45th Annual Meeting on Women's Cancer®

Tampa

March 22-25, 2014 Florida

Abstracts Presented for the 2014 Society of Gynecologic Oncology 45th Annual Meeting on Women's Cancer March 22 – March 25, 2014 Tampa Convention Center Tampa, FL

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Society of Gynecologic Oncology

Abstracts Presented for the 2014 Society of Gynecologic Oncology 45th Annual Meeting on Women's Cancer March 22 – March 25, 2014 Tampa Convention Center, Tampa, FL

Scientific Plenary I: Innovative and Practice Changing Concepts in Gynecologic Oncology
Saturday, March 22, 2014
8:25 a.m. – 9:30 a.m., Ballroom B-C
Moderator: Kathleen Moore, MD, *University of Oklahoma, Oklahoma City, OK*

1 - Scientific Plenary

Spatial analysis of geographic location and adherence to treatment guidelines for advanced-stage ovarian cancer: impact of race and socioeconomic status

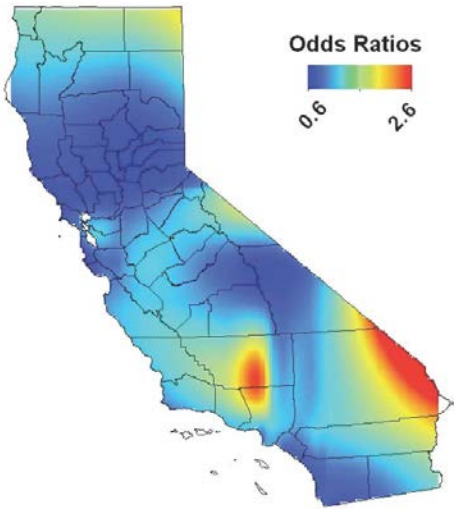
R. E. Bristow, J. Chang, A. Ziogas, H. Anton-Culver and V. M. Vieira
University of California at Irvine, Irvine, CA

Objectives: To determine the impact of geographic location of residence and proximity to a high-volume hospital (HVH) on advanced-stage ovarian cancer care adherence to National Comprehensive Cancer Network (NCCN) guidelines in relation to race and socioeconomic status (SES).

Methods: Patients diagnosed with stage IIIC/IV epithelial ovarian cancer between January 1, 1999 and December 31, 2006 were identified from the California Cancer Registry. HVHs were defined as ≥20 cases/year. Generalized additive models (GAMs) were generated to assess the effect of spatial distributions, race, and SES on adherence to NCCN guidelines, with smoothing of geographic location and adjustment for confounding variables. Addresses were geocoded to the census block centroid.

Results: A total of 11,770 patients were identified. The median age at diagnosis was 63.8 years, and 5,343 patients (45.4%) were treated according to NCCN guidelines (Figure). After controlling for disease-related characteristics, black race (OR=1.49, 95% CI=1.21-1.83) and low SES (OR=1.46, 95% CI=1.24-1.72) were associated with an increased likelihood of treatment that was not adherent to NCCN guidelines, while HVH treatment was protective (OR=0.59, 95% CI=0.53-0.66). Geographic location ≥80 km from an HVH was independently associated with an increased risk of nonadherent care (OR=1.88, 95% CI=1.61-2.19). There was an inverse linear association between SES and the proportion of patients living ≥80 km from a HVH, ranging from 6.3% (high SES) to 33.0% (low SES) ($P<0.0001$). Overall, 33.6% of patients treated at HVHs traveled ≥32 km for care compared to just 17.0% for patients treated at low-volume hospitals ($P<0.0001$). Travel distance ≥32 km to receive care was associated with an independent and statistically significant protective effect against treatment that deviated from NCCN guidelines (OR=0.80, 95% CI=0.69-0.92). White patients were significantly more likely to travel ≥32 km to receive care (21.8%) compared to blacks (14.4%), Hispanics (15.9%), and Asian/Pacific Islanders (15.5%) ($P<0.0001$).

Conclusions: Geographic proximity to a HVH and travel distance to receive treatment are independent predictors of NCCN guideline-adherent care for advanced-stage ovarian cancer. Geographic barriers to standard ovarian cancer treatment disproportionately affect racial minorities and women of low SES.



2 - Scientific Plenary

A randomized phase III trial of gemcitabine + docetaxel + bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma (uLMS): a Gynecologic Oncology Group study

M. L. Hensley[1], A. Miller[2], D. M. O'Malley[3], R. S. Mannel[4], K. Behbakht[5], J. N. Bakkum-Gamez[6] and H. Michael[7]
[1]Memorial Sloan-Kettering Cancer Center, New York, NY, [2]Gynecologic Oncology Group, Buffalo, NY, [3]The Ohio State University, Columbus, OH, [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]University of Colorado Denver, Aurora, CO, [6]Mayo Clinic, Rochester, MN, [7]Indiana University School of Medicine, Indianapolis, IN

Objectives: First-line, fixed dose-rate gemcitabine + docetaxel (GD) achieves an objective response (OR) in 35% of uLMS patients. In some cancers, the addition of bevacizumab (B) to chemotherapy has improved overall survival (OS). The primary objective of this study was to determine whether the addition of B to GD increases progression-free survival (PFS) in patients with metastatic uLMS. Secondary objectives were OR and OS.

Methods: The study was a phase III, double-blind, placebo (P)-controlled trial. Patients with metastatic unresectable uLMS, no prior cytotoxic therapy, and adequate performance status and organ function were randomly assigned to GD+B or GD+P. B 15 mg/kg or P was given on day 1. G 900 mg/m^2 over 90 minutes was given on days 1 and 8 with docetaxel 75 mg/m^2 on day 8 of each 3-week cycle. Patients with prior pelvic radiation received lower doses of GD (675/60). CT for Response Evaluation Criteria in Solid Tumors (RECIST) response was performed every other cycle. PFS, OS, and OR were compared to determine superiority. Target accrual was 130 patients to detect an increase in median PFS from 4 months (GD+P) to 6.7 months (GD+B).

Results: One hundred and two of the target 130 patients were accrued: GD+P (n=52) and GD+B (n=50). Nine patients were inevaluable for inadequate pathology, leaving 46 (GD+P) and 47 (GD+B) evaluable. No statistically significant differences in grade 3 or 4 toxicities were observed. Noted toxicities among patients on GD+B included: hypertension, grade 2 (6 patients), grade 3 (2 patients); gastrointestinal (GI) bleeding grade 1 (7 patients), grade 2 (1 patient); GI fistula, grade 3 (1 patient). Median PFS was 6.2 months for GD+P vs 4.1 months for GD+B (HR 1.14, P=0.54). At 12 months, 24.5% of patients on GD+P were progression-free vs 23.2% of patients on GD+B. Median OS was 19.4 months for GD+P and 23.3 months for GD+B (HR 1.12, P=0.71). At 12 months, 74.3% of GD+P patients were alive vs 71.2% of GD+B patients. ORs were observed in 36% of GD+P patients and 32% of GD+B patients, with mean duration of response of 7.6 months for GD+P (range, 3.8 to 30.2 months) vs 6.5 months for GD+B (range, 1.7 to 27 months). The study closed when the Data Safety and Monitoring Board determined that the observed (stratified) HR for GD+B relative to GD+P was within the futility region.

Conclusions: The addition of B to GD for first-line treatment of metastatic uLMS failed to improve PFS, OS, or OR. GD remains a reasonable first-line standard treatment for metastatic uLMS.

3 - Scientific Plenary

Comparison of the performance of human papillomavirus (HPV) primary screening strategies with cytology-based strategies: results from the ATHENA trial 3-year follow-up phase

T. C. Wright[1], M. H. Stoler[2], C. M. Behrens[3], G. Zhang[3] and A. Sharma[3]
[1]Columbia University, New York, NY, [2]University of Virginia Health System, Charlottesville, VA, [3]Roche Molecular Systems, Pleasanton, CA

Objectives: To explore the performance and clinical utility of cervical cancer screening strategies using HPV as the first-line test and to compare HPV-based strategies with cytology-based strategies

Methods: The ATHENA trial enrolled 42,209 women ≥25 years of age, of whom 40,901 were evaluable for this subanalysis. At enrollment, all women had liquid-based cytology (LBC) and HPV testing using the cobas HPV test that detects HPV16 and HPV18 separately and a pool of 12 other high-risk HPV types. Women with abnormal cytology (≥atypical squamous cells of unknown significance [ASC-US]) or high-risk HPV-positive (hrHPV+) were referred for colposcopy. Women undergoing colposcopy who did not have positive cervical intraepithelial neoplasia grade 2 (CIN2+) proceeded to the 3-year follow-up phase in which annual cytology and HPV testing were performed. During follow-up, women with ≥ASC-US cytology were referred to colposcopy but did not exit the study unless they had CIN2+. At the 3-year visit, all women underwent repeat colposcopy with cervical biopsy. For each strategy, we determined the total number of cases (baseline and during 3-year

follow-up) of CIN2+ detected as well as the number of screening tests (LBC and/or HPV tests) and the number of colposcopies required to carry out the strategy.

Results: A total of 587 cases of CIN2+ were identified at baseline and during the 3-year follow-up period. Cytology with ASC-US triage was much less sensitive for CIN2+ than any of the HPV-based strategies (Table). hrHPV primary screening with triage to colposcopy based on HPV16/18 genotyping and reflex cytology had an overall sensitivity of 80.0% and detected the most disease at the baseline screening round, but it was somewhat less efficient in terms of the number of colposcopy examinations required to identify an individual case of CIN2+. Cotesting with both cytology and hrHPV showed a marginal decrease in sensitivity (77.3%) but required nearly double the number of screening tests.

Conclusions: The 3-year follow-up data from the ATHENA trial indicate that hrHPV primary screening with triage to colposcopy based on genotyping and reflex cytology provides a more sensitive cervical screening strategy than cytology and is more efficient than cotesting.

Strategy	Screening Tests	Detected cases of CIN2+			Missed cases of CIN2+		Number of Colpos	Colpos to detect 1x CIN2+
		Total Number	*Detected at Baseline*	*Detected Years 01-03*	*Total*	*Due to LTF*		
LBC with reflex HPV for ASCUS	43,503	270	215	55	317	0	1,949	7.2
Cotesting with LBC and HPV	91,822	455	215	240	132	67	3,640	8.0
HPV with 16/18 genotyping	49,830	445	197	248	142	59	3,171	7.1
HPV with reflex cytology	54,024	443	200	243	144	61	3,138	7.1
HPV with genotyping and reflex cytology	53,820	473	283	190	114	31	3,748	7.9

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4 - Scientific Plenary

Bariatric surgery decreases the risk of uterine malignancy

K. K. Ward[1], A. M. Roncancio[2], N. R. Shah[1], M. A. Davis[1], C. C. Saenz[1], M. T. McHale[1] and S. C. Plaxe[1]
[1]UCSD Rebecca and John Moores Cancer Center, La Jolla, CA, [2]The University of Texas School of Public Health, Houston, TX

Objectives: To describe the risk of uterine malignancy among women who have had weight loss surgery.

Methods: The hypothesis for this study was that a reduced rate of uterine malignancy may be associated with previous bariatric surgery. We performed a retrospective cohort study among inpatient admissions of women ≥18 years, who were registered in the University HealthSystem Consortium (UHC) dataset from January 1, 2009 to June 1, 2013. We calculated the rate of uterine malignancy per hospital admission and compared rates according to whether diagnoses at the time of discharge included history of bariatric surgery and further, according to whether there was a diagnosis of obesity.

Results: A total of 7,431,858 admissions were recorded during the study period. Of those, 103,797 had a history of bariatric surgery and 44,345 had a diagnosis of uterine malignancy. For admissions that did not include a history of bariatric surgery, the rate of uterine malignancy was 599/100,000 (95% CI 590-610); the rate was 2.8 (95% CI 2.78-2.90) times higher among obese (1,409/100,000; 95% CI 1,380-1,440) than for nonobese (496/100,000; 95% CI 490-510) women. For admissions among patients who had a history of bariatric surgery, the risk of uterine malignancy was 408/100,000 (95% CI 370-450); the rate was 682/100,000 (95% CI 600-770) in patients with persistent obesity and 270/100,000 (95% CI 230-310) in patients who were no longer obese (relative risk 2.5; 95% CI 2.08-3.06). The relative risk of uterine malignancy in admissions for women who had prior bariatric surgery compared to obese women who had not had bariatric surgery was 0.29 (95% CI 0.26-0.32).

Conclusions: A history of bariatric surgery is associated with an approximately 70% reduced risk for uterine malignancy. This finding suggests that obesity may be a modifiable risk factor related to the development of endometrial cancer.

5 - Scientific Plenary

A cost-utility analysis of Gynecologic Oncology Group protocol 218: the importance of incorporating prospectively collected quality-of-life scores in health outcomes research

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[1]The Ohio State University, Columbus, OH, [2]San Antonio Military Medical Center, Ft. Sam Houston, TX, [3]University of California, Irvine, Irvine, CA, [4]Creighton University School of Medicine, St. Joseph's Hospital and Medical Center, Phoenix,, AZ, [5]University of Pennsylvania, Philadelphia, PA, [6]Duke University Medical Center, Durham, NC

Objectives: To estimate the quality-of-life (QOL)-adjusted cost-effectiveness of the addition of bevacizumab (B) to intravenous paclitaxel/carboplatin (PC) for the primary treatment of advanced-stage epithelial ovarian cancer.

Methods: A modified Markov state transition model of the three regimens evaluated in GOG 218 (PC, PC + concurrent B [PCB], and PC + concurrent and maintenance B [PCB+B]) was populated by prospectively collected survival, adverse event, and QOL data from the trial. Progression-free survival (PFS) and overall survival (OS) were modeled using primary event data. Severe adverse events were assigned costs using Agency for Healthcare Research and Quality data, including grade 4 hypertension and grade 3-5 bowel events that included fistula. Cost of growth factor support per cycle was incorporated. QOL scores collected using the FACT-O instrument at baseline; before cycles 4, 7, 13, and 21; and 6 months following completion of treatment were converted to utilities. QOL was assumed to be equivalent between arms from the final measured QOL time point to date of progression. All variables were modeled as mathematical distributions; a Monte Carlo probabilistic sensitivity analysis was performed to account for uncertainty in estimates.

Results: PC was the least expensive ($4,129) and least effective (mean 1.1 quality-adjusted progression-free years [QA-PFY]) regimen. PCB ($44,017 and 1.13 QA-PFY) was dominated by a combination of PC and PCB+B. PCB+B ($123,308 and 1.25 QA-PFY) was the most expensive regimen and had an incremental cost-effectiveness ratio of $757,939/QA-PFY compared to PC. In a model in which QOL was assumed to be equivalent between arms, the incremental cost-effectiveness ratio (ICER) of PCB+B was $635,120/PFY compared to PC. When using OS (rather than PFS) as an effectiveness endpoint, PCB+B had an ICER of $2,467,745/quality-adjusted life year (QALY) compared to PC.

Conclusions: In this cost-effectiveness model, the incorporation of QOL into an analysis of GOG 218 led to a change in the ICER by >$100,000/QA-PFY in favor of PC over regimens containing B compared with a model that does not include QOL. Thus, the incorporation of prospectively collected QOL data has a large impact on the cost-effectiveness of regimens in randomized, controlled trials and should be included in future studies that include health outcomes endpoints.

6 - Scientific Plenary

Evaluation of incidence and prognostic significance of newly identified hotspot mutations in DNA polymerase epsilon (POLE) in endometrial cancer: contextualizing findings from The Cancer Genome Atlas Research Network

C. C. Billingsley[1], D. E. Cohn[1], D. G. Mutch[2] and P. J. Goodfellow[1]
[1]The Ohio State University, Columbus, OH, [2]Washington University School of Medicine, St. Louis, MO

Objectives: POLE mutations characterize a subtype of endometrial cancer (EC) with a markedly increased number of somatic mutations. The Cancer Genome Atlas (TCGA) Research Network highlighted 17 (~7%) POLE-mutant cancers comprising endometrioid tumors with extremely high overall mutation rate and high incidence of microsatellite stability (MSS). The TCGA further reported that POLE mutant cases had a significantly better progression-free survival compared to POLE wild-type (WT) cases. The objective of this study was to investigate the incidence of POLE mutations and assess the clinical significance of POLE mutations in an endometrioid EC population.

Methods: Polymerase chain reaction amplification and Sanger sequencing was used to test for mutations in the exonuclease domain of POLE in 544 tumors. Demographic, clinicopathologic, and molecular data were abstracted. The relationship between POLE mutation status and clinical variables, including survival outcomes, were assessed.

Results: Mutation analysis has been completed for 304 women who had MSS tumors with analyses ongoing. The most common mutations reported by the TCGA, p.Pro286Arg and p.Val411Leu, were seen in 8 and 5 tumors, respectively. An additional mutation noted by the TCGA (p.S297F) and a novel mutation (p.P437R) were identified in 1 patient each. The combined POLE mutation rate was 4.93%. No recurrences have occurred in the POLE mutant group, while the POLE WT group has an ~12% recurrence rate.

Conclusions: We confirmed the POLE mutations described with ~5% frequency in our MSS population, similar to that reported by the TCGA. Our analysis identified a POLE mutation that has been previously reported only in colorectal cancer and never in EC. Concordant with the TCGA, there were no recurrences in the mutant group. However, understanding the true effect on survival of POLE mutations will require an analysis of a very large cohort. Conclusions about the prognostic significance of POLE mutations should be reserved until more data are available because the improved outcomes reported by the TCGA are for a very specific subset of patients and may not be generalizable to all patients with POLE mutations. Further studies are needed to fully evaluate the potential significance of POLE mutations and determine to which populations those findings may apply.

Focused Plenary I: Translational Research, Concept to Clinic
Saturday, March 22, 2014
11:00 a.m. – 12:00 p.m., Ballroom A
Moderator: Douglas A. Levine, MD, *Memorial Sloan-Kettering Cancer Center, New York, NY*

7 - Focused Plenary

Long noncoding RNA HOTAIR is associated with human cervical cancer progression

H. J. Kim, G. W. Yim, S. M. Baek, J. W. Kim and Y. T. Kim
Yonsei University College of Medicine, Seoul, South Korea

Objectives: The functions of many long noncoding RNAs (lncRNAs) in human cancers remain to be clarified. The lncRNA Hox transcript antisense intergenic RNA (*HOTAIR*), which was identified from a custom tiling array of the *HOXC* locus (12q13.13), has been reported to reprogram chromatin organization and promote breast and colorectal cancer metastasis. In this study, we examined the expression and functional role of *HOTAIR* in cervical carcinoma.

Methods: *HOTAIR* expression was determined in cervical cancer tissues (n=111) and corresponding normal tissues (n=40) by using real-time polymerase chain reaction, and its correlation with clinical parameters and prognosis were analyzed. To determine the role of *HOTAIR* in cell proliferation, migration, and invasion, RNA interference was used to knock down *HOTAIR* expression in HeLa cervical cancer cells.

Results: The expression level of *HOTAIR* in cervical cancer tissues was higher than that in corresponding noncancerous tissues. High *HOTAIR* expression correlated with lymph node metastasis, and it was a significant prognostic factor for predicting cervical cancer recurrence. Knockdown of *HOTAIR* reduced cell proliferation, migration, and invasion. Moreover, *HOTAIR* knockdown decreased the expression of vascular endothelial growth factor (VDGF) and matrix metalloproteinase-9 (MMP-9), which are important for cell motility and metastasis. Therefore, *HOTAIR* may promote tumor aggressiveness through the upregulation of VEGF and MMP-9.

Conclusions: *HOTAIR* is highly expressed in cervical cancer tissues and is associated with cervical cancer progression and prognosis. *HOTAIR* may represent a novel biomarker for predicting recurrence and prognosis and serve as a promising therapeutic target in cervical cancer.

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8 - Focused Plenary

Biological effects of metformin in a preoperative window clinical trial for endometrial cancer

K. M. Schuler[1], B. Rambally[2], M. Difurio[2], B. Sampey[3], P. A. Gehrig[2], L. Makowski[2] and V. L. Bae-Jump[2]
[1]Good Samaritan Hospital, Cincinnati, OH, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC, [3]Metabolon, Research Triangle Park, NC,

Objectives: The objective of this preoperative window clinical trial was to evaluate the antiproliferative and molecular effects of metformin in obese endometrial cancer (EC) patients.

Methods: Obese (BMI≥30) women with endometrioid EC were recruited. Once enrolled, patients began metformin at a dose of 850 mg PO once daily for 1-4 weeks before surgical staging. Using triplicate cores, a tissue microarray was constructed from paired formalin-fixed, paraffin-embedded endometrial biopsy and hysterectomy specimens before and after metformin treatment. The expression of Ki-67, a marker of cell proliferation, as well as the estrogen receptor (ER), progesterone receptor (PR), adenosine monophosphate-activated protein kinase (AMPK), and downstream targets of the mTOR pathway were measured by immunohistochemistry. Global, untargeted metabolomics was performed on serum pre- and post-

metformin treatment and matched tumor, using combined gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) techniques.

Results: Twenty patients completed the protocol. The mean duration of treatment was 14.7 days. Metformin significantly reduced Ki-67 staining based on comparison of pretreatment endometrial biopsies with posttreatment hysterectomy specimens (overall mean decrease of 11.75%, P=0.008). Sixty-five percent of patients (13/20) responded to metformin treatment, with a mean decrease in Ki-67 staining of 21.9%. Metformin treatment resulted in decreased expression of phosphorylated AMPK (60.3%, P=0.00001), phosphorylated Akt (44.2%, P=0.0002), phosphorylated S6 (51.2%, P=0.0002), and phosphorylated 4E-BP-1 (74.7%, P=0.001). Metformin decreased ER expression (65.7%, P=0.0002), but had no effect on PR expression. Metabolomic profiling of serum indicated that “responders” versus “nonresponders” to treatment appeared more sensitive to metformin’s effect on central carbon metabolism, particularly with respect to systemic lipolysis, which correlated with a shift in lipid and carbohydrate metabolism in their corresponding tumors.

Conclusions: Metformin significantly reduced proliferation in a preoperative window study in obese EC patients, with parallel effects on inhibition of the mTOR pathway. Differences were found in the metabolic effects of metformin in “responders” versus “nonresponders” to treatment. This study provides support for therapeutic clinical trials of metformin in this obesity-driven disease.

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9 - Focused Plenary

Omentin: a potential tumor suppressor in the microenvironment associated with visceral obesity

M. Onstad, C. Au Yeung, L. L. Holman, R. E. Schmandt, Q. Zhang, M. F. Munsell, S. Mok and K. H. Lu
The University of Texas MD Anderson Cancer Center, Houston, TX

Objectives: Omentin is a newly discovered adipokine secreted by the mesothelial cells of visceral adipose tissue. Its expression is inversely related to obesity, and we hypothesize that omentin may have tumor suppressor activity. We sought to compare circulating omentin concentrations in women with ovarian cancer to those in healthy controls and to explore the effect of omentin on ovarian cancer progression.

Methods: Serum samples were collected from 148 patients with serous ovarian cancer and 148 body mass index (BMI)-matched healthy controls. Circulating omentin concentrations levels were quantified by enzyme-linked immunosorbent assay. Immunohistochemistry (IHC) was used to evaluate omentin expression in cancer-associated and normal omental adipose tissues. Normal human mesothelial cells were cocultured with an ovarian cancer cell line (SKOV3) to examine the influence of ovarian cancer cells on mesothelial omentin mRNA expression. We further cultured ovarian cancer cells with conditioned media from omentin-treated adipocytes, and measured cell proliferation using MTT assays. Motility and invasion potential were evaluated using wound healing assays and invasion potential assays, respectively.

Results: In BMI-matched individuals, mean circulating omentin concentrations were significantly lower in ovarian cancer patients (416.6 vs 756.4 ng/mL, P<0.001). IHC studies correspondingly revealed that omentin expression was significantly lower in ovarian cancer-associated mesothelial cells compared to normal controls. When mesothelial cells were cocultured with ovarian cancer cells, they expressed significantly lower omentin mRNA compared to those cocultured with control media (P<0.05). In assessing omentin’s effect on cell proliferation, all cancer cell lines cultured with omentin-treated adipocytes showed a significantly lower proliferation rate compared to those cultured without omentin (P<0.05). Omentin also significantly suppressed the motility and invasion potential of ovarian cancer cells (P<0.01).

Conclusions: In patients with matched BMI, the concentration of circulating omentin was lower among women with ovarian cancer compared to controls. In addition, we showed that omentin decreases ovarian cancer cell proliferation, motility, and invasion potential. Our studies demonstrate that therapies or interventions that increase omentin may have clinical benefit.

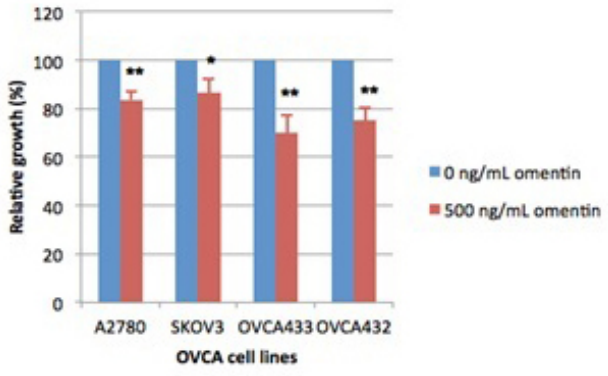

Figure 1: Ovarian cancer cells demonstrate lower proliferation rates in the presence of omentin-treated adipocytes compared to controls.
$^{**}P<0.01$; $^{*}P<0.05$.

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10 - Focused Plenary

Germline mutations in DNA repair genes in women with ovarian, peritoneal, or fallopian tube cancer treated on GOG protocols 218 and 262

B. S. Norquist[1], M. I. Harrell[1], T. Walsh[1], M. K. Lee[1], M. C. King[1], S. A. Davidson[2], R. S. Mannel[3], P. A. DiSilvestro[4], E. M. Swisher[1] and M. J. Birrer[5]
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Objectives: GOG218 and GOG262 were trials of adjuvant chemotherapy following debulking surgery for advanced ovarian, peritoneal, and fallopian tube cancers. Our objective was to deeply sequence germline DNA from patients treated on these protocols for mutations in 47 DNA repair genes to determine the frequency and spectrum of inherited mutations in a large group of ovarian cancer patients.

Methods: De-identified germline DNA samples were sequenced using a targeted capture and massively parallel sequencing test (BROCA-HR). BROCA-HR detects all types of mutations (insertions, deletions, single base-pair changes, splice site mutations, and copy number variations) in a panel of 47 genes that include *BRCA1* and *BRCA2* and other genes in the Fanconi anemia-BRCA and related pathways.

Results: A total of 950 samples have been sequenced using BROCA-HR (773 from GOG 218, 177 from GOG 262). The germline mutation rate was 213/950 (22.4%). A total of 142/950 (14.9%) had mutations in *BRCA1* or *BRCA2*, 49/950 (5.2%) had mutations in other genes associated with cancer, and 22/950 (2.3%) had mutations in candidate genes. Mutations in non-*BRCA1/2* cancer-associated genes included *BRIP1* (16), *PALB2* (7), *NBN* (6), *CHEK2* (5), *ATM* (5), *RAD51D* (5), *RAD51C* (4), *ATR* (2), *BARD1* (2), *MRE11A* (1), *SLX4* (1), *XRCC2* (1), *TP53* (1), and *PMS2* (1). Inherited loss-of-function mutations occurred in 49/191 (25.7%) genes other than *BRCA1/2*. Sequencing data from an additional 400 GOG 262 cases will be available at the time of presentation and will be correlated with clinical variables.

Conclusions: Women with advanced-stage ovarian carcinoma have a high rate of germline mutations in ovarian cancer susceptibility genes. Novel ovarian cancer genes not previously reported included *ATM, ATR, SLX4,* and *XRCC2*. Approximately 25% of mutations are missed by sequencing only *BRCA1* and *BRCA2*. Targeted capture and massively parallel sequencing allows for accurate, cost-effective detection of mutations in multiple genes simultaneously.

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11 - Focused Plenary

Molecular profiling of tumors from stage I versus stage III/IV cancer patients: a prediction signature for metastasis in Gynecologic Oncology Group 8024

Y. Casablanca[1], J. Mieznikowski[2], R. Day[3], C. A. Hamilton[4], T. P. Conrads[5], G. L. Maxwell[6], B. L. Hood[5], A. Wallace[7], G. S. Rose[8] and D. S. McMeekin[9]
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Objectives: In the United States, only 25% of patients with newly diagnosed endometrial cancer are referred to a gynecologic oncologist for subspecialty management. The objective of this study was to identify changes in molecular expression of transcripts and/or proteins that correlate with extrauterine disease.

Methods: More than 650 cases of endometrioid endometrial cancer from Gynecologic Oncology Group 210 and Duke University were screened to identify 164 eligible and evaluable patients with satisfactory transcript expression and proteomic data from laser microdissected frozen primary tumors. The sample sets were broken into a training set (n=74: 29 stage I, 27 stage IIIC, 18 stage IV, grade missing in 3 cases) and a validation set (n=80: 45 stage I, 36 stage IIIC, 9 stage IV). Wilcoxon-ranked sum testing was used to evaluate the differentially abundant transcripts and proteins. Q values were generated to adjust for multiple testing and false discovery. Candidates with a q value <0.05 moved forward for validation. Predictive accuracy was assessed by logistic regression.

Results: There were 343 differentially expressed transcripts in the training set (P<0.001) and none passed the false-discovery threshold (q<0.05). Of the 230 differentially abundant proteins in tumors with and without metastasis (P<0.05), 38 had a q value <0.05. *EPHX1, ISOC1, TOP2A, AGRIN*, and *FASN* were the top five candidates (P<0.001 and q<0.02) that passed the threshold to move to validation. The prediction model for metastasis based on grade 3 alone had an AUC of 0.619 in the training set and 0.554 in the validation set. The model with the top five candidate proteins and grade 3 had an AUC of 0.968 in the training set but only 0.714 in the validation set.

Conclusions: A predictive molecular signature for metastasis in endometrial cancer using transcript expression or protein expression analysis was not found. These data either highlight limitations reflective of selection bias or support a longitudinal metastasis hypothesis in which the metastatic lesion is not predicted by the profile of the primary tumor. Future investigative work should focus on new methodologies aimed at prediction of metastasis.

Focused Plenary II: Sexual and Geriatric Population Health
Saturday, March 22, 2014
11 a.m. – 12:10 p.m., Room 13-16
Moderator: Marcela Del Carmen, MD, MPH, *Massachusetts General Hospital/Harvard University, Boston, MA*

12 - Focused Plenary

Operative outcomes among a geriatric population of endometrial cancer patients: an ancillary data analysis of Gynecologic Oncology Group study LAP2

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[1]The University of Oklahoma, Oklahoma City, OK, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY

Objectives: The elderly population is the most rapidly growing age bracket in the United States. By the year 2020, there will be >55 million people >65 years of age (16.8% of population) and almost 80 million (21% of population) by 2040. The incidence of endometrial cancer (EC) is expected to increase with an aging population. LAP2 is one of the largest prospective trials of surgical staging in EC. This analysis sought to evaluate surgical outcomes among patients >70 year of age.

Methods: An ancillary data analysis of Gynecologic Oncology Group LAP2 was performed. Descriptive statistics were used for demographics, surgicopathologic characteristics, and complications by body mass index (BMI). Wilcoxon, Pearson, Cochran-Mantel-Haenszel, and Kruskal-Wallis tests were used for univariate and multivariate analysis.

Results: LAP2 enrolled 2,516 eligible patients with clinical stage I EC. Patients were randomized in a 2:1 fashion to laparoscopy (L/S) (n=1,630) or open surgery (XLAP) (n=886). The median age for the 2 groups did not differ at 62.8 and 62.7 years, respectively. Among patients in the L/S arm, 29.1% were >70 years of age, as were 27.2% in the XLAP arm. Patients >70 years had lower BMI (P<0.01) and were more often converted from L/S to XLAP (23.7% vs 28.6%; P=0.039). Evaluating the L/S group, the only intraoperative complication (IOC) that increased with age was injury to the bladder (P=0.032). The only postoperative complication (POC) that increased with age was wound complication (P=0.042) and hospital stay >2 days (P<0.001). Looking at XLAP, there were no differences in IOC. Several POCs increased with age, including venous thromboembolism (P=0.05), pneumonia (P=0.006), urinary fistula (P=0.004), congestive heart failure

(P=0.016), and arrhythmia (P<0.001). More readmissions (P=0.022) and postoperative deaths (P=0.005) were seen with increasing age.

Conclusions: Overall rates of complications were low in this cohort, even among the elderly. This was a highly selected population with good performance status and possibly better tolerance of surgical interventions. Even so, significant post- and perioperative complications occurred with increasing age, which should inform surgical planning and counseling for this vulnerable population.

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13 - Focused Plenary

Comparative effectiveness of radical hysterectomy in elderly women with cervical cancer

E. George, A. I. Tergas, S. N. Lewin, W. M. Burke, E. Prendergast, Y. S. Lu, T. J. Herzog and J. D. Wright
Columbia University, New York, NY

Objectives: Despite institutional studies that suggest that radical hysterectomy for cervical cancer is well tolerated in the elderly, little population-level data are available to describe the outcomes of the procedure in older women. We performed a population-based analysis to determine the morbidity, mortality, and resource utilization of radical hysterectomy in elderly women with cervical cancer.

Methods: Patients with invasive cervical cancer who underwent abdominal radical hysterectomy between 1998 and 2010 and were recorded in the Nationwide Inpatient Sample were analyzed. Patients were stratified by age <50, 50-59, 60-69, and >70 years. The association between age and the outcomes of interest was examined using chi square tests and multivariable logistic regression models to adjust for confounding variables.

Results: A total of 8,206 women were identified. The cohort included 786 (9.4%) women age 60-69 years and 462 (5.6%) women >70 years. All-cause morbidity increased from 20.9% in women <50 years to 23.1% in those 50-59 years, 29.4% in patients 60-69 years, and 31.8% in women >70 years (P<0.0001). Compared to women <50 years, those >70 years were more likely to have intraoperative complications (4.6% vs 8.9%, P=0.0004), surgical site complications (10.9% vs 17.5%, P<0.0001), and perioperative medical complications (8.3% vs 14.9%, P<0.0001). Transfusion was required in 11.0% of women <50 years compared to 23.2% in patients >70 years (P<0.0001), while a prolonged hospitalization was required in 59.5% vs 80.1% of women in these respective age groups (P<0.0001). The risk of non-routine discharge (to a nursing facility) was 0.5% in women <50 years, 2.3% in those 60-69 years, and 12.3% in women >70 years (P<0.0001). Perioperative mortality was 0.05% in women <50 years compared to 0.3% in those 60-69 years and 1.5% in those >70 years (P<0.0001).

Conclusions: Despite institutional claims that radical hysterectomy is well tolerated in the elderly, we noted higher complication rates in elderly women and a more than tenfold greater risk of perioperative mortality in women >70 years of age compared to younger women. Nonsurgical treatments should be considered in elderly women with cervical cancer.

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14 - Focused Plenary

Sexual function among older female cancer survivors

S. Chatterjee[1], D. Patel[2], E. Erekson[3] and E. S. Ratner[1]
[1]Yale University School of Medicine, New Haven, CT, [2]University of Michigan, Ann Arbor, MI, [3]Dartmouth-Hitchcock Medical Center, Lebanon, NH

Objectives: Sexual health greatly affects quality of life and may be negatively affected in cancer survivors. The aim of this study was to compare sexual function of older female cancer survivors relative to other women without a history of cancer.

Methods: We performed a cross-sectional analysis of the 2005-2006 National Social Life, Health, and Aging Project (NSHAP) database to investigate sexual attitudes and function of female cancer survivors ages 57 to 85 years. We compared sexuality in older female cancer survivors to other women and substratified by age and years since cancer diagnosis. Outcomes measured included sexual partnership, activity, frequency, attitudes and beliefs, and dysfunction.

Results: A total of 1,550 women were included in the analysis, of whom 6.5% were cancer survivors. The most common cancer was breast cancer (38.6%), followed by gynecologic malignancies (32.4%). Female cancer survivors were less likely

to report a current sexual partner (P=0.004) or sexual activity in the previous 12 months (P=0.03) and reported decreased interest in sex (P=0.04) compared to their noncancer counterparts. No differences were observed regarding types of sexual activity between cancer survivors and other women, as measured by degree of foreplay (P=0.13), vaginal coitus (P=0.10), and masturbation (P=0.90). Common sexual problems, such as vaginal dryness (P=0.36), anorgasmia (P=0.47), dyspareunia (P=0.46), lack of pleasure (P=0.15), performance anxiety (P=0.07), and avoidance of sex (P=0.19), were similar between female cancer survivors and other women. Sexual attitudes, values and beliefs, and sexual dysfunction were also similar between age groups of cancer survivors (57-64 years, 65-74 years, and 75-85 years). Female survivors within 5 years of cancer diagnosis reported increased vaginal dryness and dyspareunia compared with female cancer survivors >5 years since their diagnosis (P=0.038 and P=0.0055, respectively).

Conclusions: Although there are issues unique to female cancer survivors, such as decreased interest in sex and sexual frequency, we found that overall sexual activity and sexual attitudes were similar to the general population.

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15 - Focused Plenary

Baseline characteristics and concerns of cancer patients/survivors seeking treatment at a female sexual medicine program

C. Stabile, B. Seidel, D. J. Goldfrank, R. E. Baser, A. R. Gunn, D. S. Chi, R. F. Steed, S. Goldfarb, R. R. Barakat and J. Carter
Memorial Sloan-Kettering Cancer Center, New York, NY

Objectives: To characterize those seeking treatment at a female sexual medicine (FSM) program and examine their sexual/vaginal health issues. The program was established to address the consequences of cancer treatment on vaginal health and sexuality.

Methods: A limited waiver of authorization was obtained to evaluate the FSM Program. Demographic and medical information and FSM clinical assessment forms from 509 new visits were analyzed. The FSM clinical assessment form consists of a clinician evaluation form with the Vaginal Assessment Scale (VAS); patient-reported outcomes (PROs), including the Sexual Activity Questionnaire (SAQ), Sexual Self-Schema Scale (SSSS), and Female Sexual Function Index (FSFI); and exploratory items.

Results: Of the 509 patients**,** 493 (97%) completed PROs. Due to staff changes, 253 of these women also received pelvic examinations. Most of the women seeking treatment had histories of breast (260 [51%]) or gynecologic (190 [37%]) cancer. Other cancers included colorectal/anal (35 [7%]), skin (20 [4%]), gastric/genitourinary (17 [3%]), and hematologic (17 [3%]). Eighty-one percent of patients were married or partnered. The median age was 51.6 years (mean, 51 years). On pelvic examination, approximately two-thirds of patients had elevated vaginal pH scores (5-6.5 [35%] or 6.5+ [33%]) and minimal (62%) or no (5%) vaginal moisture. Eighty-seven patients (44%) experienced pain during their examinations (25% mild, 12% moderate, 2% severe). Fifty-three percent of patients were sexually active, but only 43% felt confident about sexual activity. The degree of concern about sexual function/vaginal health was significant, with a mean of 7.9 on a scale of 0 (not at all) to 10 (very much). Approximately half had moderate/severe dryness (133 [51%]) and dyspareunia (120 [46%]) per the VAS. The mean SSSS score was 60.7, indicating a slightly positive sexual self-view. However, 93% (429) had an FSFI score below 26, suggesting sexual dysfunction.

Conclusions: At initial consultation, women reported symptoms of vaginal dryness, pain, and sexual dysfunction. Pelvic examinations for many women revealed elevated vaginal pH, lack of moisture, and discomfort with the examination itself. Future analyses will examine changes over time. Our goal is to provide information, strategies, and support to improve symptoms while promoting confidence about sexual/vaginal health.

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16 - Focused Plenary

Evaluation of a multifaceted vaginal health program in gynecologic cancer patients experiencing sexual dysfunction: a randomized controlled trial

N. A. Onujiogu[1,2], L. A. Seaborne[1], J. K. Rash[1], S. L. Stewart[1], R. J. Chappell[1] and D. M. Kushner[1]
[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, [2]University of Illinois, Chicago, IL

Objectives: Half of patients treated for gynecologic cancer report severe, chronic sexual problems. The Vaginal Renewal™ Program (VRP) is a multidimensional vaginal health system consisting of a vibrating vaginal wand, water-based lubricant, and instructions on moisturizing and massaging the vulva and vagina. We assessed the efficacy of VRP in women with gynecologic cancers and sexual dysfunction.

Methods: This randomized, controlled trial included women with a history of gynecologic cancer and no evidence of disease who were at least 3 months from their last surgical or radiation treatment. Patients had self-reported sexual dysfunction with a suspected physical component and desire to improve their sexual function. They were randomized to either VRP or standard of care (SOC). The primary objective was to assess the 6-month change in the Female Sexual Function Index (FSFI) score. Changes in quality of life were also measured by Functional Assessment of Cancer Therapy General (FACT-G), Marinoff Dyspareunia Scale, change in vaginal length, and qualitative self-report.

Results: Twenty-nine women enrolled over 20 months: 16 in the VRP arm and 13 in the SOC arm. The primary disease sites were endometrial (48%), ovarian (34%), cervical (14%), and vulvar (3%). Sixty-three percent had stage I disease, 13% stage III, 10% stage II, and 3% stage IV. Twenty percent had received radiation. The study was closed before completion due to a drop in accrual rate. The median baseline FSFI score was 14 in the VRP arm and 13 in the SOC arm (<26 is consistent with sexual dysfunction). The FSFI score for both arms increased by 6 points over 6 months. Of the 12 self-report comments in both arms, all reported improvement in sexual experience. All women in the SOC arm completed the final surveys; half the women in the VRP arm did not.

Conclusions: Despite the mode of therapy, when clinicians pay dedicated attention to sexual dysfunction, overall sexual satisfaction of gynecologic cancer survivors improves. Patient self-report revealed comments indicating improvement in overall sexual experience. The effectiveness of the VRP system as compared to SOC were difficult to assess with these results, but they inform further study design. The impact of dedicated clinician attention to sexual dysfunction in this population should be more formally studied.

Focused Plenary III: Surgical Film Session
Saturday, March 22, 2014
11:00 a.m. – 12:10 p.m., Ballroom B-C
Moderator: Alexander Olawaiye, MD, *Magee-Womens Hospital of UPMC, Pittsburgh, PA*

17 - Surgical Film

Development and robotic dissection of a novel pelvic lymphadenectomy model

D. J. Kiely[1], W. H. Gotlieb[2], K. Jardon[3], S. Lau[2] and J. Z. Press[2,4]
[1]Université de Montréal - Hopital Notre Dame, Montreal, QC, Canada, [2]McGill University - Jewish General Hospital, Montreal, QC, Canada, [3]McGill University - Royal Victoria Hospital, Montreal, QC, Canada, [4]Pacific Gynecology Specialists, Seattle, WA

This video demonstrates an original model of pelvic lymphadenectomy for surgical simulation training. The model incorporates novel low-cost, surgeon-designed techniques to model vasculature and dissection planes. Assembly of the model and highlights of five robotic dissections by three gynecologic oncologists and two gynecologic oncology fellows are shown. This model demonstrates that complex anatomy can be simulated using a low-cost inanimate model, thereby increasing the accessibility of advanced surgical simulation in gynecologic oncology.

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18 - Surgical Film

Resection of a gastrosplenic ligament tumor in a patient with recurrent stage IA uterine papillary serous carcinoma

G. Menderes[1] and D. A. Silasi[2]
[1]Yale New Haven Health System - Bridgeport Hospital, Bridgeport, CT, [2]Yale University School of Medicine, New Haven, CT

The patient is a 56-year-old white woman who initially underwent robotic-assisted total laparoscopic hysterectomy/bilateral salpingo-oopherectomy/pelvic and para-aortic lymph node dissection and infracolic omentectomy in 2009 for stage IA papillary serous carcinoma of the uterus. Subsequently, she was treated with adjuvant chemotherapy of carboplatin/paclitaxel for 6 cycles. She had recurrence 3 years after completion of chemotherapy with a 5-cm tumor in the gastrosplenic ligament. This tumor was resected laparoscopically with robotic assistance in January 2012 and received chemotherapy after the surgery. She has been alive with disease since then. This video demonstrates the resection of the gastrosplenic ligament tumor.

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19 - Surgical Film

Robotic-assisted total intracorporeal ileal loop urinary diversion

P. C. Lim
Center of Hope, Reno, NV

The ileal loop urinary diversion procedure is an integral part of surgical treatment for central recurrent cervical cancer requiring pelvic exenteration. The procedure is typically performed via open laparotomy, which often is associated with significant blood loss, increased morbidity, and prolonged recovery. Thus, it would be ideal to perform the ileal loop urinary diversion via a minimally invasive surgical approach that is either laparoscopic or robotic-assisted. A major limitation of traditional laparoscopic-assisted urinary diversion is the inability to perform ureteroileal anastamosis, which requires fine sewing. A detailed technique of robotic-assisted complete intracorporeal ileal loop urinary diversion is described.

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20 - Surgical Film

High-resolution anoscopy for the detection of anal intraepithelial neoplasia

A. C. ElNaggar[1] and W. Likes[2]
[1]The Ohio State University, Columbus, OH, [2]University of Tennessee Health Science Center, Memphis, TN

We present the performance of high-resolution anoscopy (HRA) for the detection of anal intraepithelial neoplasia. This video depicts important landmarks of the anal canal and pathologic features of anal intraepithelial neoplasia (AIN). The patient is a 25-year-old white woman seen in June 2013 for atypical squamous cells of unknown significance (ASCUS) anal cytology with high-risk human papillomavirus. Her past medical history includes human immunodeficiency virus, cervical intraepithelial neoplasia grade 1, and vulvar intraepithelial neoplasia grade 1. She has smoked approximately half a pack per day of cigarettes for the past 9 years. Her last CD4 count was 700 and viral load was 10,000. Physical examination shows an area of abnormal vessel pattern with application of acetic acid. This area is also nonstaining with iodine. The area is biopsied and found to be mild AIN. The management is repeat HRA in 1 year.

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21 - Surgical Film

Resection of aortocaval lymphadenopathy in a patient with metastatic serous carcinoma of the fallopian tube

G. Menderes[1] and D. A. Silasi[2]
[1]Yale New Haven Health System, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT

The patient is a 51-year-old white woman who initially presented to her primary gynecologist with new-onset pelvic pain. Transvaginal/pelvic ultrasonography revealed bilateral complex adnexal masses. She was taken to operating room with these findings without any further evaluation. She underwent robotic-assisted total laparoscopic hysterectomy/bilateral salpingo-oophorectomy. Intraoperative frozen section was not requested. The woman's postoperative course was uneventful. Final pathology revealed high-grade serous carcinoma of fallopian tube origin that had metastasized to bilateral ovaries. She was referred to gynecologic oncology. After thorough counseling about pathology results and recommended treatment, she decided to proceed with a complete staging procedure. She was taken to operating room 2 weeks after the initial surgery and underwent robotic-assisted pelvic and para-aortic lymphadenectomy, with resection of aortocaval lymphadenopathy/infracolic omentectomy/peritoneal biopsies and pelvic washings. After uneventfully recovering from her second surgery, the woman is undergoing adjuvant chemotherapy.

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22 - Surgical Film

Recurrent vulvar carcinoma treated with robotic infralevator total pelvic exenteration: a minimally invasive alternative for the elderly population

J. R. Woessner and M. Moslemi-Kebria
The Cleveland Clinic, Cleveland, OH

Recurrent vulvar carcinoma has traditionally been treated with pelvic exenteration performed via laparotomy, an invasive procedure that may be associated with a high-level of morbidity. Because of this high morbidity, elderly patients are often not considered good surgical candidates. However, robotic surgery offers a minimally invasive technique. Robotic total pelvic exenteration procedures now offer the elderly patient a less morbid, minimally invasive surgical treatment alternative.

Featured Poster Session I: International Efforts in Gynecologic Cancer
Saturday, March 22, 2014
2:00 p.m. – 3:00 p.m., Rooms 13-16
Moderator: Ram Eitan, MD, *Rabin Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israe*l

23 - Featured Poster

External validation of an all-stage ovarian cancer nomogram: is BRCA status more predictive than family history?

B. Cormier[1], J. N. Barlin[2], O. Charette[1], L. Kou[3], C. Yu[3], M. W. Kattan[3], D. S. Chi[2] and D. M. Provencher[1]
[1]Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, [2]Memorial Sloan-Kettering Cancer Center, New York, NY, [3]The Cleveland Clinic, Cleveland, OH

Objectives: An all-stage nomogram to predict 5-year disease-specific mortality for epithelial ovarian cancer has been described by Memorial Sloan-Kettering Cancer Center (MSKCC). The variables used in this nomogram were age, stage, residual disease status, preoperative albumin level, histology, American Society of Anesthesia status, and family history suggestive of hereditary breast/ovarian cancer (HBOC). The aim of this study was to externally validate the nomogram using an independent patient cohort and to evaluate the predictive ability of BRCA status compared to family history suggestive of HBOC.

Methods: We examined the medical records of all consecutive patients who underwent primary surgery for epithelial ovarian cancer at our institution between July 1992 and August 2009. Patients were included if the 7 variables from the MSKCC nomogram were available and their germline BRCA mutation status was known. Concordance index (CI) and calibration plot were used to validate the existing model on our external data. To compare predictive capabilities of BRCA and HBOC, a base competing risks regression model was formed with the MSKCC data (excluding HBOC) and applied to our local data to generate a risk score for each patient. This risk score was then used with either HBOC or BRCA to build two new models from our validation data, whose CIs were compared through bootstrap resamples.

Results: A total of 304 patients were included in the final analysis. HBOC was present in 89 patients (29%), and a BRCA mutation was confirmed in 37 patients (12%). The CI of the original nomogram on our external patients was 0.670. The new models built on our data showed no difference in bootstrap-corrected CIs (0.677 for both the BRCA and the HBOC models, P=0.994).

Conclusions: The MSKCC all-stage epithelial ovarian cancer nomogram was externally validated in an independent population. Knowledge of BRCA status rather than just HBOC family history was not shown to improve the prognostic value of this tool, thereby maintaining excellent accessibility of this nomogram in clinical practice.

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24 - Featured Poster

Increased incidence and poor prognosis of breast cancer in postmenopausal women with high body mass index attending a mammography screening program in the province of Modena (Italy)

F. Sebastiani[1], L. Cortesi[1], M. Sant[2], V. Lucarini[1], C. Cirilli[1], E. De Matteis[1], I. Marchi[1], R. Negri[1], E. Gallo[1] and M. Federico[1]
[1]University of Modena and Reggio Emilia, Modena, Italy, [2]National Tumor Institute, Milano, Italy

Objectives: We conducted a study to evaluate the relationship between body mass index (BMI) and breast cancer (BC) incidence and outcome in a population of more than 14.500 postmenopausal women offered a mammography screening program (MSP) in the province of Modena, Italy.

Methods: Study population was drawn from women who participated in the MSP between 2004 and 2006. Women were subdivided in obese, overweight, and normal-weight groups according to BMI and followed until July 31, 2010, to evaluate the BC incidence. Clinicopathologic characteristics of diagnosed BC also were evaluated in different groups of patients. After BC diagnosis, patients were followed for a median of 65 months (range, 2-104), and second events (recurrences and second tumors) were registered. The 5-year event-free survival (EFS) was calculated.

Results: During a period of 73 months, 366 cases of BC occurred. Obese women had a significantly higher incidence of BC (RR=1.32; *P*=0.04) compared with normal-weight women (RR=1), their tumors were larger (27% of tumors were >T2 size), and they had more nodal involvement (38.5% of tumors were node-positive). Furthermore, a significantly higher rate of events was seen in obese women compared with overweight and normal-weight patients (17.9% vs 11.4% vs 10.8%, respectively, *P*=0.032). The 5-year EFS was 89%, 89%, and 80% for normal-weight, overweight, and obese patients, respectively.

Conclusions: Obese women had a significantly higher incidence of BC among those offered the MSP in the province of Modena. Obese women also had more second events and a poorer prognosis than nonobese women.

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25 - Featured Poster

Nutritional Risk Index as a significant prognostic factor in advanced-stage epithelial ovarian cancer patients

J. W. Yoon, G. W. Yim, S. W. Kim, E. J. Nam, S. Kim, J. W. Kim and Y. T. Kim
Yonsei University College of Medicine, Seoul, South Korea

Objectives: Ovarian cancer is a chronic, wasting disease. Nutritional Risk Index (NRI) has been reported as a simple and accurate tool to assess nutritional status. The objective of this study was to explore the association between pre/postchemotherapy nutritional risk and survival using NRI.

Methods: A retrospective data review was conducted of 212 stage III/IV ovarian cancer patients who received primary surgical staging with 6 cycles of paclitaxel plus platinum postoperative adjuvant chemotherapy. NRI was calculated with patient body weight, ideal body weight, and serum albumin value. Body mass index (BMI) was categorized by World Health Organization criteria: underweight (<18.5), normal (18.5-22.9), and overweight (23.0 and greater). Weight change was defined as the ratio of body weight at the last course of chemotherapy to presurgery body weight. Overall survival (OS) and recurrence-free survival (RFS) classified by NRI were estimated by Kaplan-Meier, and associations were assessed by Cox proportional hazards analysis adjusted for known prognostic variables (age, histology, tumor grade, residual tumor).

Results: Mean age of patients was 54 years. Mean BMI was 23.1 (overweight) and 22.5 (normal) before and after chemotherapy, respectively. Postchemotherapy weight loss (1% to 9.9%) occurred in 48% of patients. Twenty-eight percent of patients were moderately-to-severely malnourished before treatment according to NRI. During 11 years of follow-up, 117 patients had recurrences and 67 patients died. The 5-year OS and RFS were 58.9% and 37.8%, respectively, and NRI was significantly associated with survival (median survival time: 80 months). Moderately-to-severely malnourished patients before chemotherapy had lower OS (48 months) compared to normal-to-mildly malnourished patients (80 months) (*P*=0.014). Posttreatment NRI showed a similar trend in OS. Adjusted for covariates, the relative risk of death was 3.6 times higher in the moderately-to-severely malnourished group (HR=3.6, 95% CI=1.63-7.96, *P*=0.002) compared with normal-to-mildly malnourished patients. No association was seen between weight change and survival.

Conclusions: NRI is a simplified nutritional screening index that may aid as a potential prognostic factor for survival. This study documents that nutritional assessment and support should not be overlooked during patient care.

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Nonradical surgery for small early-stage cervical cancer: is it time?

G. Bouchard-Fortier, C. J. M. Reade and A. L. Covens
University of Toronto, Toronto, ON, Canada

Objectives: Radical hysterectomy is the gold standard surgical approach for invasive cervical cancer, but nonradical surgery is now being considered in women with early-stage cervical cancer to avoid morbidity. The goal of this study was to evaluate the outcomes of women with early-stage cervical cancer treated with a nonradical surgical approach.

Methods: Between March 1991 and July 2013, 51 women with early-stage cervical cancer were treated with simple hysterectomy or cone biopsy and concomitant bilateral pelvic lymphadenectomy or sentinel lymph node biopsy. Data on patient demographics, clinical stage, perioperative complications, pathology findings, and disease-free interval were collected prospectively.

Results: The median age of the woman was 34 years (range, 19-77 years). Twenty-five women had squamous cell carcinoma (SCC), 22 had adenocarcinoma (AC), and 3 had adenosquamous (AS) carcinoma. Thirty women had FIGO stage 1A1 disease, 8 women had stage IA2 disease, and 13 women had stage 1B1 disease. Twenty-two (43%) and 29 (57%) women underwent simple hysterectomy with lymphadenectomy and cone biopsy with lymphadenectomy, respectively. Median tumor size was 10 mm (range, 2-11 mm). Lymphovascular space invasion (LVSI) was present in 18 women (35%). The median depth of invasion was 2.0 mm (range, 0.6-12 mm), 2.0 mm (range, 0.1-4.5 mm), and 2.0 mm (range, 1.7-4.0 mm) for women with SCC, AC, and AS, respectively. The margins were clear in all women. Two women received adjuvant chemoradiation (one had deep stromal invasion on cone biopsy with LVSI and one had two micrometastases to pelvic nodes). More than 95% (49 of 51 women) of patients had their Foley catheter removed on the day of surgery or postoperative day 1. There were no intraoperative or postoperative complications, and the average blood loss was estimated at 143 mL. Median follow-up was 21 months (range, 1-112 months). None of the 51 women with early-stage cervical cancer developed a recurrence during their follow-up time (95% CI: 0-6%).

Conclusions: Nonradical surgery in appropriately selected early-stage cervical cancer patients appears to be associated with a very low perioperative complication rate and excellent oncologic outcomes. While large phase II and III studies are underway, this approach seems to be a safe and reasonable option in well-selected patients.

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27 - Featured Poster

Radical trachelectomy in early-stage cervical cancer: is minimally invasive surgery the new standard of care?

G. J. Rendón[1], L. R. Pareja Franco[1], M. A. Vieira[2], A. M. Nick[3], M. F. Munsell[3], L. M. Echeverri[1], K. M. Schmeler[3], M. M. Frumovitz[3], P. F. Escobar[4] and P. T. Ramirez[3]
[1]Instituto de Cancerología - Las Américas, Medellín, Colombia, [2]Barretos Cancer Hospital, Barretos, Brazil, [3]The University of Texas MD Anderson Cancer Center, Houston, TX, [4]The Cleveland Clinic Foundation, Cleveland, OH

Objectives: Radical trachelectomy is considered standard of care in patients with early-stage cervical cancer interested in future fertility. The goal of this study was to compare operative, oncologic, and obstetric outcomes in patients with early-stage cervical cancer undergoing open or minimally invasive radical trachelectomy.

Methods: A retrospective review was performed of all patients from 4 institutions who underwent radical trachelectomy for early-stage cervical cancer from June 2002 to July 2013, evaluating perioperative, oncologic, and obstetric outcomes.

Results: Of 100 patients included in the study, 42 (42.0%) had minimally invasive surgery (MIS) (laparoscopic or robotic). There were no differences in age, body mass index, race, histology, lymphvascular space invasion, or stage between the two groups ($P>0.05$). The median surgical time for MIS and laparotomy was 272 and 270 minutes, respectively ($P=0.78$). Blood loss was significantly less for MIS vs laparotomy (50 mL [10-225 mL] vs 300 mL [50-1,100 mL]) ($P<0.0001$). Length of hospitalization was shorter for MIS than laparotomy (1 day [1-3 days] vs 4 days [1-9 days]) ($P<0.0001$). Two intraoperative complications occurred: 1 bladder injury in MIS and 1 vascular injury in open surgery. The median lymph node count was 17 (5-47) for MIS vs 22 (7-48) for open surgery ($P=0.03$). There were no differences in the rate of postoperative complications (30% MIS vs 31% open surgery). Among 84 patients who preserved their fertility, 34 (40%) attempted to get pregnant. The pregnancy rate was highest in the open surgery group (51% vs 28%) ($P=0.018$). At a median follow-up of 30 months (0.3-135 months) there were 2 recurrences.

Conclusions: Radical trachelectomy via MIS results in less estimated blood loss and a shorter hospital stay. We have shown that oncologic results are similar to historical reports of radical hysterectomy.

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28 - Featured Poster

A phase III randomized clinical trial of laparoscopic (TLRH) or robotic radical hysterectomy (RRH) versus abdominal radical hysterectomy (ARH) in patients with early-stage cervical cancer: preliminary quality-of-life outcomes

A. Obermair[1], M. M. Frumovitz[2], V. Gebski[3], M. Janda[4], J. Baker[4], L. R. Pareja Franco[5] and P. T. Ramirez[2]
[1]Queensland Centre for Gynaecological Cancer, Herston, Australia, [2]The University of Texas MD Anderson Cancer Center,

Houston, TX, [3]NHMRC Clinical Trials Centre, Sydney, Australia, [4]Institute of Health Biomedical Innovation (IHBI), Brisbane, Australia, [5]Instituto de Cancerología - Las Américas, Medellín, Colombia

Objectives: No randomized controlled trials have compared open to minimally invasive surgery for early-stage cervical cancer. The LACC trial is a prospective multi-institutional trial comparing radical hysterectomy performed by an open approach with a minimally invasive approach. The objective of this report is to provide preliminary results on quality-of-life (QOL) outcomes.

Methods: Between 2008 and 2013, 271 patients were enrolled at 24 centers in 9 countries. Patients with histologically confirmed invasive squamous cell carcinoma or adenocarcinoma of the cervix, stage IA1 (with lymphovascular space involvement), IA2, and IB1 were eligible. Patients were randomly assigned to TLRH/RRH or ARH and stratified by center, disease stage, and age at diagnosis. QOL was measured at baseline, 6 weeks (early), and 6 months (late) after surgery, using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. Improvement of QOL after surgery was chosen as the primary outcome for this analysis and was defined as a 10-point increase in QOL scores from baseline to early (6 weeks) or late (6 months) time points.

Results: To date, 271 patients with a median age of 45 years (range, 22-79 years) have been enrolled (139 TLRH/RRH; 132 ARH). Baseline characteristics, such as body mass index, ECOG score, stage, and grade are well balanced between the groups. Disease was diagnosed at stage 1B1 in 91% of patients. QOL data were available for 145 patients who completed follow-up of at least 6 months postsurgery. In the early phase of recovery, patients receiving TLRH/RRH reported greater improvement in QOL from baseline compared with those receiving ARH. An improvement >10 points was noted for 15% and 7% in the physical well-being domain (early recovery) for patients who had TLRH/RRH and ARH, respectively. Improvements in the functional well-being domain (early recovery) were reported in 15% and 10% of patients who had TLRH/RRH and ARH, respectively. Improvements in QOL up to 6 months after surgery (late recovery) continued to favor TLRH/RRH, primarily in the social (27% vs 18%) well-being domain (Table).

Conclusions: These results justify continuing enrollment to the original target of 740 patients to determine equivalence/non-inferiority with respect to disease-free survival to address the benefit of TLRH/RRH as an alternative surgical procedure.

	Early QOL		Late QOL	
	TLRH/TRRH (%)	TARH (%)	TLRH/TRRH (%)	TARH (%)
Physical wellbeing				
Improvement	15	7	22	22
No change	38	30	59	59
Deterioration	46	63	19	19
Social/Functional Wellbeing				
Improvement	19	25	27	18
No change	62	52	50	68
Deterioration	19	23	23	14
Functional Wellbeing				
Improvement	15	10	33	40
No change	36	37	49	44
Deterioration	49	52	18	17
FACT-G				
Improvement	13	11	27	22
No change	60	56	51	53
Deterioration	27	33	22	24
Additional items				
Improvement	8	11	28	19
No change	58	56	57	65
Deterioration	35	33	15	16

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Long-term outcomes and survival prognostic factors in patients with positive nodes treated by neoadjuvant chemotherapy + radical surgery + adjuvant chemotherapy in locally advanced cervical cancer

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Objectives: To evaluate long-term outcomes and survival prognostic factors in patients with positive pelvic nodes treated by neoadjuvant chemotherapy + radical surgery + adjuvant chemotherapy in locally advanced cervical cancer.

Methods: Between June 2000 and September 2005, all patients with pathologically confirmed node metastasis in locally advanced cervical cancer (stage IB2-IIB) treated by neoadjuvant chemotherapy + radical surgery + adjuvant chemotherapy in the Division of Gynecologic Oncology of the Campus Bio Medico and "Sapienza" Universities of Rome were included in this retrospective analysis. All enrolled patients had pelvic nodes metastases determined after bilateral systematic pelvic lymph node dissection during radical surgery, and each received adjuvant platinum-based chemotherapy every 3 weeks. All surgical data were recorded and referred to final pathology analysis. Survival curves were constructed according to the Kaplan–Meier estimator, and differences were compared by the log-rank test. Univariate and multivariate analysis were performed to determine the association between the correlative factors and prognosis.

Results: Median follow-up was 89 months (range: 79-96 months). The overall survival rate was 62%. On multivariate analysis, only the number of nodal metastases and the lesion diameter were significant factors in determining overall survival. Rates of recurrence were also related to these factors. There was a statistically significant difference in overall survival between the patients with large cervical lesions (diameter >43 mm) and more than 3 nodes with metastases and patients with a smaller lesion and no more than 3 nodes involved (P=0.02 based on number of lymph nodes involved).

Conclusions: Neoadjuvant chemotherapy + radical surgery + adjuvant chemotherapy seems to be promising in patients with nodes metastasis in locally advanced cervical cancer. The best predictors for survival were the number of positive lymph nodes involved and the diameter of lesions.

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Prognostic value of pretreatment total-lesion glycolysis calculated by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with locally advanced cervical cancer

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Objectives: To determine the prognostic value of pretreatment total-lesion glycolysis (TLG) calculated by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with locally advanced cervical cancer who underwent concurrent chemoradiation.

Methods: The study population included prospectively enrolled patients with stage IB2-III cervical squamous cell carcinoma treated with concurrent chemoradiation. ^{18}F-FDG PET/CT scans were performed within the 2 weeks before the treatment began. We determined the mean and maximum standardized uptake value (SUVmean and SUVmax, respectively), metabolic tumor volume (MTV), and TLG in the primary tumor mass and evaluated their relationships to progression-free survival (PFS).

Results: A total of 96 patients with minimum follow-up of 1 year were enrolled. The median follow-up among survivors was 25.1 months. Univariate analysis demonstrated that both MTV and TLG showed significant association with PFS (all P<0.05). There was a significant correlation between SUVmax and PFS (P=0.013), but SUVmean did not show any correlation with PFS. Under multivariate Cox regression analysis, MTV and SUVmax were not significantly associated with PFS; only TLG was significantly associated with PFS (HR=2.62, 95% CI 1.267-5.399, P=0.003), adjusted by FIGO stage and other clinical factors.

Conclusions: TLG was an independent prognostic factor for PFS in patients with locally advanced cervical carcinoma who underwent concurrent chemoradiation. TLG might be used solely in this group of patients for individualized treatment planning.

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Comparing intensity-modulated radiotherapy and conventional external beam radiotherapy in cervical cancer

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Objectives: To compare the effects of intensity-modulated radiation therapy (IMRT) with conventional external beam radiation therapy (CXRT) on morbidity, tumor response, and quality of life (QOL) in cervical cancer patients.

Methods: Between August 2009 and February 2010, 50 patients with an age range of 20-85 years who had FIGO stage IIA-IIIB disease were prospectively randomized 2:1 to CXRT and IMRT at the Indo-American Cancer Institute. Both groups received concurrent chemotherapy (weekly cisplatin 30-40 mg/m^2) with external beam radiation (EBRT) 50 Gy/25 fractions followed by intracavitary brachytherapy at 21 Gy/3 fractions. Complications and QOL were evaluated during treatment and in follow-up with CTC 4.0 and EORTC QLQ-C30, and disease recurrence was based on pelvic examination. Analysis used chi square (X^2) at a significance level of 0.05.

Results: Average time to completion was 49 and 48 days, respectively, in CXRT and IMRT arms (P>0.05). Four patients did not complete the treatment in the CXRT. Two months after completion, 31/35 (89%) of CXRT and 15/15 (100%) of IMRT patients had complete responses (P>0.05). At 5 months, 30/35 (86%) of CXRT and 14/15 (93%) of IMRT patients had no locoregional disease (LRD); 1 IMRT patient died from distant metastasis (DM). At 18 months, 25/35 (72%) in the CXRT group and 14/15 (93.5%) in the IMRT group had no LRD or DM. At 24 months, 25/35 (72%) in the CXRT group and 14/15 (93.5%) in IMRT group had no LRD or DM. The most common acute adverse effects in the CXRT group were grade 1 vomiting/cystitis/diarrhea and grade 2 nausea/skin reactions/proctitis. One patient developed vesicovaginal fistula (VVF) after 50 Gy by EBRT. The most common acute adverse effects in the IMRT group were grade 1 nausea/vomiting/cystitis/proctitis/diarrhea. Two patients had grade 3 neutropenia in the fifth week of RT. QOL was better in the IMRT group (P<0.01) based on functional, symptom, single-item, and global scales, except for pain, insomnia, and loss of appetite. Diarrhea and financial problems were worse in the CXRT group (P<0.05). Chronic complications such as radiation-induced proctitis occurred in 5 patients, and subacute intestinal obstruction developed in 2 patients during follow-up period in CXRT vs IMRT (P<0.001).

Conclusions: IMRT is superior to CXRT, with fewer chronic adverse effects and similar acute adverse effects and treatment responses. Two patients had grade 3 neutropenia with IMRT. This is the first randomized clinical trial of these treatments in cervical cancer.

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Factors associated with recommending human papillomavirus (HPV) vaccines among nurses working in a tertiary hospital in South Africa

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Objectives: The purpose of this study was to determine factors contributing to recommending human papillomavirus (HPV) vaccination among nurses in South Africa.

Methods: This cross-sectional study was conducted among 345 nurses working at a tertiary hospital in South Africa using a self-administered anonymous questionnaire.

Results: The average age of the participants was 37.2 years. A total of 252 of the nurses (73.3%) were aware of HPV, and among these, 38.3% knew that HPV is the most common sexually transmitted virus. All the nurses knew that there is a vaccine for HPV, but only 42.7% could name both vaccines. Overall, nurses had poor knowledge about HPV infection and the HPV vaccine. The majority (90.9%) intended to recommend the vaccine to their patients. The nurses who mentioned that adolescents and young adults will accept HPV vaccination were more likely to recommend HPV vaccination to their patients (OR=57.78, P=0.031).

Conclusions: Even though nurses in this study had a low level of knowledge about HPV infection and vaccines, most were willing to recommend the vaccines for their patients. Nurses need to be educated before implementing HPV vaccination nationwide.

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Triage of women with negative cytology and positive high-risk human papillomavirus (HPV) DNA testing: an analysis of data from the SHENCCAST (Shenzhen Cervical Cancer Screening Program) II/III studies

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Objectives: To determine a management strategy for women testing negative with cervical cytology and positive for high-risk HPV (HR-HPV).

Methods: Using data from the large population-based SHENCCAST II/III, we compared the risk of cervical intraepithelial neoplasia (CIN) 3 or cancer (CIN 3+) in women with negative cytology but positive testing results for HR-HPV DNA using Cervista HPV HR or polymerase chain reaction-based MALDI-TOF, followed by secondary screening with type-specific Cervista HPV 16/18 or MALDI-TOF. The study aim was to seek the most sensitive and specific triage assay for referral for colposcopy.

Results: A total of 8,556 women had complete data. The proportion of women with negative cytology and positive HR-HPV by Cervista HR-HPV (5.30%, 453/8,556) was slightly lower than that of negative cytology and positive HR-HPV tests by MALDI-TOF (5.82%, 499/8,556, P=0.015).The proportion of women with negative cervical cytology and a positive HR-HPV by Cervista HR who had HPV-16 and/or 18 identified by Cervista HPV 16/18 (11.8%, 53/448) was less than that for women with negative cervical cytology and positive HR-HPV by MALDI-TOF who had HPV 16 and/or 18 identified by MALDI-TOF (19.4%, 97/499, P=0.001). The proportion of women with CIN 3+ within the negative cervical cytology and positive HR-HPV group who had HPV 16 and/or 18 identified by the Cervista 16/18 assay (61.5%, 8/13) was similar to that identified by the MALDI-TOF 16/18 assay (66.7%, 10/15, P=0.8). In the cytology-negative, HR-HPV-positive population, Cervista 16/18 as the HPV detection method would refer 11.8% of women for colposcopy and diagnose 61.5% of the CIN 3+, while MALDI-TOF16/18 would refer 19.4% and diagnose 66.7% of the CIN3+.

Conclusions: Cervista HPV 16/18 appears to be the superior triage test, but in resource-limited settings, an assay that includes 16/18 genotyping in the primary result (rather than a second test) may be more cost-efficient.

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Endometrial cancer: preoperative and intraoperative assessment of myometrial invasion - comparison between MRI and intraoperative examination

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Barretos Cancer Hospital, Barretos, Brazil

Objectives: The purpose of this study was to compare the myometrial invasion assessed by preoperative MRI and intraoperative examination in endometrial cancer.

Methods: Eighty-seven consecutive endometrial cancer patients from a single institution, evaluated between September 2011 and May 2013, were included. MRI was part of the preoperative routine evaluation. All underwent total hysterectomy and bilateral salpingo-oophorectomy, with the intraoperative assessment of depth of myometrium invasion performed by an experienced pathologist. The final pathology report was used as definitive diagnosis. To calculate the positive predictive value (PPV) and negative predictive value (NPV), the reports were divided in 2 categories: ≤50% and >50% myometrial invasion.

Results: All patients underwent perioperative examination, and the MRI report was available in 78 patients. MRI failed to predict the depth of myometrial invasion in the final pathology report in 50% of the cases; the perioperative assessment erred in 23%. The PPV and NPP for the MRI were 64.3% and 68%, respectively. The PPV and NPP for the intraoperative evaluation were 80% and 89.5%, respectively. Final results are shown in the Table.

Table 1. Results

		Final Pathology Report			TOTAL
		Restricted to the Endometrium	Invades ≤50%	Invades >50%	
Myometrium invasion in the MRI	Restricted to the endometrium	1	10	1	12
	Invades ≤50%	3	20	4	27
	Invades >50%	0	7	18	25
	Unspecific myometrium invasion	1	1	1	3
	Indeterminate	1	6	4	11
TOTAL		6	44	28	78
Myometrium invasion in the perioperative evaluation	Restricted to the endometrium	3	5	0	8
	Invades ≤50%	3	40	5	48
	Invades >50%	1	3	24	28
	Indeterminate	0	2	1	3
TOTAL		7	50	30	87

Conclusions: MRI showed poor accuracy in predicting myometrial invasion, although the correlation was better when MRI suggested >50% of myometrial invasion. Perioperative evaluation had a satisfactory accuracy, especially in those who had >50% myometrial invasion. These results indicate that preoperative assessment in endometrial cancer may not be reliable in predicting the extent of the surgery or the final stage.

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Cost-effectiveness of selective lymphadenectomy based on a preoperative prediction model in patients with endometrial cancer

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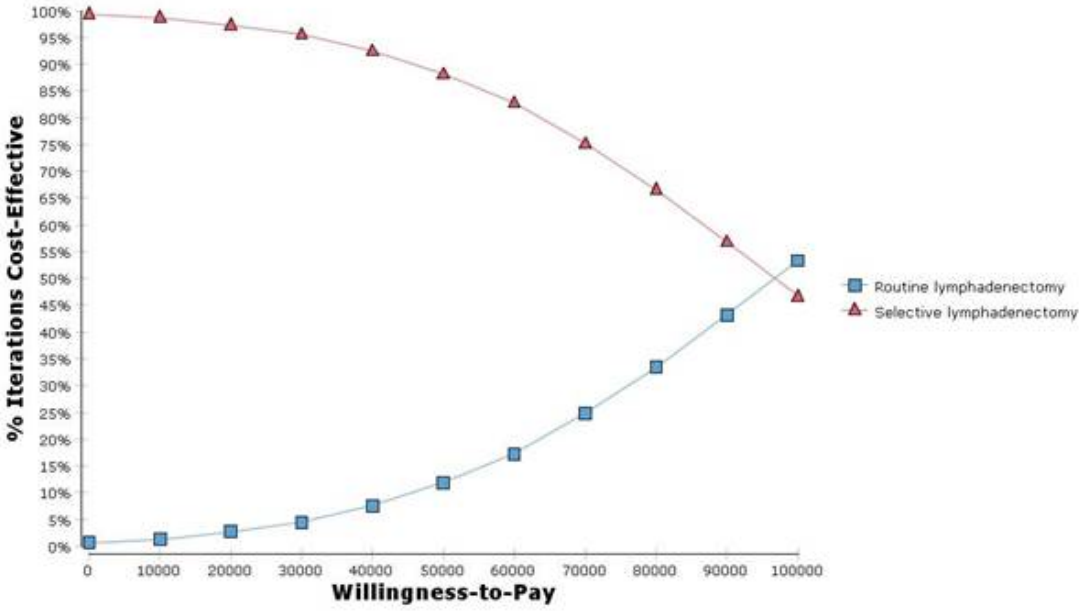
Objectives: In 2012, the Korean Gynecologic Oncology Group proposed a preoperative prediction model for lymph node metastasis using CA-125 concentrations and MRI parameters. The aim of this study was to determine the cost-effectiveness of selective lymphadenectomy based on the preoperative prediction model versus routine lymphadenectomy for patients undergoing surgery for endometrial cancer.

Methods: A modified Markov model was used to estimate the clinical and economic consequences of a newly diagnosed, apparent early-stage endometrial cancer using 2 different strategies: 1) selective lymphadenectomy, in which surgical staging is omitted for patients classified as low risk based on the preoperative prediction model and 2) routine lymphadenectomy, in which all patients undergo complete surgical staging. Published data were used to estimate the rates of adjuvant therapy and survival. The cost of diagnosis and treatment for endometrial cancer was estimated using Korean National Health Insurance database. The rates of lymph node metastasis and lymphedema, the cost of lymphedema treatment, and the performance of the preoperative prediction model were varied for sensitivity analysis.

Results: Using selective lymphadenectomy as the baseline, the incremental cost-effectiveness ratio (ICER) of routine lymphadenectomy was $98,295 per year of life saved (YLS). A one-way sensitivity analysis showed that the ICER for routine lymphadenectomy exceeded $50,000/YLS if the prevalence of lymph node metastasis was <16%, the rate of lymphedema was >6%, the cost of lymphedema care was >$9,250, or the sensitivity of the preoperative prediction model was >85%. The cost-effectiveness acceptability curve demonstrated that at a willingness-to-pay threshold of $50,000, almost 90% of samples suggested that selective lymphadenectomy is cost-effective.

Conclusions: A strategy of selective lymphadenectomy based on the preoperative prediction model was more cost-effective than routine lymphadenectomy for patients with endometrial cancer. The cost-effectiveness of selective lymphadenectomy is projected to increase generally when there is a lower rate of lymph node metastasis, a higher rate of lymphedema, a higher cost of lymphedema treatment, and higher test sensitivity.

Figure. Cost-effectiveness acceptability curve based on probability sensitivity analysis using 9999 samples.



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The impact of body mass index on radiotherapy technique in patients with early-stage endometrial cancer: a single-center dosimetric study

G. Yavas[1], C. Yavas[2], O. S. Kerimoglu[1] and C. Celik[1]
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Objectives: Obesity is a well-known risk factor for endometrial carcinoma. In obese patients, the depth to the tumor is greater compared to normal-weight patients, which can result in unwanted radiation "hot spots" and excess doses to organs at risk (OAR), making pelvic radiotherapy (RT) planning is more difficult. We sought to evaluate the impact of body mass index (BMI) on RT technique in patients with early-stage endometrial cancer.

Methods: Twenty-seven consecutive patients were divided into 3 groups based on their BMI (normal-weight=18.5-24.9, overweight=25-29.9, obese=30-39.9). Treatment plans using field-in-field (FIF) and 3-dimensional conformal RT (3D-CRT) were compared for the doses in the planning target volume (PTV); OAR volumes, including rectum, bladder, bowel, bilateral femurs, and bone marrow (BM); dose homogeneity index (DHI); and monitor unit (MU) counts required for the treatment.

Results: The FIF technique was superior to 3D-CRT with respect to the maximum and mean doses received by OAR and DHI. Subgroup analyses revealed that the mean doses received by rectum (P=0.001) and bladder (P=0.015) and the minimum dose received by right femur (P=0.025) were significantly reduced only in obese patients. The volumes of bowel and BM receiving more than the prescribed dose of 30 Gy were significantly reduced only in obese patients (P=0.023 and P=0.039, respectively). The volumes of bladder and BM receiving more than the prescribed dose of 45 Gy were significantly reduced both in overweight and obese patients (P=0.016 and P=0.046; P=0.027 and P=0.002, respectively).

Conclusions: Based on the lower maximum doses in OAR and PTV, the FIF technique appears to be more advantageous than 3D-CRT during adjuvant RT for early-stage endometrial cancer. This advantage is more prominent in obese patients.

Scientific Plenary II: Hugh R. K. Barber Lectureship: Global Efforts to End Cervical Cancer
Saturday, March 22, 2014
4:00 p.m. – 5:45 p.m., Ballroom B-C
Moderator: Adriana Bermudez, MD, *Buenos Aires University Hospital, Buenos Aires, Argentina*

37 - Scientific Plenary

Development and validation of a new HPV genotyping assay based on next generation sequencing

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Objectives: To develop an HPV assay applicable to large-scale cervical cancer screening based on next-generation sequencing (NGS) technology.

Methods: We developed a new HPV genotyping assay based on multiplex polymerase chain reaction and NGS methods. We validated this new high-risk (HR)-HPV genotyping assay on population-based self-collected samples. We trained the assay on 1,170 self-collected samples, balancing the cut-points to be most sensitive for those HR-HPV types most frequently associated worldwide with high-grade preinvasive disease and cancer. Using 4,262 separate highly validated self-collected specimens, we compared concordance, sensitivity, and specificity for ≥ cervical intraepithelial neoplasia (CIN) 2 and ≥CIN 3 of the HPV sequencing assay with that of HC2 direct-samples (physician-collected) and matrix-assisted laser desorption/ionization time-of-flight (mass spectroscopy) assay self-samples. ROC curves were constructed for decisions as to assay cut-point, and McNemar's test was used for calculations of sensitivity and specificity.

Results: All assays had a good agreement. The sensitivity for ≥CIN 2 and ≥CIN 3 (data below) of the self-sampling specimens tested by the new NGS HR-HPV genotyping assay run both on a MiSeq sequencer and a PGM sequencer was similar to that of direct sampling specimens tested by HC2 ($P>0.05$), but the specificity for ≥CIN 2 and ≥CIN 3 (data below) of the NGS HR-HPV assay was significantly higher than HC2 ($P<0.01$).

Test	**Sensitivity ≥CIN3** (%)(CI)	P-value*	**Specificity ≥CIN3** (%)(CI)	P-value*
HC2-direct	**98.5** (98.1, 98.8)	-	**88.2** (87.2, 89.1)	-
MS-self	**95.4** (94.8, 96.0)	0.63	**88.3** (87.3, 89.3)	0.72
MiSeq-self**	**96.9** (96.4, 97.4)	0.99	**90.1** (89.2, 91.0)	<0.01
PGM-self**	**98.5** (98.1, 98.8)	0.99	**89.5** (88.6, 90.4)	<0.01

***All comparisons to HC2 Direct
****Sequencing assay

Conclusions: This population-based study demonstrated the applicability of a new NGS HR-HPV assay for primary cervical cancer screening based on self-collection. The throughput (40,000+/week), accuracy, improved specificity, and low cost per case (<$5.00), with 14 high-risk genotypes reported, make the technology particularly suited for large-scale screening programs with centralized laboratories especially targeting the medically underserved.

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38 - Scientific Plenary

The community prevalence of human papillomavirus (HPV) in India and the feasibility of self-collected vaginal swabs

A. Peedicayil[1], P. Abraham[1], J. Prasad[1], S. Abraham[1], L. Jeyaseelan[1], M. Gnanamony[1], P. E. Gravitt[2] and S. Kurian[1]
[1]Christian Medical College, Vellore, Vellore, India, [2]Johns Hopkins Medical Institutions, Baltimore, MD

Objectives: The aim of this study was to determine the community prevalence of HPV infection and the feasibility of using self-collected vaginal swabs for HPV testing.

Methods: The cross-sectional study involved the Kaniyambadi block of Vellore district in India. A computer-generated list of women 30 to 50 years old was prepared, and women were randomly invited to participate in screening for cervical neoplasia. Community health workers trained in visual inspection with acetic acid obtained self-collected vaginal swabs from the participants and brought women to the cancer screening clinic where cervical samples for cytology and HPV testing were taken by a doctor. HPV testing was done by polymerase chain reaction and genotyping by the line blot assay. Quality control for the HPV testing was determined by sending samples to Johns Hopkins University, Baltimore, MD. Data analysis consisted of descriptive statistics such as proportions.

Results: The study involved 806 women, of whom 2% were nulliparous, 34% were illiterate, 0.7% had multiple sexual partners, and 3% had used oral contraception. Low-risk HPV was seen in 23 (3%) and high-risk HPV in 45 (6%) self-

collected vaginal samples. Among the clinician-collected cervical samples, low-risk HPV was seen in 25 (3%) and high-risk HPV in 9 (1%). Low-grade cervical intraepithelial neoplasia (CIN) was found in 26 (3.2%) and high-grade CIN in 10 (1.2%). There was 96% concordance between the laboratories at Vellore and Baltimore. Some women said that self-collection was inconvenient (12%) and painful (13%). Most women (71%) said that they preferred self-collection to samples being taken by a health worker or a doctor.

Conclusions: This study showed that use of self-collected vaginal samples for HPV testing is feasible and acceptable to women in India. The prevalence of high-risk HPV was low in this community.

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39 - Scientific Plenary

Difficulty with single-visit approach (SVA) for colposcopy and cervical intraepithelial neoplasia (CIN) treatment in Goma/RDC

M. K. Sahani, R. P. Hamuli and D. Tshombe
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Objectives: Cervical cancer is a major public health issue worldwide and particularly in D.R. Congo, where it is #1 cause of death by cancer. Our colposcopy unit has only been in existence for 4 months and is the only colposcopy service in the country. This study sought to inform 350 health professionals in our community and 50 funders worldwide of the challenges for SVA for colposcopy in Goma.

Methods: We are performing cervical cancer screening at Hope Medical Center (HMC) and have analyzed feasibility of SVA for colposcopy during screening. This is a descriptive and analytic study with data from screening procedure reports at HMC. Statistical tests comparing percentages has been applied to analyze our data.

Results: In the 4 months of the program's existence, 115 women have been screened. The breakdown of patients according to age is shown in the Table.

Age	20-30 years	31-40 years	41-50 years	>50 years	Total
Number	40	52	18	5	115
Percentage	34.78%	45.22%	15.65%	4.35%	100%

A significantly larger number of women with precancer were seen in the 31-40 years age group. Among 115 women screened, we have found 31(26.95%) with precancer and 84(73.04%) with negative results. World Health Organization (WHO) has an estimated 20.3% as a reference for cervical cancer prevalence in D.R. Congo. We found the difference with the WHO estimate was not statistically significant for cervical cancer situation in this local community ($Ch2=3.15$, $P=0.075972$). Among 31 women with positive results, 9 (29.03%) had CIN I, 17(54.84%) had CIN II, and 5(16.13%) had CIN III. Those with CIN II and CIN III required treatment by excision (22 women). Among those women, none agreed to treatment at first visit for the following reasons: 1) Wanted to talk first with husband before being treated (7 [31.82%]); 2) Needed to find money for treatment (13 [59.09%]); and 3) Needed to think about it before accepting treatment (2 [9.09%]). With these three reasons, statistically significantly more women were not ready to be treated at first visit because of not having money for treatment ($Chi2=12.41$, $P=0.002020$).

Conclusions: None of the women who required treatment by excision were prepared to be treated at first visit. The most common reason was not having money, which highlights the need for the colposcopy program to gain financial support from committed funders to overcome this challenge.

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40 - Scientific Plenary

Mexican Cervical Cancer Screening Study II (MECCS II): 6-month and 2-year follow-up

D. C. Starks[1], N. A. Lucybeth[2], C. Enerson[3], J. Brainard[4], N. Nagore[5], S. Belinson[6], A. Chiesa-Vottero[4] and J. L. Belinson[4]
[1]Avera Medical Group Gynecologic Oncology, Sioux Falls, SD, [2]New Hanover Medical Center, Wilmington, NC, [3]Prueba Para La Vida, Morelia, Mexico, [4]The Cleveland Clinic Foundation, Cleveland, OH, [5]Hospital de la Mujer, Morelia, Mexico, [6]Preventive Oncology International, Cleveland Heights, OH

Objectives: To determine the efficacy and tolerance of cryotherapy in a VIA triage protocol after primary human papillomavirus (HPV) screening.

Materials/Methods: This study enrolled nonpregnant, high-risk HPV (HR-HPV)-positive women between the ages of 30 and 50 years, who resided in the state of Michoacán, Mexico, and had a history of no Pap smear screening or knowledge of Pap smear results within the last 3 years. These women were initially enrolled in the MECCS II trial and were treated with cryotherapy after VIA triage. They subsequently were followed up at 6 months and 2 years for repeat VIA, colposcopy, and biopsy.

Results: A total of 291 women were treated with cryotherapy, and 226 (78%) were followed up at 6 months. Of 153 (68%) women who were HR-HPV-negative, 148 had negative biopsies, 2 had cervical intraepithelial neoplasia (CIN) 1, and 3 had no biopsies. There were no findings of ≥CIN 2. Of 73 women (32%) were HR-HPV-positive, 67 had negative biopsies, 1 had CIN 1, 2 had CIN 2, and 3 women had CIN 3. Of 137 women followed up at 2 years, 116 were HR-HPV-negative, 74 had negative biopsies, 41 had CIN 1, and 1 did not have a biopsy. Of 21 women who were HR-HPV-positive, 9 had negative biopsies, 11 had CIN 1, and 1 had no biopsy. There were no biopsies of ≥CIN2 at 2 years. Before cryotherapy, 15 (6.6%) women were ECC-positive, and 5 were referred for surgical management. Ten of the women who were ECC-positive (67%) were followed up at 6 months, and none was ECC positive. Eleven (73%) ECC-positive women were followed up at 2 years, and none had a positive ECC. In our study, VIA had a false-positive rate of 5%.

Conclusions: Cryotherapy was an effective, acceptable, and a well-tolerated means of treating cervical dysplasia in a low-resource setting.

Featured Poster Session II: Predictors of Outcomes in Ovarian Cancer/Translational Science
Sunday, March 23, 2014
6:30 a.m. – 7:30 a.m., Rooms 13-16
Moderator: John Liao, MD, PhD, *University of Washington, Seattle, WA*

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The impact and interaction of preoperative disease burden, complex surgery, and residual disease in patients with advanced stage ovarian cancer and the effect on patient survival: A GOG 182 analysis

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Objectives: To examine the effects of disease burden and complex surgery on the volume of residual disease (RD), progression-free survival (PFS) and overall survival (OS) in patients with advanced epithelial ovarian cancer (EOC) or primary peritoneal cancer (PPC) who have <1 cm of residual disease following surgical cytoreduction.

Methods: Demographic, pathologic, surgical, and outcome data were collected from GOG 182 records of EOC or PPC patients cytoreduced to <1 cm RD. Preoperative disease score (DS) and surgical complexity score (CS) were calculated using published scoring systems. The effects of DS and CS on RD and subsequent PFS and OS outcomes were assessed using multivariable logistic and proportional hazards regression methods.

Results: A total of 2,655 patients underwent primary cytoreductive surgery to <1 cm RD. Modeling estimated the probability of complete gross resection (CR) as a function of DS, CS, the DS/CS interaction, and other possible confounders. Given the DS/CS interaction, the primary effect of DS on RD remained statistically significant ($P<0.01$), while the main effect of CS was not ($P=0.23$). This finding suggests that CS did not directly affect RD but instead had an indirect effect on RD through its moderation of the DS effect. Within high-DS patients, those with high CS were significantly more likely to obtain CR than those with low CS or moderate CS ($P<0.01$ for both). Within the low-DS and moderate-DS patients, the probability of MR was not affected by CS ($P=0.68$). Repeating this model in patients from institutions in which CR rates were >40% gave similar results, suggesting no evidence for institutional bias. The effects of DS and RD status on prognosis were both statistically significant ($P<0.01$). Patients with CR had better prognoses than those with <1 cm RD ($P<0.01$). After controlling for DS, RD, an interaction term for DS/CS, performance status, age, and cell type, CS did not have any effect on PFS or OS.

Conclusions: Initial disease burden reflected in the DS is a principal determinant of RD, PFS, and OS following surgical cytoreduction. Data from the current study suggest that aggressive surgical cytoreduction provides by far the greatest benefit when CR is achieved.

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BRCA1/2 protein expression as a potential marker of the *BRCA*ness syndrome in ovarian cancer

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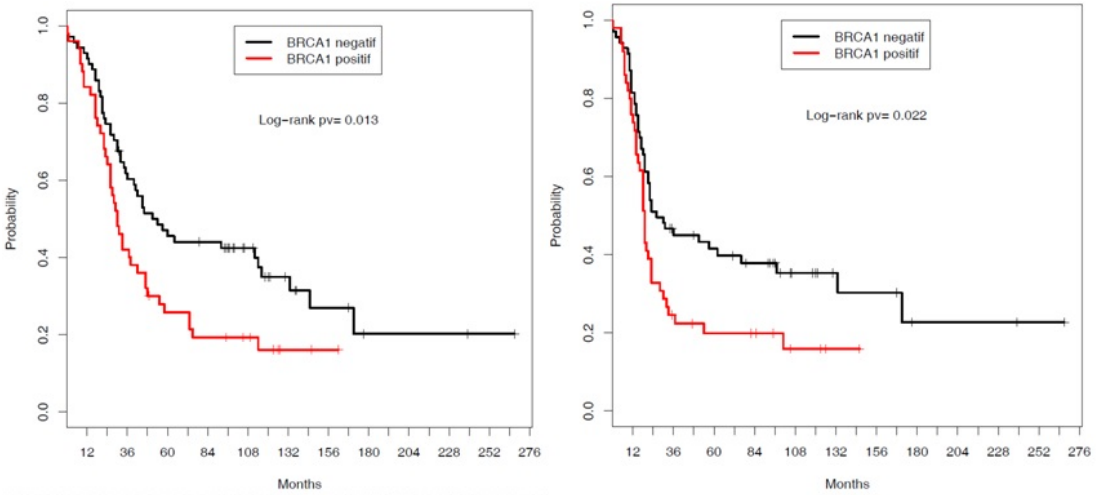
Objectives: To determine whether the level of *BRCA1/2* protein expression is one of the biologic characteristics of the *BRCA*ness clinical syndrome, we analyzed the relationship between the clinical outcome of primary ovarian cancer patients and the expression of *BRCA1/2* protein in tumor tissue. We also sought to assess the potential value of *BRCA1/2* protein expression as a prognostic and/or predictive biologic parameter in sporadic ovarian cancer.

Methods: This large retrospective cohort examined 126 patients with primary epithelial ovarian cancer (EOC). A tumor tissue fragment from each case, cryopreserved at the tumoral bank and containing high amount of tumor cells, was analyzed. Inclusion criteria were: primary ovarian cancer, FIGO stages I-IV, and primary cytoreductive surgery followed by chemotherapy with platinum or combination of taxane/platinum regimens. We used Western blot and quantitative real-time polymerase chain reaction to evaluate the abundance and the expression of *BRCA1/2*. Overall survival (OS) was calculated from date of surgery to date of death due to ovarian cancer (time in months) for patients with negative vs positive *BRCA 1/2* protein expression, low vs high grade and stage via Kaplan-Meier log rank test. Odds ratio were conducted using multivariate logistic regression, applying the proportional odds model to assess evidence of no association between *BRCA1* and other clinical parameters (age, grade, and stage) in survival analysis.

Results: Patients with absent *BRCA1* protein expression had a significantly improved OS and progression-free survival (Kaplan-Meier statistical analysis) following treatment compared with patients with positive *BRCA1* protein expression. Analysis of the *BRCA1/2* mRNA level did not demonstrate a significant link related to survival. We believe that this is related to the weak level of mRNA expression.

Conclusions: There was a poor correlation between mRNA and protein expression levels of *BRCA1* or *BRCA2*. There was no significant link between *BRCA1/2* mRNA expression level and disease outcome. There was a significant correlation between *BRCA1* loss of expression and an improved outcome for ovarian cancer. These results suggest that *BRCA1* protein expression could be one of the biologic parameters associated with the *BRCA*ness clinical syndrome.



BRCA1 Protein Expression

Kaplan-Meier survival analysis of BRCA1 protein expression, demonstrating a statistically significant improved survival for patients with absence of protein expression. (E) Overall survival P=0.013 and (F) Progression Free Survival P=0.022.

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Identification of candidate circulating cisplatin resistance biomarkers from epithelial ovarian carcinoma cell secretomes

P. N. Teng[1], G. Wang[1], B. L. Hood[1], K. A. Conrads[1], C. A. Hamilton[2], G. L. Maxwell[3], K. M. Darcy[1] and T. P. Conrads[1]
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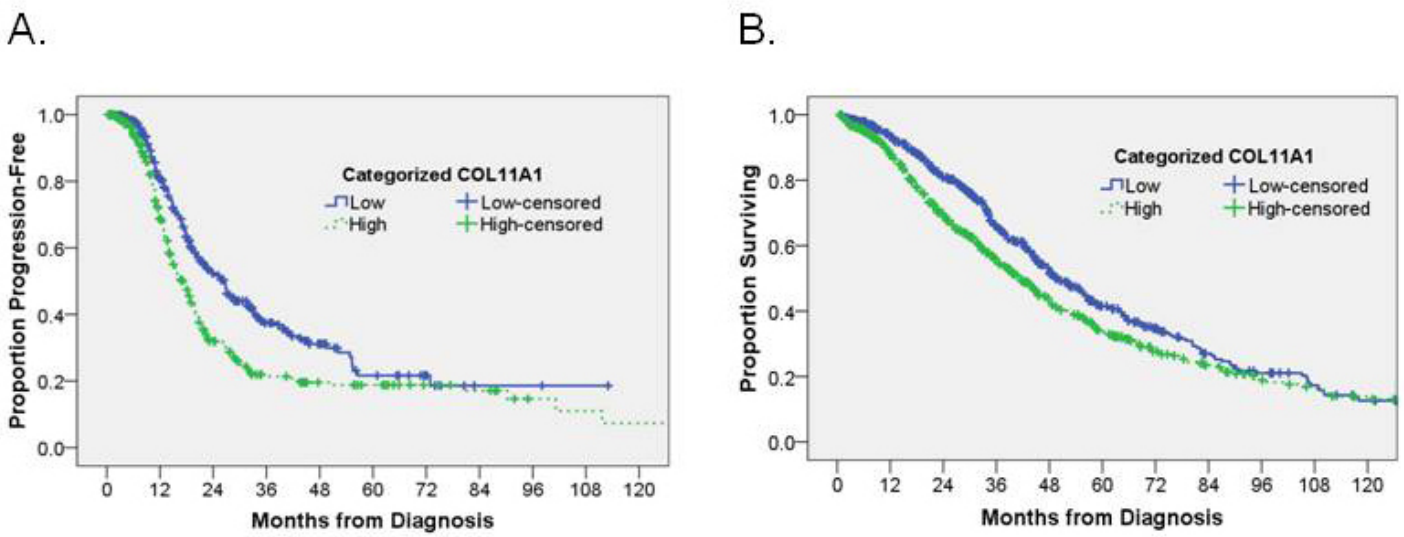
Objectives: Most patients diagnosed with advanced epithelial ovarian carcinoma (EOC) relapse with resistant disease, and there are no clinically useful biomarkers to identify or monitor this resistance. This study sought to identify differential secreted proteins collected from human EOC cell lines of varying platinum sensitivity.

Methods: Secreted proteins collected from conditioned medium from five ovarian cancer cell lines that varied in their sensitivity to cisplatin were digested with trypsin and analyzed by liquid chromatography-tandem mass spectrometry for peptide identification. Significantly altered proteins were validated in independent biologic replicates by immunoblotting. Survival analyses were performed using public gene expression data to interrogate candidate biomarkers that passed immunoblot verification to evaluate the clinical relevance.

Results: Among the 1,688 proteins identified, 16 were differentially abundant ($P<0.05$) between platinum-resistant and -sensitive ovarian cancer cell lines. Approximately 60% of the identified secretome proteins were also found in the human plasma proteome and/or were annotated in the secreted protein database. A number of the significant differential secretome proteins were verified by immunoblot, including COL11A1, which was also found to be associated with worse progression-free survival (PFS) ($n=723$, $P=0.0003$) and overall survival (OS) ($n=1,183$, $P=7x10^{-5}$), as assessed from publicly available transcript expression data from ovarian cancer tumor specimens (Figure 1).

Conclusions: Secretome proteomics of EOC cells resulted in the identification of a novel candidate biomarker, COL11A1. We have compiled publicly available gene expression data and shown that elevated COL11A1 correlates to worse PFS and OS. Due to our observation that COL11A1 is secreted from cisplatin-resistant ovarian cancer cells, this protein represents an attractive candidate for validation in sera as a biomarker of cisplatin resistance and poor outcome.

Figure 1. Kaplan-Meier plots for PFS (A) and OS (B) in ovarian cancer patients with low (≤median) or high (>median) tumor expression of COL11A1 assessed from the average of two probes (median=6.8722). There were 723 women included in the PFS and 1,183 women included in the OS analysis.



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MicroRNA 206 is associated with longer overall survival and platinum sensitivity in serous epithelial ovarian cancer

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Objectives: Most women with high-grade serous epithelial ovarian cancer (EOC) eventually develop platinum-resistant disease. MicroRNAs (miRNAs) are pleiotropic and regulate many biologic processes. Our objective was to identify and validate miRNAs associated with platinum resistance in EOC.

Methods: The Cancer Genome Atlas (TCGA) data portal and Broad Institute's Genome Data Analysis Center were used to download miRNA data and distinguish two unique patient groups within the TCGA data sets. Of 576 patients in the data sets, 257 were identified with reliable clinical information available. Sixty-eight chemoresistant patients (recurrence or progression within 6 months of completed chemotherapy) and 185 very chemosensitive patients (without recurrence for more than 12 months after completion of chemotherapy) were selected. Differentially expressed miRNA genes in the chemoresistant vs chemosensitive groups were detected by a four-way ANCOVA test, and an overall survival (OS) comparative analysis was performed. These miRNAs were validated with real-time polymerase chain reaction (PCR) in EOC lines. In vitro proliferation and colony assays were performed, and in vivo xenograft experiments are in progress.

Results: Upregulation of miR-193b* was found in the chemoresistant patient group and associated with shorter OS (Pearson's correlation coefficient [PCC] = 0.18). In contrast, miR-206 was upregulated in the chemosensitive patient group and most strongly associated with longer OS (PCC = 0.24). Real-time PCR in the paired sensitive and resistant EOC cell lines IGROV1/IGROV CP1 and 2008/2008 C13 showed higher expression of miR-206 in the sensitive EOC lines. Both proliferation and colony in vitro assays showed that miR-206 further sensitizes the IGROV1 cell line to carboplatin ($P < 0.05$).

Conclusions: Chemoresistant and chemosensitive EOC have distinct miRNA expression profiles. Specifically, miR-206 is differentially expressed in very chemosensitive patients, indicating a better prognosis, and the upregulation of miR-206 further enhances platinum sensitivity in EOC. Inhibition of genes *NOTCH3* and *c-MET* by miR-206 is associated with tumor suppression, making both of these genes potential targets for further assays.

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The significance of prior tubal occlusion in uterine papillary serous carcinoma

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Objectives: Uterine papillary serous carcinoma (UPSC) often presents with high-grade and advanced-stage disease. Compared to endometrioid type endometrial carcinoma, UPSC has a higher propensity for intraperitoneal spread and extra-abdominal disease. Transtubal exfoliation has been hypothesized as one mechanism by which UPSC spreads intra-abdominally. We sought to evaluate the significance of prior tubal occlusion among women with UPSC.

Methods: Medical records of patients diagnosed with UPSC between January 1995 and December 2010 were reviewed. Patients were separated into two groups based on the presence or absence of prior tubal ligation that preceded the diagnosis of UPSC. Groups were compared with respect to patient characteristics, histopathologic findings, stage distribution, and rates of optimal cytoreduction (<1 cm residual disease).

Results: We identified 183 patients, 29 of whom (15.85%) had a history of prior tubal ligation and 154 of whom (84.2%) did not. The tubal ligation group had a greater percentage of patients with stage I disease (72.4% vs 49.4% $P=0.072$). Groups were similar with respect to other histopathologic findings, including myometrial invasion (62.1% vs 69.5%), cervical stromal invasion (17.9% vs 23.0%), lymph-vascular space invasion (21.4% vs 37.7%), and the presence of positive lymph nodes (29.2% vs 27.0%). Patients with prior tubal ligation were significantly less likely to have adnexal involvement (93.1% vs 75.3%, $P=0.047$) and positive cytologic washings (88.5% vs 66.7%, $P=0.035$). Rates of optimal cytoreduction were similar between groups.

Conclusions: Patients with a history of UPSC and prior tubal occlusion are significantly less likely to have adnexal involvement and positive cytologic washings.

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Genome-wide association study evaluating single-nucleotide polymorphisms and outcomes in patients with advanced-stage serous ovarian or primary peritoneal cancer: a Gynecologic Oncology Group (GOG) study

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Objectives: Identification of novel pathways involved in advanced stage epithelial ovarian cancer (EOC) is essential to improve patient outcomes. This study proposes to evaluate single nucleotide polymorphisms (SNPs) associated with progression-free survival (PFS) and overall survival (OS) in patients with advanced-stage serous EOC and primary peritoneal cancer (PPC).

Methods: Patients enrolled in GOG-172 and 182 who provided specimens for translational research and consent were included in this study. Germ line DNA was evaluated with the Illumina's HumanOMNI1-Quad beadchips and scanned using Illumina's iScan optical imaging system. SNPs were analyzed for PFS and OS using Cox regression, adjusting for cell type, size, and three principal components expressing population stratification. Statistical significance was determined using Bonferroni corrected *P*-values with genomic control adjustment.

Results: The initial analysis included 1,124,677 markers in 396 patients. To obtain the final data set, quality control checks were performed and limited to patients with serous tumors and white race. A total 636,555 SNPs and 289 patients passed all the filters. Ten SNPs were identified for OS: rs295315 p-4.744e-07, rs17693104 p-4.873e-7, rs868767 p-1.186e-06, rs2050203 p-2.604e-06, rs11621975 p-3.493e-06, rs17548007 p-3.564e-06, rs202280 p-4.235e-06, rs1564271 p-5.955e-06, rs10899426 p-6.183e-06, rs4618572 p-6.310e-06. These SNPs are located on chromosomes 3, 6, 8, 10, 11, 12, 14, and 20. SNP rs7693104 is located in the *SDH2D4B* gene and rs1564271 is located in the *PDS11* gene. Ten SNPs that were identified for PFS (rs10899426 p-5.217e-08, rs6256 p-2.760e-07, rs10832063 p-1.488e-06, rs10500780 p-1.524e-06, rs281358 p-4.084e-06, rs17163580 p-4.225e-06, rs17011846 p-4.225e-06, rs227147 p-5.055e-06, rs11782341 p-7.790e-06, rs7011443 p-8.180e-06) are located on chromosomes 1, 8, 11, and 17. The genes involved include *PTH, BTBD10, DSP1, TUSC3*, and *CSMD1*.

Conclusions: We identified 10 SNPs associated with PFS and an additional 10 SNPs associated with OS in patients with advanced-stage serous EOC and PPC. The SNPs identified in this study require validation, and these preliminary findings may lead to identification of novel pathways and biomarkers.

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Developing novel aldehyde dehydrogenase inhibitors to target ovarian cancer stem cells

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Objectives: Cancer stem-like cells (CSC) are rare chemoresistant cells within a tumor with self-renewal and differentiation capacities necessary for tumor recurrence. Several studies have demonstrated that aldehyde dehydrogenase enzymatic activity (ALDH), alone and in combination with CD133, identifies a population of ovarian CSC (OvCSC). ALDH regulates stem cell processes, including the synthesis of retinoic acid, a critical regulator of cellular differentiation. ALDH is also important for cellular detoxification and resistance to chemotherapy. Based on its stem cell-specific expression and functional importance in CSC, we hypothesize that inhibitors of ALDH may act as CSC-targeted therapeutics. The objectives of this study were to identify and characterize novel ALDH inhibitors that target OvCSC.

Methods: We screened ~50 compounds with molecular analogy to the ALDH inhibitor DEAB for the ability to inhibit ALDH and deplete ovarian CSC using fluorescence-activated cell sorting (FACS). MTT, tumor sphere formation, and recovery assays were performed to assess anti-CSC toxicity. Tumor initiation studies, tumor xenograft, and patient-derived xenografts were used to confirm in vivo anti-CSC toxicity and drug safety.

Results: ALDH inhibitors UM673 and UM773 significantly restricted the growth and viability of ovarian cancer cell lines, while proving to be nontoxic to normal stem cells. FACS analysis confirmed selective reduction in the percentage of ALDH+ and CD133+ cells. This effect was synergistic with chemotherapy. Treatment with UM673 and UM773 reduced the formation of tumor spheres in both cell line and patient samples ~8-fold (range, 4-40-fold). Importantly, UM673 and UM773 reduced tumor initiation, and when combined with cisplatin, completely eliminated tumor initiation capacity. Finally, ALDH inhibitors reduced tumor cell line xenograft growth in vivo and restored chemoresponsiveness in a platinum-resistant patient-derived xenograft.

Conclusions: We have identified two novel ALDH inhibitors that selectively deplete cells expressing OvCSC markers ALDH and CD133. These compounds are highly synergistic with chemotherapeutic agents and reverse chemotherapy resistance in vivo. These studies strongly support the development of ALDH-targeted therapy for ovarian cancer.

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Wound healing gone awry: role for platelets in tumor growth after antiangiogenic therapy

J. N. Bottsford-Miller[1], M. Taylor[1], H. J. Dalton[1], R. L. Stone[2], A. M. Nick[1], A. N. Davis[1], B. Zand[1], R. A. Previs[1], V. Afshar-Kharghan[1] and A. K. Sood[1]
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Objectives: In phase III trials, vascular endothelial growth factor (VEGF)-targeted agents have offered modest improvements in progression-free survival (PFS) without affecting overall survival; over time, survival curves collapse and sometimes cross. Preclinical models suggest that antiangiogenic therapy may result in a more invasive and metastatic tumor phenotype, but the underlying mechanisms are not known.

Methods: We used an orthotopic mouse model of human ovarian cancer to test the effect of antiangiogenic therapy withdrawal on tumor growth. Mice bearing human ovarian cancer were subjected to intravital fixation, and immunofluorescence was used to examine for extravascular platelets, both in untreated animals and after treatment with pazopanib or bevacizumab. In vitro modeling included co-culture experiments measuring tumor cell proliferation, apoptosis, and invasion.

Results: Compared to untreated control, mice treated with continuous pazopanib had 64% decreased tumor growth (P=0.05); in contrast, withdrawal of pazopanib resulted in a 270% increase in tumor growth (P=0.02) compared to untreated controls. These findings were confirmed in four other models. Co-culture experiments showed that tumor cell exposure to platelets increased proliferation rates by 2.5-fold (P<0.05) and decreased apoptosis rates by up to 60% (P<0.05). Platelet co-culture increased tumor cell invasion in a normoxic (by 240%) and hypoxic (by 267%) environment (both P<0.001). In mice bearing human ovarian cancer, platelet transfusion resulted in 1.9-fold increase in mean tumor weight (P=0.04) as well as a twofold increase in microvessel density (P=0.001). Platelet depletion resulted in a 65% decrease in mean tumor weight (P=0.02). Immunofluorescence of tumor showed extravascular trafficking of platelets (69 platelets/high-power field [hpf] vs 0.69 platelets/hpf in nontumor tissue; P<0.001). Compared to controls, tumor treated with bevacizumab had a 3.5-fold increase in platelet extravasation (P=0.001), and tumor treated with pazopanib had a 1.5-fold increase in platelet extravasation (P=0.03).

Conclusions: Withdrawal of antiangiogenic agents results in increased platelet penetration into the tumor stroma and increased tumor growth. These findings have implications for new approaches aimed at improving the efficacy of antiangiogenesis therapies.

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Pathogenesis of *ARID1A*-driven gynecologic cancer

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[1]Michigan State University, Grand Rapids, MI, [2]Gynecologic Cancer Center of Excellence, Annandale, VA, [3]Walter Reed National Military Medical Center, Bethesda, MD, [4]Inova Fairfax Hospital, Falls Church, VA

Objectives: *ARID1A* is mutationally inactivated in a significant portion of gynecologic cancers. The mechanisms underlying the tumor suppressive action of *ARID1A* remain unclear, and downstream regulatory and transcriptional changes remain to be determined. These regulated genes and/or pathways may provide opportunities for targeted therapies.

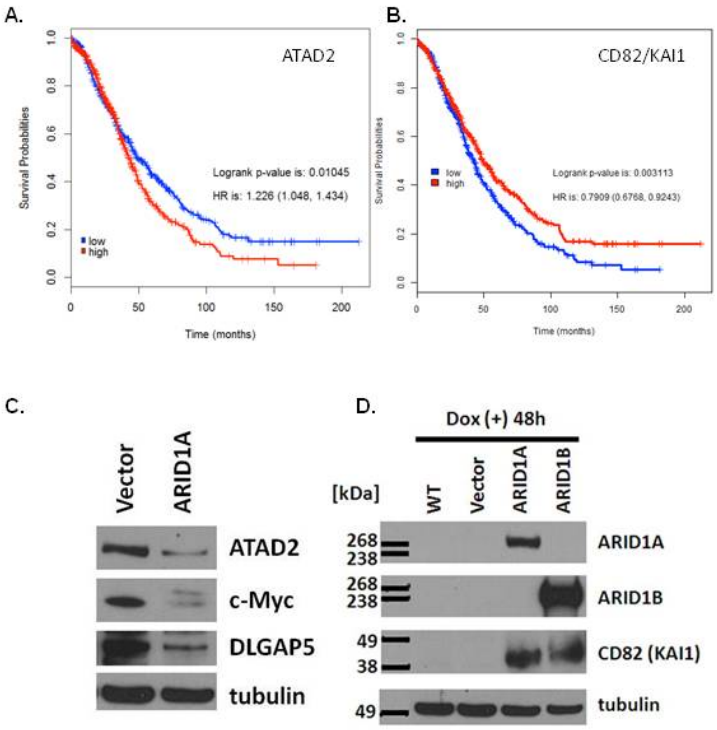
Methods: *ARID1A* mutant endometrioid and clear cell cancer cell models were functionally complimented with ectopic *ARID1A*. Genomic interactions of *ARID1A* were mapped by ChIP-seq, and the proteomic impact of *ARID1A* restoration was assessed by mass spectrometry (MS). Candidates were validated by immunoblot and quantitative polymerase chain reaction (qPCR) and examined in clinical specimens of endometrial and ovarian cancer by immunohistochemistry (IHC). Clinical significance of selected genes was analyzed using a survival tool developed in-house.

Results: We identified 3,099 *ARID1A* DNA binding peaks in *ARID1A*-restored ovarian cancer cells in or near many gene promoters, including estrogen receptor alpha (*ESR1*). Levels of *ESR1* and its target, the progesterone receptor, were restored

in *ARID1A*-expressing cells. MS-based proteomics identified 217 altered proteins (z-score <0.001). Immunoblotting and qPCR confirmed the *ARID1A*-dependent expression of *ATAD2* and *CD82*. *ATAD2* and *c-MYC* levels decreased following *ARID1A* restoration. Loss of the metastasis suppressor *CD82* depended on *TP53* and *ARID1A* expression. *ATAD2* and *CD82* correlated with poor overall survival (*P*=0.01 and 0.003, respectively). Elevated *ATAD2* was noted in ovarian cancers lacking *ARID1A* by IHC.

Conclusions: Our novel systems approach has identified clinically relevant biomarkers and pathways linked to *ARID1A* function. Several novel targets were revealed to be directly regulated by *ARID1A*, including *ESR1*, *CD82*, and *ATAD2*, all of which have direct functional roles in carcinogenesis and metastasis and offer novel opportunities for biomarker and therapeutic development.

Figure 1: Kaplan-Meier plots of show worse overall survival for high expressing ATAD2 cancers (A) and low expressing CD82/KAI1 cancers (B). Immunoblots of dox-induced ARID1A in ACI-98 ARID1A mutant cells. ARID1A-mediated decreased expression in ATAD2, c-Myc and DLGAP5 (C) and re-expression of metastasis suppressor CD82 following restoration of ARID1A or ARID1B (D).



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Natural killer cells derived from human-induced pluripotent stem cells: an “off the shelf” strategy for killing ovarian cancer

M. A. Geller, D. L. Hermanson, D. A. Knorr, L. A. Bendzick, L. J. Pribyl and D. S. Kaufman
University of Minnesota, Minneapolis, MN

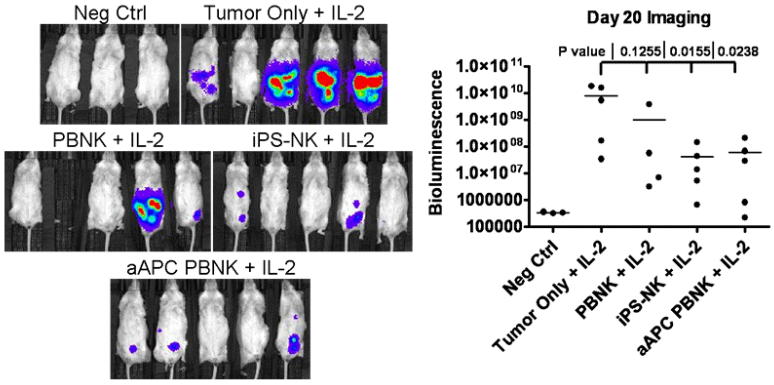
Objectives: Natural killer (NK) cells are a key part of the innate immune system and have the ability to recognize diverse types of tumors and virally infected targets. Human-induced pluripotent stem cells (iPSCs) provide an accessible, genetically tractable, and homogenous starting cell population to develop NK cells. Our goal was to evaluate in vivo anti-ovarian cancer activity of peripheral blood-NK (PBNK) cells vs NK cells derived from iPSCs.

Methods: Using “Spin-EB” in which mediated differentiation of iPSCs is followed by co-culture with artificial antigen-presenting cells (aAPC) that express membrane bound-interleukin (IL)-21, up to 10^9 NK cells were generated from a population of 10^6 undifferentiated iPSCs. A total of 2 x 10^5 GFP^+Luciferase-positive MA-148 ovarian cancer cells were injected intraperitoneally (IP) into NOD/SCID/$gc^{-/-}$ (NSG) mice. Four days later, 20 x 10^6 freshly isolated PBNK derived from healthy donor peripheral blood mononuclear cells, aAPC-expanded PBNK (aAPC PBNK), or iPSC-derived NK cells (IPS-NK) were

delivered IP (or no NK cells for controls). Mice were given IL-2 (5 ug/mouse) every other day for 4 weeks after NK cell treatment. Tumor growth was monitored weekly by bioluminescence. Mice were followed up to 55 days. There were 5 mice per group, and all experiments were performed in duplicate with similar results.

Results: IPS-NK cells were a mature NK population and phenotypically similar to PBNK cells based on standard NK cell surface antigens. PBNK cells isolated by CD3/CD19 depletion contained 30% NK cells and 70% monocytes, whereas iPSC-derived NK cells and aAPC PBNK cells were 99% pure NK cell populations. Bioluminescent imaging demonstrated that IPS-NK cells (P=0.015) and aAPC PBNK (P=0.023) had the greatest antitumor activity (See Figure). NK cells were detected IP up to 35 days after delivery. PBNK and aAPC PBNK were found in peripheral blood on days 7 and 14, but iPS-NK were not detected peripherally on days 7 or 14.

Conclusions: NK cells delivered IP have significant ovarian tumor inhibition in vivo. iPSCs provide a novel strategy to produce “off the shelf” NK cells suitable for immune therapies that show promise in ovarian cancer. Furthermore, iPSCs can be genetically engineered to express additional tumor recognition elements, such as chimeric antigen receptors, to further enhance antitumor activity.



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More is not always better: thrombocytosis contributes to impaired chemotherapy response in ovarian cancer

J. N. Bottsford-Miller[1], M. Taylor[1], H. J. Dalton[1], R. L. Stone[2], A. M. Nick[1], A. N. Davis[1], B. Zand[1], R. A. Previs[1], V. Afshar-Kharghan[1] and A. K. Sood[1]
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Objectives: Thrombocytosis in ovarian cancer patients is an independent predictor of decreased progression-free survival (PFS) and overall survival (OS), but the underlying mechanisms are not understood.

Methods: Platelet levels of patients with platinum-refractory vs -sensitive disease were assessed through front-line therapy. In vitro (proliferation and apoptosis) and in vivo (anti-GP1ba antibody, platelet transfusion, aspirin) effect of platelets on docetaxel response using ovarian cancer models were assessed.

Results: Thrombocytosis at diagnosis was associated with worse OS (median 480 vs 625 days, P=0.007) and PFS (median 386 days vs 440 days, P= 0.05). In a platinum-sensitive cohort, 50% had thrombocytosis at diagnosis, and 100% normalized platelets before initiation of chemotherapy. Conversely, all patients in a matched platinum-refractory cohort had thrombocytosis at diagnosis, and only 50% normalized during treatment. In vitro co-culture of platelets with human ovarian cancer cell lines (HeyA8, SKOV3-Ip1, and OVCAR5) increased proliferation rates by 79% to 258% (P<0.05). Co-culture of platelets with ovarian cancer cells decreased the apoptotic response to docetaxel by 20% to 67%. Use of a barrier with 0.4-mcm pores to separate platelets from tumor cells demonstrated that these effects did not require direct contact between the platelets and tumor cells. Blockade of platelet reactivity by fixation abrogated both the proliferative effect and apoptosis protection. In two orthotopic mouse models of human ovarian cancer, platelet depletion resulted in a 70% reduction in mean tumor weight compared to control (P<0.05). Compared to mice treated with docetaxel, mice treated with both docetaxel and platelet-depleting antibody had a 62% decrease in mean tumor weight (P=0.04). In contrast, platelet transfusion increased mean aggregate tumor weight 2.4-fold (P<0.05). Platelet transfusion blocked the effect of docetaxel on tumor growth (P=0.55), increased tumor cell proliferation (Ki67 index), and decreased tumor cell apoptosis (Caspase-3 activation). Pretransfusion aspirinization of the platelets blocked these effects.

Conclusions: Platelet-driven effects on chemotherapy response may explain clinical observations. These findings may lead to new therapeutic approaches.

52 - Featured Poster

Pharmacologic inhibition of the DNA damage response kinases ATR (ataxia telangiectasia and rad3 related) and ATM (ataxia telangiectasia mutated) broadly sensitizes diverse subtypes of gynecologic cancer cells to ionizing radiation

N. W. Bateman[1], P. N. Teng[1], K. A. Conrads[1], C. A. Hamilton[2], G. L. Maxwell[3], C. J. Bakkenist[4] and T. P. Conrads[1]
[1]Gynecologic Cancer Center of Excellence, Annandale, VA, [2]Walter Reed National Military Medical Center, Bethesda, MD, [3]Inova Fairfax Hospital, Falls Church, VA, [4]University of Pittsburgh, Pittsburgh, PA

Objectives: The management of gynecologic malignancies includes exposure of tumor cells to genotoxic insults, such as ionizing radiation (IR), and focuses on damaging cellular DNA and inducing subsequent cell death. Because cells possess innate mechanisms to repair DNA damage, this study focused on combining IR with inhibition of ATR and ATM, key mediators of DNA repair, to further sensitize gynecologic cancer cells to this mode of genotoxic stress.

Methods: Clonogenic survival assays: A panel of human cell line models of ovarian, endometrial, and cervical cancer was treated with drug vehicle, 5.0 μM ATR inhibitor (ETP-46464), 10.0 μM ATM inhibitor (KU55933), or a combination of ATRi and ATMi, before exposure to IR doses up to 6.0 Gy. Drug was removed 4 hours later and resulting colonies were counted when mean colony size was ≥50 cells. Western blot: ATM, ATR, and downstream canonical signaling effectors were assessed in cell lysates harvested from representative cell line models of ovarian (A2780), endometrial (HEC1B), and cervical (HELA) cancers 1 hour following treatment with inhibitors and IR exposure (2.0 Gy only) as described previously.

Results: Clonogenic survival assays revealed that inhibition of ATR and ATM increased sensitization to IR across all models of gynecologic cancer cells assessed (representative results for the endometrial cancer cell line HEC1B in Figure 1A, $n=3$ studies). This effect was further increased with combined ATR and ATM inhibitor treatments. Western blot analyses (Figure 1B) revealed activation of ATM and ATR signaling in response to IR, i.e., DMSO; + IR lane; increased p-ATM, p-Chk1, and p-Chk2. Activation of Chk1, a known downstream effector of ATR, is attenuated in ATRi-treated conditions and activation of ATM (autophosphorylation at Ser1981) and Chk2, mediated by ATM, is reduced in ATMi-treated conditions.

Conclusions: These studies revealed that inhibition of the DNA damage response kinases ATR and ATM markedly sensitizes diverse gynecologic cancer subtypes to IR. They provide evidence to support further consideration of therapies pairing modulation of DNA damage signaling with IR in the treatment of gynecologic malignancies.

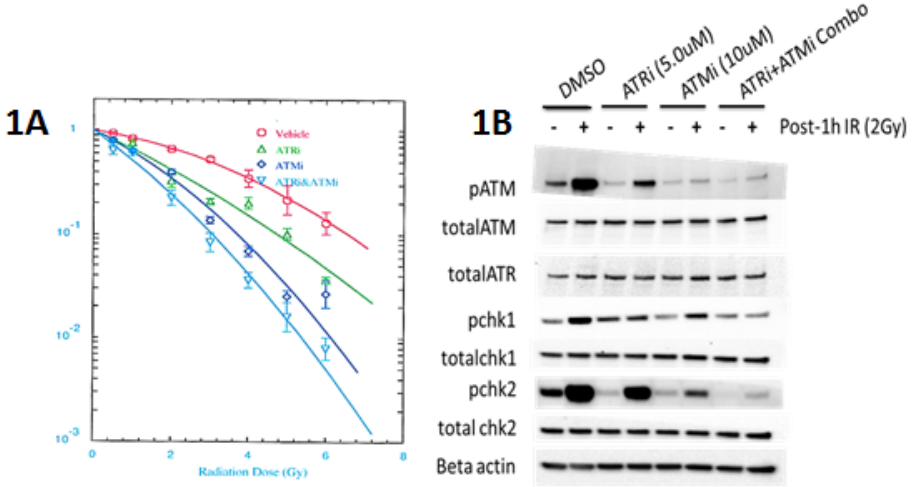


Figure 1: (A) Clonogenic survival assay of HEC1B cells in response to increasing IR exposure and treatment with ATRi and /or ATMi. (B) Western blot analysis of ATM and ATR signaling in HEC1B cells in response to IR exposure and treatment with ATRi and /or ATMi.

53 - Featured Poster

Inhibition of gamma-secretase activity in combination with carboplatin and paclitaxel precludes uterine papillary serous carcinoma growth in a primary human xenograft model

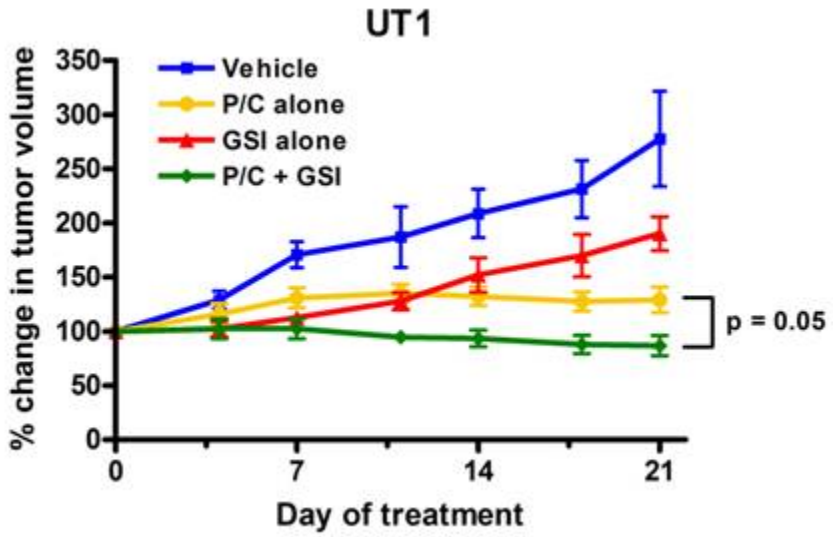
J. W. Groeneweg, T. R. Hall, L. Zhang, M. Kim, V. F. Byron, C. M. DiGloria, R. Tambouret, R. Foster, B. R. Rueda and W. B. Growdon
Massachusetts General Hospital, Boston, MA

Objectives: Uterine papillary serous carcinoma (UPSC) is an aggressive subtype of endometrial cancer that is often refractory to chemotherapy and requires innovative therapeutic strategies. Our objective was to characterize Notch1 expression in UPSC and test the γ-secretase inhibitor (GSI) MRK-003 as a single agent and in combination with standard chemotherapy in UPSC cell lines, cell line-derived xenografts, and primary tumor xenografts.

Methods: With institutional review board approval, UPSC tissue blocks derived from patients who underwent surgery from 2000 through 2012 were obtained. Clinical outcomes were correlated with immunohistochemistry for Notch1. Three nonimmortalized UPSC cell lines (ARK1, ARK2, SPEC2) were treated with increasing concentrations of GSI. Mice bearing xenografts generated from these cell lines were treated with GSI (300 mg/kg) or vehicle. Two cohorts of mice harboring primary human UPSC xenografts (UT1, UT2) were treated with vehicle, GSI, paclitaxel (15 mg/kg), and carboplatin (50 mg/kg) (P/C) or combination GSI and P/C. GSI-treated samples were analyzed by Western blot for cleaved Notch1 and quantitative polymerase chain reaction analysis of *Hes1* expression. Statistical analysis was performed using Wilcoxon rank sum and Kaplan-Meier methods.

Results: High Notch1 protein expression was observed in the cytoplasm and nucleus in 39% and 60% of UPSC samples, respectively. High cytoplasmic expression correlated with decreased overall survival ($P<0.04$). GSI administration in vitro induced a dose-dependent reduction in cell number and a decrease in expression of cleaved Notch1 protein and *Hes1* mRNA. Treatment of UPSC xenografts with GSI for 6 and 24 hours led to decreased *Hes1* mRNA expression. In addition, GSI impeded tumor growth of ARK1 and ARK2 cell line xenografts as well as UT1 primary UPSC xenografts (all $P\leq0.05$). When GSI and P/C were combined, synergistic antitumor activity was observed in UT1 xenografts ($P=0.05$).

Conclusions: These data suggest that Notch1 is expressed in a large subset of UPSC. Inhibition of the Notch pathway with GSI led to both reduced cell numbers in vitro and decreased tumor growth of UPSC xenografts. When combined with conventional chemotherapy, Notch inhibition led to heightened antitumor activity, suggesting this as a promising therapeutic strategy for future investigation.



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54 - Featured Poster

Development of a rucaparib response signature that shows in vitro predictive value to the PARP inhibitors, ABT-888 and olaparib in ovarian cancer cells

S. S. Al Rubaish[1], Y. Xiong[1], D. Marchion[1], F. Abbasi[1], S. Bush[2], I. Ramirez[2], N. Bou Zgheib[2], P. L. Judson Lancaster[1], R. M. Wenham[1] and J. M. Lancaster[1]
[1]H. Lee Moffitt Cancer Center, Tampa, FL, [2]University of South Florida College of Medicine, Tampa, FL

Objectives: Rucaparib (RUB) is a poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitor with potential activity against sporadic ovarian cancer (OVCA).To date biomarkers that reliably identify patients who will benefit from RUB

therapy do not exist. We report the development of a RUB response signature, developed using a panel of OVCA cell lines, that may predict in vitro sensitivity to other PARP inhibitors.

Methods: OVCA cell lines (*n*=27) were subjected to RUB treatment and, in parallel, gene expression analysis using the HuRSTA genechip. OVCA cell sensitivity to RUB was quantified using MTS proliferation assays. To develop a RUB response signature, gene expression profiles of the most sensitive and resistant cells were analyzed using prediction analysis of microarrays (PAM). The developed RUB response signature was evaluated in eight OVCA cell lines in the NCI60 dataset, for which sensitivity to the PARP inhibitors ABT-888 and olaparib as well as gene expression data were available.

Results: RUB exhibited antiproliferative effects against our panel of 27 OVCA cell lines, with median inhibition concentration (IC50) values ranging from 16.31 to 44.5 μM. PAM analysis of RUB-treated OVCA cells resulted in a two-gene (*CYB5R2, GSTT1*) RUB response signature. When analyzed against OVCA cells in the NCI60 database, the RUB response signature correctly predicted ABT-888 response in three of five cells (60%) and olaparib response in three of three cells (100%) using a median value threshold to determine sensitive vs resistant.

Conclusions: Strategies targeting DNA repair mechanisms provide hope for treatment of OVCA. We have identified a two-gene in vitro RUB response signature that may also be associated with in vitro response of other the PARP inhibitors ABT-888 and olaparib. Further study of this signature is required in clinical samples from patients who have received PARP inhibitors.

Scientific Plenary III: The Farr Nezhat Surgical Innovation Session
Sunday, March 23, 2014
7:45 a.m. – 9:20 a.m., Ballroom B-C
Moderator: Fidel A. Valea, MD, *Duke University Medical Center, Durham, NC*

55 - Scientific Plenary

The sensitivity of sentinel lymph nodes identified with robotic fluorescence imaging for detecting metastatic endometrial cancer: interim results from the FIRES trial

E. C. Rossi[1], A. L. Jackson[2], L. D. Kowalski[3], A. Ivanova[2] and J. F. Boggess[2]
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Objectives: Sentinel lymph node (SLN) mapping for endometrial cancer has been described as an alternative staging technique, but definitive data regarding its diagnostic accuracy are lacking. Fluorescence imaging of indocyanine green (ICG) dye is a novel feasible modality for SLN mapping. The FIRES trial (fluorescence imaging for robotic endometrial cancer sentinel node mapping) is a prospective, multicenter cohort study of comprehensively staged women with endometrial cancer. The primary objective of the trial is to estimate the sensitivity and negative predictive value (NPV) of SLNs for detecting metastatic disease.

Methods: Patients with clinical stage I endometrial cancer undergoing robotic staging received cervical injection of ICG (1 mg) and both SLN mapping and pelvic ± para-aortic (PA) lymphadenectomy. All histologies and grades were eligible. All lymph nodes were evaluated with hematoxylin and eosin sectioning. SLNs were ultrastaged with immunohistochemistry for cytokeratin. This study has ongoing recruitment at five United States centers. It is registered with Clinical Trials.gov.

Results: Seventy-five eligible patients have undergone attempted SLN mapping. The mean body mass index of the cohort is 35.2. Pelvic lymphadenectomy was performed in 72 patients (96%) and PA lymphadenectomy in 55 patients (73%). Three patients had aborted mapping and no nodes removed due to inability to perform lymphadenectomy; 64 patients (85%) had successful mapping (at least one SLN identified). Bilateral SLNs were identified in 48 of these patients (75%). The median number of SLNs was 4 (range, 2-17). A median number of 22 (range, 2-43) total LNs were removed per patient. Twelve (16%) patients had stage IIIC disease, 10 of whom mapped a SLN. Among those who mapped, nodal metastases were correctly identified in the SLNs in all cases, yielding a sensitivity and NPV of 100%. Isolated PA metastatic disease was identified in SLNs of 2 patients (3%). Sixty percent (6) of nodal metastases were identified with ultrastaging.

Conclusions: The interim results of the FIRES trial show a high degree of diagnostic accuracy for SLNs identified with robotic fluorescence imaging in women with endometrial cancer. There were no false-negative SLNs in patients who mapped. Replacement of complete lymphadenectomy with SLN biopsy is not advocated until the study's statistical endpoints have been met.

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56 – Scientific Plenary Surgical Film

Sentinel lymph node mapping for uterine cancer: a practical illustration of injection and mapping techniques

J. J. Mueller and N. R. Abu-Rustum
Memorial Sloan-Kettering Cancer Center, New York, NY

This practical surgical teaching film reviews the key steps in performing sentinel lymph node mapping, including the technique of cervical dye injection. It illustrates the two common pelvic lymphatic drainage patterns seen in early-stage uterine cancer. This instructional film uses a sentinel lymph node mapping algorithm to convey the important aspects of this procedure. The film includes narration and uses video, anatomic illustrations, and photographic examples, incorporating the use of a variety of commercially available colored dyes.

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57 - Scientific Plenary

Isolated sentinel lymph node biopsy with conservative management in women diagnosed with vulvar cancer

R. G. Moore[1], D. R. Roque[2], C. K. McCourt[1], A. R. Stuckey[1], P. A. DiSilvestro[1], J. Sung[1], M. Steinhoff[1], C. O. Granai[1] and K. M. Robison[1]
[1]Women & Infants Hospital, Brown University, Providence, RI, [2]University of North Carolina at Chapel Hill, Chapel Hill, NC

Objectives: Sentinel lymph node (SLN) dissection is a reliable method for evaluation of the inguinal lymph nodes in patients with vulvar malignancies. The objective of this study was to examine SLN evaluation alone in women with squamous cell carcinoma (SCC) of the vulva and evaluate the inguinal recurrence and complication rates.

Methods: An institution review board-approved prospective study enrolled patients with SCC of the vulva. Peritumoral injection of Tc-99 sulfur colloid and blue dye was used to identify SLNs intraoperatively. Patients with negative SLN for metastasis were followed clinically without further treatment. Patients with metastasis to an SLN underwent full groin node dissection followed by standard treatment protocols.

Results: A total of 73 women were enrolled, with 69 patients undergoing SLN dissection. Mean age was 66.9 years (range, 29-91 years) with 47 stage I , 12 stage II, 10 stage III, 1 stage IV, and 3 unstaged patients. SLN dissections were successful in 63 patients; 3 patients had a unilateral SLN with a contralateral complete node dissection and 3 had no SLN detected. Of the 111 groins evaluated with an SLN dissection, 93% (103/111) had an SLN identified, with an average of 2 SLNs per groin. Ninety-two groins had negative SLN and 11 groins had positive SLN for a metastatic rate of 10.7%. There were 57 patients with negative SLN eligible for conservative management. The median follow-up was 58.3 months. Three patients experienced groin recurrences (2 unilateral and 1 bilateral) for a recurrence rate of 5.2% (3/57). The groin recurrence rate was 4.2% (4/92). Two patients with groin recurrences had vulva recurrences preceding the groin recurrences, which were detected 21 and 10 months from the original diagnosis. The third patient had an isolated groin recurrence 13 months from diagnosis. Two of the groin recurrences were in patients with peri-clitoral lesions and one with a perianal lesion. The rate of surgical complications for the vulva was 26.3% (15/57), which included hematoma, wound breakdown, and infections. The rate of surgical complications for the inguinal incisions was 10.5% (1 cellulitis, 1 abscess, 2 lymphocele, 1 lymphedema and leg pain).

Conclusions: Isolated SLN dissection alone has a low inguinal recurrence rate with decreased complications and should be considered as an option for women with SCC of the vulva.

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58 - Scientific Plenary

Abdominal radical trachelectomy (ART): what's the role in fertility-sparing surgery for cervical malignancies?

X. Wu and J. Li
Fudan University Shanghai Cancer Center, Shanghai, China

Objectives: As abdominal radical trachelectomy (ART) becomes a favored fertility-sparing procedure, the relative contraindication of tumor size >2 cm has been questioned. We report our ART experience in patients with cervical

malignancies, describing the surgical, oncologic, and fertility outcomes and discussing the role of ART in fertility-sparing surgery for cervical malignancies.

Methods: We conducted a retrospective review of a prospectively maintained database of patients undergoing fertility-sparing ART for cervical malignancies at our institution from April 2004 to July 2013.

Results: A total of 167 patients with cervical malignancies underwent laparotomy for planned ART. Eight patients needed immediate completion of radical hysterectomy due to unfavorable intraoperative findings. Median age was 30.2 years (range, 11-44 years). Median follow-up was 39.8 months (range, 2-113 months). Histology included 19 (11.4%) adenocarcinoma, 130 (77.8%) squamous carcinoma, 8 (4.8%) adenosquamous carcinoma, and 10 (6%) cervical sarcoma. Median number of nodes evaluated was 25 (range, 12–53). Fifty-three patients with pathologic risk factors received adjuvant therapy. Sixty-seven of 106 stage IB1 cases had tumor size ≥2 cm and 61 (91%) of them had preserved fertility potential. Two recurrences were observed at 21 months and 38 months after surgery, both of which were poorly differentiated adenosquamous carcinoma. One patient with a recurrence had 4-cm tumor, and she underwent 4 cycles of adjuvant chemotherapy. The other recurrent case had a 2-cm tumor and did not receive any adjuvant treatment. Both were offered salvage surgery and they are now undergoing chemoradiation. For various reasons, only 45 patients attempted to conceive and 7 (15.5%) of them succeeded. Four delivered by cesarean section at 37-39 weeks' gestation, two miscarried, and one is still expecting.

Conclusions: Although two patients had recurrences, ART provides secured oncologic outcomes for selected patients whose tumor size is ≥2 cm. Patients in our study group had less favorable obstetric outcomes, which may be related to the radicality of the surgery as well as social, familial, and physical factors. In the future, personalized fertility-sparing surgery may be offered to patients based on their different situations.

Scientific Plenary IV: Predictors of Outcomes in Gynecologic Cancers: What Can We Learn?
Sunday, March 23, 2014
11:00 a.m. – 12:45 p.m., Ballroom B-C
Moderator: Adnan R. Munkarah, MD, *Henry Ford Health System, Detroit, MI*

59 - Scientific Plenary

A prospective trial evaluating the ability of preoperative CT scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer

R. S. Suidan[1], P. T. Ramirez[2], D. Sarasohn[1], J. Teitcher[1], S. Mironov[1], R. Iyer[2], Q. Zhou[1], H. Paul[1], M. Osaka[2] and D. S. Chi[1]
[1]Memorial Sloan-Kettering Cancer Center, New York, NY, [2]The University of Texas MD Anderson Cancer Center, Houston, TX

Objectives: To assess the ability of preoperative CT scan of the abdomen/pelvis and serum CA-125 to predict suboptimal (>1 cm residual disease) primary cytoreduction in advanced epithelial ovarian (EOC), fallopian tube (FT), and peritoneal cancer (PC).

Methods: This was a prospective, nonrandomized, dual-center clinical trial of patients who underwent primary cytoreduction for stage III-IV EOC, FT, and PC. A CT scan of the abdomen/pelvis and serum CA-125 were obtained within 35 and 14 days before surgery, respectively. Five clinical and 20 radiologic criteria were assessed, and a multivariate model predictive of suboptimal cytoreduction was developed.

Results: From July 2001 to December 2012, 669 patients were enrolled, with 350 meeting eligibility criteria. The optimal debulking rate was 75% (261 patients), and the suboptimal rate was 25% (89 patients). On multivariate analysis, two clinical and five radiologic criteria were found to be significantly associated with suboptimal debulking: ASA 3-4 (odds ratio [OR] 3.1, 95% CI 1.6-6, P=0.001), CA-125 >500 U/mL (OR 1.5, 95% CI 1.2-1.9, P<0.001), and the following CT findings: lesions in the lesser sac (OR 2.6, 95% CI 2.2-3, P<0.001), root of the superior mesenteric artery implants (OR 2.9, 95% CI 2.3-3.6, P<0.001), retroperitoneal lymphadenopathy above the renal hilum (OR 1.3, 95% CI 1.3-1.4, P<0.001), perisplenic lesions (OR 1.9, 95% CI 1.6-2.2, P<0.001), and diffuse small bowel adhesions/thickening (OR 1.8, 95% CI 1.7-1.9, P<0.001). Of the seven identified criteria, the suboptimal debulking rate of patients who had 0, 1, 2, 3, and ≥4 factors was 6%, 14%, 23%, 34%, and 53%, respectively. A receiver operating characteristic curve was generated, and a predictive model using the five CT criteria had an AUC of 0.663; the five CT criteria and the preoperative CA-125 combined had an AUC of 0.674. The most accurate model combined the five CT criteria, CA-125, and ASA, with an AUC of 0.717.

Conclusions: In two high-volume ovarian cancer centers, we identified seven factors associated with suboptimal cytoreduction, with the suboptimal rate directly proportional to the number of factors. A prognostic model combining these seven factors had a predictive accuracy of 0.717. These results may be helpful in pretreatment patient counseling.

Criteria	Optimal (*n*)	Suboptimal (*n*)	Suboptimal Rate
0	33	2	6%
1	81	13	14%
2	82	24	23%
3	44	23	34%
≥4	18	20	53%

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60 - Scientific Plenary

Predictive model for preoperative determination of microscopic residual disease at the time of primary cytoreduction in patients with advanced-stage epithelial ovarian cancer: a Gynecologic Oncology Group (GOG) 182 analysis

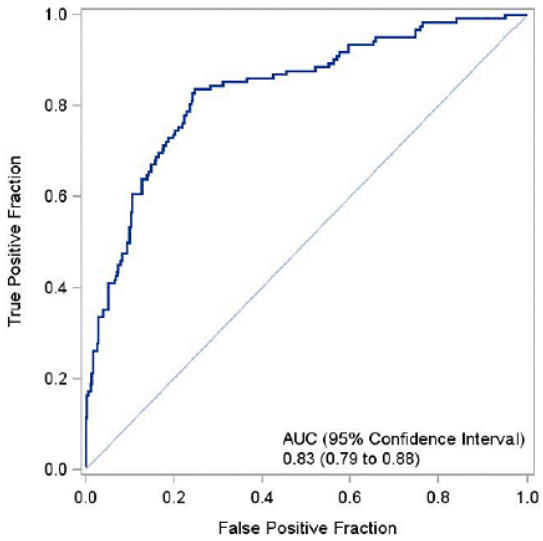
N. S. Horowitz[1], A. Miller[2], B. J. Rungruang[3], T. C. Krivak[4], S. D. Richard[5], C. A. Hamilton[6], N. Rodriguez[7], M. A. Bookman[8] and G. L. Maxwell[9]
[1]Harvard University, Boston, MA, [2]Gynecologic Oncology Group, Buffalo, NY, [3]Georgia Reagents University, Evans, GA, [4]Western Pennsylvania Hospital, Pittsburgh, PA, [5]Hahnemann University Hospital/Drexel University College of Medicine, Philadelphia, PA, [6]Walter Reed National Military Medical Center, Bethesda, MD, [7]Loma Linda University Medical Center, Loma Linda, CA, [8]University of Arizona Cancer Center, Tucson, AZ, [9]Inova Fairfax Hospital, Falls Church, VA

Objectives: Complete gross resection (CR) at primary surgery is associated with a significant survival benefit for patients with advanced epithelial ovarian cancer (EOC). Having a method to determine preoperatively in whom this can be achieved would be very helpful. Our objective was to develop a model that predicts CR.

Methods: Demographic, pathologic, surgical, and CA-125 data were collected from GOG 182 records. Patients enrolled before September 1, 2003 were used for the training model; those enrolled after constituted the validation data set. Disease score (DS) was calculated using a previously published scoring system. CR was modeled using logistic regression methods. The preliminary model was reduced using backward selection, with a retention threshold of $P<0.20$. Scores from the training model were applied prospectively to the validation data. Predictive accuracy was quantified using area receiver operating characteristic AUC from the validation data. AUC values >0.80 were considered to have utility in predicting CR.

Results: Of the 4,312 patients enrolled in GOG 182, 1,480 had preoperative CA-125 and ascites data available. The training data set consisted of 1,007 patients (234 with CR), and 473 patients (122 with CR) were used for model validation. The model fit was not significantly degraded by the backward selection ($P=0.66$). The reduced model included main effects for DS (DS-low or DS-mod) ($P<0.001$), stage ($P=0.009$), CA-125 ($P<0.001$), ascites ($P<0.001$), and stage-age interaction ($P=0.01$). AUC for the training group was 0.87. Applying reduced model scoring to the validation data resulted in AUC of 0.83 (95% CI 0.79-0.88). At the Youden Index optimal cutpoint, the sensitivity and specificity from the validation set were 0.83 and 0.75, respectively. A nomogram to estimate CR is being developed

Conclusions: This study used the largest available multi-institutional dataset to create a predictive model. Although extent of disease at presentation, stage, preoperative CA-125, ascites, and age can predict CR with a reasonable degree of accuracy, clinical parameters alone are insufficient to predict debulking status. Therefore, alternative molecular markers and advanced dynamic imaging studies need to be evaluated to help select patients for appropriate aggressive surgical cytoreduction.



61 - Scientific Plenary

Molecular predictors of residual disease in patients with ovarian cancer

S. L. Tucker[1], K. Gharpure[1], S. Herbrich[1], A. M. Nick[1], E. R. King[1], R. L. Coleman[1], J. Guenthoer[2], H. J. Dalton[1], K. A. Baggerly[1] and A. K. Sood[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Fred Hutchinson Cancer Research Center, Seattle, WA

Objectives: Gross residual disease (RD) following primary cytoreduction is the best predictor of overall survival in patients with high-grade serous ovarian cancer (HGSOC). Accurate identification of patients who will have RD has been elusive, prompting many to undergo unnecessary surgical exploration. Our goal was to identify and validate molecular markers associated with high rates of RD.

Methods: We interrogated two publicly available genomic datasets of primary HGSOC for genes consistently differentially expressed in RD and no residual disease (R0) cohorts and significant at a false-discovery rate (FDR) of 10%. Genomic expression was further validated in an independent cohort (chemonaïve ovarian tumor tissues) using quantitative reverse-transcriptase polymerase chain reaction followed by a blinded prediction of RD. A one-sided Fisher's exact test was used to compare RD rates in predicted high- and low-risk groups.

Results: In the TCGA and Tothill datasets, 491 and 189 patients, respectively, met the criteria for inclusion. As expected, survival was significantly better for patients with R0 resection compared to those with any RD. We identified 47 probesets, representing 38 different genes, significant in both datasets at 10% FDR. These included probesets for *FABP4* and *ADH1B*, which tracked tightly and showed dynamic ranges >16-fold. For these genes, there is a level of expression above which nearly all patients have RD; the distribution of expression values is roughly bimodal. In the validation cohort, using the top quartile of *FABP4* polymerase chain reaction values as a prespecified cutoff, we found 30/35 RD cases in the high-expression group and 54/104 in the low-expression group ($P=0.0002$). Our predictive method based on *FABP4*, therefore, correctly identified a cohort of patients with significantly increased rates of RD in an independent test set. Further examination of the *ADH1B* results showed that predictions using either *ADH1B* alone or in combination with *FABP4* would have produced similar results. Examining the reasons for RD in the high-risk cohort suggests a preponderance of cases with either innumerable sites of disease or unresectable disease involving vital regions.

Conclusions: High *FABP4* and *ADH1B* expression are associated with significantly higher risk of RD in HGSOC patients. Patients with high tumoral *FABP4* levels may be candidates for neoadjuvant chemotherapy.

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62 - Scientific Plenary

Ascites predicts degree of treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube, and peritoneal cancers

J. S. Ferriss[1], J. Java[2], R. A. Burger[3], M. A. Bookman[4], G. Fleming[5], B. J. Monk[6], J. L. Walker[7], H. D. Homesley[8], J. M. Fowler[9], B. E. Greer[10] and M. P. Boente[11]
[1]Temple University School of Medicine, Philadelphia, PA, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, [3]University of Pennsylvania, Philadelphia, PA, [4]University of Arizona Cancer Center, Tucson, AZ, [5]University of Chicago Medical Center, Chicago, IL, [6]University of Arizona Cancer Center, Phoenix, AZ, [7]The University of Oklahoma, Oklahoma City, OK, [8]East Carolina University, Greensville, NC, [9]The Ohio State University, Columbus, OH, [10]University of Washington Medical Center, Seattle, WA, [11]Minnesota Oncology Hematology PA, US Oncology, Edina, MN

Objectives: Bevacizumab with and following cytotoxic chemotherapy has been associated with improved progression-free survival (PFS) but not overall survival (OS) in the primary treatment of advanced ovarian, fallopian tube, and peritoneal cancers. Factors predictive of long-term efficacy have remained elusive. Because malignant ascites has been associated with expression of vascular endothelial growth factor, we investigated the value of ascites as a predictor of efficacy for bevacizumab.

Methods: Data from Gynecologic Oncology Group 0218, a double-blinded, placebo-controlled, randomized trial of standard cytotoxic chemotherapy with or without bevacizumab, were analyzed. Presence of ascites was defined prospectively as peritoneal fluid >50 cm^3 at the time of maximum surgical cytoreductive effort. Patients assigned to cytotoxic therapy plus concurrent and maintenance (≤10 months) bevacizumab (R3, $n=570$) were compared to those assigned to cytotoxic therapy alone (R1, $n=581$). Categorical variables were compared between groups by chi-square test and continuous variables by the

Wilcoxon-Mann-Whitney test. Survival was estimated by the Kaplan-Meier method, and Cox proportional hazard models were used to evaluate independent prognostic factors and to estimate covariate effects on PFS and OS.

Results: a total of 914 (79%) patients had ascites, while 237 (21%) did not. Treatment arms were balanced with respect to presence or absence of ascites and other prognostic factors. Those with ascites were more likely to have poor performance status (*P*=0.004), serous histology (*P*=0.04), higher baseline CA-125, and suboptimal cytoreduction (both *P*<0.001). Ascites was independently predictive of poor OS (HR 2.2, 95% CI 1.48-3.27, *P*<0.001). Ascitic patients on R3 had significantly improved PFS (HR 0.72, 95% CI 0.63-0.83, *P*<0.001) and improved OS (HR 0.82, 95% CI 0.7-0.96, *P*=0.01). However, nonascitic patients had no significant improvement in PFS (HR 0.77, 95% CI 0.57-1.04, *P*=0.091) or OS (HR 0.88, 95% CI 0.61-1.28, *P*=0.5).

Conclusions: Malignant ascites in women with newly diagnosed advanced ovarian cancer is phenotypic of tumor angiogenesis and, based on this secondary analysis, is an independent poor prognostic factor that may predict the population of women more likely to derive long-term benefit from bevacizumab.

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63 - Scientific Plenary

Frailty index predicts severe complications in gynecologic oncology patients

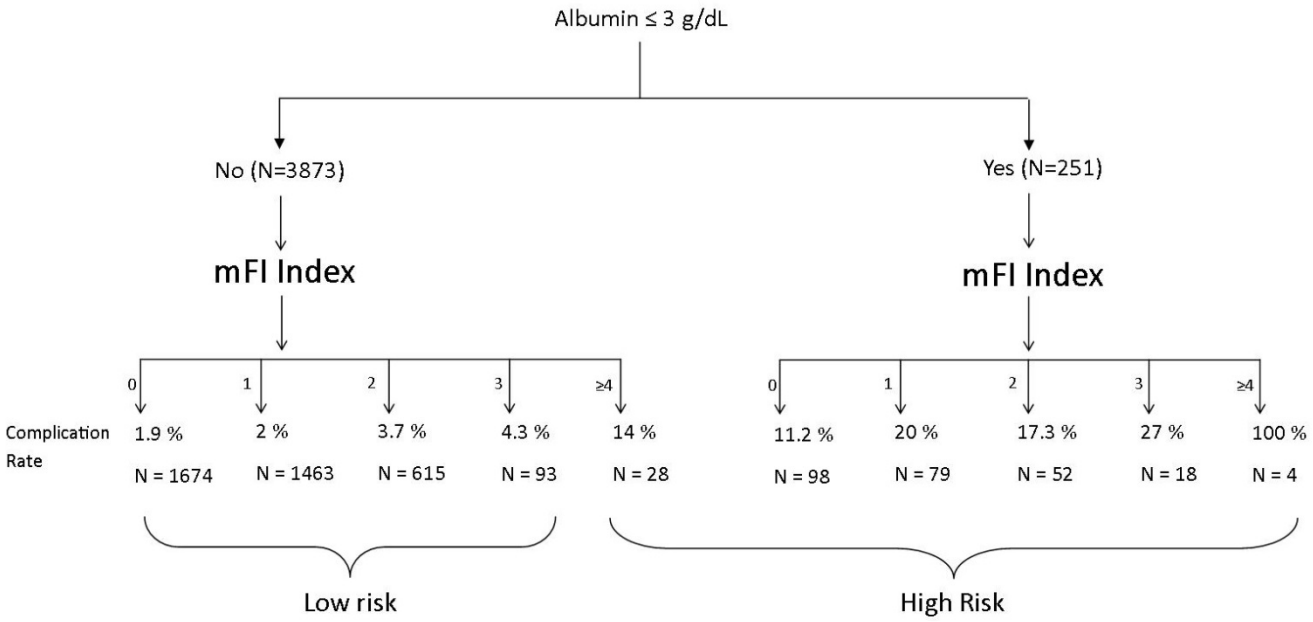
S. Uppal, E. M. Hartenbach, L. M. Barroilhet, A. N. Al-Niaimi, R. Spencer, D. M. Kushner, L. W. Rice and S. L. Rose
University of Wisconsin School of Medicine and Public Health, Madison, WI

Objectives: Patients undergoing surgery for gynecologic malignancies experience a wide range of adverse outcomes. The purpose of this study was to quantify the predictive value of frailty index on 30-day Clavien class IV (requiring critical care support) and class V (30-day mortality) complications after gynecologic cancer surgery.

Methods: Patients included in the National Surgical Quality Improvement Program (NSQIP) participant user files for 2008-2011 with a final diagnosis of gynecologic malignancy were identified. A previously described modified frailty index (mFI) was calculated, with 11 variables based on mapping the Canadian Study of Health and Aging Frailty Index and the existing NSQIP variables. Higher mFI scores indicated more severe comorbidities. Logistic regression was used to control for operative time, surgical complexity, wound classification, ASA classification, body mass index (BMI), preoperative albumin, mode of surgery, and localized vs metastatic disease.

Results: A total of 6,551 patients were identified, with 188 (2.9%) experiencing a Clavien IV or V complication. mFI scores were 0 for 2,958 (45.2%), 1 for 2,405 (36.7%), 2 for 985 (15%), 3 for 162 (2.5%) and ≥4 for 41 (0.6%) patients. The rates of Clavien IV and V complications were 2%, 2.7%, 4.4%, 7.4%, and 24.4% for mFIs of 0, 1, 2, 3, and ≥4, respectively. Variables found to be significant for predicting Clavien IV and V complications on logistic regression modeling were preoperative albumin <3 g/dL (odd ratio [OR]=6.5, 95% CI 4.31-9.96), operative time (OR=1.003, 95% CI 1.001-1.004), nonlaparoscopic surgery (OR=3.3, 95% CI 1.56-8.33), frailty index (OR score 0 = reference, score 1=1.26 (95% CI 0.81-1.95), score 2=1.91 (95% CI 1.17-3.11), score 3=2.33 (95% CI 1.05-5.19), and score ≥4=12.5 (95% CI 4.77-32.76). Taking the two preoperative factors of albumin and mFI into account, we were able to help categorize patients' level of severe morbidity and mortality following surgery (Fig 1).

Conclusions: mFI is predictive of the need for critical care support and 30-day mortality after surgery for gynecologic cancer. Such a tool could potentially be used preoperatively to identify high-risk patients, aid in preoperative decision-making, and provide increased support in the perioperative period.



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64 - Scientific Plenary

Preoperative quality of life in gynecologic oncology patients: a new predictor of operative risk?

K. M. Doll, A. C. Snavely, A. Kalinowski, D. E. Irwin, J. T. Bensen, V. L. Bae-Jump, J. F. Boggess, J. T. Soper, W. R. Brewster and P. A. Gehrig
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Objectives: To evaluate the association between preoperative quality of life (QOL) measures and 30-day postoperative morbidity and health resource utilization by gynecologic oncology patients.

Methods: We analyzed prospectively collected survey data from an institution-wide cohort study. Patients were enrolled from August 2012 to June 2013, and medical records data were abstracted (demographics, comorbid conditions, and operative outcomes). Responses from the Functional Assessment of Cancer Therapy (FACT-GP), and Patient Reported Outcomes Measurement Information System (PROMIS©) global mental (GMH) and physical health (GPH) surveys were linked to clinical data for analysis. Bivariate tests and multivariate linear regression models were used to evaluate factors associated with QOL scores (lower scores are worse).

Results: Of 186 women with suspected gynecologic malignancies, 148 (80%) were surveyed preoperatively and subsequently underwent surgery. Uterine (94 [63.5%]), ovarian (26 [17.5%]), cervical (15 [10%]), vulvar/vaginal (8 [5.4%]), and other (5 [3.4%]) cancers were represented. There were 37 (25%) cases of postoperative morbidity (PM), 18 (12%) unscheduled emergency department visits (EDV), 9(6%) unscheduled clinic visits (CV), and 17 (11.5%) hospital readmissions (HR) within 30 days of surgery. Patients who experienced PM had lower functional well-being (FWB) FACT-GP subscale (15.3 vs 18.7, P=0.01) and overall FACT-GP (74.7 vs 81.5, P=0.048) compared to those who did not. FWB remained significant on multivariate regression analysis (-3.25, P=0.02) after adjusting for anxiety/depression/chronic pain. Thirty-day HR was also associated with lower FWB (12.8 vs 18.5, P=0.01), FACT-GP (67.9 vs 81.3, P=0.008), and GPH (41.9 vs 47.2, P=0.03) scores, and each relationship remained significant after controlling for anxiety/depression/chronic pain and prior surgery. There were no differences in age, major comorbidity, prior abdominal surgery, or obesity in PM vs no-PM groups. EDV and CV were also significantly associated with lower preoperative QOL scores.

Conclusions: Lower preoperative QOL scores are significantly associated with postoperative morbidity and utilization of increased health care resources. This relationship is independent of baseline medical comorbidity and may be a novel indicator of operative risk.

Featured Poster Session III: Ovarian Cancer: Innovations and Controversies
Sunday, March 23, 2014
12:45 p.m. – 1:30 p.m., West Hall
Moderator: Anil Sood, MD, *The University of Texas MD Anderson Cancer Center, Houston, TX*

65 - Featured Poster

An evaluation of progression-free survival (PFS) and overall survival (OS) of ovarian cancer patients with clear cell carcinoma vs serous carcinoma treated with platinum therapy: a Gynecologic Oncology Group (GOG) experience

K. E. Oliver[1], W. E. Brady[2], M. J. Birrer[3], D. M. Gershenson[4], G. Fleming[5] and J. H. Farley[6]
[1]Walter Reed National Military Medical Center, Bethesda, MD, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, [3]Massachusetts General Hospital/Harvard University, Boston, MA, [4]The University of Texas MD Anderson Cancer Center, Houston, TX, [5]University of Chicago Medical Center, Chicago, IL, [6]St. Joseph's Hospital and Medical Center, Phoenix, AZ

Objectives: We examined disparities in prognosis between patients with ovarian clear cell carcinoma (OCCC) and serous epithelial ovarian cancer (SOC).

Methods: We reviewed data from FIGO stage I-IV epithelial ovarian cancer patients who participated in 12 prospective, randomized GOG protocols using platinum-based chemotherapy between 1986 and 2009. Proportional hazards models adjusted for age and stratified by protocol and treatment arm, stage, performance status (PS), and race were used to compare PFS and OS by cell type (clear cell vs serous).

Results: Of 10,803 patients enrolled, 858 were not eligible, 103 were not randomized, 311 did not receive platinum-based regimens, leaving 9,531 eligible patients, of whom 544 (6%) had OCCC, 7,054 (74%) had SOC, and 1,933 (20%) had other. Only the OCCC and SOC patients are considered here. The OCCC patients were significantly younger, more often of Asian race, had early-stage disease and good PS, and were more often optimally debulked than SOC patients. Before adjustment, OCCC patients had better PFS and OS due to better prognostic factors. There was no significant difference in PFS or OS for early-stage OCCC patients compared to high-grade SOC patients. After adjusting for age and stratifying by protocol and treatment arm, stage, performance status, and race, OCCC had significantly decreased OS (HR=1.53 [1.33, 1.76]; $P<0.001$). In early-stage disease, there was a significantly decreased treatment effect on PFS for consolidative therapy with weekly taxol vs observation in OCCC compared to SOC ($P=0.048$). For late-stage disease, OCCC had worse PFS and OS compared to SOC, with OS HR=1.66 (1.43, 1.91; $P<0.001$). For both optimal debulking (HR=1.34 [1.10, 1.63]; $P=0.003$) and suboptimal debulking (HR=3.18 [2.13, 4.75]; $P<0.001$), OCCC had a significantly poorer OS than SOC.

Conclusions: This is one of the largest analyses to date of OCCC treated uniformly under a cooperative group study. OCCC patients had better PFS and OS compared to SOC that was due to their better prognostic factors. No difference in PFS or OS was observed for early-stage OCCC vs high-grade SOC, but in late-stage disease, OCCC was significantly associated with decreased OS, which was true for both optimally and suboptimally debulked patients. Finally, treatment effect was influenced by histology.

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66 - Featured Poster

Comparative effectiveness of treatments for recurrent ovarian cancer

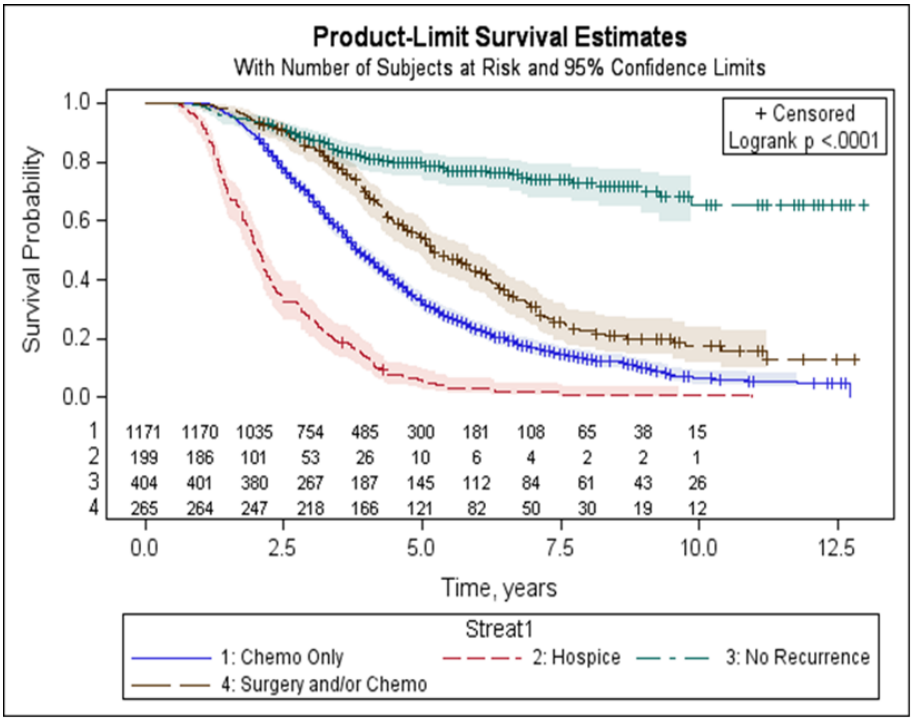
N. A. Bickell[1], P. Deb[2], M. P. Hayes[1], R. Franco[1], J. Wisnivesky[1], E. A. Howell[1], R. Sun[2] and N. Egorova[1]
[1]The Mount Sinai School of Medicine, New York, NY, [2]CUNY Hunter College, New York, NY

Objectives: Secondary cytoreductive surgery (SCS) is increasingly being performed to treat recurrent ovarian cancer. We undertook this study to compare survival between SCS vs chemotherapy vs hospice to treat recurrent ovarian cancer.

Methods: Using SEER-Medicare 1997-2007, we identified a cohort of women age 65+ years with Medicare who were diagnosed with stages III and IV epithelial ovarian cancer, treated with surgery and chemotherapy for their primary cancer, and developed recurrent cancer. Recurrent cancer was identified using claims for chemotherapy, hospice, or SCS following a 6-month treatment-free window after primary treatment. Survival time was calculated from time of first recurrence. Parametric and semi-parametric multivariate survival analyses were used to assess comparative treatment survival rates and factors affecting survival. Propensity score weighting methods were used to obtain doubly robust estimates of comparative effectiveness.

Results: Of the 35,995 women with ovarian cancer, 7,934 met the study criteria. Of these, 3,439 women underwent primary debulking surgery and chemotherapy. Of the 1,633 women who developed recurrent cancer, 72% received secondary chemotherapy alone, 16% received both chemotherapy and surgery, and 12% received hospice with no active treatment. Multivariate survival models controlling for patient demographics, cancer type, and comorbidities showed that women treated with SCS and chemotherapy survived >1 year longer than those treated with only chemotherapy and >3 years longer than those in hospice (Figure 1). The “No recurrence” group survived 4.5 years longer than women with recurrence treated with SCS. In addition to treatment type, survival is negatively affected by older age, comorbidity, black race, and living in the Midwest. Black women undergo SCS at rates similar to whites.

Conclusions: Patients with recurrent ovarian cancer treated with SCS survive longer than patients treated with chemotherapy alone. Women who are black or older at time of recurrence have worse survivals. The poorer survival of black women is likely due to greater burden of comorbidities.



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67 - Featured Poster

Short-term morbidity and mortality associated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent/advanced-stage ovarian cancer

J. C. Cripe II[1], J. Tseng[2], R. Eskander[1], S. D. Thompson[2], A. Nickles Fader[2], E. J. Tanner III[2] and R. E. Bristow[3]
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Objectives: To analyze 30-day morbidity and mortality associated with cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for recurrent/advanced-stage ovarian, fallopian tube, and primary peritoneal cancer.

Methods: A retrospective review of patients undergoing CRS and HIPEC from 2007 through 2013 at two academic medical centers was performed. Complications were graded using the National Cancer Institute Common Toxicity Criteria version 4.0. Chi square analysis was used to compare prevalence of toxicities.

Results: A total of 32 patients with a median age of 59 years (range, 42 to 79 years) were identified, with 27 (84.3%) ovarian, 3 (9.3%) primary peritoneal, and 2 (6.3%) fallopian tube cancers. Indications for surgery were: 75% (*n*=24) secondary-CRS, 18.7% (*n*=6) interval-CRS, and 6.2% (*n*=2) consolidation. HIPEC regimens included: 21 (65.6%) carboplatin, 4 (12.5%) cisplatin, 2 (6.3%) oxaliplatin, 1(3.1%) oxaliplatin + intravenous (IV) 5-fluorouracil, 1 (3.1%) doxorubicin, 1 (3.1%) cisplatin + doxorubicin. Time of infusion ranged from 30 to 90 minutes at median temperature of 42°C. The median intensive care unit and hospital stays were 1 and 8 days, respectively. The combined grade 3/4 morbidity rate was 65.6% (*n*=21). The most common causes of morbidity included: grade 3 anemia 40.6% (*n*=13), infection 18.7%

(*n*=6), and pleural effusion 12.5% (*n*=4). The 30-day readmission rate was 21.8% (*n*=7). Indications for readmission included pain, failure to thrive, infection, and pneumonia. The reoperation rate was 6.2% (*n*=2) for wound closure and intra-abdominal bleeding. Morbidity was not statistically associated with age, body mass index, surgical complexity score, preoperative hemoglobin, preoperative albumin, disease stage, or surgical setting. Full-thickness diaphragm resection/peritoneal stripping was statistically linked to grade 3 and 4 pleural effusions (*P*=0.0007).

Conclusions: Combination CRS + HIPEC is feasible in patients with recurrent/advanced-stage ovarian cancer, with 65.6% grade 3/4 morbidity and no mortalities. As with all therapeutic advancements, the potential benefits of HIPEC must be weighed against risks associated with treatment.

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68 - Featured Poster

Primary debulking surgery or neoadjuvant chemotherapy: what is the optimal treatment approach for obese patients with ovarian/fallopian tube/primary peritoneal carcinoma?

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[1]Brigham and Women's Hospital/Harvard University, Boston, MA, [2]Massachusetts General Hospital/Harvard University, Boston, MA, [3]Harvard University, Boston, MA

Objectives: To compare primary debulking surgery (PDS) with combined neoadjuvant chemotherapy and interval debulking surgery (NACT-IDS) among obese patients with ovarian/fallopian tube/primary peritoneal carcinoma.

Methods: Medical records of patients with a body mass index (BMI) ≥30 who had epithelial ovarian/fallopian tube/primary peritoneal carcinoma between January 2005 and December 2010 were reviewed. Patients were separated by PDS or NACT-IDS. Preoperative characteristics, surgical procedures, and postoperative and oncologic outcomes were compared. Surgical procedures were given a complexity score based on a previously published method.

Results: Of 117 patients, 95 (81.2%) underwent PDS and 22 (18.8%) underwent NACT-IDS. Patients undergoing NACT-IDS were more likely to have stage IV disease (63.6% vs 26.3%, *P*=0.001). The majority of patients in the NACT-IDS group had a low surgical complexity score (*n*=14, 63.6%), while more patients in the PDS group had an intermediate surgical complexity score (*n*=48, 50.5%). There were no other differences between groups with respect to preoperative characteristics or postoperative morbidity. Compared to patients undergoing NACT-IDS, those undergoing PDS had an improved progression-free survival (PFS) (15 vs 11 months, *P*=0.006) and overall survival (OS) (53 vs 32 months, *P*=0.036). Seventy-eight (66.7%) patients had a BMI<35. Within this subset of obese patients, those undergoing PDS had an improved PFS (15 vs 10 months, *P*=0.011) and OS (58 vs 32 months, *P*=0.033) compared to those undergoing NACT-IDS. Among patients with a BMI ≥35, there was no difference in PFS (14 vs 12 months, *P*=0.316) or OS (38 vs 32 months, *P*=0.640) when comparing PDS and NACT-IDS.

Conclusions: Obese patients with a BMI<35 undergoing PDS have improved oncologic outcomes compared to those undergoing NACT-IDS. Obese patients with a BMI ≥35 undergoing PDS have similar oncologic outcomes to those undergoing NACT-IDS. Complication rates were similar at all BMIs regardless of treatment approach.

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69 - Featured Poster

Launching personalized surgical therapy for advanced ovarian cancer

A. M. Nick[1], P. T. Ramirez[1], K. M. Rangel[1], K. M. Schmeler[1], P. T. Soliman[1], J. K. Burzawa[1], M. Kodama[2], K. H. Lu[1], R. L. Coleman[1] and A. K. Sood[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]Osaka University Graduate School of Medicine, Suita, Japan

Objectives: There is growing consensus that patients who benefit the most from primary cytoreduction (TRS) are those are left with no gross residual disease (R0). Current clinical evaluation methods are inadequate for predicting R0 TRS, prompting us to develop a more reliable strategy.

Methods: We developed a triage algorithm incorporating disease distribution scoring by laparoscopy (modified from Fagotti et al, *Gynecol Oncol* 2005). Preoperative defined parameters were analyzed during each procedure and scored independently by two surgeons. Scores >8 resulted in triage to neoadjuvant chemotherapy (NACT). An adjudicating faculty was used when

consensus was not met. Patient outcomes and faculty compliance were tracked prospectively under a Quality Improvement (QI) Board-approved protocol. A QI committee met weekly to review each patient undergoing assessment. R0 TRS rates following the implementation of the new practice guidelines were compared to historical R0 rates at our institution from 2007 through 2012.

Results: Between April and September 2013, 49 patients with suspected advanced ovarian cancer were evaluated (13 excluded due to medical comorbidities or extra-abdominal metastases; 3 not offered laparoscopy by their primary surgeon [94% compliance]). Thirty-three patients underwent laparoscopy with no intraoperative complications. There was 100% concordance between the two surgeons. Nineteen patients (58%) scored <8 and underwent primary TRS, with the remaining 14 (42%) undergoing NACT. The accuracy of laparoscopic assessment for predicting R0 resection was 84% (compared to a historical R0 resection rate of 44% from 2007-2012, $P<0.01$), with no difference in the time to initiation of postoperative adjuvant chemotherapy (23 days [range, 5-61 days] vs 26.5 days [range, 15-38 days], $P=0.15$). To date, six patients in the NACT group have undergone interval TRS, with a R0 rate of 100% compared to a past rate of 65% ($P=0.15$). The median time to initiation of NACT was significantly shorter following laparoscopy compared to the historical practice of referral for percutaneous biopsy (6 days [range, 1-14 days] vs 12 days [range, 0-52 days], $P<0.01$).

Conclusions: We have incorporated a new systematic approach to the surgical management of primary ovarian cancer. To date, laparoscopy appears to be a more reliable and reproducible method of determining resectability of advanced ovarian cancer.

Focused Plenary IV: Innovations in Immunotherapy
Sunday, March 23, 2014
1:45 p.m. – 3 p.m., Ballroom D
Moderator: Terri L. Cornelison, MD, PhD, *Breast and Gynecologic Cancer Research Group, DPC, National Cancer Institute, Bethesda, MD*

70 - Focused Plenary

Phase I evaluation of therapeutic HPV16 E7 vaccination before resection of HPV16+ CIN2/3

W. K. Huh[1], R. D. Alvarez[1], L. Maldonado[2], C. Wang[2], T. C. Wu[2] and C. Trimble[2]
[1]*University of Alabama at Birmingham, Birmingham, AL,* [2]*Johns Hopkins Medical Institutions, Baltimore, MD*

Objectives: The primary goal of this trial was to determine the feasibility, tolerability, and safety of pNGVL4a-CRT-E7(detox), a human papillomavirus (HPV)16 E7 vaccine, administered either epidermally (particle-mediated), intralesionally, or intramuscularly before therapeutic resection of HPV16+ cervical intraepithelial neoplasia (CIN)2/3. Secondary goals included assessment of potential clinical and biologic effects associated with this vaccination strategy.

Methods: This prospective, dose-escalation, phase I study tested two dosages of pNGVL4a-CRT-E7(detox) administered 3 times every 4 weeks before a standard therapeutic resection. Eligibility criteria included a biopsy diagnosis of CIN2/3, residual lesion after diagnostic biopsy, HPV16 positivity, and immunocompetency. Toxicity was assessed using predefined vaccine-specific toxicity criteria and CTCAE4.0 guidelines. Clinical efficacy, although not a primary aim, was assessed by evaluating histopathologic findings and by immune responses to HPV16 E7.

Results: To date, 25 women have completed the vaccination regimens. Vaccination via all three routes (particle-mediated epidermal delivery [needle-free], intralesional, and intramuscular) has been feasible and tolerable. The most common reported adverse events are injection site discomfort (particle-mediated and intramuscular cohorts); cramping (intralesional cohort); and headaches, flulike symptoms, and mild muscle/joint aches (all cohorts). All adverse events were mild and resolved without intervention. Preliminary assessment of histologic response (Table 1) suggested better efficacy in higher-dose cohorts and in patients who were vaccinated by intralesional or intramuscular routes. Viral load and immunologic response data are maturing and will be presented.

Table 1. Histologic Responses 7 Weeks After Vaccination

Route of Vaccination	Dose	Number of Completed Vaccinations to Date	Complete Response (%)
Particle-mediated	8 µg	3	0/3 (0%)
Particle-mediated	16 µg	6	1/6 (17%)
Intralesional	1 mg	3	0/3 (0%)
Intralesional	3 mg	6	2/6 (33%)
Intramuscular	1 mg	3	1/3 (33%)
Intramuscular	3 mg	4	2/4 (50%)

Conclusions: This study provides evidence that vaccination with pNGVL4a-CRT-E7(detox) at the evaluated dosages and schedule is feasible and well-tolerated. Vaccination via the intralesional or intramuscular route at the 3-mg dose appears more clinically effective.

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71 - Focused Plenary

Phase II trial of paclitaxel, 13-cis retinoic acid, and interferon-alfa-2b in the treatment of advanced stage or recurrent cervical cancer

M. Song[1], R. Di Paola[1], B. M. Cracchiolo[2], D. G. Gibbon[1], M. Hellmann[1], W. Nieves[1], A. P. Vaidya[3], A. Wagreich[1], W. Shih[1] and L. Rodriguez-Rodriguez[1]
[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, [2]Rutgers New Jersey Medical School, Newark, NJ, [3]John Theuerer Cancer Center, Hackensack, NJ

Objectives: Overexpression of bcl-2 is a mechanism of drug resistance in cervical cancer. Agents that downregulate bcl-2 may decrease tumor cell threshold and, therefore, sensitize tumor cells to chemotherapy. The objective of this multi-institutional phase II trial was to evaluate the efficacy and toxicity of paclitaxel and bcl-2 modulators (13-cis retinoic acid and interferon-alfa-2b) in patients with advanced-stage or recurrent cervical cancer.

Methods: Eligible patients had histologically or cytologically proven metastatic, recurrent, or persistent cervical cancer. Other inclusion criteria were: >18 years old; estimated life expectancy of at least 6 months; Eastern Cooperative Oncology Group performance status of 0-2; and no prior retinoids, interferon, or paclitaxel therapy. The treatment consisted of cis-retinoic acid 1 mg/kg/day PO on days 1-4 of each cycle, interferon alfa-2b SQ 6 mU/m² on days 1-4 of each cycle, and paclitaxel 175 mg/m² on day 4 until disease progression or adverse events prohibited further treatment. Each cycle repeated every 21 days. The primary endpoint was overall response rate.

Results: A total of 33 patients were enrolled from five participating institutions between March 2001 and June 2009, and 31 patients were eligible for evaluation of treatment response. Twenty-seven patients (82%) received prior concurrent chemoradiation or radiotherapy alone before study enrollment. The overall response rate was 30% (6 complete responses and 4 partial responses). Furthermore, 7 patients (21%) had stable disease. Grade 3 or 4 adverse events included neutropenia (n=16, 48%), febrile neutropenia (n=1, 3%), and anemia (n=1, 3%). There were no treatment-related deaths. The median progression-free survival was 3.4 months (95% CI, 2.0-7.4 months), and overall survival was 11.2 months (95% CI, 7.5-26.2 months). Of six patients who had complete responses, five survived >2 years.

Conclusions: Combination therapy with paclitaxel, 13-cis retinoic acid, and interferon alfa-2b is effective and safe in treating patients with advanced and recurrent cervical cancer.

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72 - Focused Plenary

Nationwide assessment of human papillomavirus (HPV) genotypes in cancers: implications for prevention and monitoring impact of current and future (9-valent) HPV vaccines in the United States

M. T. Goodman[1], E. R. Unger[2], T. Thompson[2], C. F. Lynch[3], M. Steinau[2], B. Hernandez[4], C. Hopenhayn[5], E. J. Wilkinson[6], G. C. Copeland[7] and M. Saraiya[2]
[1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Centers for Disease Control and Prevention, Atlanta, GA, [3]University of Iowa, Iowa City, IA, [4]University of Hawaii Cancer Center, Honolulu, HI, [5]University of Kentucky, Lexington, KY, [6]University of Florida College of Medicine, Gainesville, FL, [7]Michigan Department of Community Health, Lansing, MI

Objectives: Systematic surveillance to determine the type-specific prevalence of human papillomavirus (HPV) in United States (US) cancers is needed to estimate the impact of current (16/18) and proposed (31/33/45/52/58) HPV vaccines.

Methods: The Centers for Disease Control and Prevention partnered with seven US population-based cancer registries to obtain archival tissue from invasive anogenital and head and neck cancers for HPV testing (n=2,670). Demographic, clinical, and pathologic data were evaluated by anatomic site and HPV status. We used current US cancer registry data and the relative contributions of the HPV types to estimate the number of cancers that could be prevented by HPV vaccine.

Results: HPV DNA was detected in cervical and anal cancers (91%), vaginal cancers (75%), oropharyngeal cancers (70%), vulvar cancers (69%), penile cancers (63%), oral cavity cancers (32%), and laryngeal cancers (21%). Removing HPV 16/18 from the population potentially could prevent 38,000 cancers, including the majority of cervical (66%), anal (79%), oropharyngeal (60%), and vaginal (55%) cancers as well as many penile (48%), vulvar (49%), and some oral cavity (22%) and laryngeal (8%) cancers. An additional 4% to 18% (8,000) of these site-specific cancers may be prevented by the future vaccine. For most cancers, younger age at diagnosis was associated with higher HPV16/18 prevalence. HPV 16/18 distribution was similar across racial/ethnic groups, with the exception of a lower prevalence among African Americans with oropharyngeal cancers.

Conclusions: The impact of current and future HPV vaccines on US cancers can be monitored using population-based cancer registries.

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73 - Focused Plenary

Combination immunotherapy enhances survival in patients with recurrent ovarian cancer

J. L. Tanyi, E. Zsiros, C. L. Chiang, D. Torigian, M. A. Morgan, W. T. Hwang, H. L. Nisenbaum, L. Kandalaft and G. Coukos
University of Pennsylvania, Philadelphia, PA

Objectives: Cyclophosphamide and antiangiogenic therapy has been shown to enhance and synergize with immunotherapy. We designed a phase I study to evaluate the safety, immunogenicity, and clinical efficacy of combination immunotherapy by using dendritic cell (DC)-based autologous whole tumor antigen vaccination alone and in combination with bevacizumab or with bevacizumab and cyclophosphamide in patients with recurrent ovarian cancer.

Methods: The phase I, three-cohort, single-center study evaluated autologous oxidized whole-tumor cell-pulsed DC (OC-DC) vaccine administered intranodally alone or in combination with bevacizumab or bevacizumab and cyclophosphamide to patients with recurrent ovarian cancer. Patients in cohort 1 (n=5) received 5 doses of 5 to 10×10^6 DCs intranodally, and patients in cohort 2 (n=10) received the 5 doses of vaccine in combination with intravenous bevacizumab given every 2 weeks. Patients in cohort 3 (n=10) also received 5 doses of vaccine with bevacizumab plus cyclophosphamide administered the day before each vaccination. Patients with stable disease at the end of study were allowed to continue with additional maintenance vaccines. Fifty patients with recurrent ovarian cancer who received bevacizumab with cyclophosphamide as second-line treatment were used as controls.

Results: The mean age, number of prior chemotherapies, and number of prior recurrences were not statistically different across the groups. Patients received an average of seven vaccines. The vaccine was well-tolerated and only produced grade 1 toxicities. Tumor-specific T-cell responses were elicited against HER-2/neu, MUC1, NY-ESO-1, mesothelin, and WT-1 tumor antigens. Fourteen patients (56%) showed clinical benefit, with stable or no evidence of disease (40% in cohort 1, 50% in cohort 2, 70% in cohort 3) at end of study and some exhibiting durable responses. Compelling progression-free and overall survival benefits were elicited in cohort 3 as compared to cohort 1 and 2 and the control group of patients.

Conclusions: Combination therapy using autologous whole-tumor DC vaccines with cyclophosphamide and antiangiogenic agents is a promising approach that warrants further investigation.

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74 - Focused Plenary

A phase I trial of a DNA plasmid-based vaccine targeting insulin-like growth factor binding protein-2 (IGFBP-2) in patients with advanced ovarian cancer: preliminary safety and immunogenicity

J. B. Liao, D. L. Cecil, J. Reichow, S. Parker, D. Higgins, J. Childs, E. Broussard, A. Coveler, L. Salazar and M. L. Disis
University of Washington, Seattle, WA

Objectives: IGFBP-2 has emerged as an important regulator of ovarian cancer invasion and metastasis. Eradication of tumor cells expressing IGFBP-2 could prevent disease relapse or metastasis. This study assessed the safety and immunogenicity of IGFBP-2 vaccination in advanced-stage or recurrent ovarian cancer.

Methods: This was a single-arm, nonrandomized phase I study in patients with advanced-stage (III/IV) or recurrent ovarian cancer treated to a complete remission. Patients received 3 intradermal injections of IGFBP-2 DNA vaccine admixed with granulocyte macrophage colony-stimulating factor 28 days apart. Serum and blood were collected before vaccination; at the third vaccination; and at months 4, 9, and 15. Patients were monitored for 1hour after immunization. Adverse events for all systems were graded on a scale of 1 to 5 and attribution was assigned, using the Common Terminology Criteria for Adverse Events Version 4.0. Serum antibodies were measured by Western blot against recombinant IGFBP-2 protein. Peripheral blood mononuclear cells (PBMC) were assayed by interferon-g enzyme-linked immunosorbent spot (ELISPOT) for activation by IGFBP-2 peptides and recombinant protein.

Results: To date a total of 172 adverse events have been reported in 24 patients. Of 70 vaccinations administered, only 2 acute toxicities occurred during the 60-minute immediate postvaccine evaluation period. Fatigue (12.21%) and injection site reactions (10.47%) were the most commonly reported adverse events. Ninety-seven percent of all adverse events to date were grades 1-2 and 3% were grades 3-5. The single related grade 3 event was decreased lymphocyte count, which was not considered a dose-limiting toxicity. In preliminary analysis for immunogenicity, 75% of patients with pre-existing serum antibodies recognizing IGFBP-2 had augmentation of these responses detected in serum by Western blot against recombinant IGFBP-2 protein at the time of the third vaccination. Initial interferon-g ELISPOT assays performed on PBMC stimulated with IGFBP-2 recombinant protein showed increased responses in two of three vaccinated patients.

Conclusions: Preliminary data from this ongoing phase I trial support an excellent safety profile for IGFBP-2 DNA vaccination. Early data also document augmentation of IGFBP-2-specific humoral and cellular immunity in response to vaccination.

Focused Plenary V: Obesity Induced Challenges in Endometrial Cancer
Sunday, March 23, 2014
1:45 p.m. – 3:00 p.m., Ballroom A
Moderator: Angeles Secord, MD, *Duke University Medical Center, Durham, NC*

75 - Focused Plenary

The economic impact associated with caring for the morbidly obese with endometrial cancer: a nationwide study of 6,560 women

J. K. Chan[1], K. W. Blansit[1], L. M. Chen[1], R. A. Brooks[1], S. M. Ueda[1], X. Yu[2] and D. S. Kapp[3]
[1]UCSF Helen Diller Comprehensive Cancer Center, San Francisco, CA, [2]University of Memphis, Memphis, TN, [3]Stanford University, Stanford, CA

Objectives: To determine the financial charges associated with surgery, hospitalization, and postoperative care of morbidly obese endometrial cancer patients in the United States.

Methods: Data were obtained from the National Inpatient Sample (NIS) from 2010. Chi square, t-test, and linear multivariate regression analyses were used for statistical analyses.

Results: Among 6,560 patients, the median age was 62 years (range, 22-99 years). Most of the patients were white (78%), with the remainder being black (10%), Hispanic, (8%), Asian (3%), and Native American (1%). Private, Medicare, Medicaid, and uninsured were identified in 7%, 37%, 9%, and 47% of patients, respectively. Within the overall study group, 1,088 (16%) were diagnosed as morbidly obese. The mean postoperative stay for the morbidly obese was 4.0 days (range, 0-46 days) compared to 3.5 days (range, 0-81 days) for the nonmorbidly obese ($P<0.01$). Morbidly obese patients required more intensive care with mechanical ventilation (5.5% vs 1.6%, $P<0.01$). The median total hospital charges were higher for morbidly obese patients compared to their counterparts ($41,160 vs $36,650, $P<0.01$). Using a multivariate linear regression model adjusted for charges associated with insurance type, hospital type, and surgery performed, the incremental costs of treating the morbidly obese was $5,096 per patient (95% CI $2,593 - $7,598; $P<0.01$). Over the study period in the year 2010, the total additional cost of treating morbidly obese endometrial cancer patients was $5,544,448 (95% CI $2,821,582 - $8,266,910) in the NIS. Using the endometrial cancer incidence of 40,000 per year, this incremental charge is estimated to be approximately $34,652,800 (95% CI $17,361,132 - $50,871,532) per year in the United States.

Conclusions: In this economic analysis, we showed that the health care charges associated with treating endometrial cancer in the morbidly obese were significantly higher compared the nonmorbidly obese. Additional resources are needed to support specialized centers that serve this population.

76 - Focused Plenary

Complications and surgical staging of endometrial cancer with respect to obesity: a Gynecologic Oncology Group LAP2 ancillary data study

C. C. Gunderson[1], J. Java[2], K. N. Moore[1] and J. L. Walker[1]
[1]The University of Oklahoma, Oklahoma City, OK, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY

Objectives: To determine the effect of body mass index (BMI) on lymph node retrieval and perioperative complications in GOG LAP2, a randomized comparison of laparoscopic vs open surgical staging in clinically early-stage endometrial cancer.

Methods: An ancillary data analysis of GOG LAP2 was performed. Descriptive statistics were used for demographics, surgicopathologic characteristics, and complications by BMI. Wilcoxon, Pearson, Cochran-Mantel-Haenszel, and Kruskal-Wallis tests were used for univariate and multivariate analysis.

Results: A total of 2,596 women were included. BMI groups were <25 (29.5%), 25-30 (28.2%), 30-35 (21%), 35-40 (10.9%), and ≥40 (10.4%). Obese women were less likely to have any positive lymph nodes (PLN) (4.6% with BMI ≥40 vs 11.7% with BMI <25, P=0.021) or positive pelvic nodes (3.4% of BMI ≥40 vs 10.5% of BMI <25, P=0.011), but the incidence of positive para-aortic nodes did not vary by BMI (P=0.23). Intraoperative complications were similar within each surgical approach group despite BMI. Postoperative complications were more frequent with obesity (23.8% with BMI ≥40 vs 13.7% with BMI <25, P<.001), including wound infection (11.5% with BMI ≥40 vs 1.1% with BMI <25, P<0.001) and venous thrombophlebitis (0.8% with BMI ≥40 vs 0.4% with BMI <25, P=0.038). Obese women more often required postoperative antibiotics (30.3% with BMI ≥40 vs 15.8% with BMI <25, P<0.001) and hospitalization >2 days (78.9% with BMI ≥40 vs 60.7% with BMI <25, P<.001). After controlling for surgical approach, wound infection (11.5% with BMI ≥40 vs 1.1% with BMI <25, P<0.001) and postoperative antibiotic use (30.3% with BMI ≥40 vs 15.8% with BMI <25, P<0.001) were higher in obese women. All postoperative complications were more frequent in obese women converted to laparotomy vs open or laparoscopic groups.

Conclusions: The primary LAP2 analysis demonstrated higher conversion rates with escalating BMI. Given the relative rarity of PLN in high-BMI women and the increased postoperative complications with laparotomy, the value of conversion from laparoscopy to complete nodes in the morbidly obese may be limited.

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77 - Focused Plenary

The link between obesity and endometrial cancer: a lack of knowledge but an opportunity for intervention

A. F. Haggerty, K. Allison, D. B. Sarwer and C. Chu
University of Pennsylvania, Philadelphia, PA

Objectives: One third of American adults are obese (body mass index [BMI] ≥30), and the causal link between obesity and endometrial cancer is well established. However, there is a paucity of information on the effect of decreasing BMI on outcomes for affected women. Our objective was to explore patients' understanding of the relationship between obesity and endometrial cancer and to assess the acceptability of a weight loss intervention to these women.

Methods: Women with obesity and type 1 histologically confirmed endometrial cancer or endometrial hyperplasia were asked to complete a survey. The questionnaire evaluated patients' self-assessment of their BMI category, knowledge about the causality of obesity and endometrial cancer, and included questions about their diet and physical activity habits. Interest in, and feasibility of, participation in a technology-based weight loss intervention was assessed with questions about text messaging and Wi-Fi Internet capability.

Results: The 75 women who completed the survey had predominantly early stage and grade disease (72.9% stage I and 38.8% grade 1), although 22.4% had grade 3 histology. The median BMI was 35.2 (interquartile range [IQR] 32.1-41.3) and the average age was 59.5±11.15 years. The majority of patients (77.0%) were unable to categorize their BMI correctly, and 100% of those who attempted to do so incorrectly underestimated their true BMI category. More than one third (34.7%) were unaware of any association between obesity and endometrial cancer, and 43.1% responded that obesity decreased or did not change the risk of endometrial cancer. In the assessment of the feasibility of a technology-based weight loss intervention, 74.3% had text messaging capability and 65.7% had private wireless Internet access. Ultimately, 46.6% of respondents were eligible for participation in the pilot intervention, and 60% expressed interest in enrollment, with a median weight loss goal of 50 (IQR 30-90 lb).

Conclusions: Obese endometrial cancer survivors are unable to self-assess their category of obesity accurately and have a significant lack of knowledge about the link between obesity and endometrial cancer. However, these women are motivated to participate in novel electronically delivered weight loss interventions.

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78 - Focused Plenary

Novel exercise, weight-loss, and dietary approach to your life study (NEWDAY) in overweight endometrial and breast cancer survivors

M. L. McCarroll[1], S. Armbruster[1], R. J. Pohle-Krauza[1,2], A. M. Lyzen[1], N. Fagan[1], S. Min[3], G. D. Roulette[1,3], S. J. Andrews[1,3] and V. E. Von Gruenigen[1,3]
[1]Summa Health System, Akron, OH, [2]Youngstown State University, Youngstown, OH, [3]Northeast Ohio Medical University (NEOMED), Rootstown, OH

Objectives: Overweight endometrial and breast cancer survivors (CS) are at risk for premature death. Previous research in CS has demonstrated the efficacy of interventions involving traditional, "face-to-face" approaches, but there are few data on strategies that are primarily electronic and asynchronous. The purpose of the current study was to examine the effectiveness of an Internet- and Smartphone/tablet-based weight-loss application (*LoseIt!)* that included an ancillary active, health care-provider interface.

Methods: Thirty-two early-stage overweight (body mass index [BMI] ≥25) female CS were given access to *LoseIt!* and instructed to log daily food intake and volitional exercise for 1 month. BMI (and weight) and waist circumference (WC) were assessed at baseline and end of the intervention. Participants completed the Weight Efficacy Lifestyle Questionnaire (WEL) measuring self-efficacy. Healthcare provider contact points were measured using the notes section of *LoseIt*! along with push notifications to reward milestones (badges). SPSS 20.0 was used to generate descriptive statistics and to conduct Student's t-tests.

Results: Mean participant age was 58.4±10.3 years. Thirteen (41%) and 17 (53%) patients had past medical histories of endometrial and breast cancers, respectively, while 2 (6%) patients had histories of both. Significant reductions were noted between pre- and postintervention BMI (34.9±8.7 vs 33.9±8.4, P=0.0005), body weight (92.3±23.7 kg vs 90.1±22.9 kg, P<0.0001), and WC (102.7±14.9 cm vs 98.3±15.1 cm, P=0.0006). A trend toward significance was noted between pre- and postintervention total WEL scores (93.8±41.1 vs 115.1±48.1, P=0.08). There was a moderate positive correlation between total WEL scores and the amount of health care provider feedback and push notifications (r=+0.349, P=0.382).

Conclusions: These results indicate that a lifestyle intervention application is a feasible option by which to elicit short-term reductions of BMI and WC by 3% to 4%. Although these results parallel the recent SUCCEED (Survivors of Uterine Cancer Empowered by Exercise and healthy Diet) trial, it is notable that they were achieved without encumbering cost and barrier-access issues. We will continue to enroll patients until we achieve 50 completers.

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79 - Focused Plenary

Metformin and the risk of endometrial cancer: a population-based cohort study

E. M. Ko[1,2], T. Sturmer[2], J. L. Hong[2], W. Camelo[2], V. L. Bae-Jump[3] and M. J. Funk[2]
[1]University of Pennsylvania, Penn Medicine, Philadelphia, PA, [2]University of North Carolina Gillings School of Public Health, Chapel Hill, NC, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC

Objectives: Metformin may decrease the risk of developing cancer, but its role in gynecologic cancers is not yet clear. We sought to compare whether women who initiate treatment with metformin vs sulfonylureas had a lower risk of endometrial cancer.

Methods: A retrospective cohort analysis was performed using Truven Health Analytics MarketScan® Databases from 2000-2011. We identified new users of metformin or sulfonylureas and estimated HR and 95% CI with Cox Proportional Hazards, using an as-treated analytic approach. Stabilized inverse probability of treatment weights (IPTW) were used to adjust for potential confounders. Crude and IPTW-adjusted survival curves were estimated using the Kaplan-Meier method.

Results: Of 541,128 eligible women, 456,838 (84%) initiated metformin and 84,290 (16%) initiated sulfonylurea. Baseline covariates, including age, diabetes, polycystic ovarian syndrome, and endometrial hyperplasia, differed between metformin

and sulfonylurea users. Over a median follow-up of 1.2 years (interquartile range [IQR] 0.4-2.3) and a total follow-up of 2,030,914 person-years, 729 women developed endometrial cancer. Metformin use appeared to reduce the risk of endometrial cancer in the unadjusted analysis (HR 0.81, 95% CI 0.67-0.97). However, after balancing all baseline covariates using IPTW, metformin did not decrease the risk of endometrial cancer (HR 1.09, 95% CI 0.88-1.35). Multiple subgroup analyses in diabetic patients and varying age groups revealed similar nonprotective findings.

Conclusions: In this population-based cohort of more than 500,000 women, initiating antidiabetic therapy with metformin compared with sulfonylureas was not associated with the risk of developing endometrial cancer. Further studies may determine if metformin may help reduce endometrial cancer in other subsets of particularly high-risk women.

Featured Poster Session IV: Cancer in the Elderly & Underserved Populations
Monday, March 24, 2014
7:00 a.m. – 8:00 a.m., Ballroom A
Moderator: Trey Leath, MD, *University of Alabama at Birmingham, Birmingham, AL*

80 – Featured Poster

Dose delay, but not dose reduction, in chemotherapy administration is associated with decreased survival in elderly women with ovarian cancer

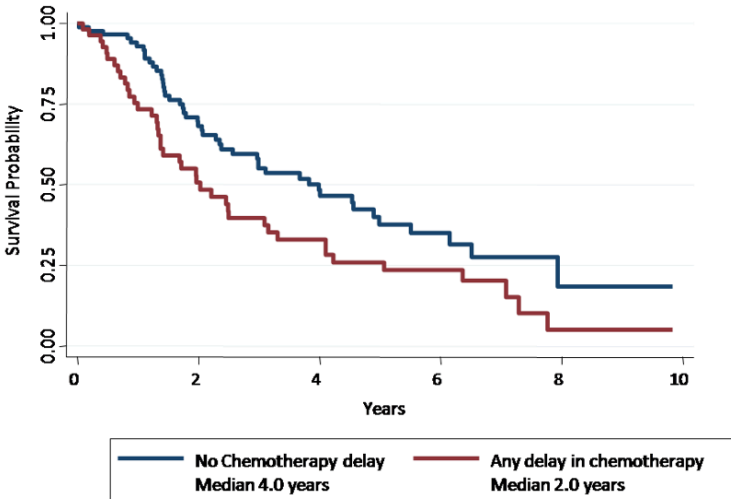
N. Joseph[1], R. M. Clark[2], M. Lee[3], K. Kopecky[4], D. S. Dizon[2] and W. B. Growdon[3]
[1]Brigham and Women's Hospital/Harvard University, Boston, MA, [2]Massachusetts General Hospital/Harvard University, Boston, MA, [3]Massachusetts General Hospital, Boston, MA, [4]Harvard Medical School, Boston, MA

Objectives: Elderly patients with ovarian cancer represent a vulnerable population that frequently demonstrates poor outcomes. The objective of this study was to characterize risk factors and treatment patterns in this population and how they relate to overall survival (OS).

Methods: After obtaining institutional review board approval, we identified all patients >65 years with stage II-IV epithelial ovarian cancer who underwent cytoreduction at our institution between the years of 2003 and 2011. Relevant clinical variables were extracted and correlated with OS. Statistical analysis was performed using logistic regression, Kaplan-Meier curves, and multivariable Cox proportional hazard models.

Results: A total of 184 patients were included in the analysis. The average age was 73 years and median ASA class was 2. Seventy-eight percent of the cohort underwent primary cytoreduction and 22% underwent neoadjuvant chemotherapy/interval debulking surgery. OS was 2.6 years (range, 1.3-6.8 years). Seventy percent of patients received a platinum doublet as initial therapy, 47% of patients underwent an initial dose reduction, 46% required at least one transfusion, and 39% experienced at least one dose delay. When modeled as both continuous and binary variables, the need for chemotherapy delay and transfusion was significantly associated with a worsened OS ($P=0.02$ and $P<0.05$, respectively). The need to reduce chemotherapy dose either initially or throughout treatment did not affect OS ($P=0.14$, $P=0.12$). Multivariate analysis, including significant variables such as age, ASA class, and disease stage, demonstrated that any delay in chemotherapy remained significant as a predictor of OS ($P= 0.029$).

Conclusions: In this study, elderly patients with ovarian cancer who underwent cytoreduction frequently required transfusion and needed dose delay. Multivariate analysis confirmed that dose delays, but not dose reductions, were independently associated with decreased OS.



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81 - Featured Poster

An American College of Surgeons-National Surgical Quality Improvement Project (ACS-NSQIP) evaluation of surgical outcomes in the elderly: endometrial cancer patients undergoing hysterectomy

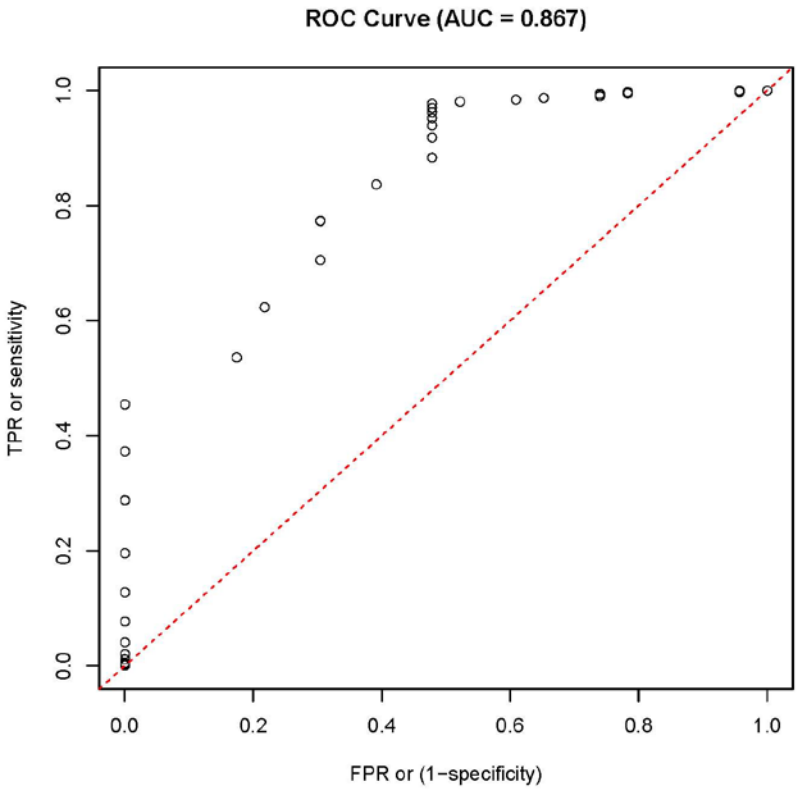
C. V. Brown[1], B. Wang[2], J. M. Scalici[2], R. P. Rocconi[2] and M. A. Finan[2]
[1]*Vanderbilt University, Nashville, TN,* [2]*University of South Alabama, Mobile, AL*

Objectives: Endometrial cancer is common in the elderly. In this study, we analyzed patients with endometrial cancer who had undergone hysterectomy to determine the effect of advanced age on postoperative outcomes.

Methods: Using the ACS-NSQIP database 2005-2011, comparative analyses were performed to determine the effect of age on preoperative characteristics, operative variables, and postoperative outcomes for patients with endometrial cancer who underwent hysterectomy. Data were analyzed using SPSS 20.0. Student t-test, chi-square test, and Fisher's exact test were used as appropriate with univariate analyses. A logistic regression analysis for risk-adjusted odds ratios (ORs) was performed.

Results: Those patients >80 years had a shorter duration of anesthesia and total operative time. The total operative time was significantly longer in the younger age group ($P<0.0001$). The elderly group also had a longer length of total surgical stay and higher incidence of pneumonia, unplanned reintubation, urinary tract infection, septic shock, wound infection, and systemic sepsis. Patients <80 years had a higher rate of deep vein thrombosis and venous thromboembolism. The elderly group had a significantly higher risk of postoperative death (odds ratio=5.31; 95% CI 2.40, 11.75; $P<0.0001$), and this was predicted by a low preoperative albumin, receiver operating characteristic with AUC of 0.867 (Figure 1).

Conclusions: The older group was significantly more ill and had a higher rate of comorbidities than the younger group, as expected. Elderly patients had a significantly higher risk of death (OR 5.3, $P<0.0001$), and this was predicted by a low albumin, particularly if <3.0 g/dL. If the patient is healthy, active, and has few comorbidities, surgery can be carried out safely with a minimal increase in morbidity in the elderly population. Caution should be exercised in the elderly with endometrial cancer, especially if they have significant comorbidities and/or albumin <3.0 g/dL.



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82 - Featured Poster

Gaps in adjuvant treatment in elderly endometrial cancer patients

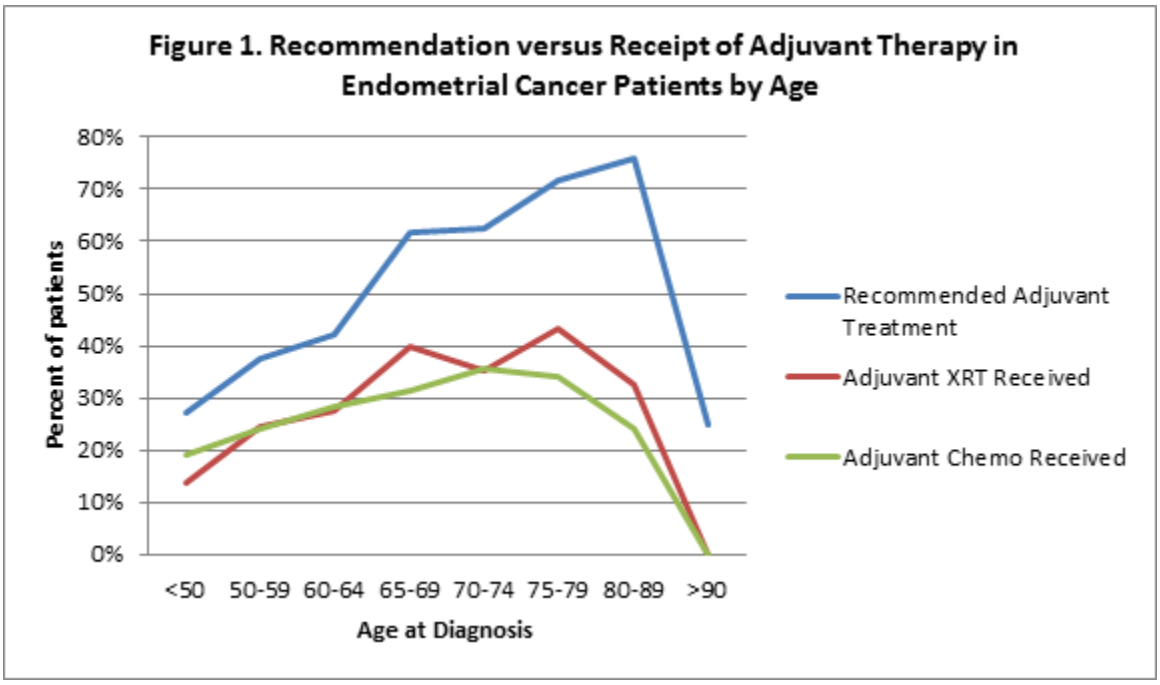
L. H. Clark[1], A. L. Jackson[1], V. L. Bae-Jump[1], P. A. Gehrig[1], L. Van Le[1] and E. M. Ko[2]
[1]*University of North Carolina at Chapel Hill, Chapel Hill, NC,* [2]*University of Pennsylvania, Philadelphia, PA*

Objectives: Previous studies of elderly endometrial cancer (EC) patients have focused on women who received treatment but have not examined the subset of elderly patients who did not receive treatment, particularly in the adjuvant setting. We sought to determine the gap between recommended and received adjuvant treatment in elderly EC patients.

Methods: Following institutional review board approval, we performed a retrospective review of all EC cases from a single tertiary care institution from 2005 to 2010. Clinical, surgical, and pathologic data were abstracted from medical records. Descriptive statistics were performed using univariate and bivariate analysis. chi-square tests were used for categorical comparisons.

Results: Of 1,064 EC patients who were reviewed, 27% (280/1064) were >70 years old. Grade 3 tumors were more common in the elderly, occurring in 62% (40/65) of octogenarians compared to 39% (333/ 854) of those 50 to 79 years and 22% (27/125) of those <50 years (P<0.001). Endometrioid adenocarcinoma was the most common in all age groups but declined from 86% (107/125) in those <50 years to 59% (38/65) of octogenarians (P<0.001). In contrast, the incidence of carcinosarcoma increased from 0.8% (1/125) in those <50 years to 15.4% (10/65) in octogenarians (P<0.001). Increasing age was associated with more advanced-stage disease, with 11% (13/125) of those <50 years having stage III/IV disease compared to 25% (16/65) of octogenarians (P=0.002). Among patients <50 years old, only 27.3% (n=30) were recommended to undergo adjuvant treatment compared to 76% (n=47) of octogenarians (P<0.001). In contrast to recommended treatment, actual receipt of adjuvant radiation peaked at only 43% among women between the ages of 75 and 79 years. Chemotherapy uptake revealed a similar trend, with even lower receipt of treatment ranging from 19% at age <50 years to 36% at age 75 (Figure 1).

Conclusions: National Comprehensive Cancer Network guidelines recommend more adjuvant treatment in elderly EC patients due to a more advanced disease stage and aggressive histopathology. However, only 50% of elderly women for whom treatment was recommended actually received it in this study. Further research may determine what criteria are appropriate for declaring under- or overtreatment in elderly EC patients, the barriers preventing elderly women from receiving guideline directed care, and where a balance between quality of life and optimal adjuvant treatment may be found.



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Improving quality of care with cervical cancer patient navigation

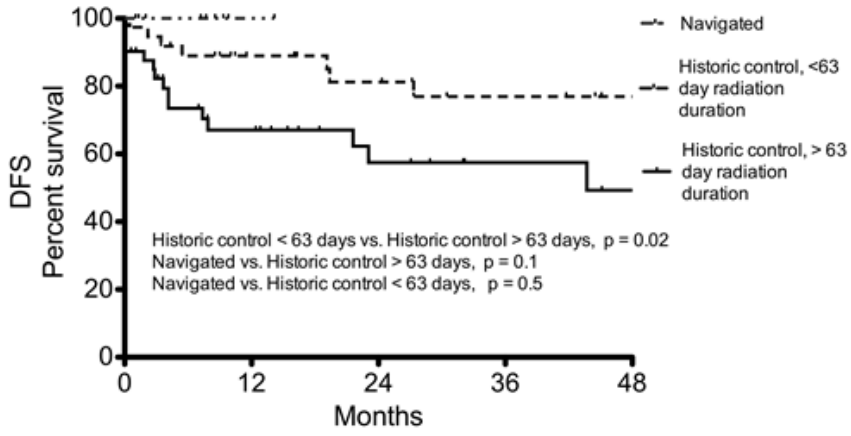
M. W. Amneus, L. M. Garcia, E. Pineda and C. H. Holschneider
Olive View-UCLA Medical Center, Sylmar, CA

Objectives: Prolonged duration of radiation treatment has been associated with poor survival outcomes in cervical cancer. Anemia during radiation therapy has also been associated with poor outcomes. Our Cervical Cancer Navigation Program (CCNP) was initiated in the spring of 2012 at an academically affiliated public teaching hospital with the aim of improving the quality of care received by cervical cancer patients. Two primary goals of the CCNP are to improve radiation duration and the management of anemia for patients undergoing primary chemoradiation (chemoXRT) for cervical cancer, hoping to thereby ultimately improve survival.

Methods: The CCNP was developed from an existing framework designed for breast cancer navigation. To date, the CCNP has navigated 50 patients through treatment. The treatment characteristics and outcomes for all patients treated with primary chemoXRT in the CCNP (n=13) were compared to a historic non-navigated control (n=79) of patients undergoing chemoXRT.

Results: The median radiation duration for CCNP patients was 55 days (range, 51-64 days) compared to 65 days (range 37-127 days) in the historic controls (P=0.01). Ninety-two percent (12/13) of CCNP patients completed treatment within 63 days compared to only 48% (38/79) of historic controls (P=0.004). None (0/13) of the patients in the CCNP started radiation with a hemoglobin (Hgb) <11 g/dL compared to 18% (13/71) of the historic controls for whom complete data were available (P=0.20). The median number of days with Hgb <11 g/dL during treatment was 1 day (range, 0-5 days) for CCNP patients and 12 days (range, 0-89 days) in the historic controls (P<0.0001). In the historic control group, patients who completed treatment within 63 days had a superior disease-free survival (DFS) when compared to those who completed treatment in >63 days (P=0.02). The DFS of the CCNP patients trended toward improvement over the historic patients treated in >63 days (P=0.1) and was similar to the historic patients treated in <63 days (P=0.5).

Conclusions: The CCNP has been successful in improving the radiation duration and management of anemia for patients undergoing primary chemoXRT for cervical cancer. This program has the potential to lead to significant improvements in patient outcomes.



84 - Featured Poster

Risk factors and impact of refusing recommended therapy in cervical cancer: a National Cancer Data Base (NCDB) study

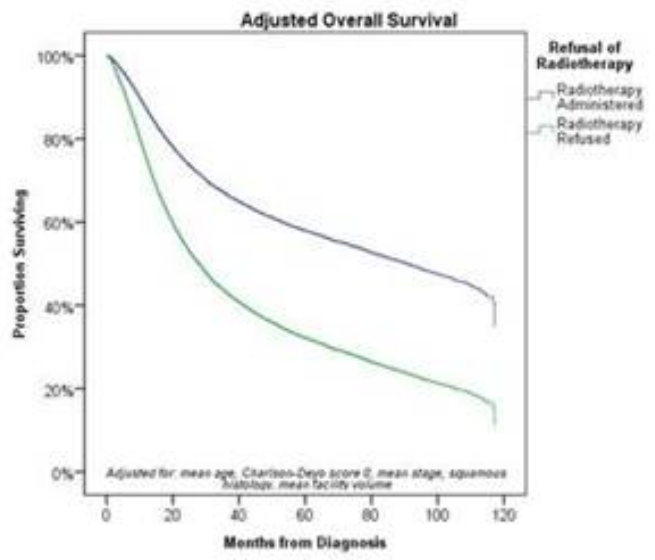
J. F. Lin[1], M. R. Rowland[1], M. M. Boisen[1], S. Beriwal[1], S. D. Richard[2], T. C. Krivak[3] and P. Sukumvanich[1]
[1]Magee-Womens Hospital of UPMC, Pittsburgh, PA, [2]Hahnemann University Hospital/Drexel University College of Medicine, Philadelphia, PA, [3]Western Pennsylvania Hospital, Pittsburgh, PA

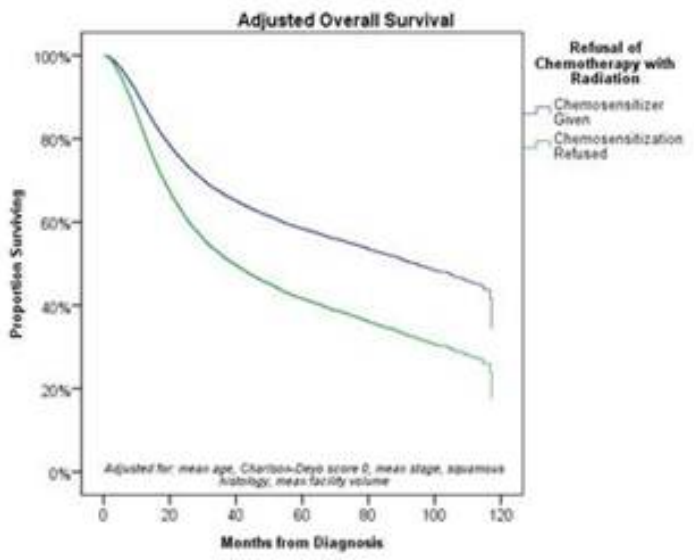
Objectives: The purpose of this study was to identify risk factors associated with patient refusal of recommended radiotherapy (RT) and chemosensitizing radiation (CCRT) as well as the impact of such refusal in patients with cervical cancer using the NCDB.

Methods: We identified all patients in the NCDB who were diagnosed with cervical cancer from January 1998 to December 2011. Patients who refused RT and CCRT were identified and compared to those who received recommended therapy. Univariate and multivariable analyses were performed using chi-square test with Bonferroni correction, binary logistic regression, log-rank test, and Cox proportional hazards modeling as indicated. Point estimates with 95% CI are reported.

Results: A total of 142,518 patients were identified, of whom 1,488 (1.0%) and 866 (0.6%) refused RT and CCRT, respectively. These patients were compared with 80,273 (56.3%) and 56,056 (39.3%) patients who received RT and CCRT, respectively. On multivariable analysis, refusal of RT was significantly associated with older age (odds ratio [OR] 1.03, 95% CI 1.02, 1.04), African-American race (OR 1.27, 95% CI 1.03, 1.56), higher comorbidity score (comorbidities) (OR 1.38, 95% CI 1.19, 1.60), higher disease stage (OR 1.14, 95% CI 1.05, 1.23), Midwest treatment facility location (OR 1.29, 95% CI 1.01, 1.64), and having had surgical therapy (OR 2.09, 95% CI 1.76, 2.50). Refusal of CCRT was significantly associated with older age (OR 1.06, 95% CI 1.05, 1.07), higher comorbidities (OR 1.20, 95% CI 1.01, 1.42), shorter distance from patient location (OR 0.85, 95% CI 0.78, 0.93), and lower facility volume (OR 0.88, 95% CI 0.79, 0.97). After controlling for age, comorbidities, stage, histology, and facility volume, refusal of RT and CCRT was associated with a 2.08 (05% CI 1.81, 2.38)- and 1.63 (95% CI 1.39, 1.91)-fold increased risk of death, respectively. These risks are greater than the risks posed by age and comorbidity independently.

Conclusions: Patient characteristics associated with frailty, African American race, and disease stage and treatment facility characteristics were associated with the refusal of recommended therapy in patients with cervical cancer and resulted in decreased survival. This study suggests that efforts should be made to improve counseling and care delivery to these populations.





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Preoperative chlorhexidine wipes reduce the risk of surgical-site infections after hysterectomy

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Objectives: Surgical-site infections (SSI) are a major cause of morbidity in surgical patients, and methods for infection control are paramount. Some literature report a decrease in skin bacterial colonization with the use of chlorhexidine gluconate (CHG) wipes. In this study, we assessed the impact of preoperative wipes on the reduction of SSI after hysterectomy.

Methods: As part of a quality assurance project, a retrospective review of SSI in women who underwent a hysterectomy for benign or malignant conditions from January 2012 to July 2013 was performed. SSI, as defined by the Centers for Disease Control and Prevention (CDC), are documented infections occurring within 30 days of the operation that are located superficially, deep, or in an organ/intra-abdominal space. We implemented the use of preoperative CHG washcloths in 2013. Patients were given the wipes at the preoperative visit with their surgeon and were instructed to use them the night before surgery and the morning of surgery. Compliance with washcloth use was documented. A standardized infection ratio (SIR) was calculated through the CDC - National Healthcare Safety Network for 2012 and for 2013. The SIR compares the actual number of SSI with the baseline in the United States. Other risk factors for infections such as body mass index (BMI) and comorbid conditions (age, hypertension, diabetes, type of hysterectomy) were assessed using a dichotomous outcome variable in a logistic regression model.

Results: In 2012, 151 hysterectomies were performed and 14 SSI were found. This provided a SSI rate of 9.27 per 100 procedures and a SIR of 4.3. Within the first 7 months of introducing CHG wipes in 2013, 82 hysterectomies were performed and 3 SSI developed. The SSI rate was 3.7 per 100 procedures and the SIR was 1.5. Patient self-reported compliance with the wipes the night before surgery and the morning of surgery was 73% and 93%, respectively. Increased BMI was the only factor that contributed to risk of SSI (P=0.041). Patient age, mode of hysterectomy, hypertension, diabetes, and coronary artery disease did not contribute to the infection risk.

Conclusions: Introduction of preoperative CHG wipes resulted in a 60% reduction of SSI in 2013 compared to 2012. Control of SSI remains a challenge throughout the health care industry, and use of these cleansing wipes should be considered before hysterectomy.

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The risk factors for readmission in postoperative gynecologic oncology patients at a single institution

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Objectives: To identify the factors that predispose patients who undergo gynecologic oncology surgery to be readmitted within 30 days of discharge.

Methods: After institutional review board approval, a 7-year retrospective review (2007–2013) was performed of all patients operated on by the University of Virginia gynecologic oncology service who were readmitted within 30 days of discharge. Abstracted data included: demographics, dates of surgery, operative details, cancer history, and relevant medical history. The readmitted patients (n=166) were compared to randomly selected controls (n=168) from the same time frame and analyzed using univariate and multivariate models. A P value of <0.05 was considered significant.

Results: In the study period, 2,993 operations were performed by the gynecologic oncology service, and 166 unique patients (5.5%) were readmitted within 30 days of discharge from their operative procedure. The univariate analysis showed a variety of factors correlated with readmission. However, only a history of psychiatric disease (P=0.029, odds ratio [OR] 1.8, 95% CI 1.06-3.04), postoperative complication (P=0.039, OR 1.91, 95% CI 1.03-3.52), and lysis of adhesions at the time of surgery (P<0.001, OR 3.64, 95% CI 1.97-6.71) remained significant on multivariate analysis. Open surgery vs laparoscopic (P=0.069), an ASA score >3 (P=0.082), and need for transfusion (P=0.080) almost reached significance. In those patients who had lysis of adhesions, the most common reasons for readmission were nausea/vomiting (37%) and infection (38%). The most common postoperative complications were infection (44%), nausea/vomiting (28%), thrombosis (6%), bowel leak (4%), and bleeding (4%).

Conclusions: Postoperative readmissions are a common problem and are increasingly important as a measure of quality. Although a psychiatric history or postoperative complication increased the risk of readmission, patients who had lysis of adhesions were at particularly high risk, primarily for gastrointestinal or infectious complications. Further investigation is needed to determine if the high-risk factors noted in this study can be modified by increased support after discharge.

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Surgeons as active leaders in the operating room: potential cost-saving behaviors

A. M. Jernigan[1], J. P. Stephens[2] and J. Knight[1]
[1]*The Cleveland Clinic Foundation, Cleveland, OH,* [2]*Case Western Reserve University, Cleveland, OH*

Objectives: Time saved in the operating room can amount to cost savings. We aimed to identify surgeon behaviors associated with a shorter preoperative phase in the operating room.

Methods: Five gynecologic oncologists rated on a Likert Scale (0-4) how frequently they use preoperative time (PT) to review images and clinical data relevant to the case, complete charting or other clinical duties, supervise positioning of a patient, or personally position the patient. A chart review was performed for all laparoscopic (L), robotic (R) and open (O) hysterectomies performed by these surgeons at one institution in 2012. PT, defined as time from induction of anesthesia to skin incision, was recorded. Mean PTs were adjusted for running multiple rooms, involvement of a fellow, and patient body mass index.

Results: Five surgeons performed 146 R, 44 L, and 76 O hysterectomies. Mean PT was longer for R compared to L or O hysterectomies (44.8 vs 40.4 vs 37.0 minutes, P<0.0003). PTs were shorter when surgeons engaged in direct preoperative care of positioning the patient (R, P=0.0001; L, P=0.009; and O P<0.0001). PTs increased when surgeons engaged in activities unrelated to preoperative care such as completing charting or other clinical duties (R, P=0.0005; O, P=0.02). Longer PTs remained associated with less active involvement in preoperative activities, even if the surgeons were using the time to perform tasks related to that patient's overall care such as reviewing clinical data and images (R, P=0.0001; L, P=0.01; O, P<0.0001) or supervising someone else positioning the patient (R, P=0.0003; L, P=0.0401; O, P=0.0074). Surgeons' active help positioning patients impacted R cases the most. Mean PT of surgeons who frequently positioned patients was 35.8 minutes compared to 44 minutes among surgeons who sometimes positioned patients (P=0003)

Conclusions: Shorter PTs were associated with surgeons actively engaged in positioning patients. This relationship is consistent across surgical modalities and is particularly strong with robotic hysterectomies. More passive activities, even supervision, were associated with longer PTs. Active involvement in preoperative care may enhance time savings and, thus, cost savings in the operating room.

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Gynecologic surgical-site infection reduction program (GSRP): a successful quality improvement project in reducing the incidence of surgical-site infection

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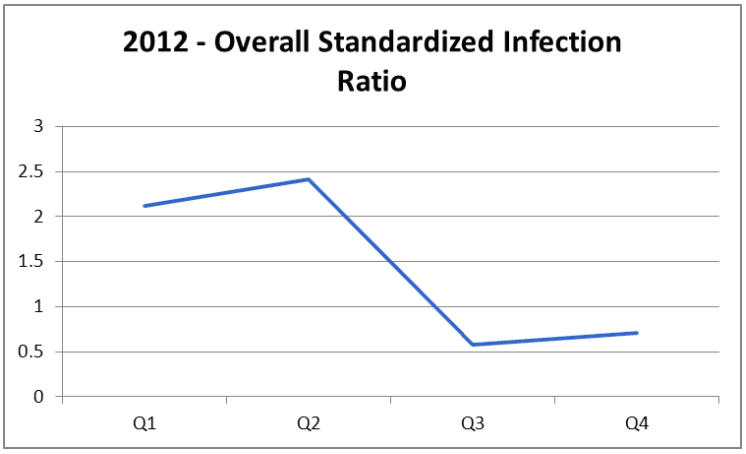
The Cleveland Clinic, Cleveland, OH,

Objectives: Surgical-site infection (SSI) is associated with significant morbidity, mortality, and health care expenditure in surgical patients. In our institution, a gynecologic SSI reduction program (GSRP) was initiated in January 2012 in response to a high SSI rate. The aim of this study was to use methodical process management tools to identify risk points that could potentially contribute to SSI, institute measures to alter those risk points to reduce the SSI rate, recognize the outcome, and sustain the improvement.

Methods: GSRP implemented a cross-functional set of interventions to target multiple risk points for infection identified within the perioperative process by a multidisciplinary team with a goal to reduce the incidence of SSI by 50%. This program created standardized protocols addressing the risk points within the entire perioperative surgical episode of care. Patients were divided into two groups: prospective group after GSIP and historic group before GSIP. Historic data were collected from our institutional National Surgical Quality Improvement Program data. The primary outcome was SSI within 30 days following surgery. Standardized incidence ratio (SIR) was calculated using the observed over the expected rate of infection for each quarter (Q1-Q4).

Results: The SSI rate in the historic group was 4.61% with SIR of 2.0. When stratified by body mass index (BMI) among the abdominal cases, obese (BMI ≥30) and underweight (BMI <18) patients had significantly higher rates of SSI compared to normal-weight patients (BMI 18-25) (19% vs 20% vs 6%, respectively, P=0.006). No difference was noted when stratified by cancer diagnosis, smoking, diabetes, corticosteroid use, intraoperative bleeding, hematocrit and albumin levels, and wound classifications. During the 12-months phase when GSRP was implemented by our institution, the SSI rate dropped from 4.61% to 1.69%, with SIR decreasing from 2.0 to 0.75. Using the hospital hysterectomy SSI surveillance data monitoring system, the SIR for SSI dropped to 2.1 during Q1 and 0.7 during Q4 (Figure 1). There was an overall reduction in the rate of SSI of 63%.

Conclusions: Initiating a new surgical quality improvement project (GSRP) significantly reduced the risk of SSI by 63%. This is an example of a systematically planned quality improvement project. GSRP is a multistep program developed by a multidisciplinary team approach.



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Characteristics of high-volume gynecologic cancer centers – framework toward centers of excellence: a National Cancer Data Base (NCDB) study

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[1]Magee-Womens Hospital of UPMC, Pittsburgh, PA, [2]Western Pennsylvania Hospital, Pittsburgh, PA, [3]University of California at Irvine, Irvine, CA, [4]University of Arizona Cancer Center, Phoenix, AZ

Objectives: Emerging evidence and health care reform encourage regionalization of cancer care into specialized centers. The goal of this study was to identify characteristics and outcomes of centers treating high volumes of gynecologic cancer patients using the NCDB.

Methods: We identified patients in the NCDB cervical, uterine, ovarian, vaginal, and vulvar -and abstracted demographic, disease, treatment, and outcome data. Case volumes were tallied for each disease site, normalized, and quartiled over all sites. Overall survival was estimated by the Kaplan-Meier method. Univariate and multivariable analyses were performed to identify factors associated with center volume and its effect on survival using chi-square test with Bonferroni correction, log-rank test, and Cox proportional hazards modeling.

Results: A total of 863,156 patients and 1,666 centers were identified. The 1st through 4th quartiles consisted of 64, 120, 235, and 1,247 centers, respectively. Top-quartile centers were more likely to be academic/research programs; no community cancer program was in the top two quartiles. Top-quartile centers were also more likely to be more than 30 miles away from their patients and more likely to perform lymphadenectomy and administer chemotherapy in patients with >stage II disease. A greater proportion of patients >71 years old as well as patients with stage IV disease were treated at the lowest quartile centers, which were also more likely to treat patients with insurance. Treatment at top-quartile centers was associated with disease-site survival advantages ranging from 2.3 to 34.1 months compared to lowest-volume centers ($P<0.0005$ for all sites except uterus $P=0.6$). Treatment at lowest-quartile centers conferred a 10% increase in adjusted mortality risk.

Conclusions: Treatment of gynecologic cancer at high-volume centers is associated with improved outcomes. Elderly and advanced-stage patients are more likely to be treated at low-volume centers, although facility volume is independently associated with improved survival, even when controlled for age, disease stage, and comorbidities. These data support regionalization of gynecologic cancer care and identify patients who may benefit from transfer to high-volume centers.

		Top 25%	2nd 25%	3rd 25%	Bottom 25%	Significance
Overall Survival (median, in months)	All	122.7	118.6	115.2	110.0	**p<0.0005**
	Cervical	117.8	114.1	111.5	102.4	**p<0.0005**
	Ovarian	49.4	45.4	42.7	32.5	**p<0.0005**
	Uterine	159.7	157.9	156.0	156.2	P=0.574
	Vaginal	72.2	69.8	60.7	38.1	**p<0.0005**
	Vulvar	136.4	125.6	130.4	134.1	**p<0.0005**
	Mortality Risk [adjusted for age, stage, CDCS; odds ratio (95% CI)]	Reference	1.02(1.001,1.05), $p=0.039$	1.03(1.01,1.05), $p=0.009$	1.10(1.07,1.12), $p<0.0005$	

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The role of adjuvant radiation and chemoradiation in single node-positive vulvar cancer

R. A. Laskey[1], M. S. Ross[1], J. F. Lin[1], P. Sukumvanich[1], T. C. Krivak[2], J. T. Comerci[1], M. Huang[1], J. Kelley[1], A. B. Olawaiye[1] and S. Beriwal[1]
[1]Magee-Womens Hospital of UPMC, Pittsburgh, PA, [2]Western Pennsylvania Hospital, Pittsburgh, PA

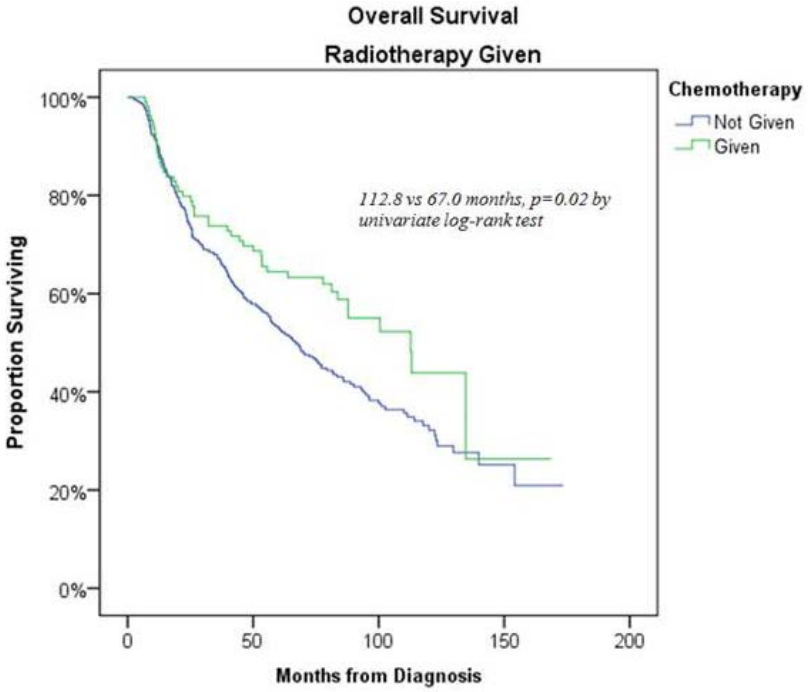
Objectives: Gynecologic Oncology Group (GOG) 37 showed the benefit of adjuvant radiation therapy (RT) for patients with positive lymph nodes (LNs). However, subset analysis failed to demonstrate an improvement in survival in patients with a single positive LN (SPLN). Currently there is no consensus on adjuvant treatment in patients with SPLN. Using the National Cancer Data Base (NCDB), we examined the impact of adjuvant RT and chemoradiation on overall survival (OS) in patients with vulvar cancer who underwent inguinofemoral lymphadenectomy and had a SPLN.

Methods: Using the NCDB, we identified patients diagnosed with vulvar cancer from January 1998 to December 2011 who underwent surgical staging with negative margins and adequate unilateral or bilateral inguinofemoral lymphadenectomy (≥6 LN per side). Demographic, clinicopathologic, treatment, and outcome data were collected. OS was determined using the Kaplan-Meier method. Univariate and multivariable analyses were performed to determine variables that affect OS.

Results: A total of 12,599 patients met inclusion criteria. SPLN was detected in 1,666 patients, of whom 660 (39.6%) had no RT data available, 504 (30.3%) received adjuvant RT (RT group), and 502 (30.1%) did not (NoRT group). The OS for the RT and NoRT groups were 67.0 and 57.0 months, respectively ($P=0.03$). One hundred and six (21%) patients in the RT group received chemosensitization, which prolonged survival to 112.8 months ($P=0.02$). However, on multivariable analysis, controlling for age, comorbidities, tumor grade, tumor size, RT, and chemoradiation, adjuvant RT (odds ratio [OR] 0.96, 95%

CI 0.715, 1.29) and chemoradiation (OR 0.76, 95% CI 0.47, 1.23) were not predictive of improved survival. Increasing age (OR 1.03, 95% CI 1.02, 1.04) and tumor size (OR 1.09, 95% CI 1.05, 1.13) were associated with an increased risk of death.

Conclusions: The use of adjuvant RT for SPLN vulvar cancer is common. Although univariate analysis showed an improvement in OS with adjuvant RT or chemoradiation over observation, when additional factors were controlled for, adjuvant therapy did not independently predict survival in patients with negative surgical margins and a SPLN following inguinofemoral lymphadenectomy. These important findings warrant further evaluation in a prospective setting.



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Barriers to human papillomavirus (HPV) vaccination: perspectives of parents of vaccine-eligible children

L. A. Meyer[1], B. Brimmage[2], M. P. Gomez[3], S. Hodgson[3], J. L. Dalrymple[3], A. Gregg[3] and M. S. Barratt[3]
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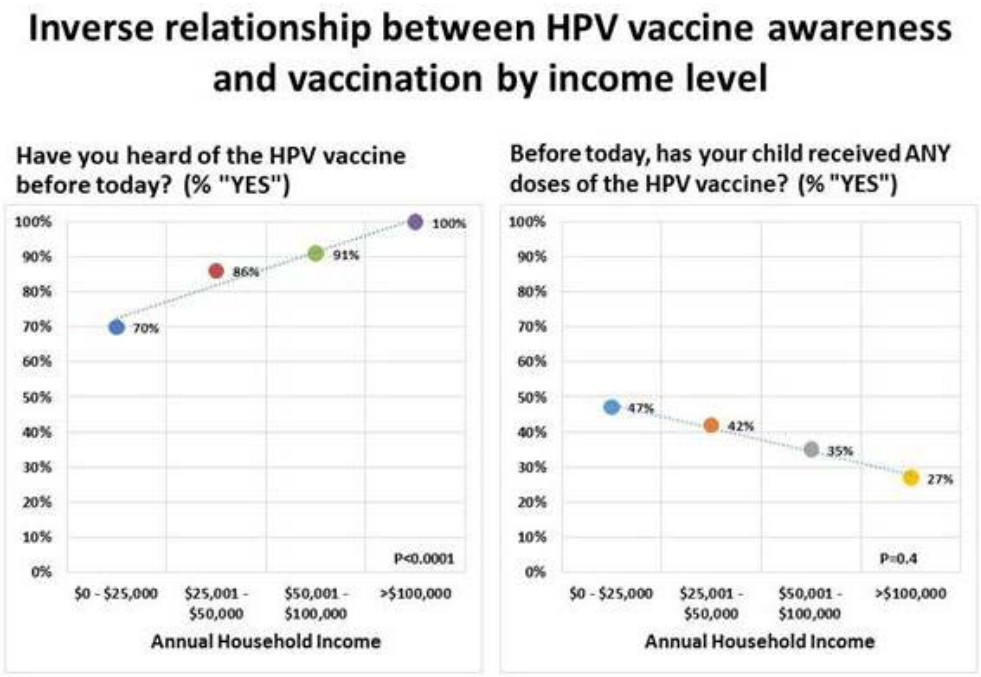
Objectives: Despite United States Food and Drug Administration approval since 2006, the incidence of HPV vaccination in the United States is still disappointingly low. We aimed to identify barriers to vaccination from the perspective of parents of vaccine-eligible children.

Methods: Following institutional review board approval, we administered a written survey in Spanish or English to parents of boys and girls aged 9 to 26 years seen at an academic urban pediatric practice. Descriptive statistics and odds ratios (ORs) were calculated, as were Fisher exact and chi-square test using VassarStats.

Results: One hundred ninety-three surveys were returned. The median age of the children was 14 years (range, 9-26 years), with 52% female and 48% male. Eighty-one percent of parents reported prior knowledge of the vaccine. Parents of boys were more likely to have heard of the vaccine than girls' parents (84% vs 69%, $P<0.01$). However, girls were more likely to have been previously vaccinated (OR 2.3, 95% CI 1.2-4.2). Private insurance coverage and high annual household income were strongly associated with knowledge of the HPV vaccine (OR 12.1, 95% CI 3.6-41.5 and OR 10.3, 95% CI 2.4-45). Non-Hispanic parents were more likely to report prior knowledge (OR 2.7, 95% CI 1.2-6.3). Fifty-one percent of parents reported that their child had been offered the HPV vaccine. There was no statistical difference in who was previously offered the vaccine by income, sex, insurance type, race, or ethnicity. Interestingly, the higher the annual household income, the less likely the child had been vaccinated (Figure 1). White children were twice as likely to not be vaccinated against HPV (OR 2.1, 95% CI 1.03-4.08). Among all respondents, the most common reasons for not vaccinating children were belief the child was not sexually active, lack of information regarding vaccine, and fear of adverse effects.

Conclusions: Multiple barriers contribute to the low HPV vaccine uptake. Half of the eligible children in our study population reported not being offered the vaccine. Health care providers need a systematic approach to HPV vaccine recommendation and delivery. Health literacy remains an issue for low-income families and those receiving Medicaid. The trend of parents

from high-income families choosing not to vaccinate their children is concerning. Targeted interventions for health care providers and parents are urgently needed.



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Human papillomavirus vaccination within a Southern California integrated health care system demonstrates disparities in adherence rates among males and females compared to national reports

G. K. Forde[1], D. Tewari[2], C. Hong[2], N. Rodriguez[2], R. E. Bristow[3] and K. S. Tewari[1]
[1]University of California at Irvine Medical Center, Orange, CA, [2]Southern California Permanente Medical Group, Irvine, CA, [3]University of California at Irvine, Irvine, CA

Objectives: To determine if the Centers for Disease Control and Prevention (CDC) reported completion rates of HPV vaccination based upon National Immunization Survey-Teen (NIS-Teen) studies is comparable between males and females using electronic health record data from a large integrated health care system.

Methods: Using Epic® health record software, 2012 clarity reports were generated for females and males receiving an initial dose of the quadrivalent HPV vaccine (HPV4). Completion rates following induction of immunity were controlled for potential attrition by updating insurance status through August 31, 2013.

Results: A total of 21,725 patients received an initial dose of HPV4 in 2012, and 3,786 (17.4%) completed the series. Maintenance of current coverage at the time of quality assurance audit was 85% and typical for this population and geographic location. Among patients followed for at least 12 months since vaccine initiation, 18.3% (n=14,391) completed the series. Of the 10,793 patients who received a second dose, 52% and 48% were females and males, respectively. Of those who initiated HPV4 uptake, males completed the series at a higher rate than females (23.5% vs 14.7%, P<0.05).

Conclusions: HPV vaccination completion rates for both females and males may be lower than previously reported through the NIS-Teen approach of the CDC, based upon electronic data abstracted from an integrated health care system recognized nationally for its success in screening/prevention programs. The data constitute one of the largest male HPV vaccination experiences and showed males having an increased adherence to vaccine protocol when compared to females. Because these findings interface with a validated information technology system, they may more accurately mirror real-world vaccine uptake. Analysis of factors that predict adherence is ongoing as cervical cancer continues to represent a highly unmet clinical need.

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Magnitude of increased lifetime risk of cervical cancer and death from cervical cancer with new screening recommendations

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[1]The Permanente Medical Group, Sacramento, CA, [2]The Permanente Medical Group, Berkeley, CA

Objectives: To quantify the potential for increased cancer and increased death from cancer if a large health maintenance organization (HMO) were to adopt the newly recommended 5-year cotesting intervals in place of the current practice of cotesting at 3-year intervals.

Methods: Recently published modeling (Kulasingham S, 2013) details the lifetime consequences for cancer incidence and mortality in the screened population using different screening intervals. This modeling was commissioned by the United States Preventive Services Task Force and was part of the evidence review for the new 5-year cotesting recommendations. The women participating in cervical cancer screening in the past 42 months in a large HMO were used as a representative population of screening participants.

Results: Currently 1,008,855 women have screened once or more in the 42 months before December 31, 2012. In a group of lifetime screening participants of this magnitude, the model predicts that 2,734 additional cervical cancers will be prevented (total 4,772 instead of 7,506), and 615 additional deaths from cervical cancer will be avoided (total 747 instead of 1,362) if we retain the current 3-year cotesting intervals instead of moving to 5-year cotesting. Every cancer prevented by staying at 3-year cotesting would require 92 additional colposcopies and treatment of 3.3 additional women for cervical intraepithelial neoplasia (CIN2)+, and every death prevented would require 410 additional colposcopies and treatment of 14.8 additional women for CIN2+.

Conclusions: Risks and benefits of screening accrue over a lifetime. The risks of loop excision appear to be substantially less than previously thought (Castanon A, 2012) and do not involve measurable perinatal mortality (Arbyn M, 2008). At no point in the publications describing the new guidelines is it acknowledged that we are now recommending more cancer and more death from cancer than the previously recommended 3-year cotesting provides, and that we are doing so presumably for the purpose of avoiding a cervical treatment that is not associated with detectable increased mortality. Recognition of the potential magnitude of the change in lifetime risk of cancer and death from cancer produced by extending screening intervals may influence institutional policy and assist patients and physicians in making informed decisions regarding screening.

Featured Poster Session V: Clinical Trials / Drug Repurposing
Monday, March 24, 2014
7:00 a.m. – 8:00 a.m., Rooms 13-16
Moderator: Carolyn Muller, MD, *University of New Mexico, Albuquerque, NM*

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Impact of age on tolerance of chemoradiation and survival for patients with local regionally advanced cervical cancer: a pooled analysis of Gynecologic Oncology Group (GOG) phase III trials

K. N. Slaughter[1], J. Java[2], F. B. Stehman[3], P. G. Rose[4], K. N. Moore[1] and P. A. DiSilvestro[5]
[1]The University of Oklahoma, Oklahoma City, OK, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, [3]Indiana University School of Medicine, Indianapolis, IN, [4]The Cleveland Clinic, Cleveland, OH, [5]Women & Infants Hospital, Brown University, Providence, RI

Objectives: To determine the effect of age on completion of and toxicities following treatment of local regionally advanced cervical cancer (LACC) in GOG Phase III trials.

Methods: Ancillary data analysis of GOG protocols 113, 120, 165, and 219 was performed. Descriptive statistics were used for demographic, clinical, and treatment characteristics according to age category. Wilcoxon, Pearson, and Kruskal-Wallis tests were used for univariate and multivariate analysis. Log rank tests were used to compare survival lengths.

Results: A total of 1,319 patients were included in this analysis, of whom 60.7% were white, 21.4% black, and 12.4% Hispanic. Fifteen percent were 60-70 years old and an additional 5% were >70 years. Sixty-six percent were enrolled with a normal performance status. Histology was squamouns in 87.4% of patients, and 54.8% had stage IIB disease and 33.9% had stage IIIB disease. Chemotherapy included cisplatin weekly, 5-fluorouracil (5-FU), hydroxyurea, cisplatin + 5-FU + hydroxyurea, and cisplatin + tirpazamine. Ethnicity varied by age, with more Hispanic and Asian patients with increasing age (P=0.014). Performance status (PS) declined with age, with more PS 1 and 2 (P=0.006). Histology and tumor stage did not differ, but tumor size was smaller with age (P=0.003). Neither the number of cycles chemotherapy received nor length of treatment or radiation dose modification varied with age. The dose to point A and B did decline with increasing age (P=0.054 and P<0.001 respectively). Grade 2 toxicities that increased with age included neutropenia (P=0.004), lymphatic (P=0.049), fevers (P=0.030), and cardiovascular (P=0.041). Grade 3 toxicities that increased with age included neutropenia (P=0.030) and cardiovascular (P=0.019). Rates and sites of recurrence did not differ by age. Progression-free survival status differed,

with increased progression or death with age (P=0.037). Only cause of death due to non-disease-related reasons increased with age (P<0.001).

Conclusions: This represents a large analysis of patients treated for LACC with chemo/radiation, approximately 20% of whom were >60 years of age. Although some significant toxicities increased with age, they did not appear to appreciably affect radiation treatment times or disease-specific survival. This suggests that older patients with cervical cancer tolerate protocol therapy similarly to younger patients and should be offered clinical trial options when appropriate.

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Do elderly women with endometrial cancer qualify for existing clinical trials?

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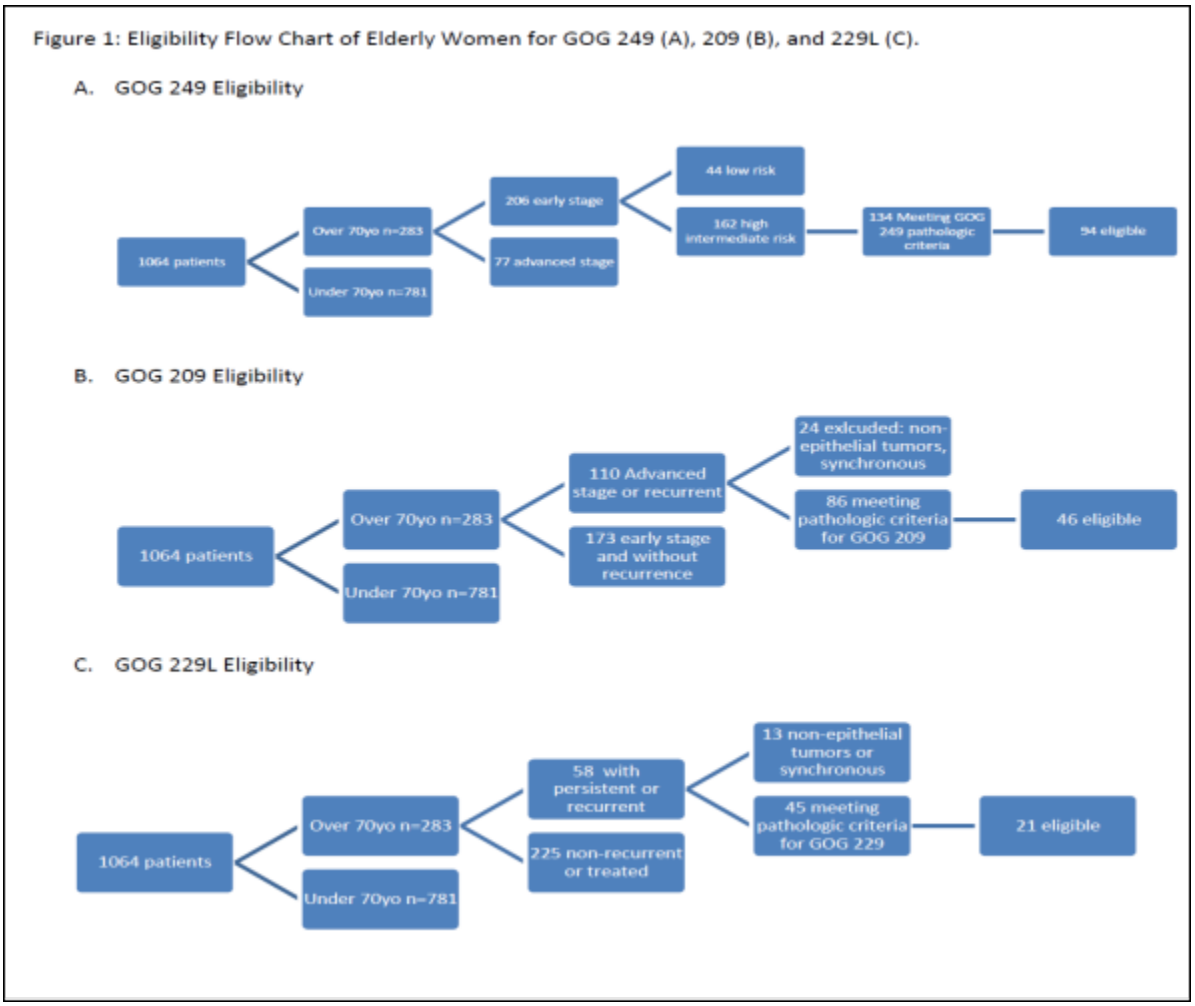
[1]University of North Carolina at Chapel Hill, Chapel Hill, NC, [2]University of Pennsylvania, Philadelphia, PA

Objectives: Elderly patients have been underrepresented in clinical trials for gynecologic cancers. We suspect that few elderly endometrial cancer (EC) patients would qualify for phase II or III trials due to comorbidities and poor functional status (FS). We sought to determine the percentage of women ≥70 years old who would meet enrollment criteria for representative Gynecologic Oncology Group (GOG) trials to better understand the gap between potential and actual enrollment of elderly women in clinical trials.

Methods: We performed an institutional review board-approved retrospective chart review of all EC cases (n=1064) from a single tertiary care institution from 2005 to 2010. We selected GOG protocols 249, 209, and 229L as representative national EC phase III trials for adjuvant treatment, for treatment of recurrent/advanced cancer, and for a phase II study, respectively. Patients ≥70 years old were evaluated for eligibility by each protocol's enrollment criteria. Descriptive statistics were performed.

Results: Patients ≥70 years old comprised 27% (n=283) of all EC cases. Of these, 47% (134/283) would have qualified for GOG 249 by pathologic criteria, but 22% (30/134) would have been eliminated due to poor FS or comorbidities (vs eliminating only 7% of patients <70 years). For GOG 209, 30% (86/283) of patients ≥70 years would have qualified by pathology, but 46% would have failed medical clearance (vs 17% in patients <70 years). For GOG 229L, 16% (45/283) of patients ≥70 years would have met pathologic criteria to qualify. Of these, 53% (24/45) were further deemed ineligible. Of those ineligible, 9% (4/45) failed medical clearance (vs 6% in patients <70 years) and 29% (13/45) had no prior chemotherapy; others were excluded for recurrences entirely treated with radiation therapy and lack of measureable disease. Overall, in the entire EC population >70 years, 9% would qualify for GOG 249, 4% for GOG 209, and 2% for GOG 229L (Figure 1).

Conclusions: Women ≥70 years accounted for >25% of all EC patients in this review. Only 9% qualified for a phase III adjuvant radiation trial and 4% for a trial for recurrent/advanced disease. Approximately 50% of the women ≥70 years who met pathologic enrollment criteria would be excluded due to complex medical disease. Further studies should examine both the applicability of trial enrollment criteria and the generalizability of past trial results to elderly women with EC.



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Patient and physician factors associated with participation in Gynecologic Oncology Group (GOG) trials in cervical and uterine cancer

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Objectives: To identify factors related to availability, eligibility, and enrollment in GOG cervical and uterine cancer trials.

Methods: Prospective observational study of women with primary or recurrent cancer of the uterus or cervix treated at a GOG institution July 19, 2010 through January 17, 2012. Patients and their physicians (MDs) completed questionnaires. Logistic regression examined the probability of availability, eligibility, and enrollment in a GOG trial. Odds ratios (OR), 95% CI, and statistically significant ($P<0.05$) results are reported.

Results: A total of 150 MDs and 781 patients at 60 sites participated. GOG trials were available for 290 patients (37% of total), of whom 150 (52%) enrolled, 102 (35%) were eligible but not enrolled, and 38 (13%) were not eligible. Academic (OR 4.6, 95% CI 1.5-13.9) or hospital-based (OR 7.1, 95% CI 3.0-16.5) practices were positively associated with trial availability. Patients of Hispanic/Latino (H/L) MDs had lower odds of having trials available (OR 0.27, 95% C.I 0.1-0.8). Patients with >4 comorbidities (OR 4.5, 95% CI 1.7-11.8) and patients of H/L MDs (OR 12.4, 95% CI 1.5-98.9) were more

likely to be ineligible for available trials. Non-white patients (O.R 7.9, 95% CI 1.3-46.1) and patients of black MDs (OR 56.5, 95% CI 1.1-999.9) had greater odds of enrolling. Modifiable patient factors related to enrollment included: feeling the trial may help them (OR 76.9, 95% CI 4.5-1000), concern about care received if not in a trial (OR 12.1, 95% CI 2.0-71.3), feeling pressure to enter a trial (OR 0.05, 95% CI 0.003-0.72), providing care to someone without pay (OR 0.13, 95% CI 0.02-0.84), and transportation difficulty (OR 0.11, 95% CI 0.02-0.53). MD factors associated with enrollment were: not believing patients would respond well to standard therapy (OR 3.6, 95% CI 1.5-8.3) or the trial would take up a lot of the patient's time (OR 3.2, 95% CI 1.3-8.1).

Conclusions: Interventions that address modifiable factors, including patient and MD beliefs, could improve the rate and diversity of enrollment in GOG cervical and uterine cancer trials.

Patient and Physician Demographics		
Ethnicity	***Patient n=781***	***Physician n=150***
Hispanic	24 (3.1%)	7 (4.7%)
Non-Hispanic	755 (96.7%)	136 (90.6%)
Unknown	2 (0.2%)	7 (4.7%)
Race		
Asian	23 (2.9%)	18 (12%)
Black	63 (8.0%)	6 (4%)
American Indian	20 (2.6%)	0
White	665 (85.1%)	123 (82%)
Native Hawaiian/Pacific Islander	2 (0.2%)	0
Unknown	8 (1.0%)	3 (2%)

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A phase II trial of intraperitoneal EGEN-001, an interleukin (IL)-12 plasmid formulated with PEG-PEI-cholesterol lipopolymer in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: a GOG study

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Objectives: The purpose of this phase II trial was to evaluate the toxicity profile, antitumor activity, and biologic effects of intraperitoneal (IP) EGEN-001 in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer.

Methods: Eligible patients had weekly IP infusion of EGEN-001 at a dose of 24 mg/m^2. Toxicity was assessed weekly using CTCAE version 4.0. Radiographic imaging was obtained within 28 days of initial treatment and after every other cycle to assess for clinical response. Co-primary endpoints were tumor response and survival without progression or going onto a subsequent therapy for at least 6 months (6-month EFS). These were evaluated using the criteria proposed by Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 guidelines. Ancillary biologic studies evaluated T-cell receptor diversity, immune cell environment, and cytokine levels.

Results: Twenty of the 22 eligible patients enrolled in the trial were treated per protocol. A total of 58 EGEN-001 cycles were administered to the 20 treated patients, with a median of 2 cycles and a range of 1-9. The most frequently associated adverse events considered either possibly, probably, or definitely related specifically to EGEN-001 treatment were nausea, vomiting, other gastrointestinal (mostly abdominal pain), and general and administration site pain. Many had fatigue, anemia, metabolism/nutrition problems, and thrombocytopenia. Three of the 20 EGEN-001-treated patients evaluable for toxicity elected to withdraw from the study, motivated in part by treatment-related toxicities. No patients achieved a partial or complete response in the entire study population (0%; 90% CI 0~10.9%). Four of the 20 treated patients had indeterminate responses (20%) because follow-up tumor measurements were not provided. Sixteen patients were evaluable for response. Seven of 20 (35%) had stable disease and 9 (45%) had progressive disease. Three patients had 6-month EFS (15%; 90% CI 4.2~34.4%). The median progression-free survival was 2.89 months and the median overall survival was 9.17 months. Translational studies are in progress.

Conclusions: IP administration of EGEN-001 at the evaluated dose and schedule had limited activity in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer and was associated with moderate toxicity. Evaluation of this agent in combination with chemotherapy is ongoing.

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Phase I trial results of a folate receptor alpha-directed cancer vaccine (E39) in ovarian and endometrial cancer patients to prevent recurrence

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Objectives: Folate receptor-alpha (FOLR-α) is an immunogenic protein that is highly overexpressed in endometrial (EC) and ovarian cancer (OC). FOLR-α expression is 20- to 80-fold higher in malignant cells compared to adult cells. We have begun a phase I/IIa clinical trial with E39, a human leukocyte antigen (HLA)-A2-restricted, FOLR-α-derived peptide, mixed with granulocyte macrophage colony-stimulating factor (GM-CSF) as an adjuvant vaccine to prevent recurrences in high-risk EC and OC patients rendered disease-free with standard-of-care therapy. Here we summarize the phase I component of the ongoing trial.

Methods: The phase I component is a 3x3, dose-escalation safety trial enrolling disease-free EC and OC patients. HLA-A2+ patients are enrolled into the vaccine group (VG) while HLA-A2- patients are being followed prospectively as an untreated control group (CG). Six monthly intradermal inoculations of either 100 mcg, 500 mcg, or 1,000 mcg of E39 + 250 mcg GM-CSF immunoadjuvant are administered during the primary vaccine series (PVS). Immunologic responses are assessed by both local reaction (LR) after each inoculation (R1-6) and delayed hypersensitivity (DTH) reaction measured prevaccination (R0) and after the PVS (R6). Recurrences are determined clinically. Data are means compared by paired, t-test, or proportional results compared by chi-square/Fisher Exact.

Results: A total of 31 patients have enrolled: 15 in the VG and 16 in the CG. There are no significant differences in age or tumor grade, stage, or nodal status between groups (all $P \geq 0.1$). Overall, the vaccine was well-tolerated (maximum local toxicity: 93% Grade (Gr) 1, 7% Gr 2; maximum systemic toxicity: 13% Gr 0, 60% Gr 1, 26.7% Gr 2). The LR increased from R1 to R2 (48.2+7.6 mm vs 78.3+8.4 mm, $P=0.01$), from R2 to R3 (78.3+8.4 mm vs 102.3+10.1 mm, $P=0.08$), and then plateaued from R3-R6 (102.3+10.1 mm vs 119.8+14.7 mm, $P=0.33$). With eight patients completing R6, DTH significantly increased from R0 to R6 (11.4+2.0 mm vs 22.7+8.1 mm, $P=0.03$). After a median follow-up of 6 months, there have been 2 recurrences (13.3%) in the VG vs 4 recurrences (25%) in the CG ($P=0.65$).

Conclusions: The maximally administered dose was well tolerated. In contrast to other FOLR-α-directed cytotoxic agents, the E39 vaccine holds the promise of an immunologic response and memory against FOLR-α-expressing recurrences without toxicity.

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Effect of *BRCA1* and *XPG* mutations on treatment response to trabectedin and pegylated liposomal doxorubicin in subjects with advanced ovarian cancer: exploratory analysis of phase III OVA-301 study

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Objectives: Both trabectedin (T) and pegylated liposomal doxorubicin (PLD) induce double-strand DNA breaks. Repair of this sublethal DNA damage is central to clinical drug resistance and involves both *BRCA1* and *XPG*. We investigated the association of *BRCA1/XPG* mutations (^{mut}) with response rate (RR), progression-free survival (PFS), and overall survival (OS) in a subset of subjects from a phase III clinical trial (OVA-301) comparing the efficacy and safety of T+PLD vs PLD alone in 672 subjects with recurrent ovarian cancer (ROC).

Methods: A candidate gene array was designed to detect 59 functional mutations based on characterization in BIC database. Association of *BRCA1/XPG* mutation status with selected clinical endpoints was determined using 2-sided log rank test (PFS and OS) or Fisher's exact test (RR) at 0.05 significance. Germline DNA samples from 264 women who failed first-line platinum-based chemotherapy, randomized (1:1) to T+PLD or only PLD were used for analysis.

Results: Overall, 41/264 subjects (16%) had *BRCA1*^{mut} (T+PLD: *n*=24 [18%]; PLD: *n*=17 [13%]) and 17/264 (6%) had *XPG*^{mut} (C/C) (T+PLD: *n*=8 [6%]; PLD: *n*= 9 [7%]). Subjects with BRCA1^{mut} had improved RR vs *BRCA1*^{wt} (37% vs 19% assessed by independent radiologist [IR]). Among *BRCA1*^{mut} subjects, T+PLD-treated had longer OS vs PLD-treated (median OS 27.3 vs 18.7 months, *P*=0.0093). Among *BRCA1*^{wt} subjects, OS was not statistically different (median OS 27.3 vs 23 months, *P*=0.4966). Overall, *BRCA1*^{mut} subjects had similar PFS to *BRCA1*^{wt} subjects, but in *BRCA1*^{mut} subjects, T+PLD-treated had longer PFS (*P*=0.0002) by IR (13.4 months) vs PLD-treated (5.5 months). No significant differences were noted between any of the *XPG* genotypes (C/C vs G/-) and RR in total population or by treatment or by platinum sensitivity. Subjects with *XPG*^{mut} had shorter OS than those with *XPG*^{wt} (median OS 17.7 vs 20.0 months, *P*=0.0363). There was no difference in OS of subjects with *XPG*^{mut} between 2 groups. In *XPG*^{mut} subjects, T+PLD-treated had shorter PFS vs *XPG*^{wt} subjects (median PFS-IR 5.2 vs 6.4 months, *P*=0.0207).

Conclusions: *BRCA1*^{mut} may predict improved outcome among T+PLD-treated subjects. Prospective evaluation of *BRCA* status is important in evaluation of DNA-damaging agents and may significantly affect the interpretation of clinical trials. *XPG* may be a biomarker of poor outcome in ROC.

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Phase II trial of pemetrexed and carboplatin in platinum-sensitive recurrent ovarian, fallopian tube, and primary peritoneal cancer

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Objectives: Despite improvements in median and overall survival (OS) using adjuvant platinum and paclitaxel-based therapy, recurrence of epithelial ovarian cancer (EOC) remains challenging. Pemetrexed is a new-generation antifolate that is a potent inhibitor of thymidylate synthase. Based on prior studies, pemetrexed is a promising agent for targeting ovarian cancer, which generally overexpresses folate receptors, and has shown synergistic preclinical efficacy in combination with platinum.

Methods: In this prospective phase II trial, patients with platinum-sensitive recurrent EOC, primary peritoneal, or fallopian tube cancer who had received at least one prior platinum and taxane-based regimen were treated with pemetrexed 600 mg/m^2 intravenous (IV) and carboplatin AUC 5 IV every 21 days for 6 cycles or until evidence of disease progression or toxicity. Response was determined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria and confirmed every 9 weeks. This is the completed data analysis of the first stage of a Simon's two-stage phase II study (NCT01001910).

Results: Of the 28 patients enrolled, 23 were evaluable for response. Of the 6 patients receiving ≤2 cycles, 5 had hypersensitivity reactions by strict protocol criteria. The median age was 64 years (range, 46-86 years). Patients completed a median of 6 cycles (range, 2-12). Five patients had a complete response (CR) and 5 had a partial response (PR) for a 43.5% (10/23) overall response rate. In addition 9 patients had confirmed stable disease and 4 pts had progressive disease. In patients who had clinical benefit (CR+PR), the median time to response was 9.8 weeks (range, 8.0-19.6 weeks). A total of 145 cycles were administered. There were 62 (42.8%) grade 3/4 hematologic toxicities and 3 (2.1%) grade 3/4 nonhematologic toxicities. The most common nonhematologic toxicities were elevations in liver function tests (*n*=3 cycles). There were 11 dose reductions and 18 dose delays due to toxicity. There were no treatment-related deaths.

Conclusions: Pemetrexed/carboplatin is a well-tolerated regimen that is comparable to other regimens for platinum-sensitive recurrent EOC and should be considered in the treatment armamentarium. While hypersensitivity was defined strictly on this protocol, the higher-than-expected rate of hypersensitivity reactions (5/28 [18%]) needs further exploration for pemetrexed and potentially for other folate receptor-targeting therapies.

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Evaluation of CA-125 response in the TRINOVA-1 study of weekly paclitaxel plus trebananib or placebo in women with recurrent ovarian cancer

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Objectives: In the TRINOVA-1 study, weekly paclitaxel+trebananib significantly prolonged progression-free survival (PFS), the primary endpoint, over paclitaxel+placebo in women with recurrent epithelial ovarian cancer (EOC). Secondary objectives were prespecified analyses of objective and CA-125 responses. Posthoc analysis compared the relationship of CA-125 response vs Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Methods: Women ≥18 years old with recurrent EOC, primary peritoneal cancer, or fallopian tube cancer, who had received one prior platinum-based treatment (progression-free interval [PFI} <12 months) were eligible. Patients were randomized to paclitaxel 80 mg/m^2 intravenous (IV) every week (QW) (3 weeks on/1 week off) plus blinded placebo IV QW or trebananib 15 mg/kg IV QW. CT/MRI were performed every 8±1 weeks for evaluation of objective response per modified RECIST v1.1. CA-125 levels were assessed every 4 weeks and evaluated for response per Gynecologic Cancer Intergroup (GCIG) criteria.

Results: A total of 919 women were randomized (trebananib/placebo, *n*=461/458), and 736 were evaluable for CA-125 response (*n*=365/371). CA-125 response rates were 56.4% (95% CI 51.2%, 61.6%) in the trebananib arm and 48.5% (95% CI 43.3%, 53.7%) in the placebo arm; the difference in response rates was 7.9% (95% CI -15.2%, -0.5%). Mean maximum percent change from baseline in CA-125 was -65.3% (95% CI -69.9, -60.7) in the trebananib arm and -49.4% (95% CI -54.9, -43.9) in the placebo arm. A total of 868 patients (trebananib/placebo, *n*=435/433) were evaluable for objective response per modified RECIST. Objective response rates (ORR) were 38.4% (95% CI 33.8%, 43.1%) for trebananib and 29.8% (95% CI 25.5%, 34.3%) for placebo; the difference in ORR was 8.6% (95% CI -15.0%, -2.1%). Mean maximum percent change from baseline in tumor burden was -26.7% (95% CI -30.4%, -23.1%) for trebananib and -14.3% (95% CI -18.3%, -10.2%) for placebo. Concordance between CA-125 response and ORR was 72% (Table). When evaluating discordance, 23% occurred among patients who had a CA-125 but not an objective response and 6% among those who had an objective response but not a CA-125 response.

Conclusions: Trebananib added to weekly paclitaxel improved objective and CA-125 response rates in recurrent EOC. While not prespecified or controlled for multiple comparisons, these improvements were significant at the 5% level. There was a high rate of concordance between CA-125 and RECIST response.

Patients Evaluable for Both RECIST and CA-125 Response, n=690	**RECIST Response**		
CA-125 Response	No	Yes	
No	294 (43%)	38 (6%)	332 (48%)
Yes	157 (23%)	201 (29%)	358 (52%)
Total	451 (65%)	239 (35%)	690 (100%)
Overall Concordance Rate	72%		
Kappa (95% CI)	0.44 (0.38, 0.50)		

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Not your mother's bisphosphonate: targeting angiogenesis in ovarian cancer

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Objectives: Bisphosphonates, known to have beneficial effects on bone and soft-tissue metastases in breast cancer, are potent inhibitors of macrophages, but their effects on the microenvironment are not fully understood. We investigated the effects of clodronate on macrophage and endothelial cell-driven angiogenesis in ovarian cancer.

Methods: Using the United States Food and Drug Administration Adverse Event Reporting System (FAERS), we broadly examined the effects of bisphosphonate use on overall cancer mortality. We examined the in vitro (endothelial cell migration, capillary formation, and cytokine secretion) and in vivo (orthotopic mouse models) effects of clodronate on angiogenesis, macrophage infiltration, and tumor growth.

Results: Using FAERS data, the overall reported death rate among ~17,000 patients with a cancer diagnosis co-medicated with a bisphosphonate was 36% lower (17.6% vs 27.7%, $P<0.0001$) than for those not receiving bisphosphonates, independent of antitumor therapy. Treatment with clodronate resulted in decreased endothelial cell secretion of interleukin (IL)-6 ($P<0.001$) and IL-8 ($P<0.001$) and a 2.5-fold reduction in cell migration compared to controls ($P< 0.001$), with only partial recovery after vascular endothelial growth factor (VEGF) stimulation. Clodronate reduced capillary formation by 1.5-fold compared to controls. In the ID8-VEGF model, clodronate-treated mice had a 5-fold decrease in tumor weight (0.05 g vs 0.3 g, $P<0.001$) compared to controls. In the SKOV3ip1 model, clodronate treatment resulted in a 3-fold decrease in tumor weight (0.35 g vs 0.96 g, $P=0.003$) and tumor nodules (5.2 vs 16, $P=0.005$) compared to controls. Immunohistochemical staining of clondronate-treated tumor sections showed a 2-fold and 1.5-fold (ID8-VEGF and SKOV3ip1, respectively) reduction in macrophage density ($P=0.001$ and $P<0.001$, respectively) compared to controls. Clodronate-treated tumor sections showed a 3-fold decrease in capillary density ($P<0.001$) compared to controls.

Conclusions: Bisphosphonates modulate tumor angiogenesis through effects on macrophages and endothelial cells and are associated with overall decreased mortality in cancer patients, independent of chemotherapeutic agents. Bisphosphonates represent an unexplored, but attractive clinical strategy in ovarian cancer, with potential for synergistic combination with other antiangiogenic agents.

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Aspirin and acetaminophen decrease the risk of cervical cancer in long-term users

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Objectives: Recent evidence demonstrates the chemoprotective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on various cancers, making them attractive tools in cancer prevention. Preclinical data point to overexpression of cyclooxygenase-2 (COX-2) in endometrial, cervical, ovarian, and breast carcinomas, where it promotes cellular proliferation and angiogenesis and inhibits apoptosis. In addition to known oncogenic properties of human papillomavirus (HPV), chronic inflammation has been shown to play a role in cervical carcinogenesis. The objective of this study was to investigate whether regular use of aspirin and acetaminophen conferred cervical cancer risk reduction.

Methods: We conducted a hospital-based, case-control study that included 565 patients with cervical cancer and 2,257 matched controls treated at a single institution. All participants completed a comprehensive epidemiologic questionnaire between 1982 and 1998. Women who reported analgesic use at least once a week for ≥6 months were classified as regular users. Frequent long-term analgesic use was defined as ≥7 tablets a week for ≥5 years. Logistic regression analysis was performed to compute crude and adjusted odds ratios (OR), with corresponding 95% CI.

Results: Compared to nonusers, frequent aspirin or acetaminophen use was associated with decreased risk of cervical cancer (OR 0.64, 95% CI 0.40-1.03, $P=0.06$ and OR 0.4, 95% CI 0.18-0.91, $P=0.03$, respectively). A marked chemoprotective effect was observed with frequent, long-term use of both aspirin (OR 0.48, 95% CI 0.24-0.95, $P=0.04$) and acetaminophen (OR 0.19, 95% CI 0.05-0.82, $P=0.03$).

Conclusions: Our findings indicate that frequent use of aspirin and acetaminophen for 5 or more years reduces the risk of cervical cancer, supporting their role in cancer prevention. The chemoprotective role of analgesics in cervical cancer opens new venue for future research elucidating molecular bases of carcinogenesis. Given the widespread use of NSAIDs and acetaminophen worldwide, further investigation in a larger sample size with better-defined dosing regimens is warranted. Taking into account the existing data on the role of chronic inflammation in persistent high-risk HPV infection, future efforts should focus on primary and secondary prevention of cervical dysplasia.

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Endometrial cancer outcomes in diabetic women treated with metformin, statins, and aspirin

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Objectives: The antidiabetic drug metformin has shown promising antitumorigenic effects in preclinical studies, and clinical trials are underway in endometrial cancer (EC) patients. Emerging evidence suggests that metformin, statins, and aspirin may improve overall survival (OS) in women with EC. Thus, our goal was to evaluate the contributory effect of statins and aspirin, in combination with metformin, on outcomes in women with diabetes mellitus (DM) and EC.

Methods: We conducted an institutional review board-approved retrospective analysis of all women treated for EC at two academic institutions between January 1997 and July 2012. Demographic and clinical data, including medication use at time of diagnosis, were abstracted from medical records. A cohort of diabetic EC patients treated with metformin was identified. Further division within this cohort included patients treated with statins or aspirin. Fisher's exact tests and Wilcoxon two-group tests were used. Cox regression modeling analyzed progression-free survival (PFS), time-to-progression (TTP), and OS.

Results: Of 1,995 women diagnosed with EC in the study period, there were 494 (25%) women with DM, who comprised the study cohort. There were 282 (57%) metformin, 232 (46%) statin, and 165 (33%) aspirin users. Metformin use was significantly associated with better OS (P<0.0002, HR 0.50, 95% CI 0.34-0.72) and better PFS (P=0.0036, HR 0.61, 95% CI 0.43-0.85), but not TTP. After adjusting for stage, grade, body mass index, age, and treatment, metformin remained significantly associated with better OS (HR 0.49, 95% CI 0.34-0.71) and better PFS (HR 0.60, 95% CI 0.43-0.84). Aspirin or statin use alone was not associated with OS, PFS, or TTP. Aspirin or statin use among metformin users had no additive benefit over metformin alone.

Conclusions: Metformin remained significantly associated with improved OS and PFS in patients with DM, and this persisted in models accounting for the use of aspirin and statins. There was no evidence of any significant association between aspirin or statin use alone among those who had DM and PFS, TTP, and OS. The resilience of metformin's association with improved outcomes further supports its potential role in EC treatment and management, particularly in the high-risk diabetic population.

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Metformin has increased efficacy under obese conditions in a novel genetically engineered mouse model of serous ovarian cancer

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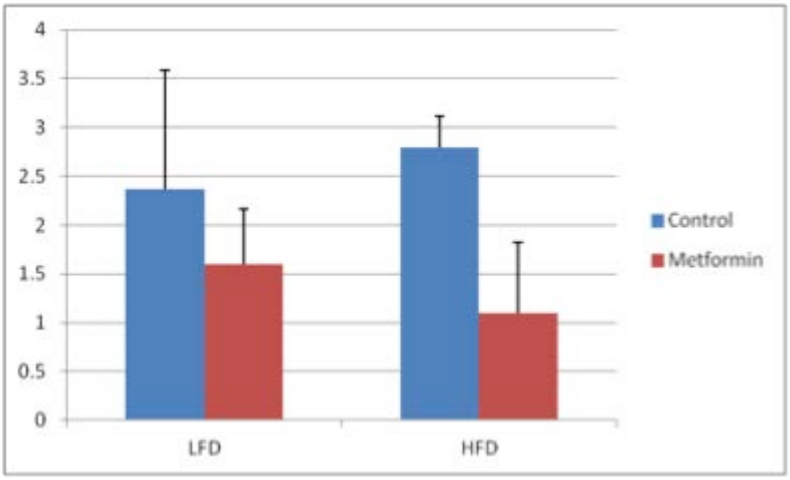
Objectives: Metformin is an antidiabetic drug with antitumorigenic effects. It is hypothesized that metformin may be more efficacious in obese and insulin-resistant cancer patients, given its favorable impact on improvement in the metabolic profile. Thus, we examined the efficacy of metformin in human ovarian cancer (OC) cell lines under varying glucose conditions well as in a genetically engineered mouse model of serous OC under obese and nonobese conditions.

Methods: The SKOV3 and IGROV1 OC cell lines were treated with metformin under low glucose (2 mM), normal glucose (5.5 mM), and high glucose (25 mM) conditions. Cell growth was determined by MTT assay. Apoptosis was evaluated by Annexin V-FITC assay. AMPK and S6 expression were documented by Western blotting. For *in vivo* studies, we used the K18-$gT_{121}^{+/-}$; $p53^{fl/fl}$; $Brca1^{fl/fl}$ (KpB) OC mouse model. KpB mice were subjected to a 60% kcal derived from fat in a high-fat diet (HFD) to mimic diet-induced obesity vs 10% kcal from fat in a low-fat diet (LFD). Mice were treated with placebo or metformin (200 mg/kg body weight daily) following tumor onset for 4 weeks (n=8-10 mice/group).

Results: As the concentration of glucose increased, phosphorylation of AMPK decreased and phosphorylation of S6 increased in the OC cell lines, signifying increased proliferative capacity and hyperactivation of the mTOR pathway with high glucose levels. Metformin was more effective in the inhibition of proliferation and induction of apoptosis under low vs high glucose concentrations. In the mice fed a HFD, metformin decreased tumor growth by 60% compared to placebo (P=0.017). In the mice fed a LFD, metformin decreased tumor growth by 32% compared to placebo (P=0.047). A comparison of the effects of metformin on mice fed a LFD vs a HFD demonstrated that metformin was more efficacious in decreasing tumor growth in the mice on the HFD (P=0.003).

Conclusions: High glucose levels may confer a growth advantage in OC cells and override some of the antiproliferative effects of metformin in vitro. *In vivo* studies demonstrate that treatment with metformin was more efficacious in inhibiting

tumor growth among mice fed a HFD. This work suggests that metformin may be a novel chemotherapeutic agent for OC treatment that is potentially more beneficial in the obese population.



Scientific Plenary V: Late-Breaking Abstracts, Abstract 106
Monday, March 24, 2014
8:15 a.m. – 9:50 a.m., Ballroom B-C
Moderator: S. Diane Yamada, MD, *University of Chicago, Chicago, IL*

106 - Scientific Plenary

Burnout is associated with decreased career satisfaction and psychosocial distress among members of the Society of Gynecologic Oncology (SGO)

K. Rath[1], L. Huffman[2], K. Carpenter[2] and J. M. Fowler[2]
[1]Ohio Health Gynecologic Cancer Surgeons, Columbus, OH, [2]The Ohio State University, Columbus, OH

Objectives: To determine the rate of burnout among gynecologic oncologists and evaluate factors associated with burnout in this population.

Methods: This study used a cross-sectional design. Current members of the SGO were sent an anonymous email survey that included 76 items measuring burnout, psychosocial distress, career satisfaction, and quality of life (QOL).

Results: Of the 1,086 members invited, 436 (40.1%) responded, and 369 of those (84.6%) completed the survey. Median age was 48 years, 66% had been practicing >10 years, 58.8% worked an average of >60 hours/week, the median number of operating room hours was 15/week, nights on call was 3/week, 77% managed chemotherapy, and 59% practiced in an academic setting. More than 32% of physicians scored above clinical cutoffs for emotional exhaustion (EE) and/or depersonalization (DP), suggesting high rates of burnout, with 30% and 10% scoring in the clinical range on EE and DP, respectively. In addition, 33% screened positive for depression (PRIME MD/PHQ2), 13% endorsed a history of suicidal ideation, 15% screened positive for alcohol abuse (CAGE), and 34% reported impaired QOL (MOS SF-12). Nonetheless, 70% reported high levels of personal accomplishment, and results suggested most were satisfied with their careers, with 89% indicating they would enter medicine again and 61% stating they would encourage their child to pursue a career in medicine. Analyses indicated that those in the high burnout category were significantly less likely to report that they would become physicians again (P=0.002) and less likely to encourage a child to enter medicine (P<.001). Burnout was also significantly associated with a positive screen for depression (P<0.001) or alcohol abuse (P=0.02), history of suicidal ideation (P<0.001), and impaired QOL (P<0.001). Interestingly, personal accomplishment scores were not significantly correlated with career satisfaction (P=0.225), depression (P>0.99), alcohol abuse (P>0.99), or suicidal ideation (P>0.99).

Conclusions: Burnout is a significant problem associated with psychosocial distress and lower levels of career satisfaction. Interventions targeted at improving QOL and treatment of depression or alcohol abuse may have an impact on burnout. However, significant barriers may exist because 44.5% of respondents reported they would be reluctant to seek medical care for depression, substance use, or other mental health concerns.

Scientific Plenary VI: Approaches to Improve Quality and Palliative Care in Gynecologic Cancers
Monday, March 24, 2014
2:30 p.m. – 3:30 p.m., Ballroom B-C
Moderator: Monique A. Spillman, MD, *University of Colorado Denver, Aurora, CO*

107 - Scientific Plenary

Hospital readmission (30-day) following surgery for advanced-stage ovarian cancer: analysis of risk factors and cost using the SEER-Medicare database

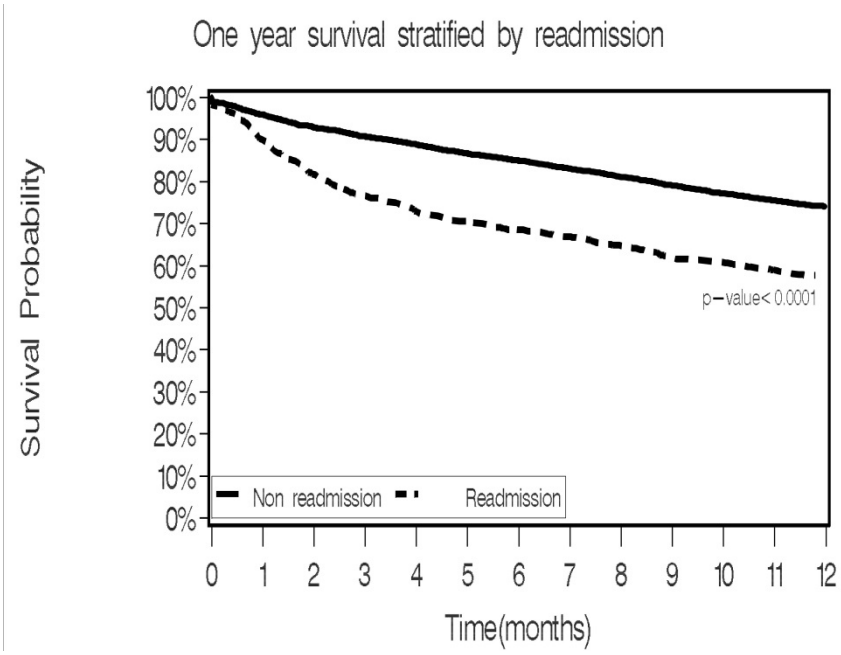
R. Eskander[1], J. Chang[2], A. Ziogas[2], H. Anton-Culver[2] and R. E. Bristow[2]
[1]*University of California at Irvine Medical Center, Orange, CA,* [2]*University of California at Irvine, Irvine, CA*

Objectives: To analyze risk factors for and costs associated with 30-day readmission after surgery for advanced-stage ovarian/primary peritoneal/fallopian tube cancer.

Methods: The Surveillance, Epidemiology and End Results -Medicare (SEER-Medicare) linked database (1992-2010) was used to evaluate readmission rates within 30-days of index surgery in patients 66 years of age and older with stage IIIC/IV ovarian/primary peritoneal/fallopian tube cancer. Multivariate logistic regression was used to identify predictors of readmission. Odds ratios (OR) were adjusted for multiple factors. Total cost of hospital stay was calculated and inflation adjusted, presented in 2010 dollars.

Results: Of 5152 eligible subjects discharged after index surgery, 888 (17.2%) were readmitted within 30 days of discharge. Mean patient age was 75 years, and the majority of patients (66.4%) had a Charlson co-morbidity score of 0. Readmission was related to surgical complications in <1% of patients. The most common diagnosis associated with readmission included, infection (34.7%), dehydration (34.3%), ileus/obstruction (26.2%), metabolic/electrolyte derangements (23.1%) and anemia (12.3%). In multivariate analysis, year of discharge was significantly associated with 30-day readmission (1996-2000 HR 1.32 95% CI 1.01-1.71; 2001-2005 HR 1.58 95% CI 1.24-2.0; 2006-2010 HR 1.73 95% CI 1.35-2.21; Referent years 1992-1995). Additionally, length of index hospital stay > 8 days (HR 1.39; 95% CI 1.18-1.64), and discharge to skilled nursing facility (HR 1.3; 95% CI 1.04-1.63) were significant predictors of 30-day readmission in multivariate analysis. When compared with patients not readmitted, those readmitted within 30 days had a significantly greater one-year mortality (41.1% vs 25.1% respectively; p<0.0001). The median cost of readmission hospital stay was $9220±$14,296, with a total cost of $9.3 million over the study period ($513,758/year).

Conclusions: Early readmission following surgery for ovarian cancer is common and due in part to modifiable factors. There is a significant association between 30-day readmission and one-year mortality. These findings may catalyze development of targeted interventions to decrease early readmission, improve patient outcomes and control health care costs.



108 - Scientific Plenary

Cost analysis comparing universal tumor testing to clinically based criteria in the evaluation of endometrial adenocarcinomas for Lynch syndrome

A. S. Bruegl[1], B. Djordjevic[2], L. Rajyalakshmi[1], K. H. Lu[1], C. C. L. Sun[1] and R. Broaddus[1]
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, [2]The Ottawa Hospital, Ottawa, ON, Canada

Objectives: Lynch Syndrome (LS) is an inherited cancer syndrome due to a mutation in a DNA mismatch repair (MMR) gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) that accounts for 1% to 6% of all endometrial adenocarcinomas. For women with LS, a gynecologic cancer is the sentinel cancer diagnosis in 50% of cases, and identification at the time of sentinel cancer diagnosis allows for screening for other LS-associated carcinomas such as colorectal cancer (CRC). CRC guidelines recommend tumor testing to evaluate all CRC tumors, regardless of family history. Guidelines for screening endometrial adenocarcinomas remain rooted in clinically based criteria. The objective of this study was to compare the direct costs of clinically based screening using Society of Gynecologic Oncology 5-10% criteria to immunohistochemistry (IHC)-based universal tumor testing in endometrial adenocarcinomas.

Methods: Clinicopathologic data for 412 sequential, unselected endometrial adenocarcinomas were collected from the electronic medical record. IHC for expression of DNA MMR proteins was performed on hysterectomy specimens. IHC loss of expression of MSH2+MSH6, MSH6, or PMS2 proteins were designated as probable LS (PLS). Polymerase chain reaction-based *MLH1* methylation was performed in tumors with IHC loss of MLH1+PMS2. Unmethylated tumors were designated PLS and methylated tumors were designated sporadic. A cost-effectiveness analysis compared the direct costs of using SGO 5-10% criteria to universal IHC testing. Costs were derived from Current Procedural Terminology codes and Medicare reimbursement fees. Genetic counseling visits, germline testing, IHC for DNA MMR proteins, and *MLH1* methylation were included in costs. Comparisons were made of total cost of screening and cost per PLS case identified.

Results: IHC was performed on 408/412 samples. Of these, 48 (10.5%) had tumor testing suggestive of LS and were designated as PLS. Ninety-seven cases met SGO 5-10% criteria and 15 (15.4%) had tumor testing consistent with a diagnosis of LS. The total cost of the SGO screening strategy in this cohort was $91,455 and $6,097/PLS case identified. The total cost of the universal testing strategy was $252,711 and $5,877/PLS case identified (Table 1).

Conclusions: Universal tumor testing of endometrial adenocarcinomas identifies more individuals at risk for LS and is a cost-effective strategy when compared to clinically based SGO 5-10% criteria.

Screening Strategy	SGO 5-10% Criteria	Universal Testing
Endometrial Cancer Patients (N = 412)		
# who undergo IHC	97	412
# who have loss of protein expression with immunohistochemistry	21	118
# who undergo *MLH1* methylation testing	13	90
# seen by genetic counselor	97	46
# probable Lynch Syndrome identified by Strategy	15	43
Estimated Costs for Screening Strategies		
Cost to screen 412 cases	$91,455	$252,711
Average cost per probable Lynch Syndrome case detected	$6,097	$5,877

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109 - Scientific Plenary

Outpatient palliative care consultation is associated with a decrease in symptom burden for women with gynecologic malignancies

R. Ruskin[1], M. W. Rabow[2], I. E. Allen[1] and L. M. Chen[2]
[1]University of California San Francisco, San Francisco, CA, [2]UCSF Helen Diller Comprehensive Cancer Center, San Francisco, CA

Objectives: To determine the impact of an outpatient palliative care consultation on symptom burden in gynecologic cancer patients.

Methods: We studied patients seen at an outpatient symptom management clinic at a single academic center from June 2007 through March 2013 who attended a follow-up visit within 90 days of their initial consultation. At each visit, patients completed a questionnaire that included the Edmonton Symptom Assessment System (ESAS). Demographic, clinicopathologic, and treatment data were obtained through chart review. Analysis of variance with multiple comparisons and chi-square statistics were used to assess changes in symptom scores and comparisons of patient subgroups.

Results: A total of 78 patients were seen for an initial consultation and at least one follow-up visit within 90 days during the study period. Thirty-five patients had at least two follow-up visits. Of these, 58% had ovarian, fallopian tube, or peritoneal cancer; 20% had uterine cancer; and 15% had cervical cancer. Stage III, IV, or recurrent cancer was documented in 81% of women. The mean age was 57 years. At study entry, 85% of patients had disease present and 62% were undergoing treatment. Sixty-two percent were white and 85% spoke English. Eight-eight percent of patients had previously undergone surgery, 87% had received chemotherapy, and 30% had received radiation. Between the initial and follow-up visit, there were statistically significant improvements in almost all symptoms ($P<0.05$), including pain (-0.94), fatigue (-0.86), anxiety (-1.35), depression (-1.59), nausea (-1.14), drowsiness (-0.49), appetite (-1.10), and shortness of breath (-0.54). There was also a small improvement in quality of life (0.09). Patients who received concurrent cancer-directed therapies were less likely to experience improvements in pain (-0.34 vs -1.48) and fatigue (-0.60 vs -1.25) compared with patients who did not receive treatment. For the subset of patients who attended at least two follow-up visits, improvements in nausea and shortness of breath after one visit persisted at the second follow-up visit. For these same patients, the symptoms of depression and drowsiness continued to improve at each visit.

Conclusions: An outpatient palliative care consultation is associated with a decrease in symptom burden for women with gynecologic malignancies.

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110 - Scientific Plenary

Predictors of palliative care consultation on an inpatient gynecologic oncology service: are we following ASCO recommendations?

C. Lefkowits[1], A. Binstock[1], M. Courtney-Brooks[1], W. Teuteberg[1], J. Leahy[1], P. Sukumvanich[2] and J. L. Kelley[1]
[1]University of Pittsburgh Medical Center, Pittsburgh, PA, [2]Magee-Womens Hospital of UPMC, Pittsburgh, PA

Objectives: To determine predictors of inpatient palliative care (PC) consultation and characterize PC referral patterns with respect to the recent ASCO recommendation to consider early PC integration for “any patient with metastatic cancer and/or high symptom burden.”

Methods: Women with a gynecologic malignancy admitted to the gynecologic oncology service between February and August 2012 were identified. Charts were reviewed for demographics, disease and treatment characteristics, presence of admission for symptom management or malignant bowel obstruction (MBO), and whether death occurred within 6 months of last admission. Statistical analysis utilized Student’s t-test for continuous variables and chi-squared test or Fisher’s exact test for categorical variables.

Results: Three hundred forty patients were identified and 82 (32%) were referred to PC. Table 1 summarizes patient characteristics and differences between patients with and without PC consultation. On multivariate logistic regression, significant predictors of PC consultation were number of admissions (>3 admissions odds ratio [OR] 17.4, 95% CI 4.2-72.7), admission for symptom management (OR 22.0, 95% CI 7.2-67.4), and death within 6 months (OR 15.7, 95% CI 5.5-44.6). Of patients referred to PC, 54% died within 6 months of last admission. Among patients with recurrent disease ($n=79$), all of whom could be considered to meet ASCO recommendations for consideration of PC integration, only 53% were seen by PC, including only 59% who had had ≥3 lines of chemotherapy.

Conclusions: Independent predictors of PC consultation included admission primarily for symptom management and death within 6 months, suggesting that the group of patients referred to PC is characterized by high symptom burden and poor prognosis. However, high-risk patients are not being captured comprehensively, as indicated by the low referral rates of subgroups included in the ASCO recommendations such as those with recurrent disease and those admitted for symptom management or MBO. Also, the majority of patients seen by PC died within 6 months, suggesting that we continue to use PC referrals primarily for patients near the end of life, rather than employing early integration, as recommended by ASCO.

Table 1. Patients Referred vs Not Referred for Inpatient Palliative Care (n=340)

	Not referred (n=258)		Referred (n=82)		
	No	%	No	%	p
Age (mean, years)	61.2		59.7		0.41*
Disease site (or ovarian vs other)					<0.001†
Ovarian	78	63.4	45	36.6	
Endometrial	133	86.9	20	13.1	
Cervical	30	66.7	15	33.3	
Vulvar/vaginal	14	93.3	1	6.7	
Stage at Dx					<0.001‡
I/II	161	88.5	21	11.5	
III/IV	84	59.2	58	40.8	
# admissions during time period					<0.001†
1-2	251	78.7	68	21.3	
≥3	7	33.3	14	66.7	
Any admission primarily for Sx control					<0.001‡
Y	10	20.8	38	79.2	
N	247	84.9	44	15.1	
Malignant Bowel Obstruction Admission					0.001‡
Y	5	35.7	9	64.3	
N	253	77.6	73	22.4	
# lines chemo by end of time period					0.001†
1-2	101	70.6	42	29.4	
≥3	15	40.5	22	59.5	
Recurrent disease by end of time period					<0.001‡
Y	37	46.8	42	53.2	
N	221	84.7	40	15.3	
Death w/in 6 months end of time period					<0.001‡
Y	19	30.2	44	69.8	
N	239	86.6	37	13.4	

†Chi-Square Test
‡Fisher's Exact Test
*Independent samples t-test

Featured Poster Session VI: Hereditary Cancer / Minimally Invasive Surgery / Obesity / Survivorship and Palliative Care
Monday, March 24, 2014
3:35 p.m. – 4:45 p.m., Ballroom D
Moderators: Laverne Mensah, MD, *Alexian Brothers Medical Group, Elk Grove Village, IL;* Cyril Spann, MD, *Emory University Medical School, Decatur, GA*

111 - Featured Poster

Interim analysis of a prospective pilot study of risk-reducing postpartum distal salpingectomy

G. L. Hsieh, K. Antony, R. Masand and M. L. Anderson
Baylor College of Medicine, Houston, TX

Objectives: To evaluate the feasibility and safety of postpartum distal salpingectomy (PPDS) as a potential strategy for preventing high-grade serous carcinomas (HGSC) and establish a standard protocol for PPDS.

Methods: After obtaining informed consent, women (age >25 years) requesting postpartum sterilization underwent PPDS using a standardized protocol optimized for limited resource settings. Procedures were performed either at cesarean section or on postpartum days 0-2 following a vaginal delivery. Only women who met state and institutional standards for surgical sterilization were enrolled. Matched cohorts of women who underwent standard-of-care postpartum tubal ligations were used as controls.

Results: To date, a total of 80 women have been enrolled. The mean age of all participants was 32.6±4.1 years (range, 27-41 years). Subjects (n=40) and controls (n=40) were similar with regard to age, body mass index, and parity. PPDS was successfully executed in 39/40 subjects without intraoperative complications. No differences in mean estimated blood loss were observed between subjects and controls undergoing modified Parkland procedure following cesarean section or modified

Pomeroy procedure following vaginal delivery as per institutional standard. Mean operative time was slightly longer for women undergoing PPDS with cesarean section (n=17) when compared to controls who underwent bilateral modified Parkland tubal ligation (105.9±9.6 minutes vs 82.0±4.3 minutes, P<0.05). Dense intra-abdominal adhesions prevented the planned procedure for one patient who underwent cesarean section as well as one control patient planned for standard tubal ligation on postpartum day 1. Infection, wound separation, or other postoperative complications were not observed.

Conclusions: PPDS is feasible and can be safely performed. Additional work is currently ongoing to better define the histology of the postpartum fallopian tube as well as determine whether PPDS can be used cost effectively to prevent high-grade serous pelvic carcinomas.

		Mean Estimated Blood Loss (mL)	Mean Operative Time (min)
s/p Vaginal Delivery	PPDS (n=23)	*22.0 ± 25.8*	*45.3 ± 13.4*
	Control (n=27)	*9.3 ± 4.7*	*40.3 ± 14.1*
s/p Cesarean	PPDS (n=17)	*837 ± 431*	*105.9 ± 29.6* **
	Control (n=13)	*1007 ± 575*	*82.0 ± 14.3*
**p<0.05			

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112 - Featured Poster

Risk management options elected by women after testing positive for a *BRCA1* or *BRCA2* variant of unknown significance mutation

C. Garcia, L. Lyon, R. D. Littell and B. Powell
Kaiser Permanente Medical Group, San Francisco, CA

Objectives: To describe and compare cancer risk-reducing behaviors in women who test positive for a *BRCA* mutation of unknown significance (VUS) and women who test positive for a known deleterious mutation.

Methods: Women who tested positive for a *BRCA* mutation from 1995-2012 were identified from a large community-based integrated health system in northern California. Exclusion criteria included loss of membership or death within 1 year of testing, prior ovarian cancer, or prior bilateral salpingo-oophorectomy. A retrospective chart review using the electronic medical record was performed. Primary outcomes were rate of risk-reducing mastectomy (RRM) and salpingo-oophorectomy (RRSO). Utilization of ovarian cancer risk-reduction strategies, including oral contraceptive (OCP) use and CA-125 and ultrasound screening, was compared with breast cancer risk reduction, including tamoxifen use and screening MRI and mammography.

Results: The mean age of the 69 VUS carriers was 50 years compared to 47 years for the 305 women with deleterious mutations. VUS women were followed for a median of 69 months from testing. Among the VUS carriers, 30% underwent RRSO and 11% underwent RRM compared to 74% and 44% for women with deleterious mutations. Women with deleterious mutations were more likely to undergo RRSO than women with VUS (OR 6.4). Use of chemoprevention with OCPs or tamoxifen was minimal for both groups. Women with a deleterious mutation were more likely to undergo cancer surveillance in the first year after testing than VUS women: 43% vs 39% for mammography (OR 2.1), 35% vs 15% for MRI (OR 6.0), 47% vs 18% for CA-125 (OR 7.7), and 45% vs 26% for ultrasonography (OR 5.0). Rates of screening fell sharply at 5 years out from testing to <10% for all surveillance measures for the deleterious group but were more stable in the VUS group. During follow-up, 54% of VUS mutations were reclassified after a median of 39 months, longer than the median time to RRSO (18.6 months) or RRM (20.1 months) for this group of women.

Conclusions: Uptake of risk-reducing surgery and breast and ovarian cancer surveillance strategies among women with VUS is lower than that of women with known deleterious mutations. Given the prognostic uncertainty and high rate of reclassification for VUS carriers, it may be best to direct efforts toward improving surveillance in this group of women.

113 - Featured Poster

Women with dual gynecologic primary cancers can have mutations in Lynch syndrome genes or *BRCA1/BRCA2,* reflecting the overlap in clinical histories between these syndromes

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[1]Myriad Genetic Laboratories, Inc., Salt Lake City, UT, [2]University of Michigan, Ann Arbor, MI

Objectives: To assess the prevalence of Lynch syndrome (LS) or hereditary breast and ovarian cancer (HBOC) in women with dual endometrial (EC)/ovarian (OC) cancers and evaluate their personal and family histories.

Methods: A commercial laboratory database was searched for women with dual OC/EC primary cancers who were tested for *MMR* and/or *BRCA* gene mutations from 2006-2012. Genetic test results, ages at diagnoses, and personal/family histories were reviewed.

Results: A total of 1,529 patients underwent LS and/or HBOC testing. Overall, 332 women had LS testing only, 845 had *BRCA* testing only, and 352 had both LS and *BRCA* testing. A total of 172 (11.2%) women were found to be mutation carriers: 126 (73.3%) by LS testing and 46 (26.7%) by *BRCA* testing. The average age at diagnosis of OC and EC in LS carriers was 44.8 years, while the average ages of diagnosis in *BRCA* carriers were 53.4 years and 50.2 years, respectively. Among LS carriers, 31.7% had personal histories of additional LS cancers. In *BRCA* mutation carriers, 28.3% had personal histories of additional HBOC cancers. Of 13 mutation-positive women with breast cancer, nine were *BRCA* carriers and four were LS mutation carriers. There was extensive overlap of the syndromes in family cancer histories in both carrier groups (Table).

Conclusions: Overall, 11.2% of women with EC/OC were found to have LS or HBOC mutations, with 73.3% of these mutations being found in LS genes. While cancer history helps guide genetic testing, many patients showed extensive overlap of LS and HBOC cancers in personal and family histories, suggesting that a panel testing approach in this patient subset may reduce the likelihood of a missed hereditary cancer syndrome diagnosis.

	Number of Patients	% of Total	HBOC-positive	Lynch-positive
Lynch Cancers Only	74	43.0	5 (6.8%)	69 (93.2%)
HBOC Cancers Only	25	14.5	19 (76.0%)	6 (24.0%)
Both Lynch and HBOC Cancers	56	32.6	16 (28.6%)	40 (71.4%)

114 - Featured Poster

Preoperative genetic testing affects surgical decision-making in breast cancer patients

E. Lokich, A. R. Stuckey, C. Raker, J. Scalia Wilbur, J. Laprise and J. Gass
Women & Infants' Hospital, Brown University, Providence, RI

Objectives: In women with newly diagnosed breast cancer, the optimal time for referral to cancer genetic specialists is unknown. The aim of our study was to determine if mutation status changes surgical decision-making in women who undergo genetic testing for *BRCA* mutations after the initial diagnosis of breast cancer.

Methods: This is a retrospective cohort study of breast cancer patients in an academic oncology program who were diagnosed between 2006 and 2012 and who had *BRCA* testing performed. Patients were identified from the hospital tumor registry. We compared women who tested positive for a *BRCA* mutation before surgery with those who tested negative. Data collected from the tumor registry included: age, race, insurance status, stage, histology, receptor status, and adjuvant treatment. Gravidity, parity, surgeon, family history, *BRCA* testing result, and surgery performed were obtained from the electronic medical record. Type of surgery was considered to be the most definitive surgery within a year of initial diagnosis. Variables were compared by *BRCA* status using chi-square or Fisher's exact test.

Results: A total of 302 women were included in the study, and 32 (10.6%) were identified as carrying a *BRCA* mutation. The median age at diagnosis was 49.6 years (range, 25-85 years). Most women had early-stage disease (55.6% T1 lesions, 72.8% node-negative). Breast-conserving surgery was undertaken in 55.6% of women and the remaining had unilateral or bilateral mastectomy. As compared to noncarriers, *BRCA* mutation carriers were more likely to have both a personal prior history of breast cancer (relative risk 2.74, 95% CI 1.08-6.98) and hormone receptor-negative tumors (56.0% vs 26.2%, P=0.002). *BRCA* mutation carriers were more likely than noncarriers to choose bilateral mastectomy with reconstruction (56.3% vs 15.9%, P<0.0001). Among *BRCA* mutation carriers, 71.9% opted for a different surgery than what was initially planned by their surgeon compared to 29% of mutation-negative patients (P<0.0001).

Conclusions: *BRCA* testing strongly influences surgical decision-making in newly diagnosed breast cancer patients. These women who meet National Comprehensive Cancer Network referral guidelines should have their genetic evaluation obtained before surgical intervention.

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115 - Featured Poster

Racial disparity in endometrial cancer patients undergoing hysterectomy: an American Cancer Society (ACS)-National Surgical Quality Improvement Program (NSQIP) evaluation of surgical outcomes

J. M. Scalici[1], J. Black[1], C. V. Brown[2], B. Wang[1], M. A. Finan[1] and R. P. Rocconi[1]
[1]University of South Alabama, Mobile, AL, [2]Vanderbilt University, Nashville, TN

Objectives: Despite improvements in the treatment of endometrial cancer (EC), significant racial disparities have persisted for years. The etiology is likely multifactorial, although previous reports suggest this disparity is partly due to African American (AA) patients being less likely to undergo staging surgery and minimally invasive surgery. Our objective was to evaluate if a racial disparity in surgical outcomes existed in patients who received surgery for EC.

Methods: The ACS-NSQIP database from years 2005 to 2011 was used to determine the effect of race on surgical outcomes for patients with EC. Comparative statistical analyses were performed to evaluate preoperative characteristics, operative variables, and postoperative 30-day morbidity and mortality.

Results: A total of 3,875 patients underwent definitive hysterectomy +/- lymphadenectomy for EC, with 90% being white (n=3,492) and 10% being AA (n=383). Groups were similar in regard to age, ASA status, and comorbid conditions. AA patients had significantly higher body mass index compared to whites (36.5 vs 34.3, P< 0.0001). Although the types of surgery performed were similar between the two groups, AA patients had significantly longer operation times (184 vs 171 minutes, P=0.003) and longer hospital stay (4.1 vs 3.1 days, P=0.046) compared to whites. Postoperative morbidity was more common in AA patients for transfusions, superficial surgical site infection, pneumonia, and sepsis. Despite binary logistic regression analysis demonstrating no significant differences between AA and white patients, AA patients were more likely to have 30-day mortality than whites (1.6 vs 0.6%, P= 0.037).

Conclusions: Although previous reports demonstrated differences in surgical procedures, our data obtained from a national database showed that AA patients received similar surgical treatments for EC. Despite similar surgical treatment, AA patients were still more likely to have 30-day morbidity as well as 30-day mortality. Considering comorbid conditions were similar between the groups, further study is warranted to elicit potential etiologies to overcome this disparity.

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116 - Featured Poster

Disparities in the use of robotic surgery in endometrial cancer based on race and socioeconomic status in the United States

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Objectives: To determine the disparities associated with the use of robotic surgery (RS) in endometrial cancer patients.

Methods: Data were obtained from the National Inpatient Sample. Chi-square and multivariate analyses were used for statistical analyses.

Results: Among 6,560 patients who underwent surgery, the median age was 62 years (range, 22 to 99 years). A total of 1,647 (25%) underwent RS, 820 (12%) had laparoscopic surgery (LS), and 4,093 (62%) had open surgery (OS). The majority were white (76%); the remainder were black (10%), Hispanic (8%), and Asian (4%). Twenty-three percent of hospitals were higher volume (>20 cases/year). RS was performed in 29% of whites, 15% of Hispanics, 12% of Blacks, and 11% of Asians ($P<0.01$). Higher-volume hospitals performed 72% of all surgeries and 84% of all RS. Moreover, these higher-volume hospitals were more likely to use RS compared with lower-volume hospitals (29% vs 14%, $P<0.01$). The percentages of patients who had RS according to income based on zip code were 21% for low (<$40,999), 25% for middle ($41,000 - $50,999), 28% for upper middle ($51,000 - $66,999), and 27% for high (>$67,000) ($P<0.01$). Based on insurance coverage, 27% of Medicare patients and 26% of private insurance had RS compared to only 14% of Medicaid patients ($P<0.01$).

Conclusions: In this nationwide analysis, endometrial cancer patients who were white, from larger-volume hospitals, and had higher income and non-Medicaid insurance were more likely to undergo RS. Further studies are warranted to better understand the barriers to receiving RS.

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The feasibility and safety of same-day discharge after robotic-assisted hysterectomy alone or with other procedures for benign and malignant indications

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Objectives: To report the feasibility and safety of same-day discharge after robotic-assisted hysterectomy.

Methods: Same-day discharge after robotic-assisted hysterectomy was initiated July 2010. All cases from then through December 2012 were captured prospectively for quality assessment monitoring. The distance from the hospital to patients' homes was determined using http://maps.google.com. Procedures were categorized as simple (total laparoscopic hysterectomy [TLH]± bilateral salpingo-oophorectomy [BSO]) or complex (TLH±BSO with sentinel node mapping, pelvic and/or aortic nodal dissection, appendectomy, or omentectomy). Urgent care center (UCC) visits and readmissions within 30 days of surgery were captured, and time to the visit was determined from the initial surgical date.

Results: Same-day discharge was planned in 200 cases. Median age was 52 years (range, 30-78 years), body mass index was 26.8 (range, 17.4-56.8), and ASA was class 2 (range, 1-3). Median distance traveled was 31.5 miles (range, 0.2-149 miles). Procedures were simple in 109 (55%) and complex in 91 (45%) cases. The indication for surgery was: endometrial cancer ($n=82$; 41%), ovarian cancer ($n=5$; 2.5%), cervical cancer ($n=8$; 4%), and non-gynecologic cancer/benign ($n=105$; 53%). One hundred fifty-seven (78%) patients had successful same-day discharge; 43 (22%) required admission. Median time for discharge for same-day cases was 4.8 hours (range, 2.4-10.3 hours). Operative time, case ending before 6 pm, and use of intraoperative ketorolac were associated with successful same-day discharge. UCC visits occurred in 8/157 (5.1%) same-day discharge cases compared to 5/43 (11.6%) requiring admission ($P=0.08$). Readmission was necessary in 5/157 (3.2%) same-day discharge cases compared to 3/43 (7.0%) requiring admission ($P=0.02$).

Conclusions: Same-day discharge after robotic-assisted hysterectomy for benign and malignant conditions is feasible and safe.

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Patterns of recurrence and survival after randomization to laparoscopy versus laparotomy in women with high-grade uterine cancer: a Gynecologic Oncology Group (GOG) study

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Objectives: To compare the clinicopathologic features, patterns of recurrence, and survival outcomes of women with high-grade uterine cancer (UC) randomized to staging via laparoscopy (LSC) vs laparotomy (LAP) in a cooperative group study.

Methods: An ancillary analysis of the LAP-2 trial, a phase III study of women with clinical stage I-II UC randomized to undergo hysterectomy and comprehensive staging via LSC or LAP, was performed. Data were collected on those with grade 3 endometrioid (ENDO) and those with type II UC: uterine serous carcinoma (USC), clear cell (CC), and carcinosarcoma (CS). Demographics, clinicopathologic features, recurrence patterns, and progression-free (PFS) and overall survival (OS) were compared by histology and surgical staging approach.

Results: We identified 753 patients: 350 had ENDO, 289 had USC, 42 had CC, and 72 had CS. LSC was performed in 507, and 246 underwent LAP. Compared with the ENDO cohort, those with type II UC were more likely to be older (69.4 vs 64.8 years, $P<0.001$), have positive peritoneal cytology (20.2% vs 7.0%, $P<0.001$), have positive lymph nodes (22.6% vs 16.9%, $P=0.05$), have higher stage disease on final pathology ($P<0.001$), and undergo a conversion to laparotomy due to metastatic disease (34.3% vs 23.3%, $P=0.008$). With a median follow-up time of 60 months, those with type II UC had higher recurrence rates (26.6% vs 13.7%, $P<0.001$), were more likely to have a multisite or extrapelvic recurrence ($P<0.001$), and had poorer PFS (59.3% vs 77.4%, $P<0.001$) and OS (65.6% vs 81.7%, $P<0.001$) than the ENDO cohort. Trocar recurrences were rare (1.5%) in the LSC cohort. Further, patterns of recurrence, PFS, and OS were not significantly different in those staged with LSC vs LAP. On multivariable analysis, age, disease stage, and type II histology were independently associated with PFS/OS. Surgical approach was not associated with survival.

Conclusions: Those with apparent early-stage type II UC have more biologically aggressive disease and poorer outcomes than their high-grade ENDO counterparts. Women with high-grade UC of any subtype staged via laparoscopy had similar patterns of recurrence and survival outcomes as those staged by laparotomy. However, the type II cohort was more likely to have metastatic disease requiring conversion to laparotomy at staging surgery.

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Is robotic-assisted surgery safe in the elderly population? An analysis of gynecologic procedures in patients ≥65 years old

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Objectives: To describe the perioperative outcomes of robotic-assisted surgery in elderly patients (≥65 years old) undergoing gynecologic procedures.

Methods: All patients ≥65 years old who were scheduled to undergo a planned robotic procedure from May 1, 2007 to May 22, 2012 were identified. Perioperative outcomes, including complications, were recorded for patients who did not require conversion to laparotomy. An institutional surgical secondary events grading system was used to assess complications. Standard statistical tests were used to compare various clinical variables among three age groups: 65-74 years (Group 1), 75-84 years (Group 2), and ≥85 years (Group 3).

Results: We identified 413 cases scheduled to undergo a planned robotic procedure. Thirty-nine (9.4%) required conversion to laparotomy: 19 (4.6%) before docking the platform and 20 (4.8%) after docking. Three hundred and seventy-four (90.6%) cases were completed robotically: 272 in Group 1, 86 in Group 2, and 16 in Group 3. Median patient age was 70 years. Median body mass index (BMI) was 28.1. A preoperative diagnosis of malignancy was documented in 63% of the cases, with the majority being endometrial cancer ($n=199$ [53%]). The procedures performed included hysterectomy (75%), unilateral/bilateral salpingo-oophorectomy (96%), lymphadenectomy (pelvic 23%, peri-aortic 19%), and sentinel lymph node mapping (38%). There was no significant difference in median BMI ($P=0.2$), estimated blood loss ($P=0.4$), operative time ($P=0.5$), or total lymph node counts ($P=0.1$) among the three groups. Median hospital length of stay was longer ($P<0.001$) in Group 3 (2 days) compared to Group 1 (1 day) and Group 2 (1 day). The overall complication rate (grades 1-5) was 10.4% and not statistically different among the three groups ($P= 0.9$). The incidence of grade 3 or greater complications (4.5%) was similar among the three groups ($P=0.897$).

Conclusions: Robotic-assisted surgery appears to be safe in an elderly patient cohort. The incidence of overall and severe complications (≥grade 3) was low and consistent with reported complication rates in other series of minimally invasive surgical approaches. Safety does not seem to be compromised with increasing age in an elderly population.

Table 1: Comparison of age groups

Variable	Group 1 (Age 65-74) N=271	Group 2 (Age 75-84) N = 86	Group 3 (Age ≥85) N= 16	*P* value
BMI, kg/m^2				
Median (range)	28.1 (17.5-58.9)	29.1 (19.0-43.6)	25.8 (19.3-50.0)	.150
Indication for surgery				
Adnexal mass	65 (24%)	16 (18.6%)	0	.018
Breast cancer/BRCA mutation	9 (3.3%)	1 (1.2%)	2 (12.5%)	
Complex atypical hyperplasia	14 (5.2%)	1 (1.2%)	1 (6.3%)	
Cervical cancer	8 (3.0%)	1 (1.2%)	0	
Cervical dysplasia	2 (0.7%)	1 (1.2%)	0	
Endometrial cancer	141 (52.0%)	51 (59.3%)	7 (43.8%)	
Ovarian cancer	11 (4.1%)	9 (10.5%)	4 (25.0%)	
Prolapse	5 (1.8%)	2 (2.3%)	0	
Other	16 (5.9%)	4 (4.7%)	2 (12.5%)	
Procedure				
Hysterectomy	193 (71.2%)	71 (82.6%)	14 (87.5%)	.052
Radical hysterectomy	6 (2.2%)	0	0	.317
Unilateral/bilateral salpingo-oophorectomy	261 (96.3%)	81 (94.2%)	15 (93.8%)	.646
Pelvic lymph node dissection	62 (22.9%)	22 (25.6%)	2 (12.5%)	.517
Peri-aortic lymph node dissection	53 (19.6%)	16 (18.6%)	1 (6.3%)	.415
Sentinel lymph node dissection	105 (38.7%)	32 (37.2%)	4 (25.0%)	.540
Other	62 (22.9%)	21 (24.4%)	8 (50.0%)	.049
Estimated blood loss, cc				
Median (range)	50 (0-850)	50 (0-300)	50 (20-200)	.376
# Pelvic lymph nodes				
Median (range)	16.5 (6-33)	12 (3-22)	8 (8-8)	.114
# Paraaortic lymph nodes				
Median (range)	5 (1-20)	7 (2-14)	2 (2-2)	.416
# Total lymph nodes				
Median (range)	20 (4-39)	15 (7-30)	10 (10-10)	.119
Operative time				
Median (range)	159 (42-476)	168.5 (57-367)	154 (69-300)	.505
Length of stay (days)				
Median (range)	1 (0-6)	1 (0-5)	2 (0-5)	<.001
Complications				
Total	29 (10.7%)	9 (10.5%)	1 (6.3%)	.852
Intra-operative	3 (1.1%)	0	0	.566
Post-operative	27 (10.0%)	9 (10.5%)	1 (6.3%)	.874
≥Grade 3	11 (4.1%)	4 (4.7%)	1 (6.3%)	.899

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The influence of obesity on disease characteristics and survival among patients with epithelial ovarian cancer

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Objectives: To evaluate the effect of body mass index (BMI) on disease characteristics and survival in patients with epithelial cancer of the ovary, peritoneum, or fallopian tube (EOC).

Methods: A retrospective chart review encompassing patients with EOC from 1996-2011 was performed. BMI was categorized using World Health Organization definitions. Data analysis used SAS version 9.2.

Results: A total of 586 patients were included. Median BMI was 27.1 (range, 13.7-67.0), with 36.5% having BMI <25, 29.3% having BMI of 25-29.9, 18% having class I obesity (BMI 30-34.9), 7.7% having class II (BMI 35-39.9), and 8.6% have class III (BMI ≥40). Most had high-grade serous histology (HGS) (68.3%) and stage III/IV disease (77.4%). The majority (89.6%) underwent primary surgery with adjuvant chemotherapy; 40% had no gross residual disease, 43.6% had ≤1 cm, and 14.2% had >1 cm residual disease. Lymphadenectomy was performed in 71.3%, and 29.1% had ≥1 radical procedure. Obese patients had similar histologies to nonobese (*P*=0.63). However, when the BMI cutpoint was raised to 35, histologic distribution became marginally different (*P*=0.06), and when the cutpoint was 40, the distribution was significantly different, with endometrioid, mucinous, and low-grade serous more common in obese patients (*P*=0.004). BMI was not associated with residual disease (odds ratio [OR] 0.9, 95% CI 0.5–1.5, *P*=0.65) or lymphadenectomy (OR 1.0, 95% CI 0.7-

1.4, *P*=0.89). Among advanced-stage patients, there was no difference in radical procedures with BMI ≥30 or <30 (30.9% vs 40%, *P*=0.07). After a median follow-up of 37.6 months (range, 0.2-147.5 months), median progression-free survival (PFS) and overall survival (OS) were 21.6 and 64.7 months, respectively. After controlling for residual disease and stage, BMI was not associated with PFS (*P*=0.52) or OS (*P*=0.67). BMI was not associated with number of total (*P*=0.31), cytotoxic (*P*=0.30), or biologic (*P*=0.84) chemotherapy regimens.

Conclusions: Class II-III obesity appears to be correlated with non-HGS histology. While some authors have demonstrated a survival detriment with obesity, our data show similar PFS and OS. However, chemotherapy dosing patterns differed with respect to weight incorporation, enabling possible undertreatment of obese patients. The relationship between BMI and non-HGS histology warrants further study, as does the potential survival impact of chemotherapy dosing based on weight.

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Differential gene expression was associated with increasing body mass index (BMI) among endometrial cancers from The Cancer Genome Atlas (TCGA) Project

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Objectives: The metabolic consequences of obesity may be critical in the development of endometrial cancer (EC). Thus, we evaluated differences in the gene expression profiles of obese and nonobese women with EC and examined the association of BMI with the integrated clusters identified in the TCGA project.

Methods: RNAseq data from the TCGA project was used to identify genes related to increasing BMI among ECs. A generalized linear model was applied for the expected gene expression in terms of BMI and other covariates that captured potential confounding effects, and appropriate false discovery rates (FDR) were controlled. Endometroid histology ECs were analyzed, with exclusion of serous or mixed histology. Four integrated clusters were previously identified in the TCGA project for EC: POLE ultramutated (POLE), microsatellite instability hypermutated (MSI), copy-number low (CNL), and copy-number high (CNH). The POLE, MSI, and CNL clusters were composed mostly of endometrioid histology tumors. BMI was compared among these three clusters.

Results: A total of 181 genes were found to be significantly up- or downregulated with increasing BMI in endometroid histology tumors (q-value<0.01), including lipoprotein lipase, insulin receptor substrate 1, insulin-like growth factor binding protein 7, and the progesterone receptor. DAVID functional annotation analysis revealed significant enrichment in "cell cycle" (adjusted *P* value for Benjamini=1.5E-5) and "DNA metabolic processes" (adjusted *P* value for Benjamini=1E-3) for those identified genes. BMI was found to be statistically different between the ECs in the MSI (mean 33.0) vs CNL (mean 35.8) cluster (*P*=0.05) and the CNL vs POLE (mean 29.8) cluster (*P*=0.006). Women with POLE tumors had significantly better progression-free survival (PFS) than those with MSI and CNL tumors and had the lowest BMI.

Conclusions: Metabolically relevant alterations in gene expression were found with increasing BMI among endometrioid ECs. BMI correlated with survival of EC subtypes, with the leanest women found in the cluster with the best PFS (POLE). Further work will focus on the investigation of the identified obesity-dependent biomarkers and potential novel targets of treatment that may be specific to obesity-driven ECs.

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The use of technology-based weight loss intervention for endometrial cancer survivors with obesity

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Objectives: Presently, more than one third of women in the United State are obese (BMI ≥30). Obesity significantly increases the relative risk of the development of both endometrial hyperplasia and cancer. However, once diagnosed, quality of survivorship of obese women is worse than that for nonobese patients. Our objective was to assess the feasibility of technology-based weight loss interventions in this patient population.

Methods: Women age >18 years with obesity (BMI ≥30) and histologically confirmed endometrial hyperplasia or type I endometrial cancer were randomized 1:1 to a technology-based delivery of a 6-month weight loss and lifestyle intervention

via either telemedicine or text messaging. The interventions were adapted from standard behavioral weight loss interventions previously used in large efficacy studies. The telemedicine arm received weekly phone calls, with weights being graphed and viewed online using a Withings© Wi-Fi scale. The text arm received 3 to 5 personalized messages per day via the Text4Diet™program. All participants maintained a 1,500 kcal/day diet, self-monitored their food intake, and received exercise goals. Psychosocial domains, including changes in dietary intake, and cancer-associated biomarkers (insulin-like growth factor binding protein-1, adiponectin, vascular endothelial growth factor, interleukin [IL]1-beta, IL2, IL6, and IL7) were assessed pre- and posttreatment.

Results: Twenty women were randomized to the pilot intervention (Telemedicine: *n*=10, Text4Diet: *n*=10), and 90% of participants have successfully lost weight. The majority had early-stage (65%) and low-grade (43.8%) endometrioid endometrial cancer, with a median age of 60.5 years. We have observed a statistically greater weight loss in the Telemedicine arm, with a median loss of 21.3 lb (range 3.4-50.4 lb, *n*=9) compared to 8.6 lb (range 0.6-25 lb, *n*=9) in the Text4Diet arm (*P*=0.0231). Analysis of cancer-associated biomarkers and psychosocial outcomes are pending and will be completed in 8 weeks when the remaining 6 subjects complete the intervention.

Conclusions: A technology-based weight loss intervention appears to be feasible in women with type I endometrial cancer and endometrial hyperplasia. Our results warrant further study in a larger and more comprehensive confirmatory trial to test its impact on longer-term prevention of recurrence of endometrial cancer.

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Maximizing minimally invasive surgical approaches in the morbidly obese patient with newly diagnosed uterine cancer

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Objectives: To assess the impact of integrating the robotic platform on the rate of minimally invasive surgery (MIS) in morbidly obese patients with newly diagnosed uterine cancer.

Methods: We identified all patients with a body mass index (BMI) ≥40 who underwent primary surgery at our institution for newly diagnosed uterine cancer from 1993 to 2012 (inclusive). Surgical approaches were categorized as laparotomy (LAP), which included all planned LAPs and cases converted to LAP from a planned minimally invasive surgery (MIS); laparoscopic (LSC); robotic (RBT); or vaginal (VAG), which were only completed vaginally. MIS included LSC and RBT cases. We identified three time periods based on the evolving use of MIS at our institution: early LSC (1993-1999), when LSC was first introduced; late LSC (2000-2008), when a greater emphasis was placed on advancing LSC; and RBT (2008-2012), when a robotics program was developed. Appropriate statistical tests were used.

Results: Of 3,163 identified cases, 426 (13%) had a BMI ≥40. Surgery was performed via LAP in 299 cases and MIS was used in 125. Only 3 (0.7%) underwent a VAG approach. Due to Gynecologic Oncology Group (GOG) LAP2 participation, morbidly obese patients were not considered for MIS, and MIS rate analysis excludes cases from 2001 to 2005 (*n*=99) but not from the perioperative outcome analysis comparing LAP to MIS overall. The rates of MIS for the early LSC, late LSC, and RBT time periods were 6%, 10%, and 57%, respectively (*P*<0.001 for three-way comparison as well as for late LSC vs RBT). The rate of MIS in 2012 was 78% (35/45) in this morbidly obese cohort, 31 of which performed with RBT. The median length of hospital stay was 5 days (range, 2-37 days) for LAP cases compared to 1 day (range, 0-7 days) for MIS cases (*P*<0.001). The rate of any complication was 36% (LAP) vs 15% (MIS) (*P*<0.001). The rate of overall wound-related complications was 27% (LAP) vs 6% (MIS) (*P*<0.001). There were no wound breakdowns in the MIS group.

Conclusions: Dedicated efforts to optimize MIS with the incorporation of the robotic platform provide a significant benefit to morbidly obese patients with newly diagnosed uterine cancer. This may have significant positive cost implications in this cohort of high-risk surgical patients.

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Obesity is associated with worse quality of life in women with gynecologic malignancies: an opportunity for improving patient-centered outcomes

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Objectives: To evaluate the effect of obesity on preoperative quality of life (QoL) in a diverse cohort of gynecologic oncology patients.

Methods: We analyzed prospectively collected data from an institution-wide cohort study. Patients enrolled from August 2012 to June 2013 had medical records abstracted (demographics and comorbid conditions). Validated QoL tools, including Functional Assessment of Cancer Therapy-General (FACT-GP) and the newly developed National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS©) global mental (GMH) and physical health (GPH) tools, were administered. Survey results were linked to clinical data. Bivariate tests and multivariate linear regression models were used to evaluate factors associated with QoL scores.

Results: A total of 186 women with ovarian, uterine, cervical, and vulvar/vaginal cancers were identified, of whom 152 (82%) were assessed prior to surgical management. Mean body mass index (BMI) was 33.5 (range, 18-62), and self-reported race included white (120 [79%]), black (22 [14%]), and other races (7 [4.6%]). Ninety-eight (64.5%) patients were obese (BMI >30). Race, cancer site, and anxiety/depression/chronic pain did not differ by obesity classification. Obese patients were more likely to be younger (57.0 vs 62.2 years, P=0.02) and have major comorbidity (33.7% vs 18.5%, P=0.059) than the nonobese. Subscales for physical (20.8 vs 23.0, P=0.04), emotional (16.4 vs 18.9, P=0.01), and social (22.3 vs 24.2, P=0.007) well-being as well as overall FACT-GP scores (76.7 vs 85.2, P=0.002) and GPH (44.9 vs 49.3, P=0.003) were significantly lower in obese vs nonobese patients. These relationships persisted with obesity classified in tertiles (<30, 30-40, >40) and with BMI as a continuous variable. Regression analyses controlling for age and major comorbidity showed obesity associated with lower FACT-GP (-5.9, P=0.056) and GPH (-3.4, P=0.03) scores.

Conclusions: Prior to surgical management, obese gynecologic oncology patients have worse baseline QoL scores on both traditional FACT-GP and the PROMIS© Global scales, independent of other comorbidity. Emerging models of QoL-based cancer outcome measures will significantly affect populations with high obesity burden.

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Cervical cancer treatment and survivorship needs: the patient's perspective

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Objectives: Previous studies have investigated quality-of-life concerns of cervical cancer survivors, but few have reported on the changing needs over time of cervical cancer patients as they transition from treatment to survivorship.

Methods: A questionnaire adapted from the Mayo Clinic Cancer Center's "Cancer Survivors Survey of Needs" was developed to assess patient areas of concerns over time, including physical effects, personal relationships, and medical care access. Patients 18 to 75 years old, who were treated for cervical cancer at a university-affiliated public teaching hospital serving a >70% Latino population, were invited to participate in the survey at the following four time points: within 6 weeks of treatment completion, 6 weeks to 6 months posttreatment, 6 months to 2 years posttreatment, and 2 to 5 years posttreatment. Patients with recurrent disease were not eligible for survey participation.

Results: To date, 93 questionnaires have been completed by 70 patients. The current cross-section of participants was distributed nearly equally over the four time points. We report on the 33% of patients who were within 6 weeks of completing treatment (early survivors) and the 24% who were 2 to 5 years posttreatment (long-term survivors). The mean score averaged over the 34 topics was 1.49 for early survivors vs 1.76 for long-term survivors (P=0.10). Out of the 34 topics queried, the following had an average score of ≥2 in both early and long-term survivors: fatigue, sleep disturbance, financial concerns, and fear of recurrence. An additional nine topics had an average score of ≥2 in the long-term survivor cohort and an additional 2 topics in the early survivor cohort (Table).

Conclusions: This is one of the first studies to document differences in concerns among early vs long-term survivors of cervical cancer. Understanding the changing needs of cancer survivors over time is critical for the successful development and implementation of cancer navigation and survivorship programs.

Changing Areas of Concern: measured on a scale ranging between 0 to 5 (0 = no concerns and 5 = extreme concerns)			
Topic	**Early Survivors** $\bar{x}$ (SD), n=31	**Long-term Survivors** $\bar{x}$ (SD), n=22	**P-value**
Dental Health	1.19 (1.78)	3.00 (1.85)	**<0.001**
Health Insurance	0.77 (1.45)	2.62 (2.38)	**0.001**
Genetic counseling	1.06 (1.73)	2.32 (2.25)	**0.03**
Bone health	1.10 (1.68)	2.14 (1.93)	**0.04**
Neuropathy	1.29 (1.72)	2.32 (1.99)	0.05
Bowel problems	1.34 (1.65)	2.36 (2.01)	0.05
Loss of strength	1.68 (1.80)	2.64 (1.94)	0.07
Concern regarding long-term effects of treatment	2.16 (1.81)	1.25 (2.05)	0.10
Finding support resources	1.29 (1.85)	2.05 (2.24)	0.18
Returning to work	2.29 (2.36)	1.55 (2.18)	0.29
Balance/walking	1.81 (1.74)	2.14 (1.88)	0.51

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A prospective study of the preferences of women with ovarian cancer

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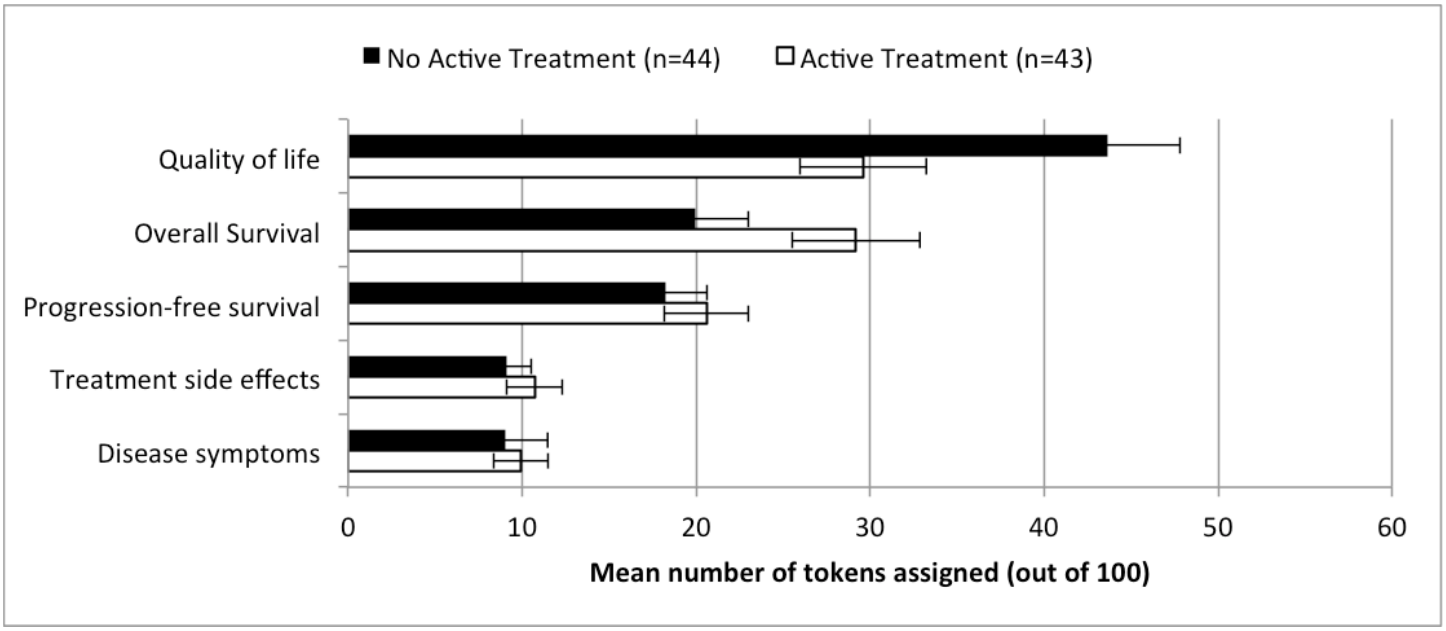
Objectives: To evaluate preferences among women with epithelial ovarian cancer (EOC) for specific outcomes in the context of chemotherapy treatment.

Methods: Eighty-nine women with advanced EOC were enrolled in a prospective study of preferences for five attributes of EOC and its treatment: quality of life (QOL), adverse effects of treatment, symptoms of ovarian cancer, progression-free survival (PFS), and overall survival (OS). Subjects indicated their relative concern about each attribute using Likert scales, ranking, and allocating 100 "tokens." In a fixed-choice scenario, two treatments were described: standard intravenous (IV) chemotherapy (every 3 weeks for 18 weeks, no change in blood pressure, 1% risk of bowel leakage, PFS 22 months) and standard IV chemotherapy plus concurrent and maintenance "medication" (representing an antiangiogenic agent every 3 weeks with chemotherapy for 18 weeks, then every 3 weeks for 9 months; hypertension requiring a new medication; 3% risk of bowel leakage; PFS 24 months). Results were analyzed for the entire cohort and by each subject's clinical and treatment status.

Results: The current status of 87 subjects was: on initial chemotherapy (n=18), on chemotherapy for recurrence (n=25), not on active treatment/never recurred (n=27), not on active treatment/previously recurred (n=17). The relative rankings of the five attributes were: 1. QOL, 2. OS, 3. PFS, 4. adverse effects of treatment, 5. symptoms of disease. On average, women on chemotherapy assigned fewer tokens to QOL (30 vs 44, P=0.01) and more tokens to OS (29 vs 20, P=0.06) than women not on chemotherapy (Figure). Women without recurrence had lower concern about adverse effects of treatment than women who had ever recurred (Likert scores 2.56 vs 3.40, P<0.01). In the fixed-choice scenario, 64/87 (74%) subjects chose standard chemotherapy over standard therapy+maintenance; this preference did not differ by active treatment status (P=0.51) or recurrence status (P=0.65).

Conclusions: QOL is the most important consideration to women with ovarian cancer but is of relatively lower concern to women currently on active treatment. When presented with schedules, adverse event profiles, and PFS associated with each regimen, 75% of women with ovarian cancer prefer a standard chemotherapy regimen without prolonged maintenance therapy.



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127 - Featured Poster

Predicting 6- and 12-month risk of mortality in patients with platinum-resistant advanced-stage ovarian cancer: toward development of a nomogram to guide palliative referrals

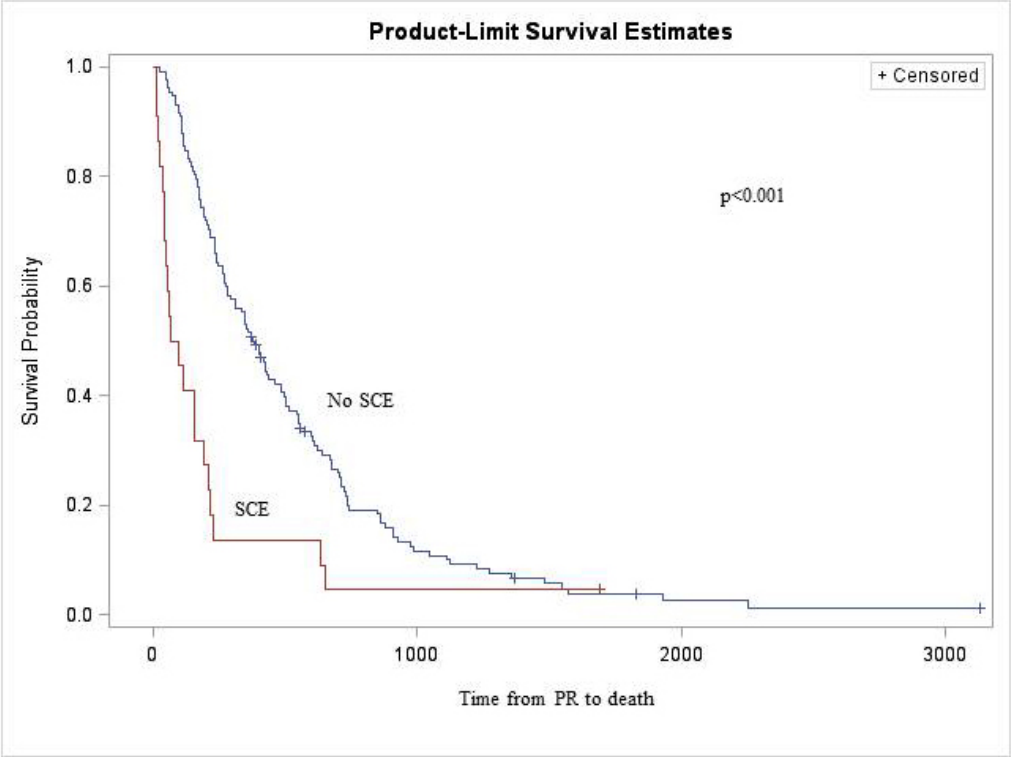
M. Lopez-Acevedo, G. Samsa, P. S. Lee and L. J. Havrilesky
Duke University Medical Center, Durham, NC

Objectives: To develop a predictive model to identify a group of patients with recurrent or progressive ovarian cancer and a prognosis of <6 to 12 months who might benefit from immediate referral to hospice or palliative care.

Methods: We retrospectively identified patients with advanced-stage epithelial ovarian cancer who had platinum-resistant disease (PR) and were treated at our institution between 2000 and 2011. PR was defined by the time of the most recent recurrence or progression: <6 months from the last platinum-containing regimen. Survival was defined as time from development of PR disease to death. A backward stepwise logistic regression was used to develop the predictive model. Eight previously studied clinical and pathologic factors (age, stage, hemoglobin, platelets, albumin, time from diagnosis to PR, comorbidity score, debulking status) were included as candidate predictors as well as the presence of a significant clinical event (SCE), which was defined as a malignant bowel obstruction, pleural effusion, or ascites occurring on or before the first date of developing PR disease and after initial diagnosis. To avoid including marginally important predictors, a *P* value of <0.005 was required for inclusion in the final model.

Results: A total of 154 patients with platinum-resistant advanced-stage epithelial ovarian cancer were identified. After diagnosis of PR, 106/154 (69%) survived <6 months and 71/154 (46%) survived <12 months. Although various predictors were statistically significant ($P<0.05$) when considered in isolation, in multivariate analysis, only SCE was retained. Only 32% of patients with an SCE survived 180 days in comparison with 75% of patients without an SCE; for 365-day survival, the corresponding figures were 14% with SCE and 52% without SCE.

Conclusions: In this predictive model, the occurrence of a SCE was the strongest predictor of death within 6 and 12 months of platinum-resistant disease. Patients who develop platinum-resistant ovarian cancer and who have suffered from bowel obstruction, pleural effusion, or ascites should be considered for immediate referral to palliative or hospice care.



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Clinical triggers for inpatient palliative care consultation in gynecologic oncology: a needs assessment

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Objectives: (1) To create consensus-based clinical triggers for inpatient palliative care (PC) consultation for a gynecologic oncology service and (2) to perform a needs assessment of the potential impact of implementing the triggers.

Methods: Based on literature review, collaboration between gynecologic oncology and PC faculty and the American Society of Clinical Oncology (ASCO) recommendation to consider early PC integration for “any patient with metastatic cancer and/or high symptom burden,” we identified four triggers for inpatient PC consultation. All admissions to the gynecologic oncology service between February and August 2012 were identified. Demographics, clinical information, and presence of PC consultation triggers were extracted from the medical record. Descriptive statistics were used to characterize admissions meeting PC triggers, Student’s t-test to compare continuous variables, and chi-square test or Fisher’s exact test to compare categorical variables.

Results: Our triggers for inpatient PC are (1) admission primarily for symptom management, (2) stage IV disease, (3) pelvic exenteration, and (4) malignant bowel obstruction. A total of 340 unique patients admitted with gynecologic cancer were identified, of which 76 (22%) had at least one admission meeting a trigger. Patients meeting triggers were significantly more likely to have ovarian cancer (59% vs 30%, $P<0.001$), recurrent disease (51% vs 15%, $P<0.001$), at least one nonelective readmission within 30 days (excluding postoperative complications) (17% vs 8%, $P=0.025$), and death within 6 months of last admission (39% vs 13%, $P<0.001$). Over the same time period, these patients had 614 admissions, of which 98 (16%) met at least one trigger. Of admissions meeting triggers, 61.2% were referred to PC, mean length of stay (LOS) was 5.69 days (mean LOS all admissions during that time period: 3.93 days), and mean time from admission to PC consultation was 1.6 days. See Table 1 for data by trigger.

Conclusions: The creation of consensus-based clinical triggers for inpatient PC is a feasible approach to standardizing PC referral. Patients meeting our triggers represent a group appropriate for PC consultation per ASCO recommendations. Almost 40% of the admissions meeting triggers did not have PC referral, leaving room for improvement with implementation of the triggers.

Table 1: Admissions meeting palliative care consultation triggers

Trigger	Number of admissions meeting trigger*	% seen by palliative care	Mean Length of Stay	Mean time admission to PC consultation (days)	% dying within 6 months	% dying within 3 months
Admission for symptom management	54	74.1%	4.7	1.6	38.9	31.5
Stage IV disease	50	30.0%	5.0	1.6	28.0	24.0
Malignant bowel obstruction	14	57.1%	9.1	2.6	42.9	42.9
Pelvic exenteration	7	71.4%	12.4	0.8	28.6	28.6

*Numbers will not add up to total number of admissions meeting at least one trigger (n=98) because one admission can meet more than one trigger

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Assessment of palliative care training in gynecologic oncology: a Gynecologic Oncology Fellows Research Network study

R. Eskander[1], K. Osann[2], E. L. Dickson[3], L. L. Holman[4], J. A. Rauh-Hain[5], L. A. Spoozak[6], E. Wu[7], A. Nickles Fader[8] and K. S. Tewari[2]
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Objectives: To assess the quality and quantity of palliative care education/training in gynecologic oncology fellowship programs.

Methods: A self-administered, 103-item online questionnaire, adapted from prior hematology/oncology research, was distributed to current gynecologic oncology fellow and candidate members of the Society of Gynecologic Oncology (SGO) during the 2013 academic year. It focused on eight domains in end-of-life (EOL) training. Descriptive statistics and bivariate and multivariate analyses were performed.

Results: Of 201 fellow and candidate members who received the survey, 74.1% (*n*=149) responded. Respondents were primarily women (75%) and white (76%). Only 11% of respondents participated in a palliative care rotation, while 91% reported exposure to a palliative care specialty service during training. Respondents rated the overall quality of teaching received on management of ovarian cancer significantly higher than management of patients at EOL, independent of level of training (8.25 vs 6.23 on a 1-10 scale; $P<0.0005$). Notably, 46% reported never being observed discussing transition of care from curative to palliative with a patient, and 56% never received feedback about technique regarding discussions on EOL care. When asked to recall their most recent patient who had died, 80% reported enrollment in hospice, with 83% of referrals occurring within 4 weeks of death. Those fellows reporting higher-quality EOL education were significantly more likely to feel prepared to care for patients at EOL and address complications of end-stage disease ($P<0.0005$). Lastly, mean ranking of preparedness increased significantly with the number of times a fellow reported discussing changing goals from curative to palliative and the number of times he/she received feedback from an attending ($P<0.0005$).

Conclusions: Gynecologic oncology fellows and candidate members reported insufficient palliative care education during fellowship training. Those respondents reporting higher-quality EOL training felt significantly more prepared to care for dying patients and to address complications commonly encountered in this setting. Incorporation of a comprehensive palliative care curriculum in fellowship may better equip trainees to handle EOL care.

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130 - Featured Poster

Too much, too late: aggressive measures and the timing of end-of life care discussions in women with gynecologic malignancies

M. Zakhour[1], L. Labrant[1], B. J. Rimel[1], C. Walsh[1], A. J. Li[1], B. Y. Karlan[2] and I. Cass[1]
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Objectives: To describe the timing of end-of-life (EOL) discussions and the use of aggressive measures in women who died of progressive gynecologic malignancies at a single institution.

Methods: An institutional review board-approved retrospective chart review identified 136 patients who died of gynecologic cancer between 2010 and 2012 with ≥1 documented interaction with their treating oncologist in the last 6 months of life. Aggressive measures were defined as chemotherapy within the last 14 days of life; emergency department (ED) visits, hospital, and intensive care unit (ICU) admissions within the last 30 days of life; and inpatient deaths. Utilization of hospice care and how often and where EOL conversations occurred as documented in the medical record from inpatient and outpatient encounters were recorded.

Results: Ninety-seven (71%) patients had a documented EOL conversation. Eighteen (19%) of these patients had this discussion as outpatients at a median of 22 days before death. Of the 79 who had an EOL conversation while inpatients, 27 (34%) died in hospital, with a median time to death of 9 days. Twelve (9%) patients died in the ICU. Two additional patients died in hospital without any documented EOL discussion. Thirteen patients (10%) had chemotherapy in the last 14 days of life. In the last 30 days of life, 54 (40%) were evaluated in the ED, 66 (49%) were admitted into hospital (median length of stay, 11 days), and 16 (12%) were admitted to the ICU (median length of stay, 8 days). At the time of death, 55 (40%) patients were enrolled in outpatient hospice care. The mean amount of time in hospice was 28 days, but half of the patients initiated hospice within the last 14 days of life.

Conclusions: Because EOL care discussions rarely occurred in the outpatient setting, an inpatient encounter became the trigger for a discussion of hospice and code status. Evaluation in the ED frequently resulted in escalation of care. Earlier EOL care discussions resulted in less aggressive measures. These data highlight the need for earlier EOL care discussions for women with progressive gynecologic cancers.

	EOL discussion >30 days before death (*n*=33)	No EOL discussion >30 days before death (*n*=103)	*P*
ED visit last 30 days	9 (27%)	45 (44%)	0.1
Inpatient last 30 days	9 (27%)	57 (55%)	0.005
Chemo last 14 days	0 (0%)	13 (13%)	0.04
Died in hospital	4 (12%)	25 (24%)	0.2
Received hospice care	21 (64%)	34 (33%)	0.002

Focused Plenary VI: Clinical Trials in Gynecologic Oncology: A Focus on Targeted Therapies
Monday, March 24, 2014
3:45 p.m. – 4:45 p.m., Ballroom B-C
Moderator: Robert Wenham, MD, MS, *H. Lee Moffitt Cancer Center, Tampa, FL*

131 - Focused Plenary

A phase I study of veliparib (ABT-888) in combination with carboplatin and gemcitabine in subjects with advanced ovarian cancer

H. J. Gray[1], M. Cristea[2], K. M. Bell-McGuinn[3], L. P. Martin[4], M. W. Dudley[5], W. P. Munasinghe[5], V. L. Giranda[5], Y. Luo[5], M. D. McKee[5] and G. Fleming[6]
[1]University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA, [2]City of Hope National Medical Center, Duarte, CA, [3]Memorial Sloan-Kettering Cancer Center, New York, NY, [4]Fox Chase Cancer Center, Philadelphia, PA, [5]AbbVie, Inc., North Chicago, IL, [6]University of Chicago Medical Center, Chicago, IL

Objectives: Veliparib (V) is an oral inhibitor of poly(ADP-ribose) polymerases (PARP)-1 and -2. V delays the repair of DNA damage induced by chemotherapeutic agents and increases the sensitivity of tumor cells to DNA-damaging agents in vitro. BRCA-deficient tumors are more sensitive to PARP inhibitors when used as monotherapy or in combination with DNA-damaging agents. Preclinically, V has demonstrated single-agent activity in BRCA-deficient tumor models and has shown robust potentiation of carboplatin (C), gemcitabine (G), and the combination of C/G. This study established the maximum

tolerated dose (MTD) for V in combination with C/G and evaluated safety and tolerability of combination therapy followed by maintenance V in a cohort of patients with advanced ovarian cancer.

Methods: Eligibility criteria included patients with metastatic or unresectable solid tumors for which C/G was a treatment option. During the study, eligibility was amended to limit prior chemotherapy regimens to ≤2 in the past 5 years. V was administered orally twice a day (BID) on days (D) 1-21, C AUC 4/G 800 mg/m^2 on D1, and G 800 mg/m^2 on D8 of a 21-day dosing cycle. Granulocyte colony-stimulating factor was permitted ad lib. When C/G was stopped, patients could receive V maintenance therapy until progression.

Results: A total of 62 patients (53 female, median age 52 years) were enrolled. Fifty-eight patients had prior chemotherapy (1-6 regimens, median 2), and 51 had prior platinum. Treatment cycles (range/ median) were 1-28/5 for V, 2-10/5 for C, and 2-10/4 for G, and 28 patients stayed on maintenance V (1-23 cycles). Ovarian cancer was the most common tumor type in patients receiving <MTD (n=30) and those receiving ≥MTD (n=9). Among ovarian cancer patients, all received prior platinum. Germline *BRCA* mutations were known in 24 ovarian cancer patients. At MTD, grade 3/4 adverse events seen in ≥2 patients were neutropenia and thrombocytopenia. Other frequent adverse events at MTD were nausea, constipation, diarrhea, fatigue, and vomiting. The preliminary efficacy for the ovarian cancer group is summarized in the Table.

Conclusions: V combined with C and G followed by V maintenance therapy was well-tolerated, with a safety profile similar to C and G alone. The MTD and recommended phase II dose was V 250 mg BID (D1-21) combined with C AUC 4.0 (D1) and G 800 mg/m^2 (D1, 8). Promising antitumor activity was observed in BRCA-deficient ovarian cancer patients.

Ovarian cancer subgroup (n=total pts)	PR / CR	Response rate (evaluable pts, %)	Median decrease tumor diameter (%)	Progression Free Survival (median [95% CI], mos.)
Dose < MTD (n=30)	10 / 2	52%	-65.5%	7.6 [5.2, 10.3]
Dose ≥ MTD (n=9)	3 / 0	38%	-60.7%	Not yet reached
gBRCA mutation (n=24)	10 / 1	58%	-64.6%	8.2 [5.2, 14.3]
gBRCA wildtype/unknown (n=15)	3 / 1	33%	-60.7%	5.9 [2.4, 10.0]

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132 - Focused Plenary

Analysis of intermediate clinical endpoints from a Phase II trial of olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC)

U. A. Matulonis[1], P. Harter[2], C. Gourley[3], M. Friedlander[4], I. B. Vergote[5], G. J. S. Rustin[6], A. Fielding[7], S. Spencer[7], T. W. Ho[8] and J. A. Ledermann[9]
[1]Dana-Farber Cancer Institute, Boston, MA, [2]Kliniken Essen-Mitte, Essen, Germany, [3]University of Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom, [4]Prince of Wales Hospital, Randwick, Australia, [5]University Hospital, Leuven, Leuven, Belgium, [6]Mount Vernon Hospital, Middlesex, United Kingdom, [7]AstraZeneca, Macclesfield, United Kingdom, [8]AstraZeneca, Wilmington, DE, [9]University College London, London, United Kingdom

Objectives: Previously we reported that maintenance treatment with the oral poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitor olaparib (400 mg BID) until Response Evaluation Criteria in Solid Tumors (RECIST) progression led to a significant progression-free survival (PFS) improvement vs placebo in patients with PSR SOC (HR=0.35, 95% CI 0.25–0.49, P<0.00001; Ledermann et al. *NEJM.* 2012), with the greatest clinical benefit observed in patients with a *BRCA1/2* mutation (BRCAm) (HR=0.18, 95% CI 0.11–0.31, P<0.00001; Ledermann et al. ASCO. 2013). At an interim analysis of overall survival (OS; 58% maturity), no significant benefit was seen in either the overall population or in BRCAm patients. To determine whether the clinically meaningful PFS improvements persist with further follow-up, lead to a meaningful delay in chemotherapy, and are maintained beyond the first RECIST progression, we performed exploratory analyses of intermediate clinical endpoints (time to first subsequent therapy or death [TFST]; time to second subsequent therapy or death [TSST]) from this randomized, double-blind, phase II trial (NCT00753545).

Methods: Exploratory analyses were conducted at the time of the interim OS analysis (data cut-off [DCO]: 26 Nov 2012). Analyses were performed for the overall patient population and by *BRCA1/2* mutation status, which had been determined for 254/265 (95.8%) patients after retrospective testing of blood samples and archival tumor samples. Intermediate clinical endpoints were defined as the time from randomization to the relevant event or death.

Results: Results from the exploratory analyses are presented in the Table. At DCO, 84/136 patients (61.8%) in the olaparib arm and 107/129 (82.9%) in the placebo arm had received at least one subsequent therapy following progression; subsequent therapies included a PARP inhibitor in 16/129 patients (12.4%) in the placebo arm, potentially confounding the interim OS analysis.

Conclusions: In this phase II study, olaparib maintenance monotherapy delayed the time to first subsequent treatment compared with placebo, and the benefits of olaparib therapy persisted beyond the first RECIST progression. For both TFST and TSST, significant benefits in favor of olaparib were observed in the overall patient population and in both the BRCAm and BRCAwt subgroups. The benefits of olaparib treatment were greatest in the BRCAm subgroup.

	Overall population (n=265)		BRCAm (n=136)		BRCAwt (n=118)	
	Olaparib (n=136)	Placebo (n=129*)	Olaparib (n=74)	Placebo (n=62)	Olaparib (n=57)	Placebo (n=61)
TFST						
Events†	95	118	46	54	45	59
Median, months	13.4	6.7	15.6	6.2	12.9	6.9
HR (95% CI)	0.40 (0.30–0.52)		0.33 (0.22–0.50)		0.45 (0.30–0.67)	
P	<0.00001		<0.00001		0.00009	
TSST						
Events†	88	108	42	49	42	55
Median, months	19.1	14.8	23.8	15.2	17.1	14.7
HR (95% CI)	0.53 (0.40–0.71)		0.44 (0.29–0.67)		0.64 (0.42–0.96)	
P	0.00001		0.00013		0.033	
OS						
Events	77	77	37	34	36	41
Median, months	29.8	27.8	34.9	31.9	24.5	26.2
HR (95% CI)	0.88 (0.64–1.21)		0.73 (0.45–1.17)		0.99 (0.63–1.55)	
P	0.442		0.192		0.957	

BRCAwt, patients with no known BRCAm or a variant of unknown significance (a non-deleterious mutation)

*n=128 for analyses of TFST and TSST

†Includes deaths

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133 - Focused Plenary

Results of Gynecologic Oncology Group (GOG) 229K: a phase II trial of BIBF-1120 for women with advanced, recurrent, or metastatic endometrial carcinoma

D. S. Dizon[1], M. Sill[2], J. M. Schilder[3], K. F. McGonigle[4], Z. Rahman[5], D. S. Miller[6], D. G. Mutch[7] and K. K. Leslie[8]
[1]Massachusetts General Hospital/Harvard University, Boston, MA, [2]Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY, [3]Indiana University School of Medicine, Indianapolis, IN, [4]Northwest Hospital & Medical Center, Women's Cancer Care of Seattle, Seattle, WA, [5]St. Francis Hospital and Medical Center, Hartford, CT, [6]University of Texas Southwestern Medical Center, Dallas, TX, [7]Washington University School of Medicine, St. Louis, MO, [8]University of Iowa Hospitals and Clinics, Iowa City, IA

Objectives: Patients who present with advanced, recurrent, or metastatic endometrial cancer have limited treatment options, which highlights the critical need to evaluate new therapies. Because of the proven activity of other angiogenesis inhibitors in gynecologic cancers (e.g., bevacizumab and aflibercept), we conducted this phase II trial of BIBF 1120, a potent

small-molecule triple-receptor tyrosine kinase inhibitor of platelet-derived growth factor receptor a and b, fibroblast growth factor receptor 1/3, and vascular endothelial growth factor receptor 1-3, in this population. The objectives were to: estimate progression-free survival (PFS) for at least 6 months, estimate the proportion of patients who have objective tumor response (complete or partial), and determine the nature and degree of toxicity. Estimates of PFS and overall (OS) survival were secondary objectives.

Methods: This was a 2-stage, single-arm phase II study. Eligible patients were treated with single-agent BIBF-1120 at a dose of 200 mg twice a day. All patients were required to have at least one target lesion for determination of response using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. All patients required informed consent before treatment, and all institutions obtained institutional review board approval before enrolling patients.

Results: Of 37 patients enrolled, 32 were evaluable. There were zero complete and three partial responses for an overall response rate of 9.4% (90% 2-sided CI 2.6 ~ 22.5%). Seven patients (21.9%; 90% 2-sided CI 10.7 ~ 37.2%) were progression-free for at least 6 months, with two patients continuing on study at the time of this abstract. Serious toxicity included the following grade 3 events: gastrointestinal toxicity (5), neutropenia (1), edema (1), hypertension (1), and liver function abnormalities (3).

Conclusions: BIBF-1120 lacked sufficient activity as a single agent to warrant enrollment to the second stage. However, preclinical data indicate it may be synergistic with paclitaxel in a population of patients enriched for specific p53 mutations that result in a loss of function. Therefore, we propose that further evaluation of BIBF-1120 is warranted, preferably in a randomized phase II design enriched for patients with a high likelihood of p53 mutations.

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134 - Focused Plenary

Outpatient treatment of malignant ascites in patients with advanced gynecologic carcinomas: a single-institution experience with intraperitoneal application of the trifunctional monoclonal antibody catumaxomab

C. M. Kurbacher, O. Horn, J. Lepique, C. Schweitzer, S. Herz and J. A. Kurbacher
Gynecological Center Bonn-Friedensplatz, Bonn, Germany

Objectives: Catumaxomab (CATU) is a trifunctional monoclonal antibody approved in the European community for the treatment (Tx) of malignant ascites related to carcinomas expressing epithelial cell adhesion molecule (EpCAM). Recently, most CATU Tx is performed in a hospital. We report on our single-institution experience with an outpatient CATU Tx in patients who have peritoneal carcinomatosis due to various gynecologic carcinomas.

Methods: A total of 26 patients with advanced gynecologic tumors were included in this retrospective analysis: epithelial ovarian cancer (13), metastatic breast cancer (6), endometrial cancer (3), other (4). Patients had failed a median of four prior systemic Tx (range: 1-12). Before starting CATU, EpCAM positivity was confirmed by immunohistochemistry. CATU was administered via an intraperitoneal (IP) catheter system, with four planned increasing doses (i.e., 10, 20, 50, and 100 µg) given at 4-day intervals over an every 2 weeks treatment period. Supportive Tx comprised metamizole (1 g/day) and granisetrone (3 mg/day). Adverse effects were scored according to the CTCAE 4.0 scale. Puncture-free survival (PuFS) was calculated from start of CATU to the next puncture due to malignant ascites, death, or loss to follow-up. Overall survival (OS) was calculated from start of CATU to death from any reason or loss to follow-up.

Results: CATU was completely administered in an outpatient setting to all patients. Seventeen patients (65.4%) received all four planned applications; another four patients (15.4%) received three instillations. Outpatient Tx with CATU was generally well tolerated. Secondary hospitalization (fever [1], abdominal pain/subileus [1], infection [1], generally deteriorated condition [5]) was necessary in seven patients (26.9%). Subsequent punctures following CATU were necessary in only five patients (19.2%). Median PuFS was 97 days and median OS was 109 days. Eleven patients (42.3%) were able to undergo subsequent systemic Tx (1-3 protocols) after IP CATU. Seven patients are still alive and free from subsequent punctures after a maximum of 812 days from start of CATU.

Conclusions: Outpatient IP CATU treatment of malignant ascites in selected patients suffering from various EpCAM-positive gynecologic malignancies is feasible and effective. Moreover, CATU allows for subsequent antineoplastic Tx in a substantial proportion of patients.

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135 - Focused Plenary

R-ketorolac as a GTPase inhibitor: phase 0 intraperitoneal pharmacokinetic and biologic activity in ovarian cancer patients

C. Muller, L. G. Hudson, S. R. Kenney, Y. Guo, M. Gaede, S. F. Adams, T. Rutledge and A. Wandinger-Ness
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Objectives: GTPases Rac1 and Cdc42, which regulate cell adhesion and migration, are constitutively active and overexpressed in ovarian cancer. A high throughput screen and cheminformatics identified the R- enantiomer of select nonsteroidal anti-inflammatory drugs as inhibitors of Rac1/Cdc42, which was confirmed in cell-based assays and in vivo xenograft models. Using R/S-ketorolac for postoperative pain management, we assessed the pharmacokinetic distribution of the ketorolac racemates in the peritoneal cavity and posttreatment GTPase inhibitory effects on ovarian cancer cells retrieved from the postoperative peritoneal cavity and peritoneal fluid cytokines.

Methods: Eligible patients for this "phase 0" study had suspected advanced-stage ovarian, fallopian tube, or primary peritoneal cancer with planned optimal cytoreductive efforts. Ascites was obtained for biologic studies. Secondary eligibility was met if "ovarian cancer" was confirmed, an intraperitoneal (IP) port was placed, there was no active bleeding or therapeutic anticoagulation, and there was good postoperative organ function. The recommended dose of intravenous ketorolac was administered. Blood and peritoneal fluid were obtained at T=0, 1 hour, 6 hours, and 24 hours. R- and S-ketorolac concentrations in serum and peritoneal fluid were measured by high-performance liquid chromatography. GTPase inhibitory activity was measured in peritoneal tumor cells, and ascites cytokines were profiled.

Results: To date, 26 women met first eligibility. Eight (30.7%) patients met secondary criteria and received ketorolac. Eighteen patients (69.2%) failed secondary eligibility due to other or noncancer (n=10), suboptimal debulking, no ascites or no IP port (n=4), postoperative clinical ineligibility (n=2), no surgery (n=1), or withdrawn consent (n=1). R-ketorolac peaked in the peritoneal cavity at 6 hours compared to serum at 1 hours and was enriched compared to the S-enantiomer. Postoperative ketorolac treatment inhibited GTPase activity in retrieved ovarian cancer cells and decreased proinflammatory cytokines (interleukin-6 and -10) in peritoneal fluid.

Conclusions: R-ketorolac has favorable distribution in the peritoneal cavity. GTPase inhibition is seen after peak peritoneal R-ketorolac in postoperative patients and may inhibit cytokines. The postoperative accessed IP compartment is a valid system to study biologic effects of select drug targets in ovarian cancer.

Scientific Plenary VII: Ovarian Cancer Clinical Trials: Endpoint Validation and Practice-Changing Results
Tuesday, March 25, 2014
7:30 a.m. – 9:00 a.m., Ballroom B-C
Moderator: Robert Burger, MD, *University of Pennsylvania, Philadelphia, PA*

136 - Scientific Plenary

A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline *BRCA1* or *BRCA2* mutation – a Gynecologic Oncology Group study

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Objectives: Veliparib is a potent small-molecule inhibitor of poly ADP (adenosine diphosphate)-ribose polymerase (PARP)-1 and PARP-2 that is cytotoxic in tumor cells with deficiencies in homologous recombination, particularly those that have mutation in *BRCA1* or *BRCA2*. We sought to estimate the clinical activity (proportion with tumor response [RR]) and toxicity of single-agent veliparib in women carrying a germline mutation in *BRCA1* or *BRCA2*.

Methods: Women with recurrent or persistent epithelial ovarian, peritoneal, or fallopian tube cancer were eligible for participation if they carried a germline mutation in *BRCA1* or *BRCA2* and had measurable disease. Up to three prior regimens were allowed, but prior use of a PARP inhibitor was an exclusion. Veliparib was administered at 400 mg po BID with up to two dose level reductions for toxicity. One cycle was 28 days. The two-stage trial design was capable of detecting a 25% RR with 90% power while controlling alpha=10% (at a 10% assumed null RR). With a sample size of 50 patients, eight or more patients with response were sufficient to declare the regimen clinically interesting.

Results: Of 52 enrolled patients, two were ineligible because of clerical error (1) and inadequate pathology (1). The median age was 57 years (range, 37–94 years). There were 14, 18, and 18 patients with 1, 2, and 3 prior therapies, respectively. Thirty patients were platinum-resistant and 20 were platinum-sensitive. The median number of cycles administered was 5.5 (range, 1-16). There was one grade 4 thrombocytopenia. Grade 3 adverse events were: fatigue (*n*=3), nausea (2), leukopenia (1), neutropenia (1), dehydration (1) and ALT (1). Grade 2 events in >10% of patients were: nausea (46%), fatigue (26%), vomiting (16%), and anemia (14%). In total, 24 patients (48%) had dose reductions. The confirmed RR was 26% (90% CI: 16%-38%, complete response: 1, partial response: 12). RR in platinum-resistant and platinum-sensitive patients was 20% and 35%, respectively. The most common reason for treatment discontinuation was disease progression (46%). Eighteen patients are alive without progression; five with stable disease are taking study therapy. Median progression-free survival is 8.11 months (90% CI: 5.45-8.77). The proportion of patients event-free at 6 months was 44%. Median overall survival is inestimable at this time.

Conclusions: Veliparib is active among *BRCA*-positive women with measurable recurrent ovarian cancer and demonstrated sufficient clinical efficacy and tolerance to warrant further investigation.

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137 - Scientific Plenary

Final analysis of overall survival in OCEANS, a randomized phase III trial of gemcitabine, carboplatin, and bevacizumab followed by bevacizumab until disease progression in patients with platinum-sensitive recurrent ovarian cancer

C. Aghajanian[1], B. A. Goff[2], L. R. Nycum[3], Y. Wang[4], A. Husain[4] and S. V. Blank[5]
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Objectives: OCEANS met its primary endpoint, a statistically significant improvement in progression-free survival (PFS) with the addition of bevacizumab (BV) to gemcitabine/carboplatin (GC) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer (OC) (HR=0.484). Results from the final analysis of overall survival (OS) are presented here.

Methods: Patients had first recurrence of Plat-S OC, primary peritoneal cancer (PPC), or fallopian tube cancer (FTC), no prior BV, ECOG PS of 0 or 1, and measurable disease. Patients were randomized to arm A: GC (G [1,000 mg/m^2, days 1 and 8] and C [AUC 4, day 1], q 21 days for 6–10 cycles) + concurrent placebo (PL; q 21 days), followed by PL until disease progression (PD) or unacceptable toxicity or to arm B: GC + concurrent BV (15 mg/kg q 21 days), followed by BV until PD or unacceptable toxicity. The primary endpoint was investigator-assessed PFS by Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included objective response, OS, and safety.

Results: A total of 484 women (242/arm) were enrolled. At the time of the final OS analysis with 353 deaths (72.9% of patients; PL arm: 176; BV arm: 177), median follow-up was 57.5 months among all patients. Median OS in the PL arm was 32.9 months and in the BV arm was 33.6 months (HR: 0.952; 95% CI: 0.771–1.176). Data on subsequent anticancer therapy were also analyzed, with 91.3% of patients in the PL arm and 88.8% in the BV arm receiving subsequent anticancer therapy. Up to 14 lines of therapy were delivered to patients to date, including front-line and OCEANS regimens, with a median of five in both arms. Subsequent BV use was reported in 43.9% and 26.0% of patients who received any subsequent anticancer therapies in the PL and BV arms, respectively. Updated safety analyses revealed no change in safety results from prior reports.

Conclusions: In OCEANS, median OS in both arms was considerably longer than the 18 months predicted based on prior data and used for the study design. OS was similar between arms, with an HR of 0.952.

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138 - Scientific Plenary

Health-related quality-of-life analysis from the TRINOVA-1 study of weekly paclitaxel plus trebananib or placebo in women with recurrent ovarian cancer

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Objectives: In a randomized placebo-controlled phase III study (TRINOVA-1), trebananib plus weekly paclitaxel significantly improved progression-free survival (PFS) compared with weekly paclitaxel alone in patients with recurrent epithelial ovarian cancer (EOC). A secondary objective of TRINOVA-1 was to evaluate the impact of trebananib on patient-reported outcomes and ovarian cancer-specific symptoms.

Methods: Eligible women were ≥18 years with recurrent EOC and primary peritoneal or fallopian tube cancer. They had received one prior platinum-based regimen (platinum-free interval <12 months). Patients were randomized to paclitaxel 80 mg/m^2 intravenous (IV) every week (3 weeks on/1 week off) plus blinded trebananib 15 mg/kg IV every week or placebo IV every week. FACT-O and FACT-O ovarian cancer-specific subscale (OCS) questionnaires were completed at weeks 1, 5, 9, 13, 17, and every 8 weeks thereafter. Changes from baseline in instrument scores were summarized by time point. A pattern mixture model was used to evaluate drop-out patterns (early treatment [≤25 weeks] vs late treatment [>25 weeks]) in the change from baseline in FACT-O and OCS.

Results: A total of 919 patients were randomized (trebananib/placebo, *n*=461/458). In the FACT-O analysis set (trebananib/placebo, *n*=392/412), instrument completion rates at weeks 1, 9, 17, 25, and 97 were 100%/100%, 83%/83%, 65%/57%, 43%/35%, and 1%/0%, respectively; in the OCS analysis set (*n*=401/416), instrument completion rates were 100%/100%, 83%/84%, 65%/58%, 43%/36%, and 1%/0%, respectively. The results are summarized in the Table. Change from baseline in FACT-O and OCS scores was similar between treatment arms, with similar changes observed in individual subscale scores for FACT-O. Pattern mixture model estimates (least squares means estimate of the difference between treatment arms; a positive value favors the trebananib arm) indicated that the change in scores was similar between treatment arms for both instruments.

Conclusions: Trebananib added to weekly paclitaxel significantly prolonged PFS and did not improve or worsen patient-reported outcomes or ovarian cancer-specific symptoms.

	Trebananib 15 mg/kg QW + paclitaxel	Placebo + paclitaxel
Mean (±SD) change from baseline		
FACT-O		
Week 17	−2.4±17.0	−0.2±15.1
Week 25	−2.1±16.7	−1.6±14.2
OCS		
Week 17	−0.6±5.4	−0.4±5.1
Week 25	−0.7±5.4	−0.9±4.6
Pattern mixture model estimate (95% CI) of the treatment effect		
FACT-O		
Early drop-out	−2.4 (−4.6 to −0.3)	
Late drop-out	−1.7 (−5.3 to 2.0)	
OCS		
Early drop-out	−0.7 (−1.4 to 0.0)	
Late drop-out	0.2 (−1.0 to 1.3)	

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139 - Scientific Plenary

Health-related quality of life associated with every-3-week paclitaxel vs dose-dense weekly paclitaxel in combination with carboplatin with or without bevacizumab for primary ovarian cancer: Gynecologic Oncology Group study 262

B. J. Monk[1], H. Huang[2], R. T. Penson[3], S. A. Davidson[4], M. L. Pearl[5], D. M. O'Malley[6], D. P. Bender[7], M. P. Boente[8], L. P. Martin[9], J. K. Chan[10], J. L. Walker[11] and C. K. McCourt[12]
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Objectives: To compare health-related quality of life (HRQOL) associated with dose-dense weekly paclitaxel (ddT) compared to every-3-week paclitaxel in combination with carboplatin (q3T) with or without bevacizumab (bev).

Methods: Patients were randomly allocated to intravenous paclitaxel 175 mg/m² every 3 weeks + carboplatin (AUC=6) x 6 cycles or paclitaxel 80 mg/m² weekly + carboplatin (AUC=6) x 6 cycles and prospectively stratified by whether their treatment would include bev 15 mg/kg every 3 weeks followed by maintenance until progression. HRQOL was assessed with the FACT-O TOI, using a linear mixed model with adjustment for baseline score and age. Assessment time points were before

cycles 1, 4, 7, 13, and 22. Chemotherapy-induced peripheral neuropathy and abdominal discomfort were evaluated with the FACT/GOG-NTX short subscale and the FACT/GOG-Ad subscale. Hypotheses were tested at a significance level of 1.67% to account for multiple comparisons.

Results: We report HRQOL scores from 604 newly diagnosed, previously untreated patients who opted for cytoreductive surgery before initiating chemotherapy. The QOL surveys were completed by 96%, 91%, 87%, 82%, and 78% of surviving patients before cycles 1, 4, 7, 13, 22, respectively. After adjusting for baseline scores, patients receiving ddT reported decreased QOL (1.43 points lower; 98.33% CI: -0.87 ~3.72; *P*=0.14) over the duration of the study compared to those receiving q3T. The maximum decrease in FACT-O TOI scores was 2.7 points (98.33 CI: -0.27 ~5.56; *P*=0.028) after the completion of 6 cycles of chemotherapy. More than 80% of patients reported peripheral neuropathy. The neuropathy symptoms were worse among patients receiving ddT and persisted throughout the study period. Less abdominal discomfort was reported during and after chemotherapy by all patients and was not statistically different between the two arms. A post-hoc, hypothesis-generating analysis of HRQOL scores among the 16% of subjects not receiving bev will be presented.

Conclusions: Dose-dense weekly paclitaxel did not decrease the HRQL significantly compared to q3T. However, patients receiving ddT reported worse peripheral neuropathy compared to those receiving q3T.

Scientific Plenary IX: Multimodal Therapy and Predictors of Response
Tuesday, March 25, 2014
10:25 a.m. – 11:50 a.m., Ballroom B-C
Moderator: Anuja Jhingran, MD, *The University of Texas MD Anderson Medical Center, Houston, TX*

140 - Scientific Plenary

Concurrent chemoradiation with paclitaxel in high-risk endometrial cancer patients after surgery: a Korean Gynecologic Oncology Group study

S. M. Hwang, H. Cho, D. B. Chay, S. Kim and J. H. Kim
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Objectives: To evaluate the efficacy and toxicity of concurrent chemoradiation with weekly paclitaxel in patients with high-risk endometrial cancer.

Methods: A total of 47 patients aged 18 to 80 years with a histologic diagnosis of high-risk endometrial endometrioid carcinoma entered this phase II study. Inclusion criteria were stages IC G3, IIB, IIIA (patients with positive washing without other unfavourable prognostic factors were omitted), IIIB, and IIIC disease. The radiation therapy (RT) plan consisted of a total dose of 50.4 Gy, given in five fractions per week (1.8 Gy: daily dose) for 6 weeks. Paclitaxel (P) at a dose of 60 mg/m^2 was infused intravenously in 250 mL of normal saline for 1 hour once weekly during RT for 5 weeks. Three further cycles of paclitaxel at a dose of 80 mg/m^2 were given weekly at the end of RT.

Results: There was no life-threatening toxicity. The overall 5-year relapse-free survival was 81.8% (95% CI, 65.2–90.9). The 5-year overall disease-specific survival was 88.4% (95% CI, 71.1–95.6).

Conclusions: These results, based on a larger series, support our previous data that paclitaxel plus RT may represent an effective and well-tolerated treatment for high-risk endometrial cancer patients.

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141 - Scientific Plenary

Multimodal therapy improves progression-free survival in patients with stage I-III uterine carcinosarcoma: a multi-institutional study

E. L. Dickson[1], R. Isaksson Vogel[1], P. A. Gehrig[2], S. R. Pierce[2], L. J. Havrilesky[3], A. A. Secord[3], J. Dottino[3], A. Nickles Fader[4], S. Ricci[4] and M. A. Geller[1]
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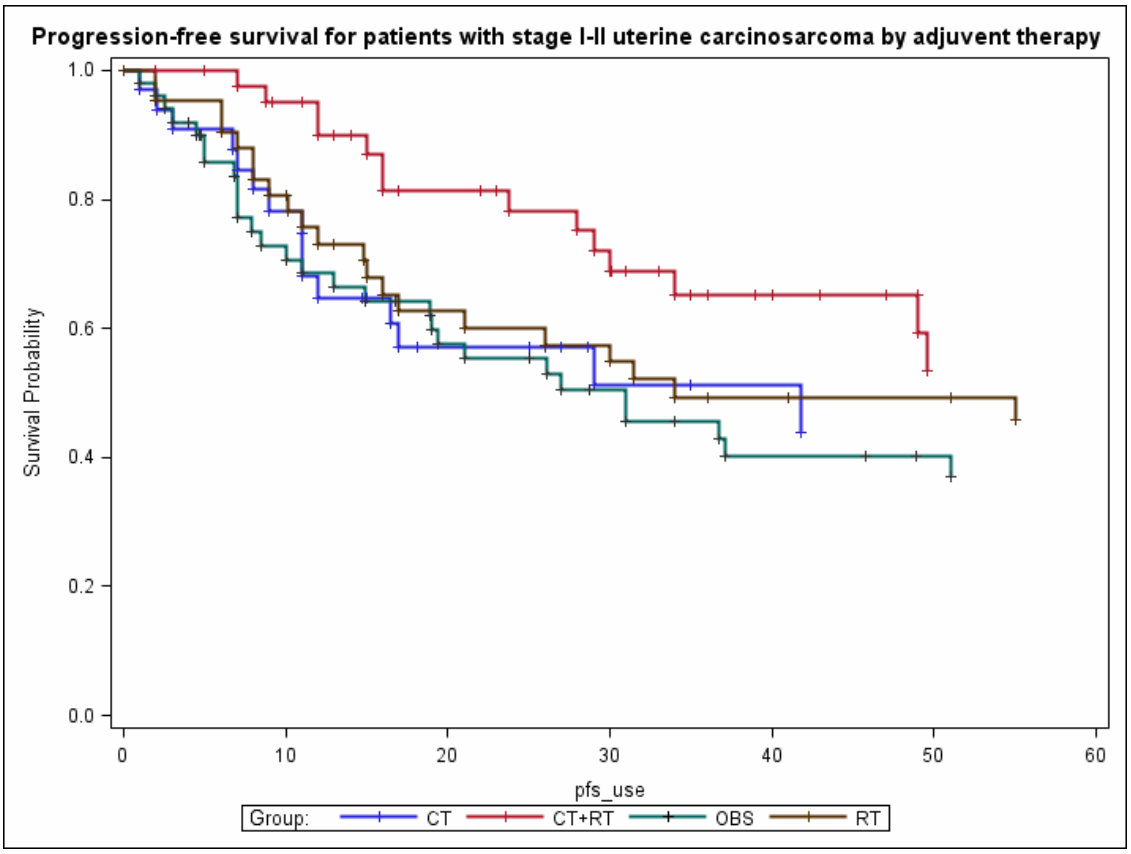
Objectives: To evaluate the impact of adjuvant therapy received after primary surgery for stage I-III uterine carcinosarcoma (CS).

Methods: A multicenter retrospective study of women with stage I-III uterine CS diagnosed from January 1, 1997 to December 31, 2012 was conducted. Analyses were grouped by stage (I/II and III). Data collected included demographics, pathology, adjuvant therapy, and outcomes. Patients were categorized according to adjuvant therapy received: observation (OBS), radiation (RT) alone, chemotherapy (CT) alone, or multimodal therapy (CT + RT). Overall survival (OS) and progression-free survival (PFS) were calculated from date of diagnosis to event or censored at last follow-up. Kaplan Meier methods and log-rank tests compared OS and PFS by therapy type. Multivariate Cox proportional hazards models included potential confounders: clinic site, cancer history, residual disease, lymphovascular space involvement, stage, age at diagnosis, parity, and year of diagnosis.

Results: A total of 274 patients were identified: 173 with stage I/II and 101 with stage III disease. Among those with stage I/II disease, 50 (30%) received OBS, 33 (20%) CT, 42 (25%) RT, and 43 (26%) CT+RT. Treatment was borderline statistically significantly associated with OS and PFS (Figure 1) in those with stage I/II disease; these associations became statistically significant after adjustment (P=0.011 and 0.036, respectively). OBS was associated with significantly lower OS. Patients receiving CT+RT had significantly improved PFS compared to those receiving CT (HR 0.36; P=0.012). Among patients with stage III disease, 10 (10%) received OBS, 34 (34%) CT, 21 (21%) RT, and 35 (35%) CT+RT. Treatment was statistically significantly associated with OS and PFS before and after adjustment (adjusted P=0.003 and 0.002, respectively). OBS was associated with significantly lower OS and PFS. Evidence suggested that receiving CT+RT was associated with improved OS and PFS compared to receiving CT (HR 0.50; P=0.107 and HR 0.58; P=0.164, respectively), although these associations are not statistically significant.

Conclusions: Multimodality therapy for women with stage I/II uterine CS is associated with improved PFS and may improve OS and PFS in those with stage III uterine CS. A clinical trial in this population is warranted to evaluate these results further.



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142 - Scientific Plenary

A cost-effectiveness analysis of four chemotherapy regimens used in the treatment of platinum-sensitive recurrent epithelial ovarian carcinoma

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[3]University of Miami, Miami, FL, [4]University of Miami Miller School of Medicine, Miami, FL, [5]South Miami Gynecologic Oncology Group, Miami, FL, [6]Zilonis Health, Inc., Miami, FL

Objectives: Compare the cost-effectiveness of four current chemotherapy treatments for platinum-sensitive recurrent epithelial ovarian carcinoma (EOC).

Methods: A Markov transition model was constructed using a hypothetical cohort of 500 women (median age, 60 years) to compare four National Comprehensive Cancer Network-recommended treatment regimens for platinum-sensitive recurrent EOC: carboplatin/paclitaxel (C/P), carboplatin/gemcitabine (C/G), C/G with bevacizumab (C/G+B), and carboplatin/pegylated liposomal doxorubicin (C/PLD). These treatments were chosen because each is supported by phase III trials. An indirect treatment comparison methodology was used to obtain useful evidence of the difference in treatment effects of each regimen. Progression-free survival (PFS) and overall survival (OS) data were used for survival comparisons. The time horizon of the model was 30 years. Cost calculations were based on data from Medicare and published literature and on median cycle number from each trial. Published values of health utilities for each of the states were used for quality-life year (QALY) calculations. Cost-effectiveness ratios were calculated for each regimen and expressed as three incremental cost-effectiveness ratios (ICER): ICER per month PFS, ICER per month OS, and ICER per QALY. Reported rates of grade 3/4 toxicities from each trial were added to the cost of each treatment. Cost, survival, and toxicity rate were varied over a range for sensitivity analysis.

Results: G/C was the most cost-effective regimen. The cost for treating one woman with 6 cycles of G/C ranged from $1,140 with no toxicity to $7,030 with toxicities at the reported rate. Treatment with G/C produced a dominant ICER of $236,318 per month PFS. Dominant ICER means the treatment is both less expensive and more effective. For each PFS month gained over the next most cost-effective option, >$200,000 was saved. G/C was also the dominant strategy for OS, with an ICER of $72,213 per month OS. When adjusted for health utility, G/C was again the dominant strategy, resulting in an ICER of $20,443 per QALY.

Conclusions: G/C was the most cost-effective regimen in this model, resulting in a dominant ICER for PFS, OS, and QALY. G/C resulted in a savings of >$20,000 per QALY saved compared to the next most cost-effective regimen. C/PLD and C/G+B were not cost-effective in this model.

Table 1. Costs for each additional quality life year gained

TREATMENT	QALY GAINED (in months)	COST (in $)	CER ($/QALY)	ICER (in $)
Carbo/Gem/Bev	42.688	20,172,078.30	472,543	1,358,594
Carbo/PLD	33.896	8,227,231.34	242,718	714,217
Carbo/Taxol	30.685	5,933,322	193,365	20,443
Carbo/Gem	39.932	5,744,267	143,849	**-(20,443)***

CER, cost effectiveness ratio; QALY, quality life year; ICER, incremental cost effectiveness ratio
*** Negative value denotes savings**

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143 - Scientific Plenary

Prospective validation of pooled clinical prognostic factors in patients with recurrent and advanced cervical cancer: a Gynecologic Oncology Group (GOG) study

K. S. Tewari[1], M. Sill[2], B. J. Monk[3], H. J. Long[4], R. T. Penson[5], H. Huang[2], L. M. Landrum[6], A. Oaknin[7], H. Michael[8], D. H. Moore[9], M. M. Leitao[10], L. M. Ramondetta[11] and T. J. Reid[12]
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Objectives: In GOG 240, the incorporation of bevacizumab significantly increased overall survival (OS). In this study, we also reported that the topotecan-paclitaxel (TP) backbone was found to be neither superior nor inferior to cisplatin-paclitaxel (CP) for efficacy. The National Comprehensive Cancer Network recently listed the cisplatin-paclitaxel-bevacizumab triplet for cervix cancer. A principal objective of GOG 240 was to prospectively validate previously identified pooled clinical prognostic factors (Moore criteria) and use them to study the chemotherapy backbones.

Methods: Potential negative prognostic factors included black race, performance status (PS) 1, measureable disease in the pelvis, prior cisplatin, and progression-free interval <365 days. Risk scores were assigned as follows: low risk (1 factor), intermediate risk (2 factors), high risk (>3 factors). Each test of association with response, progression-free survival, and OS was conducted at the 5% level of significance. Logistic regression and survival analysis were used to determine whether the factors were prognostic or could be used to guide therapy (i.e., CP or TP backbone).

Results: For the entire study cohort (*n*=452), black race, PS, prior cisplatin, and the score were significantly associated with response. For those treated with the CP backbone, response was significantly associated with PS, prior cisplatin, and score. For those treated with the TP backbone, only prior cisplatin affected response significantly. Response for low-risk group was 67% (CP) vs 46% (TP); for the intermediate-risk group, 48% (CP) vs 38% (TP); for the high-risk group, 16% (CP) vs 21% (TP). Median OS for low risk was 26 months (CP) vs 20 months (TP); for high risk, median OS was essentially the same (8.21 vs 8.25 months). The estimated HRs for death were 1.18 (low), 1.11 (intermediate), and 0.84 (high).

Conclusions: The Moore criteria have been prospectively validated in this population, but the risk score is not useful in selecting the chemotherapy backbone to use. The TP backbone could be more desirable among those with higher-risk scores, but these results are not significant, and any OS benefit from TP in high-risk patients is likely to be modest (e.g., HR=0.84). It is now important to determine if these criteria can identify a high-risk cohort unlikely to benefit from antiangiogenesis therapy.

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144 - Scientific Plenary

High-risk patients with recurrent/advanced cervical cancer may derive the most benefit from antiangiogenesis therapy: a Gynecologic Oncology Group (GOG) study

K. S. Tewari[1], M. Sill[2], D. H. Moore[3], H. J. Long[4], R. T. Penson[5], H. Huang[2], L. M. Landrum[6], A. Oaknin[7], H. Michael[8], B. J. Monk[9], L. M. Ramondetta[10], T. J. Reid[11] and M. M. Leitao[12]
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Objectives: Vascular endothelial growth factor (VEGF) has emerged as an important therapeutic target in advanced cervical cancer. GOG 240 met one of its primary endpoints with the regimens administering the anti-VEGF monoclonal antibody bevacizumab (B), which was associated with significantly improved overall survival (OS). A prospective objective of GOG 240 was to study antiangiogenesis therapy in different risk cohorts using validated prognostic markers known as the Moore criteria.

Methods: Negative prognostic factors included black race, performance status (PS) 1, measureable disease in the pelvis, prior cisplatin, and progression-free interval (PFI) <365 days. Risk scores were derived according to the model: low risk (1 factor), intermediate risk (2 factors), high risk (>3 factors). Scores were assessed in patients treated with chemotherapy alone (C) and chemotherapy plus anti-VEGF therapy (C+B). Each test of association with response rate (RR), progression-free survival, and OS was conducted at the 5% level of significance. Logistic regression and survival analysis was used to determine whether the factors were prognostic or could be used to guide therapy.

Results: In the low risk group, RR was 52% (C) vs 63% (C+B); for intermediate risk, it was 36% (C) vs 51% (C+B). In high risk, RR was 13% (C) vs 23% (C+B). Median OS for low risk was essentially the same (21.8 months C vs 23.0 months C+B); for high risk, median OS was 6.3 months (C) vs 12.1 months (C+B). The estimated HRs for death were 0.96 (low), 0.67 (intermediate), and 0.54 (high). A model-based interaction term was not significant between treatment with B and score for response, OS, and PFS. Models without an interaction term indicated that both B and score were highly significant.

Conclusions: The Moore criteria are prognostic, but evidence is lacking for their utility as a guide for personalized treatment. There is clinical benefit to receiving B in all risk categories, including high-risk patients. Interestingly, patients at the highest risk levels appear to derive the most benefit from the incorporation of antiangiogenesis therapy. The need to combine these validated clinical prognostic factors with as yet unidentified molecular biomarkers to identify patients likely to be refractory to anti-VEGF therapy is implicit.

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145 - Scientific Plenary

A comparative analysis of the treatment strategies for advanced ovarian cancer

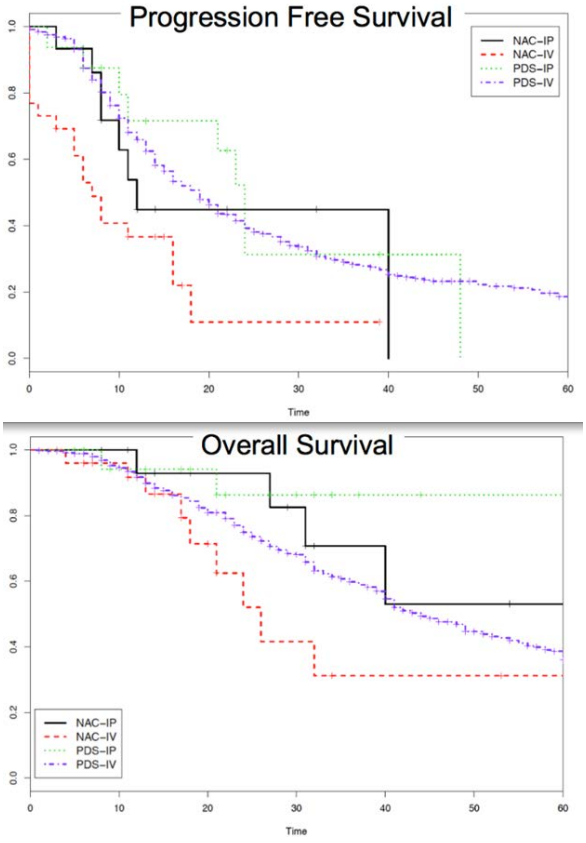
J. M. Scalici, D. DeCotis-Smith, B. Wang, M. A. Finan and R. P. Rocconi
University of South Alabama, Mobile, AL

Objectives: The advent of neoadjuvant chemotherapy (NAC) and intraperitoneal (IP) chemotherapy as treatment options for ovarian cancer allows multiple treatment strategies. The objective of our study was to evaluate the efficacy of the multiple treatment strategies currently used for ovarian cancer.

Methods: In this retrospective review, advanced-stage ovarian cancer patients were stratified into four groups based on the treatment received: primary debulking surgery followed by adjuvant intravenous (IV) chemotherapy (PDS-IV), primary debulking surgery followed by adjuvant intraperitoneal (IP) chemotherapy (PDS-IP), neoadjuvant chemotherapy with interval debulking surgery followed by IV chemotherapy (NAC-IV), and neoadjuvant chemotherapy with interval debulking surgery followed by IP chemotherapy (NAC-IP). Statistical comparison was performed using appropriate tests.

Results: Among 627 identified patients, 562 were treated with PDS-IV, 19 with PDS-IP, 26 with NAC-IV, and 20 with NAC-IP. Groups were similar in age; race; body mass index; and disease stage, histology, and grade. Median progression-free survival was 19 months for PDS-IV, 24 months for PDS-IP, 7 months for NAC-IV, and 12 months for NAC-IP. Median overall survival (OS) was 44 months for PDS-IV, 109 months for PDS-IP, 26 months for NAC-IV, not yet achieved for NAC-IP. OS was statistically worse for the NAC-IV group ($P<0.01$), but the other groups were similar in comparison. When comparing all IP vs all IV chemotherapy, irrespective of timing (NAC or adjuvant), the IP group had a significantly improved survival ($P<0.01$). When comparing all PDS vs all NAC, there was no difference in OS. Using multivariate Cox regression analysis, survival correlated with age >66 years ($P=0.002$), stage ($P<0.001$), and optimal debulking ($P<0.01$). Suboptimal debulking was associated with a 156% higher recurrence risk compared to optimal debulking.

Conclusions: Our results confirm that IP chemotherapy significantly improves survival for ovarian cancer patients and should be used whenever possible. The timing of surgery (primary vs interval) does not appear to affect survival. Therefore, maximal efforts for optimal debulking should be pursued to improve patient outcomes. Based on these data, NAC followed by IP chemotherapy in select patients is a feasible treatment strategy.



146 - Poster Session A

The BCL2 antagonist of cell death (BAD) signaling pathway and phospho-BAD protein levels are associated with triple-negative breast cancer clinical development and clinical outcome

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Objectives: Triple-negative breast cancer (TNBC) accounts for approximately 10% to 20% of all breast cancer cases and disproportionately affects younger women, African Americans or Hispanics, and those with a *BRCA1* gene mutation. Hormonal receptor status limits efficacy of hormonal therapy, such that cytotoxic therapy is a mainstay of treatment. Response to chemotherapy is a critical determinant of survival for patients with TNBC, although the molecular basis for chemoresponse remains to be fully delineated. We sought to explore the role of the BAD apoptotic pathway and protein in TNBC.

Methods: Using principle component analysis to summarize BAD apoptotic pathway expression, we compared TNBC vs non-TNBCs and also TNBC vs non-TNBC cell lines. Immunofluorescence and Western blot analyses were used to evaluate the expression of phospho-BAD (pBAD) protein and the kinases and phosphatases known to influence the phosphorylation status of BAD in TNBC cells. MTS survival assays evaluated the effects of BAD pathway inhibition on TNBC cell line chemosensitivity.

Results: Expression of the BAD apoptotic pathway distinguished the expression profiles of triple-negative (n=56) and estrogen receptor-positive (ER+) (n=56) primary breast cancer specimens (P=0.01) and cell lines (ER+: MCF-7, 3.85; T47D, 2.65; triple-negative: MDA-231, -3.47; BT549, -2.62; Hs578t, -5.17) (P=0.01). Further, expression of the BAD apoptotic pathway was associated with relapse-free survival in two breast cancer clinic-genomic datasets (n=286, P=0.01; n=155, P=0.02). TNBC specimens from patients categorized as short-term survivors (<36 months) expressed higher levels of pBAD [serine-112, -136, -155] than long-term survivors (>36 months). TNBC cell lines demonstrated higher levels of pBAD and BAD pathway kinases and lower levels of BAD phosphatase, PP2C, than ER+ cells. Inhibition of the BAD pathway in TNBC cells decreased pBAD expression and increased cytotoxic agent-induced growth arrest.

Conclusions: The BAD pathway is associated with the triple-negative breast cancer phenotype and may influence overall patient survival. Our data suggest that the BAD pathway may be an attractive therapeutic target to reverse TNBC chemoresistance and prolong survival.

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147 - Poster Session A

Analysis of the effect of adjuvant radiotherapy on outcome and complications after radical hysterectomy in FIGO stage IB1 cervical cancer patients with intermediate risk factors

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Objectives: There are no definitive criteria for patients with FIGO stage IB cervical cancer who may benefit from adjuvant therapy after radical hysterectomy because each study has a specific protocol. According to the recent annual report of cervical cancer treatment in Japan, 34.9% of stage Ib1 patients received postoperative adjuvant therapy. Thus, the aim of this study was to clarify the efficacy of adjuvant therapy and complications after radical hysterectomy in patients with FIGO stage Ib1 cervical cancer with intermediate risk factors.

Methods: Between January 2005 and December 2009, the medical records of 89 stage IBI patients with intermediate risk factors (i.e., tumor size 2-4 cm, lymphvascular involvement, and/or deep stromal invasion >1/2) who were treated with radical hysterectomy were enrolled for this retrospective study. The patients were grouped according to the adjuvant therapy received: 60 patients, no further treatment (NFT); 18 patients, radiation treatment (RT); 6 patients, concurrent chemoradiotherapy (CCRT); 5 patients, chemotherapy (CT) (Table). The significance of the clinical outcomes and complications for each group were analyzed.

Results: After an average follow-up of 6.0 years, only one patient who received RT and had three risk factors developed recurrence. All but one of the other patients who received RT, CCRT, or CT had two or three risk factors. Lymphedema and

other complications such as bowel obstruction and urinary disturbance occurred significantly more often in patients who received RT or CCRT.

Conclusions: The criteria of intermediate risk factors for Gynecologic Oncology Group (GOG) 92 have been adopted as the basis of other clinical studies. However, the GOG criteria are complicated in practice, and we defined simpler criteria. The findings of this study suggest that RT and CCRT after radical hysterectomy are not associated with benefits in patients who have intermediate risks. RT and CCRT appear to particularly increase the incidence of lymphedema and other complications. Because the results were obtained in a nonrandomized retrospective study, a prospective randomized study is needed to solidify the conclusions.

Patients characteristics of intermediate-risk cervical cancer

Risk factor	Adjuvant therapy		
	NFT	RT/CCRT	CT
	n=60	n=24	n=5
MS	24	1	0
SI	11	0	0
LVSI	1	0	0
MS+SI	12	4	1
MS+LSVI	4	4	0
SI+LSVI	2	0	0
MS+SI+LSVI	6	15	4

Abbreviations: NFT=no further treatment RT=radiation therapy
CCRT=concurent chemoradiotherapy CT=chemotherapy
MS=mass size SI=stromal invasion
LVSI= lymphovascular space involvement

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148 - Poster Session A

The impact of multiple high-risk factors on survival outcome of surgically treated early-stage cervical cancer

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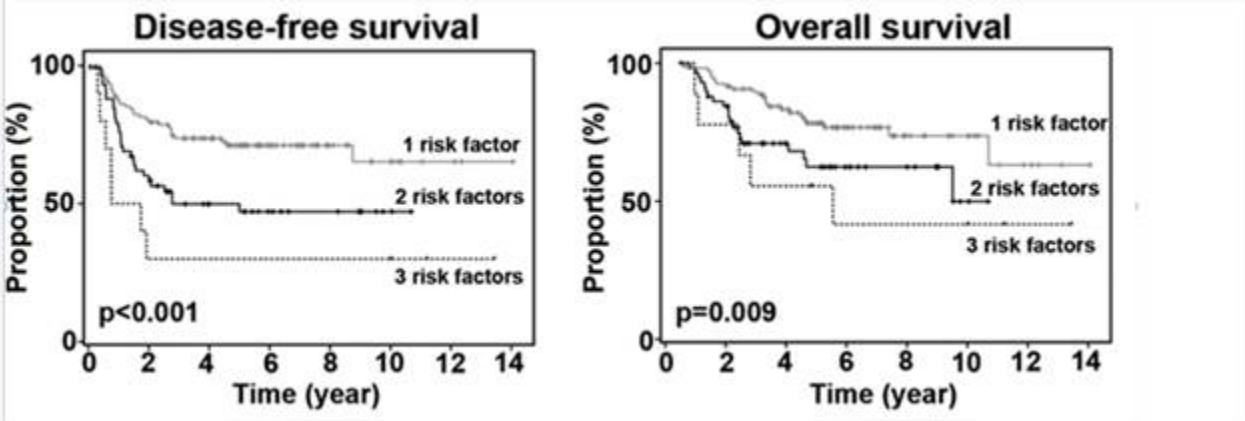
Objectives: Surgical-pathological risk factors obtained from radical hysterectomy specimen are valuable in the management of early-stage cervical cancer to identify a subset of patients who will benefit from adjuvant therapy. However, the significance of multiple high-risk factors on survival is not well elucidated.

Methods: A retrospective study was conducted for surgically treated cervical cancer patients (stage IA2-IIB, *n*=540). Surgical-pathological risk factors were examined, and tumors expressing ≥1 high-risk factors (nodal metastasis, parametrial involvement, or positive surgical margin) were eligible for analysis (*n*=177 [32.8%]). Survival analysis was performed based on the number of high-risk factors and the type of adjuvant therapy.

Results: Among 177 cases, 68 (38.4%) expressed multiple high-risk factors (2 risk factors, *n*=58 [32.8%]; 3 risk factors, *n*=10 [5.6%]). Five-year progression-free survival (PFS) for 1, 2, and 3 high-risk factors were 71.2%, 50.3%, and 30%, respectively (*P*<0.001) and were 78.2%, 62.3%, and 55.9%, respectively, for overall survival (OS) (*P*=0.009). Postoperatively, 101 (57.1%) patients received concurrent chemoradiotherapy (CCRT) and 76 (42.9%) received radiotherapy alone (RT). CCRT was beneficial for tumors expressing only a single high-risk factor: hazard ratio (HR) for CCRT over RT alone for PFS and OS were 0.27 (95% CI 0.13-0.57, *P*=0.001) and 0.31 (95% CI 0.13-0.72, *P*=0.007), respectively. The benefit of CCRT diminished when tumors expressed multiple high-risk factors: HR for PFS and OS were 0.72 (95% CI 0.37-1.38, *P*=0.32) and 0.78 (95% CI 0.36-1.73, *P*=0.55), respectively.

Conclusions: Special consideration of the significance of multiple high-risk factors merits further investigation in the management of surgically treated early-stage cervical cancer.



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149 - Poster Session A

Cervical adenocarcinoma in situ with coexisting squamous cell lesions: impact on recurrence

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Objectives: To assess the relative incidences of cervical adenocarcinoma in situ (AIS) and squamous cell carcinoma in situ (sCIS) and to determine the impact of coexisting squamous cell lesions on outcomes in patients with cervical AIS.

Methods: We performed a retrospective review of patients diagnosed with AIS or sCIS who underwent conization at a university hospital between 2000 and 2011.

Results: A total of 1,184 patients with cervical carcinoma in situ were included. The ratio of sCIS to AIS was 16:1. Among 71 patients with AIS, AIS with coexisting squamous cell lesions and AIS alone were detected in 41 patients (58%) and 30 patients (42%), respectively. The Papanicolaou smear results before conization in patients with AIS and coexisting squamous cell lesions showed squamous, glandular, and combined cell abnormalities in 93%, 2%, and 2% of patients, respectively, whereas the Papanicolaou smear results of patients with AIS alone showed squamous, glandular, and combined cell abnormalities in 37%, 43%, and 10% of patients, respectively ($P<0.001$). During the median follow-up of 57.1 months, five episodes of AIS recurrences and one episode of invasive recurrence occurred. The recurrence rate was significantly higher in patients with AIS alone than in patients with AIS and coexisting squamous cell lesions (17% vs 2%; $P=0.043$).

Conclusions: Patients with AIS alone on conization sample are more likely to experience recurrence, whereas patients with AIS and coexisting squamous cell lesions may be treated conservatively.

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150 - Poster Session A

A new suggested pattern-based clinical classification system for endocervical adenocarcinoma

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Objectives: According to FIGO classification, endocervical adenocarcinoma (EAC) staging is based on tumor depth of invasion (DOI). Because EAC spreads primarily by lymphatic dissemination, treatment of patients with EAC needs to address not only the primary tumor size but also the adjacent tissues and lymph nodes (LNs). The objective of this study was to investigate other pathologic factors that could better identify those patients at risk of developing LN metastases.

Methods: A retrospective review of records of patients with EAC treated in our institution. Data regarding clinical and pathologic features, such as DOI, tumor size, lymphovascular invasion (LVI), and pattern of tumor invasion, were defined. Suggesting a newly devised system, the above parameters were categorized as followed: Pattern A: well-confined glands, disregarding DOI; Pattern B: early invasion of stroma, originating from well-confined glands; Pattern C: spread, destructive invasion.

Results: A total of 103 women aged 21 to 79 years (mean, 50.67 years) were identified with EAC. All patients were staged between IA2 and IV, with DOI ranging from 3.5 to >40 mm; LVI was documented in 42 cases. To compare the standard staging method using DOI criteria and the suggested new method with patterns, we created the following table:

	Patients	**Patients with Pos LN**	**Total LN**	**# Pos LN**	**Stage I**	**Stage II - IV**
Standard Method	103	15 (14.6%)	2281	35 (1.53%)	65 (63.1%)	38 (36.9%)
Pattern A	20 (19.4%)	0 (0%)	451	0 (0%)	20 (100%)	0 (0%)
Pattern B	35 (33.9%)	4 (11.4%)	680	10 (1.5%)	25 (71.4%)	10 (28.6%)
Pattern C	48 (46.7%)	11 (22.9%)	1150	25 (2.2%)	20 (41.6%)	28 (58.3%)

Conclusions: As shown, a percentage of the 19.4% of patients (Pattern A, stage I) would not need LN resection, according to the suggested histologic classification for EAC. Moreover, patients with Pattern B characteristics rarely have LN metastases because 71.4% of them have stage I disease. In contrast, patients with Pattern C should receive aggressive treatment because 22.9% of them have LN involvement. Additionally, most patients who have higher-stage disease have tumors in Pattern C. Therefore, our data suggest that this new pattern-based method of classifying EAC could be clinically significant because it is simple and consistent.

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151 - Poster Session A

Differentiation between high- and low-grade cervical intraepithelial neoplasia by p16 immunoexpression

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Objectives: Inter-rater disagreement may occur when differentiating high-grade from low-grade cervical intraepithelial neoplasia (CIN) in clinical routine. The use of p16 immunohistochemistry could help the pathologist to differentiate these two presentations of CIN.

Methods: We performed a retrospective analysis of all consecutive cone specimens from patients who underwent surgical treatment for CIN between July 2009 and February 2011. The pathological results were classified into low-grade CIN and high-grade CIN, and these two groups were compared with p16 immunohistochemistry. p16 was considered positive when 75% of the neoplasia had moderate or strong staining. Categories were compared by means of chi-square test. A *P* value <0.05 was considered significant.

Results: Among 277 women, 20 (7.2%) of cone specimens showed low-grade CIN and 257 (92.8%) showed high-grade CIN. In low-grade CIN histology group, 18 (90%) had negative p16 stain and 2 (10%) had positive p16 stain. In the high-grade CIN group, 72 (28%) had negative p16 stain and 185 (72%) were positive. The difference between the two groups was statistically significant (*P* <0.0001) (Table 1).

Conclusions: The use of p16 immunohistochemistry had the capacity to differentiate high-grade from low-grade CIN, and this tool should be used clinically to reduce inter-rater disagreement.

Table 1. Distribution of p16 Staining by CIN Histology

CIN Histology		p16 negative *n* (%)	p16 positive *n* (%)		*P* value
Low-grade		18 (90%)	2 (10%)		<0.0001
High-grade		72 (28%)	185 (72%)		

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Risk factors for cervical intraepithelial neoplasia (CIN) recurrence in patients with positive cone margins

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Objectives: Positive cone margins are an important factor related to CIN recurrence after conization, but not all women with these findings will have recurrences. We evaluated the risk factors associated with CIN recurrence after surgical treatment in patients with positive cone margins.

Methods: Ninety-seven women who underwent surgery between July 2009 and February 2011 due to CIN and who had positive surgical margins at final pathology reports were analyzed. Clinical (age, tobacco consumption, and parity) and pathologic (histopathologic diagnosis and glandular extension) factors and biomarkers (high-risk human papillomavirus (HPV) detection by COBAS test® in the pretreatment cytology and p16 immunoexpression in the surgical specimen) were evaluated by univariate and multivariate analyses to determine the predictors of recurrence in 2 years.

Results: The median follow-up was 22.6 months (range, 0.7 -37.5 months). There were 33 recurrences of CIN after treatment (34.0%). The 2-year disease-free survival rate was 66.3% (95% CI 56.3% - 76.3%). After univariate analysis, positive HPV-16, tobacco consumption, and age were considered for multivariate analysis. In multivariate analysis (Table 1), the single independent risk factor for recurrence was tobacco consumption (HR 3.5, 95% CI 1.6 – 7.6, *P*=0.002).

Conclusions: Women with tobacco consumption and positive surgical margins at conization had a higher risk of recurrence. Tobacco cessation is strongly recommended in this population.

Table 1. Multivariate Analysis (Cox Model)

VARIABLE	CATEGORY	*n*	HR	95% CI	*P* Value
HPV-16	No	35	1.0	Reference	
	Yes	53	2.3	1.0 – 5.2	0.056
Tobacco consumption	No/in the past	52	1.0	Reference	
	Yes	36	3.5	1.6 – 7.6	0.002
Age	≤30 years old	21	1.0	Reference	
	31–45 years old	40	2.0	0.7 – 6.3	0.217
	>45 years old	27	2.8	0.9 – 9.3	0.083

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153 - Poster Session A

The diagnostic utility of HR-HPV as a predictor of cervical cancer recurrence

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Objectives: To identify the role of cervicovaginal HR-HPV testing in predicting cervical cancer recurrence.

Methods: This was a retrospective study of all patients who underwent HR-HPV testing as part of their routine surveillance for cervical cancer. Demographic information such as age, body mass index (BMI), smoking status, cancer stage, initial treatment, and results of surveillance cytology were also collected. Standard statistical analyses, including chi-square test and multivariable logistic regression, were performed. All analysis was performed using IBM SPSS 19.0 (Armonk, NY).

Results: A total of 134 patients were identified. Squamous cell carcinoma was the most common histology (79.9%), followed by adenocarcinoma (14.9%). The majority (69.4%) of the cohort had bulky disease (FIGO IB2 and beyond) and was treated primarily with chemoradiation and brachytherapy. Mean follow-up time was 26.4 months, and 9.7% of patients had a disease recurrence. Of patients who recurred, 46% had tested positive for HR-HPV during their surveillance compared to 11% of patients who did not recur (relative risk 4.93, P <0.05). On multiple logistic regression controlling for patient age, race, initial stage, smoking status, treatment modality, and abnormal cervicovaginal cytology during surveillance, HR-HPV status remained significantly predictive of disease recurrence (odds ratio 9.207, P <0.05, 95% CI 1.334-63.564). Using 2 X 2 table analysis, we found that while cervicovaginal cytology has limited specificity and sensitivity in predicting recurrence (Spec 53.72%, 95% CI 44.43% to 62.82%; Sens 69.23%, 95% CI 38.6% to 90.72%), the combination of cytology with HR-HPV testing increases the specificity of testing (Spec 93.39%, 95% CI 87.37% to 97.09%; Sens 38.46%, 95% CI 14% to 68.36%).

Conclusions: Persistence of HR-HPV after cervical cancer treatment is a significant risk factor for disease recurrence. At present, HR-HPV testing is not routinely used during surveillance for cervical cancer, but this study suggests that large, prospective trials investigating the role of HR-HPV and cytology co-testing in cervical cancer surveillance are needed.

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154 - Poster Session A

Synaptonemal complex protein 3 is a prognostic marker in cervical cancer

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Objectives: Synaptonemal complex protein 3 (SCP3), a member of the Cor1 family, is preferentially upregulated in various cancer cells. Its onocogenic potential and clinical significance, however, have not yet been characterized. We investigated the oncogenic role of SCP3 and its relationship with phosphorylated AKT (pAKT) in cervical neoplasias.

Methods: The functional role of SCP3 expression was investigated by overexpression or knockdown of SCP3 in NIH3T3 cells for in vitro and in vivo studies. Furthermore, we examined SCP3 expression in tumor specimens from 581 cervical neoplasias patients by immunohistochemistry and analyzed the correlation between SCP3 expression and clinicopathologic factors or survival.

Results: Overexpression of SCP3 promoted AKT-mediated tumorigenesis in the NIH3T3 cell line model both in vitro and in vivo. Functional studies demonstrated that the C-terminal region of human SCP3 is important for AKT activation and its oncogenesis. High expression of SCP3 was significantly associated with tumor stage (P=0.002) and tumor grade (P<0.001), and SCP3 activation was positively associated with expression of pAKT in cervical neoplasias. Survival times for patients with cervical cancer with both SCP3 and pAKT overexpression (median, 134.0 months, n=68) were significantly shorter than those for patients with low expression of either SCP3 or pAKT (161.5 months, n=108), as determined by multivariate analysis (P=0.020).

Conclusions: Our findings suggest that SCP3 plays an important role in the progression of cervical cancer through the AKT signaling pathway, supporting the possible use of SCP3 as a novel promising cancer target for cervical cancer therapy.

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155 - Poster Session A

MICA/B and ULBP1 natural killer group 2 member D (NKG2D) ligands are independent predictors of prognosis in cervical cancer

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Objectives: NKG2D recognizes a diverse array of cellular ligands of the MIC and ULBP/RAET family and is thought to play an important role in mediating the activation of anticancer immune response. In this study, we investigated the clinical significance of NKG2D in the pathogenesis of cervical cancer.

Methods: We assessed the expression of all MICA/B, ULBP1, ULBP2, ULBP3, RAET1E, and RAET1G proteins in archival tumor tissue specimens from 200 cervical cancers, 327 high-grade cervical intraepithelial neoplasias (CINs), 99 low-grade CINs, and 541 matched nonadjacent normal cervical epithelial tissues via immunohistochemical staining.

Results: MICA/B, ULBP1, and RAET1E expressions were higher in cervical cancer than in low-grade CIN ($P<0.001$, $P=0.012$, $P=0.013$, respectively) and normal cervix (all $P<0.001$). Among these markers, expression of ULBP1 differed significantly, depending on the patient's FIGO stage ($P=0.010$) and tumor size ($P=0.045$). ULBP1 expression was correlated with MICA/B ($P<0.001$) and ULBP2 expression ($P=0.002$) in cervical cancer. While MICA/B+ or ULBP1+ showed improved disease-free survival time ($P=0.027$ and $P=0.009$, respectively) compared with that of a low-expression group, RAET1E+ or RAET1G+ showed shorter survival time ($P=0.018$ and $P=0.029$, respectively). However, the ULBP1+ group showed significantly longer overall survival time ($P=0.009$). Multivariate analysis indicated that MICA/B+/ULBP1+ (HR=0.16, $P=0.015$), ULBP1+ (HR=0.31, $P=0.024$), tumor stage (HR=3.60, $P=0.010$), and lymph node metastasis (HR=2.71, $P=0.032$) are independent prognostic factors of disease-free survival in cervical cancer.

Conclusions: We demonstrated that MICA/B and ULBP1 expressions are significantly increased in cervical cancer, which is consistent with an immunoediting mechanism that selects tumor cells that have lost or reduced expression of NKG2D ligands. Furthermore, the combination of MICA/B and ULBP1 was found to be an independent predictor of survival, suggesting value in clinical assessment.

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156 - Poster Session A

Impact of treatment time on chemoradiotherapy in locally advanced cervical carcinoma

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Objectives: The adverse effect of treatment prolongation beyond 8 weeks with radiotherapy in cervical cancer has been established. Clinical data also show that cisplatin increases the biologically effective dose of radiotherapy. There are no data on the effect of overall treatment time in patients with locally advanced cervical cancer treated with concomitant chemoradiotherapy (CCRT) from the Indian population. The study aimed to study the feasibility of concurrent chemotherapy and interspaced brachytherapy during the course of external radiotherapy to reduce the overall treatment time and compare normal tissue toxicity and locoregional control with a conventional schedule.

Methods: Between January 2009 and March 2012, 50 patients registered in the gynecologic oncology clinic of the Institute Rotary Cancer Hospital who had locally advanced cervical cancer (FIGO stage IIB-IIIB) were enrolled. In this randomized, controlled study, patients were randomly allocated to treatment arms based on a computer-generated random number. Arm 1 ($n=25$) treatment consisted of irradiation of the whole pelvis to a dose of 50 Gy in 27 fractions and weekly cisplatin 40 mg/m^2. High-dose rate intracavitory radiotherapy (HDR-ICRT) was performed within 1 week of completing external beam radiation therapy (EBRT). The prescribed dose for each session was 7 Gy to point A for three insertions at 1-week intervals. Arm 2 ($n=25$) treatment consisted of irradiation of the whole pelvis to a dose of 50 Gy in 27 fractions. Intracavitary radiation therapy was performed with 40 Gy and 7 Gy delivered to point A for three insertions (days 23, 30, 37) at 1-week interval. Cisplatin 20 mg/m^2/day was administered from days 1 through 5 and days 24 through 28. Overall treatment time ranged from the first day of EBRT to the last day of HDR brachytherapy. Locoregional response was assessed at 1, 4, and 6 months.

Results: The mean age was 51.8.and 48.8 years in Arm 1 and Arm 2, respectively. The mean treatment time in the two arms was 65 days (range, 54-101 days) and 48 days (range, 42-60 days), respectively. The response rates and toxicities were comparable.

Conclusions: In the setting of concurrent chemoradiotherapy, a shorter treatment schedule and overall treatment time of 48 days may be feasible by interspacing brachytherapy during external irradiation. Detailed patient characteristics, clinical profiles, and treatment outcomes will be presented.

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Makorin ring finger protein 1 (MKRN1) as an adjunct marker in liquid-based cervical cytology

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Objectives: To test the ability of MKRN1 to detect cervical lesions in a screening setting and its use as a surrogate marker of human papillomavirus (HPV) infection.

Methods: We conducted **PRO**spective specimen collection and retrospective **B**linded **E**valuation **(PROBE)** study. Four hundred patients were enrolled (200 patients with normal findings and 200 patients with abnormal findings, including 63 atypical squamous cells of unknown significance (ASCUS), 57 low-grade squamous intraepithelial lesion (LSIL), 46 high-grade squamous intraepithelial lesion (HSIL), and 34 atypical squamous cells - cannot exclude HSIL (ASC-H). MKRN1 immunostaining on cell block sections, HPV hybrid capture, and real-time polymerase chain reaction (PCR) were performed and analyzed with pathologic results.

Results: Comparison of the number of MKRN1 immunoreactive cells/1,000 cells exhibited a significantly higher mean count in HSIL (8.20±1.28) than other cytologic groups. The mean count of LSIL (1.29±0.27) was significantly higher than that of the negative group (0.81±0.43). ASC-H and HSIL combined group showed a significantly higher mean count (6.98±1.31) than other groups. The mean count of MKRN1 immunoreactive cells/1,000 cells was significantly higher in HPV16-positive samples (3.78±0.81) than in samples containing infections with other types (0.91±0.37) or HPV-negative samples (1.08±0.45). Receiver-operating characteristic curves yielded test accuracy (area under curve) of 0.74, 0.80, 0.87, and 0.92 for ASCUS, LSIL, ASC-H/HSIL, and HSIL, respectively. Threshold for 95% sensitivity was at 0.007, 0.009, 0.099, and 0.465 immunopositive cells/1,000 cells for ASCUS, LSIL, ASC-H/HSIL, and HSIL, respectively. The 95% specificity threshold for the detection of HSIL was at 1.89 immunopositive cells/1,000cells.

Conclusions: MKRN1 immunostaining on cell block sections of cervical cytology specimens showed distinct correlation patterns with biopsy results. The accuracy and diagnostic indices of the test are good when compared with those of other techniques. As part of screening procedures, MKRN1 immunostaining could be used as an adjunct to liquid-based cytology to identify HSIL and as a surrogate marker of HPV infection.

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158 - Poster Session A

High rates of cervical intraepithelial neoplasia (CIN) 3 in young women undergoing immediate excisional procedure for high-grade squamous intraepithelial lesion (HSIL) cytology

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Objectives: New guidelines for the management of abnormal cervical cytology in women <25 years old recommend against the use of immediate excisional procedures (commonly referred to as see-and-treat) for HSIL cytology. The objective of this study was to compare rates of CIN 3 between women 21 to 24 years and women ≥25 years undergoing see-and-treat procedures.

Methods: Following institutional review board approval, women treated with an immediate loop excisional procedure (LEEP) for HSIL cytology at our university-based colposcopy clinic from 2008-2013 were identified. Data collected included age, race, parity, smoking status, method of contraception, history of abnormal cytology, HIV status, and LEEP pathology. Cohorts were compared with the Student's t-test and chi-square test.

Results: A total of 369 women were included in the analysis. The mean age was 29.8 years (standard deviation, 7.2; range, 21-56 years), with 97 women (26.3%) ages 21 to 24 years. Race broke down as 189 (51.2%) white, 143 (38.8%) black, and 30 (8.1%) Hispanic. One hundred eighty-six (50.4%) women were current or past smokers. The median parity was 2 (range, 0-9). The rate of CIN 3 in all women undergoing see-and-treat LEEP for HSIL cytology was 65.9% (95% CI 60.8-70.5). The rate of CIN 2 was 15.2% (95% CI 11.9-19.2). Three women (1.1%) had invasive carcinoma. There was no significant difference in the rate of CIN 3 in women 21 to 24 years old compared to women ≥25 years (73.3% vs 63.2%, P=0.09). Within this see-and-treat population, there was no correlation between CIN 3 and age, race, smoking, parity, contraception, or HIV status.

Conclusions: Most women undergoing see-and-treat LEEP for HSIL cytology have CIN 3. In this large cohort, there was no difference in rate of CIN 3 in women <25 years compared to women ≥25 years, suggesting that see-and-treat remains a valid option for the prevention of invasive disease in young women.

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159 - Poster Session A

Fertility-sparing surgery after high dose-dense neoadjuvant chemotherapy: critical view of experiences with 25 patients

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Objectives: To examine the effect of dose-dense neoadjuvant chemotherapy (NAC) in saving fertility in women with early-stage cervical cancer.

Methods: Twenty-five women with early-stage cervical cancer and a strong desire to save fertility who did not fulfill standard criteria for fertility-sparing surgery (tumor >2 cm or infiltrating >50% of stroma) were included this prospective study. NAC was given to all patients in 10-day intervals: cisplatin plus ifosfamide in squamous cell cancer or plus doxorubicin in adenocarcinoma. Patients underwent laparoscopic lymphadenectomy and vaginal simple trachelectomy after NAC. Women with positive lymph nodes or inadequate free surgical margins underwent radical hysterectomy.

Results: No residual disease was found in 6 women (24%), microscopic disease in 8 women(32%), and macroscopic tumor in 11 women (44%). Positive nodes were found in 2 women (8%). Eight women (32%) lost fertility. Four women (23.5%) had recurrences after fertility-sparing surgery (radical hysterectomy was recommended to one of them due to close margins, but she refused) and two of them died of disease (11.8%). Fertility was spared in 17 women, 11 planned pregnancy, and 8 became pregnant. Six women delivered eight babies (six term and two preterm deliveries). There were two miscarriages in the second trimester (in one woman) and one in the first trimester. One woman underwent four unsuccessful cycles of in vitro fertilization, one did not become pregnant, and one had recurred before pregnancy.

Conclusions: Response to NAC and extension of residual disease seem to be the most important prognostic factors and should be considered before undertaking fertility-sparing surgery after NAC. This work is supported by grant MZCR - NT 13166.

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160 - Poster Session A

Efficacy of adjuvant chemotherapy after radical hysterectomy in FIGO stage IB-IIA cervical cancer: Comparison with adjuvant RT/CCRT using Propensity Scores

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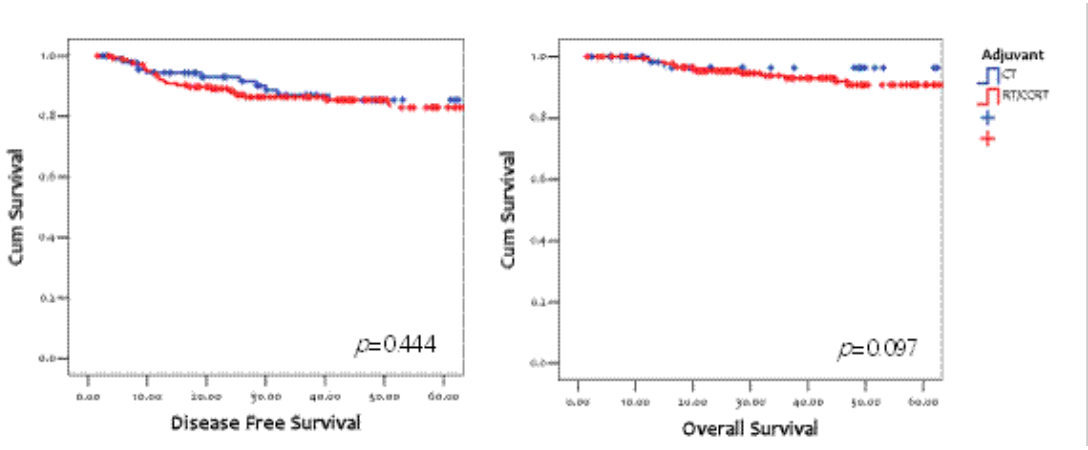
Objectives: To verify the clinical efficacy of adjuvant chemotherapy (AC) in FIGO stage IB-IIA cervical cancer.

Methods: In this study, 276 cervical cancer patients were enrolled, who received radical hysterectomy (RH) and adjuvant therapy at Asan Medical Center between 1991 and 2012. Ninety-four patients received AC and 182 received adjuvant RT/CCRT (AR). The therapeutic outcomes and adverse effects in both arms were compared. To reduce the impact of treatment selection bias and potential confounding factors, we performed rigorous adjustment in characteristics of patients by use of the weighted Cox proportional hazards regression models using the inverse-probability-of-treatment weighting (IPTW). The propensity scores (PS) were estimated by multiple logistic-regression analysis.

Results: During 45.5 months of median follow-up duration, 41 patients (14.9%) had recurrences and 18 patients (6.5%) died of disease. In multivariable analysis, parametrial invasion (PMI) and lymph node metastasis (LNM) significantly affected recurrence (PMI HR 2.479, 95% CI 1.211-5.074, P=0.01; LNM 1.97, 95% CI 1.045-3.712, P=0.04). However, only LNM significantly affected death (HR 3.007, 95% CI 1.111-8.137, P=0.03). After IPTW matching, HR for recurrence did not significantly differ in both arms (P=0.49), but the HR of death was significantly higher in patients treated with AR (HR 4.82, 95% CI 1.254-18.524, P=0.02). Disease-free survival and overall survival were not significantly different between patients in both arms (P=0.444, 0.097, respectively) (Figure 1). In addition, patients treated with AC had a much lower prevalence of long-term complications (lymphedema: n=10 [45.5%] vs 49 [70.0%], P=0.03; ureter stricture: none vs 11 [15.7%], P=0.04).

Conclusions: AC has the equivalent therapeutic effect to AR in patients with FIGO stage IB-IIA cervical cancer. With a much lower incidence of long-term complication after adjuvant therapy, AC can be an alternative adjuvant treatment option, especially in younger patients.



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161 - Poster Session A

Less radical surgery than radical trachelectomy or radical hysterectomy in patients with stage I cervical cancer

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Objectives: The purpose of this pilot study was determine the feasibility and safety of less radical surgery, laparoscopic lymphadenectomy with sentinel lymph node identification (SLNI), followed by large cone simple trachelectomy (fertility-sparing group) or vaginal hysterectomy type A (non-fertility-sparing group).

Methods: From January 1999 to June 2012, 196 women with squamous or adenocarcinoma (tumor size <20 mm in largest diameter and infiltration <50% of the cervical stroma) underwent laparoscopic SLNI, frozen section (FS) with laparoscopic lymphadenectomy, or only SLNI in 36 cases (18%). Node-negative women underwent conservative fertility-sparing surgery (64 cases) or vaginal hysterectomy (116 cases).

Results: Sixteen women had positive lymph nodes (8.2%). FS of SLN was positive in 13 cases (12 metastases, 1 micrometastases). Radical hysterectomy type C2 was performed in all cases. Three cases had false-negative FS; all had micrometastases on final histopathology. One of them underwent radical hysterectomy and two underwent adjuvant chemoradiotherapy. Two recurrences were diagnosed in node-positive patients (12%), both of whom died of disease. The other 14 node-positive patients are without evidence of disease. Two local recurrences were observed in the conservative fertility-sparing group (3%), and one of the patients died. Adenocarcinoma was diagnosed in one woman after fertility-sparing procedure that was done for squamous cancer. One recurrence was observed in the hysterectomy non-fertility-sparing group (1%).

Conclusions: Less radical surgery with large cone or simple trachelectomy or hysterectomy type A combined with SLNI with laparoscopic pelvic lymphadenectomy can be a feasible and safe method in small-tumor volume early cervical cancer.

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162 - Poster Session A

A study of safe criteria for radical trachelectomy in cervical cancer patients to prevent recurrence and catastrophic consequences: a multicenter study

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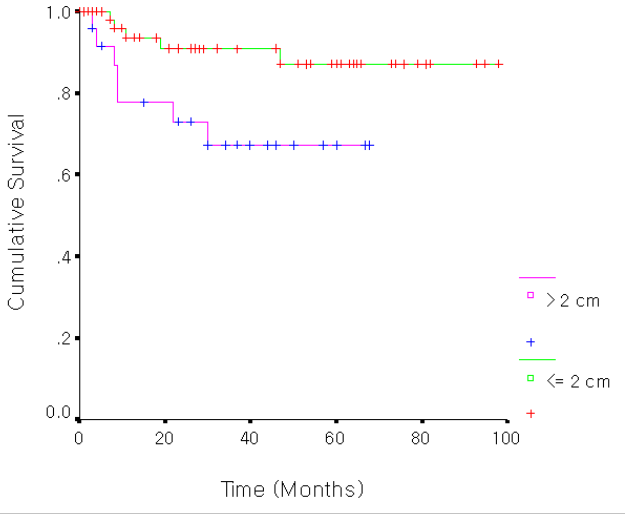
Objectives: Radical trachelectomy (RT) is increasingly used for patients with early cervical cancer as an alternative to radical hysterectomy when women want to preserve their fertility. The objective of this study was to evaluate oncologic and

obstetric outcomes of RT, to analyze the distinct relapse patterns of RT using minimally invasive techniques, and to determine the safety criteria for RT in the treatment of cervical cancer.

Methods: Clinicopathologic data for the current study were obtained from tumor registry databases of two institutions - Asan Medical Center and Ajou University Hospital - between October 2004 and July 2013. A total of 85 patients with early-stage cervical cancer treated by laparoscopic (LRT) were identified. All patients underwent RT using laparoscopy combining 70% laparoscopic and 30% vaginal approaches.

Results: The median age at diagnosis was 31 years (range, 22-43 years) and the median parity was 0. Most patients had stage IB1 (85.9%) cervical cancer and squamous cell carcinoma (82.4%). Mean tumor size was 1.2 cm (range, no visible-4.4 cm) and 25 (29.4%) patients had tumors >2 cm. At a mean follow-up of 35 months (range, 0-98 months), 12 patients had recurred after the initial treatment (14.1%) and there were four (4.7%) deaths. Locoregional relapse was most common in the uterus, vagina, pelvic peritoneum, or pelvic lymph nodes. Large tumor size (>2 cm), close endocervical margin from tumor, and direct contact of tumor with uterine elevator during the procedure were potential risk factors associated with disease recurrence. The recurrence rate was significantly higher in patients with tumor >2 cm compared to those with tumor <2 cm (8.3% vs 28.0%). There was a statistically significant difference in 3-year disease-free survival rates between the two groups (91% vs 67%, *P*=0.03).

Conclusions: This study suggests the paramount importance of patient selection in RT. Selection of candidates for RT should be limited to those with small-volume disease. To prevent locoregional relapse, meticulous surgical skills are required. More generous use of adjuvant chemotherapy might be of help in these high-risk patients after RT. Further studies are needed to confirm our results.



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163 - Poster Session A

Less radical surgery for early-stage cervical cancer: can cold knife cone specimens help identify those at low risk for parametrial involvement?

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Objectives: Many have tried to identify a low-risk group of cervical cancer patients in whom the rate of parametrial involvement (PI) is so low that parametrectomy can be eliminated. The goal of this study was to identify risk factors for PI and evaluate features of cold knife cone (CKC) specimens that may predict PI.

Methods: Patients with FIGO IA2-IIA cervical cancer treated with radical hysterectomy (RH) and pelvic lymph node (PLN) dissection from 2000 to 2010 were retrospectively identified. Pathology reports from CKC and RH specimens were reviewed for tumor size, presence of PI, lymph vascular space invasion (LVSI), depth of stromal invasion (DOI), and lymph node positivity (LNP). PI was defined as direct extension or metastatic spread (LVSI or parametrial LN).

Results: A total of 267 patients were evaluated. The majority (76%) of patients were stage IB1 with squamous cell histology (71%). The incidence of PI was 16% overall, 35% in IB2 and 15% in IB1. PI was via metastasis in most (67%) of cases. Patients with PI were more likely to have residual carcinoma after CKC, DOI >50%, and LVSI (*P* values <0.001). PI was

more frequent with larger tumors (median 4 cm vs 3 cm, *P*<0.001) and LNP (*P*<0.001). Of the 118 (44%) patients treated with CKC, nine (8%) had PI on RH. Those with PI were more likely to have LVSI on CKC (88% vs 34%, *P*=0.005) and dysplasia or carcinoma on endocervical curettage (ECC) (71% vs 40%, *P*=0.041). The risk of PI with a positive ECC was 21%. There were no statistically significant differences in CKC tumor size or margin status. In logistic regression analysis, positive PLN and LVSI were predictive of PI (Table).

Conclusions: The incidence of PI in early-stage cervical cancer is not negligible and commonly occurs as the result of metastasis rather than direct extension. While LNP and LVSI are predictors of PI, other CKC factors are not predictive. There may be a small group of patients who can be spared parametrectomy, but additional research is needed.

Table. Probability of PI based on multivariable logistic regression

Right PLN	Left PLN	LVSI	N	Probability	95% CI	
Negative	Negative	No	131	5.1	2.6	9.8
Negative	Negative	Yes	46	17.8	10.0	29.8
Negative	Positive	No	6	12.7	4.6	30.5
Negative	Positive	Yes	9	37.0	18.4	60.5
Positive	Negative	No	4	19.1	7.3	41.5
Positive	Negative	Yes	13	48.7	28.6	69.3
Positive	Positive	No	2	39.0	16.7	67.0
Positive	Positive	Yes	21	72.0	53.8	85.0

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164 - Poster Session A

Adenocarcinoma indicates more favorable prognosis with cervix cancer

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Objectives: To describe the difference in recurrence and survival patterns in patients with adenocarcinoma (AC) subtypes vs squamous cell carcinoma (SCC) of the cervix.

Methods: A retrospective chart review was performed of consecutive patients treated for cervix cancer from January 1999- to October 2011, with analysis was limited to SCC and AC subtypes (ACA; composite of AC, adenosquamous, and villoglandular histologies). Descriptive, clinicopathologic, and survival data were collected. SAS 9.2 was used for statistical analyses.

Results: Of the 465 patients who met study criteria, 424 (91%) had SCC or ACA. Patients with SCC were older (median 46 vs 43 years, *P*=0.024), had higher Charlson comorbidity scores (median 4 vs 3, *P*<0.0001), more tobacco abuse (current smokers: 48% vs 24%, *P*<0.0001), and less often had private insurance or Medicare (49% vs 68%, *P*=0.0007), but had similar body mass indices (BMI) (median 27.3 vs 28.3, *P*=0.48) and racial distribution (77% vs 81% Caucasian, *P*=0.59) compared to patients with ACA. Patients with SCC had higher stage (stage IIIA-IVA: 20% vs 5%, *P*<0.0001) and higher-grade tumors (grade 2/3: 67% vs 50%, *P*<0.0001) than patients with ACA. Accordingly, SCC pts less often met Gynecologic Oncology Group low- or intermediate-risk groups for adjuvant therapy following radical hysterectomy (21% vs 58%, *P*<0.0001) and more often received radiation (74% vs 43%, *P*<0.0001) or chemotherapy (70% vs 38%, *P*<0.0001). Additionally, patients with SCC more often had positive pelvic nodes (43% vs 15%, *P*<0.0001) or any positive lymph nodes (43% vs 15%, *P*<0.0001). Overall survival (OS) was longer in patients with ACA than patients with SCC, with 5-year survival periods of 72% vs. 60 % (*P*=0.008); patients with SCC more often experienced disease recurrence (27% vs 16%, *P*=0.015) and did so more quickly (median not met, *P*=0.004) than patients with ACA. After controlling for stage, tobacco use, and race, histology remained a significant predictor of OS (*P*=0.034).

Conclusions: ACA appears to represent an inherently more favorable cervix cancer subtype with respect to disease distribution, risk of recurrence, and OS, in contrast to the commonly held belief that ACA represents a poor prognostic feature. Counseling should be tailored to reflect histology as an integral portion of risk stratification.

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165 - Poster Session A

Diagnosis of adenocarcinoma in situ (AIS): changing trends and the impact of human papillomavirus (HPV) testing

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Objectives: Co-testing with a combination of cytology and HPV testing is now considered the preferred cervical cancer screening approach for women >30 years. Because HPV testing has become more widely used, some institutions have seen an increase in the diagnosis of AIS. The objective of this study was to evaluate trends in the diagnosis of AIS at our institution since 2000 and investigate the potential impact of HPV testing on this trend.

Methods: All consecutive cases of histologically confirmed AIS diagnosed at our institution from 2000 to 2013 were collected and the records reviewed. Specific screening histories were obtained from 2005 (when HPV testing commonly used) to 2013 (to date). A proportion Z-test was used to compare incidence rates of AIS.

Results: From 2000 to 2004, the average yearly incidence of histologically confirmed AIS was 1.2/10,000 liquid-based cervical cytology (LBC) specimens. From 2005 to 2009, incidence increased to 1.7, and increased further to 2.9/10,000 LBC from 2010 to 2013 to date. This trend was statistically significant ($P<0.001$). Screening histories of 97 women with AIS diagnosed from 2005 to 2013 were reviewed. Of the 97 women, 56 (58%) had a documented LBC result in the year preceding AIS diagnosis, and 48 had an HPV (Hybrid Capture 2) result. Of the 48 HPV tests, 46 (96%) were positive, 1 was insufficient, and 1 was negative. Thirteen of the 56 (23%) preceding LBC were negative for intraepithelial lesion or malignancy (NILM); 11 of the 13 women with NILM had documented HPV results, all of which were positive. Thirty-seven women had a second LBC in the 3 years preceding AIS, and 24 (65%) were NILM. These women had 22 HPV tests, all of which were positive, including 15 women with NILM. Twenty women had a third LBC in the 3 years preceding AIS, of which 15 (75%) were NILM. HPV had been obtained in eight of these women, all of which were positive.

Conclusions: A more than doubling of the average yearly incidence of AIS per 10,000 LBC occurred at our institution from 2000 to 2013 (to date). A significant proportion of AIS diagnosed since the introduction of HPV cotesting for screening were diagnosed in women with NILM who were HPV-positive, suggesting that the addition of HPV to cervical cancer screening protocols improves the detection of AIS.

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166 - Poster Session A

Prognostic role of maximum standardized uptake value of metastatic pelvic lymph node in patients with early-stage cervical cancer for the prediction of distant metastasis

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Objectives: To evaluate the role of maximum standardized uptake value (SUVmax) of metastatic pelvic lymph node measured by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with early-stage cervical cancer to predict future distant metastasis.

Methods: A total of 213 patients with stage I-IIA cervical cancer who had underwent radical hysterectomy and pelvic lymphadenectomy from January 2007 to December 2011 were enrolled in this study. All patients underwent preoperative ^{18}F-FDG PET/CT scan within 2 weeks of surgery. SUVmax and clinical and pathologic data were retrieved from medical chart review.

Results: The median follow-up period was 15.6 months. The SUVmax of 152 primary tumor masses and 79 metastatic pelvic lymph nodes were analyzed; the SUVmax could not be analyzed in 52 patients due to absence of data. The median SUVmax was 8.75 (range, 1 to 41) for the primary tumor and 5.95 (range, 2 to 25) for the pelvic lymph node. When multiple lymph nodes were identified, only the lymph node with the highest SUVmax was used. Lymph nodes in patients who later developed distant metastasis had higher SUVmax values than those who did not develop distant metastasis (3.2 vs 1.80, $P<0.0007$). When the cutoff value of SUVmax for the primary tumor was set at 8.0 by receiver operating curve analysis, it was not associated with future distant metastasis ($P=0.16$). In contrast, when the cutoff value of SUVmax for the lymph nodes was set at 7.0, it showed significant association with future distant metastasis ($P=0.015$).

Conclusions: SUVmax of metastatic pelvic lymph nodes, not just lymph node metastasis itself, in patients with cervical cancer has a predictive role for future distant metastasis. It might help clinicians develop individualized treatment plans.

167 - Poster Session A

Weekly ixabepilone with or without concurrent bevacizumab in the treatment of platinum/taxane-resistant endometrial and ovarian cancers: an institutional experience

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Objectives: Ixabepilone for endometrial/ovarian cancer has been evaluated as a single agent in phase II studies (Gynecologic Oncology Group [GOG] 129P, GOG 126M) and is currently under investigation in conjunction with carboplatin/bevacizumab (GOG 86P). This study describes the institutional experience of weekly ixabepilone ± biweekly bevacizumab in treatment of platinum/taxane-resistant endometrial and ovarian cancers.

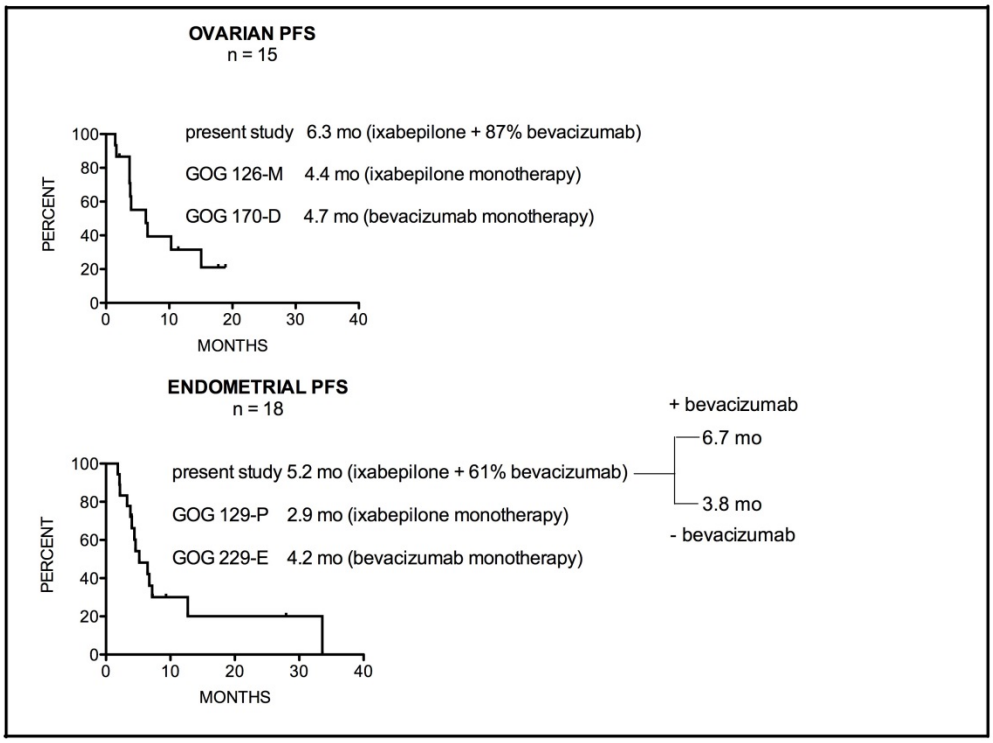
Methods: Patients who received ≥2 cycles of ixabepilone (16-20 mg/m^2 on days 1, 8, 15) ± bevacizumab (10 mg/kg on days 1, 15) of a 28-day cycle were identified retrospectively.

Results: Thirty three (18 endometrial, 15 ovarian) patients were included (Table). Patients received a mean of 4.8±1.9 cycles; the initial course is ongoing in three patients. Among endometrial cancer patients, one (5.6%) exhibited a complete response (CR), three (16.7%) exhibited partial responses (PR), and five (27.8%) had disease stabilization (SD). Among ovarian cancer patients, one (6.6%) exhibited a CR, two (13.3%) had PR, and five (33.3%) showed SD. Median progression-free survival (PFS) for endometrial and ovarian cohorts was 5.2 and 6.3 months and median overall survival (OS) was 9 months and not reached, respectively. Approximately 73% of patients received concurrent bevacizumab (11 endometrial, 13 ovarian). PFS and OS in patients who received concurrent bevacizumab were twice that of patients who did not (6.7 vs 3.8 months and 9.6 vs. 4.6 months, respectively), although this failed to reach significance (Figure 1). Toxicities were recorded in 20% and were grade 1-2. There were 18 deaths (14 endometrial, 4 ovarian). Median follow-up was 3.45 years (range, 1.3-15.3 years).

Conclusions: Ixabepilone shows encouraging activity in patients with platinum/taxane-resistant endometrial/ovarian cancers. Weekly dosing + biweekly bevacizumab is well-tolerated and may offer improvement in PFS. Additional investigation and long-term follow-up are warranted.

TABLE 1	**ENDOMETRIAL (*n*=18)**		**OVARIAN (*n*=15)**	
MEDIAN AGE, years (range)	63 (33-81)		53 (34-77)	
MEDIAN PRIOR LINES OF CHEMOTHERAPY	3		4	
	%	***n***	**%**	***n***
STAGE				
- I	38.9	7	0	0
- II	0	0	6.7	1
- III	11.1	2	53.3	8
- IV	44.4	8	0	0
- unstaged	5.6	1	0	0
- neoadjuvant	0	0	40.0	6
HISTOLOGY				
- serous	27.7	5	73.3	11
- clear cell	5.6	1	13.3	2
- endometrioid	50.0	9	6.7	1
- sarcoma	5.6	1	0	0
- undifferentiated	11.1	2	0	0
- borderline			6.7	1
RACE				
- white	77.7	14	93.3	14
- black	5.6	1	6.7	1
- Hispanic	11.1	2	0	0
- Asian	5.6	1	0	0

Figure 1



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168 - Poster Session A

A dose-dense paclitaxel and carboplatin regimen is highly active in the treatment of recurrent and advanced endometrial cancer

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[1]University of Chicago, Chicago, IL, [2]Northshore University Health System, Evanston, IL, [3]Inova Fairfax Hospital, Falls Church, VA

Objectives: To evaluate the efficacy and toxicity of dose-dense paclitaxel and carboplatin for recurrent and advanced endometrial cancer.

Methods: Single-institution retrospective analysis (2001-2013) of outcomes associated with administration of a regimen of carboplatin (AUC 5 on day 1) and paclitaxel (80 mg/m^2 on days 1, 8, 15) of a 28-day cycle in women with advanced (stage III-IV with measurable disease) and recurrent endometrial carcinoma. Primary endpoints included response rate (RR), progression-free interval (PFI), and overall survival (OS). PFI was calculated from date of onset of the dose-dense regimen to recurrence, and OS was calculated from date of original diagnosis of endometrial cancer to the date of death.

Results: Fifteen women with recurrent disease and three women with advanced disease were evaluable. Fourteen women with recurrent disease had previously received platinum-based chemotherapy and/or radiation as part of their initial treatment. The women with advanced disease received dose-dense therapy as their upfront treatment regimen. The overall RR was 94.4% (nine complete responses [CR] and eight partial responses [PR]). Among the women with recurrent disease, there was a 100% response rate (eight CR, seven PR). Two of three women with advanced disease responded (one CR, one PR). Median follow-up time for the cohort was 34.4 months (range, 11-73 months). The median PFI for all subjects treated was 11 months and the median OS was 54 months. For those with recurrent disease, PFI was 14 months and OS was 54 months. In the recurrent disease cohort, the OS was 19.5 months when calculated from the initiation of dose-dense treatment. Patients with advanced disease had a PFI and OS of 7.7 and 13.3 months, respectively. The most common toxicities were fatigue and anemia. Thirteen women had mild neuropathy, but only two required alteration of therapy due to symptoms. Three women required a dose reduction during their course of treatment.

Conclusions: A dose-dense paclitaxel and carboplatin regimen is highly active for women with recurrent and advanced-stage endometrial adenocarcinoma. The regimen appears especially active in the setting of recurrence. Given the high response rate compared to historical controls and general tolerability of this regimen, it is an excellent option for patients with recurrent endometrial cancer.

169 - Poster Session A

Oxaliplatin is a safe alternative therapeutic option for patients with recurrent gynecologic cancers following hypersensitivity reaction to carboplatin

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Objectives: To determine the tolerability and efficacy of oxaliplatin following severe carboplatin hypersensitivity reaction in comparison with its conventional analogue cisplatin in patients with recurrent gynecologic malignancies.

Methods: Forty-six patients with recurrent cancers of the ovary, endometrium, and cervix were treated with platinum-based chemotherapy from 2006 to 2011 and developed hypersensitivity reactions to carboplatin. Oxaliplatin was substituted for carboplatin in 27 patients; 19 patients were retreated with cisplatin. Clinicopathologic variables, toxicity, and time to failure were analyzed retrospectively using descriptive statistics, Fisher's exact, and independent sample permutation t-tests.

Results: The median number of carboplatin cycles (6 vs 7.5 cycles, P=0.93) and cumulative dose before reaction (980±662 mg vs 686±579.6 mg, P=0.49) were similar in the oxaliplatin and cisplatin groups, respectively. Non-life-threatening hypersensitivity reaction to oxaliplatin eventually occurred in 2/27 patients. There were no reactions to cisplatin. The median number of oxaliplatin/cisplatin cycles was six in both groups. The rate of complete response to therapy was 34.62% (oxaliplatin) and 31.58% (cisplatin); stable disease on imaging was seen in 50% and 36.84% of oxaliplatin- and cisplatin-treated patients, respectively (P=0.46). Exposure to oxaliplatin resulted in less neurotoxicity than cisplatin (25.93% vs 68.42%, P=0.01). Both regimens were well tolerated by patients; the median number of prior chemotherapy lines in the oxaliplatin- and cisplatin-treated groups was two. The median time to failure was 8.4 months in the oxaliplatin group and 7.6 months in the cisplatin group (P=0.99).

Conclusions: Platinum-based chemotherapy remains the cornerstone treatment in the setting of disease relapse with long disease-free interval. Our data suggest that salvage therapy with oxaliplatin following hypersensitivity reaction to carboplatin is associated with excellent tolerability and time to failure comparable to cisplatin. When further administration of carboplatin is precluded, oxaliplatin represents a safe and effective treatment strategy. The significantly lower neurotoxicity profile makes it an attractive alternative to cisplatin.

170 - Poster Session A

Distribution of ovarian cancer recurrence following intravenous (IV) and intraperitoneal (IP) adjuvant chemotherapy after upfront cytoreductive surgery

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Objectives: Information regarding ovarian cancer recurrence patterns after different chemotherapy administration routes is limited and remains to be further characterized. The objective of this investigation was to examine the differences in recurrence patterns in women who received IV and IP adjuvant chemotherapy following an upfront cytoreductive or staging surgical procedure for epithelial ovarian cancer (EOC).

Methods: A retrospective review of all women diagnosed with ovarian cancer from January 2005 to December 2010 was conducted at two institutions. Patient charts were reviewed and clinical data abstracted from the records. Recurrence was classified as IP, hepatic, nodal, and extra-abdominal. Statistical analyses were used to associate patterns of recurrence with route of chemotherapy administration and determine progression-free and overall survival.

Results: We identified 327 patients who underwent upfront surgery followed by either IV or IP adjuvant platinum-based chemotherapy. The majority of this cohort (n=229, 70%) received IV chemotherapy. Patients who received IP chemotherapy had a higher rate of optimal cytoreduction compared to women who received IV chemotherapy (98% vs 76%, P<0.001). Within our study group, 258/327 (78.9%) patients had recurrence of their malignancy. Of these, 71 (27.5%) received IP chemotherapy and 187 (18.3%) received IV chemotherapy (P=0.06). When patients who received IP chemotherapy were compared to those who received IV, there was no difference in the rate of IP recurrence (72.4% vs 76.2%, P=0.5), hepatic

recurrence (5.7% vs 10.4%, *P*=0.2), lymph node recurrence (20.6% vs 39.1%, *P*=0.2), distant recurrence (47.8% vs 38.4%, *P*=0.1), and pleural/lung recurrence (8.6% vs 7.3%, *P*=0.7). Median survival in our study group was 67 months. Patients who received IP chemotherapy had an improved survival compared to those who received IV chemotherapy (logrank *P*<0.001). Median survival in the IV chemotherapy group was 51 months. The median survival in the IP chemotherapy group had not been reached at the time of data retrieval.

Conclusions: Based on our study, there is no statistical difference between recurrence patterns in patients who receive IV or IP platinum-based chemotherapy after upfront cytoreductive surgery.

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171 - Poster Session A

A dose a day keeps the cancer away: metronomic albumin-bound paclitaxel and topotecan has potent antitumor activity in ovarian cancer

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Objectives: There is growing recognition of the important role of metronomic chemotherapy for cancer treatment. Based on their unique antiangiogenic effects, we tested the efficacy of combination chemotherapy with albumin-bound paclitaxel (ABP), which stimulates thrombospondin-1, and topotecan, which inhibits hypoxia-inducible factor 1-alpha, at metronomic dosing in ovarian carcinoma.

Methods: We examined the effects of ABP and topotecan in vitro (MTT) and in vivo using SKOV3ip1, HeyA8, and HeyA8-MDR orthotopic mouse models of ovarian cancer. We also examined effects on proliferation (Ki67), apoptosis (TUNEL), and angiogenesis (MVD) in tumor samples obtained at necropsy.

Results: In vitro cytotoxicity assays revealed similar effects (median inhibition concentration [IC50]=20-60 nM) with maximum tolerated dosing (MTD) and metronomic dosing of ABP on HeyA8 tumor cells (*P*<0.05). In vivo therapy experiments using the SKOV3ip1 and HeyA8 tumor models demonstrated that treatment with metronomic ABP alone and in combination with metronomic topotecan resulted in significant reductions in tumor weight (62% and 96%, respectively) as compared to controls (*P*<0.01). Combination treatment with metronomically dosed ABP and topotecan further reduced tumor growth by 82% compared to topotecan alone (*P*<0.01). In the chemoresistant tumor model, HeyA8-MDR, metronomically dosed monotherapy with either cytotoxic agent had a modest effect on tumor growth, but combination therapy decreased tumor burden by 74% when compared to controls (*P*<0.01). Metronomic ABP monotherapy resulted in reduced cell proliferation (*P*<0.001), reduced tumor angiogenesis (*P*≤0.01), and increased apoptosis (*P*<0.01).

Conclusions: Metronomically dosed ABP and topotecan offer a highly effective and novel therapeutic approach in ovarian carcinoma that merits further clinical development.

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172 - Poster Session A

Nanoparticle albumin-bound (nab) paclitaxel therapy in patients with primary and recurrent ovarian, fallopian tube, and primary peritoneal carcinoma

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Objectives: To evaluate the use of nab-paclitaxel in patients with ovarian, primary peritoneal (PP), and fallopian tube carcinomas (CA) in the primary and recurrent setting.

Methods: A single-institution retrospective analysis of women who received nab-paclitaxel with or without any additional cytotoxic agents was performed in patients with ovarian/PP/fallopian tube CA. Response was determined by measurable disease or by assessment of serial CA-125 measurements in both the primary and recurrent setting.

Results: Nineteen patients were identified; 5 (26%) received nab-paclitaxel in the primary setting and 14 (74%) in the recurrent setting. Most of the patients had a diagnosis of ovarian CA (*n*=17, 89%), with 1 PP and 1 fallopian tube CA. Of the patients who received nab-paclitaxel in the primary setting, all 5 developed a prior paclitaxel hypersensitivity reaction, 1 in

the neoadjuvant setting. All of the primary nab-paclitaxel patients received combination treatment with a platinum (4 carboplatin, 1 cisplatin) for a mean of 5.2 cycles/patient. Four of the 5 patients (80%) had a complete response to treatment, with median progression-free survival (PFS) of 9 months (range, 0.3-21 months) and median overall survival (OS) of 15 months (range, 2-25 months) noted for the group. Of the 14 patients who received nab-paclitaxel in the recurrent setting, only 1 had had a prior paclitaxel hypersensitivity reaction. Nine patients (64%) were platinum-sensitive and 36% were platinum-resistant. This was a heavily pretreated group, having received a median of 3.5 prior lines of treatment and a median of 4.5 cycles (range, 1-12 cycles) of nab-paclitaxel in the recurrent setting. The majority of patients (9/14 [64%]) received single-agent nab-paclitaxel, 1 received combination treatment with carboplatin and 4 with bevacizumab. The overall response rate was 71% (10/14), with 4 complete responses and 6 partial responses. One patient had stable disease and 3 had progression of disease. Median PFS was 9.2 months and median OS was 57 months. Nab-paclitaxel was well tolerated in this overall group of 19 patients, with neuropathy noted in 2 cases, one of which necessitated changing treatment to docetaxel, and muscle spasms in one additional patient.

Conclusions: Nab-paclitaxel is active in both primary and recurrent ovarian cancer, with an overall response rate of 71% in the recurrent setting and a tolerable toxicity profile.

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173 - Poster Session A

Serum antibodies recognizing hypoxia-inducible factor 1-alpha and platinum sensitivity in ovarian cancer

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Objectives: Antibody immunity against ovarian cancer antigens has been shown to predict disease outcome. Overexpression of hypoxia-inducible factor 1-alpha (HIF-1α) protein in ovarian cancer patients has been associated with response to platinum-based chemotherapy. We hypothesized that serum antibodies recognizing overexpressed HIF-1α in ovarian cancer patients could predict primary platinum sensitivity.

Methods: Serum samples collected from ovarian cancer patients (n=47) at the time of their initial surgery and from healthy donors (n=58) were analyzed by enzyme-linked immunosorbent assay for immunoglobulin (Ig)G antibodies to human recombinant HIF-1α protein. The median IgG antibody level of the ovarian cancer patients was used as positive cuff-off. Both positive and negative serum samples were confirmed with recombinant protein by Western blot. Age, stage, grade, histology, surgical outcome, primary platinum response, and overall survival (OS) were correlated with serum IgG antibody levels.

Results: Serum HIF-1α-specific IgG antibody levels in ovarian cancer patients were similar to those of healthy donors (mean 0.49 µg/mL vs 0.37 µg/mL, P=0.19). Patients had primarily stage III/IV disease (94%), had serous histology (85%), and were optimally debulked (74%). The median HIF-1α-specific IgG antibody of the cancer group was 0.34 µg/mL (range, 0–4.7 µg/mL). Primary platinum-sensitive patients (n=28) had significantly higher IgG antibody levels than primary platinum-resistant patients (n=19) (mean 0.70 µg/mL vs 0.17 µg/mL, P=0.003). Presence of HIF-1α-specific immunity, defined by IgG level ≥0.34 µg/mL, yielded a positive predictive value of 86% for primary platinum sensitivity. Multivariate logistic regression revealed that HIF-1α-specific IgG antibody levels ≥0.34 ug/mL was an independent predictor of primary platinum sensitivity (odds ratio 7.02, 95% CI 1.26 – 39.1, P=0.026). There was a trend toward significance in improved OS in patients with HIF-1α-specific IgG immunity (n=21) (median 42.6 months vs 33 months, P=0.06).

Conclusions: Both normal donors and cancer patients exhibited detectable serum IgG immunity to HIF-1α protein. However, increased IgG antibody immunity in ovarian cancer patients, which suggests a tumor-associated humoral immune response, is prognostic for primary platinum sensitivity.

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174 - Poster Session A

Is it equivalent? A comparison of the clinical activity of Lipodox compared to Doxil in the treatment of recurrent ovarian cancer

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Objectives: In response to the critical shortage of Doxil in the United States, the United States Food and Drug Administration (FDA) approved temporary importation of Lipodox (doxorubicin hydrochloride liposome injection) from Sun Pharma Global FZE in India. Temporary importation of unapproved foreign drugs is considered when shortages of the FDA-

approved drug are critical to patients. The efficacy and safety of substituting Doxil with Lipodox is unknown. Our hypothesis, based on clinical observation, was that the two agents are not equivalent. The primary objective in this study was to compare toxicity, the objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST), and time to progression (TTP) of Lipodox to Doxil.

Methods: This retrospective study compared patients with recurrent ovarian cancer receiving Lipodox to matched patients who received Doxil. All patients prescribed Lipodox between February 2012 and November 2012 were identified using pharmacy dispensing records. A total of 330 patient profiles from an existing de-identified Doxil database were used as matched controls 3:1 based on age, stage, platinum sensitivity, and number of prior treatments. Patients receiving combination regimens were excluded.

Results: A total of 40 recurrent ovarian cancer patients received Lipodox, and data were compared to 120 matched control Doxil patients. In this study, 42.5% of the Lipodox patients were switched to Doxil when it was available. Thus, 17 patients received combination Lipodox/Doxil. Patient demographics are described in Table 1. The OR for 23 patients who received only Lipodox was 4.3% compared to 31.8% for patients who received combination Lipodox/Doxil and 18% in matched controls. Among platinum-sensitive patients, 100% progressed in the Lipodox group compared to 22.2% in the Lipodox/Doxil group and 78.4% in matched Doxil controls. The mean TTP was 4.1±2.9 months for Lipodox only, 7.5±5.1 months for Lipodox/Doxil (*P*= 0.01), and 6.2±7.2 months in matched controls (*P*=0.17). Toxicity was similar in the Lipodox groups and control group.

Conclusions: The data suggest that Lipodox may not have equal efficacy compared to Doxil for treatment of recurrent ovarian cancer. Formal prospective clinical studies comparing the two products are warranted before Lipodox can be deemed an equivalent substitution for Doxil.

Patient demographics	Lipodox Only (N=23)	Lipodox/Doxil (N=17)	Historical Controls Doxil Alone (3:1, N=120)
Mean Age [#+/-SD (Range)]	62.2 [+/-8.8(45-77)]	61.4 [+/-12.1 (38-80)]	60.7 [+/-10.7 (33-87)]
Mean BMI [#+/-SD (Range)]	25.4 [+/-6 (16.5-40.8)]	29.1 [+/-7.4 (20.0-45.6)]	28.1 [+/-7.1 (15.4-51.0]
Race	White=17 Hispanic=1 Black=2 Asian=3	White=12 Hispanic=2 Black=2 Asian=1	White=94 Hispanic= 14 Black= 8 Asian= 4
Mean # of Comorbities [#+/-SD (Range)]	2 [+/-1 (0-5)]	2 [+/-2 (0-8)]	2 [+/-2 (0-8)]
Number Platinum-Sensitive at time of Lipodox/Doxil Treatment	9	10	57
Number Platinum-Resistant at time of Lipodox/Doxil Treatment	14	7	63
Mean Number of Prior Regimens [#+/-SD (Range)]	3 [+/-2 (1-9)]	3 [+/-2 (1-8)]	4 [+/-2 (1-9)]
Number of Patients with Prior Doxil	2	3	0
Mean Number of Cycles "Liposomal Doxorubicin" Received [#+/-SD (Range)] * = p< 0.00001 Lipodox vs combine Lipodox/Doxil; ^p=0.01 Lipodox vs Matched controls; # p=0.25 Combined Lipodox/Doxil vs Matched Controls	*^ 3 [+/-3 (1-13)]	#7 [+/-5 (2-15)]	5 [+/- 4 (1-29)]

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175 - Poster Session A

Semi-quantitative human papillomavirus virus (HPV) viral load correlates with the presence and grade of preneoplastic lesions of the uterine cervix in patients with atypical squamous cells of undetermined significance (ASCUS) cytology

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Objectives: This cross-sectional observational study was performed to evaluate the prognostic significance of HPV viral load, expressed in relative light units (RLUs), in patients with ASCUS cytology.

Methods: Among 1,520 women diagnosed with ASCUS at Konkuk University Hospital from August 2005 to December 2012, 489 underwent HPV DNA testing using the commercially available Hybrid Capture 2 (HC2®) assay, following the manufacturer's instructions. A total of 349 ASCUS cases with HPV infection detected using HC2®were histologically diagnosed. A colposcopically directed punch biopsy was performed on acetowhitened areas. Endocervical curettage biopsy and random cervical punch biopsy in four quadrants were performed in unsatisfactory colposcopy cases. In negative colposcopy cases, random cervical punch biopsy in four quadrants was performed. We evaluated the correlation between viral load, expressed in RLUs, and the severity of cervical lesions.

Results: "Negative" cases, cervical intraepithelial neoplasia (CIN)1, and CIN2+ (CIN2/CIN3) accounted for 162 (46.4%), 135 (38.7%), and 52 (14.9%) of cases, respectively. The mean patient age was 40.4±12.3 years and did not differ among the three groups (P=0.510). The median RLU values for negative, CIN1, and CIN2+ cases were 42.68 (range, 0.84-2368.30), 146.45 (range, 0.92-2701.47), and 156.43 (range, 2.20-1563.62), respectively. There was a significant correlation between RLU values and the severity of cervical lesions (P<0.001). The cutoff values of RLUs to detect CIN1+ (CIN1/CIN2/CIN3) and CIN2+ were 6.73 (sensitivity 95%, specificity 29%) and 45.64 (sensitivity 80%, specificity 44%), respectively. Of the 60 cases with RLU values <6.73, seven (11.7%) had CIN1+. In total, 17 of 52 CIN2+ cases (32.7%) had RLU values <45.64.

Conclusions: The HPV viral load in ASCUS cases significantly correlated with the severity of cervical lesions. However, this study showed large overlapping of viral loads between the grades of cervical lesions. In ASCUS cases, RLUs were not an accurate predictor of immediate cervical lesions, possibly because HPV infections with a high RLU could persist and develop into cervical lesions in the future.

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176 - Poster Session A

Narrative medicine: using reflective writing workshops to help house staff address the complex and challenging nature of caring for gynecologic oncology patients

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Objectives: Trainees in obstetrics/gynecology have been shown to have high levels of burnout. Perceived loss of control, mental overload, and lack of time may lead to burnout and decreased empathy, which can negatively affect patient care. The care of patients with gynecologic malignancies may be particularly challenging because of both emotional issues raised and the demanding workload. We assessed burnout, empathy, and perceptions of the service culture among our house staff and created a narrative medicine curriculum to explore these issues.

Methods: An electronic survey was distributed to residents and gynecologic oncology fellows that included the Maslach Burnout Inventory (MBI) and questions about their perspectives on caring for oncology patients. The MBI, a validated 22-item questionnaire, includes three subscales of burnout: Emotional Exhaustion, Depersonalization and Personal Accomplishment. A curriculum of workshops was developed using short stories and poems that addressed relevant themes as well as reflective writing prompts and group discussion to help house staff explore these issues. The curriculum was introduced into the protected mandatory didactic time. House staff completed feedback forms following each workshop.

Results: Twenty-seven house staff completed the survey. House staff showed high levels of burnout on the MBI on the subscales of Emotional Exhaustion and Depersonalization, but high levels of Personal Accomplishment (Table 1). A narrative medicine curriculum with sessions on death and dying, making mistakes, coping mechanisms, and professional calling was introduced. Four sessions take place each calendar year, with 10 to 21 house staff present at each session. Residents completed feedback forms, with 99% responding that they enjoy the workshops and 97% finding them relevant to their work. Among house staff interviewed, 95% stated they would participate again.

Conclusions: Obstetrics/gynecology house staff suffer from high emotional burnout, despite a high sense of personal accomplishment. A curriculum of reflective workshops tailored to address the challenge of caring for patients with gynecologic malignancies has been incorporated into scheduled didactic sessions, and measurement of effect is ongoing.

Table 1					
Year of training N (%)	**PGY1**	**PGY2**	**PGY3**	**PGY4**	**Fellow**
	7 (26)	6 (22)	5 (19)	6 (22)	3 (11)
I am considering specializing in gynecologic oncology N (%)	**Yes**		**No**		
	6 (22)		21 (78)		
Maslach Burnout Inventory Score Mean (SD), interpretation	**Emotional Exhaustion**	**Depersonalization**	**Personal Accomplishment**		
	27.5 (8.94), HIGH Burnout	15.8 (4.05), HIGH Burnout	40.04 (4.04), LOW Burnout		
Questionnaire Responses N (%)	**Strongly Disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly Agree**
I should be able to give bad news without feeling upset	1 (4)	8 (30)	4 (15)	11 (41)	3 (11)
I feel comfortable discussing end-of-life care with patients	0	3 (11)	5 (19)	17 (63)	2 (7)
I should be stronger than my patients about the emotional impact of their disease	0	1 (4)	12 (44)	10 (37)	4 (15)
Caring for patients with cancer is difficult for me	1 (4)	6 (22)	7 (26)	13 (48)	0
It is inappropriate to show emotion to a patient	7 (26)	15 (56)	3 (11)	2 (7)	0
Working on the gynecologic oncology service is overwhelming	5 (19)	12 (44)	8 (30)	2 (7)	0

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177 - Poster Session A

Evaluating an adnexal mass using a multivariate index assay and imaging

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Objectives: To investigate the relationship between imaging and the multivariate index assay (MIA) OVA1 in predicting the likelihood of ovarian malignancy before surgery.

Methods: Subjects were recruited in two related prospective, multi-institutional trials involving 44 sites across the United States. All women had ovarian imaging, biomarker analysis, and surgery for an adnexal mass. Imaging included ultrasonography, computed tomography scan, or magnetic resonance imaging. Ovarian tumors were classified as high risk for solid or papillary morphology, ascites, or metastases. Biomarker and imaging results were correlated with surgical findings.

Results: Of the 1110 women enrolled with an adnexal mass on imaging, 1,024 were evaluable. There were 255 malignancies and 769 benign tumors. High-risk findings were present in 59% of 1,232 imaging tests and 61% of 1,024 MIA tests. The risk of malignancy increased with MIA score; similarly, the likelihood of malignancy was higher for high-risk compared to low-risk imaging. Sensitivity and specificity for predicting malignancy was 98% (95% CI 96-99) and 27% (95% CI 24-30) for imaging "OR" MIA and 80% (95% CI 74-84) and 72% (95% CI 69-76) for imaging "AND" MIA, respectively. Only 1.6% of ovarian tumors were malignant when both tests were low risk. Logistic regression analysis revealed the following combined test performance: sensitivity 93%, specificity 54%, positive and negative predictive value 40% and 96%, respectively.

Conclusions: The MIA can be combined with a simplified imaging strategy to better assist in surgical planning for an ovarian tumor.

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178 - Poster Session A

Is hysterectomy safe after concurrent radiochemotherapy of cervical cancer?

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Objectives: To assess the safety of hysterectomy after concurrent radiochemotherapy of cervical cancer.

Methods: We reviewed 30 cervical cancer patients with FIGO IB1-IIIB stage disease, who underwent hysterectomy after concurrent radiochemotherapy in Beijing Cancer Hospital and assessed operating time, intraoperative blood loss, and postoperative complications.

Results: Twenty-eight of 30 cervical cancer patients had squamous carcinoma; the other two had adenocarcinoma. Eight patients had residual disease confirmed by postoperative pathology. Two patients underwent pelvic lymphadenectomy in addition to hysterectomy. The mean intraoperative blood loss was significatively more for these patients than for the others without pelvic lymphadenectomy (600 mL vs 100 mL, $P<0.05$). The mean operating time was 90 minutes. Rectovaginal fistula was found in two patients: one was FIGO IIIB and one was IB2. No patients recurred.

Conclusions: Hysterectomy after concurrent radiochemotherapy is relatively safe and perhaps helpful for reducing the central recurrence.

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179 - Poster Session A

Determinants of pelvic and para-aortic lymph node metastasis in endometrial cancer and its role in tailoring lymphadenectomy

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Objectives: Complete lymphadenectomy may be omitted in selected cases in which the risk of lymph node spread is low (low-risk cancer). In this study, we aimed to study the various clinicopathologic variables affecting lymph node metastasis, to evaluate the incidence and distribution of pelvic lymph nodes (PLN) and para-aortic lymph node (PALN) metastases in endometrial cancer, and to study intraoperative and postoperative complications of pelvic and para-aortic lymphadenectomy.

Methods: Our study included 78 patients with endometrial cancer between June 2005 and May 2011. The surgical procedure involved peritoneal cytology, total or radical hysterectomy, and bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy. Statistical analysis was performed using Fisher's exact probability test, and $P<0.05$ was considered statistically significant.

Results: Positive LN metastasis was diagnosed in 41% of patients: 23% with PLN and PALN metastasis, 10.3% with PLN metastasis only, and 7.7% with PALN metastasis only. The most commonly involved PLN groups were internal iliac and obturator LNs (67.9% and 61.5%). In the aortic area, the most commonly involved group (66.6%) was the preaortic LNs (supra- and inframesentric). PLN and PALN metastasis in stages III and IV was significantly higher than in stages I and II. Myometrial invasion, cervical invasion, adnexal metastasis, and lymphovascular invasion were significantly correlated with PLN metastasis, while myometrial invasion, adnexal metastasis, and lymphovascular invasion were significantly correlated with PALN metastasis. Postoperative complications were observed in 50 patients (64.1%). The most common complication was pelvic lymphocysts in 46.1%. Ileus and deep venous thrombosis were seen in 7.6%. None of the complications resulted in death.

Conclusions: Our findings suggest that systemic lymphadenectomy can be omitted in endometrial carcinoma patients who have favorable clinicopathological determinants (stage I, endometroid type, myometrial invasion<50%, and absence of lymphovascular invasion) because of low risk for LN metastasis and to avoid perioperative complications. However, these results should be confirmed in prospective large-scale, randomized clinical trials.

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180 - Poster Session A

Perioperative thromboembolism prophylaxis: how much is enough?

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Objectives: Determine the incidence of venous thromboembolism (VTE) in a single institution and identify a subgroup of patients who may benefit from prolonged VTE prophylaxis after discharge.

Methods: A retrospective review was carried out of perioperative care of women undergoing major surgery for gynecologic cancer and treated in accordance to a standardized perioperative thromboprophylaxis management between 2008 and 2010. Comprehensive data from the entire perioperative course were collected from hospital and outpatient records. Univariate, multivariate, and logistic regression analysis were used to identify risk factors associated with VTE. Costs of diagnostic tests and therapy were calculated applying published 2012 Medicare rates.

Results: A total of 285 patients met inclusion criteria. VTE occurred in 6 patients (2.1%). The mean demographics were: age 61 years, body mass index 31, 227 minutes of anesthesia, 169 minutes of surgery, 305 mL of estimated blood loss (EBL), and length of stay (LOS) of 2.78 days. Metastasis was present in 90 (32%) of patients. Significant variables by univariate analysis were presence of metastasis (P= 0.013), higher EBL (P=0.004), and increased LOS (P=0.008). Multilogistic regression linked prolonged LOS (P=0.002) with the risk of VTE, which increased to 8.5% if LOS was >3 days. A published study of a similar hypothetical population estimated a 10% decrease in VTE incidence (1.9%) with prophylaxis extending to 30 days postsurgery. Applying this information to our population would decrease the rate of VTE from six to five patients. Total cost of prophylaxis and treatment of VTE in our population was $185,565. If extended prophylaxis had been used, the cost would have been $441,928. Thus, the cost of preventing one VTE and two diagnostic tests with this treatment approach would increase by $256,363.

Conclusions: The incidence of VTE in our institution using our standardized perioperative protocol is low. Patients with metastatic disease and an LOS >3 days were at highest risk of developing a VTE. Continued prophylaxis after discharge should be considered for these patients. Extended prophylaxis for all women undergoing major surgery for cancer is not cost-effective.

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181 - Poster Session A

Malignant endometrial polyps in uterine serous carcinoma: does size matter?

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Objectives: Uterine papillary serous carcinoma (UPSC) can present with extrapelvic metastasis in the setting of limited intrauterine disease. We sought to evaluate clinical and pathologic parameters, such as polyp size, and their impact on outcome in stage 1A USC patients with cancer limited to a polyp vs those in whom disease involved the endometrium.

Methods: From 2002 to 2013, relevant clinical and pathologic information were retrospectively extracted in 129 patients with pure UPSC, with the disease limited to a polyp and/or endometrium without extrauterine spread. Separately, data were collected for patients with UPSC limited to a polyp in the endometrium and with extrapelvic spread (stage IVB). Logistic regression was used to compute the odds ratio (OR) in continuous and categorical variables via SAS v9.1.

Results: Twenty-seven patients had stage IA USC without any myometrial invasion (Table 1). Fourteen patients (52%) had tumor confined to a polyp (polyp group [PG]), with three patients having focal polyp stromal involvement. Thirteen patients had tumor limited to the endometrium (endometrial group [EG]) with (n=5) or without (n=8) polyp involvement. The median follow-up period was 31.6 months (range, 1-163 months). No patients had evidence of lymphovascular involvement (LVI). Patients in the PG had significantly less expression of the progesterone receptor (PR) than those in the EG. Significantly fewer patients received adjuvant treatment in the EG (6/13 [42.8%]). Recurrence was rare, with one patient in the PG recurring distally in her lungs after receiving external beam radiation therapy at 29 months after diagnosis and none in the EG. Comparing our cohort to a group of stage IVB patients with polyp-only disease in the uterus, the polyp diameter was significantly larger in those with abdominal metastasis (P=0.009). Logistic regression analysis showed that with every 1 cm increase in malignant polyp size, the odds of having disease limited to the endometrium decreased by almost twofold (OR 0.502, 95% CI 0.285-0.883, P=0.017). Polyps that were >2 cm had 10 times likelihood of having metastasis when compared to polyps <2 cm (OR 10.2, 95% CI 1.885 – 55.2, P=0.007).

Conclusions: Full surgical staging is important in patients with UPSC involving an endometrial polyp, especially in those whose polyps are >2 cm. Our limited data may affect the overall management of this select group of women with UPSC.

Table 1: Characteristics of patients with USC confined to a polyp or endometrium:

	Endometrim Group (n=13) (%)	Polyp Group (n=14) (%)	P-value
Age (yr)	66.5	69	NS
Body Mass Index (kg/m^2)	36.2	28.5	0.002
Polyp size (cm)	1.6	2.7	NS
Breast Cancer History	1	0	NS
ERα			
Positive	7 (78%)	9 (82%)	NS
Negative	2 (22%)	2 (18%)	
Unknown	4	3	
PR			
Positive	8 (88.9)	6 (60%)	0.001
Negative	1 (11.1)	4 (40%)	
Unknown	4	4	
Treatment			
Chemotherapy	6 (42.8%)	11 (84.6%)	0.001
Radiation	5 (35.7%)	10 (76.9%)	0.001
Recurrence	0	1 (7.1%)	

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182 - Poster Session A

Trends in patient care after discontinuation of daily progress checklists after transition to electronic patient documentation: evaluation of prophylactic compliance and surgical outcomes among gynecologic oncology patients

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Objectives: To evaluate the impact of the discontinuation of checklists at the daily progress note among gynecologic oncology patients after transition to electronic patient management.

Methods: We previously demonstrated at our institution that the use of checklists in the daily progress notes on the gynecologic oncology service resulted in a significant decrease in the length of stay during an admission, decreased nonsurgical admissions, and increased the use of compression stockings and sequential compression devices as well as deep vein thrombosis (DVT) and peptic ulcer disease (PUD) prophylaxis. Since implementing checklists into daily notes, our institution has transitioned to an electronic system for documentation and no longer incorporates these checklists. We wished to assess the impact of this change. Average length of stay, compliance with prophylactic guidelines, reason for admission, and readmission rate were compared among the following time intervals: preimplementation period of 6 months before introduction of the checklist, postimplementation period of 6 months after implementation of the checklist, immediate postdiscontinuation period 6 months after removal of the checklist, and 1 year postdiscontinuation of the checklist.

Results: Discharge summaries were evaluated (267 preimplementation, 225 postimplementation, 229 immediate postdiscontinuation, and 208 1 year postdiscontinuation.) DVT prophylaxis was given to 55% of the preimplementation group, 76% of the postimplementation group, 87% of the immediate postdiscontinuation group, and 81% of the 1 year postdiscontinuation group (P=0.000). PUD prophylaxis administration increased from 52% in the preimplementation group to 88% in the postimplementation group compared with 91% in the immediate postdiscontinuation group and 76% in the 1 year postdiscontinuation group (P=0.000). Nonsurgical admissions decreased from 41% in the preimplementation group to 32% in the postimplementation group compared with 29% in the immediate postdiscontinuation group and 34% in the 1 year postdiscontinuation group (P=0.105).

Conclusions: The use of checklists in daily progress notes enhanced patient care by improving compliance with prophylactic guidelines as well as improving surgical outcomes. This enhancement can be maintained after discontinuation of checklist use, likely due to increased vigilance in the immediate discontinuation period and standardization of clinical pathways.

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183 - Poster Session A

Preoperative hypoalbuminemia is a risk factor for 30-day morbidity after gynecologic malignancy surgery

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Objectives: To determine the relationship between preoperative hypoalbuminemia and the development of complications after gynecologic cancer surgery as well as postoperative bowel function and hospital stay.

Methods: The medical records of 533 patients undergoing elective gynecologic cancer surgery in our institution during 2005 and 2013 were reviewed. The patients had serum albumin assessed preoperative. Albumin <3.5 g/dL was defined as hypoalbuminemia. All peri- and postoperative complications within 30 days after surgery, time to resumption of normal diet, and length of hospital stay were analyzed.

Results: The median patient age was 51 years (range, 13-85 years). Eighty patients (15%) had hypoalbuminemia. Hypoalbuminemic patients had significantly higher consumption of alcohol (>2 standard drinks per day) (P=0.009), higher rate of ascites development (P<0.001), lower ASA score (P<0.001), and more advanced-stage disease (P=0.005) compared with nonhypoalbuminemic patients. The overall complication rate within 30 days after surgery was 20.3%. Hypoalbuminemic patients were more likely to develop at least one postoperative complication compared to nonhypoalbuminemic patients (34.3% vs 17.8%, P=0.022). Time to resumption of normal diet in hypoalbuminemic patients and length of hospitalization were significantly longer than that in nonhypoalbuminemic patients (3.3 days vs 2.6 days, P=0.005; 9.0 days vs 10.0 days, P=0.014, respectively). In univariate analysis, age, ASA, laparoscopic approach, hypoalbuminemia, complexity of surgery, and operation time were risk factors for postoperative complications. In multivariate analysis, age >50 years (odds ratio [OR] 2.478, 95% CI 1.310-4.684, P=0.005), operation time (OR 1.006, 95% CI 1.002-1.009, P=0.006), and hypoalbuminemia (OR 2.367, 95% CI 1.021-5.487, P=0.044) remained significant risk factors.

Conclusions: Preoperative hypoalbuminemia in patients undergoing elective surgery for gynecologic malignancy is an independent predictor of postoperative morbidity. Although the causes of hypoalbuminemia are multifactorial, identification of this subset of patients and preoperative optimization of nutritional status may improve surgical outcomes in this high-risk population.

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184 - Poster Session A

Factors associated with clinical trial screening failures in gynecologic oncology

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Objectives: Low enrollment of adult cancer patients in clinical trials is an ongoing challenge in cancer research. In general, about 3% to 5% of adults diagnosed with cancer enroll in a clinical trial. Our objective was to determine factors associated with clinical trial screening failures in women diagnosed with a gynecologic malignancy at a large urban university health system.

Methods: A retrospective review was conducted of women with gynecologic malignancies who presented to a large university system between December 2009 and December 2012. All patients identified were potential candidates for clinical trials. Data collected included demographics, socioeconomic status, medical history, and recorded reasons for screening failure.

Results: A total of 245 patients were identified as candidates for a clinical trial. Of these, 40% chose to participate in a clinical trial, with 60% declining. The median age of those who participated was 53.6 years and of nonparticipants was 56.4 years (P=NS). There were more screening failures at time of primary diagnosis (120/182 [66%]) than for recurrent cancer (28/63 [44%]) (P=0.003). Eighty percent of patients declined phase I trials compared with 42% declining phase II and 65% declining phase III trials (P=0.006). There was no statistically significant difference in nonparticipation rate based on hospital setting, payor status, language, race, family history of cancer, presence of medical comorbidities, response to prior treatment, substance abuse history, history of recent surgery, or whether the trial offered was placebo-based. Of the nonparticipants, 51% declined study due to perceived harm, 17% were ultimately deemed ineligible, 17% had extensive comorbidities, 7% due to socioeconomic barriers, 7% due to noncompliance, and 1% due to language barriers.

Conclusions: Significantly more screening failures for clinical trials occurred when trials were offered at primary diagnosis or were phase I. The majority of patients declining clinical trials did so based on perceived harm from enrolling in a clinical

trial. Our findings underscore the importance of education and social assistance when offering clinical trials to patients with limited socioeconomic support.

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185 - Poster Session A

Prediction model for 30-day morbidity after gynecologic malignancy surgery

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Objectives: To construct a preoperative nomogram predicting 30-day morbidity after gynecologic malignancy surgery.

Methods: The medical records of 533 patients who underwent elective gynecologic cancer surgery in our center from 2005 to 2013 were reviewed. All peri- and postoperative complications within 30 days after surgery were registered and classified according to the definitions of the National Surgical Quality Improvement Program (NSQIP). To investigate independent predictors of 30-day morbidity, a multivariate Cox regression model with backward stepwise elimination was used. A nomogram based on this Cox model was developed and internally validated by bootstrapping. Its performance was assessed by using the concordance index and a calibration curve.

Results: The median patient age was 51 years (range, 13-85 years). Thirty-day morbidity was seen in 107 (20.3%) patients. Multivariate regression analysis revealed that age >50 years (odds ratio [OR] 2.455, 95% CI 1.291-4.670, *P*=0.006), operation time (OR 1.006, 95% CI 1.002-1.010, *P*=0.007), and serum albumin level (OR 0.397, 95% CI 0.200-0.787, *P*=0.008) were independent predictors of postoperative morbidity. The nomogram incorporating these three predictors demonstrated good discrimination and calibration (concordance index=0.743, 95% CI 0.665–0.820).

Conclusions: Thirty-day morbidity after gynecologic cancer surgery could be predicted by age >50 years, operation time, and serum albumin level. If externally validated, the constructed nomogram could be valuable for predicting operative risk for the individual patient.

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186 - Poster Session A

Gynecologic oncology fellow perspectives on research and career development symposia: a Gynecologic Oncology Fellows' and Allied Health Professionals' Research Network (GOFRN) survey study

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Objectives: To understand gynecologic oncology fellows' attitudes and goals regarding collaborative research and career development.

Methods: An online 38-question survey was sent to attendees of the inaugural GOFRN Research Symposium at the Society of Gynecologic Oncology (SGO) 44th annual meeting. This day-long symposium focused on career development and research methodology for fellows and included a faculty lecture series, a survey design workshop, and discussion of cooperative group research. Descriptive analysis was performed, normality tested, and univariate analysis performed using either chi-square or Fisher's exact tests.

Results: The overall response rate was 67.4% (58/86 in attendance). Demographic information is summarized in Table 1. Most respondents were female (75%) and in their second year of fellowship (38.6%). Overall, fellows were "extremely" or "very" (84%) satisfied with the symposium, with the faculty lectures rated as the best part of the symposium (64%). Fellows believed an ideal future symposium would be 5 to 6 hours long (44%), contain three to four lectures (51.7%), and focus on one to two development topics (35.4%). Themes of free-text responses included fellows' desire to discuss collaborative research with other institutions (27.0%), becoming involved in clinical trials (24.3%), more discussion of work-life balance from female mentors (18.9%), and early career development (16.2%). GOFRN was felt to be "a novel way to establish collaborative relationships to research rare tumors and investigate quality outcomes and comparative effectiveness research". Fellows also expressed a desire for the GOFRN to become "an innovative network to investigate surgical and treatment disparities in the United States." The majority of respondents (91.1%) were interested in becoming involved with the GOFRN and believed it would positively affect their careers.

Conclusions: Gynecologic oncology fellows have clear ideas about symposia related to medical education. There is a strong desire to participate in substantive, fellow-directed programming at the SGO Annual Meeting and other educational forums and to become involved in cooperative group research while still in training. Further studies regarding the impact of training networks like the GOFRN on fellows' academic career development are needed.

Table 1: Demographic data from GOFRN survey of SGO annual meeting symposium respondents

Age (median, min-max)		33, 30-40
Gender	Male Female	25% 75%
Region	Northeast Midwest South West	31.6% 31.6% 22.8% 14.0%
Year in Fellowship	Before fellowship 1 2 3 4	7.0% 33.3% 38.6% 15.8% 5.3%
Length of Fellowship Program	3-Year 4-Year	67.9% 32.1%
Currently on Research Rotation	No Yes	42.9% 57.1%
Have Performed Research	No Yes	5.3% 94.7%

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187 - Poster Session A

Assessment of primary care providers' current clinical practices in determining a woman's risk for ovarian cancer

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Objectives: Ovarian cancer is the gynecologic cancer with the highest mortality rate, yet it is also a disease with known hereditary risk factors and, more recently, a better-defined set of symptoms in early-stage disease. The purpose of this study was to assess primary care practitioner knowledge of ovarian cancer risk factors, current usage of standardized tools, and the willingness to adopt a clinical decision rules algorithm into their daily practice regarding the identification of women who are at increased risk for ovarian cancer.

Methods: A survey was sent via email to 481 primary care practitioners using an online survey tool. Topics addressed included: history-taking practices, hereditary and symptomatic risk factors for ovarian cancer, and willingness to adopt a clinical decision rules algorithm into their daily practice regarding the identification of women who are at increased risk for ovarian cancer.

Results: Preliminary data from 79 respondents was presented at the 2013 New England Association of Gynecologic Oncologists Annual Meeting. Final data are now available from 179 practitioners (37% response rate). The demographics of those who responded are: 37% family medicine, 11% obstetrics and gynecology, 18% internal medicine, and 9% nurse practitioner/physician assistant. Only 20% of respondents reported that they were aware of an ovarian cancer symptom index. With regards to hereditary nonpolyposis colorectal cancer (HNPCC) screening, 5% of respondents knew either the Amsterdam II Criteria or the Revised Bethesda Criteria, but only 1.5% reported using either criteria in clinical practice. With regards to family history, most respondents reported rarely asking questions that specifically evaluate for an increased risk of *BRCA* mutation. Sixty-seven percent answered that they would be willing to use a standardized patient questionnaire, and 72% were willing to use an electronic medical record tool.

Conclusions: Primary care practitioners in our population are underutilizing available standardized tools for detecting women at risk for ovarian cancer. There also appears to be strong support from practitioners for the creation of a standardized patient history questionnaire or electronic medical record tool to aid in increasing the capture rate of these women.

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188 - Poster Session A

A new Lynch syndrome: what is the role for polymerase D1 mutations in hereditary endometrial cancer?

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Objectives: Current guidelines for genetic testing referral for Lynch syndrome (LS) fail to accurately identify endometrial cancer (EC) patients at risk for germline mutations in mismatch repair (MMR) genes. In addition, some patients report a family history consistent with LS but have microsatellite stable (MSS) tumors. Recent studies have shown a hotspot mutation in exon 12 (S478N) of polymerase D1 (*PolD1*) in families with a preponderance for colon (CRC) and EC but with MSS tumors. Our study objective was to evaluate a cohort of EC patients who met criteria for genetic counseling referral (SGO 5-10%) for increased risk of LS and MSS tumors for germline mutations in *PolD1*.

Methods: Patients with a diagnosis of EC, clinical features meeting SGO 5-10% criteria, and intact immunohistochemical staining (IHC) for MMR proteins were identified from a large unselected retrospective database. Clinicopathologic data for patients were collected through a retrospective chart review. DNA was extracted from white blood cells (WBC) available in the gynecologic oncology tumor bank, and bidirectional Sanger sequencing was performed with site-specific primers for exon 12 of *PolD1* (S478N).

Results: A total of 412 patients treated for EC from 2004-2011 with available IHC staining for Lynch associated proteins (MLH1, MSH2, MSH6, PMS2) were identified retrospectively. Of these, 88 (21.4%) patients met SGO 5-10% criteria, had intact IHC staining for all four proteins, and were presumably MSS. Thirty-eight patients had WBC available in the gynecologic oncology tumor bank. The majority of patients had stage I disease (71.1%), were grade 2 (60.5%), and had endometrioid histology (81.6%). Sixteen patients (42.1%) had a significant personal and/or family history of CRC, and nine patients (23.7%) reported a family history of EC, all with MSS tumors. Two patients (5.3%) reported a family history that met Amsterdam II criteria but had no identifiable Lynch mutation. No patients in our patient cohort had germline mutations in *PolD1* S478N on germline sequencing.

Conclusions: Despite being a hotspot mutation, no mutations in *PolD1* S478N were identified in our patient cohort. More extensive mutational analysis is ongoing for novel mutations in *PolD1* and other candidate genes that could be responsible for cases of hereditary EC.

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189 - Poster Session A

Prevalence and clinical predictors of germline *PTEN* mutation in endometrial cancer patients with Cowden and Cowden-like syndrome

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Objectives: Endometrial cancer (EC) has been recently recognized as a major cancer component in Cowden syndrome (CS). Germline *PTEN* mutation causes CS and CS-like (CSL) phenotypes, including high risks of breast, thyroid, endometrial, and other cancers. The aim of this study was to identify the prevalence and clinicopathologic features predictive of germline *PTEN* mutation in CS and CSL patients with EC.

Methods: CS or CSL patients with EC were prospectively enrolled from 2005 to 2011. All patients had comprehensive *PTEN* analysis. PTEN and downstream proteins were analyzed from patient-derived lymphoblast lines. *PTEN* Cleveland Clinic scoring system (CC score) is a regression-based system that gives a priori prediction of germline *PTEN* mutation based on certain clinical features, roughly mirroring phenotypic load and age at diagnosis.

Results: Of the 371 patients who met the inclusion criteria, 26 (7%) had germline pathogenic *PTEN* mutation (*PTEN*+), 19 (5%) had variants of unknown significance (*PTEN*_VUS), and the remaining 326 (88%) had no mutation or VUS (*PTEN*-). *PTEN*+ were significantly younger than *PTEN* VUS and *PTEN*- patients (mean age, 44 vs 52 vs 54 years, respectively, $P<0.001$). *PTEN*+ had significantly higher mean CC score compared to *PTEN*_VUS and *PTEN*- patients (30 vs 6.7

vs 7.7, respectively, *P*<0.001). Among *PTEN*+, 62.5% had the lowest quartile of blood PTEN protein level compared to 25% each for *PTEN*_VUS and *PTEN*- patients (*P*=0.01). Significant clinical predictors of germline *PTEN* mutation included age >50 year (odds ratio [OR] 6.1, 95% CI 1.4-26.2, *P*=0.015 for age <30 years and OR 4.4, 95% CI 1.7-11.2, *P*=0.001 for age 30-50 years), macrocephaly (OR 14.4, 95% CI 5.6-37.6, *P*<0.001), higher CC score (OR 1.35 for each 1-unit increment in CC score, 95% CI 1.2-1.5, *P*<0.001), PTEN protein level at the lowest quartile compared to PTEN protein level at the highest quartile (OR 5.1, 95% CI 1.1-24.6, *P*=0.039), and coexisting renal cancer (OR 5.7, 95% CI 1.86-17.55, *P*=0.002).

Conclusions: We found germline *PTEN* mutation in 7% of CS/CSL patients with EC. EC diagnosed before age 50 years, macrocephaly, lowest blood PTEN protein levels and/or prevalent renal cancer predict for presence of germline *PTEN* mutation and should alert the treating physician to potential heritable risk and referral for genetic counseling and cancer risk management.

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190 - Poster Session A

Germline *SDHB/C/D* variation and *KLLN* promoter methylation in endometrial cancer patients with Cowden and Cowden-like syndrome

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Objectives: Endometrial cancer (EC) has been recognized as a major cancer component in Cowden syndrome (CS), which is classically associated with germline *PTEN* mutations. Germline *SDHB/C/D* (*SDHx*) variation and *KLLN* promoter methylation have been recently reported in CS and CS-like (CSL) patients. The aim of this study was to identify the prevalence and clinico-athologic features predictive of germline *SDHx and KLLN* alterations in CS and CSL patients with EC.

Methods: CS or CSL patients with EC were prospectively enrolled from 2005 to 2011. All patients had comprehensive *PTEN, SDHB/C/D* mutation/variation, and *KLLN* methylation analyses. *PTEN* Cleveland Clinic scoring system (CC score) is a weighted regression-based risk calculator that gives a priori risk of germline *PTEN* mutation roughly reflecting phenotypic load and age of onset.

Results: Of the 367 patients who met the inclusion criteria, germline *SDHx* and *KLLN* promoter methylation (*KLLN*-Me+), respectively, were found in 36/367 (9.8%) and 24/228 (10.5%) of informative samples. No differences in the frequencies of germline *SDHx* variation or *KLLN*-Me+ were found between *PTEN* mutation-positive and *PTEN* mutation-negative patients (9.1% vs 9.2%, *P*=0.9 and 13% vs.9%, *P*=0.16, respectively). *KLLN*-Me+ patients were a mean 12 years younger than *KLLN*-Me-negative patients (44 vs 52 years, *P*=0.018). Further, *KLLN*-Me+ patients had higher mean CC scores compared to *KLLN* Me-negative patients (14 vs 10.6, *P*=0.01). Clinical predictors of germline *KLLN* promoter methylation were younger age (odds ratio [OR] 1.25 for each 5 years younger, 95% CI 1.04-1.50, *P*=0.015) and higher CC score (OR 1.03 for each 1-unit increment in CC score, 95% CI 0.99-1.07, *P*=0.09). There was no difference in clinical characteristics among CS/CSL patients with EC stratified by germline *SDHx* variation status.

Conclusions: Germline *SDHx* variation and *KLLN* promoter methylation occurred in 9.8% and 10.5% of CS/CSL patients with EC. *KLLN*-Me+ patients were younger at presentation and had higher CC scores. Our data suggest that earlier EC presentations in the context of increased phenotypic load are predictive of *KLLN* methylation in CS/CSL who have EC. Thus, high-risk cancer surveillance and prophylactic surgery of the uterus may be considered for *KLLN*-ME+ patients similar to those with *PTEN* mutations.

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191 - Poster Session A

PD-0332991, a cyclin-dependent kinase 4/6 inhibitor, is an active agent in uterine cancer cells

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Objectives: Uterine cancer is the most common gynecologic malignancy and has limited therapeutic options in the recurrent setting. PD-0332991 is a potent, orally active cyclin-dependent kinase (CDK) 4/6 inhibitor currently under investigation in many clinical trials. The best responses to PD-0332991 have been identified in retinoblastoma (*RB1*) wild-type cells. The Cancer Genome Atlas data on endometrial cancer indicate that 90% of tumors are *RB1*wild-type, suggesting therapeutic applicability. We aimed to establish benchmark sensitivities of uterine cancer cells to PD-0332991.

Methods: We measured the effects of PD-0332991 on proliferation and *RB1* phosphorylation in a panel of six uterine cancer cell lines. Well-characterized *RB1*-proficient and mutant cancer cell lines served as positive and negative controls, respectively. XTT Cell Proliferation assays were performed to assess drug sensitivity. Immunoblotting was performed to evaluate protein expression of total RB1, phosphorylated RB1, and total CDKN2A (p16).

Results: The majority of uterine cancer cells tested were sensitive to PD-0332991. Leiomyosarcoma cell lines were the most sensitive to PD-0332991, with median inhibition concentration (IC_{50}) values of ~0.25 µM. Endometrial cancer cell lines had more variable response to PD-0332991, with IC_{50} values ranging from 1 to 4 µM. Decreased phospho-RB1 and increased p16, detected by immunoblotting, corresponded to the drug's inhibitory effect on proliferation.

Conclusions: PD-0332991 has an antiproliferative effect in uterine cancer cell lines. As expected, most *RB1*-proficient cell lines were sensitive to the drug, with leiomyosarcomas being more sensitive than endometrial cancer cell lines. Data from our preliminary experiments suggest that PD-0332991 could be an active agent in the treatment of uterine cancer. Ongoing studies will determine if these effects are cell cycle-dependent, leading to a G1/S phase arrest and result in overexpression of *RB1*-depedent downstream effectors.

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192 - Poster Session A

Exome sequencing identifies germline mutations involving novel single nucleotide polymorphisms within DNA repair pathway genes in uterine serous carcinoma

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Objectives: The Cancer Genome Atlas (TCGA) identified uterine serous carcinoma (USC), an aggressive variant of endometrial cancer (EC), as sharing many genomic characteristics with basal-like breast and high-grade serous ovarian cancers, suggesting molecular crosslink between these tumor types. Defects in components of DNA repair pathways, such as the FANCONI (FA) and mismatch repair (MMR) genes, are responsible for numerous hereditary malignancies, including breast and ovarian carcinoma. Our objective was to perform an integrated genomic analysis of potential germline mutations of known tumor suppressor genes in pure USC with clinical and histopathologic correlation.

Methods: We prospectively collected paired tumor (T) and non-tumor (NT) tissue in seven chemotherapy-naive patients diagnosed with USC during their initial surgical staging between 2010 and 2013. We performed target capture and massively parallel genomic sequencing for 45 common tumor suppressor genes, including those within the FA and MMR pathways. Missense mutations with at least two out of three algorithms predicting a deleterious function were included in the final analysis.

Results: Table 1 describes characteristics of the seven patients. We identified 64 germline mutations, 27 of which were predicted to have deleterious function. Eighty-five percent (6/7) of samples had at least one mutation within the FA pathway, with the most commonly mutated genes being *ATM* (2/7), *NBN* (2/7), *RAD50* (1/7), and *RAD51D* (1/7). Forty-three percent (3/7) of our samples had at least one germline mutation within the MMR pathway: 3/7 in *MSH2*, 1/7 in *MLSH1* and *PMS1*, and 1/7 in *MUTYH*. In addition, we report two novel missense mutations with loss of heterogeneity in *WRAP53*, a gene involved in telomere synthesis that also regulates p53 induction upon DNA damage, and *PGPEP1*, a gene whose role in cancer genetics has not yet been elucidated.

Conclusions: Our preliminary data expand the emerging genomic platform of USC tumorigenesis by suggesting that a select group of women with USC carry germline mutations in DNA repair pathways such as FA and MMR. These findings may help with risk stratification for these patients. Because defective DNA repair pathways also render cells sensitive to radiotherapy and selected chemotherapies, our data may help to risk-stratify individualize treatments for women with UPSC.

Table 1: UPSC Patient Characteristics (n=7)

Mean Age at Diagnosis	75
Mean BMI	27.6
Race	
Black (Non-hispanic)	5 (71.4%)
Other (Hispanic)	2 (28.6%)
Stage	
I/II	2(28.6%)
III/IV	5(71.4%)
Recurrence of Disease	5(71.4%)
Treatment	
Carboplatin/Paclitaxel (3-6 Cycles)	7(100%)
Radiation Therapy	7(100%)
Platinum	
Sensitive	2(28.6%)
Resistent	4(57.1%)
Unknown	1(14.3%)
Mean Progression Free Survival	11.3 months
Mean Overall Survival	14.3 months
Personal History of Breast Cancer	3(42.9%)
Family History of Cancer (1st degree)	
Breast	2(28.6%)
Ovarian	1(14.3%)
Colon	1(14.3%)
None	3(42.9%)
Receptor Status on Immunohistochemistry	
ER+	3(42.9%)
PR+	3(42.9%)
Her2+	2(28.6%)

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193 - Poster Session A

Breast cancer risk with hormone replacement after risk-reducing Salpingo-oophorectomy in BRCA mutation carriers: does it abrogate the benefit?

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Objectives: Premenopausal risk-reducing salpingo-oophorectomy (RRSO) in *BRCA* mutation carriers is associated with a significant reduction in the risk of breast cancer. Given symptoms of surgically induced menopause, some women consider use of systemic hormone replacement therapy (HRT) after RRSO. Available data regarding the impact of this approach on subsequent breast cancer risk is, however, limited by ascertainment biases and incomplete information about the type and duration of HRT. Our objective was to prospectively determine in a well-characterized cohort if the breast cancer risk reduction conferred by premenopausal RRSO in *BRCA* mutation carriers is abrogated by the use of systemic HRT.

Methods: From June 17, 1995 through June 13, 2012, 422 unaffected women with breast tissue at risk and ovaries in situ were identified as having a deleterious *BRCA1* or *BRCA2* mutation and enrolled on an institutional review board-approved prospective follow-up study. One hundred eight of these women underwent premenopausal RRSO. The use of HRT post-RRSO and the occurrence of new breast cancer through June 10, 2013 were obtained by annual questionnaire, telephone contact, and medical record review. Impact of HRT use on subsequent breast cancer risk was analyzed using a Cox proportional hazards model.

Results: Following premenopausal RRSO, 41 of 108 women used systemic HRT (12 estrogen only, 29 estrogen plus progesterone) for a median of 34.9 months. During a median follow-up of 31.8 months, breast cancer was diagnosed in four of the 41 women who chose to use HRT after RRSO and in eight of the 67 women who did not use HRT after RRSO. After controlling for age at RRSO, there was no significant difference in the incidence of breast cancer whether or not women used HRT following RRSO (HR=0.84, 95% CI 0.25-2.88, P=0.78).

Conclusions: Results of early follow-up of this prospective series suggest that use of HRT after premenopausal RRSO in *BRCA* mutation carriers is not associated with an increased risk of subsequent breast cancer.

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194 - Poster Session A

A *KRAS* hot spot mutation correlates with *MLH1* methylation in endometrial carcinomas with microsatellite instability: a potential triage tool for Lynch syndrome evaluation

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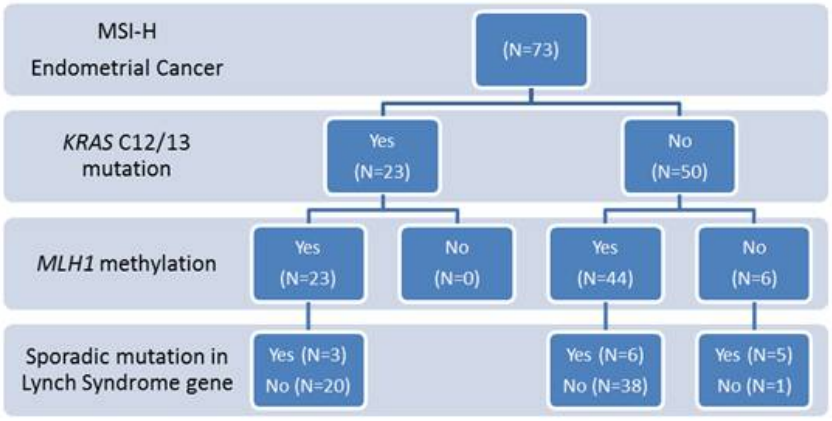
Objectives: In colorectal carcinomas with microsatellite instability (MSI), the presence of a *BRAF* V600E mutation is highly predictive of sporadic *MLH1* methylation and the absence Lynch syndrome (LS). Our objective was to determine whether a similar predictor exists in endometrial carcinoma.

Methods: Data from endometrial carcinoma patients profiled by The Cancer Genome Atlas (TCGA) were downloaded from CBioPortal. Somatic gene mutation rates were analyzed and compared among MSI-high (MSI-H) tumors with and without *MLH1* methylation. Standard statistical tests were applied.

Results: Among 245 endometrial carcinomas, 73 (29%) were MSI-H. All MSI-H tumors were endometrioid (100%), grade was evenly distributed (28% G1, 33% G2, 38% G3), and the majority were early stage (79% stage I). Sixty-seven of 73 (92%) MSI-H tumors had *MLH1* methylation. Among 11 genes with a somatic mutation rate of >20% in MSI-H tumors, only *ARID1A*, *KRAS*, *PIK3R1,* and *PTEN* were mutated at a higher rate in tumors with *MLH1* methylation, and only *KRAS* demonstrated a hot spot for recurrent mutations. Among 23 tumors with a *KRAS* codon 12 or 13 (C12/13) mutation, all 23 (100%) had *MLH1* methylation. In this group, somatic mutations in an LS gene (*MLH1*, *MSH2*, *MSH6,* or *PMS2*) were found in 13% (3 of 23). Among six tumors with no *KRAS* C12/13 mutation and no *MLH1* methylation, somatic mutations in an LS gene were found in 83% (5 of 6) (Figure). Mutations in *BRAF* were infrequent in endometrial carcinoma.

Conclusions: A *KRAS* hot spot mutation in codon 12 or 13 correlates highly with *MLH1* methylation in the endometrial cancer dataset from TCGA. Further work is necessary to determine the germline mutation status of the LS genes in these cases. Absence of germline LS mutations would suggest *KRAS* testing as a potential triage tool to identify sporadic cases in the evaluation of endometrial carcinomas with microsatellite instability. This could avoid the expense of full gene sequencing of the LS genes.

Figure:



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195 - Poster Session A

Genetic mutations and characteristics of “resistant” *BRCA1* and *BRCA2* carriers cohort

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Objectives: We describe the genetic mutations and demographic, reproductive, and environmental characteristics of a cohort of *BRCA1/2* mutation carriers who did not develop cancer and had not undergone any prophylactic surgery before the age of 65.

Methods: We reviewed 5,021 patients from the PROSE (Prevention and Observation of Surgical Endpoints) Consortium database of *BRCA1/2* mutation carriers. We evaluated the age distribution of ovarian and breast cancer incidence in the PROSE database of those ≥65 years, including those >90th percentile of the PROSE cohort. We identified *BRCA1/2* mutation carriers ≥65 years, who were never diagnosed with breast or ovarian cancer and had not undergone any prophylactic or risk-reducing surgeries. The demographic, reproductive, environmental risk factors, and genetic mutation characteristics were reviewed.

Results: We identified 38 patients who fulfilled the criteria. Fourteen patients carried *BRCA1* (0.44%% of the 3,172 total *BRCA1* carriers in PROSE) and 23 patients carried *BRCA2* (1.21% of the 1,894 total *BRCA2* carriers in PROSE). One patient carried both mutations. Twenty-six (68.4%) women were Caucasian and 10 (26.3%) were Jewish. The mean follow-up period from testing was 9.8 years. The mean age of menarche was 12.8 years. Nine women were nulliparous, and the average parity of the rest was 3.8. Eleven (29.0%) women used oral contraception, and 14 (36.8%) women used hormone replacement therapy for an average of 87.7 months. The *BRCA1/2* mutations observed were:

Conclusions: A greater proportion of *BRCA2* than *BRCA1* carriers were without cancer. These data begin to characterize a unique subgroup of *BRCA1/2* mutation carriers who appear to be resistant to developing cancer. Studying the genetic mutation characteristics as well as the modifiable risk factors of this unique group will provide further insight into the risk assessment process in *BRCA* carriers.

BRCA1	Frequency
1559insA (FS, PTC)	1
185delAG	2
2671delAA (FS, PTC)	1
3604delA	1
3747insA	1
5382insC	1
5385insC	1
916delTT	1
Cys61Gly (MS, MS)	1
Q563X (NS, PTC)	1
Q780X	1
c.1505_1509delTAAAG	1
c.5152+1G>T (S, IFD)	1
del exons 1-23	1
Total	15

BRCA1 Mutation Type	Frequency	Percentage
Frameshift	7	63.64
Nonsense	2	18.18
Splice	1	9.09
Missing	1	9.09
Total	11	

BRCA2	Frequency
279delAC (FS, PTC)	2
3036del4 (FS, PTC)	1
4706del4 (FS, PTC)	2
5950delCT (FS, PTC)	1
6174delT (FS, PTC)	8
6503delTT (FS, PTC)	1
7231del5 (FS/S?, unknown)	1
8765delAG (FS, PTC)	1
886delGT (FS, PTC)	1
9325insA (FS, PTC)	1
K944X	1
N/A	1
R245X	1
R2659K (8204G>A) (S, IFD)	1
Y1313X	1
Total	24

BRCA2 Mutation Type	Frequency	Percentage
Frameshift	14	77.78
Nonsense	2	11.11
N/A	2	11.11
Total	18	

196 - Poster Session A

Gene expression profiles of high-grade serous ovarian cancers in patients with normal CA-125 levels at the time of recurrence

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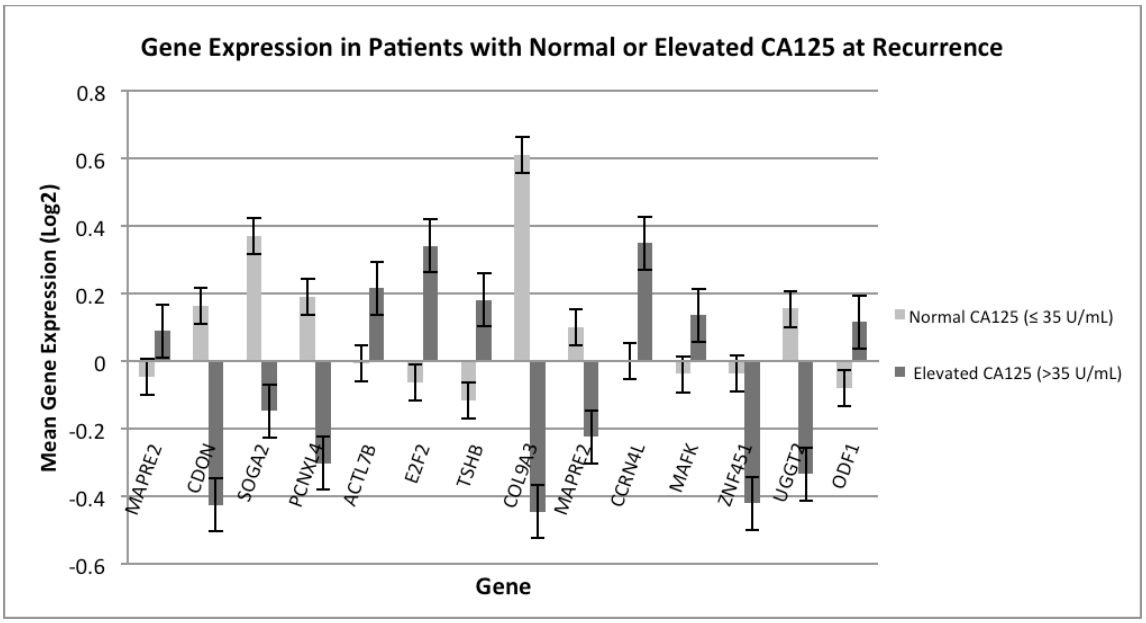
Objectives: CA-125 is a useful tool for monitoring response to therapy and recurrence in patients with high-grade serous ovarian cancer (HGSOC). However, 15% to 20% of patients have normal levels of CA-125 at the time of recurrence, limiting the prognostic ability of CA-125 in this population. We aimed to determine differences in gene expression profiles of tumors from patients with and without elevated CA-125 levels at the time of recurrence.

Methods: Patients with stage IIIC or IV HGSOC who underwent primary surgical cytoreduction and initial platinum-based chemotherapy were identified from The Cancer Genome Atlas (TCGA). All patients had platinum-sensitive, radiographic-confirmed recurrent disease. Patients were stratified into two groups: those with elevated CA-125 (>35 U/mL) and those with normal CA-125 (≤35 U/mL) at time of recurrence. Gene expression profiling was performed using 1 Agilent and 2 Affymetrix expression microarray platforms. Expression data were combined across microarrays using factor analysis for genes present on all array platforms. Gene expression levels for 11,864 genes were analyzed. Mean gene expression was compared using student t-test and significance was defined as $P<0.001$.

Results: Data were available for 21 patients with normal CA-125 (≤35 U/mL) and 32 patients with elevated CA-125 (>35 U/mL) at the time of recurrence. There were no statistical differences in mean age (56 years, STD 11 years) or median time to recurrence (13 months, range 6-50 months) between the two study groups. Of the 11,864 genes analyzed, 14 showed a statistically significant difference in expression between the two groups (Figure); six genes had increased expression and eight genes had decreased expression in patients with normal CA-125 levels at recurrence. The gene functions were consistent with known CA-125/MUC16 biology, including regulation of transcription and DNA binding, which would affect growth, mobility, and invasion.

Conclusions: Gene expression profiles vary between advanced-stage, platinum-sensitive HGSOC patients who recur with and without elevated CA-125 levels. These findings may indicate inherent differences in tumor biology. Further evaluation of the functional significance of this variable gene expression may lead to better stratification and monitoring approaches based on primary tumor genomics.

Figure:



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197 - Poster Session A

Association of in vitro chemotherapy drug resistance assays in ovarian cancer patients with *BRCA1/2* mutations

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Objectives: To evaluate performance of an in vitro chemotherapy drug response assay in *BRCA1/2*-deficient patients with primary ovarian cancer (OVCA).

Methods: Retrospective review of newly diagnosed OVCA patients undergoing primary staging/debulking surgery with performance of commercially available in vitro chemosensitivity assays (CSTA). All patients were offered genetic counseling and testing. Progression-free survival (PFS) and overall survival (OS) were analyzed. Comparative analysis was performed using Fisher's exact test. PFSs were analyzed using Kaplan-Meier curves.

Results: A total of 140 patients met inclusion criteria and had adequate follow-up information. Deleterious mutations in *BRCA1* and BRCA2 were found in 8.6% (12/140) and 6.4% (9/140) of patients, respectively, with 25.7% (25/140) patients negative for *BRCA* mutation. The remaining 59.3% (83/140) declined testing. All patients underwent primary chemotherapy with a platinum agent and a taxane. The mean age at diagnosis was 55 and 61 years in *BRCA1/2* mutated and negative/not tested patients (neg/NT). The majority of patients were diagnosed with stage III/IV disease: 71.4% (15/21) *BRCA and* 80.7% (96/119) neg/NT patients. *BRCA1/2* patients had a trend toward improved PFS when compared to PFS in neg/NT (19 vs 26) (P=0.08). There were no statistically significant differences in CTSA between *BRCA1/2* and neg/NT patients: carboplatin (73.7% response vs 61.6% response, P=0.43), cisplatin (64.3% vs 49.3% P=0.39), carboplatin with paclitaxel (80% vs 80%, P=1.00), carboplatin with docetaxel (83.3% vs 85.3%, P=1.00), carboplatin with gemcitabine (77.3% vs 76.7%, P=1.00), doxorubicin (20.0% vs 33.7%, P=0.37), gemcitabine (35.0% vs 32.3%, P=0.80), paclitaxel (57.9 vs 56.4%, P=1.00), and docetaxel (37.5% vs 34.4%, P=0.78).

Conclusions: In this review of primary OVCA patients tested with CTSA, no significant difference in chemosensitivities based on *BRCA* mutation status was observed. Although *BRCA* mutation has been linked to increased platinum sensitivity, this was not demonstrated based on the drug assay. An in vivo mechanism not evaluated by in vitro assay may account for clinically observed increased platinum sensitivity.

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198 - Poster Session A

Inhibition of chaperone-mediated autophagy may be a novel approach to increase platinum susceptibility in ovarian cancer cell lines

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Objectives: Chaperone-mediated autophagy (CMA) assures lysosomal degradation of specific damaged cytosolic proteins. Our group has previously shown that CMA is upregulated in different types of cancer cells and is required for lung and melanoma tumor growth. We hypothesized that upregulation of CMA may underlie chemotherapy resistance in serous ovarian cancer by removing cellular damage generated by the treatment.

Methods: CMA and macroautophagy (MA) activity were assessed in ovarian cancer cell lines with different sensitivities to cisplatin and in formalin-fixed tumor specimens using biochemical and image-based procedures. Markers of both pathways were measured by immunoblot, immunofluorescence, and immunohistochemistry (IHC). MA activity was assessed by LC3B flux assay and CMA activity using a photoactivatable fluorescent reporter. CMA was inhibited using RNA interference against LAMP-2A, the CMA lysosomal receptor. Changes in protein expression between knockdown cells and control were assessed. Cell proliferation and cell viability were measured using standard assays to analyze changes in susceptibility to chemotherapy.

Results: Tumor IHC revealed significantly increased expression of LAMP-2A for all ovarian cancer stages, while LC3 was decreased in all stages compared to control. MA activity was comparable in control and platinum-sensitive cell lines, but it was reduced in the platinum-resistant cell line. CMA markers and activity were increased in the ovarian cancer cells compared to control but most notably in the platinum-resistant cell line. Blockage of CMA by LAMP-2A knockdown decreased proliferation rates of both cancer cell lines and partially restored cisplatin sensitivity in the platinum-resistant cell line. We are currently investigating the molecular changes induced by the blockage of CMA in the platinum-resistant cells that contributed to their increased sensitivity.

Conclusions: Inhibition of chaperone-mediated autophagy may be a novel approach to increase chemotherapy susceptibility of platinum-resistant ovarian cancers.

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199 - Poster Session A

The management of peritoneal surface malignancies: single-center initial experience

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Objectives: Peritoneal carcinomatosis (PC) has been traditionally considered a terminal disease, with median survivals reported in the literature of 6 to 12 months. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have gradually gained acceptance as the standard of care in the management of selected cases of PC. Excellent results have been achieved in well-selected patients, but there is a very steep learning curve when starting a new program.

Methods: A program for the multidisciplinary treatment of peritoneal surface malignancies of gastrointestinal or gynecologic origin was initiated in January 2010 at the American University of Beirut Medical Center. Patients enrolled in the program were treated using multimodality therapy with combinations of systemic therapy, cytoreductive surgery (CRS), and HIPEC. We present the results of our initial experience using a retrospective review of a prospectively collected database.

Results: Twenty-three patients were treated with CRS and HIPEC. There were 10 male and 13 female patients. The most common indication (35%) was PC of colorectal origin, followed closely by pseudomyxoma (30%), ovarian malignancies (22%), gastric cancer (8%), and mesothelioma (4%). The mean duration of surgery was 480 minutes. Mean Peritoneal Cancer Index was 26. Twenty-one (91%) patients had a complete cytoreduction. Major morbidity and mortality rates were 35% and 4.3%, respectively. Mean hospital stay was 16 days. At a mean follow-up of 18 months, median survival has not been reached.

Conclusions: We report the successful establishment of an active peritoneal surface malignancy multidisciplinary treatment program with excellent early results that are comparable to those published by reputable centers in the literature. Careful patient selection, a multidisciplinary approach, and proper surgical training and technique are essential for the success of such a program.

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200 - Poster Session A

The mTOR inhibitor RAD001 exhibited more efficacy against ovarian cancer ascites after pharmacologic inhibition of Mirk kinase

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Objectives: The PI3K/PTEN/Akt/mTOR pathway is one of the most frequently deregulated signaling pathways in ovarian cancer and is often responsible for the chemoresistance characterizing recurrent ovarian cancers. Several inhibitors of this pathway have shown limited clinical responses due to upregulation of other survival pathways in complex feedback loops. Because pharmacologic inhibition of mTOR causes Akt or PI3K upregulated expression of Mirk/dyrk1B kinase, we determined whether pharmacologic inhibition of Mirk kinase would enhance the toxicity of mTOR inhibitors toward ovarian cancer ascites taken from patients. Mirk is expressed in most ovarian cancers, and depletion or pharmacologic inhibition of Mirk forces ovarian cancer cells to enter the cycle with elevated reactive oxygen species (ROS) levels, leading to cell death.

Methods: Ascites were maintained as nonadherent multicellular aggregates or spheroids by culture in serum-free spheroid media in ultralow-attachment dishes. Specimens were obtained from eight patients with newly diagnosed epithelial ovarian cancer.

Results: A Mirk/dyrk1B kinase inhibitor increased the sensitivity of three ovarian cancer cell lines to the mTOR inhibitor RAD001 (everolimus). Spheroids from these lines, like ascites spheroids, were largely quiescent, mostly in G0/G1, and enriched in Mirk/dyrk1B kinase and the quiescence proteins p130/Rb2 and the CDK inhibitor p27. Inhibition of Mirk/dyrk1B kinase led to a decrease in spheroid quiescence markers, an increase in ROS levels, and up to a sevenfold decrease in spheroid volume and viable cell numbers. Significantly, treatment of eight of eight patient-derived ovarian cancer ascites with a Mirk/dyrk1B kinase inhibitor together with the mTOR inhibitor RAD001 led first to an induction of apoptosis markers, then to a disruption of spheroid structure, and finally to loss in viable tumor cells. The Mirk inhibitor, at the concentration that killed patient-derived ovarian cancer ascites cells in vitro, had no detectable toxicity in mice, but reduced the size of xenografts up to threefold.

Conclusions: The mTOR inhibitor RAD001 was more effective against ovarian cancer ascites when Mirk/dyrk1B kinase was inhibited.

201 - Poster Session A

The usefulness of ovarian cancer risk scoring in the discrimination of an isolated pelvic mass

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Objectives: Treatment by a gynecologic oncologist improves survival for women with ovarian cancer. When patients present with a pelvic mass, risk-scoring systems are commonly applied to predict the likelihood of benign vs malignant disease based on menopausal status, tumor markers, and ultrasound findings. The objective of this study was to determine the usefulness of the Risk of Malignancy Index (RMI) to guide appropriate referral in patients with an isolated pelvic mass using a prospective population-based cohort.

Methods: All patients presenting to our institution from February 2011 through November 2012 with known ovarian cancer, *BRCA* mutations, or a pelvic mass were approached for inclusion in this prospective cohort study. Patients with an isolated pelvic mass were evaluated using surgical/pathological data and tumor marker/imaging findings. Patients were eligible if computed tomography scan showed lymphadenopathy <2 cm or mild-moderate ascites, but ineligible if there was obvious evidence of metastatic disease. The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of the RMI were determined.

Results: Eighty-two patients presented with a solitary pelvic mass and no evidence of metastatic disease. The mean age was 56±14 years, and 64% were postmenopausal. The median CA-125 values was 54 U/mL (range, 3 – 1,953 U/mL) and 31 U/mL (range, 2 – 479 U/mL) for patients with and without a confirmed malignancy, respectively. The sensitivity, specificity, PPV, and NPV of the RMI were 84%, 53%, 49%, and 86%. False-negative scores included Ewing sarcoma, metastatic colorectal cancer, and two stage I ovarian cancers (clear cell and low-grade serous). Fifty percent of false-positive scores were borderline ovarian tumors. If borderline tumors were considered malignant, the sensitivity, specificity, PPV, and NPV were 76%, 63%, 74%, and 65%.

Conclusions: RMI scoring in the setting of an isolated, unilateral pelvic mass has low specificity and predictive value. Although the majority of malignancies are identified, guiding referral to specialized centers for surgical management, 50% of such referred cases will be misclassified, affecting hospital resources. Meanwhile, the minority of malignant pelvic masses that continue to be misclassified may lose the opportunity for appropriate surgical staging at the time of primary surgery.

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202 - Poster Session A

Do high-grade stage I ovarian cancers benefit from adjuvant chemotherapy?

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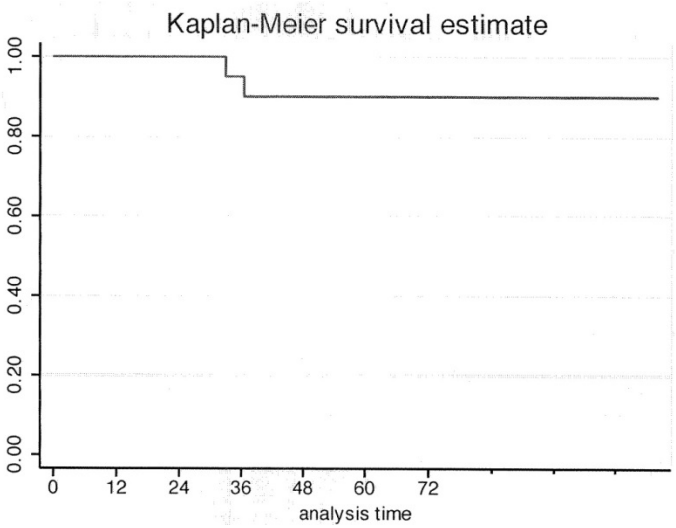
Objectives: Approximately 30% of patients with ovarian cancer are diagnosed with early-stage disease. Those with stage IC high-grade or clear cell histology have as high as 40% risk of recurrence. This high recurrence rate has led many clinicians to offer adjuvant treatment, despite lack of definitive proof of efficacy. Our objective was to review the results of patients with high-grade stage I ovarian cancer managed without adjuvant treatment.

Methods: A retrospective chart review identified patients with newly diagnosed stage I high-grade ovarian cancer, including serous, clear cell, and endometroid histology, who underwent comprehensive surgical staging. We excluded all patients with stage II or greater, low-grade or mucinous histology, incomplete surgical staging, neoadjuvant chemotherapy, previous radiation therapy, postsurgery adjuvant treatment, or other malignancy.

Results: Thirty-three patients with FIGO surgical stage I high-grade ovarian cancer were identified (16 stage IA, 9 stage IB disease, and 8 stage IC). Fourteen were clear cell, seven endometroid, five serous, and seven mixed histology. After a median follow-up of 40 months (range, 7-116 months), nine patients (27%) recurred. The median time to recurrence was 19 months (range, 1-69 months). At last contact, of the nine patients with recurrences four (44%) were alive with disease, three (33%) had no evidence of disease, and two had died of disease (22%). The 2- and 5-year overall survival was 100% and 90%, respectively (Figure 1).

Conclusions: The recurrence rates of stage I high-risk epithelial ovarian cancer that is completely staged without adjuvant treatment appear to be comparable to those of treatment arms reported in the literature. A proportion of these patients can be salvaged at recurrence, yielding a high overall survival. A randomized study of high-grade fully staged ovarian cancer patients managed with and without adjuvant therapy is warranted.



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203 - Poster Session A

Risk factors for progression to invasive carcinoma in patients with borderline ovarian tumors

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Objectives: To identify risk factors for progression to invasive carcinoma in patients with borderline ovarian tumors (BOTs).

Methods: We performed a retrospective review of all patients treated and followed for BOTs between 1996 and 2011. Multivariate Cox proportional hazard model was performed to identify independent risk factors for progression to invasive carcinoma.

Results: A total of 364 patients were identified. During the median follow-up of 53.8 months, 31 patients (8.5%) developed recurrent disease: 12 (3.3%) had recurrent disease with progression to invasive carcinoma and 19 (5.2%) had recurrent disease with borderline histology. Disease-related death (7/364 [1.7%]) was observed only in patients with progression to invasive carcinoma. Multivariate analysis showed that independent risk factors for progression to invasive carcinoma were advanced disease stage (hazard ratio [HR] 5.59, P=0.005), age ≥65 years (HR 5.13, P=0.037), and the presence of microinvasion (HR 3.71, P=0.047). These three factors were also independently related to overall survival.

Conclusions: Although patients with BOTs have an excellent prognosis, the risk of progression to invasive carcinoma and, thereby, death remains. Therefore, physician should pay closer attention to BOT patients with risk factors (i.e., advanced disease stage, older age, and microinvasion) and undertake more careful surveillance for progression to invasive carcinoma.

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204 - Poster Session A

Clinicopathological prognostic factors for recurrence in adult granulosa cell tumor of the ovary

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Objectives: Granulosa cell tumor (GCT) accounts for <5% of all ovarian malignancies, and 95% of them occur after 30 years of age (adult type). The aim of this study was to evaluate prognostic factors for recurrence in GCT.

Methods: A retrospective review of the records of patients with adult GCT of the ovary treated in our institution from 1996 through 2011 was conducted. Clinical, pathological, and survival data were collected. Kaplan-Meier and Cox proportional hazards analyses along with receiver operating characteristic curve analysis were used to identify the predictions for recurrence and determine the cutoff value of continuous variables for predicting recurrence.

Results: A total of 48 women whose mean age was 54.4 years (SD=18.6 years) participated in the study; 64.6% of them were postmenopausal. In 45.8% of the cases, cystic tumor was found preoperatively via ultrasonography; in 22.9% of cases, solid tumor was identified. Intraoperative rupture of tumor occurred in 12.5% of the patients; surgical staging was completed in 58.3% (18.8% had pelvic lymphadenectomy). Only six (12.6%) had stage IIB to IIIC disease; the majority had stage IA (64.4%). Mitotic index was 4 or more in 39.6% of the patients, and nuclear atypia was moderate to high in 72.5%. The mean follow-up period was 8.8 years (SD=4.6), with median equal to 8.1 years (interquartile range from 5.0 to 12.9 years). During the follow-up period, disease recurrence occurred in seven patients (14.6%), none of whom died. The cumulative recurrence-free rate for the first 2 years was 97.9% (SE=2.1%), for 5 years was 93% (SE=3.9%), and for 10 years was 80.4% (SE=6.8%). Cox analysis showed a significant association of tumor size, stage, and mitotic index with the risk for recurrence. Age, menopause, ultrasonogaphy findings, CA-125, intraoperative rupture of tumor, pelvic lymphadenectomy, surgical staging, and nuclear atypia were not significantly associated with recurrence-free survival, but were independent predictors.

Conclusions: Recurrence in GCT appears to be associated with tumor size and stage as parameters of clinical prognostic importance. Mitotic index seems to be the only significant pathologic prognostic factor.

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205 - Poster Session A

Use and duration of chemotherapy and its impact on survival in early-stage ovarian cancer

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Objectives: Although 5-year survival for early-stage ovarian cancer is favorable, prognosis at recurrence is poor, necessitating appropriate initial management. We examined the patterns of care and the impact of the duration of chemotherapy on survival for women with early-stage ovarian cancer.

Methods: Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified a cohort of women 65 years of age with stage I-II ovarian cancer diagnosed from 1991 to 2007. Patients were categorized as low-risk (non-clear cell histology, stage IA or IB, grade 1 or 2) or high-risk (clear cell histology, grade 3, or stage IC or II). We used multivariable logistic regression and Cox proportional hazards models to determine predictors of chemotherapy and the effect of chemotherapy use and duration on survival.

Results: Among 1,844 women with early-stage ovarian cancer, 790 (43%) underwent lymphadenectomy. Among low-risk patients, 26% (86/337) received adjuvant chemotherapy, and the use of chemotherapy increased with time. Among high-risk patients, 71% (793/1124) received adjuvant chemotherapy; 28% had ≤3 months of treatment, and 72% had >3 months of treatment. Older patients were less likely to receive chemotherapy while those with higher stage and grade disease were more likely to receive chemotherapy (P<0.05 for all). Among high-risk patients, the duration of chemotherapy did not affect overall (HR 1.08, 95% CI 0.83-1.41) or cancer-specific (HR 1.26, 95% CI 0.88-1.81) survival.

Conclusions: Practice patterns are widely divergent in treating early-stage ovarian cancer patients. Most patients are not completely surgically staged. Extended-duration chemotherapy does not appear to affect survival with high-risk disease.

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206 - Poster Session A

Clinical response to anti-estrogen therapy in platinum-resistant ovarian cancer patients and the role of tumor estrogen receptor expression status

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Objectives: To determine the progression-free interval (PFI) for patients with platinum-resistant ovarian cancer receiving anti-estrogen therapy and to correlate PFI with estrogen receptor (ER) expression in tumor specimens.

Methods: This is a retrospective cohort study of platinum-resistant epithelial ovarian, fallopian tube, and primary peritoneal cancers treated with tamoxifen or an aromatase inhibitor (AI) at our institution from January 1999 to January 2012. Patient data were abstracted from medical records. Median PFI on anti-estrogen therapy was calculated and a 95% CI was constructed by bootstrapping. Relationships of PFI with disease characteristics were examined using one-way ANOVA or Pearson correlation. ER status of tumor specimens was assessed by immunohistochemistry (IHC) using the Allred score. PFI was compared between ER status groups with the Mann-Whitney test.

Results: A total of 103 patients met inclusion criteria: 79% were prescribed tamoxifen and 21% were prescribed an AI. Patients had a mean of four prior chemotherapy regimens (range, 1-14). Median PFI for anti-estrogen treatment was 4.0 months (range, 1-49 months), with a 95% CI of 3.0, 5.0, which was comparable to the published PFI for gemcitabine (median PFI 2.8-5.0 months) and liposomal doxorubicin (median PFI 4.8-5.7 months). Fourteen percent of patients were prescribed a second anti-estrogen agent, with median PFI of 4.0 months (range, 1-15 months). PFI was independent of stage, number of prior treatments, and type of anti-estrogen therapy. ER status was obtained for 56 patients. Nine had been determined to be ER-positive prior to therapy. IHC was performed on 47 patients who received hormonal therapy with unknown ER status, and 31 were ER-positive. PFI was not significantly different between ER-positive (median 4.0 months) and ER-negative (median 2.0 months) status (P=0.09).

Conclusions: This is the largest study to date on the use of anti-estrogen therapy for women with heavily pretreated, platinum-resistant ovarian cancer. The median PFI of 4.0 months is comparable to that seen with standard cytotoxic therapies, and long-term responders were seen. Responses were seen in patients whose tumors were ER-negative. Thus, given the low adverse effect profile of anti-estrogen therapy, this treatment approach should be considered for all platinum-resistant ovarian cancer patients.

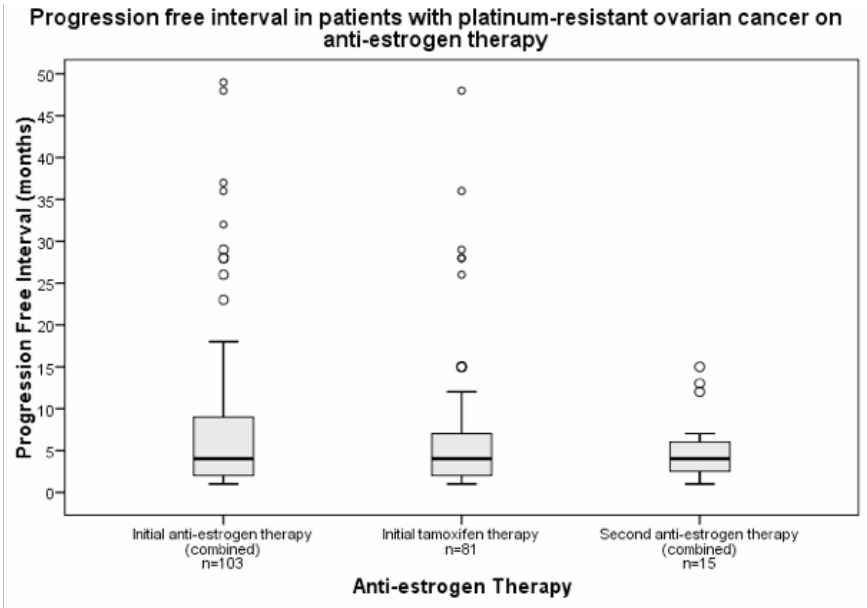

Figure 1. Progression free interval in patients with platinum-resistant ovarian cancer on anti-estrogen therapy. Boxplot demonstrating PFI following initial anti-estrogen therapy, initial therapy with tamoxifen specifically, and second anti-estrogen therapy. Horizontal black line demonstrates the median, grey box represents the 25% and 75% margins, and vertical lines the range. Outliers are shown with open circles.

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207 - Poster Session A

Impact of lymphovascular space invasion (LVSI) on survival of stage I epithelial ovarian cancer

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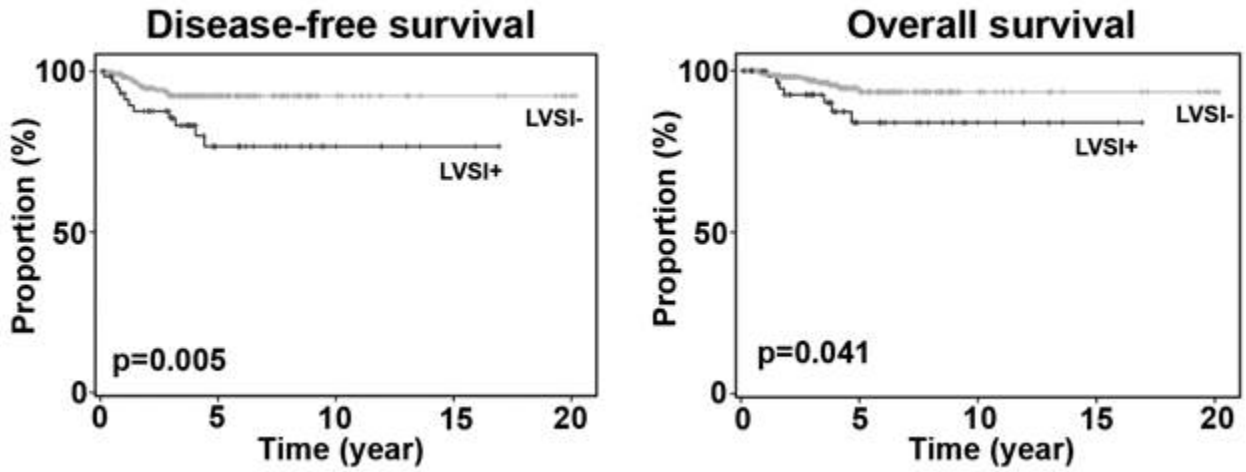
Objectives: Although early-stage ovarian cancer seems to have a generally decent prognosis, identifying any tumor marker associated with increased risk of recurrence can aid in guiding management. The aim of study was to evaluate the impact of LVSI on survival of early-stage epithelial ovarian cancer patients.

Methods: A multicenter retrospective study was conducted of patients with stage IA-C epithelial ovarian cancer who underwent primary cytoreductive surgery including lymphadenectomy. Histopathology slides for ovarian tumors were examined by gynecologic pathologists, and LVSI was assessed as present or absent. Survival analysis was performed examining tumoral factors.

Results: Among 312 cases evaluated for the analysis, LVSI was detected in 63 (20.2%, 95% CI 15.7-24.6) cases of stage I epithelial ovarian cancer and associated with histology type (endometrioid 9.1%, low-grade serous 10.5%, mucinous 19.3%, high-grade serous 27.8%, and clear cell 28.2%, *P*=0.019), grade (low vs high, 15.0% vs 24.7%, *P*=0.046), and stage (IA-B vs IC, 14.3% vs 23.5%, *P*=0.057). LVSI was significantly associated with decreased survival outcomes: 5-year progression-free survival (PFS) of 76.3% vs 92.4% (*P*=0.005) and overall survival of 84.0% vs 93.6% (*P*=0.041). LVSI remained a significant variable associated with decreased PFS (HR 2.30, 95% CI 1.01-5.21, *P*=0.047) after controlling for other significant variables, including age (≥50 vs <50 years, *P*=0.39), histology (high-grade serous vs others, *P*=0.28), grade (high vs low, *P*=0.22), stage (IC vs IA-B, *P*=0.33), and adjuvant chemotherapy (yes vs no, *P*=0.72).

Conclusions: LVSI is an important histologic feature to identify a subgroup of patients with increased risk of recurrence in stage I epithelial ovarian cancer.



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208 - Poster Session A

Preoperative predictors which impact the survival and outcome of secondary cytoreduction in ovarian cancer

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Objectives: To examine a variety of factors that may influence the feasibility of optimal and complete secondary cytoreductive surgery (SCRS) and to characterize the prognostic factors that correlate with improved survival in a single-institutional cohort of patients who underwent SCRS.

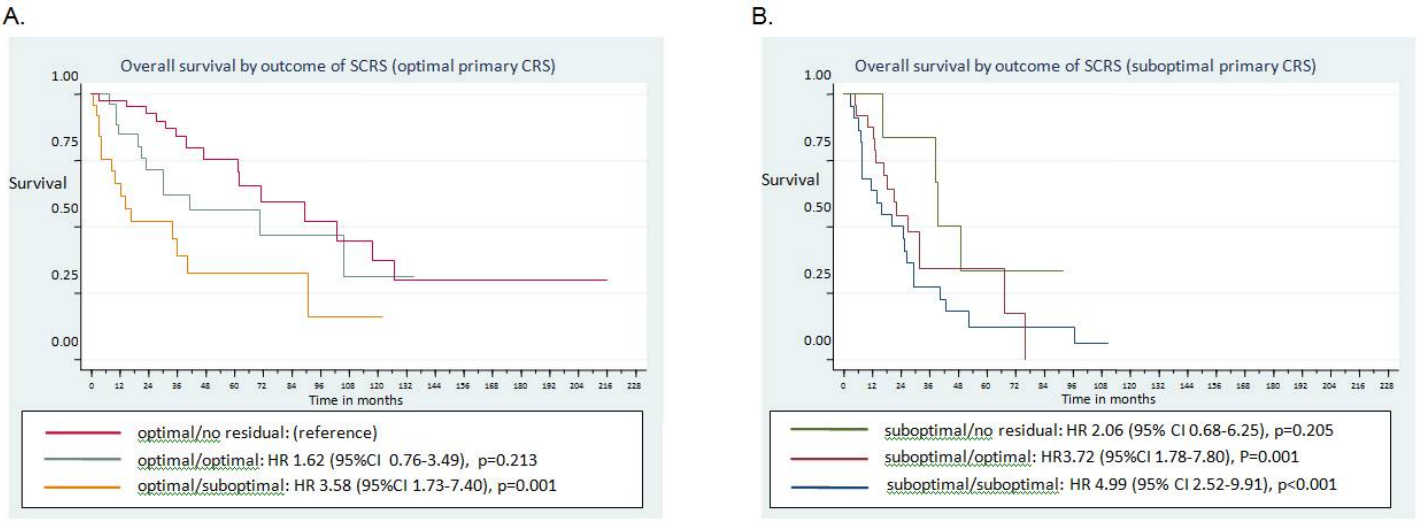
Methods: A retrospective cohort study of patients who underwent surgical exploration for recurrent epithelial ovarian cancer (EOC) at our institution between January 1985 and December 2010. Institutional review board approval was obtained before initiation of the study.

Results: Of 181 patients who underwent surgery for histologically documented recurrent EOC, 148 were included for analysis due to completeness of data. The median follow-up was 30 months from date of SCRS (range, 0.43-216.16 months). Platinum sensitivity was more likely to result in complete (as opposed to suboptimal) cytoreduction at SCRS (odds ratio [OR] 3.94, 95% CI 1.41-11.11, *P*=0.009). Suboptimal cytoreduction at primary surgery was more likely to result in suboptimal cytoreduction at SCRS (OR 5.28, 95% CI 1.97-14.13, *P*=0.001). Size of largest tumor implant >4 cm was associated with increased likelihood of suboptimal SCRS (OR 5.77, 95% CI 1.02 – 32.70, *P*=0.048). Overall survival analysis using Kaplan-Meier curves showed a survival advantage for complete cytoreduction vs optimal cytoreduction vs suboptimal

cytoreduction. Outcome of SCRS affected survival regardless of outcome of primary surgery, with no statistically significant difference in survival between optimal/complete and suboptimal/complete groups (HR 2.06, 95% CI 0.68-6.25, *P*=0.205), while suboptimal SCRS was associated with worse survival regardless of primary cytoreduction outcome (HR 3.58, 95% CI 1.73-7.40, *P*=0.001 and HR 4.99, 95% CI 2.52-9.91, *P*<0.001 for optimal/suboptimal and suboptimal/suboptimal groups, respectively) (Figure 1). Location of largest implant in upper abdomen (as opposed to mid-abdomen and pelvis) and presence of ascites at SCRS were associated with shorter overall survival.

Conclusions: Preoperative factors affect the outcome of SCRS. Complete cytoreduction at SCRS was associated with improved overall survival regardless of outcome of primary surgery, although complete cytoreduction was less likely to be achieved if primary cytoreduction was suboptimal.

Figure 1



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209 - Poster Session A

Tumor microvessel density does not correlate with bevacizumab response in recurrent ovarian cancer

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Objectives: To evaluate the significance of tumor microvessel density (MVD) on response to bevacizumab chemotherapy in recurrent ovarian cancer.

Methods: We identified patients treated with bevacizumab for recurrent ovarian cancer off trial from 2005 to 2012. We then counted the MVD of original surgery ovarian tumor slides by immunohistochemical staining with CD31, a pan-endothelial marker. MVD was assessed by averaging three areas of high cross-section vessel count on light microscopy at high power (x200). Counts were performed by two independent, blinded physicians. Charts were reviewed for clinical data. Response was analyzed both as a dichotomized variable using Gynecologic Cancer Intergroup (GCIG) CA-125 criteria and as a continuous variable using the number of bevacizumab cycles received as a proxy for response. Data were analyzed by Fisher's exact test, Wilcoxon rank-sum test, and Spearman correlation coefficients.

Results: We had 38 patients with evaluable original tumor specimens whose mean age at time of bevacizumab initiation was 63.7 years. All patients had stage III or IV disease, with the majority having serous histology (92%). The median number of prior chemotherapy regimens was 3.5 (range, 2-9), with 34 patients (87.5%) having platinum-resistant disease. Eight patients received neoadjuvant chemotherapy before surgical debulking. The median number of bevacizumab cycles was 4.5 (range, 2-28), and 47% were given along with a second chemotherapeutic agent. The mean MVD was 24.6 (range, 8.7-53.7). There was no correlation of CD31-MVD either as a continuous variable or in MVD tertiles with response to bevacizumab by number of completed bevacizumab cycles (*P*=0.9). Similarly, there was no correlation with MVD when patients were classified as responders vs nonresponders by CGIG criteria. Response to bevacizumab was also not predicted by use of neoadjuvant chemotherapy, a second agent, or platinum resistance. We are currently evaluating MVD measured by CD105, a proliferating endothelial cell marker found specifically on cells that undergo neovascularization, and its relationship with drug response.

Conclusions: Despite its antiangiogenic mechanism of action, clinical response to bevacizumab in recurrent ovarian cancer was not predicted by tumor microvessel density.

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210 - Poster Session A

Outcome and response to neoadjuvant chemotherapy in patients with advanced stage Müllerian cancer in *BRCA1/2* mutation-positive compared to mutation-negative women

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Objectives: To evaluate the clinical outcome in patients with germline *BRCA1/2* mutation (BRCA-mut+) who received neoadjuvant chemotherapy for advanced stage Müllerian cancer compared to patients with no germline *BRCA* mutation (BRCA-mut-).

Methods: Patients who received neoadjuvant chemotherapy (NAC) for advanced-stage Müllerian carcinoma in 2000 through 2013 were identified. Demographic, clinicopathologic, and genetic testing results as well as treatment and outcome data were extracted from medical records. All patients received platinum-based chemotherapy. Progression free-survival (PFS) was calculated from date of last chemotherapy to date of progression/recurrence or last follow-up (censored). Overall survival (OS) was calculated from date of diagnosis to date of death or last follow-up (censored). Chi-square and Welch t-tests and Kaplan-Meier survival curves were used.

Results: Of the 195 patients who received NAC, 32 had germline *BRCA1/2* testing. Of these 32, 10 were BRCA-mut+ (two *BRCA1* and eight *BRCA2*) and 22 were BRCA-mut-. There was no significant difference in age (P=0.31), stage of presentation (P=0.81), number of comorbidities (P=0.1), number of NAC cycles (P=0.72), adjuvant chemotherapy cycles (P=0.57), and surgical factors that included rates of optimal tumor reductive surgery (P=0.47) and bowel resection (P=0.97). Complete tumor-reductive surgery was reported in 29% of BRCA-mut+ vs 15% of BRCA-mut- (P=0.30). There was a trend toward an improved PFS among BRCA-mut+ compared to BRCA-mut- patients (median 15.3 vs 5.9 months), but this difference was not statistically different (P=0.45). Further, no difference in OS was noted between BRCA-mut+ and BRCA-mut- patients (median 61.4 vs. 54.9 months, P=0.14).

Conclusions: Patients with germline *BRCA1/2* mutations had a trend to more frequent complete tumor-reductive surgery and improved PFS. Patients with germline *BRCA1/2* mutation treated with neoadjuvant chemotherapy had an OS comparable to patients treated with primary cytoreductive surgery and adjuvant chemotherapy based on historic data. However, these data need to be validated in a larger prospective series of patients tested for *BRCA1/2* mutations.

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211 - Poster Session A

MK-2206 sensitizes *BRCA2* mutant ovarian adenocarcinoma to cisplatin and poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitor therapy

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Objectives: Platinum resistance is a common obstacle in the treatment of epithelial ovarian cancer (EOC). Activation of the Akt pathway promotes platinum resistance, while inhibition of Akt sensitizes chemoresistant cells. Patients with *BRCA* mutant EOC and, thus, a defect in the homologous recombination repair (HRR) pathway, demonstrate greater platinum and olaparib sensitivity than *BRCA* wild-type patients. MK-2206, an allosteric inhibitor of Akt phosphorylation, has been shown to sensitize a variety of cell types to other antitumor agents. This study examined the differential effects of Akt inhibition with cisplatin and olaparib therapy in *BRCA2* mutant vs wild-type EOC.

Methods: MTS colormetric assays were conducted using PEO1, a chemosensitive *BRCA2* mutant serous ovarian adenocarcinoma, and PEO4, a restored *BRCA2* wild-type line from the same patient after chemotherapeutic resistance developed. Cells were treated 24 hours after plating and incubated continuously with drug combinations for 72 hours. Western blotting assessed the impact of drug treatment on the activation of Akt and its downstream targets.

Results: In PEO1, MK-2206 demonstrated moderate-to-strong synergy with cisplatin and olaparib at all doses while demonstrating antagonism at all doses in PEO4. Baseline phospho-Akt activity in untreated cells is upregulated in PE01. MK-2206 prevents the cisplatin- and olaparib-induced Akt activation in the *BRCA* mutant PEO1 cells.

Conclusions: *BRCA* mutant ovarian adenocarcinoma cells upregulate baseline Akt activity to enhance survival in the absence of HRR. As a result, *BRCA* mutants are more sensitive to Akt inhibition in the absence of cytotoxic agents. Higher Akt activity is also required to withstand cytotoxic agent-induced DNA damage, leading to strong synergy between MK-2206 and cisplatin or olaparib therapy in *BRCA* mutants. MK-2206 shows promise as a chemosensitization agent in *BRCA* mutant EOC and merits clinical investigation in this patient population.

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212 - Poster Session A

HNF1B contributes to resistance to oxidative stress through modification of metabolism in ovarian clear cell carcinoma

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Objectives: Ovarian clear cell carcinoma (OCCC) exhibits unique characteristics, including overexpression of HNF1B and antioxidant activities such as chemoresistance and development in endometriotic cysts. Cancer cell-specific metabolism (the Warburg effect) confers resistance to oxidative stress by suppressing the mitochondrial TCA cycle, thus leading to decreased production of intracellular reactive oxygen species (ROS). The aim of this study was to verify our hypothesis that HNF1B mediates resistance to oxidative stress in OCCC through a particular metabolic process.

Methods: Between sh-*HNF1B* or sh-*SLC3A1* and control cells, we assessed intracellular ROS level, median inhibition concentration (IC50) to ferric nitrilotriacetate (FeNTA; Fe-mediated inducer of oxidative stress) and comprehensive metabolomics using CE-TOFMS.

Results: Suppression of *HNF1B* was associated with reduced IC50 to FeNTA and increased intracellular ROS ($P<0.05$) in OCCC cell lines. Comprehensive metabolic analyses using capillary electrophoresis time-of-flight mass spectrometry showed that knockdown of *HNF1B* was associated with decreased intracellular lactic acid ($P<0.05$), increased pyruvic acid ($P<0.01$) and increased citric acid ($P<0.01$), indicating that *HNF1B* increases anaerobic glycolysis while suppressing the TCA cycle, consistent with the Warburg effect. Glutathione, another major antioxidant molecule, was significantly decreased in the *HFN1B* knockdown cells ($P<0.0005$). A quantitative intracellular glutathione assay confirmed that intracellular glutathione was decreased by *HNF1B* knockdown ($P<0.05$). Cysteine is known to be the rate-limiting metabolite of glutathione synthesis and is mainly imported to cell as cystine. Cystine transporter *SLC3A1* was significantly downregulated by *HNF1B* knockdown ($P<0.0001$). Suppression of *SLC3A1* induced downregulation of intracellular glutathione levels and upregulation of intracellular ROS activity.

Conclusions: *HNF1B* confers resistance to oxidative stress mechanistically driven by decreased TCA cycle activity combined with increased intracellular glutathione through increased expression of cystine transporter *SLC3A1*. Further investigation of this mechanism may lead to development of new therapeutic modalities against OCCC.

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213 - Poster Session A

Utility of serum folate-binding protein as a biomarker in the monitoring and treatment of ovarian cancer

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Objectives: Folate receptor type alpha (FRα) is expressed in nonmucinous adenocarcinomas of the ovary. Tumor FRα is the precursor to serum folate-binding protein (sFBP), a potential clinical tool to monitor tumor FRα expression. There is inadequate quantitative data on the expression patterns of sFBP in ovarian tumors, the relationship of relative sFBP levels to tumor expression of FRα, or the comparative status of sFBP and CA-125 in patient sera, which prompted the current study.

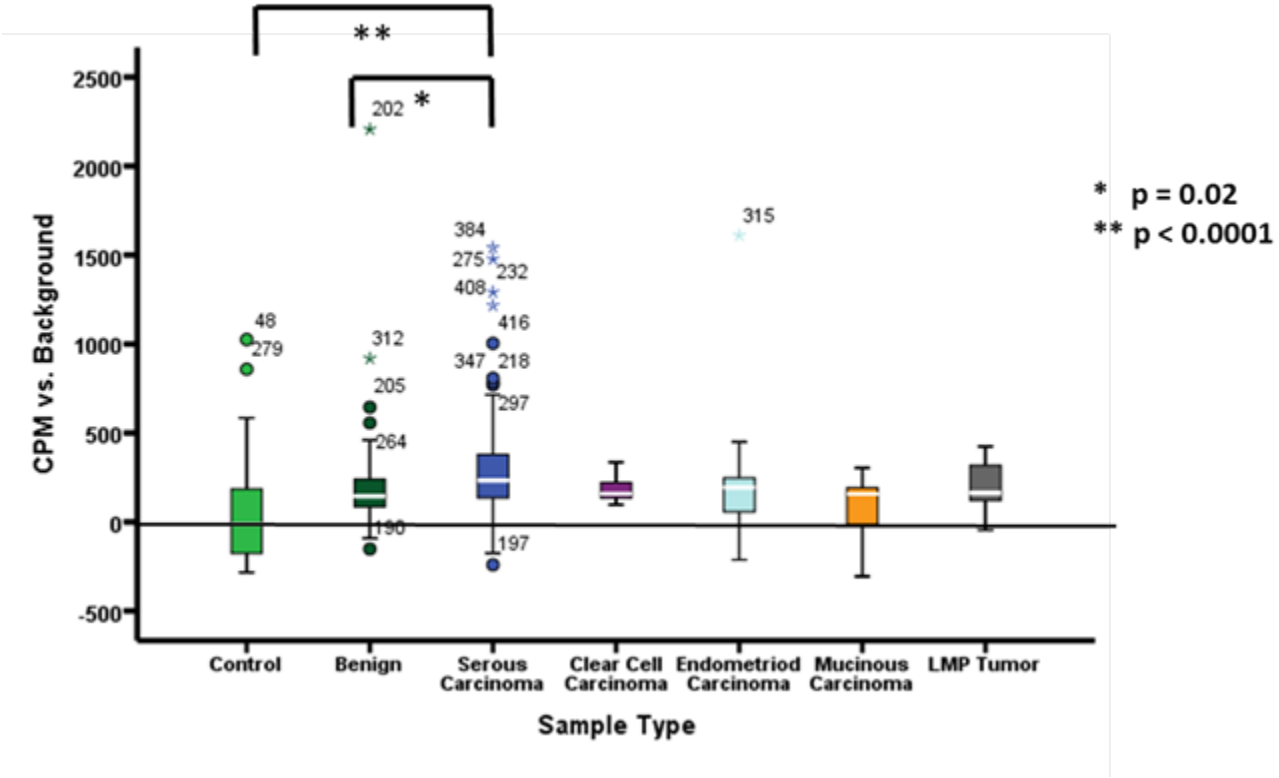
Methods: sFBP was assayed in sera from healthy volunteers ($n=128$), patients with benign ovarian pathology ($n=84$), and patients with epithelial ovarian carcinoma at initial diagnosis ($n=181$) using a radioactive folate-binding assay optimized to detect <5 fmol of sFBP in 10 uL of serum. CA-125 was measured in a random subgroup of patients with serous carcinoma ($n=40$) to determine correlation with sFBP. Finally, tissue expression of FRα was evaluated in a subset of carcinomas by immunohistochemistry (IHC) with H-score analysis. Analysis was performed using one-way ANOVA and Pearson correlation coefficient.

Results: The median sFBP value for serous adenocarcinoma was both the highest and significantly different from both normal patients and benign histologies ($P=0.0001$ and $P=0.02$) (Figure 1). As predicted, patients with mucinous carcinomas

did not have an elevated sFBP level when compared to patients with benign pathology or healthy controls (P=0.6). The relative sFBP levels reflected tumor expression of FRα in the subset of patients examined by IHC H-score. In samples in which sFBP and CA-125 were compared, there was no overlapping expression patterns when compared by the Pearson correlation coefficient (P=0.4).

Conclusions: sFBP can be measured reliably to femtomolar amounts in small volumes of human serum. It appears to be a reliable marker to estimate tumor FRα expression, and given the distinct patterns of CA-125 and sFBP, combining both may allow for improved initial diagnosis and early detection of recurrence of ovarian carcinoma. Measurement of sFBP should also be considered in predicting response to FRα-targeted therapies. Studies are currently underway to further identify its ultimate utility in these roles.

Figure 1. Serum Folate Binding Protein levels from patient samples.



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214 - Poster Session A

BCL2 antagonist of cell death (BAD) gene sequence and functional analysis of phosphorylation sites in ovarian cancer

N. Bou Zgheib[1], Y. Xiong[2], D. Marchion[2], I. Ramirez[1], S. Bush[1], P. L. Judson Lancaster[2], A. Hakam[2], R. M. Wenham[2], S. M. Apte[2] and J. M. Lancaster[2]
[1]*University of South Florida College of Medicine, Tampa, FL,* [2]*H. Lee Moffitt Cancer Center, Tampa, FL*

Objectives: The BAD pathway was found to influence the response of ovarian cancer (OVCA) cells to cisplatin, likely via modulation of BAD protein phosphorylation. The biologic features that influence OVCA BAD protein phosphorylation status remain to be delineated. We sought to study BAD gene phosphorylation sites for sequence variants as determinants of OVCA response to platinum-based therapy and to define the relative importance of major BAD protein phosphorylation sites on the resistance of OVCA cells to carcinoma in situ (CIS)-induced apoptosis.

Methods: OVCA cells (n=41) and primary OVCAs (n=108) were evaluated for DNA sequence variants in the apoptosis-related phosphorylation sites of the BAD gene. Polymerase chain reaction was used to amplify the major phosphorylation sites known to regulate BAD protein function as well as the BH3-domain. DNA sequencing was performed on the AB3130 Genetic Analysis System using BigDye 3.1 dye terminator chemistry according to manufacturer's instructions. Comparative sequence analysis of *BAD* exons was performed using DNAStar Lasergene 8 software. OVCA cells were evaluated for changes in CIS-induced growth arrest and cell death after transfection pFlag-600 vectors harboring full-length *BAD* with serine (S) to alanine (A) (*BAD-S112A, BAD-S136A, BAD-S155A*; non-phosphorylatable), or glutamic acid (E) (*BAD-S112E, BAD-S136E*, *BAD-S155E*; phosphorylation mimic) mutations in the apoptosis-related phosphorylation sites.

Results: Comparative sequence analysis of the *BAD* gene in OVCA cells and primary samples failed to identify any mutation. Overexpression of the nonphosphorylatable isoforms of BAD protein (*BAD-S136A* or *BAD-S155A)* increased CIS-induced apoptosis when compared to mock-transfected or wild-type *BAD*-transfected cells. In contrast, overexpression of the phosphorylation mimicking isoforms of BAD protein (*BAD-S136E* or *BAD-S155E)* decreased the apoptotic response to CIS treatment.

Conclusions: OVCA *BAD* gene sequence appears to be preserved in vitro and in vivo. Posttranslational events likely influence *BAD*, OVCA cell apoptotic signaling, and subsequent sensitivity to cytotoxic challenges. Defining the molecular basis for the development of OVCA resistance to chemotherapy may identify opportunities to develop targeted therapies.

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215 - Poster Session A

Incidence of lymph node metastasis in comprehensively staged clear cell carcinoma grossly confined to the ovary

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Objectives: The primary objective of this study was to assess the rate of lymph node (LN) metastasis in comprehensively staged (>10 LNs retrieved) ovarian clear cell carcinoma (OCCC) clinically confined to the ovary. The secondary objective was to determine factors associated with LN metastasis.

Methods: We identified all cases of OCCC treated at our institution from January 1995 to December 2011. From this cohort of patients, we only included cases with disease confined grossly to the ovary that had surgical staging performed. Various clinicopathologic data were abstracted from electronic medical records. The association of certain factors with LN metastases was tested. Appropriate statistical tests were performed.

Results: We identified 155 cases of OCCC, of which 131 (85%) met criteria for inclusion in this analysis. Of these cases, 88 (67%) were staged within our institution; the remaining cases were staged elsewhere. Median patient age was 51 years (range, 30-83 years). Median total LN count was 19 (range, 0-74). Eight (6.1%) patients had LN metastases**.** Data were then analyzed in cases in which ≥10 LNs were retrieved (n=91). Six (6.6%) of these cases had LN metastasis. LN metastasis was noted in 2/15 (13%) cases with positive cytology compared to 3/71 (4%) with negative cytology (P=0.2). LN metastasis was noted in 3/22 (14%) cases with tumor extension onto ovarian surface compared to 3/65 (4.6%) without surface involvement (P=0.2). Additional factors such as ascites and peritoneal, omental, and fallopian tube involvement were tested, with no meaningful differences observed. A “high-risk” group of cases in which cytology was positive and there was growth on the ovarian surface was identified. LN metastasis was noted in 2/6 (33%) of these high-risk cases compared to 3/80 (4%) not at high risk (P=0.04).

Conclusions: Women who underwent comprehensive staging for clinical stage I OCCC had an LN metastasis rate of 6% to 7%. These results suggest that patients with both ovarian surface involvement and positive cytology have the greatest risk of LN involvement. This may influence clinical decision-making in whether to stage patients with incidental OCCC found after salpingo-oophorectomy.

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216 - Poster Session A

The role of secondary cytoreduction in patients with recurrent low-grade serous ovarian carcinoma

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Objectives: Although the benefit of secondary cytoreductive surgery (SCRS) is well-established in the general setting of epithelial ovarian cancer, its utility in patients with low-grade serous ovarian cancer (LGSOC) is unknown. We, therefore, sought to determine the benefit of SCRS in patients with LGSOC and whether cytoreduction to no gross residual disease affects survival.

Methods: A single-institution retrospective chart review was conducted in patients with recurrent LGSOC who underwent SCRS between 1995 and 2012. Data that included demographics, survival, chemotherapy, disease characteristics at the time of surgery, residual disease, and operative complications were collected. Overall survival (OS) and progression-free survival (PFS) were calculated. Kaplan-Meier and log-rank tests were used to examine survival outcomes.

Results: We identified 43 patients with LGSOC who underwent SCRS. Median age at diagnosis was 41 years. Most patients (86%) had stage III or IV disease at initial diagnosis and received adjuvant chemotherapy after primary surgery (88%). Only 51% were disease-free at the end of primary treatment, with 85% of patients left with gross residual disease at the time of initial debulking. The median number of months between primary tumor debulking and SCRS was 33.2. Of 43 patients who underwent SCRS, 33 (78%) had gross residual disease at the conclusion of surgery. The median PFS for patients with no gross residual disease has not yet been reached; for patients with gross residual disease, PFS was 10.5 months (P=0.009 compared to no gross residual). Median OS for patients with no gross residual disease at SCRS was 168 months compared to 89 months for patients with gross residual disease (P=0.15). Median OS from the time of SCRS for patients with no gross residual disease was 93.6 months compared to 45.8 months for those with gross residual disease (P=0.15). Complications occurred in 39% of patients after SCRS; there were no deaths directly attributable to surgery.

Conclusions: There is potential benefit to SCRS in patients with recurrent LGSOC, a relatively chemoresistant disease. Efforts to maximally cytoreduce patients should be made because patients with no gross residual disease had a better PFS and a trend toward better OS. Efforts are underway to determine whether certain selection criteria can identify ideal candidates for SCRS.

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217 - Poster Session A

Significance of serum CA-125 level as a prognostic factor after the first cycle of chemotherapy in patients with advanced serous epithelial ovarian cancer

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Objectives: To evaluate the prognostic differences in patients with advanced serous epithelial ovarian cancer according to measured serum CA-125 levels before surgery and after each cycle of chemotherapy.

Methods: The study included 188 patients who had undergone staging laparotomy, had been diagnosed as having International Federation of Gynecology and Obstetrics stage IIc-IV serous epithelial ovarian cancer, and who had received postoperative adjuvant chemotherapy (≥6 cycles) at the Yonsei University Affiliated Severance Hospital and Gangnam Severance Hospital between April 2000 and March 2013. The effect of serum CA-125 levels measured before surgery and after each cycle of chemotherapy on overall and disease-free survival was analyzed. Patients' information was obtained from medical records, and the Cox proportional hazard model was used to evaluate statistical significance.

Results: Patients were divided into four quartile groups. Univariate analysis showed that the hazard ratio for overall survival was 10.3 times higher in the upper quartile group that was composed of patients with the highest 25% of CA-125 levels (CA-125 >124.75 U/mL) after the first cycle of chemotherapy than in the lower quartile group that was composed of patients with the lowest 25% of CA-125 levels (CA-125 ≤23.5 U/mL) (P<0.001). Further, the HR for disease-free survival was 5.5 times higher in the upper quartile group than in the lower quartile group (P<0.001). In multivariate analysis, the serum CA-125 levels measured after the first cycle of chemotherapy were the most important prognostic factor for overall and disease-free survival (P<0.001). Additionally, in terms of overall and disease-free survival, the quantity of ascites (P=0.022 and P=0.001, respectively) and the CA-125 level after the sixth cycle of chemotherapy (P=0.046 and P=0.033, respectively) were the most significant prognostic indicators.

Conclusions: The serum CA-125 level after the first cycle of chemotherapy was the most significant prognostic factor in the prediction of overall and disease-free survival in patients with advanced serous epithelial ovarian cancer.

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218 - Poster Session A

The Charlson Comorbidity Index predicts survival in women with epithelial ovarian cancer independent of surgical debulking status

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Objectives: To determine if patient comorbidities affect progression free survival (PFS) and overall survival (OS) in patients with epithelial ovarian cancer (EOC).

Methods: Eligible subjects for this retrospective cohort study included women diagnosed with EOC between 2004 and 2009 who received primary treatment and follow-up at our institution. After institutional review board approval, records were reviewed for demographics, tumor characteristics, recurrence, survival, and comorbidity as quantified by the Charlson Comorbidity Index (CCI). The CCI is a validated predictor of hospital mortality and includes 19 separately weighted medical conditions. For our analysis, patients were separated into three categories based on a CCI of 0, 1, or 2+. Survival was calculated using Kaplan-Meier estimates and compared with the log-rank test. Cox proportional hazards were used to compare clinical variables with likelihood of survival.

Results: Of the 367 women included in the study, 225 (61%) had a CCI of 0, 99 (27%) had a CCI of 1, and 43 (12%) had a CCI of ≥2. Compared to women with a CCI ≥1, women with a CCI of 0 were more likely to be younger, white, and have private insurance. A CCI of 0 was not associated with an increased rate of optimal debulking (relative risk 1.01, 95% CI 0.71-1.42). PFS and OS varied significantly based on CCI. Median PFS for women with a CCI of 0, 1, or 2+ was 18.8, 12.1, and 9.7 months, respectively (P<.005). Median OS for women with a CCI of 0, 1, or 2+ was 46.5, 33.1, and 20.4 months, respectively (P<.005). On multivariable analysis adjusting for age, race, grade, stage, and debulking status, a CCI ≥1 was independently associated with a greater hazard for progression (HR 1.16, 95% CI 1.04-1.28) and death (HR 1.19, 95% CI 1.07-1.34).

Conclusions: Patient comorbidities, as measured by the CCI, are independently associated with a lower PFS and OS in women with EOC. Future clinical trials may need to include the CCI or other predictor of outcome as a stratification variable.

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219 - Poster Session A

Targeting *PI3K/AKT* signaling and the *TR3/NR4A1* receptor in ovarian cancer

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Objectives: The high incidence of disease recurrence following platinum-based therapy indicates an urgent need for new treatments in advanced ovarian cancer. The phosphatidylinositol 3-kinase (PI3K) pathway is aberrantly activated in one-third of high-grade serous ovarian cancers. Discovering key downstream targets of PI3K signaling will guide strategies to improve clinical response to PI3K inhibitor therapy. We recently showed that the *PI3K/AKT* pathway negatively regulates the *TR3/NR4A1* immediate-early gene in ovarian cancer apoptosis. Cisplatin and direct-binding TR3 activators stimulate apoptosis by promoting nuclear-mitochondrial translocation of TR3 and/or transactivation of TR3 transcription. Therefore, combined TR3 activators with PI3K inhibitors to test the hypothesis that they will cooperatively suppress ovarian cancer cell survival.

Methods: Ovarian cancer cell lines (*PIK3CA*-mutant SKOV3, *PI3KCA*-amplified OVCAR3, *PIK3CA*-wild-type OVCAR8, and isogenic *A2780* parental and cisplatin-resistant A2780CP20) were treated with the TR3 activator cytosporone B (CsnB), the PI3K inhibitor BYL719, or both. Sulforhodamine B colorimetric assays measured cell viability. Western blot and immunofluorescence assays measured expression levels and subcellular localization of TR3, phospho-AKT, and the apoptotic markers cleaved PARP and cytochrome C release. A luciferase reporter plasmid bearing the NurRE response element measured TR3 DNA binding. Experimental groups were compared by two-tailed Student's t test.

Results: As single agents, CsnB and BYL719 reduced cell viability in all cell lines in a dose-dependent manner. Cell lines with activated *PI3K* were most sensitive to BYL719-mediated inhibition of cell viability and phospho-AKT. When CsnB and BYL719 were combined, there was a significant decrease in viability and increase in apoptosis markers in all cell lines compared to each drug alone. Augmented apoptosis by combination treatment involved upregulated TR3 expression, with corresponding increases in association of TR3 with mitochondrial Hsp60 and cytochrome C release, and TR3 DNA binding.

Conclusions: These studies highlight the potential of combination activation of TR3 and PI3K inhibition as a novel therapeutic strategy in cisplatin-resistant ovarian cancer.

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220 - Poster Session A

Forkhead box M1 (*FOXM1*) gene expression inversely correlates with survival and targeting *FOXM1* improves cytotoxicity of paclitaxel and cisplatinum in platinum-resistant ovarian cancer ascites cells ex vivo

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Objectives: Aberrantly activated *FOXM1* leads to uncontrolled cell proliferation, and dysregulation of the *FOXM1* transcription network occurs in 87% of ovarian cancer cases. We have previously demonstrated that thiostrepton, a thiazole antibiotic, decreases *FOXM1* expression, and adding thiopstrepton to standard paclitaxel/cisplatin chemotherapy showed a synergistic cytotoxicity in ovarian cancer cell lines. We sought to determine if *FOXM1* expression correlates to survival in platinum-resistant patients and if targeting this pathway can improve the efficacy of paclitaxel and cisplatinum in human ovarian cancer ascites cells ex vivo.

Methods: A Cox regression analysis was performed on *FOXM1* mRNA expression data from a subgroup of 151 patients from The Cancer Genome Atlas (progression-free survival <12 months). Human ovarian cancer ascites cells from five patients were treated with paclitaxel/cisplatinum/thiostrepton or a combination for 48 hours and cytotoxicity was assessed by flow cytometry. Drug combination effects were determined by calculating the combination index (CI) values using the Chou and Talalay method (CI <0.9=synergy, CI 0.9-1.10=additive, and CI >1.10=antagonism). Quantitative reverse transcriptase polymerase chain reaction was performed to determine changes in *FOXM1* expression and its downstream targets.

Results: In a subgroup of platinum-resistant patients from The Cancer Genome Atlas, high *FOXM1* mRNA expression correlated with worse overall survival (24 months vs 33 months, P=0.017). In ascites cells from three patients with platinum-resistant tumors and one tumor of unknown platinum response, *FOXM1* mRNA expression was upregulated compared to normal ovarian tissue. Treatment with thiostrepton decreased *FOXM1* mRNA expression and the downstream targets *CCNB1* and *CDC25B* in all five patients. Combination therapy with paclitaxel, cisplatinum, and thiostrepton showed synergy in three of the four patients with platinum-resistant disease (CI 0.40-0.83).

Conclusions: Aberrantly activated *FOXM1* correlates with worse survival in patients with platinum-resistant tumors. Thiostrepton improves the cytotoxic effect of paclitaxel and cisplatinum in ascites cells from platinum-resistant patients. *FOXM1* expression may be a useful marker for prognosis, and targeting this pathway may lead to novel therapeutics for epithelial ovarian cancer.

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221 - Poster Session A

A mycobacterial heat shock protein 70-based fusion protein targeting mesothelin induces dendritic cell maturation and cross-presentation in a murine model of ovarian carcinoma

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Objectives: Failure of current ovarian cancer immunotherapy is believed to result from poor induction of dendritic cell (DC) maturation and antigen presentation. We developed a novel immunotherapeutic agent linking a single-chain antibody variable fragment (scFv) targeting mesothelin (MSLN), a surface glycoprotein expressed at high levels in ovarian cancer, to *Mycobacterium tuberculosis* (MTB) heat shock protein 70 (Hsp70), which is a potent immune activator known to bind to CD40 on DCs. We evaluated its ability to induce DC maturation and cross-presentation of tumor-associated antigens.

Methods: To investigate DC maturation, unsorted and low-CD40 bone marrow-derived dendritic cells (BMDCs) isolated by cell sorting were stimulated with scFvMTBHsp70 fusion protein and then assessed for expression of DC maturation markers by flow cytometry. To study cross-presentation, FVB mice were immunized intradermally with scFvMTBHsp70. Lymphocytes from harvested skin-draining lymph nodes were restimulated ex vivo with tumor-associated antigens before assessment of CD4+ and CD8+ T-cell Granzyme B production.

Results: In vitro, the scFvMTBHsp70 fusion protein significantly (P<0.05) induced BMDC expression of maturation markers. Interaction of the MTBHsp70 portion with CD40 is a likely but not exclusive mechanism of signaling. Tumor-specific Granzyme B production by CD4+ and CD8+ T-cells from mice immunized with the fusion protein was significantly enhanced (P<0.05), but high-dose immunization induced immunosuppression and decreased subsequent Granzyme B production (P<0.05).

Conclusions: The ability of scFvMTBHsp70 to induce DC maturation and potent tumor-specific CD4+ and CD8+ T-cell responses is crucial to overcoming tumor-mediated immune latency in ovarian cancer and rescue DC maturation and function from tumor-induced defects in cases where many other immunotherapies have failed. This new cancer immunotherapy bypasses complex ex vivo manipulation of patient cells and has the potential to be a cost-effective and powerful tool at optimal doses, especially when used in combination with other agents that modulate the inhibitory tumor microenvironment.

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222 - Poster Session A

Pelvic magnetic resonance imaging diagnosis correlates with pathology of adnexal masses

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Objectives: Given the frequent use of pelvic magnetic resonance imaging (MRI) at our institution to further characterize indeterminate pelvic masses, we sought to evaluate the accuracy of MRI in women with subsequent surgical resection of a complex adnexal mass. The primary objective of our study was to determine the accuracy of pelvic MRI in differentiating benign and malignant adnexal pathology compared to the final surgical pathology in a cohort of women who underwent both a pelvic MRI for an adnexal mass and subsequent surgical management. Our secondary aim was to determine the accuracy with which MRI can detect type-specific ovarian histopathology compared to the final histopathology subtype and determine the frequency of discrepancy.

Methods: We performed a retrospective cohort study of women who underwent pelvic MRI with a diagnosis of an adnexal mass between June 2008 and 2010 at our tertiary care institution. The radiologic interpretations (benign or malignant) and the favored specific histologic subtype on MRI reports were abstracted from the medical records. The radiologic diagnoses were then compared to the diagnoses by surgical pathology.

Results: Data from 237 patients who underwent pelvic MRI were included, of whom 41.35% underwent surgical intervention for the adnexal mass. Pelvic MRI had a sensitivity of 95.0% and specificity of 94.1% for diagnosis of malignancy when compared to available pathology (n=88). The predicted specific histologic subtype by MRI (n=84) was accurate in 56/57 women (98.25%) with an anticipated benign diagnosis and in 23/27 women (85.19%) with an anticipated malignancy. The correlation between a benign diagnosis from MRI and benign final surgical pathology was 0.74 (P<0.001).

Conclusions: In our tertiary care center, MRI is used to further characterize indeterminate adnexal masses and can accurately differentiate benign vs malignant adnexal masses. The specific diagnosis on MRI was also highly correlative with the final histopathology. The majority of the cohort (59%) was managed expectantly based on reassuring results of the MRI. MRI offered diagnostic value, more detailed patient counseling, appropriate subspecialty referral and surgical planning, and reassurance to pursue conservative management of benign masses by MRI, such as when patients are poor surgical candidates.

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223 - Poster Session A

The presence of endometriosis is associated with improved survival in epithelial ovarian cancer

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Objectives: To characterize ovarian cancers associated with endometriosis and to evaluate the prognostic impact of the presence of endometriosis.

Methods: Ovarian cancer cases from a single institution diagnosed between 2000 and 2013 were examined and specimens reviewed by two pathologists for the presence of endometriosis. Ovarian cancer cases with and without endometriosis were compared to determine the clinical factors associated with endometriosis and the prognostic significance of the presence of endometriosis. Two-sample T-tests, chi-square tests, multivariable logistic regression, and Cox proportional hazards models were used for statistical analysis.

Results: Among 139 epithelial ovarian cancers diagnosed between 2000 and 2013, there were 49 (35%) with endometriosis and 90 (65%) without endometriosis. The distribution of histologies of ovarian cancers with endometriosis was 43% endometrioid, 23% clear cell, 20% mixed, 8% mucinous, and 6% serous. Ovarian cancer cases with endometriosis were more likely to be confined to the pelvis (89% vs 41%, P<0.0001) and diagnosed with lower-grade tumors (41% vs 21%, P=0.014). Younger age and earlier stage independently predicted the presence of endometriosis (P=0.0011 and P<0.0001, respectively). Ovarian cancer patients with endometriosis had improved progression-free survival (HR=0.20, P<0.0001) and overall survival (HR=0.18, P=0.025) compared to patients without endometriosis. After controlling for tumor stage and age at diagnosis, however, endometriosis was not an independent predictor of survival.

Conclusions: Patients with ovarian cancer and endometriosis have younger age at diagnosis, earlier-stage and lower-grade disease, and disease distribution limited to the pelvis compared to patients without endometriosis. Ovarian cancers with

endometriosis have a more favorable prognosis with improved progression-free survival and overall survival due to these clinical factors, but endometriosis had no independent prognostic significance in our study population.

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224 - Poster Session A

Characterization of primary platinum resistance in an era of biologic agents and novel chemotherapeutic design

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Objectives: Primary platinum resistance (PPR) confers a poor prognosis for patients with epithelial ovarian carcinoma (EOC). Median overall survival (OS) is 12 months. Given the increased use of biologic agents, we sought to examine the characteristics and outcomes of patients with PPR EOC in the modern treatment era.

Methods: Patients with EOC from 2000-2010 were retrospectively reviewed. PPR was defined as not achieving complete response (CR) with primary therapy or documented recurrence <6 months from the end of therapy. Medical records were abstracted for clinicopathologic variables, treatment, and outcomes. Data were abstracted using SAS 9.2.

Results: A total of 538 patients were identified, 186 (34%) of whom had PPR and 156 (84%) of whom had high-grade serous carcinoma (HGSC). The median age of patients who had PPR was 63 years, 3.7% received primary chemotherapy, 11.3% received neoadjuvant chemotherapy (NACT), and 84.9% underwent primary debulking. Optimal debulking was achieved in 76%. Median progression-free survival was 4.3 months. On multivariate analysis, neither residual disease, histology, age, primary treatment nor clinical trial was associated with PPR. The use of NACT was associated with PPR (HR 5.53; 95% CI 1.02, 30.04; P=0.048). Following development of PPR, the median number of treatment regimens was three. The Median number of cytotoxic agents was three and biologic agents were 1.5. Use of biologic agents differed by histology. Patients with acquired platinum resistance had a median overall survival (OS) of 18.3 months vs 13.8 months for those who had PPR. Platinum-sensitive patients had an OS of 115.9 months. Patients with PPR and HGSC had nearly twice the median OS as those with non-HGSC (15.1 vs 8.7 months, P=0003). Use of maintenance therapy following primary chemotherapy was associated with increased OS in HGSC (32.3 vs 13.8 months, P=0.036) but not for non-serous histologies (4.3 vs 6.0 months, P=0.37). Among all patients with PPR, 37.7% had an OS probability >24 months and 15.9% had an OS probability >48 months.

Conclusions: PPR in the modern treatment era still confers a poor prognosis. Maintenance therapy was associated with an improved OS, which needs to be further elucidated. Although some patients with PPR survive well beyond the reported median, efforts aimed at eliminating any modifiable risk factors for PPR are important as is further development of effective salvage strategies to convert more patients to survival beyond the 12-month mark.

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225 - Poster Session A

Primary debulking surgery in stage IIIC and IV ovarian cancer results in improved survival compared to those undergoing neoadjuvant chemotherapy with interval cytoreduction

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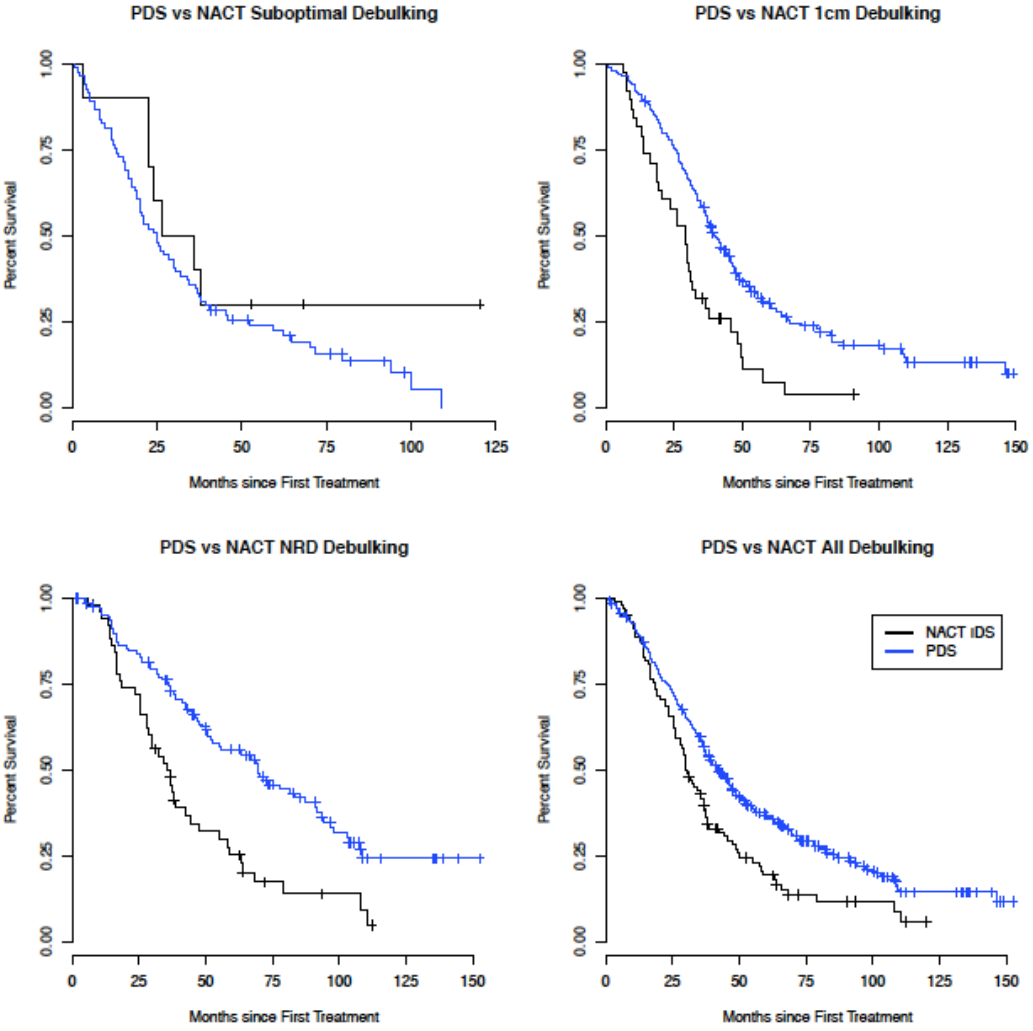
Objectives: The timing of surgical cytoreduction for advanced epithelial ovarian cancer (EOC) has been questioned in recent studies. At our institution, we maintain a surgically aggressive posture favoring primary debulking surgery (PDS). The purpose of this study was to determine the clinical outcomes of this approach in patients with advanced ovarian cancer.

Methods: We identified all women diagnosed with FIGO stage IIIC/IV EOC who underwent debulking surgery at a single institution between the years of 2000 and 2009. The decision to perform PDS vs neoadjuvant/interval debulking surgery (NACT/IDS) was based on the attending physician's judgment. Residual disease was stratified into three categories: suboptimal (>1 cm), optimal (<1 cm), or no gross residual disease (NRD). Chemotherapy reflected standard protocols. Chart review extracted relevant clinical variables and appropriate statistical analyses were performed.

Results: A total of 492 women were included in the analysis. Eighty percent (*n*=393) underwent PDS; the remaining 20% (*n*=99) had NACT/IDS. Patients undergoing NACT/IDS were significantly older (*P*=0.013) and more likely to have stage IV disease (*P*<0.001). Of patients undergoing PDS, 79.4% were optimally cytoreduced and 32.1% were debulked to NRD. In the NACT/IDS cohort, 90.8% were optimally cytoreduced, with 51.5% debulked to NRD. Patients who underwent PDS had a higher surgical radicality score than those undergoing NACT/IDS (*P*<0.001), but there was no difference in the number of perioperative complications (*P*=0.29) or ability to tolerate chemotherapy (*P*=0.91). Regardless of group. cytoreduction to NRD resulted in decreased risk of death (HR 0.50, 95% CI 0.36-0.69). However, on multivariate analysis, PDS demonstrated a survival advantage over NACT/IDS (overall survival of 69.6 months [range, 52.5-91.50 months] vs 35.4 months [range, 28.1-47.6 months]).

Conclusions: In a high-volume academic center, primary debulking surgery for advanced ovarian cancer is feasible and safe for the majority of patients. Patients who are resected to NRD have a lower risk of dying from their cancer. Furthermore, patients who are NRD after PDS have almost double the median survival of those undergoing NACT/IDS, even when controlling for age and disease stage.



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226 - Poster Session A

Hypomethylation signature enriches stem properties and predicts poor prognosis for ovarian cancer patients

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Objectives: The clinical significance of epigenetic effects in ovarian cancer stem cells remains largely unexplored. In this study, we aimed to discover novel DNA methylation in ovarian cancer cells with stem properties and test its potential as a prognostic biomarker.

Methods: We compared the methylomic profiles between an ovarian cancer initiating cell line (CP70sps) and their parental line (CP70) by bead arrays. Quantitative real-time polymerase chain reaction (QRT-PCR), quantitative methylation-specific PCR (QMSP), and pyrosequencing were used for the validation of gene expressions and DNA methylation. The prognostic significance of candidate methylation genes was tested using tissues from our institute and methylation data from The Cancer Genome Atlas (TCGA). We also characterized the effects of one gene on stem properties and malignant phenotypes.

Results: We identified *ATG4A* and *HIST1H2BN* as potential candidate genes. Methylation status of both genes by QMSP was tested in 168 ovarian cancer tissues, which revealed independent prognostic significance of *ATG4A* and *HIST1H2BN* methylation for progression-free survival (PFS) and overall survival (OS). Kaplan-Meier analysis and multivariate Cox regression analysis showed that patients with low-level methylation of *ATG4A* and *HIST1H2BN* had poor PFS (HR 1.8, 95% CI, 1.0-3.6, $P<0.05$) and OS (HR 1.7, 95% CI, 1.0-3.0, $P<0.05$), which was the same as validation in an independent cohort. TCGA ovarian cancer database validated the prognostic significance of this hypomethylation signature. Overexpression of *ATG4A* in cells increased their stem properties, providing an indication of its biological function.

Conclusions: Our data demonstrated that the hypomethylation of *ATG4A* and *HIST1H2BN* is an independent prognostic biomarker for ovarian cancer patients and may provide a novel therapeutic target for ovarian cancer consisting of a more stem-like phenotype enriched by *ATG4A*.

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227 - Poster Session A

Hyperthermic intraperitoneal chemotherapy in the treatment of ovarian, fallopian tube, and peritoneal cancer: an analysis of recurrence patterns and survival

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Objectives: To evaluate patterns of recurrence and survival in patients with epithelial ovarian (EOC), fallopian tube cancer (FTC), and primary peritoneal cancer (PPC) treated with hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods: We performed a retrospective review of patients at two academic institutions with EOC, FTC, and PPC who underwent HIPEC from November 2002 to April 2013 and completed all postoperative therapy. Demographics, pathology reports, treatment characteristics, recurrence patterns, and time to progression were evaluated.

Results: Nineteen patients with a median age of 54 years (range, 43–73 years) received HIPEC with adequate follow-up. Diagnoses included: EOC ($n=16$), PPC ($n=2$), and FTC ($n=1$). The majority of patients had stage IIIC (63%) or IV disease (16%). HIPEC was administered in the following settings: interval cytoreduction (26%), consolidation (11%), secondary cytoreduction (47%), and tertiary or greater cytoreduction (16%). All patients achieved a complete gross resection during cytoreductive surgery at time of HIPEC. HIPEC regimens included: carboplatin ($n=13$), cisplatin ($n=3$), oxaliplatin ($n=1$), cisplatin/doxorubicin ($n=1$), and mitomycin C ($n=1$). For patients undergoing interval cytoreduction or consolidation, the median time from diagnosis to HIPEC was 5.1 months (range, 3.2–7.3). For patients undergoing HIPEC for recurrent disease, the median treatment-free interval from last therapy was 18.0 months (range, 1.0–40.0). Thirteen patients (68%) recurred following HIPEC. The location of first recurrences included: pelvis (77%), abdomen (31%), abdominal lymph nodes (23%), liver (8%), extra-abdominal lymph nodes (8%), lung (8%), and other (8%). Of the seven patients who received HIPEC following interval cytoreduction or consolidation, four (57%) recurred at a median of 49.4 months (range, 14.6–68.4), with two deaths (29%). Of the 12 patients who received HIPEC following secondary or tertiary cytoreduction, nine (75%) recurred at a median of 19.6 months (range, 9.6–33.4), with five deaths (42%).

Conclusions: In a highly selected group of patients with advanced EOC, FTC, and PPC, HIPEC appears to confer a favorable prognosis. Administration of HIPEC during cytoreductive surgery warrants further study in the setting of a clinical trial.

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228 - Poster Session A

A “REST-less” phenotype is associated with favorable recurrence-free survival in ovarian cancer

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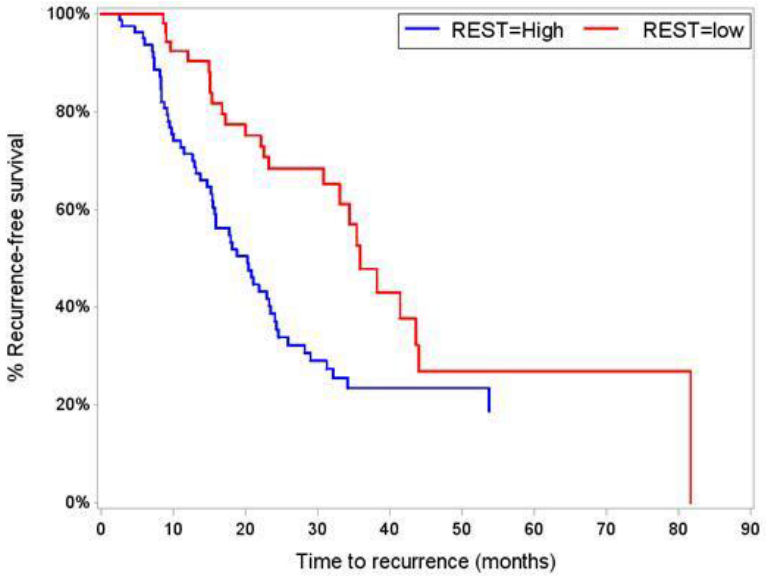
Objectives: The transcription repression element 1 (RE1) silencing transcription factor (REST) appears to act as a tumor suppressor in epithelial carcinomas, including colon, breast, prostate, and small cell lung cancer, where decreased REST

expression has been associated with more aggressive disease. In neural tumors, however, REST acts as an oncogene. The role of REST in ovarian cancer has yet to be fully characterized. The objective of this study was to determine the expression of REST expression in ovarian cancer and its association with tumor characteristics and clinical outcome.

Methods: Protein microarray analysis of ovarian cancer tissue was used to determine protein expression levels for REST and FANCD2 (a homologous recombination protein previously associated with early ovarian cancer recurrence and platinum resistance). REST expression was validated by Western blot. Tumor characteristics and clinical data were analyzed for correlation with levels of protein expression for 160 patients with ovarian cancer, using chi square and Kaplan-Meier methods.

Results: In 160 patients, 65 (41%) had tumors with no REST expression. REST expression was not associated with tumor grade, stage, or histologic subtype. Patients with no REST expression showed a more favorable recurrence-free survival curve, with median time to recurrence for REST-less tumors of 20.3 months compared to 35.8 months for REST-expressing tumors (P=0.002). REST expression was positively correlated with FANCD2 expression (P=0.003), though FANCD2 was not associated with prognosis or tumor characteristics in this cohort.

Conclusions: REST has been shown to have tissue-dependent expression, acting as either a tumor suppressor or oncogene. In contrast to what has been observed in other epithelial cancers, decreased REST expression may be associated with a more favorable prognosis in ovarian cancer. Further knowledge of the role of REST in ovarian cancer could allow for novel therapeutic regimens.



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229 - Poster Session A

Subcellular localization of AT-rich interactive domain1A protein expression is associated with survival in epithelial ovarian and peritoneal carcinoma

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Objectives: Mutation and loss of nuclear AT-rich interactive domain1A (*ARID1A*) expression, a known tumor suppressor, has been reported in a significant portion of gynecologic cancers. Our investigations detected aberrant cytoplasmic *ARID1A* localization in a subset of ovarian carcinomas. This investigation characterized decreased survival associated with cytoplasmic *ARID1A* and explored the molecular mechanism and oncogenic impact of this mis-localization.

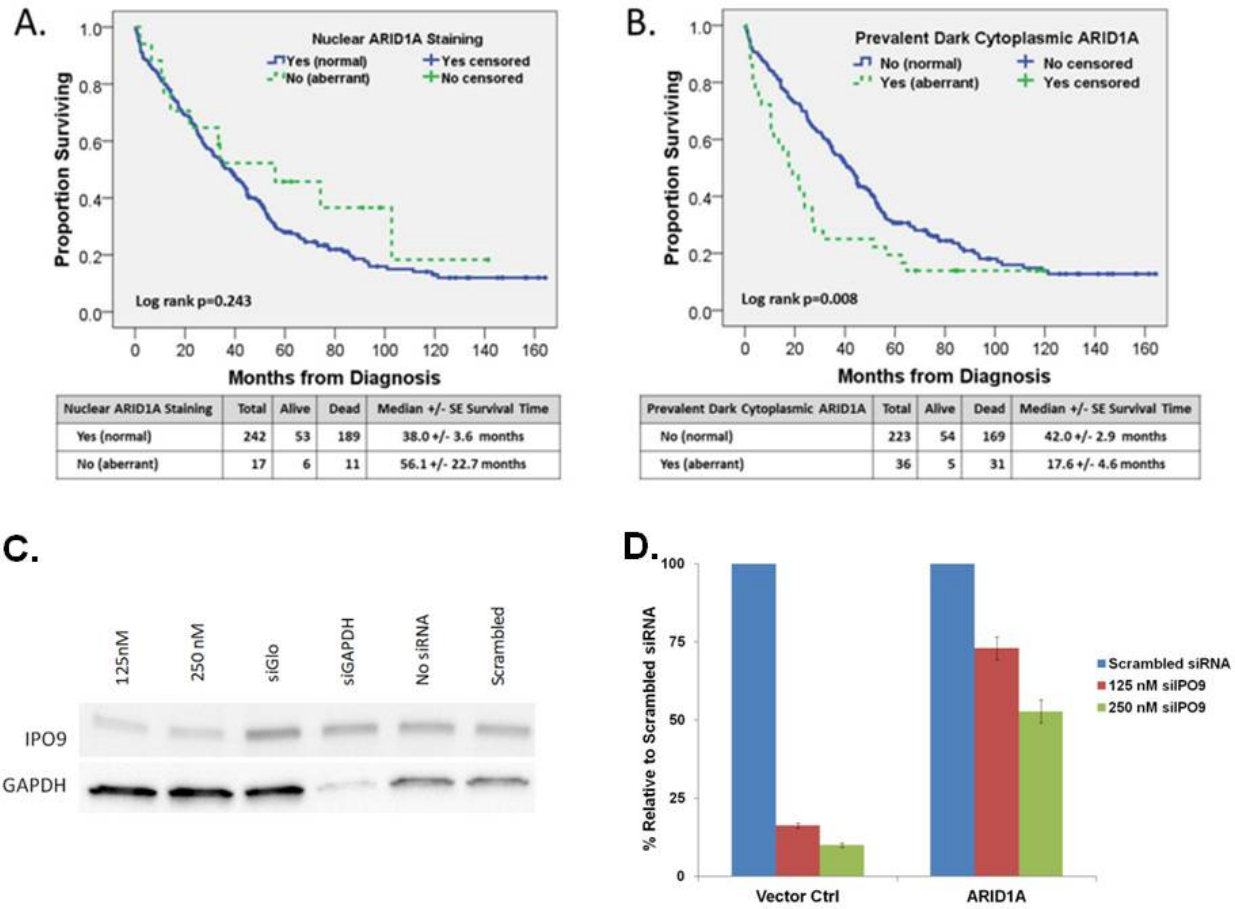
Methods: Expression and cellular compartmentalization of *ARID1A* was evaluated by immunohistochemistry in tissue microarrays (TMA) containing tumor from 259 epithelial ovarian carcinoma cases (EOC) and associations with clinical

characteristics or survival were evaluated. Deep DNA sequencing, immunoprecipitation (IP), siRNA, flow cytometry, proliferation assays, and mass spectrometry (MS) were employed for molecular and functional characterization in ovarian clear cell carcinoma cell lines.

Results: Loss of nuclear *ARID1A* was observed in 17 cases (6.6%) but was not associated with survival (Figure 1A, *P*=0.243). Prevalent cytoplasmic immunoreactivity (≥40% of cores for a case) was observed in 36 cases (13.9%); was more common in mucinous (50%), clear cell (42%), and serous (11%) histotypes; and was associated with worse survival (Figure 1B, *P*=0.008). Prevalent cytoplasmic *ARID1A* was an independent predictor of worse survival (adjusted HR 1.530, 95% CI 1.017-2.301, *P*=0.041), with a 2-year shorter median survival (*P*=0.008). Survival stratified by both cytoplasmic and nuclear staining was distinct (*P*<0.001) and median survival times spanned more than 5 years. *ARID1A* IP followed by MS identified key trafficking proteins, including importin 9 (*IPO9*). Blocking nuclear import of *ARID1A* in ovarian cancer cells (Figure 1C) was associated with increased cytoplasmic localization and increased proliferation (Figure 1D).

Conclusions: Aberrant cytoplasmic localization of *ARID1A* is independently associated with decreased patient survival and increases cellular proliferation in vitro.

Figure1: Kaplan-Meier curves for groups displaying or lacking *ARID1A* immunoreactivity in the nucleus (A), prevalent cytoplasmic staining (B). Silencing of importin-9 by siRNA (C) increases proliferation in TOV21G ovarian cancer cells expressing *ARID1A* (D).



Nuclear ARID1A Staining	Total	Alive	Dead	Median +/- SE Survival Time
Yes (normal)	242	53	189	38.0 +/- 3.6 months
No (aberrant)	17	6	11	56.1 +/- 22.7 months

Prevalent Dark Cytoplasmic ARID1A	Total	Alive	Dead	Median +/- SE Survival Time
No (normal)	223	54	169	42.0 +/- 2.9 months
Yes (aberrant)	36	5	31	17.6 +/- 4.6 months

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230 - Poster Session A

An analysis of short-term morbidity associated with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer

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Objectives: To evaluate the short-term morbidity associated with intraoperative HIPEC in patients with ovarian cancer (OVCA).

Methods: We performed a single-institution retrospective case series of all patients who underwent HIPEC for treatment of OVCA from October 2011 to June 2013. Perioperative variables, adverse events, and complications from time of HIPEC to 30 days postoperatively were identified.

Results: Twenty patients with a median age of 57 years (range, 37-81 years) received intraoperative HIPEC during the study period: 4 (20%) as consolidation therapy at time of second-look surgery, 5 (25%) at the time of interval surgical cytoreduction, and 11 (55%) at the time of secondary surgical cytoreduction. All patients had a Gynecologic Oncology Group performance status of 0 or 1. The most common tumor histology was high-grade papillary serous (n=17). Choice of chemotherapeutic agents was dictated by previous treatment response; the most common regimen administered was a combination of paclitaxel and cisplatin (n=12). Extent of surgery varied, although most had radical cytoreductive procedures, including 13 bowel resections, 7 splenectomies, and 3 partial liver resections. There were no intraoperative complications. All patients were observed postoperatively in the surgical intensive care unit. The most common postoperative adverse events were: need for transfusion (n=10), anemia (n=7), and fever (n=7). Five (25%) patients required readmission within the 30-day postoperative period (1 case of pyelonephritis, 1 small bowel obstruction, 1 anastamotic leak, and 2 wound infections). Only one patient required reoperation within 30 days (for an anastamotic leak). There were no postoperative deaths.

Conclusions: Our data suggest that not only is the incorporation of intraoperative HIPEC feasible, but it is also associated with acceptable 30-day morbidity rates that are similar to those seen in surgical resection for OVCA without intraoperative chemotherapy. Further investigation into determining oncologic and survival outcomes is warranted.

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231 - Poster Session A

Correlation of positron emission tomography (PET) with CA-125 levels in predicting recurrence in ovarian cancer

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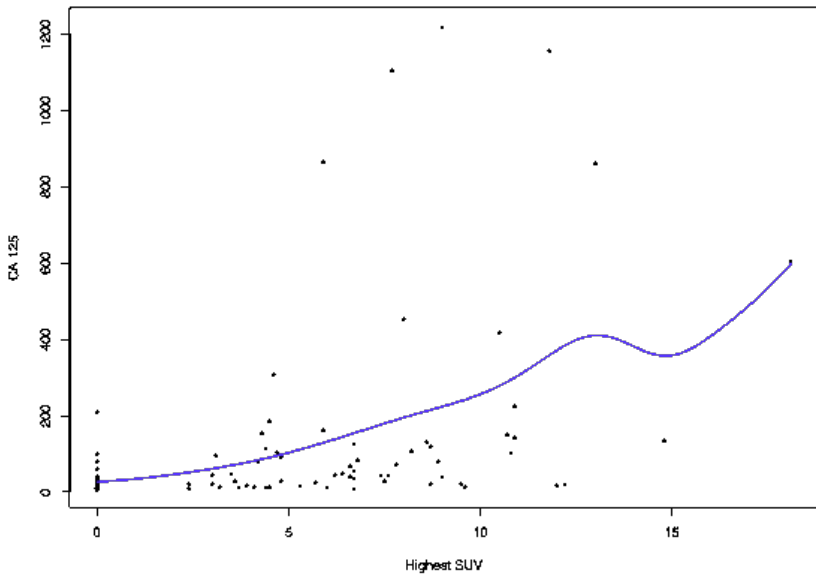
Objectives: CA-125 levels during chemotherapy have been demonstrated to predict response to therapy and recurrence in ovarian cancer patients. However, elevations of CA-125 are seen in only 80% of ovarian cancers. As such, some have advocated the use of PET hyperactivity as an equal indicator of response to therapy and predicting recurrence. Our objective was to evaluate the correlation of PET scans with CA-125 levels in predicting recurrent ovarian cancer.

Methods: A retrospective review of ovarian cancer patients with CA-125-positive disease was performed from 2009 to 2012. Demographics, treatment data, CA-125 levels, PET/computed tomography (CT) results and survival outcomes were abstracted. Standardized uptake value (SUV) of the index lesions was compared to CA-125 level at the time of imaging via Spearman's rank correlation coefficient with a non-parametric smoothing technique to determine the relationship.

Results: A total of 356 patients with newly diagnosed ovarian cancer were identified, and a total of 143 PET/CT scans were performed in 59 patients during surveillance. The mean age was 62.0 years, with the majority of patients being white (93%) and having stage III disease (69%) of papillary serous histology (71%). Mean CA-125 level at time of diagnosis was 1,367 U/mL (range, 35-9,771 U/mL). During surveillance, 55 CA-125 levels were positive (>35 U/mL), with mean level of 118 U/mL (range, 8-14,677 U/mL). PET scans demonstrated recurrent disease in 60 of 142 (42%) PETs performed, with a mean SUV of target lesion of 8.6 (range 2.4-60.3). Of the 60 positive PET SUVs, 19 (32%) were determined in patients with negative CA-125 levels at time of recurrence. Spearman's rank correlation coefficient demonstrated a statistically significant moderate-to-strong correlation of PET SUV with CA-125 level (0.59, P<0.0001) with non-parametric smoothing technique determining a linear to exponential relationship.

Conclusions: PET SUV demonstrated a significant correlation with CA-125 levels in patients with CA-125-positive ovarian cancer. Additionally, PET scans were helpful in determining recurrence in patients with normal CA-125 levels at the time of recurrence. PET is an accurate predictor of recurrence of ovarian cancer but needs further study to determine the impact on current clinical management.



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232 - Poster Session A

Identification of differentially expressed miRNAs in ovarian cancer from endometriosis in the same patient

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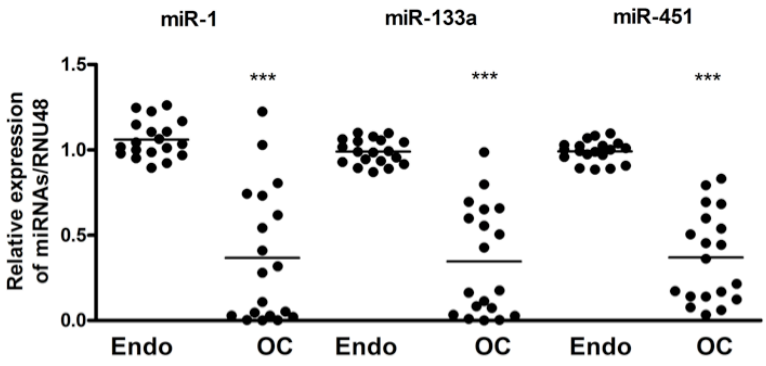
Objectives: Endometriosis has a known association with ovarian cancer. Micro RNAs (miRNAs) are small noncoding RNAs that play an important role in biologic and pathologic processes and are now used as diagnostic and prognostic markers in various cancers. The role of miRNAs in ovarian cancer and endometriosis is unclear. The aim of this study was to recognize a possible role for miRNAs in distinguishing ovarian cancer and endometriosis by comparing the miRNA profiling of ovarian cancer in patients with endometriosis.

Methods: We identified 19 cases of ovarian carcinoma with endometriosis in the same patient from our database. Nine were endometrioid, eight serous, and two clear cell carcinoma. Microscopic foci of endometriosis and ovarian cancer were selected and macrodissected. The miRNA expression profiling was performed initially from pooled RNA samples from ovarian cancer and endometriosis from all cases through LC Sciences using array technology. Later, the abnormal expression of selected miRNAs was validated in individual cases by quantitative real-time PCR (qRT-PCR).

Results: The miRNA profiling demonstrated deregulation of >1,000 miRNAs in ovarian cancer of which the top seven were further validated by qRT-PCR. The expression of tumor suppressor miRNAs miR-1, miR-133a, and miR-451 were reduced significantly in ovarian cancer, while the expression of the oncogenic miRNAs miR-141, miR-200a, miR-200c, and miR-3613 was elevated significantly in ovarian cancer (Figure). Conversely, miRNAs for oncogene and tumor suppressor gene expression in endometriosis showed a reverse trend.

Conclusions: There are significant differences between ovarian cancer and associated endometriosis at the level of miRNA transcription. Both tumor suppressor miRNAs (1, 133a, 451) and oncogenic miRNAs (141, 200a, 200c, 3613) are possible molecules that distinguish ovarian cancer from its associated endometriosis. These miRNAs should be studied further to identify their role as possible biomarkers in the development of ovarian cancer in patients with endometriosis.



Tumor Suppressor miRNAs were significantly reduced in OC (ovarian cancer) compared to respective Endo (endometriosis). ***P= 0.0001

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233 - Poster Session A

Cancer-testis antigen expression is shared between epithelial ovarian cancer tumors

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Objectives: Cancer-testis (CT) antigens have been proposed as potential targets for cancer immunotherapy. The presence of these antigens is known to be heterogeneous, with no single antigen found to be universally expressed. Current data from gene expression profiles in many types of tumors suggest that antigen sharing between allogeneic tumors of the same type may be a generalizable phenomenon. We hypothesized that there is antigen sharing between epithelial ovarian cancer (EOC) tumors. Our objective was to evaluate the expression of a panel of 20 CT antigens in EOC tumor specimens, and to determine if antigen sharing occurs between tumors.

Methods: RNA was isolated from EOC specimens, EOC cell lines, and benign ovarian specimens. Real-time polymerase chain reaction analysis was performed to determine the expression level and the biologic relevance of 20 CT antigens, including NY-ESO-1, MAGE-A3/A4, GAGE, LAGE, PIWIL-2, and CT-45.

Results: A total of 62 EOC specimens (47 primary ovarian tumors and 15 metastases), 8 ovarian cancer cell lines, and 3 benign ovarian tissues were evaluated for CT antigen expression. The majority of the specimens were high-grade (62%), serous (68%), and advanced-stage (73%) and were obtained at primary debulking surgery (81%). Fifty-eight (95%) of the EOC tumors analyzed expressed at least one of the CT antigens evaluated. The median number of CT antigen expressed was four (range, 0-17). Higher-grade tumors (2 and 3) expressed three or more CT antigens (both 72% vs 25% of grade 1, P=0.04). The most frequently expressed CT antigen were MAGE A4 (67%), SP17 (47%), GAGE (47%), and MAGE A1 (40%). Antigen-sharing analysis showed the following: 9 tumors shared only one antigen with 62% of the evaluated specimens, 5 tumors shared up to two antigens with 74%, 11 tumors shared up to three antigens with 71%, and 37 tumors shared four or more antigens with 82%. Five tumors expressed >10 CT antigens, which were shared with 90% of the tumor panel.

Conclusions: We detected expression of at least one of the 20 tested CT antigens in 95% of EOC tumor specimens. However, not a single antigen was universally expressed across all samples. The degree of antigen sharing between tumors increased with the total antigens expressed. These data suggest that a multi-epitope vaccine for the immunotherapy of EOC will be more broadly applicable than a single-epitope approach.

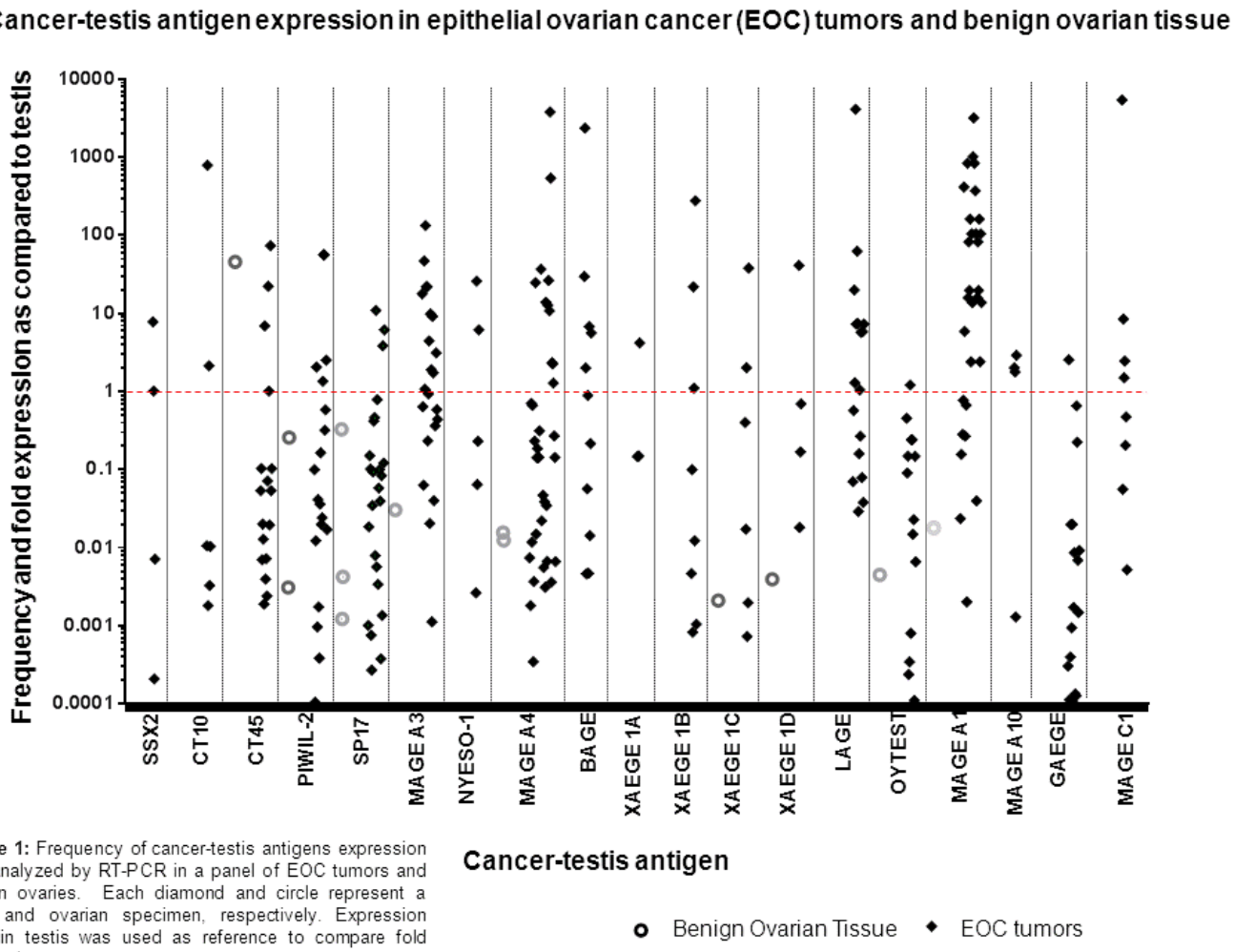

Figure 1: Frequency of cancer-testis antigens expression was analyzed by RT-PCR in a panel of EOC tumors and benign ovaries. Each diamond and circle represent a EOC and ovarian specimen, respectively. Expression level in testis was used as reference to compare fold expression.

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234 - Poster Session A

Reliability and reproducibility of ^{99m}Tc-etarfolatide for identification of patient folate receptor status

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Objectives: The folate receptor (FR) is expressed on most epithelial ovarian cancers, and FR expression can be a negative prognostic factor in this setting. Several folate receptor-targeting drugs have been developed, including vintafolide, a small-molecule drug conjugate of folate and desacetylvinblastine. ^{99m}Tc-Etarfolatide (EC20) is a small molecular-weight folate receptor-targeted companion single-photon emission computed tomography (SPECT) imaging agent that can be used for noninvasive real-time assessment of functionally active FRs and as a companion diagnostic for vintafolide. In a previous randomized phase II study, vintafolide showed clinical activity in platinum-resistant ovarian cancer (PROC) and ^{99m}Tc-etarfolatide had utility for selecting patients most likely to benefit from vintafolide therapy. This study assessed the reliability and reproducibility of the folate receptor status assessment by measuring inter-reader agreement among five readers.

Methods: Target lesions of 60 patients with PROC were selected at the treatment sites based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. According to the read protocol, SPECT images of these patients were individually assessed for ^{99m}Tc-etarfolatide uptake by five central nuclear medicine physicians. Each reader independently evaluated, for each patient, the percent of target lesions that were FR-positive. Inter-reader agreement was assessed for patient classification relative to different FR thresholds [e.g., FR(100%) vs FR(<100%) and FR(>0%) vs FR(0%)]. The primary analysis was to estimate Fleiss' kappa statistic for each FR threshold. Secondary objectives included measuring pairwise agreement and assessing reader consistency.

Results: Five-reader agreement was at least 73% and Fleiss' Kappa was at least 0.69 for both the FR(100%) and FR(0%) thresholds.

Conclusions: ^{99m}Tc-etarfolatide imaging is a reliable and reproducible method to identify patients with FR-positive lesions. This reproducibility is critical to the ongoing phase III study (PROCEED) in which only FR-positive patients determined by ^{99m}Tc-etarfolatide scan receive vintafolide.

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235 - Poster Session A

HGF/c-Met axis drives cancer aggressiveness in the neoadjuvant setting of ovarian cancer

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Objectives: Ovarian cancer is the most lethal gynecologic malignancy. Recently, neoadjuvant chemotherapy (NACT) has been clinically tested as alternative approach for the management of ovarian cancer patients. A biologic predictor helpful in selecting patients for NACT would be desirable. Indeed, chemotherapy has a strong impact in modifying tumor biology and rendering it more aggressive. This study was aimed at identifying actionable mechanisms of resistance to NACT.

Methods: Expression of a panel of microRNAs was screened in a discovery set of 85 patients. Analysis of the potential targets was conducted in the same RNAs by calculating significant correlations between microRNAs and genes. Quantitative fluorescent immunohistochemistry was employed in a validation set of 109 patients. Pre- and post-NACT specimens were analyzed in multiple cores of tumor from formalin-fixed paraffin embedded material (FFPE).

Results: MiR-193a-5p was significantly overexpressed in the NACT setting. Analysis of its potential targets demonstrated that this microRNA is also significantly correlated with the expression levels of *HGF* and *MET* genes. Analysis of protein expression in samples taken before and after NACT demonstrated that both *HGF* and *c-Met* are increased after NACT. Patients who relapse shortly after NACT exhibited the highest relative basal expression of both *HGF* and *c-Met*, while the opposite phenomenon was observed in the best responders.

Conclusions: These findings demonstrate that NACT-refractory patients express activation of the *HGF/c-Met* pathway. *HGF/c-Met* expression may help select eligible patients for this modality of treatment. Moreover, inhibitors of this pathway may improve the efficacy of NACT.

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236 - Poster Session A

Hitting the right mark: nonoverlapping *Notch* and *PI3K* alterations in ovarian cancer

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The University of Texas MD Anderson Cancer Center, Houston, TX

Objectives: The *Notch* and *PI3K/AKT* pathways are known to play critical roles in the progression of cancer and have been identified as important therapeutic targets in multiple tumor types. Therefore, we sought to identify the relationship between specific gene alterations in the *Notch* and *PI3K/AKT* pathways and their potential clinical relevance in ovarian cancer.

Methods: Genomic alteration information (mRNA expression, mutation, and copy number) was obtained from cBio Cancer Genomic Portal. Additionally, we downloaded clinical data from The Cancer Genome Atlas (TCGA). Extracted information included age, stage, histologic grade, residual disease, and overall and progression-free survival.

Results: A total of 315 samples were available for analysis. When we examined genes in the *Notch* pathway, 29% (90) had amplification and/or upregulation of *Notch 3* or *DLL3* genes. Within the *PI3K/AKT* pathway, 13% (41) had amplification and/or upregulation of *AKT1* or *PIK3R3* genes. Interestingly, gene alterations in either pathway were typically mutually exclusive. Only 4% (12) of tumors had amplification and/or upregulation of genes in both *Notch* and *PI3K* pathways. When excluding these cases with overlapping alterations, *Notch 3/DLL3* amplification and/or upregulation (n=78) correlated with significantly poorer overall survival compared to patients with upregulation and/or amplification of *AKT1/PIK3R3* (n=29) (median survival 36.2 months vs 63.5 months, P=0.0024). There was no significant difference in residual disease, histologic grade, or clinical stage between the two groups (Fisher test was performed). The group with *Notch 3/DLL3* alterations had a higher median age of 63 years vs 53 years (P=0.015) (Wilkinson rank sum test performed).

Conclusions: Amplification and/or upregulation of *Notch 3* and *DLL3* genes were associated with worse patient survival when compared to amplification and/or upregulation of *AKT1* and *PIK3R3*. Given that *Notch* and *PI3K* pathway inhibitors are currently being tested in clinical cancer trials, these data could have implications for personalized cancer therapy.

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237 - Poster Session A

Clinicopathologic benchmark for prognostic modeling of advanced epithelial ovarian cancer long-term survival: a Gynecologic Oncology Group (GOG) analysis

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Objectives: Reliably predicting long-term survival (LTS) in epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC) may allow greater individualization of adjuvant treatment. Our objective was to determine clinicopathologic factors associated with 10-year survival in advanced EOC and PPC patients and develop a predictive model identifying these patients.

Methods: Demographic, surgical, and clinicopathologic data were abstracted from GOG 182 records. LTS was defined as date of death or last follow-up >120 months. Bootstrap methods were used to develop predictive models. The preliminary model included main effects for age, performance status, ascites, preoperative disease score (DS), surgical complexity score (CS), residual disease (RD), stage, pretreatment CA-125, and all second-order interactions (a total of 53 covariates). This model was reduced by backward selection in 2000 bootstrapped data sets. Covariates retained in at least 70% of the bootstrapped models comprised the final model. Predictive accuracy was quantified using optimism-adjusted area under the receiver operating characteristic curve (AUC).

Results: Of 4,312 patients enrolled in GOG 182, 3,699 had adequate annotation to assign DS and RD. After censoring, 2,815 patients and 195 LTS remained for this analysis. The secondary model included all main effects plus interaction terms with RD and both ascites and age. These interaction terms were removed because of low representation in the bootstrap sets and a lack of statistical significance when refit with the original data. Age and DS were also dropped from the final model because they were not statistically significant and did not change the model fit. Full-reduced model chi-square tests showed no loss of fit between the full and final (main-effects) models. The final model had AUC=0.726 when fit to the original data; the optimism-adjusted AUC was 0.722 (0.714 to 0.726).

Conclusions: Despite developing a model using extensive demographic, surgical, and clinicopathologic data, we were unable to reliably predict LTS. The AUC established in this study provides a benchmark for development of more accurate predictive models that include molecular features alone or in combination with other characteristics.

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238 - Poster Session A

Serum antibodies recognizing *BRCA1* at time of diagnosis and primary platinum resistance in ovarian cancer

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Objectives: To establish *BRCA1* as a tumor-associated antigen in ovarian cancer and ascertain the relationship of serum antibodies recognizing *BRCA1* with primary platinumresistant and refractory disease.

Methods: Ovarian cancer patients were tested for serum antibodies recognizing *BRCA1* using MCF7 cell lysates by Western blot and immunoprecipitation with densitometry quantitation. Serum concentrations >2 standard deviations above the mean of normal donors were considered positive and confirmed by Western blot using recombinant protein. Serum was obtained at diagnosis and stored at -80°C. Patients who progressed within 6 months of completing therapy were classified as platinum-resistant and those who progressed >6 months after completing therapy were classified as platinum-sensitive. Platinum-refractory patients failed to achieve at least a partial response.

Results: Of 49 ovarian cancer patients, 7 (14.3%) had confirmed serum antibodies recognizing *BRCA1* at time of diagnosis. None of 49 normal donors had confirmed antibodies recognizing *BRCA1* (P=0.03) (odds ratio [OR]: 8.167, 95% CI 0.9647-

69.13). In 20 ovarian cancer patients with platinum-refractory (*n*=5) or platinum-resistant disease (*n*=15), 30% had antibodies to *BRCA1*. In the 29 with platinum-sensitive disease, 3.4% had antibodies to *BRCA1*. Ovarian cancer patients who proved to be primary platinum-resistant or -refractory were more likely to possess elevated levels of serum antibodies recognizing *BRCA1* at time of diagnosis than patients with primary platinum-sensitive disease (*P*=0.014)(OR 12.00, 95% CI 1.313-109.7). Mean serum concentrations of *BRCA1* antibodies were more than fivefold higher in patients who were primary platinum-resistant or -refractory compared to those who proved to be platinum-sensitive. There was no difference in the rate of germline *BRCA1* mutations in primary platinum-resistant or -refractory patients with antibodies and those without.

Conclusions: The detection of serum antibodies recognizing *BRCA1* in ovarian cancer patients establishes it as a novel tumor-associated antigen and a potential target for immune-based therapies. Elevated levels of serum *BRCA1* antibodies in ovarian cancer patients at the time of diagnosis may identify patients at increased risk of having a primary platinum-resistant or -refractory phenotype.

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239 - Poster Session A

Prognostic significance of the number of postoperative intraperitoneal chemotherapy cycles for patients with advanced epithelial ovarian cancer

R. S. Suidan, Q. Zhou, A. Iasonos, R. O'Cearbhaill, D. S. Chi, K. C. Long, E. J. Tanner III, J. Denesopolis, R. R. Barakat and O. Zivanovic
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Objectives: A combination of intravenous (IV) and intraperitoneal (IP) chemotherapy is associated with a survival advantage for patients with optimally resected advanced epithelial ovarian cancer compared to IV therapy alone. In Gynecologic Oncology Group (GOG) 172, only 42% of patients in the IV/IP arm received all 6 planned cycles, mainly due to toxicity. Despite this, the IV/IP arm was associated with increased survival. The purpose of this study was to evaluate the prognostic significance of the number of IV/IP cycles administered.

Methods: Data were analyzed for all patients with stage IIIB-IV ovarian, fallopian tube, and primary peritoneal cancer who underwent optimal primary cytoreduction followed by platinum-based chemotherapy at our institution between January 2005 and July 2011. Eligible patients had a minimum of 1 cycle of IV/IP treatment as part of their postoperative chemotherapy. A landmark analysis at completion of IV/IP chemotherapy was performed to associate progression-free (PFS) and overall (OS) survival with IV/IP treatment cycles.

Results: A total of 201 patients treated with at least 1 IV/IP cycle were identified over the study period. Twenty-three patients (11%) received 1 to 2 cycles of IP chemotherapy, 42 patients (21%) received 3 to 4 cycles, and 136 patients (68%) received 5 to 6 cycles. A total of 187 patients (93%) received cisplatin-based IP chemotherapy, while 14 patients (7%) received carboplatin-based IP chemotherapy. Of the 201 patients, 162 started with IV/IP chemotherapy, while 39 started with IV and later transitioned to IV/IP chemotherapy. The median PFS and OS for the entire cohort were 25 and 75 months, respectively, with a median follow-up of 46 months. There was no significant difference in 5-year PFS for patients who received 1 to 2 cycles (17%), 3 to 4 cycles (30%), or 5 to 6 cycles (16%) (*P*=0.21). There was no significant difference in 5-year OS for patients who received 1 to 2 cycles (50%), 3 to 4 cycles (58%), or 5 to 6 cycles (52%) (*P*=0.33). Of the 88 patients (44%) who received <6 IP cycles, the most common reasons were: poor performance status (17 [19%]), gastrointestinal symptoms/dehydration (10 [11%]), and renal/metabolic toxicity (9 [10%]).

Conclusions: In our study, we did not detect a significant survival difference between patients who received 1 to 2, 3 to 4, or 5 to 6 cycles of IV/IP chemotherapy. Patients who receive <6 cycles of IV/IP chemotherapy as part of their postoperative treatment may still have a survival benefit.

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240 - Poster Session A

Venous thromboembolism carries a particularly grave prognosis with epithelial ovarian cancer

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Objectives: To analyze survival with preoperative vs postoperative venous thromboembolism (VTE) in patients with epithelial ovarian cancer (EOC).

Methods: A retrospective chart review was performed consisting of patients treated for stage I-IV EOC from January 1996 to June 2011. Demographic, clinicopathologic, and treatment characteristics were recorded. VTE was dichotomized as preoperative (pre-op) or postoperative (post-op). SAS 9.2 was used for statistical analyses.

Results: Among the 586 patients who met study criteria, the median age was 63 years (range, 17-94 years), 88% were white, and 87.9% had performance status=0 at diagnosis. Median body mass index (BMI) was 27.1 (range, 13.7-67.0). Underlying hypertension was present in 42.3%, and 10.8% had diabetes mellitus. Most (68.7%) had high-grade serous histology and advanced-stage (III/IV) disease (61.6%) and underwent lymphadenectomy (71.2%). Four percent had a pre-op VTE and 13.7% had a post-op VTE. Of the patients with pre-op VTE, 62% had pulmonary emboli vs 83% of patients with post-op VTE. Platelet count did not differ with pre-op (P=0.26) or post-op (P=0.06) VTE, but CA-125 levels were higher in patients with both pre-op (median 478 U/mL vs 242 U/mL, P=0.046) and post-op VTE (473 U/mL vs 227 U/mL, P=0.0015) as compared to patients without VTE. Patients with post-op VTE were more likely to have had any radical procedure (49.4% vs 24.7%, P<0.001) as well as individual radical procedures such as colon resection (40.3% vs 16.6%, P<0.0001), splenectomy (11.8% vs 3.9%, P=0.008), and diaphragm stripping (14.3% vs 3.7%, P<0.001). Pre-op VTE was unrelated to PFS (P=0.11) but was associated with attenuated OS (median 19.7 months vs 66.0 months; HR 2.5, 95% CI 1.5-4.3, P=0.0007). Post-op VTE was associated with both shortened PFS (median 14.4 months vs 25.9 months; HR 1.5, 95% CI 1.2-2.0, P=0.002) and OS (median 47.6 months vs 83.9 months; HR 1.6, 95% CI 1.2-2.2, P=0.004). Upon multivariate analysis adjusting for age, stage, histology, performance status, and residual disease, pre-op VTE remained predictive of OS (P=0.01) but not PFS, although post-op VTE was associated with shorter PFS (P=0.004) and OS (P=0.006).

Conclusions: Both pre-op and post-op VTE appear to have a detrimental effect on OS of patients with EOC. However, it is unclear whether VTE is an inherent poor prognostic marker or if improved VTE prophylaxis and treatment may enable similar survival to patients without these events.

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241 - Poster Session A

Solitomab, an EpCAM/CD3 bispecific antibody (BiTE®), is highly active against primary chemotherapy-resistant ovarian cancer cell lines in vitro and fresh tumor cells ex vivo

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Objectives: Chemotherapy-resistant ovarian cancer remains an incurable disease. Solitomab is a novel bispecific single-chain antibody that targets the epithelial antigen EpCAM on tumor cells and also contains a CD3-binding region. We evaluated the in vitro activity of solitomab against multiple primary chemotherapy-resistant epithelial ovarian carcinoma cell lines and malignant tumor cells in ascitic fluid.

Methods: EpCAM expression was evaluated by real-time polymerase chain reaction (RT-PCR) and flow cytometry in 10 primary ovarian serous (OSC) cell lines and 10 fresh ovarian tumor cell cultures from ascitic fluids collected from patients with chemotherapy-resistant disease. The potential activity of solitomab against Ep-CAM/TROP-1-positive tumor cells was evaluated by flow cytometry, proliferation, and 4-hour chromium-release cell-mediated cytotoxicity assays.

Results: High expression of Ep-CAM/TROP-1 was detected by RT-PCR and flow cytometry in >90% of the ovarian tumors tested. Ep-CAM/TROP-1-positive chemotherapy-resistant ovarian cancer cell lines were found highly resistant to natural killer cell-mediated killing after exposure to peripheral blood lymphocytes (PBL) in 4-hour chromium-release assays (mean killing ± SEM, 3.48%±0.62%; range, 0% to 12.7%). In contrast, after incubation with solitomab, Ep-CAM/TROP-1-positive chemotherapy-resistant ovarian cancer cells become highly sensitive to T-cell cytotoxicity (mean killing ± SEM of 28.2%±2.05%; range, 10% to 50.7%; P<0.0001) by PBL. No killing was noted after incubation of EpCAM-positive cell lines with control BiTE. Ex vivo incubation for 96 hours of autologous tumor associated lymphocytes (TAL) with EpCAM-expressing malignant cells in unmanipulated ascitic fluid with solitomab resulted in a significant increase in TAL expression of the T-cell activation markers CD25 (interleukin-2 receptor alpha) and human leucocyte antigen (HLA)-DR, increased secretion of interferon-gamma, and proliferation of CD8 + TAL (P=0.01) as well as a dramatic reduction in the number of viable ovarian tumor cells in the ascitic fluid.

Conclusions: Solitomab may represent a novel, potentially highly effective targeted agent for the treatment of chemotherapy-resistant/refractory ovarian cancer patients overexpressing Ep-CAM/TROP-1.

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242 - Poster Session A

Inhibition of *HIF1a* promotes paclitaxel efficacy in CD133+ ovarian carcinoma cells

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Objectives: The cell surface protein *CD133* demarcates an ovarian cancer-initiating cell (CIC) population. CD133+ cells are chemoresistant relative to CD133- ovarian cancer cells and are enriched in recurrent ovarian cancer. Our objective was to determine if metabolic characterization of CD133+ vs CD133- cells could be used to identify novel CD133+ cell targets for therapy.

Methods: We analyzed gene expression microarray data from 34 ovarian cell lines for the proportion of CD133+ cells that was known. 41M, SKOV8, OVCAR4 ovarian cancer cell lines were sorted into CD133+ and CD133- subpopulations (n=4 replicates) by flow cytometry, and metabolic profiling of these cells was performed by Metabolon, Inc. (Durham, NC). The in vitro median inhibition concentrations for paclitaxel and/or noscapine (IC50 values) were determined and the Combination Index (CI) was calculated to determine if there is an additive, synergistic, or antagonistic effect between drugs.

Results: Gene set enrichment analysis showed enrichment of CD133+ vs CD133- cells with *HIF1A* target genes (FDR q=0.078). By metabolic profiling, trans-4 hydroxyproline (a product of *HIF1A* hydroxylation in the pathway leading to *HIF1A* degradation) was consistently decreased in CD133+ vs CD133- cells, approaching significance for 41M cells (P=0.121). These results suggest that the ability to sustain higher levels of *HIF1A* in CD133+ cells may be due to hindered *HIF1A* degradation. Moreover, glucose and glycolytic metabolites were elevated in CD133+ vs CD133- OVCAR4 cells ($0.1<P<0.2$). CD133+ cells were more resistant to paclitaxel than their CD133- counterparts (IC50: 4.20 nM vs. 3.79 nM, P=0.013). Treatment of these cells with the *HIF1A* inhibitor noscapine reduced *HIF1A* mRNA expression by 53.51%. Combined treatment with paclitaxel and noscapine was synergistic (CI 0.46).

Conclusions: *HIF1A*-related metabolic differences along with differences in glucose uptake and utilization may be hallmarks of an ovarian cancer stem cell phenotype. Our results suggest that the *HIF1A* pathway is a potential therapeutic target in CD133+ CIC cells.

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243 - Poster Session A

The utilization of positron emission tomography (PET) scans in ovarian, fallopian tube, and primary peritoneal carcinoma patients may be associated with improved overall survival

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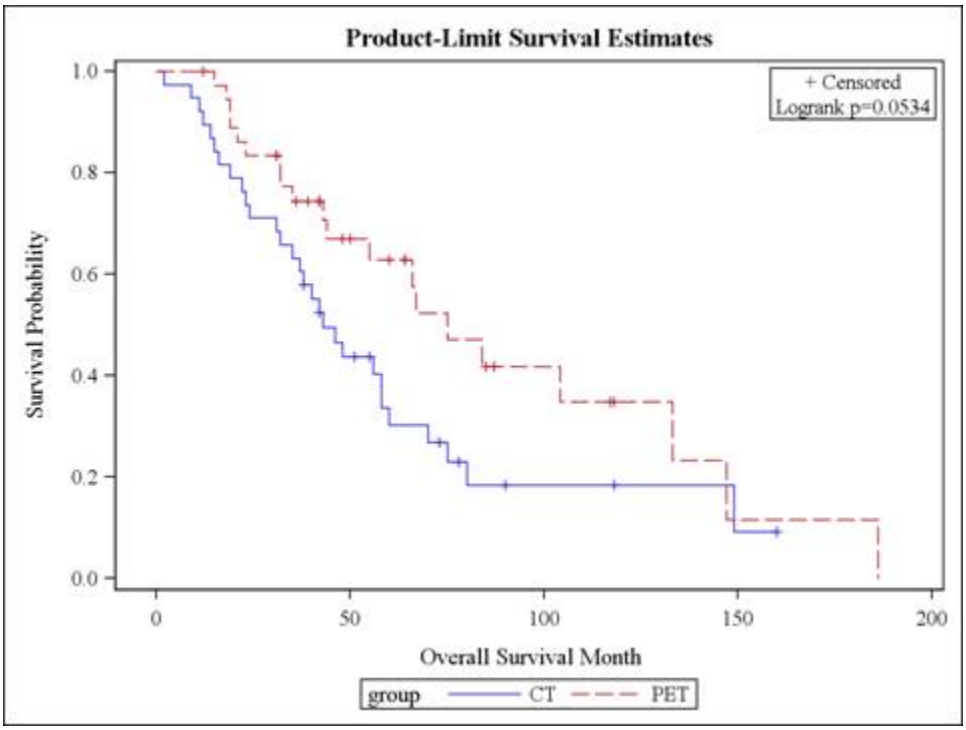
Objectives: To evaluate the practice patterns and use of positron emission tomography (PET) scans in patients with ovarian, primary peritoneal (PP), and fallopian tube carcinoma (CA) during treatment and surveillance vs routine CT scans alone as a prognostic factor for overall survival.

Methods: A retrospective analysis of women who underwent a PET scan at any point during their course of treatment or surveillance for ovarian, PP, and fallopian tube CA was performed and compared to patients who underwent CT scans only. Univariate analysis was performed using the Wilcoxon and chi-square tests. Kaplan-Meier and Cox proportional hazard regression was used for survival analysis.

Results: A total of 174 PET scans were performed in 58 patients. However, 19 of these patients had a diagnosis of another malignancy and were excluded from analysis. Of the remaining 39 patients, 120 PET scans were performed for an average of 3 PET scans/patient. The majority of PET scans were ordered by medical oncologists (75%), followed by gynecologic oncologists (16%), radiation oncologists (7%), and non-oncologic physicians (3%). The main reasons for obtaining a PET study were to evaluate treatment response (45%), surveillance (28%), follow-up CT findings (18%), and evaluate symptoms/increasing CA-125 (8%). On further analysis, the 39 PET scan patients were compared to an equal number of matched CT control patients. There were no differences in age, histology, stage, grade, or debulking status between the PET and the CT control group. However, on Kaplan-Meier evaluation, there was a statistically significant difference in overall survival in those patients who underwent a PET scan at some point during their treatment or surveillance (overall survival [OS]=75 months) vs those patients who only had CT scans for evaluation (OS=43 months, P=0.05) (Fig 1). Controlling for age, histology, stage, grade, and debulking status, Cox regression was applied to assess the effect of PET and CT on OS. Similarly, the CT control group was associated with a worse prognosis with an HR of 1.95 (95% CI 1.015 – 3.761, P=0.045) compared to the PET scan group.

Conclusions: The use of PET scans in the evaluation of ovarian, PP, and fallopian tube CA patients may be associated with improved OS compared to patients who only undergo CT scans. Larger studies are needed to evaluate the role of PET scans in ovarian cancer.



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244 - Poster Session A

Prognostic factors for overall survival in recurrent ovarian, fallopian tube, and peritoneal cancer patients treated with bevacizumab: a multisite study

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Objectives: To determine prognostic factors for overall survival (OS) in patients treated with bevacizumab (BEV) for recurrent ovarian, fallopian tube, and peritoneal cancers.

Methods: A multisite retrospective review of patients treated with BEV for recurrent ovarian, fallopian tube, or peritoneal cancer from 2001 to 2012 was performed. Age at diagnosis, stage, histology, grade, surgical outcome, primary platinum response, number of chemotherapy regimens after primary adjuvant chemotherapy but prior to BEV treatment, interval from completion of primary adjuvant chemotherapy to starting BEV treatment, and survival outcomes were abstracted. Cox proportional hazards regression was used to identify independent prognostic factors for OS (from BEV treatment start), using log-rank test.

Results: Of 161 patients identified, 131 consecutive women with complete medical records were available for analysis. Patients were treated with BEV alone (n=6) or with concurrent cytotoxic chemotherapy (n=125). A total of 107 deaths (82%) were identified, with median OS of 23.8 months. Factors associated with improved OS included age <60 years (n=66) at primary diagnosis (median 33.1 months vs 16.9 months, P=0.021), receiving 1 cytotoxic chemotherapy regimen (n=23) for recurrence prior to initiation of BEV (median 33.7 months vs 22.2 months for 2 regimens vs. 20.1 months for ≥3 regimens vs 18.8 months for no regimen, P=0.018), and having platinum-sensitive disease (n=74) following initial adjuvant chemotherapy (median 34.6 months vs 13 months, P<0.001). Primary platinum sensitivity was an independent predictor of improved OS (P<0.001). Receipt of 1 prior chemotherapy regimen, but not 0, 2, 3, or more prior regimens, was an independent predictor of improved OS (P=0.025), despite no significant difference in proportions of platinum-sensitive patients in these groups. Time from completion of primary adjuvant chemotherapy to starting BEV was not significantly associated with OS (P=0.679) nor independently predictive of OS (P=0.681).

Conclusions: Patients who are initially platinum-sensitive appear to benefit most from BEV-based regimens for recurrent disease. An optimal window of opportunity may exist for the use of BEV in the ordinal selection of treatments for recurrences that demands further study.

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245 - Poster Session A

Prognostic factors in malignant ovarian germ cell tumors

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Objectives: To analyze the clinicopathologic factors and their relation to survival in malignant ovarian germ cell tumors (MOGCT).

Methods: We retrospectively analyzed 78 patients treated for MOGCT from February 1980 to October 2012 in the Department of Gynecologic Oncology, AC Camargo Cancer Center.

Results: The median age was 16 years and median tumor size was 17 cm. There were 34 dysgerminomas, 15 yolk sac tumors, 10 immature teratomas, 5 embryonal carcinomas, 2 choriocarcinomas, and 12 mixed germ cell tumors. FIGO tumor staging was as follows: 43.1% stage I, 4.2% stage II, 38.9% stage III, and 8.3% stage IV. Of the stage IIIC disease, 39.3% were due to lymph node metastasis. The median follow-up was 73 months, and 26.8% of patients had residual tumor after surgery. Adjuvant chemotherapy and radiotherapy were performed in 64.1% and 17.9% of cases, respectively. The 5-year progression-free survival (PFS) was 83.1%, and all recurrences occurred in the first 2 years of follow-up. The 5-year overall survival (OS) was 80.6%, and there was no death after the third year of follow-up. Stage I had 5-year OS of 96.6%, whereas stages III and IV had 71% and 40%, respectively. Fertility-sparing surgery did not affect survival (P=0.805). Pure dysgerminoma histology had better survival compared to non-dysgerminomas (P=0.052). Further, lymph node dissection did not affect survival even for dysgerminoma (P=0.41). Bilateral ovarian involvement (18.1% of cases) also correlated to worse survival (P=0.022), and tumor size >10 cm had worse but not statistically significant survival (P=0.081). Presence of residual tumor after surgery negatively affected OS (P<0.001). However, no variable retained the negative impact of OS in multivariate analysis.

Conclusions: MOGCT have overall good prognosis, but macroscopic residual disease may negatively affect survival.

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246 - Poster Session A

A comparison of primary intraperitoneal chemotherapy to consolidation intraperitoneal chemotherapy in optimally resected advanced ovarian cancer

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Objectives: At our institution, patients with advanced epithelial ovarian cancer who had primary debulking followed by intravenous (IV) chemotherapy were historically offered second-look surgery and consolidation treatment with intraperitoneal (IP) chemotherapy if no or minimal disease was found at second look. With the publication of Gynecologic Oncology Group (GOG) 172, this management approach changed to giving primary IV/IP chemotherapy immediately after primary cytoreduction. The purpose of this study was to compare survival outcomes for patients who received primary IV/IP chemotherapy to patients who received IV followed by consolidation IP chemotherapy.

Methods: We identified all patients who underwent optimal primary cytoreduction (residual disease ≤1 cm) followed by platinum-based chemotherapy for stage IIIB-C ovarian, fallopian tube, and primary peritoneal cancer at our institution between January 2001 and July 2011. Patients were included if they received IV followed by consolidation IP chemotherapy (January 2001 to December 2005) or primary IV/IP chemotherapy (January 2005 to July 2011). Appropriate statistical tests were used.

Results: Of the 242 patients who met inclusion criteria, 180 (74%) received primary IP chemotherapy and 62 (26%) received consolidation IP chemotherapy. There were no differences between the groups in age, stage, tumor grade, ASA, preoperative albumin, or complete gross resection rate. The IP consolidation group had a significantly greater median preoperative CA-125, platelet count, and presence and amount of ascites at presentation. The primary IP group had a significantly greater number of patients with serous histology. The median progression-free survival (PFS) was significantly

greater for the primary IP group (25.8 months vs 21.1 months; HR 0.73, 95% CI = 0.53-0.99, *P*=0.048). The median overall survival (OS) was also significantly greater for the primary IP group (74.5 months vs 57.9 months; HR 0.58, 95% CI 0.39-0.86, *P*=0.008). After controlling for preoperative CA-125, platelet count, ascites, and histology, there was no significant difference in PFS (*P*=0.21), although OS was still significantly greater in the primary IP group (*P*=0.046).

Conclusions: In our analysis, primary IV/IP chemotherapy was associated with improved OS compared to IV followed by consolidation IP chemotherapy in patients with optimally cytoreduced advanced ovarian cancer.

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247 - Poster Session A

Nomogram predicting 5-year progression-free survival after secondary surgical cytoreduction for platinum-sensitive recurrent ovarian cancer

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Objectives: Patients who undergo secondary surgical cytoreduction (SSCR) for platinum-sensitive epithelial ovarian cancer (EOC) have variable disease courses. Prior studies have focused on prognostic factors for overall survival in this setting. Our objective was to identify prognostic factors for progression-free probability (PFP) and to develop a nomogram that predicts the probability of recurrence at 5 years that could be applied to an individual patient.

Methods: From January 1991 to November 2009, all EOC pts who underwent SSCR for first recurrence were identified. We excluded patients who recurred <6 months from the date of their last platinum therapy or if second-line chemotherapy was given prior to SSCR. Attempt at SSCR was required in all cases. Eleven clinical and pathologic variables available at the time of SSCR were investigated. PFP was calculated in months from date of SSCR to date of second recurrence or last follow-up. Multivariable Cox proportional hazards rates regression analysis was performed using significant factors on univariate analysis. Bootstrapping was used for internal validation of the nomogram. The concordance index (CI) was calculated to quantify the model's discrimination ability.

Results: We identified 198 patients who underwent SSCR for their first recurrence. The median age was 56 years (range, 27-80 years). Breakdown by initial stage of disease was: I (31), II (29), III (132), IV (6). There were 128 serous, 44 endometrioid, 12 clear cell, 6 mucinous, 5 carcinosarcoma, and 3 other histological types. Residual disease after SSCR was: 0 (114), <5 mm (26), <10 mm (14), >1 cm (44). Recurrence occurred in 162 patients after SSCR during a median follow-up of 45.4 months (range, 1.2-234.7 months). A nomogram was constructed using four significant variables. Internal validation was performed using bootstrapping, and the model was shown to have a 95% CI of 0.667.

Conclusions: We identified four prognostic factors for PFS after SSCR for recurrent EOC: number of recurrence sites, residual disease after SSCR, disease-free interval, and *BRCA* status. Using these four predictor variables, we developed a nomogram to predict an individual patient's 5-year PFP. With external validation, this tool may be helpful in patient counseling, postoperative management, and determining clinical trial eligibility.

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248 - Poster Session A

Lymphadenectomy in stage I ovarian granulosa cell tumors improves overall survival

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Objectives: Granulosa cell tumors are staged according to International Federation of Gynecology and Obstetrics ovarian cancer staging guidelines with stage being the most important prognostic factor. Previous small, retrospective reviews have suggested that lymph node dissection can be eliminated from the staging process for early stage disease given the rarity of metastatic disease to the lymph nodes. The objective of this study is to determine the effect of lymphadenectomy on overall survival in patients with stage I ovarian granulosa cell tumors.

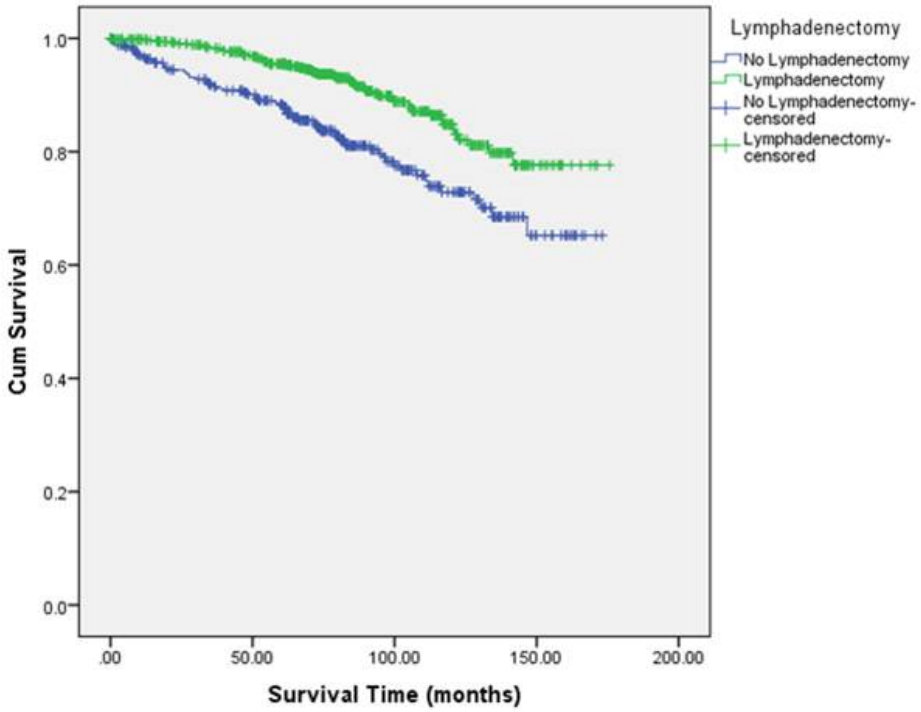
Methods: Patients with granulosa cell tumors of the ovary were identified from the National Cancer Data Base between 1998 and 2011. Patients with clinical stage T1/N0/M0 and pathologic stage T1/NX or NO/M0 disease were divided into those who underwent a lymph node assessment and those who did not. Demographic data, clinical and pathologic details, adjuvant

treatment, and vital status were extracted. Student's t-test, Chi-square or Fisher's exact test was used for all univariate analysis. Overall survival (OS) was calculated using the Kaplan-Meier method and compared using the log-rank test.

Results: Out of 3060 patients with ovarian granulosa cell tumors identified, only 46 (1.5%) had documented lymph node involvement. There were 1693 patients with stage I disease and 1609 who had data recorded regarding the performance of lymph node dissection. Of evaluable stage I patients, 975 (57.6%) had lymph node assessment and 634 (37.4%) did not. These groups were no different with regards to age, race, Charlson/Deyo comorbidity score, tumor grade, LVSI, type and frequency of adjuvant therapy. Patients who underwent lymphadenectomy had a larger mean tumor size (11.2 vs 9.5 cm, p< 0.001). The 5-yr and 10-yr overall survival (OS) for those with stage I disease who had lymphadenectomy was 98.8% and 95.7% compared to 94.4% and 87.5%, respectively for those who had no lymph node assessment, translating into a mean OS of 157.4 vs 140.2 months (p<0.001)(Figure 1).

Conclusions: Metastatic lymph node involvement is rare in ovarian granulosa cell tumors. However, even among patients with stage I disease, lymphadenectomy appears to confer an overall survival advantage indicating that abandonment of routine lymphadenectomy based on retrospective studies may be premature.

Figure 1. Overall Survival for patients with Stage 1 Granulosa Cell Tumor of the ovary based on performance of lymphadenectomy



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249 - Poster Session A

Risk of second primary breast cancer among women with epithelial ovarian cancer compared to fallopian tube cancer

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Objectives: Women with a history of epithelial ovarian cancer (EOC) have a significantly increased risk of developing a second primary breast cancer and vice versa. The risk in women with fallopian tube cancer (FTC) is unknown. The aim of this study was to compare the risk of second primary breast cancer after first primary EOC and FTC.

Methods: The Surveillance, Epidemiology, and End Results (SEER) Program data for all 18 registries from 1988 through 2010 was reviewed to identify women with EOC and FTC. To minimize misclassification of metastases or undetected synchronous cancers, women with EOC and FTC who developed second primary breast cancers 4 months after the diagnosis of EOC or FTC were identified. Continuous variables were evaluated by Student's t test or Wilcoxon-Mann-Whitney test, as appropriate. Categorical variables were evaluated by chi-square test. Impact of tumor site on survival was analyzed using the Kaplan-Meier method. Factors predictive of outcome were compared using the Cox proportional hazards model.

Results: Of 63,790 women included in this analysis, 61,565 (96.5%) women had EOC and 2,225 (3.5%) had FTC. The mean age at diagnosis was 59±15 years for women with EOC and 63±12.0 years for FTC (*P*<0.001). Patients with EOC had a higher rate of stage III (30% vs 18%, *P*<0.001) and IV disease (24.5% vs 8%, *P*<0.001). The time to diagnosis of secondary breast cancer was significantly longer in women with EOC (64 months vs 44.4 months, *P*<0.001). Women with EOC were less likely to develop breast cancer compared to those with FTC (1.2% vs 2.2%, *P*<0.001), and the 5-year breast cancer diagnosis rate was lower in women with EOC (1.3% vs 2.7%, *P*=0.001). After controlling for age at diagnosis of EOC or FTC, original stage, race, marital status, SEER registry, surgery, radiotherapy, grade, and histology, women with EOC were less likely to develop a secondary breast cancer (HR 0.64, 95 CI 0.47-0.89). In the whole population, women who developed a secondary breast cancer had an improved 5-year survival rate compared to women who did not develop breast cancer (83.5% vs 47.3%, *P*<0.001).

Conclusions: Women with FTC were more likely to develop a secondary primary breast cancer. Women who developed breast cancer after diagnosis of EOC or FTC had an improved survival compared to women who do not did not.

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250 - Poster Session A

Predicting overall survival after secondary surgical cytoreduction for platinum-sensitive recurrent ovarian cancer: a prognostic nomogram

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Objective: Patients with platinum-sensitive epithelial ovarian cancer (EOC) recurrence who undergo secondary surgical cytoreduction (SSCR) have heterogeneous outcomes. Our objective was to identify prognostic factors for overall survival (OS) to develop a nomogram that could predict OS for an individual patient undergoing SSCR.

Methods: We identified all EOC patients who underwent SSCR for their first recurrence at our institution from January 1991 to November 2009. We excluded all patients who recurred <6 months from their last platinum therapy and those who had second-line chemotherapy before SSCR. OS was calculated based on the date of death or follow-up. We analyzed 11 clinicopathologic variables. A Cox proportional hazards model then stepdown was employed to construct a predictive nomogram for internal validation (95% CI). Bootstrapping was used to correct optimistic bias.

Results: Among 198 eligible patients, the median age was 56 years (range, 27-80 years). Initial stage III-IV disease was identified in 138 (70%) patients. Histologies included 128 serous, 12 clear cell, 44 endometrioid, 6 mucinous, 5 carcinosarcoma, and 3 other. Residual tumor after primary cytoreduction was: 0 (78 patients), 5 mm (45), 10 mm (40), and >10 mm (35). Residual disease after SSCR was: 0 (114 patients), <5 mm (26), <10 mm (14), and >10 mm (44). With a median follow-up of 40.6 months (range, 1.2-180.6 months), 125 deaths were observed. The median time to death was 53.6 months. Five significant prognostic factors for OS were identified on multivariable analysis: disease-free interval, CA-125 level, ASA score, number of recurrence sites, and residual disease after SSCR. A nomogram using these five variables was constructed with bootstrapping for internal validation and shown to have a 95% CI of 0.719 (Figure).

Conclusions: We identified five prognostic factors for OS at the time of SSCR for recurrent platinum-sensitive EOC. Using these predictor variables, we developed a nomogram to predict an individual patient's OS after SSCR with a 95% CI of 0.719. With external validation, this tool may be helpful in patient counseling, selection for SSCR, postoperative management, and determining clinical trial eligibility.

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251 - Poster Session A

Acquired platinum resistance among women with high-grade serous epithelial ovarian cancer

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Objectives: Following primary chemotherapy, patients are categorized as either primary platinum-sensitive (PPS) or acquired platinum-resistant (APR). Eventually, PPS patients develop resistance to platinum therapies and can be characterized as APR. We sought to examine the natural history of APR as compared to primary platinum resistance (PPR).

Methods: Medical records of patients with high-grade serous ovarian cancer (HGS-OVCA) treated at a single institution from 2000 through 2010 were reviewed. PPR was defined as not achieving complete response (CR) with primary platinum therapy or recurrence <6 months from the end of therapy. APR was defined as CR with primary platinum therapy and subsequent therapy with a platinum agent resulting in progressive disease (PD) or recurrence within 6 months. Demographics, therapeutic modalities, and survival outcomes were abstracted and analyzed.

Results: Of 348 patients identified with HGS-OVCA, just over half (*n*=178) were PPS, while 23.3% (*n*=81) were PPR and 20.4% (*n*=71) were APR. Patients with APR had a median age of 61 years (range, 31-87 years). Stage III disease was diagnosed in 75% of patients. The majority of APR patients underwent primary debulking (86%); 13% received neoadjuvant therapy. The median number of therapy regimens was 4 (range, 2-11), with a median of 4 (range, 2-8) cytotoxics and 1 (range, 0-6) biologic. After a median follow-up of 4 years, patients with APR had a median primary progression-free survival (PFS) of 21.3 months and a median overall survival (OS) of 61.4 months. When calculated from the date of APR, OS was approximately 21 months compared to 15 months for PPR pts. There was no difference in median OS for APR patients based on prior number of platinum-containing regimens received (*P*=0.26). Mean length of time to develop APR was approximately 38 months, which was similar to that for patients who received maintenance therapy in the upfront setting and those who did not (37.7 months vs 37.5 months, *P*=0.98). Once APR, 10% of patients survived more than 4 years. Participation in clinical trials (*P*=0.006) and longer primary PFS (*P*=0.009) were associated with prolonged OS for patients with APR, while younger age (*P*=0.04), clinical trial participation (*P*=0.02), and number of biologic agents (*P*=0.006) predicted longer OS for PPR patients.

Conclusions: Prognosis following development of APR, while not as dire as for PPR, is still poor. Referral of these patients to clinical trials of biologic and targeted agents appears to be the best option for PPR and APR patients.

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252 - Poster Session A

Differential expression of *Rad51* and *NAC1* proteins in primary, metastatic, and recurrent high-grade serous ovarian cancer

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Objectives: *Rad51* interacts with *BRCA1/2* genes and plays a central role in the homologous recombination pathway essential for repair of DNA double-strand breaks. On the other hand, *NAC1* is a transcriptions repressor that has been reported to be associated with early recurrence and chemotherapy resistance. The objective of this study was to evaluate the expression of *Rad51* and *NAC1* proteins in primary, metastatic, and recurrent high-grade serous ovarian cancer.

Methods: A total of 248 cases of high-grade serous ovarian cancer, including 79 primary (PT), 86 metastatic (MT) (from lymph nodes, omentum, and liver) ,and 83 recurrent tumors (RT) following initial adjuvant chemotherapy and secondary tumor reductive surgery were constructed into tissue microarray. Immunohistochemical staining (IHC) using antibody against *Rad51* and *NAC1* proteins was performed. Nuclear and/or cytoplasmic expression was evaluated for *Rad51* and *NAC1* based on the intensity of staining (graded 0-3). Grade 0 was considered as negative expression and grades 1 through 3 were considered as positive expression. Chi-square test was used for statistical analysis.

Results: The expression of *Rad51* protein was found in 11.4% (9/79) of PT. This expression increased to 55.8% (48/86) among MT and 45.8% (38/83) among RT (*P*=3.9). Moderate-strong *Rad51* expression was found in 2/7 (28.5%) of PT, 18/45 (37.5%) of MT, and 10/38 (26%) of RT. *Rad51* expression was significantly higher in MT (*P*<0.05) and RT (*P*<0.05) compared to PT, but there was no difference in *Rad51* expression between MT and RT (*P*=0.21). In contrast, expression of *NAC1* was higher in PT 64.6% (51/79) and MT 75.3% (64/85) compared to RT 29.8% (25/84) (*P*=5.6). Moderate-strong *NAC1* expression was found in 12/51 (23.5%) of PT, 19/64 (30%) of MT, and 4/25 (16%) of RT. Positive expression of *NAC1* was significantly lower in the RT compared to both PT (*P*<0.05) and MT (*P*<0.05), but no difference in *NAC1* expression was found between PT and MT (*P*=0.17).

Conclusions: *Rad51* protein expression was significantly higher in metastatic and recurrent compared to primary ovarian tumors. On the other hand, *NAC1* expression was significantly lower in recurrent compared to primary and metastatic tumors. Further data correlating expression of these two proteins with clinical outcome are currently under investigation.

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253 - Poster Session A

Radiation therapy for recurrent clear cell ovarian carcinoma

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Objectives: Given the relative chemoresistant nature of clear cell gynecologic cancers, radiation therapy (RT) has been explored as an adjuvant treatment. We investigated the utility of radiation to treat recurrent clear cell carcinoma of the ovary.

Methods: A retrospective chart review of cases of recurrent ovarian clear cell carcinoma (CCC) was conducted from 1994 to 2012. Clinicopathologic factors were extracted and evaluated using Student t-test, Fisher's exact tests, Kaplan-Meier and Cox regression analyses. Patients were excluded if they had mixed tumors, synchronous primary tumors, or inadequate clinical data.

Results: Fifty-five patients had recurrent ovarian CCC, and 23 of these patients received RT (41.8%) at some point in their treatment. Tumors were initially 27% stage I, 9% stage II, 59% stage III, and 5% stage IV. Between those who received RT and those who did not, there was no difference in age, stage, optimal debulking, platinum response, or the number of patients who received >3 cycles of chemotherapy. A focal recurrence was more common in the group that was treated with radiation therapy (60.9% vs 12.5%, *P*=0.0004). The median time from diagnosis to receiving RT was 26 months, and most patients received RT after 1 or 2 cycles of chemotherapy (78.3%). Of patients who received RT, 73.9% had surgery with or prior to their treatment. The most common type of RT delivered was external beam radiation therapy to the pelvic field (72%). Despite receiving RT at variable times during their treatment course, RT showed a significant benefit in 5-year overall survival (74% vs 45%, *P*=0.008). In a multivariate analysis of multiple prognostic factors, only platinum sensitivity and RT treatment were significantly associated with improved overall survival (HR 0.08 and 0.15, respectively).

Conclusions: In this cohort of patients, two factors were associated with improved survival: platinum-sensitive disease and RT. Our study adds further support for the use of RT to treat recurrent disease.

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254 - Poster Session A

An analysis of the survival outcomes of video-assisted thoracic surgery in the primary management of patients with advanced ovarian, tubal, and peritoneal cancer

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Objectives: Since 2000, our institutional policy for patients who present with a moderate-to-large pleural effusion and presumed advanced ovarian cancer has been to perform video-assisted thoracoscopic surgery (VATS) to rule out large-volume intrathoracic disease. Patients with unresectable >1 cm intrathoracic disease were treated with neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS); those with no or ≤1 cm intrathoracic disease (at initial VATS evaluation or after intrathoracic cytoreduction) had abdominal primary debulking surgery (PDS). The objective of this study was to determine the progression-free (PFS) and overall survival (OS) of this management strategy.

Methods: We identified all women with advanced-stage high-grade serous carcinoma who underwent a VATS procedure as part of their primary management. The decision to proceed with PDS vs NACT was made by the attending gynecologic oncologist. All pertinent clinical information was collected from the electronic medical records and appropriate statistical tests were performed using SPSS v21.

Results: Between 2000 and 2012, 70 women met inclusion criteria. PDS was attempted following VATS in 42 (60%) cases, while NACT and IDS was performed in 28 (40%) cases. Median age and follow-up time for those patients treated with PDS vs NACT were similar. There were no complications related to the VATS procedure. Optimal cytoreduction (residual disease ≤1 cm) was achieved in 32/42 (76%) of the PDS cases and 27/28 (96%) of the NACT/IDS cases. Median PFS was improved for those patients who had VATS followed by PDS (16 months; range, 12-20 months) compared to those who had NACT/IDS (8 months; range, 5-11 months) (*P*<0.001). Similarly, median OS for women who had VATS was greater for those who had PDS than for those who had NACT/IDS at 55 months (range, 37-74 months) vs 35 months (range, 29-42 months) (*P*=0.05).

Conclusions: The management strategy of triaging patients with moderate-to-large pleural effusions to PDS vs IDS identified a subset of patients who had significantly longer PFS and OS rather than automatically assigning them to NACT due to stage IV extraperitoneal disease.

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255 - Poster Session A

Canine scent-specific detection of serous ovarian cancer

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Objectives: There are currently no effective screening measures for ovarian cancer, the deadliest of all gynecologic malignancies. Dogs have 1 million to 10 million times the ability of humans to detect aromas. Search and Rescue (SAR) dogs are trained to detect trace amounts of scents associated with cadavers, bombs, and drugs. We have enlisted dogs to determine if they can be trained to identify a scent specific to serous ovarian cancer and discriminate between cancer and benign conditions.

Methods: Five SAR dogs were initially imprinted on a scent from multiple samples of fresh ovarian cancer tissue. The animals were trained using a specific verbal command associated with the ovarian cancer smell. Only positive rewards were used in the training. The animals were further trained to not respond to the aromas of multiple benign fresh ovarian tissues. Once imprinting was complete, the animals were exposed to urine from either affected or benign women.

Results: The dogs were able to imprint on a scent specific to ovarian cancer within 3hours of training, the time to produce imprinting fell dramatically with each animal. Once the animals could discriminate the aroma produced by serous ovarian cancers and benign ovarian tissue, they were exposed to urine. The animals were 100% accurate in determining benign or malignant scent in the urine, which included specimens from patients to whom the dogs were not previously (i.e., had not previously smelled the patients' tumors).

Conclusions: This study illustrated the ability to train SAR dogs to detect a scent specific to ovarian cancer and to detect this aroma in urine. This work is been expanded to a large prospective study to determine the sensitivity and specificity of this method as a screening. It is hoped that this will ultimately result in a reduction in mortality from ovarian cancer by early detection.

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256 - Poster Session A

Robotic and open cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of recurrent ovarian carcinoma

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Objectives: To evaluate the feasibility and tolerability of hyperthermic intraperitoneal chemotherapy (HIPEC) following robotic or open cytoreduction for recurrent ovarian cancer.

Methods: In a single-institution pilot study, patients underwent optimal cytoreductive surgery in combination with HIPEC followed by consolidation chemotherapy from September 2011 to May 2013. Optimal cytoreduction was defined as no lesion >1 cm. Adverse and oncologic outcomes were measured. Standard statistical analysis was used.

Results: Thirteen patients with a median age of 52 years (range 20-86 years) were identified. The median number of chemotherapy regimens prior to HIPEC was 3 (range, 1-12 regimens). A median of 2 platinum-containing regimens were administered prior to HIPEC (range, 0-5 regimens). Median CA-125 at the time of HIPEC was 256 U/mL (range, 13–8,543 U/mL). Seven (54%) patients were platinum-sensitive at the time of HIPEC. Six (46%) patients underwent robotic optimal cytoreductive surgery. The following cytotoxic agents were used during HIPEC: mitomycin in 6 patients (46%), cisplatin and paclitaxel in 4 (31%), carboplatin in 2 (15%), and paclitaxel in 1 (8%). There were no intraoperative complications or adverse events attributable to HIPEC therapy. Median hospital stay was 8 days (range, 1-25 days). All patients received consolidation chemotherapy following their cytoreduction and HIPEC. At a median follow-up of 4 months (range, 1-7 months), the progression-free survival free and overall survivals have not been reached.

Conclusions: In select patients, robotic and open cytoreductive surgery in combination with HIPEC is feasible and safe. The optimal candidate and chemotherapy regimen have yet to be defined. Preliminary survival data suggest efficacy. Further investigation for the role of robotic cytoreduction and HIPEC is warranted.

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257 - Poster Session A

Development of flow cytometric predictive biomarker assay for response to PARP inhibitor (PARPi) therapy in high-grade serous ovarian cancer (HGSOC)

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Objectives: Approximately 50% of HGSOC are deficient in homologous recombination (HRD). Understanding which HGSOC have HRD is of therapeutic importance to triage women to PARPi-based therapy. *γH2AX* and *RAD51* have been employed individually as surrogate measures of DNA double strand break (DSB) damage and repair, respectively, but neither alone has been proven a predictive biomarker. Quantification of both *γH2AX* and *RAD51* using a high throughput measure, such as a flow cytometric method, can allow determination of homologous recombination (HR) competence (low *γH2AX/RAD51* ratio) and incompetence (high *γH2AX/RAD51* ratio). We hypothesized HRD, described by a high ratio, will predict susceptibility to PARPi in HGSOC.

Methods: A sensitive and reproducible flow cytometry method was developed and validated using dual-color immunofluorescence (IF). Phorbol myristate acetate and ionomycin were used to stimulate peripheral blood mononuclear cells (PBMCs) for 4 hours before an up to 48-hour treatment with carboplatin 50μM/olaparib 10μM. PBMC samples from healthy blood donors were obtained from the National Institutes of Health Clinical Center Blood Bank. Changes in *RAD51, γH2AX*, and *MRE11*, a protein involved in the initial process of HR, were examined over time. Cycloheximide treatment during stimulation was performed to test if there was de novo production of *MRE11* in response to injury.

Results: Flow cytometry measures of HRD demonstrated that changes in *γH2AX* and *MRE11* can be assessed reliably in the setting of DNA damage and repair. *γH2AX* expression increased over the first 36 hours of treatment, and *MRE11* increase in expression was delayed, starting at 36 hours. Cycloheximide treatment significantly decreased *MRE11* induction but not *γH2AX* induction ($P=0.003$), indicating de novo production of *MRE11* in response to DNA injury. Preliminary IF results support the findings of the flow cytometry. Further validation studies using IF are ongoing. PBMC samples from patients in an olaparib/carboplatin study (NCT01445418) will be examined and correlated to outcome and toxicity.

Conclusions: Dual-label flow cytometry to measure the *γH2AX/MRE11* intensity ratio is a promising tool with which to predict DSB repair competence (high ratio) and incompetence (low ratio). Validation using PBMCs from olaparib/carboplatin patients is pending. Prospective confirmation will be needed.

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258 - Poster Session A

Incorporation of porcine adenovirus 4 fiber protein enhances infectivity of adenovirus vector on dendritic cells: implications for immune-mediated cancer therapy

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Objectives: Dendritic cells (DCs) loaded with tumor antigen are capable of eliciting a T-cell-mediated antitumor immune response. Human adenovirus serotype 5 (HAdV5) has been used in human studies for gene delivery and antigen loading but has limited infection in DCs, which lack the proper receptors. Addition of the porcine fiber knob (PK) from porcine adenovirus type 4 to HAdV5 allows the virus to deliver genetic material via glycosylated surface proteins and bypasses the wild-type HAdV5 receptor. In this study, we explored the potential therapeutic applications of an adenovirus with PK tropism (Ad5-PK) against mesothelin-expressing ovarian cancer for ex vivo dendritic cell antigen loading.

Methods: Human DCs were cultured from healthy donor peripheral blood mononuclear cells (PBMCs). HAdV5 and Ad5-PK viruses were generated containing luciferase, green fluorescent protein (GFP) (Ad5GFP1 or Ad5GFP1-PK), or a single chain trimer (SCT) plasmid encoding an immunogenic nine-amino acid mesothelin peptide (Ad5-9SCT or Ad5-9SCT-PK). Luciferase activity was measured in relative light units. GFP and SCT expression was detected via FACS analysis. Mouse models and SKOV-3 cells were used to demonstrate T-cell specificity and tumor antigen responses via interferon gamma (INF-ɣ) detection ELISpot.

Results: Ad5-PK showed increased infectivity and gene transfer over HAdV5 and previously tested modified adenoviruses, including Ad5/3 and Ad5FF/CD40L ($P<0.003$). The CD141+ DC subset, a key subset for activation of naïve CD8+ T cells, showed a sevenfold increase ($P<0.0001$) in GFP expression after infection with Ad5GFP1-PK compared to Ad5GFP1. Ad5-

9SCT-PK increased DC expression of tumor-specific SCT by a factor of 20 over Ad5-9SCT-infected DCs ($P<0.0001$). Vaccination of mice with the Ad5-9SCT-PK resulted in enhanced T-cell-mediated IFN-ɣ release in response the mesothelin antigen ($P=0.001$). Compared to Ad5-9SCT, mouse splenocytes boosted ex vivo with Ad5-9SCT-PK-infected DCs had a 50% increase in INF-ɣ release when exposed to mesothelin-expressing SKOV-3 ovarian cancer cells.

Conclusions: Ad5-PK is a promising tool for cancer immunotherapy because it improves infectivity, gene transfer, protein expression, and subsequent T-cell activation in DCs compared to wild-type HAdV5 viruses.

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259 - Poster Session A

Magneto-electric nanoparticles as field-controlled nano-electroporation sites for high specificity

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Objectives: High-specificity targeted delivery of antineoplastic drugs would be a significant breakthrough in ovarian cancer. Intraperitoneal delivery through a surgically implanted catheter has shown improved survival rates. However, catheter complications and toxicity have precluded widespread adoption of this means of delivery. To address this challenge, we hypothesized that magneto-electric nanoparticles (MENs) loaded with the drug(s) could serve as highly localized nano-electroporation sites to enable high-specificity, high-efficacy delivery. These new devices provide unprecedented energy-efficient, dissipation-free, and high-specificity control at the subcellular level. Unlike the conventional chemistry-based approaches, the new technology exploits the difference in physical (electric) properties between the tumor and healthy cells to determine the required specificity. The intravenously administrated drug-loaded MENs can be directed to the intraperitoneal tumor via external low-energy fields.

Methods: Using the hydrothermal method, 30-nm $CoFe_2O_4$-$BaTiO_3$ core-shell MENs were prepared. Paclitaxel (PTX) was loaded on MENs using standard chemistry. The kinetics of the field-controlled process were studied with nanocharacterization methods such as atomic force microscopy/magnetic force microscopy, Fourier transform infrared spectroscopy, mass spectrometry, fluorescence imaging, and ionizing radiation absorption. Cell culture experiments were performed using SKOV-3 cell lines.

Results: MENs served as localized nano-electroporation sites that “opened” the local pores in the cancer cell membranes on demand via application of a low-energy magnetic field (<100 Oe at 0 Hz) to allow the drug-loaded MENs inside the cytosol (with >80% coverage) without affecting the surrounding healthy cells. The drug penetrated through the tumor cell membrane and completely eradicated the cells within a 24-hour period without affecting the normal cells. The penetration field was reduced from >100 Oe to <30 Oe by increasing the frequency to 1,000 Hz. The cell viability (>98%) was maintained at the nanoparticle densities up to 100 mcg/mL.

Conclusions: The significance of this study in ovarian cancer is to develop a noninvasive means of administering intraperitoneal high-specificity chemotherapy for treatment of both localized and metastatic disease.

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260 - Poster Session A

Treatment of epithelial ovarian cancer with *HE4*-targeted antisense phosphorothioligos (PTOs)

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Objectives: The protein *HE4* is overexpressed in epithelial ovarian cancer and is clinically correlated with platinum resistance and poor prognosis. In animal models, *HE4* promotes human xenograft tumor growth and platinum resistance. Specifically designed phosphorothioligos (PTOs) can be used to target gene products (mRNA) that are overexpressed in cancer cells and used as targeted therapeutics. We examined the use of PTOs targeting *HE4* to determine their cytotoxic and antiangiogenic properties. We also examined the synergistic properties of PTOs with cisplatin for treatment of ovarian cancer.

Methods: PTOs targeting *HE4* were used to knock down *HE4* expression in ovarian cancer cell lines (SKOV3, OVCAR8). *HE4* expression was examined by Western blot. MTS assays and immunohistochemistry for TUNEL were performed to determine cell viability after treatment with PTOs and PTOs + cisplatin. Expression of cleaved poly ADP (adenosine diphosphate)-ribose polymerase (PARP), a marker of apoptosis, was examined by Western blot after treatment of cell lines with PTOs. Angiogenesis markers, including vascular endothelial growth factor (VEGF), VEGF-R2, focal adhesion kinase (FAK), and

phosphorylated epidermal growth factor receptor (P-EGFR) were examined by Western blot. Protein-protein interaction of *HE4* with VEGF-R2 was determined by colocalization and coimmunoprecipitation (co-IP).

Results: SKOV3 and OVCAR8 cells treated with PTOs had 73% to 87% reduced cell viability compared to controls. Additionally, PTOs acted in synergy with cisplatin by reducing resistance and inducing apoptosis. PTO treatment of SKOV3 and OVCAR8 mouse human xenograft tumors displayed increased apoptosis, as shown by TUNEL staining (25% vs 5% in controls). Treated cells also expressed cleaved PARP, a marker of apoptosis, which was not detectable in controls. *HE4* co-precipitates with VEGF-R2. PTO treatment of SKOV3 and OVCAR8 cells leads to decreased expression of angiogenesis factors, including VEGF (75% decrease compared to control), VEGF-R2 (53% to 99% decrease compared to control), FAK (61% decrease compared to control), and P-EGFR (96% decrease compared to control).

Conclusions: *HE4*-targeted antisense PTOs increased apoptosis and reduced angiogenesis in ovarian cancer cells and human xenograft tumor models. *HE4*-targeted PTOs can restore cisplatin-induced cytotoxicity in platinum-resistant ovarian cancer cell lines. These findings provide a promising target for treatment of *HE4* overexpressing epithelial ovarian cancer.

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261 - Poster Session A

Intraperitoneal administration of alpha-emitting isotopes

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Objectives: Alpha-emitting radionuclides recently were reported to be effective against microscopic carcinoma in clinical studies. This study presents a method of producing an alpha-emitting radionuclide, Bi-212, for clinical use and in vitro and in vivo studies supporting intraperitoneal (IP) administration of Bi-212 against microscopic ovarian cancer.

Methods: We developed a cation-ion exchange system based on the natural decay and regrowth of the isotope Pb-212 to produce millicuries of activity for IP clinical use. We compared the relative biological effectiveness (RBE) of Bi-121 against cell lines grown in monolayer and spheroids compared to x-ray and P-32 therapy. The effectiveness of IP treatment with Bi-212 of tumor-bearing mice inoculated IP with Ehrlich-Lettre ascites tumors was determined. Studies determined the biodistribution and toxicity associated with IP administration of Bi-212. Based on these studies, doses of Bi-212 necessary for eradication of microscopic ovarian cancer after IP administration while minimizing toxicity were determined.

Results: Our developed method provided adequate doses for clinical use. The calculated yield over a 24-hour period yielded 7.635 mCi of Bi-212 for each mCi of the parent isotope Lead-212 loaded onto the column. The actual yield of Bi-212 was up to 20 mCi of activity per elution. Bi-212 showed a higher RBE than x-ray therapy. The RBE was 1.4 for P-32, 1.5 for x-ray, and 3.19 for Bi-212 therapy. Imaging rabbits up to 3 hours after IP instillation of B-212 in 200 mL of saline showed even distribution in the peritoneal cavity, with 80% of the activity remaining in the peritoneal cavity. Bi-212 is effective in eradicating intraabdominal tumors in Ehrich-Lettre ascites-bearing mice. A cure with no evidence of disease at 3 months was documented in 40% of mice. Based upon these in vitro and in vivo studies, toxicity to normal human tissue is acceptable after IPadministration. A contemplated dose of 100 mCi to a human produces an alpha dose to any organ of <15c GY.

Conclusions: The alpha-emitter Bi-212 is a feasible radionuclide for treatment of microscopic ovarian carcinomas confined to the peritoneal cavity.

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262 - Poster Session A

Impact of new oncolytic herpes simplex virus for cervical cancer therapy

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Objectives: Cervical cancer is the third most common cancer in women and the seventh overall, with a worldwide incidence of approximately 530,000 and mortality of approximately 275,000, according to a database of the Agency for Research on Cancer (IARC) in 2008. One requirement of new treatments is to improve pathologic outcome. Oncolytic herpes simplex virus type 1 (HSV-1) is a promising strategy for cancer treatment. Accumulating evidence indicates that, aside from the extent of replication capability within the tumor, the efficacy of an oncolytic HSV-1 depends on the extent of induction of host antitumor immune responses. We analyzed the therapeutic potential of a third-generation of oncolytic HSV-1 termed T-01 for cervical cancer in mouse model.

Methods: We investigated the in vitro cytotoxicity reaction in human and mouse cervical cancer cell lines (TC-1, SKG-IIIa, CaSki, and HeLa). We analyzed TC-1 cell lines in vivo in immune-competent models and HeLa cell lines in immune-deficient models. Animals were challenged with a lethal dose of TC-1 or HeLa 17 days after the first intratumoral (i.t.) administration of T-01 was performed. T-01 was administered i.t. a 4- to 5-day intervals for 6 cycles.

Results: T-01 has great cytotoxicity for human and mouse cervical cancer cell lines. In addition, our results indicate that administration of T-01 produced the greatest antitumor effects for both cancer models. Furthermore, in immune-competent models, we found an increase of the number of cancer-specific CD8+ T-cells in the spleens of mice treated with T-01 compared with the control treated mice.

Conclusions: Our data suggest that T-01 is an effective treatment in a cervical cancer model that potentially may be translated into the clinical area.

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263 - Poster Session A

BRCA1 mutation determines the impact of profilin1 in ovarian cancer cell motility

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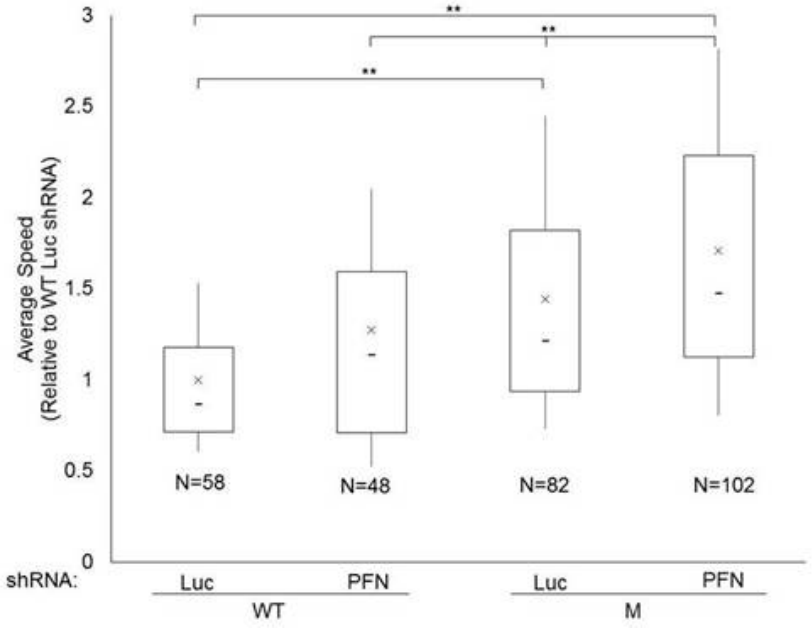
Objectives: Functional loss of *BRCA1* has been implicated in genomic instability and cancer progression. Profilin1 (*PFN1*) is an actin cytoskeleton-associated protein whose downregulation promotes breast cancer cell motility/invasion and dissemination. *PFN1* has not been studied in ovarian cancer, so we analyzed the expression and function of *PFN1* in a *BRCA1* mutant and wild-type (WT) cell lines and patient tumors.

Methods: A proteomic analysis was conducted on a cell line derived from a patient with papillary serous ovarian cancer with a known mutation in *BRCA1* (UWB1.289) and compared to its isogenic partner with *BRCA1* function restored (UWB1.289+BRCA). This analysis was also performed on tumor samples from patients with germline *BRCA1* mutations (n=13). *PFN1* expression in cell lines and tumor samples was assessed by immunoblot and fluorescence immunohistochemical (IHC) staining methods. Cell motility of *BRCA1*-deficient vs restored cell lines, with and without shRNA-mediated *PFN1* knockdown, was assessed by time-lapse videomicroscopy of randomly migrating cells.

Results: Comparison of differentially expressed proteins revealed increased expression of *PFN1* associated with *BRCA1* deficiency in both cell line and tumor samples, which was further confirmed by Western blot and IHC analyses. Motility studies demonstrated that *BRCA1* restoration in WT cells increased the random motility of mutant cells. *PFN1* knockdown enhanced motility in WT cells but not in *BRCA1*-deficient conditions (Fig 1).

Conclusions: The association of a functional connection between *PFN1* and *BRCA1* status and ovarian cancer cell migration has not been previously reported. While *BRCA1* has been extensively studied in the context of DNA repair, there is emerging evidence that *BRCA1* proteins may play a role in cell migration. Our findings demonstrate that: 1) *BRCA1* positively influences ovarian cancer cell motility, and 2) *BRCA1* status determines the role of *PFN1* role in ovarian cancer cell motility, suggesting a possible novel mechanism and association between *PFN1*, *BRCA1,* and ovarian cancer cell motility. Future studies should explore whether *PFN1* downregulation enhances the metastatic potential of ovarian cancer cells with intact *BRCA1* function and whether *PFN1* may serve as a possible therapeutic target.

Figure 1. Ovarian Cancer Cell Motility in BRCA1-Mutant (M) and Wild-type (WT) Cells with Luciferase (Luc) control and PFN1 Knockdown (PFN shRNA) ** p<0.01



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264 - Poster Session A

Yes-associated protein (YAP) functions as a proto-oncogene and promotes radiation resistance in endometrial cancer

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Objectives: YAP is a transcriptional coactivator that has a key role in organ size and oncogenesis by regulating cell proliferation and apoptosis. Recently, its relevance to the estrogen/progesterone receptors and radioresistance has been reported. However, the clinical and biological significance of YAP is still unknown in endometrial cancer (EMCA). We hypothesized that YAP activation could contribute to tumor progression and response to radiation in EMCA.

Methods: YAP nuclear and cytoplasmic expression was analyzed in 146 primary EMCA tissues by immunohistochemistry. Statistical analysis was conducted to assess the association of staining levels with demographic data. Biological functions of YAP were evaluated by cell proliferation assay, soft agar assay, and flow cytometry, comparing findings between YAP-inhibited cells and control cells. EMCA cells transfected with either control siRNA or YAP-specific siRNA were exposed to increasing doses of radiation and clonogenic assay was performed.

Results: Immunohistochemical results demonstrated that increased nuclear expression was significantly associated with body mass index, tumor grade and stage, and lymphovascular space involvement in type 1 cancer ($n=117$) ($P=0.01$, $P<0.0001$, $P=0.007$, and $P=0.0006$, respectively), but there were no significant correlations in type 2 cancer ($n=29$) (Table 1). YAP inhibition by siRNA in the HEC1B EMCA cell line resulted in a significant decrease in cell proliferation compared to the control cells at 72 hours after transfection ($P<0.05$). YAP inhibition similarly resulted in a suppression of anchorage-dependent growth in soft agar assay ($P=0.015$) and induced a significant accumulation of cells in G0/G1 phase in cell cycle analysis ($P=0.002$). Inhibition of YAP resulted in enhanced radiation sensitivity in clonogenic assay, with a dose enhancement factor at 10% survival (DEF0.1) of 1.36 in the HEC1B cell line.

Conclusions: Because YAP functions as a transcriptional coactivator, its differential localization in the nucleus of cancer tissues and its impact on cell proliferation could have important consequences with respect to its role as a proto-oncogene in EMCA. YAP overexpression could be useful as a prognostic indicator or therapeutic target and may predict radiation insensitivity for patients with EMCA.

Table1

Association of YAP expressions in nucleus with clinicopathological factors in type1 and type2 endometrial cancers.

		Type1 cancer (n=117) Nuclear YAP expression low (n=72)	high (n=45)		Type2 cancer (n=29) Nuclear YAP expression low (n=11)	high (n=18)	
Age (year)	mean (range)	63.3 (40-89)	63.8 (44-82)	N.S.[a]	66.4 (47-85)	68.0 (55-79)	N.S.[a]
BMI	mean (range)	34.4 (19.4-70.4)	39.6 (19.1-64.3)	p=0.01[a]	37.8 (19.8-54.7)	34.2 (18.4-85.4)	N.S.[a]
Ethnic group	White	74	44		10	18	
	Other races	0	1	N.S.[b]	1	0	N.S.[b]
Grade	1	52	13		0	0	
	2/3	20	32	p<0.0001[b]	11	18	N.S.[b]
Stage	1	65	31		6	10	
	2/3/4	7	14	p=0.007[b]	5	8	N.S.[b]
LVSI	Abesent	67	30		7	6	
	Present	5	15	p=0.0006[b]	4	12	N.S.[b]

BMI; Body mass index
LVSI; Lymphovascular space involvement
N.S.; not significant
(a): Student's t-test
(b): Chi squqre test (there is no <10 number in data) / Fisher's exact test (there is <10 number in data)

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265 - Poster Session A

Somatic mutations in small cell carcinoma of the ovary

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Objectives: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare, highly aggressive form of ovarian cancer primarily diagnosed in young women. Due to the unmet need for better therapeutic options, we performed DNA sequencing to define the somatic mutational landscape of SCCOHT.

Methods: DNA and RNA were extracted from eight formalin-fixed, paraffin-embedded (FFPE) samples with available tissue that met pathologic criteria for SCCOHT. Paired tumor and normal samples underwent target capture and massively parallel DNA sequencing to a minimal coverage depth of 300X. Identified somatic mutations were all validated with Sanger sequencing of genomic DNA, and expression of the mutants was confirmed through sequencing of RNA transcripts. Proteins were extracted from available frozen tumor, resolved by SDS-PAGE electrophoresis, and blotted with appropriate antibodies. An anti-Brg1 (*SMARCA4*) antibody was optimized for immunohistochemistry (IHC) use in FFPE sections.

Results: All patients (median age, 22 years; range, 18-40 years) had exclusive and uniform *SMARCA4* somatic mutations out of 279 key cancer-associated genes sequenced. All variants detected were functional bi-allelic mutations, including splice site, nonsense, and frameshift mutations. All mutations were independently confirmed, and RNA sequencing demonstrated expression of the identified variants. Immunoblotting of two available protein lysates confirmed loss of *SMARCA4* protein. IHC performed on four available cases with somatic mutations showed loss of expression in tumor cells, with retention of expression in nonmalignant stromal cells used as internal controls. *SMARCA4* somatic mutations have been reported in 3% of 4,910 tumors sequenced by The Cancer Genome Atlas. The probability of identifying *SMARCA4* mutations in all eight sequenced samples is 8.7 x 10-13.

Conclusions: Massively parallel DNA sequencing identified uniform mutations in *SMARCA4* in all cases of SCCOHT examined. *SMARCA4* is a member of the SWI/SNF chromatin-remodeling complex that regulates many aspects of cellular transcription. The bi-allelic mutations function as classic tumor suppressors, suggesting their importance in malignant transformation. These results suggest that canonical mutations in *SMARCA4* may be an important therapeutic target for further investigation.

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266 - Poster Session A

Detection of ovarian cancer biomarkers in routine Pap tests by mass spectrometry-based proteomic techniques

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Objectives: To determine whether ovarian cancer cells shed proteins that can be detected in residual Pap test fluid by mass spectrometry (MS)-based proteomic techniques.

Methods: The residual fluid from discarded Pap tests from women with normal cytology was used to optimize the methodology for sample preparation prior to analysis by MS. Cells were removed by centrifugation and the protein concentration of the cell-free supernatant was determined. The protein composition of individual samples was visualized by separating the proteins on SDS-PAGE gels followed by silver staining. Proteins were trypsinized, and the resulting peptides were fractionated followed by analysis with tandem MS.

Results: The average volume of the residual Pap tests was 1.5 mL, and the average protein concentration was 160 ug/mL. The number of peptides and proteins present in Pap tests was determined by searching the MS data against the Human Uniprot database. More than 250 proteins were identified in samples pooled from 40 patients with normal cytology. Similar studies were conducted with residual Pap tests from individual women, allowing a “Pap Core Proteome” to be defined for the cervicovaginal fluid of women with normal cytology. When the proteins were classified according to cellular localization and biological function, >50% of the proteins were extracellular or plasma membrane proteins. Pap tests from women with ovarian cancer contained several proteins that were not identified in the “Pap Core Proteome” from women with normal cytology, suggesting their role as ovarian cancer biomarkers.

Conclusions: We have developed a protocol for processing residual Pap test fluid so as to optimize protein recovery and subsequent identification of proteins by MS. In most cases, residual Pap test fluid contained a sufficient amount of protein for analysis by MS. We have identified a “Pap Core Proteome” comprising ~200 proteins that represent the proteins found in the cervicovaginal fluid of women with normal cytology. We have also identified proteins that are unique to women with ovarian cancer. Ongoing studies with residual Pap tests and cervical swabs obtained from additional ovarian cancer patients will allow us to define a “Pap Core Proteome” for ovarian cancer patients and validate new biomarkers for ovarian cancer.

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267 - Poster Session A

Inhibition of autophagy by vaginal fluid from women with malignant adnexal masses

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Objectives: Noninvasive protocols to accurately predict malignancy in women presenting with an adnexal mass remain limited. Since inhibition of autophagy is a characteristic of ovarian cancer, we assayed vaginal fluid from women undergoing a preoperative evaluation of an adnexal mass for the ability to inhibit autophagy.

Methods: Vaginal fluid was obtained from 54 women referred for evaluation of an adnexal mass and from 24 healthy women. Aliquots were incubated for 48 hours with peripheral blood mononuclear cells (PBMCs) from healthy female donors. The cells were lysed and assayed for cytoplasmic levels of p62 by enzyme-linked immunoassay. p62 is an autophagy component whose intracellular concentration is inversely proportional to the extent of autophagy induction (high p62 = inhibition of autophagy). The final pathologic diagnosis was obtained after completion of laboratory testing. The mean p62 levels from samples of women with different diagnoses were compared using the Mann-Whitney test.

Results: Mean p62 levels were higher in PBMCs incubated with vaginal samples from 14 women with malignant mass (9.2 pg/ml) than in samples from 6 women with a borderline mass (4.2 pg/mL), 34 with a benign mass (3.1 pg/mL), and 24 healthy controls (1.7 pg/mL)(P<.0034 malignant vs all others). Vaginal samples from women with endometrioid, serous, and or mucinous ovarian cancers all inhibited autophagy. The final p62 level was unrelated to the age or body mass index of the vaginal fluid donor.

Conclusions: Vaginal fluid from women with a malignant adnexal mass inhibited induction of autophagy in PBMCs to a greater extent than vaginal fluid from women whose adnexal mass was negative for malignancy. Further analysis of additional women with different histologic types of cancer, the comparative analysis of the accuracy of autophagy inhibition vs circulating tumor markers in diagnosing a malignancy, and/or identification and measurement of the autophagy inhibitory component(s) may form the basis of a new noninvasive test to aid in the preoperative triage of women with adnexal masses and to detect early stage ovarian cancer.

268 - Poster Session A

Frequent inactivation of the *XAF1* tumor suppressor gene in human ovarian cancer by aberrant promoter CpG sites hypermethylation

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Objectives: XIAP-associated factor 1 (*XAF1*) is a tumor suppressor that has been known to exert proapoptotic effect. The *XAF1* gene is located at 17p13.2, and its mRNA is ubiquitously expressed in all normal adult and fetal tissues but is absent or present at very low level in multiple human tumors.

Methods: To explore the candidacy of *XAF1* as a tumor suppressor in ovarian tumorigenesis, we investigated the expression and mutation status of the gene in six ovarian cancer cell lines and 16 tumor tissues.

Results: *XAF1* transcript was easily detectable in all noncancerous ovarian tissues we examined. In contrast, however, its expression was not found or very low in 50% (3/6) of cancer cell lines and in 37.5% (6/16) of primary tumors. Whereas somatic mutations of the *XAF1* gene were not detected, its mRNA expression was reactivated in no- or low-expression tumor cells following 5-aza-2-deoxycytidine treatment. Furthermore, bisulfite DNA sequencing analysis revealed that aberrant methylation at 7 CpG sites located in the 5' proximal region of the promoter is tightly associated with decreased mRNA expression, indicating that CpG sites hypermethylation of this promoter region is critical for the transcriptional silencing of *XAF1*.

Conclusions: Together, our study suggested that epigenetic silencing of *XAF1* by aberrant promoter methylation may contribute to the development and/or malignant progression of human ovarian tumors.

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269 - Poster Session A

Enhanced gynecologic cancer cell killing through pharmacologic inhibition of the ataxia telangiectasia and *Rad3*-related kinase

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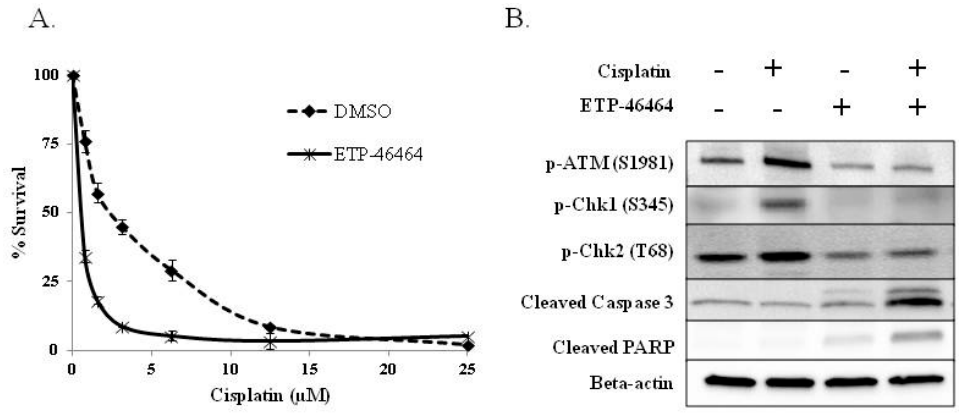
Objectives: Platinum-based chemotherapy is the mainstay of treatment for gynecologic malignancies, but the development of resistance renders platinum agents less effective in the recurrent setting. The archetypal alkylating-like agent cisplatin forms DNA crosslinks that, if they persist, produce single- and double-strand breaks. The ataxia telangiectasia mutated and Rad3-related (ATR) protein kinase is a key enzyme in the DNA damage response (DDR), activating checkpoint kinase 1 (Chk1) that facilitates cell cycle arrest for the commencement of DNA repair. We hypothesized that pharmacologic inhibition of ATR would significantly enhance cisplatin-mediated cell killing.

Methods: The half maximal inhibitory concentrations of cisplatin in the presence and absence of a selective ATR inhibitor (ETP-46464) were determined by MTS assay in undifferentiated (A2780 and A2780-CP20) and serous (OVCAR3, OV90) ovarian, endometrial (KLE, HEC1B), and cervical (HeLa, SiHa) cancer cell lines. The impact of inhibiting ATR on select effectors of cell cycle, apoptosis, and DDR, including phospho-ATM (S1981), phospho-Chk1 (S345), phospho-Chk2 (T68), cleaved caspase 3, and cleaved PARP, were monitored by immunoblotting.

Results: Significantly enhanced cisplatin-mediated cell killing (by 54% to 99%) was observed in all seven gynecologic cell lines cotreated with ETP-46464 (Figure 1A). Cotreatment of cells with cisplatin and ETP-46464 resulted in suppressed levels of phospho-ATM, -Chk1, and -Chk2 (Figure 1B). Further, the enhanced cisplatin-mediated cell killing by ETP-46464 cotreatment was attributed to enhanced apoptosis signaling, as indicated by elevated levels of cleaved caspase 3 and PARP1 (Figure 1B).

Conclusions: Pharmacologic inhibition of ATR significantly enhances platinum sensitivity in all gynecologic cancer cell lines tested. These results suggested that ATR represents a key signaling node centrally involved in cisplatin resistance in gynecologic cancer cells and represents an attractive candidate for molecularly targeted therapy.

Figure 1. A2780 co-treated with cisplatin and vehicle control or ATR inhibitor were assayed for A) cell proliferation at 72 h and B) immunoblotted for DNA damage sensor and effectors phospho-ATM, -Chk1and -Chk2 at 3 h, as well as apoptosis markers cleaved caspase 3 and PARP1 at 24 h.



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270 - Poster Session A

HE4 interacts with sex hormones in epithelial ovarian cancer

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Objectives: HE4 is a biomarker that is overexpressed in epithelial ovarian cancer (EOC). The biological functions of HE4 in EOC are not known. Several prior studies have suggested that HE4 overexpression promotes EOC growth and chemoresistance. Hormonal-responsive elements present within the HE4 promoter region can influence expression of HE4 in ovarian cancer. This study was designed to determine if hormones alter HE4 expression and if HE4 interacts with hormone receptors.

Methods: To determine the impact of androgens and estrogens on HE4 and its spatial expression, SKOV3 and OVCAR8 ovarian cancer cell lines were treated with testosterone, dihydrotestosterone, estrogen, or tamoxifen. Cells were stained with HE4 antibody and images recorded. Cellular levels of HE4 and estrogen receptor (ER) were measured with Western blotting. Protein-protein interaction of HE4 with ER was determined by co-localization and co-immunoprecipitation (co-IP). MTS assays were performed to determine cell viability after treatment with tamoxifen.

Results: We observed that both androgens and estrogens mediated nuclear translocation of HE4 in SKOV3 and OVCAR8 cell lines. Co-IP indicated that HE4 interacted with estrogen receptor-α. Stable overexpression of HE4 resulted in depletion of ER in SKOV3 cells (decrease of 52% to 100% compared to controls). HE4 co-localized with ER in normal tissues but not in EOC tissues. EOC tissues showed nuclear ER staining compared to normal ovarian tissues where staining was cytoplasmic. Treatment of ovarian cancer cell lines with androgens increased HE4 expression (increase of 76% compared to controls). HE4 overexpressing ovarian cancer cell clones treated with tamoxifen had 60% cell viability compared to 37% in controls.

Conclusions: Our studies clearly showed the biological cross-talk of HE4 with sex hormones in ovarian cancer cell lines. Future studies will define how androgen- and estrogen-mediated HE4 nuclear translocation affect EOC tumor progression and chemoresistance in EOC.

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271 - Poster Session A

Novel mechanisms of chemoresistance in ovarian cancer: the role of tunneling nanotubes

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Objectives: The biologic mechanisms of chemotherapy resistance in ovarian cancer remain unclear. Intercellular communication may play an undetermined but critical role in this process. Tunneling nanotubes (TnTs), which are long, thin, actin-based cytoplasmic extensions that mediate intercellular transfer of cellular cargo, represent a novel candidate to explain the evolution of resistance in malignant ovarian cells. Potential cargos of interest include ERCC1, a nucleotide excision repair protein associated with resistance to cisplatin in ovarian cancer cell lines, and microRNAs (miRNAs) 29b and 199a, which are upregulated in cisplatin-resistant ovarian cancer cells. The purpose of this study was to investigate transfer of cargo between susceptible and chemoresistant cells.

Methods: We cultured platinum-sensitive (A2780) and -resistant (C200 and SKOV3) ovarian cancer cells as well as normal ovarian epithelial cells (IOSE). SKOV3 cells were transfected with either GFP-labeled ERCC1 or Alexa488-labeled miRNA 29b and 199a and examined for intercellular transfer via TnTs connecting distant SKOV3 or co-cultured IOSE stromal cells. In separate experiments, SKOV3 cells treated with doxorubicin were co-cultured with A2780 cells to assess the ability of TnTs to act as a conduit for transmission of therapeutic drugs.

Results: A hyperglycemic, low-serum, acidic medium stimulated TnT formation between A2780 and platinum-resistant cell lines (C200 and SKOV3) as well as between SKOV3 and stromal IOSE. ERCC1-GFP, miRNA 29b, and miRNA 199a were transported via TnTs from SKOV3 cells to each other and to IOSE cells. TnTs-mediated transfer of doxorubicin from SKOV3 to A2780 cells induced cell death in recipient drug-naïve cells (Figure 1).

Conclusions: TnT formation is stimulated in conditions of cellular stress and creates direct cytoplasmic connections between connected cells in vitro. Our data suggested that these conduits facilitate cellular exchange between platinum-sensitive and -resistant ovarian cancer cells as well as between ovarian cancer cell lines and normal ovarian epithelial stromal cells. Using currently available therapeutic agents to target TnTs and disrupt this communication provides a novel approach to overcoming the clinically significant problem of platinum resistance in ovarian cancer.

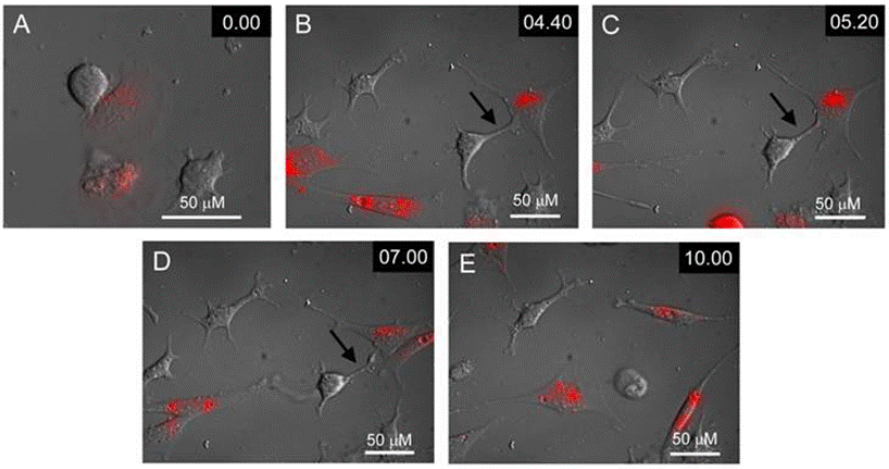

Figure 1: Tunneling nanotubes facilitate the transfer of drug therapy between chemo sensitive and chemo resistant cells. A) A2780 chemo sensitive cell line co-cultured with SKOV3 doxorubicin labeled cells. B) TnT formation between A2780 and SKOV3 cells. C) Transfer of doxorubicin from SKOV3 to A2780 cells. D) Separation of A2780 and SKOV3 cells, after transfer of doxorubicin. E) Cell death of A2780 cell.

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272 - Poster Session A

FBxW7 duality in ovarian cancer: novel insight into ovarian cancer pathogenesis

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Objectives: *FBxW7* is a tumor suppressor gene that has been shown to be linked to ubiquitin-dependent proteolysis and regulation of the G1-S cell cycle checkpoint. In this study, we characterized the functional and prognostic significance of *FBXW7* in ovarian cancer.

Methods: Platinum-sensitive (A2780) and -resistant (C200 and SKOV3) ovarian cancer cell lines were used. Ovarian cancer cell lines were transfected with *FBxW7* constructs using Lipofectamine 2000^{tm}. Quantitative polymerase chain reaction was performed to determine levels of gene and microRNA expression. Cell proliferation assays and fluorescence-activated cell sorting were performed to determine cell proliferation and viability. A tissue microarray was used for immunohistochemical (IHC) staining using *FBxW7* antibody. Tissue stains were scored manually. Staining was correlated with patient outcomes to calculate overall survival and progression-free survival using Kaplan-Meier methods and log-rank tests.

Results: Upregulation of *FBxW7* in platinum-sensitive cell lines decreased the substrates of *FBxW7* ubiquitination, such as cMYC, Notch, and JUN. However, similar levels of *FBXW7* expression did not decrease these substrate levels in platinum-resistant cell lines. microRNAs associated with stemness and chemoresistance also had differential profiles with *FBxW7* transient transfection. Cell proliferation assays also highlighted differences between these sensitive and resistant cell lines. For tissue array analysis, 516 samples were used for *FBXW7* IHC staining. The majority of tissue samples had high-grade serous (206 [40.2%]) histology. The majority of samples had *FBxW7* staining of high intensity (273 [52.9%]). There was no relationship between overall survival or progression-free survival and *FBxW7* tissue staining in the total group. However, when analyzing only the high-grade serous histology, there was a trend of *FBXW7* higher expression being associated with better progression-free survival (P=0.051).

Conclusions: Our studies suggested that *FBxW7* has a dual role in ovarian cancer cell lines, having less effect on those cell lines associated with chemoresistance. In ovarian tumor tissues, there was a trend for elevated levels of *FBxW7* expression and better progression-free survival. Further studies on *FBxW7* and its role in ovarian cancer pathogenesis are warranted.

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273 - Poster Session A

Progestin and vitamin D suppress growth of ovarian cancer in vitro and in vivo

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Objectives: To evaluate the efficacy of progestin and vitamin D on inhibition of ovarian carcinogenesis.

Methods: In vitro: Progesterone receptor-expressing ovarian cancer cells (OVCAR-3-PGR) were treated with vehicle (control), progestin (15 to 30 µM progesterone), with or without 100 nM of vitamin D analog (CB1089) for 2, 3, or 6 days. Viability was tested using an MTS assay. To measure apoptosis, cells were fixed, stained with TUNEL, and assessed by flow cytometry. In vivo xenografts: OVCAR-3-PGR cells ($5x10^6$) were injected subcutaneously into each flank of athymic nude mice (n=80). When tumors were palpable and >1 mm^3, the mice were divided into four treatment groups receiving the following interventions: control, progestin (depot medroxyprogesterone acetate [DMPA], 2 mg/mouse), 0.15 µg/kg/day CB1089 via an Alzet osmotic pump, or combined DMPA and CB1089. Mice were euthanized at 4 weeks; tumors were measured and weighed. Data were analyzed by ANOVA with statistical significance defined at P<0.05.

Results: Isobolographic analysis demonstrated that OVCAR-3-PGR cells treated with combined progesterone and CB1089 underwent synergistic inhibition of cell proliferation as compared to treatment with progesterone or CB1089 alone. Furthermore, there was a significant twofold increase in apoptosis in cells treated with both progesterone alone and the combination of vitamin D and progesterone as compared with controls (P<0.01). In the ovarian cancer xenografts, 68 mice grew evaluable tumors (85%, n=15-18 per group), yielding a total of 111 tumors. We observed a decrease in overall growth of the tumors in the treated groups vs controls, with percent decreases in weight in the DMPA, CB1089, and DMPA/CB1089 of 90%, 31%, and 69%, respectively. Mean tumor volumes exhibited corresponding **Results:** DMPA 13.3±3.1 mm^{3,} CB1089 101.2±20.3 mm^{3,} DMPA/CB1089 43.5±10.8 mm$^{3,\text{ and}}$ control 139.2±42.5 mm^3.

Conclusions: Progestin and vitamin D synergistically and dose-dependently inhibited cell proliferation and initiated apoptosis in ovarian cancer cells. This combination deserves further evaluation for inhibition of ovarian carcinogenesis.

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274 - Poster Session A

The *PI3K* inhibitor GDC-0941 is synergistic with lapatinib and mediates endocrine sensitivity in uterine papillary serous carcinoma via AKT

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Objectives: Ligand-independent estrogen signaling is known to interact with components of the phosphoinositide 3-kinase (*PI3K*) pathway, such as AKT. Dysregulation of *PI3K* is implicated in hormonal sensitivity. We sought to determine the effect of *PI3K* activity in mediating endocrine sensitivity in uterine papillary serous carcinoma (UPSC).

Methods: Drug effect on cell proliferation was calculated via Calcusyn in patient-derived UPSC cell lines ARK 1 and 2. *PI3K* mutation was analyzed after laser capture microdissection of tumor DNA in seven consecutive patients with UPSC. Protein expression via Western blot was correlated prospectively with clinical parameters.

Results: Table 1 shows cell line baseline characteristics and median inhibition concentration (IC_{50}) to various drugs. Fulvestrant, an estrogen receptor (ER) antagonist, rendered the cells significantly more resistant to taxol in ARK1 and 2 (P=0.035, P=0.021, respectively). This was associated with a concomitant decrease in pER^{S167} and pAKT^{S473} that was independent of baseline ER expression and *PI3K* mutation status (Figure 1). In ARK2, a cell line that is ER-, disrupting AKT signaling via the *PI3K* inhibitor GDC-0941 or with the erbB inhibitor lapatinib was synergistic with fulvestrant (Combination Index $(CI)_{50}$ of 0.441 and 0.229, respectively). Independent of *HER2* amplification or *PI3K* mutation, lapatinib and GDC-0941 exhibited synergistic cytotoxicity in both cell lines (CI_{50} of 0.577 in ARK 1 and 0.233 in ARK 2). Finally, *PI3K* mutation and pAKT^{S473} expression were analyzed in seven tumor samples. While none had *PI3K* mutation, patients who were chemoresistant had significantly lower expression of baseline pAKT^{S473} in their tumor samples than those who were chemosensitive.

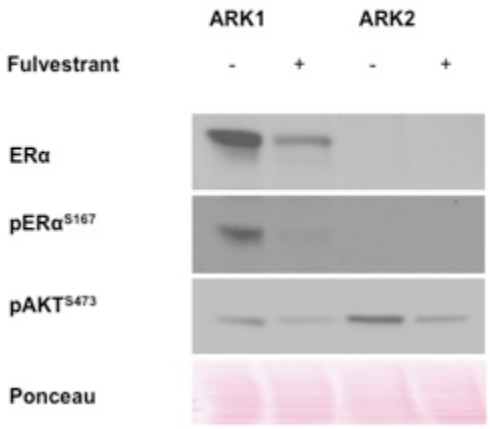
Conclusions: Dysregulation of the *PI3K* pathway via upstream erbB amplification or downstream constitutive activation of AKT may be important in mediating endocrine and taxol sensitivity in UPSC. pAKT^{S473} may be a biomarker of drug sensitivity. The combination of *PI3K* inhibitor and lapatinib was synergistic and warrants further investigation.

Table 1

	ARK1	**ARK2**
PI3KCA mutation	Exon 9	null
ERα (WB)[a]	Yes	No
pERα167 (WB)	YES	No
pHER (WB)	No	Yes
IC_{50} nM (mean ± STD)[b]		
GDC-0941	93.1±5.9	271±116.5
Lapatinib	No effect	135.6±29.2
Fulvestrant	No effect	No effect
Taxol	4.6±1.9	7.8±5.6
Cisplatin	1103±65.7	2632.6±1797.9

[a] *western blot;* [b]*drug dose achieving 50% cell kill*

Figure 1: The effect of Fulvestrant on ER and AKT activity in UPSC cell lines



275 - Poster Session A

Subcellular localization and function of insulin-like growth factor 2 (IGF2) in uterine carcinosarcoma

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Objectives: To evaluate IGF2 expression and localization in uterine carcinosarcoma (CS) compared to normal endometrium and to test the function of IGF2 in CS cell lines.

Methods: Under institutional review board approval, tumor and normal endometrial tissues were obtained from 30 CS patients and 17 benign hysterectomy specimens from postmenopausal women. Immunohistochemistry was performed using an anti-human IGF2 antibody (Abcam), with positive and negative controls confirming specificity. A pathologist quantified staining intensity (SI) and percentage positive (PP) cells in the tissues, converted to an H-score (product of SI and PP) for each compartment: stroma cytoplasm, stroma nucleus, epithelium cytoplasm, and epithelium nucleus. The effect of IGF2 depletion by siRNA vs control siRNA was tested in a CS cell line (CS99) and a primary cell line (CS16) derived from fresh CS tissue. Knockdown was confirmed by real-time quantitative polymerase chain reaction, and cellular proliferation was measured by counting cells with a Millipore Scepter. Data were analyzed using one-way ANOVA with Tukey post-test, or unpaired t-test, with $P<0.05$ deemed significant.

Results: Median age of CS patients was 68.5 years; FIGO stage distribution was stage I (12 patients), stage II (0), stage III (10), and stage IV (8). Stromal cytoplasmic IGF2 expression was significantly elevated in CS compared to normal ($P<0.001$). Epithelial cytoplasmic IGF2 expression was also elevated in CS compared to normal ($P=0.01$). In contrast, epithelial nuclear IGF2 expression was decreased in CS compared to normal ($P=0.0001$), while stromal nuclear IGF2 expression was similar in CS and normal. Patients with stage III/IV CS had higher stromal cytoplasmic IGF2 compared to patients with stage I CS ($P<0.05$). IGF2 depletion by either of two unique siRNAs decreased cellular proliferation, with an average reduction in cell number compared to control siRNA of 74% in CS99 (at 3 days) and 68% in CS16 (at 5 days).

Conclusions: Subcellular localization of IGF2 was altered in CS compared to normal endometrium, characterized by higher cytoplasmic expression in CS. Cytoplasmic IGF2 was further increased in patients with metastatic disease, suggesting a role in disease progression. In tissue culture, CS cells are dependent on IGF2 for proliferation, indicating that IGF2 is a potential therapeutic target.

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276 - Poster Session A

The HMG-CoA reductase inhibitor simvastatin exhibits antitumorigenic and antimetastatic effects in ovarian cancer

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Objectives: HMG-CoA reductase inhibitor use in women with ovarian cancer has been shown to improve survival, yet the molecular mechanisms underlying this clinical finding are unknown. We sought to evaluate the effects of simvastatin on cell proliferation, apoptosis, cellular stress, and adhesion/invasion in human ovarian cancer cell lines and ovarian primary culture.

Methods: Two human ovarian cancer cell lines (SKOV3 and HEY) were used. Cells for primary culture were obtained from four patients who underwent cytoreductive surgery. Cell proliferation was assessed by MTT assay. Cell cycle progression was evaluated by Cellometer. Apoptosis was evaluated by Annexin V-FITC assay using Cellometer. Invasion was demonstrated by a transwell invasion assay. HMGCoA activity and cell adhesion were assessed by enzyme-linked immunosorbent assay. Effects of simvastatin on HMGCoA, phosphorylated-S6, phosphorylated-p42/p44, pan-S6, pan-p42/44, BIP, PERK and calnexin expression were documented by Western immunoblotting. Mitochondrial DNA damage was confirmed by quantitative polymerase chain reaction.

Results: Simvastatin inhibited cell proliferation in a dose-dependent manner in both ovarian cancer cell lines within 48 to 72 hours of exposure (median inhibition concentration [IC50] range of 8-16 nM, $)P<0.001$-0.05). Treatment with simvastatin resulted in G1 cell cycle arrest, induction of apoptosis, cellular stress, and reduction in the enzymatic activity of HMG-CoA reductase. Western immunoblot analysis demonstrated that simvastatin decreased phosphorylation of S6 and p42/44 and increased BIP, PERK, and calnexin expression within 18 hours of exposure. In parallel, treatment with simvastatin reduced cell adhesion ($P<0.001$-0.02) and invasion ($P<0.001$-0.05) and increased mitochondrial DNA damage in both cell lines. Cell proliferation was also inhibited by simvastatin in a dose-dependent manner in primary ovarian cancer cells (4/4; IC50 range, 6-25 nM).

Conclusions: Simvastatin potently inhibited ovarian cancer cell growth via G1 arrest, caused cellular stress, and increased apoptosis. These antitumorigenic effects may be partially mediated through inhibition of the mTOR and MAPK pathways. Thus, statins may have a role in the treatment of ovarian cancer and may be worthy of further exploration in clinical trials.

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277 - Poster Session A

Simvastatin, an HMG-CoA reductase inhibitor, exhibits antimetastatic and antitumorigenic effects in endometrial cancer

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Objectives: Statin use has been associated with improved overall survival in women with endometrial cancer. However, whether this is due to direct biologic effects or due to overall improved health is not clear. Thus, we evaluated the effects of simvastatin on cell proliferation, apoptosis, cellular stress, and adhesion/invasion in human endometrial cancer cell lines and endometrial primary culture.

Methods: Two endometrial cancer cell lines (ECC-1 and Ishikawa) were used. Cells for primary culture were obtained from five patients who underwent endometrial cancer staging surgery. Cell proliferation was assessed by MTT assay. Cell cycle progression was evaluated by Cellometer. Apoptosis was evaluated by Annexin V-FITC assay using Cellometer. Invasion was demonstrated by a transwell invasion assay. Reactive oxygen species and cell adhesion were assessed by enzyme-linked immunosorbent assay. Effects of simvastatin on phosphorylated-S6, phosphorylated-p42/p44, pan-S6, and pan-p42/44 expression were documented by Western immunoblotting. Mitochondrial DNA damage was confirmed by quantitative polymerase chain reaction.

Results: Simvastatin significantly inhibited cell proliferation in a dose-dependent manner in both ECC-1 and Ishikawa within 48 to 72 hours of exposure (median inhibition concentration [IC50] range of 15-18 nM, $P<0.001$-0.05). Treatment with simvastatin resulted in G1 cell cycle arrest, induction of apoptosis, cellular stress, and reduction in the enzymatic activity of HMG-CoA reductase. Western immunoblot analysis demonstrated that simvastatin decreased phosphorylation of S6 and p42/44 expression within 18 hours of exposure. In parallel, treatment with simvastatin reduced cell adhesion ($P<0.001$-0.03) and invasion ($P<0.01$-0.03) and increased mitochondrial DNA damage in both cell lines. Cell proliferation was also inhibited by simvastatin in a dose-dependent manner in primary endometrial cancer cells (5/5; IC50 range, 8-25 nM).

Conclusions: Simvastatin potently inhibited endometrial cancer cell growth via G1 arrest, cellular stress, mitochondrial DNA damage and increased apoptosis. These antitumorigenic effects may be partially mediated through inhibition of the mTOR and MAPK pathways. These findings are of particular interest because many women with endometrial cancer also have cardiovascular risk factors that could be mitigated by statin use.

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278 - Poster Session A

Binary methylation of human papillomavirus (HPV) L1 and death-associated protein kinase (DAPK) as biomarkers of progression in cervical carcinogenesis

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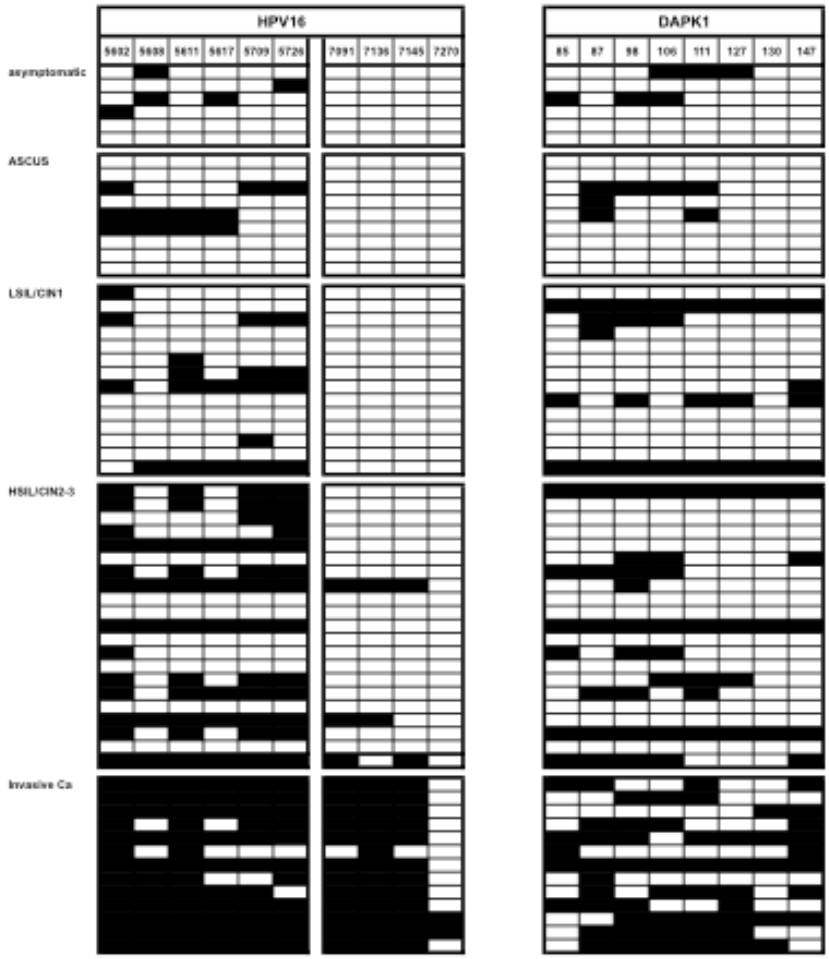
Objectives: Most patients with high risk HPV DNA and/or abnormal cytology do not develop cervical cancer and are often subjected to repetitive testing and biopsies. The invasive phenotype of oncogenic HPV is dependent upon integration, which is difficult to measure directly. Neoplastic transformation is facilitated through DNA methylation, which silences key viral replication sequences (e.g., capsid protein L1), allowing for expression of the viral oncogenes E6 and E7. Similar epigenetic phenomena may also result in aberrant signaling of the death-associated protein kinase (DAPK) tumor suppressor gene product, further promoting cervical carcinogenesis. We studied oncogenic *HPV L1* and *DAPK* methylation as biomarkers for progression.

Methods: From October 1, 2009 to May 30, 2010, 505 consecutive patients seen at a university-affiliated dedicated colposcopy clinic provided informed consent to have a liquid-based cytologic sample undergo HPV genotyping and biomarker methylation detection. Methylation status of *HPV L1* and cellular *DAPK* was determined indirectly using bisulfide modification and then correlated to severity of cervical dysplasia. All molecular biologists were blinded to clinical information.

Results: High-risk subtypes included HPV16, 18, 31, and 45 (n=102). The full spectrum of cytologic and histologic aberrations were present from benign, atypical squamous cells of undetermined significance, and low- and high-grade squamous intraepithelial lesion to all grades of cervical dysplasia and invasive carcinoma. Methylation of both genes was significantly lower with benign histology and progressively increased with worsening histology (P<0.05) (Figure 1). Methylation of both biomarkers was most pronounced in cervical carcinoma.

Conclusions: Bisulfide modification constitutes a high-throughput method to detect methylation of viral and cellular genes critical for neoplastic transformation and may serve as a molecular triage for patients with low-grade cytology/early dysplasia. Because *DAPK* is also a mediator of interferon-induced cell death, the immunotherapeutic implications of this readily identifiable target are implicit.

Figure 1. Methylation of HPV 16 and DAPK. Columns represent dinucleotides with potential for methylation. Black = methylated.



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279 - Poster Session A

Targeting myeloid cells in the tumor microenvironment as a strategy to enhance vaccine efficacy in epithelial ovarian cancer

N. V. Kolomeyevskaya, N. Khan, M. Grimm, K. Singel, K. S. Grzankowski, S. Abrams, K. O. Odunsi and B. H. Segal
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Objectives: Ovarian cancer vaccine development is hampered by the availability of powerful immune adjuvants that can induce sustained innate immunity and augment adaptive cellular responses in the tumor-bearing host. Accumulation of myeloid cells in the tumor microenvironment is a known obstacle to durable antitumor immunity. We evaluated the strategy of vaccination with the novel TLR9/NOD2 ligand (MIS-416) followed by myeloid cell depletion in the murine model of epithelial ovarian cancer (EOC).

Methods: Mice (*n*=80) were inoculated with ovalbumin (OVA)-expressing syngeneic ovarian cancer cell line. Adoptive transfer of transgenic CD8+ T-cells recognizing OVA was performed, followed by MIS-416 vaccination and administration of monoclonal anti-CD11b+ antibody. Decisions about euthanasia based on morbidity were made blinded to treatment. Survival and tumor burden were compared among all experimental groups. Immunologic endpoints were assessed using flow cytometry at the time of early and advanced disease.

Results: Immunosuppressive macrophages and granulocytic myeloid-derived suppressor cells, $CD11b^{+}Ly6G^{+}Ly6C^{low}$, accumulated in the local tumor environment as a function of disease burden. MIS-416 vaccination reduced gross tumor burden (*P*=0.0011) and delayed time to euthanasia (*P*=0.0001). Further augmentation of survival in MIS-416-immunized mice was noted after partial myeloid (CD11b+) cell depletion with anti-CD11b antibody (*P*=0.0013). No effect on tumor progression was seen with administration of anti-CD11b without vaccine. Accordingly, MIS-416 induced clonal expansion of cytotoxic CD8+ lymphocytes (0.01% vs 10.9%), guiding them toward the tumor microenvironment; increased the population of CD11b+CD11c+ dendritic cells (38% vs 68%); and decreased the population of immunosuppressive M2 macrophages, $CD11c+CDF4/80+CD206^{high}$, (3% vs 59%).

Conclusions: These findings established the proof of principle that myeloid depletion can enhance vaccine efficacy in the murine model of EOC. Further studies of myeloid cell phenotypes in the EOC microenvironment may predict time to relapse and identify patients who are likely to benefit from vaccination followed by myeloid depletion.

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280 - Poster Session A

Cytokine profiling of ascites identifies macrophage inflammatory protein-beta and tumor necrosis factor–alpha as predictors of progression-free survival in patients with epithelial ovarian cancer

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Objectives: The epithelial ovarian cancer (EOC) microenvironment is characterized by accumulation of various cytokines produced by tumor cells and myeloid-derived suppressor cells. Their complex interaction leads to suppression of T-cell proliferation as well as activation and recruitment of tumor-associated macrophages and regulatory T-cells that ultimately potentiate tumor evasion. EOC ascites represents a complex heterogeneous matrix where these cytokines modulate interactions between neoplastic cells and the host immunity. The aim of this study was to determine whether the presence of immunosuppressive cytokines in EOC ascites correlates with aggressive tumor phenotype and progression-free survival.

Methods: EOC ascites was collected from 64 patients with ovarian, primary peritoneal, and fallopian tube cancer at the time of primary cytoreductive surgery. Luminex multiplex assay was performed to determine levels of 13 cytokines: Granulocyte colony-stimulating factor (G-CSF), granulocyte-monocyte colony stimulating factor (GM-CSF), interleukin (IL)-8, IL-1β , IL-6, IL-17α, monocyte chemoattractant protein (MCP)-1, MCP-3, macrophage-derived chemokine (MDC), macrophage inflammatory protein (MIP)-1α, MIP-1β, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF). Median levels of expression were computed for each analyte. Progression-free survival (PFS) was determined based on low and high levels of cytokine expression using Kaplan-Meier analysis.

Results: Decreased levels of MIP-1 β (≤56 pg/ml) and TNF-α (≤39 pg/ml) in EOC ascites correlated with improved 5-year-PFS: MIP-1β = 28% vs 8%, *P*=0.01; TNF-α= 24% vs 4.7%, *P*=0.007, respectively. We did not observe statistically significant survival benefit in patients with differential expression of the other cytokines. High levels of G-CSF (≥126 pg/mL) were associated with an improved 5-year PFS of 26% that approached statistical significance at *P*=0.047.

Conclusions: Our data indicated that accumulation of MIP-1β and TNF-α in EOC ascites predicts poor survival, pointing to the role of these cytokines in potentiating an immunosuppressive tumor microenvironment. Evaluation of cytokine expression signatures in EOC ascites is a novel strategy that can promote discovery of biomarkers and putative therapeutic targets.

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281 - Poster Session A

Expression of *GPER*, *ERβ*, *ERα*, and *PR* in gynecologic sarcomas

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Objectives: G protein-coupled estrogen receptor (GPER/GPR30) and estrogen receptor (ER) β are prognostic biomarkers in ovarian and endometrial carcinoma. The objective was to evaluate these receptors in gynecologic sarcomas.

Methods: Patients treated for gynecologic sarcoma from 1995 through 2010 were identified and clinicopathologic data abstracted from medical records. Immunohistochemistry was performed using antibodies to GPER, ERβ, ERα, and progesterone receptor (PR). The staining intensity and percentage of positive cells were scored and expression levels compared using H-scores (product of intensity and percentage positive cells). Correlation between receptor H-scores was evaluated by Pearson's correlation coefficient. Fisher's exact test was used for measures of association between clinicopathologic variables and receptor status. Overall survival (OS) was estimated using the Kaplan-Meier method, and differences in survival between receptor status was assessed using the log rank test.

Results: A total of 27 patients with gynecologic sarcoma were identified. Clinicopathologic data are shown in Table 1. Fifteen patients recurred, with a median time to recurrence of 2.3 years. The recurrence-free interval was similar in patients with receptor-positive and -negative disease ($P>0.05$ for ERα, ERβ, PR, and GPER). Positive PR expression was associated with improved OS ($P=0.05$), while no association with OS was observed for ERα, ERβ, and GPER. There was a strong correlation between ERα and PR expression ($P=0.006$) and between ERβ nuclear and cytoplasmic expression ($P<0.0001$) and a borderline correlation between PR and ERβ ($P=0.06$). There were also associations between histologic subtype and nuclear staining of ERβ ($P=0.04$), where 19 out of 22 leiomyosarcomas stained positively, and between stage and GPER, where 12 out of 21 stage I/II sarcomas stained positively ($P=0.05$).

Conclusions: In contrast to our prior findings in ovarian and endometrial carcinoma, GPER expression is associated with early-stage disease in gynecologic sarcomas and is not a prognostic factor for recurrence or survival. ERβ is frequently expressed in leiomyosarcomas but also does not correlate with recurrence or survival. Consistent with other reports, PR expression is a favorable prognostic factor in sarcoma patients.

Table 1

Variable	Median (standard deviation)
Age at diagnosis (years)	52 Range: 29-81
BMI (kg^m^2)	30.8 (6.9)
Ethnicity	
Caucasian	6 (22.2)
African American	14 (51.9)
Hispanic	2 (7.4)
Asian	1 (3.7)
Other	2 (7.4)
Missing	2 (7.4)
Gravity	3 [0-6]
Parity	2 [0-4]
Histology	
Leiomyosarcoma	21 (77.8%)
Adenosarcoma	4 (14.8%)
Other	2 (7.4%)
Stage (new FIGO)	
I	16 (59.3%)
II	5 (18.5%)
III	0 (0.0%)
IV	1 (3.7%)
Unstaged	4 (14.8%)
Grade	
1	3 (11.1%)
2	1 (3.7%)
3	21 (77.8%)
Missing	2 (7.4%)

Ovarian cancers with nuclear special AT-rich sequence-binding protein 1 and cytoplasmic AT-rich interactive domain-containing protein 1A are rare, drug-resistant, and deadly

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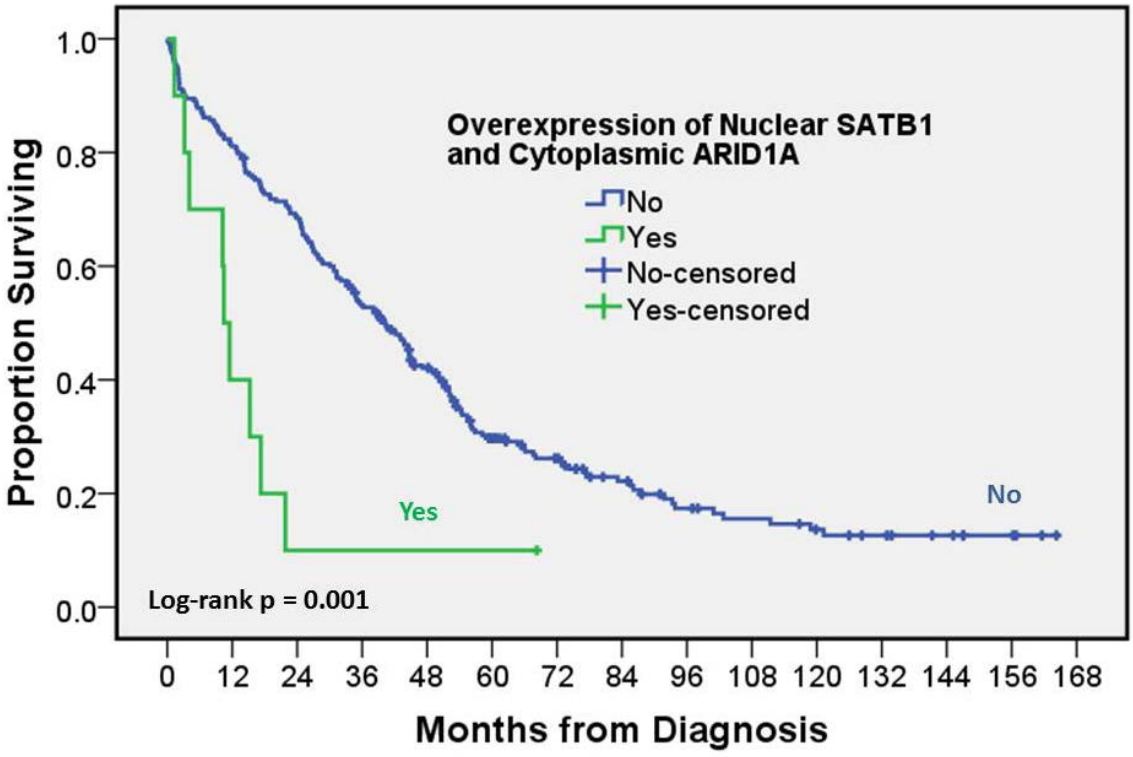
Objectives: Proteomics and RNA sequencing studies were recently performed in the isogenic platinum-sensitive A2780 and the platinum-resistant A2780-CP20 ovarian cancer cells, which revealed that the special AT-rich sequence binding protein 1 (*SATB1*), a master chromatin organizer, was highly overexpressed in platinum-resistant vs –sensitive cells by four- and ninefold at the protein and transcript level, respectively. Cytoplasmic localization of the AT-rich interactive domain 1A protein (*ARID1A*), another chromatin remodeling factor, was recently shown to be associated with poor survival in a subset of ovarian cancers. This study tested the hypothesis that ovarian cancers that overexpress nuclear *SATB1* and cytoplasmic *ARID1A* are drug-resistant and deadly.

Methods: Expression of nuclear *SATB1* and cytoplasmic *ARID1A* was evaluated by immunohistochemistry in a tissue microarray (TMA) comprising 248 women with epithelial ovarian or peritoneal cancer with at least three evaluable cores. Associations with drug resistance and survival were analyzed.

Results: Although overexpression of nuclear *SATB1* and cytoplasmic *ARID1A* were rare and observed in 4% of epithelial ovarian cancers (10/248), women with these defects had a 4.9-fold increased odds of drug resistance (95% CI 1.3-17.9, *P*=0.017), worse progression-free survival (HR 2.8, 95% CI 1.5-5.3, *P*=0.002), and worse overall survival (HR 2.9 , 95% CI 1.5-5.7, *P*=0.002). Median survival was 30 months shorter (10 months vs 40 months, *P*= 0.001) for those with nuclear *SATB1* and cytoplasmic *ARID1A* compared with their counterparts (Figure 1). Presence of both nuclear *SATB1* and cytoplasmic *ARID1A* expression was an independent predictor of worse progression-free survival (adjusted HR 2.4, 95% CI 1.3-4.7, *P*=0.008) and overall survival (adjusted HR 2.8, 95% CI 1.4-5.5, *P*=0.004).

Conclusions: Ovarian cancers with nuclear *SATB1* and cytoplasmic *ARID1A* are rare, drug-resistant, and deadly.

Fig 1. Median survival time for patients with nuclear SATB1 and cytoplasmic ARID1A (green line) compared to patients without this pattern of expression.



283 - Poster Session A

Putative events in the development of clear cell ovarian carcinoma from endometriosis: an evaluation using immunohistochemistry and gene expression profiling

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Objectives: To use known protein markers and gene expression profiling to evaluate the timing of events and molecular markers in the development of ovarian clear cell carcinoma (OCCC) from endometriosis.

Methods: ANOVA with post hoc Tukey's multiple comparisons test was used to determine the significance of *hKIM-1, ARID1a*, *HNF-1β*, *PTEN*, and *ER* immunohistochemical staining in a series (n=158) of malignant ovarian neoplasms, endometriosis, and normal ovarian tissues. Seven patient-matched sets (containing a primary OCCC, adjacent endometriosis, and distant endometriosis) were analyzed for marker expression along the progression continuum. Gene expression profiles were obtained from microdissected endometriotic and tumor features from four of the patient-matched formalin-fixed, paraffin-embedded (FFPE) sets. Significance analysis of microarrays and linear models for microarray data packages were used to rank significant differentially expressed genes.

Results: OCCC displayed elevated expression of *hKIM-1* (P<0.0001) and *HNF-1β* (P=0.002) and lower expression of *ARID1a* (P<0.0001), *PTEN* (P<0.0001), and *ER* (P<0.0001). On post hoc analysis, *PTEN* was significantly lost in both endometriotic and invasive tumor tissues. *HNF-1β* expression was significantly greater, while expression of *ARID1a* and *ER* was significantly lower when comparing OCCC to endometriosis. For the primary OCCC within the matched sets, expression of *hKIM-1* (P<0.0001) and *HNF-1β* (P=0.0001) was greater and expression of *ER* (P<0.0001) was less when compared to both distant and adjacent areas of endometriosis. Analysis of gene expression profiles of materials microdissected from ER-stained FFPE samples to distinguish endometriotic tissues from primary tumors resulted in identification of genes such as *GPX3* and *EFF1A2* that were known highly expressed in OCCC. Immunohistochemical validation studies showed significantly elevated expression of novel signaling proteins *Patched 2* and *Protein Phosphatase 1* in OCCC.

Conclusions: Loss of *PTEN* expression is an early event during the transformation of OCCC from endometriosis, while *HNF-1β* expression and loss of *ER* expression are associated with the ultimate transformation of OCCC from endometriosis. The identified novel markers may play a role in endometriosis-associated OCCC and provide potential targets for investigation.

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284 - Poster Session A

Selective activation of *Notch3* in high-grade serous ovarian cancer

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Objectives: *Notch3* alterations are strongly associated with poor survival of patients with high-grade serous ovarian cancer (HGSOC), but the biologic significance is not well understood and was tested here.

Methods: We tested the biological significance of *Notch3* activation in high-grade serous ovarian cancer (HGS-OvCa) using in vitro and in vivo orthotopic models of ovarian cancer and investigated the mechanisms by which *Notch3* was selectively activated using functional assays.

Results: Cleaved *Notch3* (NICD3) was selectively expressed in a panel of ovarian cancer cells tested by Western blot analysis. In vitro functional studies showed that *Notch3* siRNA induced apoptosis and G2/M phase arrest in *NICD3*-positive cells (OVCAR3, OVCAR5, and A2780) but not in *NICD3*-negative cells (SKOV3, SKOV3TR, and IGROV1). We also found that the *NICD3*-positive cells were more sensitive to treatment with a gamma secretase inhibitor (GSI) than were the NICD3-negative cells. *NICD3* expression was the critical determinant of response to *Notch*-targeted therapy. Furthermore, we detected that silencing *Notch3* significantly inhibited the growth of HGS-OvCa and induced apoptosis in *NICD3*-positive ovarian cancer models (P<0.05) but not in NICD3-negative cancer (SKOV3 model). In the *NICD3*-positive A2780 model, *Notch3* siRNA or paclitaxel alone weighed 74.1% (P<0.01) and 75.7% (P<0.01) less, respectively, than controls. Combining *Notch3* siRNA and paclitaxel reduced tumor weight by 99.3% compared to the controls (P<0.01). In the *NICD3*-negative SKOV3 model, *Notch3* silencing did not affect tumor growth. *Jag1* stimulation could induce *Notch3* proteolysis in NICD3-negative SKOV3ip1 cells compared with controls. The endocytosis inhibitor dynasore, a cell-permeable inhibitor of dynamin, reduced NICD3 expression in a time- and dose-dependent manner and significantly induced apoptosis in Jag1/NICD3-positive cells compared to Jag1/NICD3-negative cells (P<0.01).

Conclusions: Our results identified previously unknown mechanisms underlying *Notch3* signaling and point to new, biomarker-driven approaches for therapy.

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285 - Poster Session A

PARP inhibition synergizes with anti-CTLA-4 immune therapy to promote rejection of peritoneal tumors in mouse models of ovarian cancer

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Objectives: Because poly-ADP-ribose polymerase-inhibitors (PARP-i) disrupt DNA repair, we hypothesized that they would alter the immunophenotype of cancer cells and sensitize tumors to immunotherapeutic modalities. We tested the therapeutic efficacy of a PARP-i alone or combined with monoclonal antibody blockade of the co-inhibitory T-cell receptor CTLA-4 in two ovarian cancer models.

Methods: The immunophenotype of ovarian tumor cells exposed to PARP-i in vitro was evaluated using flow cytometry. The therapeutic and immunomodulatory effects of PARP-i in combination with anti-CTLA4 antibody were tested in mice injected intraperitoneally (IP) with $5x10^6$ ovarian cancer cells (ID8 or *BRCA1*-BR5AKT) on Day 0. Survival rates were compared among groups of five mice receiving PARP-i daily for 3 weeks beginning on Day 3, anti-CTLA4 administered as two IP injections on days 4 and 11, or both. Control animals received sham injections and nonspecific immunoglobulin. In parallel experiments, mice were euthanized at day 14 or 25 after tumor challenge, and IP T-cells were evaluated with flow cytometry.

Results: PARP-i upregulated *Fas* and *MHC-I* on surviving tumor cells in vitro. In mice inoculated with *BRCA1*-BR5AKT or ID8 cells, a survival benefit was seen with combined PARP-i and anti-CLTA-4 treatment ($P<0.05$) compared with PARP-i or anti-CTLA4 alone. In time-point analyses, all groups had peritoneal carcinomatosis on day 14, although mice receiving CTLA-4 only or CTLA-4 and PARP-i demonstrated tumor regression by day 25. On day 14, mice receiving anti-CTLA4 alone or in combination with PARP-i had a higher percentage of both CD4+ and CD8+ effector memory cells ($CD44+CD62^{lo}$) compared with other groups. On day 25, the number of memory T-cells remained highest in animals receiving both anti-CTLA-4 and PARP-i.

Conclusions: We have demonstrated that PARP-i exposure alters the immunophenotype of ovarian cancer cells. In keeping with this, treated animals had an increase in effector memory T-cells in the peritoneal tumor environment, and exposure to PARP-i enhanced the therapeutic effect of anti-CTLA4 antibody. We conclude that PARP-i synergizes with anti-CTLA-4 to promote immune-mediated tumor rejection in ovarian cancer models, and this combination should be considered for further testing.

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286 - Poster Session A

Tumor cells surviving the cytotoxic effect of paclitaxel are sensitized to anti-cancer peptide PNC-27

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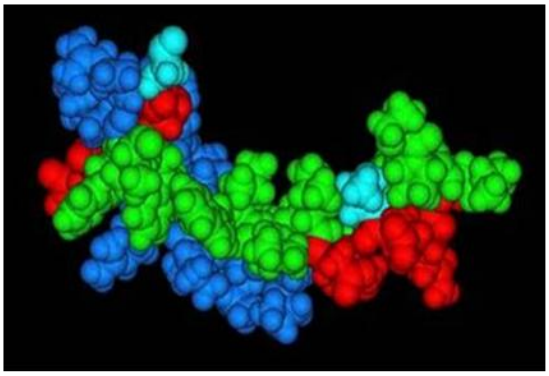
Objectives: Paclitaxel targets tumor cells in the M phase of the cell cycle. Cells in other phases survive the insult and repopulate the tumor. PNC-27 is a peptide synthesized of amino acids of the p53-HDM2-binding domain that kills various cancer cell lines. In this study, we assessed the sensitivity of ovarian cancer cells that survive treatment with paclitaxel to PNC-27.

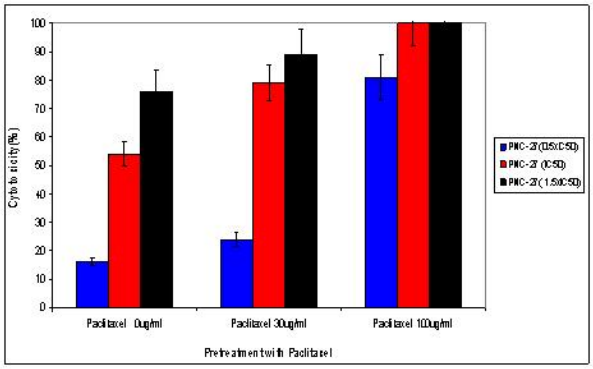
Methods: Murine ovarian cancer cells (ID8) were maintained in DMEM media. For measurement of cytotoxicity in vitro, cells were exposed for 12 hours to paclitaxel at various concentrations. After 12 hours, the drug-containing medium was removed and the cells were cultured for 24 hours in medium containing various concentrations of PNC-27. Viability was assessed with the use of MTT assay. Survival fractions were plotted against drug concentrations, and the data were fitted to logistic dose-response curves. The 50% inhibitory concentration (IC50) was obtained from the fit parameters that achieved the lowest x^2 value. Isoeffective combinations were used to create isobolograms. A Monte Carlo simulation (10^3 replications) was conducted to assess the interaction between paclitaxel and PNC-27 in a binomial regression model.

Results: A 12-hour exposure to paclitaxel rendered incomplete killing, and a maximal cytotoxicity of 80% was reached at 100 ug/mL. Cells were more responsive to increased exposure time than to increased dose, and 100% cytotoxicity was obtained at 48 hours. PNC-27 mediated comprehensive, dose-dependent killing. The IC50 for a 24-hour exposure was 58 ug/mL, while 100% cytotoxicity was achieved at 300 ug/mL. ID8 cells surviving paclitaxel demonstrated increased susceptibility to PNC-27. The killing effect of PNC-27 at a low dose (½ IC50) increased from 16% in control cells to 80% after exposure to paclitaxel at 100 ug/mL ($P<0.05$). The IC50 of PNC-27 for cells surviving treatment with paclitaxel at various doses was lower as compared to the untreated cells. Isobologram for dose combinations that were isoeffective at the level of maximal cytotoxicity reached by paclitaxel alone indicated a synergistic effect between the two agents (Monte Carlo simulation**,** $P<0.05$).

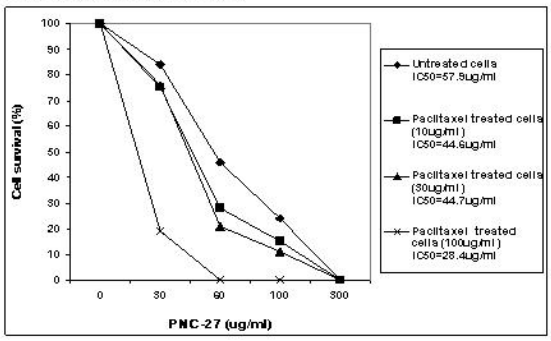
Conclusions: Our data demonstrated *in vitro* synergism between PNC-27 and paclitaxel. PNC-27 could eliminate cells surviving paclitaxel and provide survival benefit.



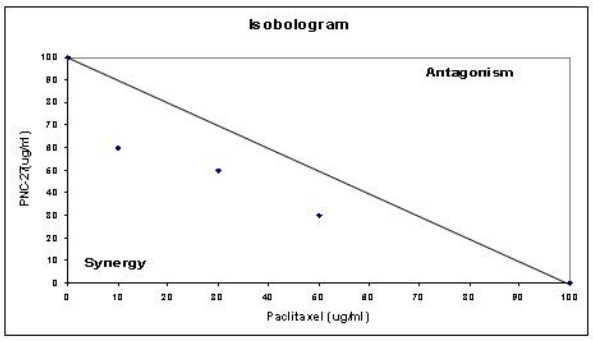
1A. Space filling model showing amphipathic structure of PNC-27.Green: hydrophobic domains, red: hydrophilic, neutral, or negatively charged residues, blue: positively charged residues. Amino terminus is on the right, carboxy terminus on the left.



1B. Increased sensitivity of surviving Paclitaxel cells to PNC-27



1C.Dose response curves of PNC-27 for cells treated with Paclitaxel at various concentrations



1D. Isobologram (IC80) demonstrating synergy between Paclitaxel and PNC-27

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287 - Poster Session A

Testing the accuracy of mutation detection for the prevention of ovarian neoplasia: the TAMPON study

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Objectives: Given that the intra-abdominal cavity communicates with the vagina through the urogenital tract, it is reasonable to consider that tumor cells might be exfoliated into the vagina. Our objective was to determine if tumor cells could be detected in the vagina of women with known ovarian cancer through digital genomic analyses of *TP53* in DNA samples collected by placement of a vaginal tampon.

Methods: After institutional review board approval, women undergoing surgery for a suspicious pelvic mass were included in this pilot feasibility study. Patients placed a vaginal tampon 8 to 12 hours prior to surgery. The tampon was removed in the operating room and cells were extracted from the tampon. Primary tumor was also collected. DNA was extracted from both

the tumor and the tampon-collected cells. Somatic *TP53* mutations in primary tumors and in DNA extracted from vaginal cells were identified through a digital genomics technique, termed SafeSeq, capable of detecting rare mutant alleles in a complex mixture of mutant and wild-type DNA.

Results: Eight patients with stage IIIC high-grade serous ovarian cancer were included. *TP53* mutations were identified in all of the tumor samples. Mutational analysis of the tampon specimen DNA revealed detectable mutations in three patients (38%), although three patients in whom a mutation was not detected in the vagina had a prior tubal ligation. The fraction of mutant alleles in the tampon sample ranged between 0.095% and 0.113%. In all three subjects, the tumor and the vaginal DNA harbored the exact same *TP53* mutation, demonstrating that the mutated cells in the tampon specimen originated from the tumor.

Conclusions: In this pilot study, ovarian cancer cells were detected in the vaginas of women with ovarian cancer through deep sequencing of DNA extracted from vaginal tampons. With further development, this technology holds promise for screening for this deadly disease.

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288 - Poster Session A

Dual *HER2* targeting impedes growth of *HER2* gene-amplified uterine papillary serous carcinoma xenografts

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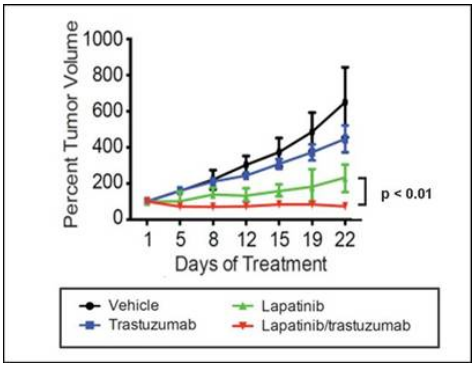
Objectives: Uterine papillary serous carcinoma (UPSC) is an aggressive tumor with a high rate of *HER2* gene amplification. Since combination anti-HER2 therapy has shown efficacy in other *HER2*-amplified cancers, we measured the combined effect of lapatinib and trastuzumab on the growth of tumor xenografts derived from human UPSC cell lines and primary human UPSCs.

Methods: Human UPSC cell lines (ARK2, SPEC2) and prospectively collected tissue from two UPSC patients undergoing primary surgery (ENCA1, ENCA2) were obtained. *HER2* protein expression and gene amplification were assessed in all samples. ARK2, SPEC2, ENCA1, and ENCA2 cells were injected subcutaneously into female NOD/SCID mice. Tumor formation was monitored regularly and mice were randomized into four treatment arms (5 mice/arm) once tumor volume reached 200 to 400 mm^3. Lapatinib (100 mg/kg) was dosed by oral gavage 6 out of every 7 days, and 10 mg/kg trastuzumab was administered by intraperitoneal injection 3 times a week. Tumor size was monitored every 3 days. Posttreatment analysis of xenografts was carried out by immunohistochemistry and Western blot. Wilcoxan ranksum testing was used to compare xenograft growth across treatment arms.

Results: ARK2- and ENCA1-derived xenografts exhibited *HER2* gene amplification and 3+ protein expression. SPEC2- and ENCA2-derived xenografts were disomic for *HER2* with 1+ protein expression. In all xenografts, trastuzumab exhibited no single-agent antitumor efficacy. Dual administration of trastuzumab and lapatinib resulted in significant synergistic activity ($P<0.01$) only in those xenografts exhibiting *HER2* gene amplification. Effective anti-HER2 therapy was associated with decreased *Ki67* expression and decreased phosphorylation of AKT and ERK. In the non-*HER2* amplified models, no alterations in downstream signaling were observed and no tumor response was manifested.

Conclusions: Our data suggested that single-agent trastuzumab has no antitumor activity in UPSC, even in the setting of *HER2* gene amplification. When administered in concert with lapatinib, however, trastuzumab demonstrated significant synergy in the *HER2* gene-amplified models. Dual targeting of *HER2* may be a promising avenue for future investigation in *HER2*-amplified UPSC.



289 - Poster Session A

Use of *SRC* pathway activation in predicting dasatinib activity in ovarian cancer

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Objectives: To determine if genomic biomarkers, including *SRC* pathway activation, can predict dasatinib antiproliferative activity in ovarian cancer.

Methods: Eighteen ovarian cancer cell lines were treated with single-agent dasatinib and dose-response curves were constructed. The cell lines were stratified into dasatinib-sensitive and dasatinib-resistant cohorts based on median inhibition concentration (IC50) values. Pretreatment gene expression profiles were used to assess for associations between *SRC* pathway activation as well as other genomic biomarkers and dasatinib's antiproliferative effect. *SRC* pathway expression was determined from the normalized array data by an 85-gene *SRC* signature decomposed into three factors based on singular value decomposition. A Bayesian probit regression model was fit to the three factors (Monte Carlo Markov Chain algorithm) and the *SRC* pathway activation level was scored.

Results: Seven cell lines were considered dasatinib-sensitive (IC50 <400 nmol), while 11 were dasatinib-resistant (IC50 >400 nmol) (IC50 range, 0.1-5,000 nmol). *SRC* pathway activation ranged from 15% to 83%. There was a marginal association between dasatinib activity and *SRC* pathway activation (P=0.1). Specifically, cell lines that exhibited very low *SRC* activation (lowest quartile) were more likely to be sensitive to dasatinib. In contrast, cell lines with the highest *SRC* pathway activation (top quartile) were likely to be dasatinib-resistant. There was no association between dasatinib antiproliferative activity and other previously reported molecular markers for dasatinib activity (annexin-1, IGFBP2, SRC, YES1, LYN, EPHA2, CAV1/2, or MSN).

Conclusions: *SRC* pathway activation may be indicative of dasatinib activity in ovarian cancer. However, further evaluation is needed to identify the gene(s) within this pathway that are most predictive of dasatinib activity.

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290 - Poster Session A

Analysis of the immune cell composition in serous ovarian cancer

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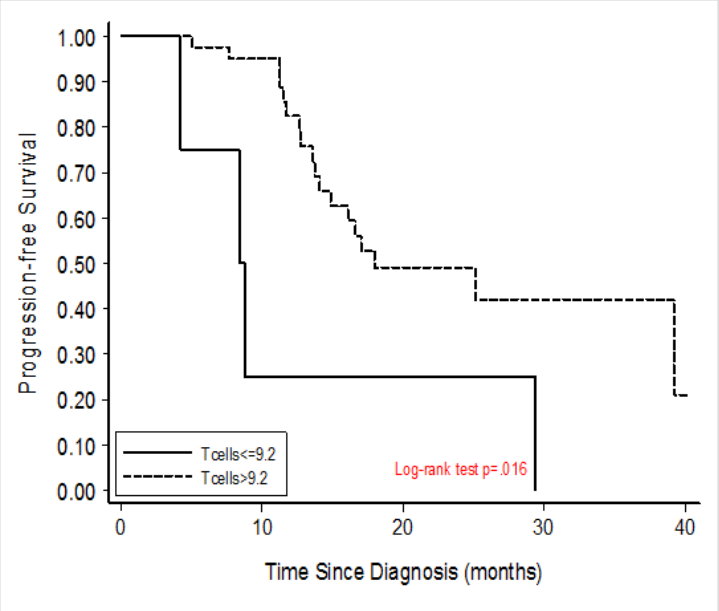
Objectives: To assess the immune cell composition in serous ovarian cancer by flow cytometry and its association with progression-free survival.

Methods: Fresh tumor samples from an institutional review board-approved human ovarian cancer tumor bank were enzymatically digested and analyzed by flow cytometry. A total of 89 samples (83 tumor and 6 ascites) from primary and recurrent ovarian cancer were analyzed for frequency of tumor cells and leukocytes among viable cells using 7AAD, EpCAM, CD45, CD3, CD19, and CD14. Descriptive statistics, Wilcoxon rank sum tests, Kaplan-Meier curves, log-rank test, and Cox regression models for progression-free survival were performed using Stata statistical software.

Results: Across all samples (n=89), the median frequency of EpCAM+ cells was 20.7% (range, 0% to 78%), and among CD45+ leukocytes, the median frequency of T-cells was 36.7% (range, 5% to 87%), of B-cells was 3.3% (range, 0% to 28%), and of monocytes was 19.1% (range, 0% to 77%). Compared to the matched solid tumor sample from the same patient, ascites fluid gave higher frequencies of T-cells but lower frequencies of EpCAM+ cells and monocytes. Of the patients undergoing primary surgery (n=50), those who had received neoadjuvant chemotherapy (NACT) (n=6) had much lower frequencies of EpCAM+ cells (0.8% vs 27.8%, P<0.001) and monocytes (7.6% vs 23.5%, P<0.05) compared to those who had not received NACT (n=44). The frequency of T-cells was not statistically different between these groups. The same pattern was seen when recurrent and primary cancer samples previously exposed to chemotherapy were combined (n=39) and compared to samples not exposed to chemotherapy (n=44) (EpCAM+: 16.8% vs 27.8%, P=0.03 and monocytes: 16.9% vs 23.5%, P=0.02). Trends toward worse progression-free survival with lower frequencies of T-cells was observed and met statistical significance comparing the lowest 10% percentile T-cell group with the upper 90% percentile group (HR 3.66, 95% CI 1.19-11.29, P=0.024) (Figure).

Conclusions: Tumor and immune cell frequency analysis by flow cytometry was feasible and gave information pertinent to immune-based therapy. While intratumoral EpCAM+ cells and monocytes were decreased in patients exposed to chemotherapy, T-cell frequencies were preserved. Furthermore, this analysis suggests worse progression-free survival in patients with low T-cell frequencies.



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291 - Poster Session A

Patient-derived tumor xenograft model (“avatar mice”) for gynecologic cancer

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Objectives: Patient-derived tumor xenograft model (Avatar mice) may provide more accurate and reliable information about individual patients' tumor biology when compared with established cell line model. This study was designed to study the development of Avatar mice and their genetic and phenotypic stability for gynecologic cancer including ovarian, endometrial and cervical cancer.

Methods: Small pieces (3 x 3 x 3 mm) of human gynecologic cancer tissue (n=94) were meticulously grafted under renal capsules of female BALB/C-nude mice within 2 h of surgical removal. Grossly visible tumor tissues serially transplanted for 2~5 generations. After the development of tumor in mice, phenotypic and genetic comparisons were performed between primary tumor and corresponding transplantable xenografts using H&E, Ion Torrent (AmpliSeq Cancer Panel), and array-comparative genomic hybridization (aCGH) analysis.

Results: Total tumor tissue engraftment rate was 37.2% (35/94) including ovarian cancer 32.8% (21/64), cervical cancer 47.6% (10/21) and endometrial cancer 44.4% (4/9). The mean time to the development of first generation in mice was 6.6 month in ovarian, 5.5 month in cervical and 4 month in endometrial cancer. Comparison of primary and Avatar tumor tissues showed highly similar histopathologic features. Moreover, analysis of Ion Torrent and aCGH indicated that all examined mutation and genomic alterations found in primary cancer tissues were precisely replicated in the corresponding Avatar tumors.

Conclusions: Avatar mice for human gynecologic cancer can be developed as a method of subrenal capsule implantation and have very similar phenotypic and genetic alteration of the original tissues. This has the potential to provide a very effective tool for future personalized therapy and for conducting translational gynecologic cancer research.

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292 - Poster Session A

The microenvironmental effects of endometriosis on VCAM1 and IL-10 expression in early stage epithelial ovarian cancer

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[1]University of Virginia Health System, Charlottesville, VA, [2]University of Virginia Medical Center, Charlottesville, VA, [3]University of South Alabama, Mobile, AL, [4]University of Virginia School of Medicine, Charlottesville, VA, [5]University of Virginia, Charlottesville, VA

Objectives: We have previously shown that vascular cellular adhesion molecule-1 (VCAM1) is overexpressed in the peritoneum of advanced epithelial ovarian cancer (EOC) patients but not in stage I EOC. VCAM1 is also highly expressed in endometriosis. Interleukin (IL)-10 is thought to promote EOC development and inhibit endometriosis. We hypothesized that VCAM1 and IL-10 are involved in the development of endometriosis-associated EOC.

Methods: Seventeen patients with stage I EOC and endometriosis were identified. Tissue samples were stained with a VCAM1-specific antibody and compared to samples from 24 patients with only stage I EOC and 25 with only endometriosis. Specimens from 10 patients with EOC and endometriosis, 6 with endometriosis only, and 8 with EOC only were stained with an IL-10-specific antibody. All samples were read by one blinded pathologist. VCAM1 was scored as positive or negative and IL-10 as the percentage of positive cells. The effect of group on VCAM1 and IL-10 were evaluated with a regression and the Jonckherre-Terpstra test (for IL-10)**.** VCAM1's effect on IL-10 was evaluated with a regression.

Results: VCAM-1 was positive in 56% of endometriosis, 29% of EOC, and 24% of EOC and endometriosis samples. The frequency of VCAM1 expression was higher in patients with only endometriosis compared to those with only EOC (P=0.042) or endometriosis and EOC (P=0.049). There was no difference in VCAM1 expression between patients with EOC only and those with EOC and endometriosis. The median percentage of IL-10 positive cells was 18% in endometriosis, 30% in EOC, and 85% in endometriosis and EOC. IL-10 expression was higher in patients with endometriosis and EOC compared with endometriosis alone (P=0.049), and there was minimal difference between patients with only endometriosis compared with only EOC (P=0.18) or EOC alone vs EOC and endometriosis (P=0.053). After adjusting for group, IL-10 expression was 24% lower when VCAM1 stained positive (P=0.16)

Conclusions: Our findings support prior results that the incidence of VCAM1 expression is more frequent in endometriosis than stage I EOC. The observation that coexisting endometriosis and stage I EOC had low VCAM1 and high IL-10 expression raises the possibility of exploiting this pattern as a marker of the transition from benign to malignant disease. Further study with larger populations is needed to confirm this observation.

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293 - Poster Session A

Serum omentin concentration is a potential biomarker for complex atypical hyperplasia and endometrioid endometrial cancer

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Objectives: Omentin is an adipokine secreted by the stromal cells of visceral fat. Serum levels of omentin are inversely correlated with body mass index (BMI) and insulin resistance. Given that endometrioid endometrial cancer (EEC) is an inflammatory state associated with obesity and insulin resistance, serum omentin may be a biomarker for the development of EEC. The objective of this study was to evaluate serum omentin in patients with complex atypical endometrial hyperplasia (CAH) or EEC as compared to controls.

Methods: Serum omentin of 74 patients with CAH, 74 patients with EEC, and 148 controls was measured in triplicate with a commercially available enzyme-linked immunosorbent assay kit. CAH and EEC patients were matched to controls by BMI and menopausal status. Serum was obtained from a tumor bank and clinical data were reviewed. Paired t-tests were used to compare the mean omentin concentration between cases and controls.

Results: The median age of patients was 59.5 years, 77.1% were postmenopausal, 74% were white, 17.2% were diabetic, and the median BMI was 31.1. EEC patients had a lower mean omentin concentration than controls (575.8 ng/mL vs 673.1 ng/mL, P=0.02). Similarly, patients with CAH had a lower omentin level than controls (359.6 ng/mL vs 723.2 ng/mL, P<0.001). When evaluated by BMI group, the mean omentin level between EEC patients and controls was different for only patients with a BMI <25. Omentin concentration between women with CAH and controls was significantly different for patients with a BMI <25 or a BMI >30 (Table).

Conclusions: Serum omentin concentration was significantly decreased among women with CAH and EEC when compared with BMI-matched controls. Interestingly, omentin levels were lower in both normal-weight EEC and CAH patients as

compared with normal-weight controls. These findings may have significant clinical implications for the use of omentin as a biomarker of CAH and its progression to EEC in these women and should be further investigated.

Table: Mean Omentin Between Cases and Controls by BMI Group

	EEC		Controls		
BMI	***n***	**Omentin (ng/mL)**	***n***	**Omentin (ng/mL)**	***p***
<25	21	667.73	21	954.06	<0.001
25 to 30	15	474.31	15	593.30	0.177
>30	38	564.98	38	550.64	0.802
Total	74	575.76	74	673.77	0.02
	CAH		**Controls**		
BMI	***n***	**Omentin (ng/mL)**	***n***	**Omentin (ng/mL)**	***p***
<25	17	438.32	17	995.94	0.002
25 to 30	16	354.79	16	652.42	0.068
>30	41	328.78	41	637.96	<0.001
Total	74	359.57	74	723.32	<0.001

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294 - Poster Session A

mTOR complex inhibition as a novel therapeutic strategy in high-grade papillary serous ovarian cancer

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Objectives: To compare mTOR complex 1 inhibition (RAD001) vs mTOR complex 1/2 inhibition (PP242) as single agents and with carboplatin (CPP) in a preclinical model of serous ovarian cancer (OVCA).

Methods: In vitro: OVCAR3 and SKOV3 cell lines were exposed to RAD001 or PP242 as single agents, vehicle, CPP alone, and RAD001 or PP242 followed by CPP. Colony-forming assays (CFAs) were performed and quantified. mRNA levels of *AKT*, downstream targets of mTOR and the DNA repair response (*ATR, ATM*, *BRCA1/2*), were quantified by quantitative real-time polymerase chain reaction (qRTPCR). Immunoblots characterized the protein expression of key components of mTOR and DNA repair pathways. Non-parametric analyses were used to compare results across groups on SPSS. In vivo: OVCAR3 cells expressing F-Luciferase were injected intraperitoneally into SCID-BG mice. At 15 weeks postinjection, mice were exposed to the treatment conditions described previously for 4 weeks. Tumor growth and response to treatment were assessed using bioluminescence imaging (IVIS). Results were analyzed on Living Image and Prism6.

Results: In vitro: OVCAR3 and SKOV3 cells are highly sensitive to mTOR inhibition. CFAs showed significantly decreased colony counts and diameter in groups exposed to either PP242 or RAD001 vs control, an effect that was potentiated by CPP (Figure 1). qRTPCR revealed a significant decrease in *4EBP1* mRNA with mTOR inhibition ($P<0.0001$) but no change in other biomarkers. Although treatment with both mTOR inhibitors resulted in decreased expression of *p-S6* by immunoblots, treatment with the dual inhibitor (PP242) caused a decrease in *p-AKT, p-4EBP1*, total and p-*CHK1*, and total and p-B*RCA1*. The levels of these proteins were not changed by addition of CPP, despite the significant effect observed in the functional assay (CFA). In vivo: Treatment with CPP + PP242 was associated with a longer median survival than other treatment groups (Table 1). A decrease in tumor burden was seen on IVIS, and tumor flux (photons/sec) at the end of treatment was significantly lower in mice treated with CPP+PP242 compared to other groups ($P<0.0001$).

Conclusions: Our preclinical model supported the concurrent use of dual mTOR inhibitors and platinum chemotherapy in the treatment of OVCA. mTOR complex 1/2 inhibition impaired the DNA repair response and correlated with improved survival in a murine model.

Figure 1: Colony Formation Assay

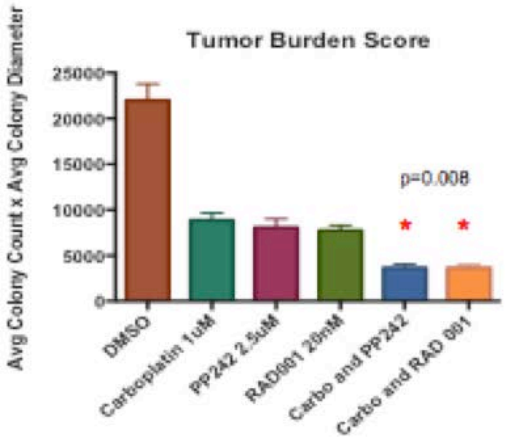

Table 1: PP242 + CPP is Associated with Improved Median Survival (Days) in a Murine Model

	Carboplatin	Carbo+RAD001	Carbo+PP242	RAD001	PP242	Vehicle
Median Survival (days)	28	15.5	36.5	21	24	20

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295 - Poster Session A

Curated Ovarian Database-derived identification of genes predicting survival in primary serous epithelial ovarian cancer

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Objectives: To use a clinically annotated ovarian cancer transcriptome database and develop biostatistical pipelines to triage and prioritize transcripts that are most prognostic and predictive for survival in patients with serous epithelial ovarian cancer (EOC).

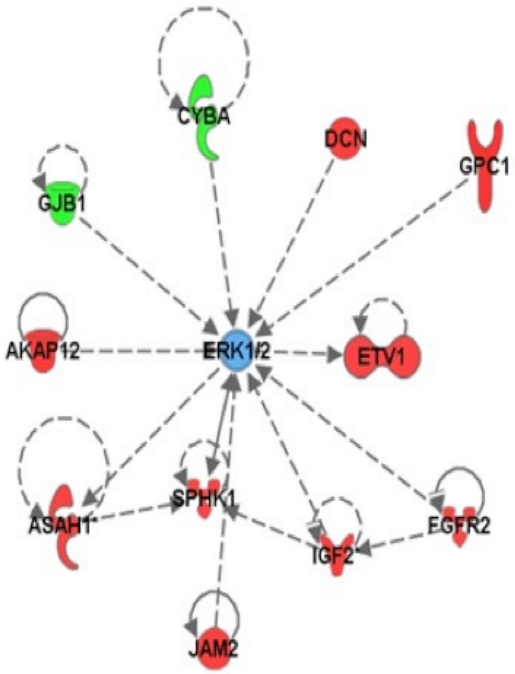
Methods: CuratedOvarianData, representing 2,970 specimens from 23 sources in 11 platforms, was downloaded using the Bioconductor R language package and Combat batch corrected. Biostatistical pipelines were implemented from transcript expression data corresponding to frozen primary serous EOCs to triage 22,277 probe sets controlling for multiple testing and false discovery ($q<0.05$). Cox regression modeling ($n=1,183$) for overall survival (OS) was performed on average gene expression data evaluated as a continuous variable and categorized at the median as low (≤ median) vs high (> median). Kaplan-Meier plots with log-rank testing ($n=1,183$) and logistic regression prediction modeling for 10-year OS ($n=733$) were performed on categorized probe sets. Significant probe sets underwent Ingenuity Pathway Analysis (IPA).

Results: A total of 191 (0.9%) probe sets surpassed the triage threshold and were significantly associated with OS by all methods. These probe sets predicted 10-year OS with 87% individual and 96% combined accuracy, outperforming any previously reported survival prediction models in EOC. IPA identified shared network pathways between significant probe sets, including 11 that regulate ERK 1/2, a member of the pro-oncogenic MAP kinase cascade (Figure).

Conclusions: The 191 probe sets had strong prognostic value and predictive accuracy in primary serous EOC and warrant prospective validation. Through IPA of these probe sets, the known correlation between the MAP kinase cascade and carcinogenesis was validated, supporting it as a target for therapeutic intervention in serous EOC.

Figure: Green = HR < 0.77, Red = HR > 1.31

Gene	Hazard Ratio High vs. Low	Survival High vs. Low (months)
CYBA	0.72	11.00
GJB1	0.71	15.35
DCN	1.37	-4.93
GPC1	1.46	-13.09
ETV1	1.34	-8.50
FGFR2	1.33	-6.91
IGF2	1.39	-9.49
JAM2	1.36	-8.46
SPHK1	1.33	-9.30
ASAH1	1.33	-10.10
AKAP12	1.40	-12.53



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296 - Poster Session A

Cytokine-induced killer cells from ovarian cancer patients expanded ex vivo in the presence of IL-7 improve survival in a xenograft mouse model of ovarian cancer

S. B. Ingersoll[1], M. Srivastava[1], G. Ali[1], Z. Mohiuddin[1], E. R. Boone[1], S. Ahmad[1], R. K. Banks[2], N. J. Finkler[1], J. R. Edwards[3] and R. W. Holloway[1]
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Objectives: To determine the therapeutic effect of cytokine-induced killer cells (CIK) from ovarian cancer (OC) patients, expanded in the presence or absence of interleukin (IL)-7 in a xenograft mouse model of OC.

Methods: Peripheral blood mononuclear cells (PBMC) were isolated from OC patients and expanded ex vivo for 15 days in IL-2, IL-12, and anti-CD3 antibody with or without IL-7. CIK activity against SKOV3-AF2 OC cells was confirmed in vitro; only CIK with >35% cytotoxicity were used for mouse studies. Female athymic mice (n=54) were injected intraperitoneally (IP) with SKOV3-AF2 ($1x10^6$). On day 7 post-tumor cell injection, mice were injected IP with $5x10^6$ CIK expanded with IL-7 (CIK+IL7) or without IL-7 (CIK-IL7) from one of two independent donors. IL-2 (4,000 U) was injected IP on day 7 and continued thrice weekly. Mice were monitored for signs of distress, weighed weekly, and sacrificed when they became moribund due to tumor burden, at which point ascitic fluid (AF) and solid tumor (ST) were measured and collected.

Results: After 15-day cultures in IL-2, IL-12, and anti-CD3, OC patients' PBMC generated large numbers of CIK with or without IL-7 (139-fold expansion with vs 94-fold without, P<0.05). CIK cytotoxicity averaged 47.5% for the mouse studies. Mice tolerated all combinations of CIK and IL-2, as evidenced by no significant weight loss during the study. Mice that received CIK+IL7 in combination with IL-2 showed a significant improvement in survival (average time to sacrifice 16.6 weeks, P<0.05) compared to mice that received no treatment (7.8 weeks), IL-2 (7.5 weeks), or CIK+IL7 (5.6 weeks). Mice treated with CIK-IL7 in combination with IL-2 did not show a significant improvement in survival (11.1 weeks, P>0.05) compared to control mice or mice treated with CIK-IL7 (8.9 weeks) alone. No difference was observed in the incidence and volume of AF or ST weight between treatment groups at time of sacrifice.

Conclusions: CIK from OC patients generated ex vivo in a cytokine cocktail plus IL-7 improved survival in an OC mouse model similar to our previously reported results that healthy donor PBMC plus IL-2 improve survival. Data demonstrated that PBMC from OC patients, which lack cytotoxic activity, can generate large numbers of potent effector cells and support further investigation of CIK as an immunotherapeutic option for OC.

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297 - Poster Session A

Wnt pathway inhibition by niclosamide: a therapeutic target for ovarian cancer

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Objectives: The Wnt/Î²-catenin pathway regulates cellular proliferation and differentiation and plays a role in chemoresistance. Niclosamide, United States Food and Drug Administration-approved salicyclamide derivative used for the treatment of tapeworm infections targets the Wnt/Î²-catenin pathway. Therefore, the objective of this study was to investigate niclosamide as a potential therapeutic agent for ovarian cancer.

Methods: Five ovarian cancer cell lines were treated with niclosamide (0.1 to 5 ÂµM) alone or in combination with carboplatin (5 to 150 ÂµM). Tumor cells isolated from the ascites of 34 patients with primary ovarian cancer were also treated. Cell viability was assessed using the ATP-lite assay. The levels of LRP6, Axin 2, Cyclin D, survivin, and cytosolic free Î²-catenin were determined using Western blot analysis. Cell lines were treated with Wnt3A ligand and niclosamide, and Wnt transcriptional activity was measured by the TOPflash reporter assay.

Results: Combination treatment produced increased cytotoxicity compared to single agent treatment in all ovarian cancer cell lines and in 32/34 patient samples. Western blot analysis showed a decrease in phosphorylated LRP6, Axin 2 expression, and the level of cytosolic free Î²-catenin in five patient samples. A significant reduction of Wnt/Î²-catenin signaling was confirmed by TOPflash assay in both parental (P=0.05) and chemoresistant cell lines (P=0.009), in addition to nine patient samples.

Conclusions: This study demonstrated that niclosamide is a potent Wnt/Î²-catenin signaling inhibitor by causing a decrease in LRP6, Axin 2 expression, cyclin D1, survivin, and cytosolic free Î²-catenin. Targeting the Wnt/Î²-catenin pathway led to decreased cellular proliferation and increased apoptosis. Niclosamide displayed excellent antitumor activity in ovarian cancer cell lines and in ovarian cancer cells from patient ascites. These findings warrant further research of this drug and other niclosamide analogs as a treatment option for ovarian cancer.

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298 - Poster Session A

PARP therapy for the genetically unstable: a preclinical evaluation of PARP inhibitors in the treatment of MSI-H endometrial tumors

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Objectives: Approximately 35% of endometrial tumors demonstrate high levels of microsatellite instability (MSI-H) resulting from germline defects in DNA mismatch repair (MMR) genes or methylation of the *MLH1* gene promoter. Previous preclinical and clinical studies have shown a benefit of poly ADP ribose polymerase (PARP) inhibition in the treatment of cancers with defects in homologous recombination as well as tumors with *PTEN* deficiency. In addition, preclinical studies in colon cancer have shown that cells with *MSH3* deficiency and MSI are sensitive to PARP inhibition. Our objective was to evaluate the efficacy of olaparib, an oral PARP inhibitor, in the treatment of MSI-H endometrial tumors.

Methods: To evaluate the effect of olaparib on endometrial cancer cells in vitro, cell viability (MTT) assays were performed. Cells were treated with olaparib at concentrations ranging from 0 to 100 uM. Cell lines included in our preliminary analysis were Hec59 (MSH2 null), Ishikawa (PTEN null), and Hec1A (KRas G13D mutation). The absorbance of the purple formazan product catalyzed by metabolically active cells was recorded at a wavelength of 590 nm and 620 nm. The change in the optical density (ΔOD) measured at these two wavelengths was used to calculate the mean median inhibition concentration (IC50) for cell lines treated with olaparib.

Results: Olaparib significantly inhibited the viability of Hec59 cells in a concentration-dependent manner, with a significant decrease in relative cell viability at a concentration of 5 uM (P=0.002). In contrast, Hec1A cells had a significant decrease in relative cell viability at a concentration of 50 uM (P=0.01), and Ishikawa cells had no significant concentration-dependent

decrease in cell viability (Figure 1). The mean IC50 for Hec59 cells was 0.281 uM. The mean IC50 for Hec1A and Ishikawa cells was 9.24 uM and 6.892 uM, respectively.

Conclusions: These preliminary studies suggested that cells with deficient MMR and/or high levels of MSI are more susceptible to PARP inhibition compared to cells with intact MMR. Further studies are ongoing to investigate PARP inhibition in MSI-H endometrial tumors.

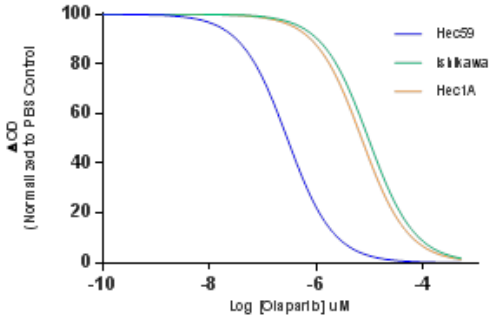

Figure 1. Dose-response curves for olaparib treatment over 48 hours in Hec59, Ishikawa, and Hec1A cells. Hec 59 cells (MSH2 null) showed increased sensitivity to treatment with olaparib.

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299 - Poster Session A

Copy number variation and mutations associated with ovarian cancer chemoresponse

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Objectives: A complete understanding of the biologic basis of ovarian cancer (OVCA) chemoresponse remains elusive. Previously explored genome-wide expression changes associated with OVCA chemoresponse identified three significant molecular pathways: O-glycan biosynthesis, *RAB1A* regulation, and *MAPK* signaling. We hypothesized that copy number variation (CNV) and DNA sequence mutations affect gene expression of these pathways involved in chemoresponse. We sought to detect gene gains, losses, and mutations between OVCA patients with complete (CR) versus incomplete response (IR) to primary platinum-based chemotherapy.

Methods: We identified gene gain and losses in patients with CR (n=321) and IR (n=136) using data from The Cancer Genome Atlas (TCGA). Using comparative genomic hybridization (CGH) and genomic identification of significant targets in cancer (GISTIC) analysis, we identified candidate pathway genomic regions that exhibited significant gains and losses in patients with CR and IR. We also identified which genomic regions with gains/losses also presented positive correlation with gene expression. Finally, we integrated mutation analysis of genes with significant gain and loss from the candidate pathways from 88 samples.

Results: Patients with CR presented gain of copy number in the following genomic regions encoding for candidate pathways genes: 3q26.2, 8q12.1, 8q24.13-q24.21, 11q13.5-q14.1, 12p12.1-p11.23, and 19q13.12-q13.2. Interestingly no loss was identified in the candidate encoding regions. IR patients also presented gain of copy number on some of the same candidate encoding regions: 8q24.21, 12p12.1, and 19p13.13; and presented loss at 2q24.1 and 12p13.33. We identified 78 genes with positive correlation between gain of CNV and expression in CR patients. IR presented positive correlation between 11 genes with gain CNV and 1 gene with CNV loss (*WNK1*). Mutations were detected in 35% of genes from the candidate genomic regions with CNV.

Conclusions: No loss of CNV was identified in the candidate encoding regions for patients with CR. Patients with IR presented loss of CNV at 2q24.1 and 12p13.33 regions, which also correlated with decreased *WNK1* expression. CNV and mutations within these candidate genomic regions may aid in understanding the biologic basis of individual response to OVCA treatment.

300 - Poster Session A

Ovarian cancer ascites stem cell population compared to primary tumor

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Objectives: Cancer stem cells (CSCs) are involved in metastasis and recurrence, and the Wnt pathway is important in CSC proliferation. Because ovarian cancer patients often recur with ascites, we sought to evaluate CSC markers and LRP6, a membrane receptor for Wnt ligands, in ascites compared to ovarian tumor specimens.

Methods: With institutional review board approval, ascites and tumor were obtained from ovarian cancer patients and tumor cells/spheres were isolated from ascites via centrifugation. Flow cytometry for *ALDH1A1* and *CD133* expression was performed. For each ascites sample, the population of ALDH-/CD133+, ALDH+/CD133-, double-negative, and double-positive was determined. Pathology was confirmed on tumor from the same patients and formalin-fixed paraffin-embedded slides were made. Both the ascites and tumor were stained for *ALDH1A1, CD133*, and *LRP6* by immunohistochemistry (IHC). The intensity of the stain (1+ to 3+) was multiplied by the percentage of positive cells to calculate an H-score (0-300).

Results: Twenty-six ascites samples were analyzed by flow cytometry. Ninety-six percent had some cells positive for *ALDH1A1* (1.6% to 54.1%). Eighty-one percent stained *CD133*-positive. By IHC, *CD133* had minimal expression in ascites and tumor. Twelve of fifteen ascites samples stained positive for both *ALDH1A1* and *LRP6*. There was a correlation between the H-scores of these, although given the small numbers, it was not statistically significant. Fifty percent (16/32) had at least one tumor site positive for *ALDH1A1* compared to 93% of the stained ascites samples. Fifty-nine percent of patients had at least one tumor site stain positive for *LRP6* compared to 94% of the ascites. Fifteen patients had tumor and ascites that could be compared by IHC. In almost all pairs (13/15), the H-score for *LRP6* in the ascites was greater than in the tumor, and in 12/15 patients the *ALDH1A1* H-score was greater in ascites. The mean ascites H-score was 95.3 for *ALDH1A1* and was 52.0 for the primary tumor. The mean H-score was 141.6 for LRP6 in ascites compared to 57.8 for tumor ($P=0.077$).

Conclusions: The Wnt pathway is active in CSCs and is a potential target in ovarian cancer. The CSC marker *ALDH1A1* and *LRP6*, the receptor for Wnt ligands, showed a higher expression in ascites compared to tissue samples by IHC.

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301 - Poster Session A

HSP90 inhibition decreases ovarian cancer cell proliferation and potentiates platinum sensitivity

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Objectives: Heat shock protein 90 (Hsp90) is a chaperone protein that assists other proteins to fold/refold during stress, transportation, and degradation. A multitude of established ovarian cancer (OVCA) oncoproteins are clients of the HSP90 chaperone system. As such, *HSP90* is an attractive OVCA chemotherapeutic target. We evaluated the effect of AUY922, an HSP90 inhibitor, on OVCA cell proliferation and platinum-sensitivity. Further, we explored the molecular signaling pathways associated with *AUY922* response.

Methods: OVCA cell lines were treated with AUY922 alone ($n=19$) and in combination with carboplatin ($n=12$). In parallel, Affymetrix expression analyses (HuRSTA genechip) were performed on pretreatment cells. Sensitivity was quantified using MTS proliferation assays. Pearson's correlation was calculated for gene expression and AUY922 median inhibition concentration (IC50) values, and differentially expressed genes were subjected to pathway analysis. Identified AUY922 response pathways were evaluated for associations with survival from OVCA in five external clinico-genomic datasets from 969 patients.

Results: AUY922 exhibited antiproliferative effects against all tested OVCA cells and significantly decreased carboplatin IC50 in 69% (9/13) of OVCA cells. Twenty-four pathways were associated with AUY922 sensitivity (false discovery rate <0.1, $P<0.01$), nine of which may influence overall survival from OVCA in one or more dataset: androstenedione and testosterone biosynthesis ($P=0.001$), protein folding and maturation/angiotensin system ($P=0.01$), FXR-regulated cholesterol and bile acids cellular transport ($P<0.001$), cytoskeleton remodeling/TGF,WNT ($P=0.01$), role of ASK1 under oxidative stress ($P=0.03$), cytoskeleton remodeling/keratin filaments ($P=0.03$), regulation of endothelial nitric oxide synthase activity in endothelial cells ($P=0.02$), LRRK2 in neuronal apoptosis ($P<0.001$), and signal transduction/AKT signaling ($P=0.02$).

Conclusions: AUY922 exhibited significant antiproliferative effects against OVCA cells and potentiated carboplatin-sensitivity. Our data provided insights into the molecular basis for AUY922 activity against OVCA cells and identified pathways associated with clinical outcome.

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302 - Poster Session A

Expression profiles of *LKB1/AMPK* in endometrial cancer specimens as a potential biomarker for targeted metabolic drug therapy

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Objectives: *LKB1* is the major kinase phosphorylating the AMP-activated protein kinase (*AMPK*), a primary modulator of cell growth that exerts its effects through the mTOR signaling pathway. It has previously been shown that metabolic drugs (metformin/phenformin) selectively induce apoptosis via *AMPK*-dependent or -independent pathways. We sought to determine baseline expression profiles of *LKB1* and *AMPK* in endometrial cancer patients (for which no data exist) as a potential biomarker for metabolic drug therapy.

Methods: In this institutional review board-approved pilot study, we analyzed 94 endometrial cancer specimens for expression profiles of *LKB1* and *AMPK*. Frozen tissue sections were quantified for protein concentration by Bradford Assay spectroscopy. Samples were analyzed by SDS-PAGE. Clinical and pathologic data were abstracted from patient medical records.

Results: The median patient age at diagnosis was 67 years. Staging was: 81.0% stage I, 7.4% stage II, 10.6% stage III, and 1.1% stage IV. Histology was 32% grade 1, 58.5% grade 2, and 5.9% grade 3. Forty-nine of 94 cases (52.1%) expressed *LKB1*, while 37 of 94 (39.4%) expressed *AMPK*, suggesting a significant loss of expression (and hence function) in approximately 50% (*LKB1*) and 60% (*AMPK*) of cases examined. Tumor angiogenesis is a well-established property of cancer cells, so endometrial cancer specimens were further characterized for the expression of major angiogenic targets, *VEGFR2* and its co-receptor, *NRP-1*. Strong *NRP-1* expression was observed in 73.4% (69/94) of specimens investigated compared with only 14.9% (14/94) with *VEGFR2* expression.

Conclusions: Loss of *LKB1/AMPK* expression appears to occur in approximately 50% of endometrial cancer cases. Consequently, *LKB1* status of endometrial cancer tumors could potentially serve as a reliable biomarker to stratify patients who may benefit from targeted metabolic drugs, such as metformin. Aberrant *NRP-1* expression may provide an additional target.

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303 - Poster Session A

Radioimmunotherapy targeting human papillomavirus E7 oncoprotein demonstrates therapeutic potential and limited toxicity

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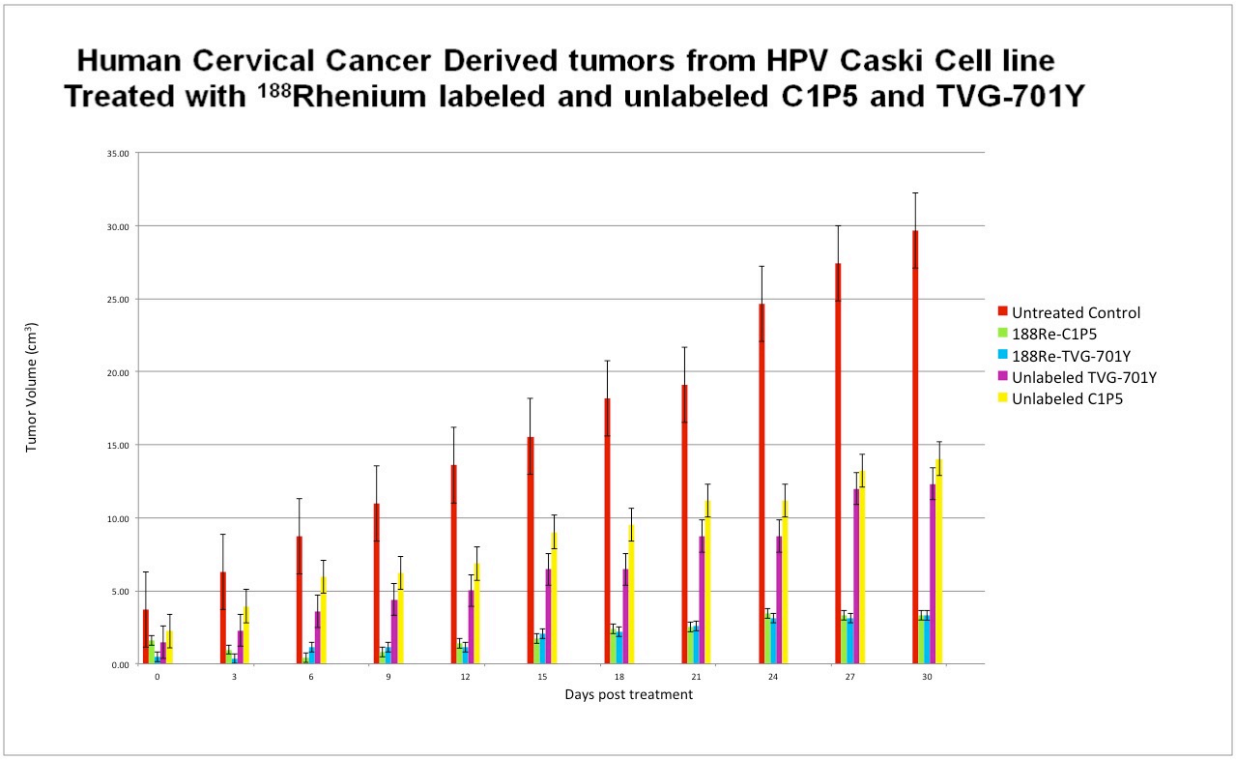
Objectives: To determine the effect and relative toxicity of radioimmunotherapy (RIT) using ^{188}Rhenium-labeled E7 monoclonal antibody (^{188}Re-TVG-701Y) compared to the published efficacy of ^{188}Rhenium-labeled E6 monoclonal antibody (^{188}Re-C1P5) in a human cervical cancer tumor model.

Methods: CasKi human cervical cancer cells expressing both E6 and E7 oncoproteins, were implanted on the flank of balb/c nu/nu mice and allowed to grow to tumor size of 3 to 5 mm. The mice were randomized to five treatment groups: untreated controls,^{188}Re-C1P5, ^{188}Re-TVG-701Y (300 µCi of^{188}Re), unlabeled TVG-701Y, and unlabeled-C1P6. Therapy was administered as a single intraperitoneal injection. Tumors were measured in three dimensions over a 30-day observation period, during which time weekly blood draws were performed and white blood cell and platelets counted. After 30 days, 13 tumor samples were fixed, embedded, and stained for E6 and E7 oncoproteins and evaluated for the presence, proportion, and intensity of uptake compared to the untreated controls.

Results: Tumor growth inhibition was noted in all treatment groups compared to untreated controls. The most significant effect was noted in those mice treated with RIT: ^{188}Re-C1P5 and^{188}Re-TVG-701. It should be noted that unlabeled antibodies also mediated an effect with respect to untreated controls, which is an important addition to the therapeutic profile. Treatment with both radiolabeled and unlabeled antibody resulted in a qualitative decrease in the staining of the target E6 or

E7 antigen when compared to the untreated group. There was no significant trend in the development of neutropenia or thrombocytopenia in any of the treated groups.

Conclusions: We have demonstrated for the first time that RIT against E7 decreases the expression of E6 and E7 oncoproteins. It inhibits tumor growth and the tumorgenicity of human papillomavirus. RIT specifically targeting viral oncoprotein may offer a novel targeted therapy for the treatment of cervical cancer with limited toxicity to the bone marrow.



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304 - Poster Session A

ALDH1A1 maintains ovarian cancer stem-like cells' properties by regulating *KLF4/p21*-mediated signaling cascade

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Objectives: The cancer stem cell (CSC) theory of chemoresistance proposes that the proportion of CSCs correlate to enhanced chemoresistance and early disease recurrence. Therefore, novel therapeutics aimed at the innate molecular pathways responsible for this resistance would be paramount to overcoming platinum resistance in ovarian cancer.

Methods: In addition to ALDEFLUOR functional cell sorting, ALDH shRNA knockdown models were established to evaluate the role of aldehyde dehydrogenase (ALDH) in ovarian cancer stem cell-like property and platinum resistance in various ovarian cancer cell lines and primary ovarian cancer tissue models.

Results: ALDH+ cells displayed stem cell-like characteristics of invasive phenotype, increased clonogenic potential, and a threefold overexpression of transcription factor KLF4. Likewise, ascites from advanced-stage ovarian cancer patients exhibited significantly higher levels of ALDH activity compared to their benign counterparts ($P< 0.01$). Correspondingly, patients with the ascites of ALDH high-yielding cell population demonstrated significantly lower progression-free survival compared to those yielding ALDH low-yielding cell population (3 months vs 9 months, $P=0.003$). Isotype specific knockdown of *ALDH1A1* significantly attenuated clonogenic potential of A2780/CP70 platinum-resistant cells and sensitized them to carboplatin. Further biochemical analysis in *ALDH1A1* knockdown cells revealed significantly fivefold lower levels of *KLF4* and *p21* and fourfold upregulation of pro-apoptotic *BAX* contributing to cell-cycle arrest in G2 phase and ultimately leading to apoptotic cell death. Additionally, we observed the induction of DNA repair protein poly ADP ribose polymerase (PARP) in carboplatin-treated cells, implicating its role in repair of single-strand breaks generated during the process of platinum-DNA adducts contributing to platinum resistance. Notably, about a twofold reduction ($P= 0.012$) in PARP levels was observed in *ALDH1A1* knockdown cells, leading to increased DNA damage and restoring platinum sensitivity.

Conclusions: Our data supports an *ALDH1A1*-mediated platinum resistance mechanism in ovarian cancer via a *KLF4/p21*-mediated cell cycle arrest and enhanced PARP-mediated single-strand DNA repair. Based on these results, targeted inhibition of this pathway warrants further study.

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305 - Poster Session A

A Hedgehog pathway smoothened inhibitor demonstrates synergy with carboplatin in ovarian cancer via a dual process of receptor enrichment plus regulation of DNA damage processing

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[1]University of South Alabama Mitchell Cancer Institute, Mobile, AL, [2]University of South Alabama, Mobile, AL, [3]University of Alabama at Birmingham, Birmingham, AL

Objectives: Inhibitors of Hedgehog (Hh) signaling at the level of Gli transcription factors are known to regulate DNA damage response and repair genes. This interaction potentially could play an important role in tumor response to platinum drugs. Our objective was to determine if the combination of a novel smoothened inhibitor (SMOi) with carboplatin could be effective for ovarian cancer treatment.

Methods: A novel SMOi (BMS-833923) was evaluated in combination with carboplatin in numerous ovarian cancer cell lines by MTS cell survival assays and Calcusyn software for calculating statistical synergy by Combination Index (CI). DNA damage response and repair genes were assessed based on Hh mediator status using a pharmacologic inhibitor of SMO.

Results: Significant cell death (92%) was demonstrated with the combination of SMOi + carboplatin with median inhibition concentration doses of each agent in numerous ovarian cancer cell lines. Calcusyn calculations determined that multiple dose combinations resulted in synergy with a CI range of 0.3 to 0.49 (synergy defined as CI <1). This synergy was enhanced fivefold with sequential therapy of priming the cells with carboplatin, followed by SMOi. Evaluation of potential etiologies of sequential therapy revealed a dose-dependent carboplatin-induced upregulation of the Hh ligand, SHH, and a decrease in Gli1. Upregulation of SHH led to enrichment of the SMO receptor on cancer cell surface primary cilia, thereby enhancing SMO inhibition. Additionally, SMO inhibition negatively regulated many genes involved in platinum-induced DNA damage processing.

Conclusions: The combination of a novel SMO inhibitor + carboplatin demonstrated synergy in ovarian cancer treatment. Sequential therapy of carboplatin then SMOi enhanced this efficacy via a dual process of SHH-regulated enrichment of SMO receptors to primary cancer cell cilia combined with a negative regulation of DNA damage processing.

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306 - Poster Session A

Pharmacologic inhibition of polo-like kinase 1 enhances paclitaxel-based cell killing in taxol-resistant ovarian cancer cells

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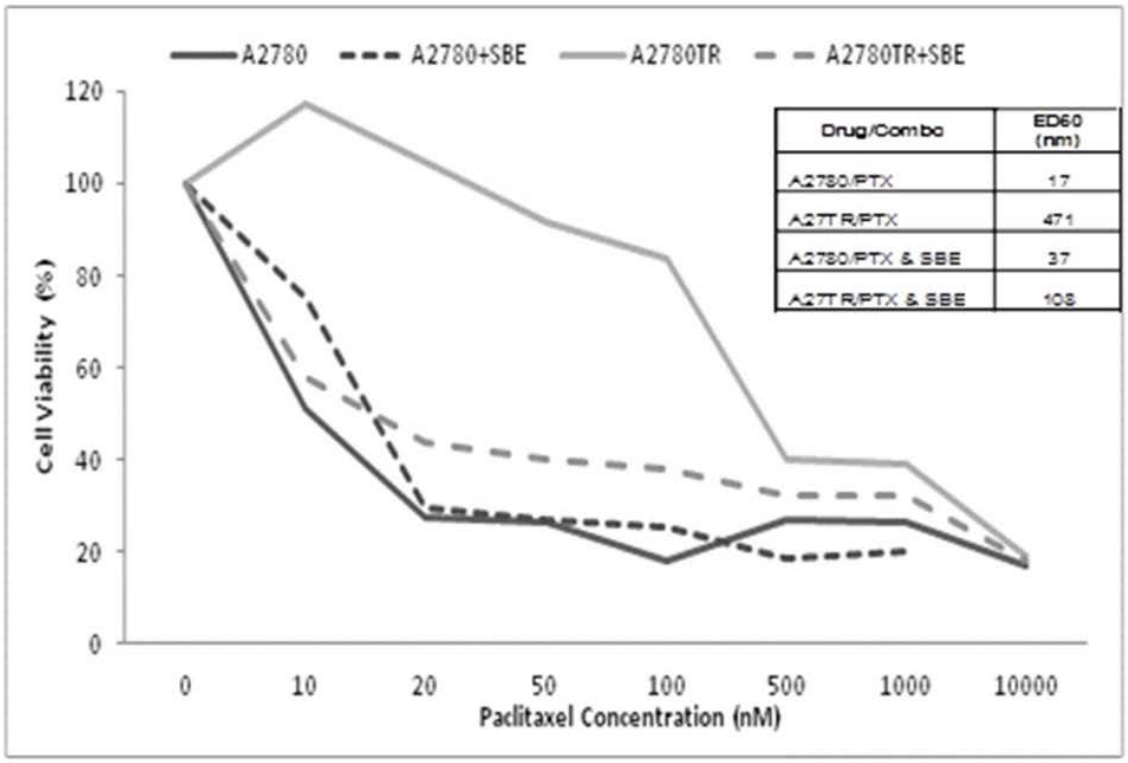
Objectives: Platinum- and taxol-based chemotherapy is the hallmark of treatment for most ovarian cancer patients, but many develop chemoresistance. Although previous analyses of taxol resistance have implicated altered tubulin and P-glycoprotein, translation into clinical practice has been limited. This investigation aimed to redress these limitations through unbiased proteomics to identify novel molecular mechanisms that contribute to taxol resistance.

Methods: A2780 ovarian cancer cells were exposed to increasing paclitaxel concentrations and a resistant phenotype, A2780TR, was achieved. Protein isolates were analyzed by mass spectrometry (MS)-based proteomics. Wilcoxon non-parametric testing was used to identify significantly differential abundant proteins from spectral count-based protein abundance measures. Immunoblotting was used to selectively monitor protein and posttranslational modification abundances. The impact of cotreatment of cells with paclitaxel and multiple pharmacologic polo-like kinase 1 (PlK1) inhibitors, including SBE13 and BI2536, was determined by cell proliferation assays.

Results: The taxol-resistant A2780TR cell line was 50-fold more resistant to taxol than the A2780 parent line. MS-based proteomics identified significantly elevated levels of *Plk1* in A2780TR compared to A2780 ($P=3.9 \times 10^{-7}$), which was validated in biological replicates by immunoblot analyses. Selective pharmacologic inhibition of *Plk1* by SBE13 (Figure 1) and BI2536 (data not shown) resulted in significantly enhanced paclitaxel-mediated cell killing in taxol-resistant ovarian cancer cells.

Conclusions: *Plk1* is overexpressed in taxol-resistant ovarian cancer cells. Treatment of A2780TR cells with Plk1 inhibitors increased their sensitivity to paclitaxel. Although several Plk1 inhibitors have been previously assessed as monotherapy in clinical trials, we hypothesize that *Plk1* inhibition in combination with paclitaxel may be a novel therapeutic option in taxol-resistant patients.

Fig 1: Selective pharmacologic inhibition of Plk1 with SBE13 significantly enhances taxol-based cell killing in taxol-resistant ovarian cancer cells.



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307 - Poster Session A

Establishment and combined genomic and proteomic characterization of patient-derived ovarian cancer cell lines

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Objectives: The majority of currently used ovarian cancer (OvCa) cell lines lack molecular resemblance to the OvCa tissues from which they were derived, therefore representing poor research models. Establishment of more accurate OvCa cell lines is an immediate and urgent need in basic research and is a requisite step in achieving personalized cancer treatment. Our objective was to define the efficacy and efficiency of a recently described novel technique for immortalizing tumors cells from patient-derived tissue. This method has not been previously evaluated in OvCa, and our study is the first to combine genetics and proteomics to establish the molecular profile of these patient-derived ovarian cell lines (PDOvCaCL).

Methods: Cells were harvested from surgical tumor samples and propagated in specially prepared medium containing Rho kinase inhibitor and layered onto irradiated murine feeder cells. Passaged cell lines were then compared to the original tumor using microscopy, karyotype analysis, quantitative real-time polymerase chain reaction (qRT-PCR), Western blot, whole-exome (WES) and whole-transcriptome (RNA-Seq) sequencing, and proteomic analysis.

Results: We have propagated >40 unique PDOvCaCL from tumors representing major OvCa histologies (i.e. serous, clear cell, malignant mixed Müllerian tumor, borderline, and granulosa cell. A representative number of these cell lines have been propagated in excess of 30 passages. Cell lines were successfully harvested from >50% of attempted tumors. Microscopic examination, qRT-PCR, and Western blot analysis demonstrated that all cell lines derived from epithelial tumors retained their epithelial characteristics and markers. Proteomic analysis indicated that <5% of the total proteins measured demonstrated notable quantitative differences between the PDOvCaCL and their respective tumor samples. WES and RNA-Seq analysis is currently underway.

Conclusions: We have successfully established multiple cell lines using this protocol and have shown that these patient-derived cell lines remain epithelial in nature, with a proteomic expression closely resembling the original tumor. In the future, evaluation with regard to WES and RNA-Seq will be added to this analysis for the purpose of fully establishing the molecular profile of these cell lines.

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308 - Poster Session A

Initial investigation of combined single-photon emission computed tomography (SPECT) and magnetic resonance (MR) imaging of a human ovarian tumor xenograft using ^{123}I-bevacizumab

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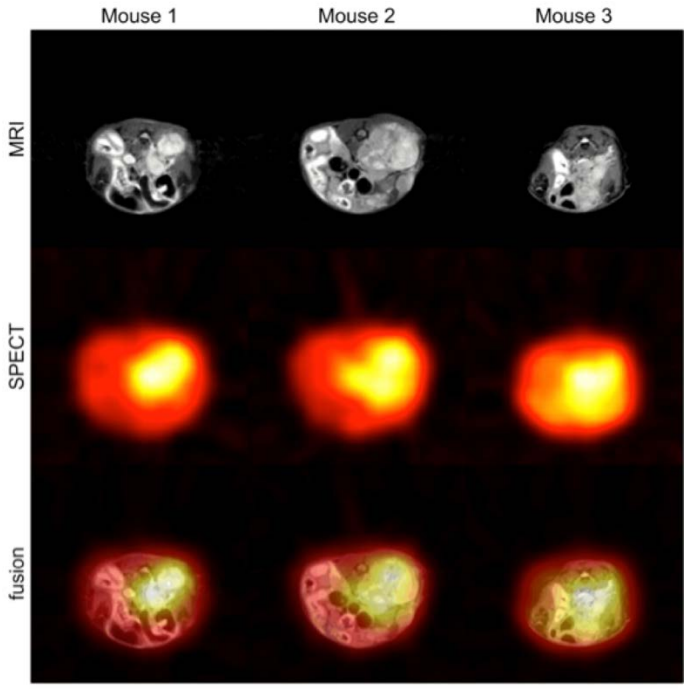
Objectives: To determine the feasibility of detecting ^{123}I-labeled bevacizumab by nuclear SPECT and anatomic MRI in an ovarian cancer mouse model.

Methods: SKOV3ip1 cells were injected via the intraperitoneal route into female NCr nude mice ($1.5x10^6$ million cells/200 uL), and 7T-MRI was performed weekly under ketamine anesthesia until measurable tumors (5 to 10 mm) were detected. A combination of 1 mg bevacizumab/2 mCi sodium ^{123}I in solution was mixed over iodination beads. Mice were injected with 1 mCi of ^{123}I-bevacizumab. Combined SPECT, employing a nuclear radiation detector consisting of 50.8×50.8×5 mm of cadmium-zinc-telluride (CZT) crystal with electronic readout and MRI was performed at 12, 24, 36, and 48 hours after injection.

Results: Measurable tumors were detected at 5 to 6 weeks postinjection, and all animals developed ascites. MR images were optimal when acquired using a two-dimensional fat-suppressed spin-echo pulse sequence with the following parameters: repetition time (TR) = 3.5 s, echo time (TE) = 30 ms, field of view = 40×40 mm, matrix = 256×256, slice thickness = 1 mm, number of averages = 2. ^{123}I-bevacizumab localized to measurable peritoneal tumors in the three mice that were imaged (Figure 1). The optimal uptake time was 24 hours postinjection. Fifteen mice died following either administration of ketamine or injection of ^{123}I-bevacizumab. All had ascites and intravascular volume depletion determined by tail vein collapse, and all had extensive miliary carcinomatosis at necroscopy.

Conclusions: Detection of radiolabeled bevacizumab was feasible by SPECT imaging. This specific animal model was suboptimal for preclinical development due to miliary distribution of nonmeasurable tumors and moribund condition of animals when tumors were measurable. We are now employing a larger animal (RNU rat) and larger tumors (HeyA8) for further development.



309 - Poster Session A

Identification of microscopic ovarian tumor foci utilizing a novel imaging device in a murine ovarian cancer model: an opportunity to improve optimal cytoreduction

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Objectives: In patients with advanced ovarian cancer, resection of all gross residual disease is associated with a significant improvement in survival. Disease remaining either as infiltrative or microscopic tumor deposits is a challenge to identify. Detection of this disease during cytoreductive surgery may lead to a more thorough reduction of cancer burden. We evaluated the performance of a fluorescent molecular imaging agent, LUM015 (Lumicell, Wellesley, MA), which is activated by cathepsin enzymes in the tumor, and a wide field-of-view imaging device (Lumicell) to detect sub-millimeter residual cancer clusters in an mouse model for ovarian cancer.

Methods: Orthotopic ovarian cancer mouse models were generated with ovarian cancer cell lines CP70 and SKOV3 (n=10). Tumor growth was followed by luciferase imaging until full abdominal spread had occurred. Once the tumor disseminated, the imaging agent LUM015 (3.52 mg/kg) was injected. Mice were euthanized and tumor debulking performed. After debulking, the abdominal wall was dissected in four quadrants, organs were harvested, and all were imaged with the LUM device. Features exhibiting high fluorescence were marked and dissected, prepared into slides for pathologic correlation with LUM015 fluorescence imaging.

Results: In 36 tissues from orthotopic ovarian cancer mouse models, the imaging system detected tumor. The imaging system detected sub-millimeter cancer cell clusters that could not be identified with visual inspection. In parallel, the imaging system is being evaluated in a phase I clinical trial in sarcoma and breast cancer patients. Five patients have been injected with LUM015 and completed the trial with no adverse events observed. Postoperative examination of the tissue using the LUM imaging device shows excellent correlation between fluorescence signal and pathology identification of tumor.

Conclusions: With a cathepsin-activated fluorescence imaging molecule (LUM015) and a wide field-of-view imaging device, we detected microscopic residual ovarian cancer tumors in orthotopic xenograft models after debulking grossly with high sensitivity. Translation of this imaging technology into the clinical setting may help surgeons detect microscopic or infiltrative residual tumor during the debulking procedures in patients with advanced ovarian cancer.

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310 - Poster Session A

An analysis of current treatment practice in uterine papillary serous and clear cell carcinoma at two high-volume cancer centers

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Objectives: Despite the rarity of uterine papillary serous (UPSC) and clear cell carcinoma (CCC), they contribute disproportionately to endometrial cancer death. Sufficient clinical information regarding treatment and prognosis is lacking. The aim of this study was to evaluate treatment outcomes in a rare cancer cohort based on the experience at two tertiary care cancer centers.

Methods: Clinicopathologic data were retrospectively collected on 279 patients with UPSC and CCC treated between 1995 and 2011. All patients with papillary serous and clear cell histology who underwent surgical staging were included. Kaplan-Meier survival estimates were calculated using STATA 11.0.

Results: Initial staging documented stage I in 40.9% of patients and stages III and IV in 52.3% of patients. Median follow-up was 31 months (range, 1-194 months). Tumor histology was pure papillary serous in 139 patients (49.8%), and 77 patients (27.6%) had tumors with pure clear cell histology. Optimal debulking was achieved in 92.1% of patients. Overall (OS) and progression-free survival (PFS) at 5 years were 63.2% and 51.9%, respectively. OS by stage was as follows: stage I=76.7%, stage II=68.0%, stage III=54.6%, and stage IV=41.7%. OS and PFS were not affected by mode of surgery (open vs robotic approach: OS HR 0.68, 95% CI 0.28-1.62; PFS HR 0.78, 95% CI 0.40-1.56). Adjuvant treatment was associated with improved OS in stages IB-II (HR 0.14, 95% CI 0.02-0.78, P=0.026) but did not affect survival in stage IA disease. The performance of a periaortic lymph node dissection was associated with improved PFS in stage III disease (HR 0.39, 95% CI

0.15-0.98, *P*=0.044), but not in stages I-II disease. There was a trend toward improved OS in stage III patients who underwent complete periaortic lymph node dissection, but this did not reach statistical significance.

Conclusions: Survival in UPSC and CCC is diminished in comparison to the more common endometrioid carcinomas. Minimally invasive surgical staging appears a reasonable strategy for patients with non-bulky disease and was not associated with diminished survival. Adjuvant treatment improved 5-year survival in stages IB-II disease but did not affect outcome in stage IA disease. The therapeutic role of periaortic lymph node dissection in this patient cohort remains unclear.

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311 - Poster Session A

Incidence of ovarian metastases in uterine leiomyosarcoma and optimal surgery

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Objectives: Uterine leiomyosarcoma (LMS) is a rare malignant tumor. The primary method of treatment for LMS is surgery. The efficacy of chemotherapy and radiotherapy is questionable. The aim of our study was to establish the incidence of ovarian metastases and the optimal extent of surgery for uterine leiomyosarcoma in patients of different ages.

Methods: A retrospective chart review involved 198 patients with LMS treated at the N.N. Blokhin Russian Cancer Research Center, Moscow, Russia, from 1970 to 2010. Patients with LMS had a median age at diagnosis of 48 (16±0.7) years. Surgical treatment alone was performed in 126 patients (63.6%). Combined treatment of either surgery+postoperative chemotherapy or surgery+radiotherapy was performed in 60 patients (30.3%). Complex treatment (surgery+chemotherapy+radiotherapy) was performed in 13 (6.5%) patients.

Results: We observed an association between ovarian preservation and improved survival: overall 5-year survival in patients with ovarian preservation and those who underwent oophorectomy was 87.3±8.4% and 49.0±5.3%, respectively (*P*<0.05). We did not observe ovarian metastases in any of 198 patients included in this study. Furthermore, the frequency of distant metastases in radically treated patients was 22.2% higher in patients with ovaries removed compared to patients with ovarian preservation during the primary surgery (59.7% and 37.5%, respectively) (*P*<0.05).

Conclusions: According to our data, the optimal surgery for LMS is total abdominal hysterectomy in women of reproductive age and total abdominal hysterectomy with bilateral salpingo-oophorectomy in postmenopausal women.

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312 - Poster Session A

Prognostic factors and outcomes in endometrial stromal sarcoma with the 2009 FIGO staging system: a multicenter review of 114 cases

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Objectives: To assess prognostic factors associated with disease-related survival in endometrial stromal sarcoma (ESS) using the 2009 FIGO staging system.

Methods: From January 1990 to January 2012, 114 patients with ESS were identified at the Samsung and Asan Medical Center and data were retrospectively analyzed.

Results: Ten (8.7%) patients died of the disease and 33 (28.9%) patients relapsed. The 5- and 10-year overall survival (OS) rates for the entire cohort were 92.6% and 87.1%, respectively, and the 5- and 10-year recurrence-free survival (RFS) rates were 71.8% and 52.1%, respectively. The estimated median survival after recurrence for the 33 patients who relapsed was 133 months (95% CI, 7.7–258.4) and 5-year survival after recurrence was 68.9%. Stage I disease (*P*=0.006), estrogen and/or progesterone receptor (ER/PR) positivity (*P*=0.0027), and no nodal metastasis (*P*=0.033) were associated with a good prognosis for OS in the univariate analysis. Ovarian preservation was an independent predictor for poorer RFS (HR 6.5, 95% CI 1.23–34.19, *P*=0.027). Positivity for ER/PR (HR 0.05, 95% CI 0.006–0.4, *P*=0.006) and cytoreductive resection of recurrent lesions (HR 0.14, 95% CI 0.02–0.93, *P*=0.042) were independent predictors of better survival after recurrence.

Conclusions: Disease stage, expression of ER/PR, and nodal metastasis were significantly associated with OS in ESS. Bilateral salpingo-oophorectomy as the primary treatment and cytoreductive resection of recurrent lesions should be considered for improving survival of patients with ESS.

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313 - Poster Session A

Is rad/let/met more than just a catchy name? A preclinical evaluation of everolimus, letrozole, and metformin in recurrent endometrial cancer

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Objectives: A phase II clinical trial of everolimus (E) and letrozole (L) in patients with recurrent endometrial cancer (EC) showed an objective response rate (ORR) of 31% and a clinical benefit rate (CBR) of 49%. Interestingly, patients on metformin (M) had an ORR of 44.4% and a CBR of 77.8%. Previous studies in breast cancer have shown cross-talk between the PI3K and estrogen receptor (ER) pathways, with non-genomic activation of ER by S6 kinase 1. In addition, our laboratory has previously shown that M promotes mislocalization of *KRas* and is growth inhibitory in EC harboring *KRas* mutations. Our objectives were to evaluate the addition of M to E and L in cells harboring *PTEN* loss and *KRas* mutations and to evaluate cross-talk between the PI3K and ER pathways in vivo.

Methods: Following bilateral oophorectomy, 80 female nude mice were injected intraperitoneally with Ishikawa (*PTEN* null) cells. Mice were divided into eight treatment groups (n=10/group): control, M alone, L alone, E alone, M+L, M+E, E+L, and M+E+L. Gross tumor weight was used as a marker of treatment effect, and mouse weight and serum alanine aminotransferase (ALT) were used as markers of therapeutic toxicity. Tumor cell proliferation was quantified by immunohistochemical (IHC) staining for *Ki67*. Phospho-S6rp (pS6rp) IHC was used to evaluate *PI3K* signaling.

Results: Animals treated with E alone (0.205, P=0.006), M+E (0.229, P=0.013), E+L (0.074, P=0.0004), and M+E+L (0.223, P=0.016) had significantly lower tumor weights compared to control mice (0.661), with the greatest effect seen in E+L-treated mice. There were no differences in tumor weight seen in the remaining treatment groups (Figure 1). There were no differences in mouse weight or serum ALT between any treatment groups. Animals treated with E+L (0.43, P=0.043) had significantly lower cellular proliferation compared to controls (0.58). Animals treated with E alone (3.89, P=0.002) and E+L (2.56, P=0.0001) had decreased expression of *pS6rp* on IHC compared to controls (7), with the largest decrease in expression seen with the combination of E+L.

Conclusions: E and L in combination had the greatest effect on tumor weight and downregulation of *pS6rp* signaling in *PTEN* null, *KRas* wild-type tumors. Further studies are ongoing in *KRas* mutant xenografts to evaluate the addition of M and characterize the effect of E and L in decreasing nongenomic ER activity.

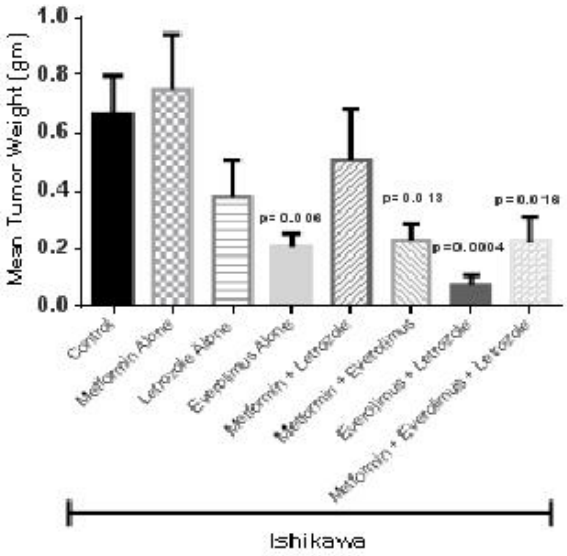

Figure 1. Mean mouse tumor weight in grams by treatment group.

314 - Poster Session A

Defining optimal combinations of PI3K/Akt/mTOR and Ras/Raf/MAPK pathway inhibitors for use in endometrial cancer

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Objectives: The PI3K/Akt/mTOR and Ras/Raf/MAPK signaling network are activated in endometrial cancer (EC) via multiple mechanisms. Many agents have been developed to target different components, yet single-agent therapy, particularly with rapalog, has yielded underwhelming clinical results. Complex feedback mechanisms may contribute to lack of response. Thus, we assessed the efficacy of different PI3K pathway inhibitors in combination with MEK inhibitor (MEK-i) in EC cell lines.

Methods: Combinations of MEK-i with various PI3K pathway inhibitors, namely rapalog, mTORC1/2 inhibitor (mTORC1/2-i), Akt inhibitor (Akt-i), pan-PI3K inhibitor (PI3K-i), and p110β-specific inhibitor (p110β-i), were evaluated in EC cell lines. Biological efficacy was determined from proliferation assays, drug interaction analyses, immunoblot profiles to identify predictive biomarkers, cell fate studies, and epithelial-to-mesenchymal transition (EMT) gene expression.

Results: Combining various PI3K pathway inhibitors with MEK-i resulted in additive/synergistic interactions across all EC cell lines. Cells that were resistant to single agents demonstrated the most profound synergy, the mechanism of which may relate to the finding that PI3K pathway inhibition in these cells induced *ERK* phosphorylation that was mitigated when combined with MEK-i. Except for one cell line that underwent drug-induced cell death, synergy was associated with suppression of proliferation, as determined by cyclin expression and flow cytometry. Akt-i/MEK-i and p110β-i /MEK-i combinations had the weakest efficacy. mTOR-i/MEK-i and PI3K-i/MEK-i combinations suppressed mesenchymal gene expression and increased levels of epithelial marker E-cadherin. Protein expression profiles showed phospho-Akt levels were variably suppressed by different agents and not reflective of single-agent or combined efficacy. Dephosphorylation of S6 ribosomal protein was highly predictive of combined drug efficacy.

Conclusions: These data support therapeutic strategies for EC that target both axes of the PI3K/MAPK signaling network. Dual targeting of MEK-i with either mTORC1/2-i or PI3K-i was the most promising approach in terms of ability to suppress cell proliferation and reverse mesenchymal-like gene expression signatures.

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315 - Poster Session A

Effective endometrial cancer screening method using liquid-based cytology

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Objectives: Endometrial carcinoma is one of the most common malignancies in the female genital tract in developed countries. Recommendations regarding screening for endometrial cancer have long been controversial in many countries. For example, transvaginal ultrasonographic examination of the uterus is too expensive and endometrial biopsy (EB) is invasive and painful. In Japan, endometrial cytology has been applied as one of important screening method in endometrial cancer, but the present endometrial cytology (conventional cytology [CC]) has some problems, which are high inadequate slides rate, low sensitivity, and low specificity. Therefore, we have attempted to develop new endometrial cytology using liquid-based cytology (LBC). This study sought to determine whether LBC can overcome some problems of EB or CC.

Methods: For this study, 641 endometrial cytologic specimens were collected directly by using brush (Honest Brush Super). Two samples (LBC and CC) in 641 patients were made and EB in 47 of 641 also was performed within 3 weeks. The diagnoses were made by a pathologist and three cytopathologists. We compared three methods (LBC, CC, EB) for inadequate rate, sensitivity and specificity.

Results: LBC (7.2%) was significantly lower in inadequate rate than CC (17.6%) and EB (14.9%). LBC had much better effect than CC for patients aged 20 to 69 years. The sensitivity of LBC was 84.0% and CC was 84.0%. The specificity of LBC was 73.0% and CC was 67.6%. Sensitivity and specificity for the two methods did not have statistically significant differences.

Conclusions: LBC could overcome high inadequate rate and showed high quality diagnostic results. This study suggested the possibility of using LBC as screening method in endometrial cancer, which will be evaluated in the future.

316 - Poster Session A

A comparison of colorimetric versus fluorometric sentinel lymph node mapping during robotic surgery for endometrial cancer

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Objectives: Near-infrared imaging with indocyanine green (ICG) has been proposed as an improved method to detect sentinel lymph nodes (SLN) in patients undergoing primary surgery for endometrial cancer (EC). Our objective was to compare the ability to detect SLNs using fluorometric imaging with ICG versus colorimetric imaging with isosulfan blue (ISB) in women undergoing robotically assisted total laparoscopic hysterectomy (RA-TLH) for EC or complex atypical hyperplasia (CAH).

Methods: All patients underwent SLN mapping during RA-TLH for EC or CAH between 2012 and 2013. Four milliliters of either ISB (10 mg/mL) or ICG (1.25 mg/mL) were injected into the cervical stroma (1 mL deep and 1 mL superficial, at 3 and 9 o'clock) immediately prior to placement of a uterine manipulator. Retroperitoneal spaces were dissected for either direct visualization of ISB or fluorometric imaging to assess for ICG. SLNs were removed for permanent analysis with hematoxylin and eosin stain. Completion lymphadenectomy was performed according to institutional protocols. The ability to detect SLNs in bilateral pelvic sidewalls was compared for ICG vs ISB using the chi-square test.

Results: SLN mapping was performed in 33 patients during RA-TLH for either EC (30) or CAH (3). SLNs were identified bilaterally (55%), unilaterally (27%), or neither (18%). SLNs were identified in 45 of 66 hemipelvises (68%). The mean number of SLNs retrieved per hemipelvis was 2.0 (range, 1-5). SLNs were identified in the hypogastric (87%), external iliac (13%), and common iliac chains (2%). Of 18 patients undergoing ICG mapping, 13 (72%) mapped bilaterally compared to 5 of 15 (33%) patients undergoing ISB mapping (P=0.04). Of 18 patients undergoing ICG mapping, 29 of 36 (81%) hemipelvises mapped compared to 16 of 30 (53%) hemipelvises of 15 patients undergoing ISB mapping (P=0.03). Thirteen patients underwent staging lymphadenectomy and only one had positive non-SLNs; however, a positive SLN was identified in the same hemipelvis. No false-negative results were noted.

Conclusions: SLN mapping techniques can be used to delineate uterine lymphatic drainage in most patients undergoing RA-TLH for EC. Fluorescence imaging with ICG appears to be superior to colorimetric imaging with ISB in patients undergoing SLN mapping for EC. A prospective multi-institutional trial to establish the false-negative rate of SLN mapping for EC is warranted.

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317 - Poster Session A

Survival impact of cytoreduction to microscopic disease for advanced-stage cancer of the uterine corpus

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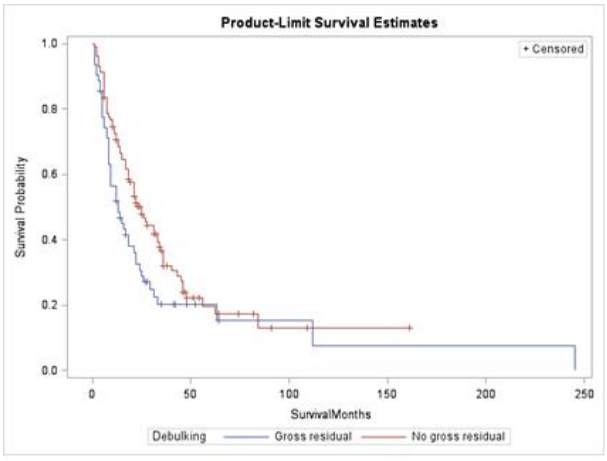
Objectives: To assess the impact of cytoreduction to no gross residual disease (RD) on overall survival (OS) in patients with stage III-IV uterine carcinosarcoma (MMMT), papillary serous/clear cell (UPSC/CC), and endometrioid carcinoma (EC).

Methods: We retrospectively identified 168 patients who underwent primary surgery for advanced uterine cancer between 1984 and 2009 in two teaching hospitals in Brooklyn, New York. Histology, stage, grade, RD, adjuvant therapy, age, race, and OS were collected. OS was calculated using the Kaplan–Meier method. Predictive factors were compared using the log rank test and Cox regression analysis.

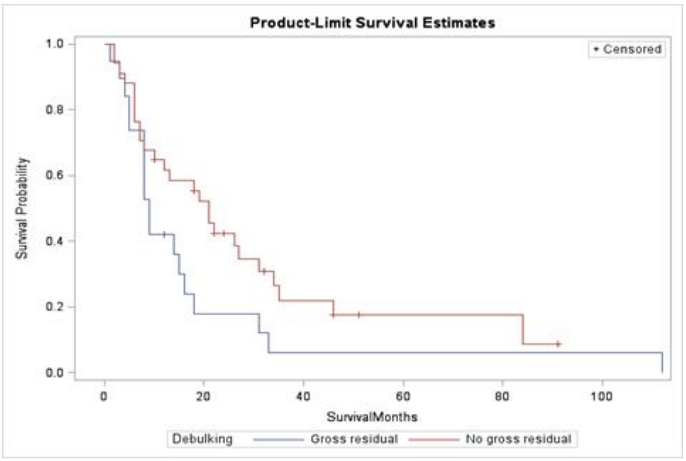
Results: The cohort included 54 patients with MMMT (stage III, n=31; stage IV, n=23), 54 patients with UPSC/CC (stage III, n=20; stage IV, n=34), and 60 patients with EC (stage III, n= 45; stage IV, n=15). Complete gross resection was achieved in 64% of patients with MMMT, in 53% of patients with UPSC/CC, and in 68% of patients with EC. There was no interaction between pathology type and feasibility of complete cytoreduction (P=0.390). No gross RD was associated with a median OS of 25 months (95% CI 18, 33) vs 13 months (95% CI 8, 18) in patients with gross RD (P=0.037). Within each pathology type, the absence of gross RD was associated with a trend for improved survival. OS was 21 months (95% CI 8, 31) for patients with MMMT when complete gross resection was achieved vs 9 months (95% CI 5, 16) for those with gross RD. OS was 22 months (95% CI 11, 31) for patients with UPSC/CC and no gross RD compared to 12 months (95% CI 6, 22) for patients with gross RD. Lastly, for patients with EC, OS was 36 months (95% CI 17, 46) if no gross RD vs 21 months (95% CI 9, 63) for patients with gross RD. Comparisons within each histologic type did not reach P<0.05. On multivariate

analysis, predictors of increased mortality were gross RD (HR 2.0 during first year postsurgery; 95% CI 1.1, 3.7; P=0.019), stage IV disease (HR 1.8; 95% CI 1.1, 3.1; *P*=0.025), and age (HR 1.04 per year of age; 95% CI 1.02, 1.07; *P*=0.002).

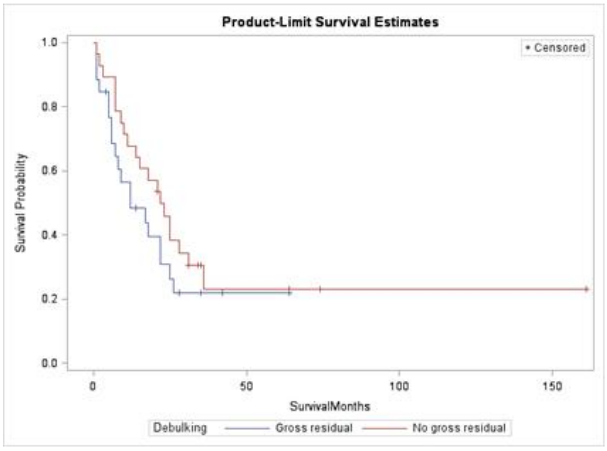
Conclusions: Cytoreductive surgery to no gross RD was associated with improved OS in advanced uterine cancer. This effect was uniform among histologies. There was no interaction between pathology type and feasibility of complete cytoreduction.



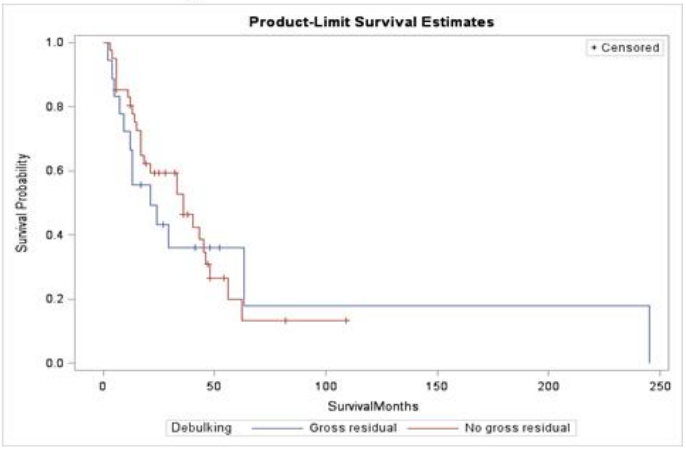
1A- All histologies, *p=0.037*



1B-Carcinosarcoma, *p=0.081*



1C-Serous/Clear cell, *p=0.281*



1D-Endometrioid, *p=0.766*

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318 - Poster Session A

Successful identification of high-risk grade 1 endometrial cancer utilizing MRI, CA-125 and BMI before surgery: a prospective quality improvement initiative

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Objectives: Accurate preoperative prediction of those patients with grade 1 endometrial cancer who would benefit from systematic lymphadenectomy would facilitate preoperative planning and surgical efficiency. We, therefore, adopted a quality improvement protocol to identify high-risk patients with preoperative magnetic resonance imaging (MRI), CA-125, and body mass index (BMI). The primary objective of this study was to evaluate the predictive value of our protocol in identifying patients with high-risk uterine features on final pathology.

Methods: In February 2012, we implemented a protocol whereby patients with grade 1 endometrial cancer, BMI <45, CA-125 >30 U/mL, or any of several MRI features (tumor volume of >36 mm^2, >50% myometrial invasion, cervical or adnexal metastasis, pelvic lymphadenopathy) underwent a systematic lymphadenectomy at the time of surgery. Patients with BMI >45 were treated outside this protocol. Institutional review board approval was obtained to analyze sensitivity, specificity,

and positive and negative predictive values to predict the presence of high-risk uterine features on final pathology. These were defined as: grade 2 or 3, >50% myometrial invasion, lymphovascular space invasion, and/or cervical or adnexal involvement.

Results: One hundred consecutive patients underwent the protocol over 15 months. Mean age was 59.6 years (range, 28-84 years) and BMI was 35.2 (range, 28.4-59.8). On final pathology, 25/100 (25%) had high-risk uterine factors, and 35/100 (35%) underwent systematic lymphadenectomy with the hysterectomy and bilateral salpingo-oophorectomy. The preoperative protocol had a false-negative rate of 4/100 (4%). Sensitivity, specificity, and positive and negative predictive values were 84%, 81.3%, 60%, and 93.9%, respectively. In the subset of patients ≥40 years of age and with a BMI >30, the false-negative rate was 1/66 (1.5%). Sensitivity, specificity, and positive and negative predictive values were 93.3%, 80.4%, 58.3%, and 97.6%, respectively (Table).

Conclusions: Applying this preoperative protocol with BMI, MRI, and CA-125 in patients with grade 1 endometrial cancer was highly predictive of the need for systematic lymphadenectomy. This protocol has the potential to improve surgical planning, utilization, and efficiency. It may also obviate the need for frozen section and decrease preoperative uncertainty.

Table

			Pre-operative protocol (MRI, CA125)					
Patients			Sensitivity	Specificity	Positive perdition value	Negative prediction value	Positive likelihood ratio	Negative likelihood ratio
All patients	N	100	84%	81.3%	60%	93.85% FN=4/100 (4%)	4.5 (2.27-7.49)	0.2 (0.08-0.49)
	Age	59.6 (28-84)						
	BMI	35.2 (28.4-59.8)						
Patient >40 years BMI>30	N	66	93.3%	80.4%	58.3%	97.6% FN= 1/66 (1.5%)	4.76 (2.69-8.43)	0.08 (0.01-0.55)
	Age	60.9 (42-84)						
	BMI	38.7 (30.4-59.8)						

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319 - Poster Session A

Extent of lymph node dissection and overall survival in patients with uterine carcinosarcoma, papillary serous, and endometrioid adenocarcinoma

I. Alagkiozidis[1], J. Jaffe[1], M. Lozano[1], B. Mize[1], C. Gorelick[2], G. M. Salame[1], O. Abulafia[1] and Y. C. Lee[1]
[1]SUNY-Downstate, Brooklyn, NY, [2]NY Methodist Hospital - Affiliate of Cornell Medical College, Brooklyn, NY

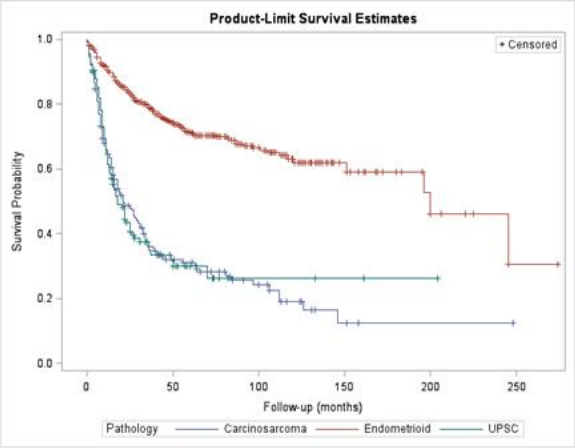
Objectives: To evaluate the interaction between extent of lymph node dissection (LND) and overall survival (OS) in patients with various histologic types of uterine cancer.

Methods: We retrospectively identified 834 patients who had primary surgery in our institution for uterine carcinosarcoma (MMMT), papillary serous (UPSC), or endometrioid carcinoma (EC) between 1984 and 2009. Stage, grade, total lymph node count (LNC), positive LNC, adjuvant therapy, age, race, and OS were collected. OS was calculated using the Kaplan–Meier method. Predictive factors were compared with the log rank test and Cox regression analysis.

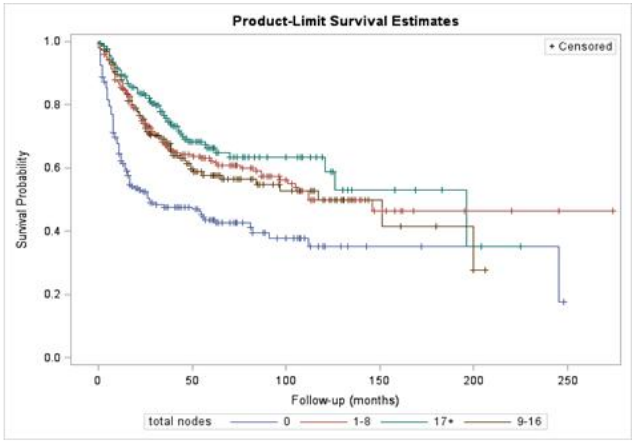
Results: The cohort included 158 patients with MMMT, 115 patients with UPSC, and 561 patients with EC. Of the cohort, 38% of the patients had stage III or IV disease. Median OS was 21 months for MMMT, 18 months for UPSC, and 200 months for patients with EC. LND was performed in 73% of patients with MMMT, 68% of patients with UPSC, and 79% of patients with EC. LND was performed in 82% of stage I-II and in 68% of stage III-IV cases. The median total LNC was 13 (range, 1-75), and there was no significant difference in the total LNC among the different histologies. In patients with stage III and IV

disease who had LND, the rate of positive LN was higher in UPSC (29%) and MMMT (19%) as compared to EC (15%) (P<0.01). In the group with positive LN, a moderately positive association between the total and positive LNC was present (Pearson coefficient 0.34, P<0.001). The cohort was divided in quartiles based on the total LNC and a Kaplan-Meier survival analysis was performed. A continuum of improved OS was noted in correlation with increased LNC. OS was 27 months for the group with 0 nodes, 112 months for the group with 1-8 nodes, 117 months for the group with 9-16 nodes, and 196 months for the group with >17 nodes. Doubling the total LNC was associated with a 28% risk of death reduction (HR 0.724, 95% CI 0.66-0.794, P<0.001) for the first year and 14% risk reduction (HR 0.858, CI 0.761-0.967, P=0.012) for the second year. This effect was independent of stage, histology, type of adjuvant treatment, age, and race.

Conclusions: In this cohort, the performance of LND was associated with improved OS. The extent of the LND was inversely correlated with the risk of death for the first 2 years. This effect appears to be uniform across pathology types.



1A. Survival by histology, p<0.001



1B. Survival by total LN count. The 0 nodes quartile differed from all others (p<0.001), the other quartiles did not differ significantly from one another (p>0.25)

Year of follow-up	HR	95% CI		p-value
1	0.724	0.660	0.794	<.001
2	0.858	0.761	0.967	0.012
3	0.970	0.814	1.156	0.736
4	1.285	0.985	1.677	0.064
5	0.868	0.646	1.165	0.346
6+	0.964	0.776	1.199	0.744

1C.Risk of death reduction associated with increasing(x2) LNC

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320 - Poster Session A

Analyzing the learning curve of robotic-assisted sentinel lymph node dissection for endometrial cancer

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Women's Cancer Center, Carol G Simon Cancer Center, Morristown, NJ

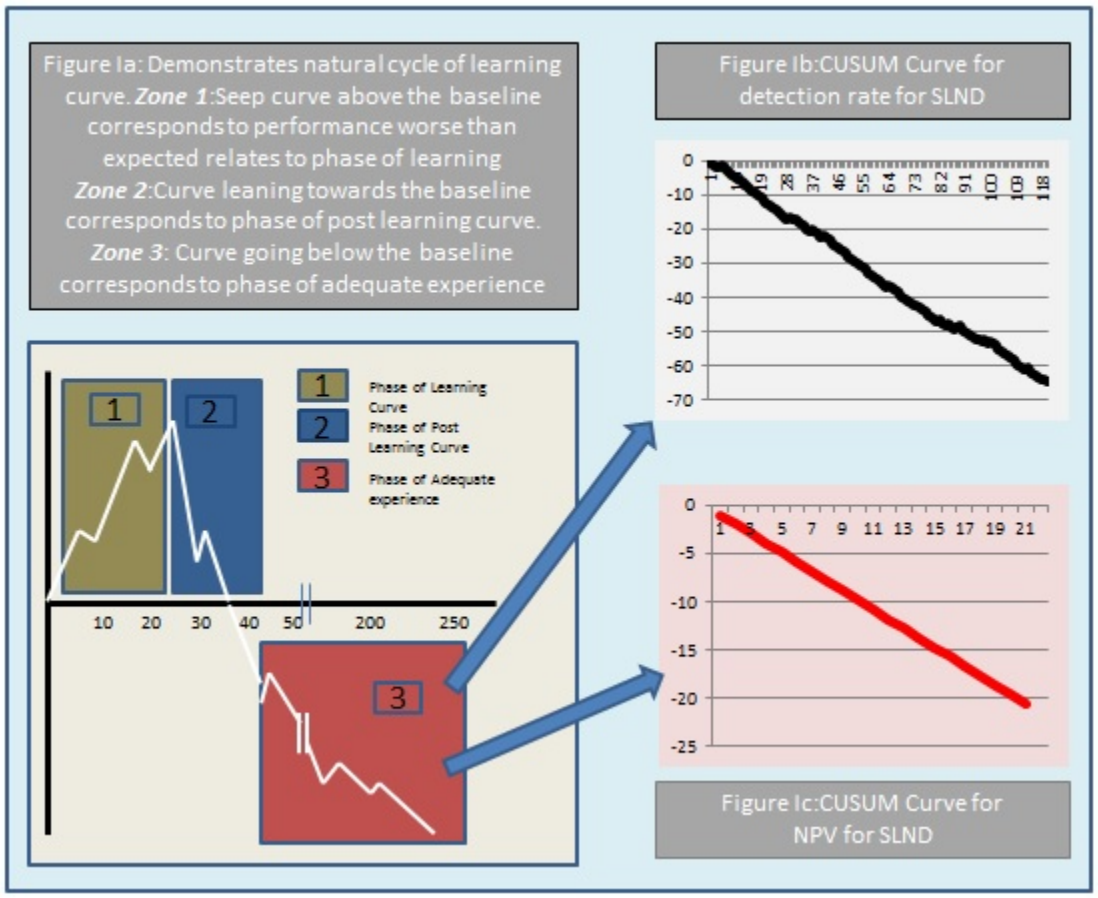
Objectives: Wide-ranging controversy surrounds performing lymphatic staging for endometrial cancer (EC). Sentinel lymph node dissection (SLND) has emerged as a feasible option not only to avoid comorbidities associated with regional lymphadenectomy but to aid in determining which patient population would benefit from adjuvant therapy. However, performing SLND with minimally invasive technique such as robotics involves a learning curve that has exceptionally high challenges. We sought to evaluate the learning curve of SLND with robotic-assisted laparoscopic hysterectomy for EC.

Methods: A retrospective database of the patients who underwent cervical blue dye injection followed by intraoperative SLN mapping performed by single surgeon with an experience of >500 robotic procedures was reviewed. SLN was initially

examined by routine hematoxylin and eosin stain if negative, with ultrastaging by immunohistochemistry (IHC). CUSUM curve of failure for the learning curve was constructed for detection rate (DR) and negative predictive value (NPV) by using following formula: Sn=Σ (Xi – Xo), where Xi=0 for a success and 1 for an observed failure. Xo is the predicted risk of failure.

Results: A total of 120 patients with EC underwent Robotic SLND without any conversion to open procedure between April 2011 and June 2013. Only 1 of 120 patients underwent SLND for fertility preservation. The DR for SLND was 86% (103/120). Bilateral SLN were detected in 52% (62/120). Positive nodes were identified in 8% (10/120) of the patients. SLN and regional lymphadenectomy were performed in 17.5 % (21/120) cases and the NPV was 100%. CUSUM curve for DR (Figure 1B) and NPV (Figure 1C) trended below the baseline from the beginning, corresponding to zone 3 of adequate experience in Figure 1A.

Conclusions: This is the largest cohort for robotic SLND for EC. Our results demonstrated that the initial expected learning curve can be surpassed, and SLND by robotic-assisted procedure for DR and NPV can be mastered with an adequate prior experience in robotic surgery. However, further large studies are required to confirm the DR and NPV for SLND with robotic-assisted procedures for EC.



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321 - Poster Session A

Does ultrastaging improve detection of micrometastasis for early-stage endometrial cancer?

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Objectives: The prognostic value of lymph node dissection for all patients with endometrial cancer (EC) remains controversial. Sentinel lymph node dissection (SLND) avoids a full lymphadenectomy with its associated increased morbidity, but it offers additional prognostic information that may help to better determine adjuvant therapy. The value of ultrastaging the SLN to reveal micrometastasis remains unclear. The objective of this study was to evaluate a large series of patients who underwent SLND for EC and to determine the impact of ultrastaging on lymph node positivity.

Methods: We performed a retrospective analysis of patients who underwent SLND for EC using the robotic platform. All patients underwent intraoperative sentinel lymph node mapping by injecting blue dye in the cervix followed by robotic SLND. SLN was initially examined by routine hematoxylin and eosin stain and, if negative, ultrastaging by immunohistochemistry (IHC). Micrometastases (tumor deposits >0.2 mm and ≤2 mm) and isolated tumor cells (≤0.2 mm) were classified as low-volume ultrastage-detected metastases.

Results: Between April 2011 and June 2013, 120 patients with EC underwent SLND. Demographic and pathologic characteristics are shown in Table 1. The detection rate for at least one SLN was 86% (103/120) and for bilateral SLNs was 52% (62/120). Out of those, SLNs were positive in 8% (10/120) of the patients. Of those with SLN (+), 50% (5/10) were by detected ultrastaging (IHC) alone. Of the patients who were positive by ultrastaging alone, 80% had deep myometrial invasion and 80% had lymphvascular space invasion. No patients had positive regional nodes without SLN (+). The false-negative predictive value (1-negative predictive value) of a SLN (-) was 0.

Conclusions: Our study represents a large series of robotic SLND for EC. Ultrastaging of SLND detected additional low-volume micrometastasis that otherwise remained undetected. The clinical significance of detection of micrometastasis of SLN for EC remains to be investigated.

Table 1:

Age (Median) in years	62(25-87)
BMI(Median) in Kg/mt^2	32 (18-76)
Surgical Approach	
Robotic	100%
Histology	
Endometrioid	87%
Serous	3%
Clear cell	2%
Carcinosarcoma	5%
Mixed	3%
FIGO Stage	
I	88%
II	3%
III	8%
IV	1%

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322 - Poster Session A

Predicting model for lymph node metastasis using preoperative tumor grade, transvaginal ultrasound, and serum CA-125 level in patients with endometrial cancer

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Objectives: To evaluate the predicting model for lymph node metastasis using preoperative tumor grade, transvaginal ultrasound (TVS), and serum CA-125 level in patients with endometrial cancer.

Methods: Between January 2000 and February 2013, we identified 172 consecutive patients with surgically staged endometrial cancer. TVS was performed by an expert gynecologic radiologist in all patients. All patients had complete staging surgery, including bilateral pelvic and para-aortic lymphadenectomy, and were staged according to the 2009 FIGO classification. Various clinicopathologic data were obtained from medical records and retrospectively analyzed.

Results: Of 172 patients, 138 presented with stage I (118 IA, 20 IB), 12 had stage II, 18 had stage III (2 IIIA, 1 IIIB, 8 IIIC1, 7 IIIC2), and 2 had stage IV diseases. The majority of patients had endometrioid adenocarcinoma (88.4%), and the remaining (12.6%) had non-endometrioid histology. Eighteen patients (10.5%) had lymph node metastasis. Deep (≥50%) myometrial invasion on preoperative TVS, high serum CA-125 level (≥35 U/mL), and preoperative grade 3 tumors were significant preoperative factors predicting lymph node metastasis. There was no significant association between preoperative histology and lymph node metastasis. We calculated the simple model predicting lymph node metastasis based on preoperative tumor grade, TVS findings, and CA-125 level using logistic regression analysis. With the cut-off point of 1.5, the sensitivity and specificity of this model were 94% and 57%, respectively (AUC 0.84, 95% CI 0.74-0.93, P<0.01).

Conclusions: Preoperative tumor grade, myometrial invasion on preoperative TVS, and CA-125 can accurately predict lymph node metastasis in endometrial cancer patients. The current study suggested the possibility that TVS could be used for preoperative evaluation strategy in the low-resource countries instead of expensive imaging modalities such as MRI or positron emission tomography-CT.

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323 - Poster Session A

Outcomes in node-positive low-grade endometrioid endometrial carcinoma

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Objectives: The extent to which lymph nodes (LNs) should be evaluated in low-grade (1-2) endometrioid endometrial cancer is widely debated. Some providers use preoperative imaging, others use the Mayo criteria, still others use sentinel lymph nodes and/or full lymphadenectomy. We sought to characterize treatment patterns and oncologic outcomes in this node-positive population to further inform the discussion regarding LN dissection.

Methods: We identified endometrial cancer cases treated surgically at our institution from February 1994 to July 2012. Those with endometrioid histology and FIGO grade 1 or 2 disease on final pathology were considered low-grade and included. The cohort was then restricted to LN-positive patients. Because the study period spanned our transition to the sentinel lymph node (SLN) program, positive nodes were those identified via full lymphadenectomy and/or SLN mapping.

Results: Among the 107 patients who met inclusion for evaluation, the median age was 61 years (range, 33-86 years), median tumor diameter was 3.8 cm (range, 0-10.2 cm), and myometrial invasion was <50% in 56 cases (52.4%). Notably, 11.5% of evaluable patients had a maximum tumor diameter ≤2.0 cm and myoinvasion <50%. Peritoneal washings were negative in 83 (77.6%). Lymphovascular invasion (LVI) was present in 87 cases (81.3%). Seventy-nine patients (73.8%) had positive pelvic LNs, and 28 patients (26.2%) had positive para-aortic LNs. Adjuvant therapy was as follows: no treatment, 7 (6.5%); radiation (RT) alone, 17 (15.9%); chemotherapy alone, 22 (20.6%); chemoradiation, 59 (55.1%); and hormonal blockade, 2 (1.9%). With a median follow-up of 44.1 months (range, 3-164 months), 17 (16%) patients recurred, and 13 patients (12%) died of disease. The 5-year disease-specific survival (DSS) for all patients was 84.6% (SE 4.5%). For those who received RT alone, the 5-year DSS was 61.8% (SE 13.8%) compared to 90.4% (SE 3.8%) for those who received chemotherapy +/- radiation therapy (P=0.08).

Conclusions: Node-positive low-grade (1-2) endometrial cancer carries significant risk for disease recurrence and death. The addition of chemotherapy to adjuvant treatment may improve survival compared to radiation therapy alone. It is critical, therefore, to continue to employ a strategy for nodal evaluation in low-grade patients to offer those with positive lymph nodes the potential benefit of appropriate adjuvant therapy.

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324 - Poster Session A

Age-adjusted Charlson comorbidity index is a prognostic factor in patients with early-stage uterine carcinoma: a study with 1,132 patients

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Objectives: The impact of competing medical comorbidity on survival endpoints in women with early stage endometrial carcinoma (EC) is not well studied. The study goal was to use a validated comorbidity scoring system to determine its impact on recurrence-free (RFS), disease-specific (DSS), and overall survival (OS) in patients with early-stage EC.

Methods: For this institutional review board-approved study, we reviewed our prospectively maintained uterine cancer database of 1,720 patients. We identified 1,132 patients with endometrioid carcinoma FIGO stages I-II who underwent hysterectomy from 1987 through 2011. Age-adjusted Charlson comorbidity index score (AAC) at time of hysterectomy was retrospectively calculated by physician chart review. Median AAC score for the study cohort was 3 (range, 0-15). Diabetes mellitus was the most common associated condition in 23.4% of the study cohort. Based on AAC score, patients were grouped as follows: 0-2 (group 1, n=379), 3-4 (group 2, n=532) and >4 (group 3, n=221). Univariate and multivariate modeling with Cox regression analysis was used to determine significant predictors of OS and DSS. Kaplan-Meier and log-rank test methods were used to evaluate survival endpoints.

Results: After a median follow-up of 80 months, 262 deaths were recorded: 42 from EC (16%) and 220 (84%) from other causes. By AAC grouping, the 5-year RFS, DSS, and OS were 95%, 98%, and 97% for group 1; 89%, 95%, and 87% for group 2; and 86%, 95%, and 72% for group 3 ($P<0.0001$). On multivariate analyses, higher AAC score, lymphovascular space invasion (LVSI), higher tumor grade, and involvement of the lower uterine segment were significant predictors of shorter DSS and OS. On multivariate analysis for RFS, only high tumor grade and LVSI were significant predictors.

Conclusions: Comorbidity score was as important as pathologic features for predicting DSS and OS in patients with early-stage uterine EC. Furthermore, higher AAC scores were independent prognostic factors for worse survival and should be considered as a stratification factor in any prospective clinical trial for patients with EC.

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325 - Poster Session A

Nodal selection during side-specific lymphadenectomy in cases of failed sentinel node mapping

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[1]Memorial Sloan-Kettering Cancer Center, New York, NY, [2]Thomas Jefferson University Hospital, Philadelphia, PA

Objectives: Side-specific lymph node dissection (SS-LND) has been advocated in sentinel lymph node (SLN) algorithms when SLN mapping fails on one side. We report our experience with SS-LND in the setting of unilateral mapping.

Methods: We identified all cases of endometrial cancer treated surgically at our institution from September 2005 through December 2011 in which SLN mapping was performed successfully. Successful mapping was defined as having SLN detection in at least one side of the pelvis. Surgical and pathologic data were abstracted, including the specific anatomic nodal basin(s) to which the patient mapped: obturator, hypogastric, external iliac, common iliac, and aortic.

Results: Of 508 patients who underwent surgical staging with successful SLN mapping, 154 (30.3%) mapped unilaterally and underwent a SS-LND on the contralateral (non-mapped) side, comprising our study group. Median age was 62 years (range, 34-87 years), and median body mass index was 28.7 (range, 16.6-49.0). The surgical approach was open in 36.4% of cases, laparoscopic in 20.8%, and robotic in 42.9% of cases. Final histology was as follows: endometrioid, 120 (77.9%); serous, 24 (15.6%); carcinosarcoma, 5 (3.2%); and clear cell, 5 (3.2%). The median number of LNs removed on the non-mapped side was 7 (range, 1-46). A positive non-SLN was discovered during side-specific LND in 7 (4.5%) of 154 cases. Of these, the positive lymph node(s) were identified in the basin symmetric to the contralateral SLN in five cases. When the hypogastric and obturator basins were considered one anatomic site, an additional one case identified the positive non-SLN in the symmetric basin. Therefore, in six of seven cases (85.7%) where a positive non-SLN was identified during SS-LND, the positive LNs were identified in the same basin as the SLN on the successfully mapped side. Limiting the SS-LND to those basins that mapped on the contralateral side would have missed 1 positive LN in 154 cases (0.6%); notably, in that case, the SLN was positive and, therefore, the patient would have been upstaged and treated regardless.

Conclusions: Positive non-SLNs were rare in our cohort. Focusing the SS-LND to the symmetric basin(s) in the setting of a unilateral mapping appeared to identify the majority of positive lymph nodes and may decrease the morbidity associated with a complete pelvic lymphadenectomy.

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326 - Poster Session A

Taking it up a Notch: implications for outcomes in endometrial cancer

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The University of Texas MD Anderson Cancer Center, Houston, TX

Objectives: The Notch pathway plays a critical role in cell-to-cell communication, proliferative signaling, and cell differentiation but can have oncogenic or tumor suppressive effects. We analyzed the clinical significance of this pathway in endometrial cancer.

Methods: We accessed clinical, somatic mutations, and reverse phase protein array (RPPA) data from The Cancer Genome Atlas (TCGA) to perform integrated analyses and determine the clinical significance of Notch pathway aberrations in endometrial cancer patients. Genomic alteration information for these patients (mRNA expression, mutation, and copy number) was obtained from cBio Cancer Genomic Portal. In this cohort, we also identified concomitant *PI3K/AKT* abnormalities. Clinical information extracted included age, body mass index, tumor histology, tumor grade, clinical stage, estrogen(ER)/progesterone(PR) receptor status, and overall survival.

Results: A total of 232 samples were available for analysis. Within the Notch pathway, 18.1% of evaluable samples had amplification or upregulation of *Notch2/Notch3* and/or *DLL3* genes, which was significantly correlated with worse overall survival ($P=3.08e^{-7}$). Median ERα, ERα(pS118), and PR RPPA levels were significantly higher for patients with no abnormalities or mutations present in *Notch2/Notch 3* and/or *DLL3* than those with amplification and/or upregulation of these genes ($P=0.0016$, $P=0.0002$, and $P=0.003$, respectively). Of the 52 identified mutations in *Notch2/Notch3* and/or *DLL3*, 92.3% and 7.7% were missense and nonsense mutations, respectively. Overexpression or amplification of mRNA involved in the *PI3K/AKT* pathway was present in 108 (46.5%) of the evaluated endometrial tumors. Of these, only 35 tumors (32.4%) had concomitant *Notch2/Notch3/DLL3* mRNA overexpression or amplification.

Conclusions: Upregulation or amplification of *Notch 2, Notch 3*, and/or *DLL3* genes predicted a more aggressive clinical course for endometrial cancer patients. Given the non-overlapping expression of *PI3K/AKT* and *Notch* pathways, personalized options for targeted therapy could be considered for each group.

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327 - Poster Session A

Prognostic factors of lymph node involvement in endometrioid endometrial cancer: a SEER analysis

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Objectives: Prior studies from the Mayo Clinic have identified a subset of women with endometrial cancer who have low probability of nodal metastasis. The objective of this investigation was to evaluate the risk of nodal metastasis in patients with endometrial cancer using the Mayo criteria in a population-based analysis.

Methods: Data from the Surveillance, Epidemiology, and End Results (SEER) registry for endometrial cancer cases diagnosed between 1988 and 2009 were reviewed. Patient and tumor characteristics as well as lymph node involvement were abstracted from the database. Patients considered at low-risk for nodal metastasis according to the Mayo criteria had the following characteristics: <50% myometrial invasion, tumor size <2 cm, and grade 1 or 2 endometrioid histology. Patients not meeting these criteria were considered at high risk for nodal involvement.

Results: The final study group consisted of 19,329 women with surgically staged endometrial cancer of whom 18,294 (94.6%) had stage I disease and 1,035 (5.3%) stage IIIC disease. A total of 4,095 (21.1%) patients were found to be at low risk and 15,234 (78.9%) at high risk for nodal metastasis. Patients with high-risk criteria were older (62.4 years vs 59.8 years, $P<0.001$) and more frequently African American (6.4% vs.4.7%, $P<0.001$). Women with low-risk features were associated with a 1.4% risk for lymph node metastasis compared to 6.4% in patients with high-risk features ($P<0.001$). When myometrial invasion was removed from the analysis and only size and grade were considered, women with low-risk pathologic features were associated with a 2.4% risk of lymph node metastasis compared to 6.3% in patients with high-risk features ($P<0.001$). The overall rate of lymph node involvement in grade 1 endometrial cancer with <50% myometrial invasion was 1.3% ($n=6,215$).

Conclusions: In a population-based analysis, women with low-risk endometrial cancer ,as defined by the Mayo criteria, had a low rate of lymph node metastasis. When myometrial invasion was removed from the analysis, the low-risk population retained a small overall risk of lymph node metastasis. Given the low rate of lymph node metastasis in grade 1 tumors with <50% invasion, the Mayo criteria could be expanded to include all grade 1 tumors independent of size.

Table 1. Lymph node metastasis by tumor grade and size, tumor invasion <50% of myometrium.

Size of Tumor	Grade 1 (n = 6215)	Grade 2 (n = 5556)	Grade3 (n = 2591)
None	0.00% (0/5)	0.00% (0/1)	0.00% (0/2)
Microscopic	0.00% (0/256)	0.00% (0/65)	0.00% (0/28)
1 cm	1.11% (9/810)	2.61% (13/498)	4.15% (9/217)
2 cm	0.90% (12/1,328)	2.12% (24/1,132)	3.52% (17/483)
3 cm	1.02% (14/1,373)	2.00% (28/1,402)	3.36% (20/595)
4 cm	1.55% (17/1,099)	3.39% (37/1,090)	5.33% (28/525)
5 cm	2.27% (14/618)	3.55% (23/648)	8.93% (31/347)
> 5 cm	2.34% (17/726)	5.56% (40/720)	10.66% (42/394)

Recurrence and survival in patients with uterine papillary serous carcinoma: do prior breast cancer and tamoxifen exposure influence outcomes?

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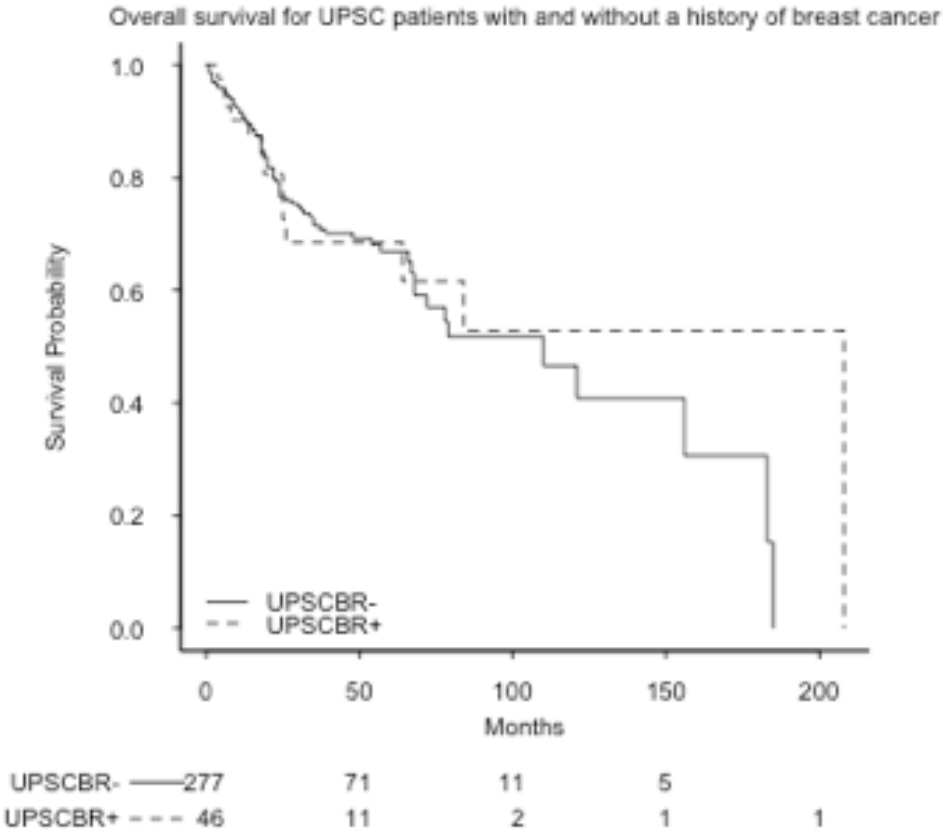
Objectives: To evaluate progression-free survival (PFS) and overall survival (OS) outcomes in women diagnosed with uterine papillary serous carcinoma (UPSC) who have had (UPSCBR+) or not had (UPSCBR-) a prior history of breast cancer and to correlate their outcomes to prior tamoxifen use.

Methods: Data were collected for all women diagnosed with UPSC at two academic institutions between January 1997 and July 2012. Patient demographics, tumor histology, stage, and treatments were recorded. Patients were divided into two groups: those with and without a personal history of breast cancer. Within the UPSCBR+ cohort, we identified those with a history of tamoxifen use. Cox regression modeling was used to explore associations of selected covariates of interest on the time-to-event outcomes of PFS and OS.

Results: Of 323 patients with UPSC, 46 (14%) were UPSCBR+, 15 (33%) of whom had a history of tamoxifen use. UPSCBR+ patients were older than the UPSCBR- group, with a median age of 72 years (interquartile range [IQR] 65-81) vs a median age of 68 years (IQR 62-74, *P*=0.004). UPSCBR+ women showed no significant difference in either PFS or OS compared to those who were UPSCBR- (PFS, *P*=0.72; OS, *P*=0.71). After controlling for age, there was still no evidence of a difference between the two groups. Within the UPSCBR+ cohort, there was no difference in PFS or OS between those who had or had not used tamoxifen (PFS, *P*=0.83; OS, *P*=0.95).

Conclusions: There was an association between breast cancer and UPSC with regard to incidence. We did not find convincing evidence of an appreciable difference in PFS or OS in the UPSCBR+ and UPSCBR- patient groups. Although tamoxifen use is a known risk factor for developing UPSC, we did not demonstrate significant OS or PFS differences in women who took tamoxifen. Our findings should be encouraging to those with these two cancer diagnoses and has implications for appropriate counseling.



329 - Poster Session A

Expression of DNA repair proteins in endometrial cancer predicts disease outcome

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Objectives: The consequences of defective homologous recombination (HR) are have not been systematically explored in endometrial cancer (EC). However, it is clear that defects in HR and other DNA repair pathways are important contributors to the effectiveness of current therapies in other tumor types. We hypothesized that a subset of ECs may harbor anomalies in HR pathways and that defects in HR or other DNA repair pathways could influence clinical outcome in these patients. Our objective was to define the *BRCA*-ness profile of EC and determine whether *BRCA1, PARP, FANCD2, PTEN, H2AX*, and *ATM* protein expression correlated with response to treatment, disease recurrence, and recurrence-free survival (RFS).

Methods: Protein microarray analysis of endometrial tissue was used to determine protein expression levels for defined DNA repair proteins: *PARP1, γH2AX, ATM, FANCD2, PTEN*, *BRCA1*, and *p53*. Correlation with clinical and pathologic parameters in 357 patients with EC (type I and type II) was analyzed using chi-square, Kaplan-Meier method, Cox proportional hazard model, and cumulative incidence function.

Results: In type I EC, PARP1+, ATM+, and FANCD2+ were associated with high tumor grade (P=0.031, P=0.0045, P=0.0062, respectively); γH2AX+ and FANCD2+ with advanced tumor stage (P=0.0004, P=0.0085); γH2AX+, FANCD2+, and p53+ with the presence of lymphovascular invasion (P=0.0004, P=0.0042, P=0.0098, respectively); and γH2AX+ and ATM+ with tumor recurrence (P=0.0203, P=0.0465, respectively). In type II EC, only PARP1+ was associated with tumor stage (P=0.0310). Patients with p53+ or FANCD2+ were 2.11 times more likely to recur (P=0.007), with a 5-year RFS probability of 71.4% in comparison to 85.5% for the other patients. Patients with p53+ or FANCD2+ had a 5-year overall survival of 66.46% in comparison to 78.5% for other patients. Finally, patients with ATM+ and p53+ or FANCD2+ were 1.77 time more likely to recur (P=0.024), with a 5-year RFS probability of 68% vs 80.3% for the other patients.

Conclusions: Patients with concomitantly high levels of *ATM* and *FANCD2* or *p53* protein expression were at increased risk of recurrence of endometrial cancer.

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330 - Poster Session A

Lack of genomic predictors of recurrence in uterine carcinoma

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Objectives: Using the comprehensive genomic characterization of uterine carcinoma by The Cancer Genome Atlas (TCGA), we sought to determine whether genomic features could be used to predict recurrence.

Methods: We downloaded data from TCGA and cBioPortal. Because of the low rate of endometrial cancer recurrence, we sought to compare genomic characteristics between extreme clinical phenotypes. We compared two groups: patients with stage I/II cancers with recurrences between 6 and 12 months from diagnosis (early recurrence group) and patients with stage III/IV cancers with no evidence of recurrence for at least 24 months (late remission group). We evaluated differences in histology, *MLH1* methylation, microsatellite instability (MSI), and somatic mutation spectrum between the two groups. Standard statistical analyses were applied.

Results: Histopathologic characteristics of the comparison groups are listed in the Table. Six patients with stage I tumors had recurrences between 6 and 12 months and 15 patients with stage III/IV tumors remained disease-free between 27 and 97 months. When comparing the early recurrence to the late remission group, we did not find any difference in rate of somatic mutations in *TP53* (17% vs 47%, P=0.2), *PIK3CA* (33% vs 40%, P=0.8), *PIK3R1* (67% vs 47%, P=0.4), *PTEN* (67% vs 60%, P=0.8), *KRAS* (16% vs 20%, P=0.8), *CTNNB1* (33% vs 13%, P=0.3), or *ARID1A* (16% vs 33%, P=0.4). There were no differences in the rates of *MLH1* methylation or MSI between the two groups (33% vs 20%, P=0.5). There were no *POLE* mutations in the early-recurrence group (0%) compared to 3 (20%) in the late-remission group, but this was not a significant finding (P=0.2).

Conclusions: Using the most extreme phenotypes of early-stage patients developing early endometrial cancer recurrence compared to late-stage patients achieving long-lasting clinical remissions, we were unable to define a genomic profile that

differentiated between the two groups. Our inability to define a genomic predictor of recurrence may be limited by heterogeneity of surgical effort and adjuvant therapy use as well as the relatively low recurrence rate in uterine carcinoma. An effort to collect longer-term follow-up data by TCGA would be useful for future efforts to define genomic predictors of outcome in uterine carcinoma.

Table: Patient characteristics

	Early recurrence (n = 6)	Late remission (n = 15)
Stage I	6 (100%)	0
Stage II	0	0
Stage III	0	14 (93%)
Stage IV	0	1 (7%)
Endometrioid grade 1	3 (50%)	4 (27%)
Endometrioid grade 2	1 (17%)	2 (13%)
Endometrioid grade 3	1 (17%)	4 (27%)
Serous	1 (17%)	5 (33%)
Disease free survival, range	Recurrence 6 – 12 months	Disease-free 27 – 97 months

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331 - Poster Session A

Genomic characterization of grade 3 endometrial carcinoma

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Objectives: Grade 3 endometrial carcinomas are heterogeneous. We sought to use the comprehensive genomic characterization of uterine carcinomas by The Cancer Genome Atlas (TCGA) to identify genomic classifiers predictive of outcome.

Methods: Data from 230 genes involved in growth, survival, and DNA repair pathways were downloaded from the TCGA endometrial cancer study and correlated with clinical data. Standard statistical analyses were performed with STATA.

Results: Among 242 uterine tumors with complete histology and stage information, 48 (20%) were grade 3 (G3) endometrioid. G1/2 endometrioid cancers were characterized by early stage, low rates of somatic mutation, and low rates of genomic instability. Serous cancers were characterized by later stage, low rates of somatic mutation, and almost universal genomic instability. In contrast to G1/2 and serous tumors, G3 tumors were more heterogeneous. G3 tumors had higher rates of somatic mutations (71% categorized as high or highest), but 21% clustered with serous tumors based on copy number abnormalities. *MLH1* methylation increased with endometrioid tumor grade (28% in G1, 33% in G2, 54% in G3) and was absent in serous tumors (0%). Eighteen percent of G3 tumors were characterized as *POLE* ultramutated (vs 7% of G1, 6% of G2, and 0% of serous) and 53% were *MSI* hypermutated (vs 26% of G1, 31% of G2, and % of serous). Somatic mutations were found at a significantly higher frequency in G3 tumors. Mutated genes were almost universally found more commonly in *POLE* ultramutated tumors. After excluding *POLE* subtype tumors, 19 of 230 genes were mutated at a frequency of >10%. The most frequently mutated genes were *PTEN* (70%), *PIK3CA* (57%), *PIK3R1* (49%), *KRAS* (34%), *TP53* (31%), *ARID1A* (31%), *CTNNB1* (18%) and *ATR* (18%). In the copy-number high subtype, mutations were found in *TP53* (100%), *PIK3R1* (55%), *PIK3CA* (44%), *PTEN* (22%), and *KRAS* (22%) but never in *CTNNB1* (0%) or *ARID1A* (0%). No gene mutations were found to predict recurrence or survival.

Conclusions: G3 endometrioid uterine cancers are the most heterogeneous subtype of endometrial carcinomas, with higher rates of somatic mutations, *POLE* mutations, and *MLH1* methylation and more variations in copy number profiles than G1/2 or serous tumors. Due to the low rate of recurrences, we were unable to identify any genomic predictors of outcome.

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332 - Poster Session A

Efficacy of adjuvant therapy in women with stage IIIC2 endometrial cancer

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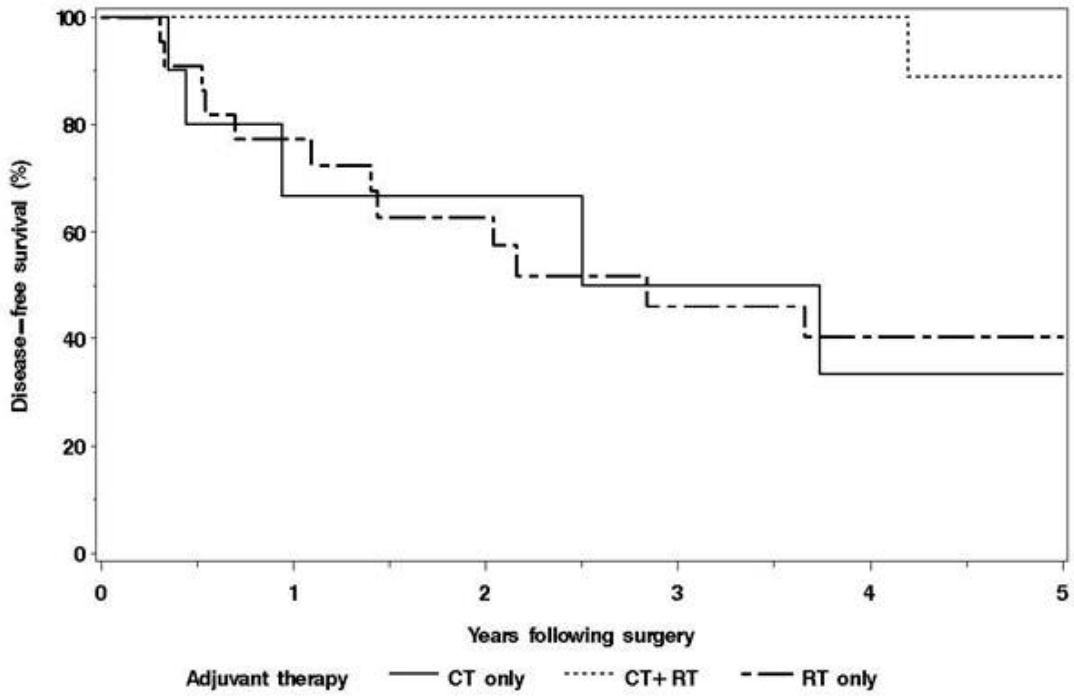
Objectives: To determine the effectiveness of adjuvant therapies in managing endometrial cancer (EC) patients with documented stage IIIC2 disease.

Methods: Patients electing primary surgical management for their EC during the time interval 1984 through 2008 formed the index population for this study. Disease-free (DFS) and overall (OS) survivals within the first 5 years were analyzed using Kaplan-Meier and Cox proportional hazards models.

Results: Among 835 EC patients undergoing para-aortic lymphadenectomy (PA LND), stage IIIC2 was documented in 81 (10%). While 12 patients elected to forego adjuvant treatment, external beam radiotherapy (RT) was administered to 26 (32%), chemotherapy (CT) to 18 (22%), CT+RT to 19 (23%), and 6 (7%) had insufficient details of therapy. The RT field included the PA node-bearing region in 34 patients (42%). The 5-year DFS and OS were 46% and 42%, respectively. Considering only patients undergoing adjuvant therapy, multivariable regression analysis demonstrated lymphovascular space invasion (LVSI) and cervical stromal invasion to be independent predictors of compromised DFS ($P<0.01$). Advancing age and LVSI correlated with worse OS ($P<0.01$). Stratifying all 81 patients by histological subtype, the 5-year estimated DFS and OS for nonendometrioid histology ($n=22$) was 33% and 23%, respectively, compared to 51% and 48%, respectively, for endometrioid histology ($n=59$) ($P=0.17$ for DFS and $P=0.06$ for OS). Different adjuvant strategies did not influence outcomes among nonendometrioid patients. However, among patients with endometrioid histology, CT+RT favorably affected DFS in comparison to CT or RT alone (Figure). This association retained significance for both DFS and OS in multivariable models ($P<0.05$).

Conclusions: CT+RT may improve outcomes of endometrioid stage IIIC2 EC, while new strategies are needed for nonendometrioid stage IIIC2 EC.

Figure: Recurrence rates by types of adjuvant therapy in stage IIIC2 endometrioid EC



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333 - Poster Session A

Variations in practice for the management of high-risk histologic subtypes in endometrial cancer: a CHREC (Consortium of High Risk Endometrial Cancer) Canadian project

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Objectives: High-risk histologic subtypes of endometrial cancer are underrepresented in randomized, controlled trials, and no level I evidence exists to guide management. The objective of this study was to examine practice patterns and outcomes in a large cohort of high-risk endometrial cancers.

Methods: This retrospective cohort study included patients with grade 3 endometrioid (G3E), serous (SC), clear cell (CC), and carcinosarcoma (CS) from seven cancer treatment centers in Canada between 2000 and 2012. Data collection included age, surgical staging, adjuvant treatment, location of relapse, and overall survival (OS).

Results: This cohort included 1,246 cases of high-risk endometrial cancers (402 G3E, 438 SC, 93 CC, 247 CS and 66 mixed subtypes). G3E cancers had a superior OS when compared to the other subtypes, with a median follow up of 33.3 months ($P<0.0001$). A wide variation in practice exists among the institutions. Surgical staging rates ranged from 36.8% to 100%, adjuvant radiation rates ranged from 10% to 78.9%, and adjuvant chemotherapy rates ranged from 16.5% to 100%. Differences in OS among institutions were observed for G3E but not for other subtypes, despite differences in management. Multivariate analysis found surgical staging to be significant for OS. A separate analysis was performed on those who had undergone appropriate surgical staging ($n=926$ [74.3%]). In this cohort, 41.7% were stage 1 and 34.3% were stage 3C or 4. Recurrence rates were as follows: stage 1A 13.3%, 1B 15.8%, II 31.3%, IIIA/B 49.6%, IIIC 48.8%, and IV 61.3%. Adjuvant treatment significantly reduced recurrence in two scenarios: adjuvant radiation for stage 1B G3E ($P=0.044$) and adjuvant chemotherapy for stage 1A serous cancers ($P=0.03$). When inadequately staged patients were removed from the analysis, the survival difference in G3E among institutions disappeared.

Conclusions: A lack of robust data to guide clinical management has resulted in a wide variation in practice for the management of high-risk endometrial cancers. G3E cancers have an improved survival compared to other subtypes. Variations in management do not appear to affect outcome for CS, CC, or SC, but may for G3E. Coordinated multi-institutional studies will be required to optimize treatment strategies for high-risk endometrial cancers.

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334 - Poster Session A

Proteomic profiling of stage I endometrial cancers: a signature of early-stage recurrence in GOG 8016

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Objectives: Approximately 12% to 27% of stage I endometrial cancers recur, and currently there are no accurate tests for identifying these patients. The study was designed to create and internally validate a prediction model based on protein expression in tissue for identification of stage I endometrial cancer patients destined to develop disease recurrence.

Methods: Frozen primary tumor from 313 women with stage I endometrioid endometrial cancer underwent pathologic review to identify specimens with limited necrosis (<50%) and high neoplastic cellularity (>20%). Eligible cases were randomized to discovery or validation cohorts prior to laser microdissection and proteomics. The discovery and validation cohorts were to be composed of 130 and 78 cases with 50% events. Wilcoxon ranked sum testing was used to identify differentially abundant proteins.

Results: The discovery cohort was actually made up of 72 non-recurrences and 42 recurrences (19 stage IA, 66 stage IB, and 29 stage 1C; 38 grade 1, 47 grade 2, 25 grade 3, and 4 missing grade; 69 with acceptable pelvic and para-aortic lymphadenectomy based on Gynecologic Oncology Group [GOG]-210 criteria). A total of 1,594 proteins were identified in laser microdissected tumor cells in the discovery cohort ($n=114$). Although GSN, ADAR, CHD4, NT5C, KRT14, and KRT16 were all statistically significant ($P<0.001$), after adjusting for false discovery using q-value adjustment, none of the identified candidate biomarkers met the threshold to move on and determine whether the candidate biomarkers accurately distinguished between the groups on the basis of protein expression.

Conclusions: Proteomic analysis of primary tumor from recurrent and non-recurrent stage I endometrial cancer tumors did not reveal proteins that could delineate between the two groups. These data suggest that the primary tumor may not contain a tissue-based protein signature that can be used to predict recurrence in stage I endometrial cancer.

335 - Poster Session A

Combined modality adjuvant therapy for FIGO stage IIIC endometrial carcinomas

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Objectives: To report the feasibility and safety of same-day discharge after robotic-assisted hysterectomy.

Methods: Same-day discharge after robotic-assisted hysterectomy was initiated In July 2010. All cases from then through December 2012 were captured prospectively for quality assessment monitoring. The distance from the hospital to patients' homes was determined using http://maps.google.com. Procedures were categorized as simple (total laparoscopic hysterectomy [TLH] ± bilateral salpingo-oophorectomy [BSO]) or complex (TLH ± BSO with sentinel node mapping, pelvic and/or aortic nodal dissection, appendectomy, or omentectomy). Urgent care center (UCC) visits and readmissions within 30 days of surgery were captured, and time to the visit was determined from the initial surgical date.

Results: Same-day discharge was planned in 200 cases. Median age was 52 years (range, 30-78 years), body mass index was 26.8 (range, 17.4-56.8), and ASA was class 2 (range, 1-3). Median distance traveled was 31.5 miles (range, 0.2-149 miles). Procedures were simple in 109 (55%) and complex in 91 (45%) cases. The indication for surgery was: endometrial cancer (n=82 [41%]), ovarian cancer (n=5 [2.5%]), cervical cancer (n=8 [4%]), and nongynecologic cancer/benign (n=105 [53%]). A total of 157 patients (78%) had successful same-day discharge; 43 (22%) required admission. Median time for discharge for same-day cases was 4.8 hours (range, 2.4-10.3 hours). Operative time, case ending before 6 PM, and use of intraoperative ketorolac were associated with successful same-day discharge. UCC visits occurred in 8/157 (5.1%) same-day discharge cases compared to 5/43 (11.6%) requiring admission (P=0.08). Readmission was necessary in 5/157 (3.2%) same-day discharge cases compared to 3/43 (7.0%) requiring admission (P=0.02).

Conclusions: Same-day discharge after robotic-assisted hysterectomy for benign and malignant conditions is feasible and safe.

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336 - Poster Session A

Pelvic sentinel lymph node mapping and aortic nodal status in endometrial cancer: does infrarenal aortic lymph node metastasis really occur in isolation?

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Objectives: To evaluate infrarenal (IR) aortic nodal status in relation to pelvic sentinel lymph nodes (SLN) in patients with clinical stage I endometrial cancer (EC).

Methods: Eighty patients with EC (April 2011 to August 2013) underwent robotic-assisted laparoscopic hysterectomy and pelvic SLN biopsies followed by systematic pelvic and aortic lymphadenectomy to the left renal vein. Data were gathered prospectively. SLN were ultrasectioned and evaluated with both hematoxylin and eosin (H&E) and immunohistochemistry (IHC) stains. The dataset was examined for perioperative and clinicopathologic factors, including presence of lymph node (LN) metastasis. The disease status of pelvic SLN mapped with isosulfan blue (ISB) and/or indocyanine green (ICG) using near-infrared imaging was compared to IR aortic node pathology.

Results: The mean patient age was 65.9±12.0 years, body mass index was 33.8±8.4, height was 65.3±10.6 inches, operative time was 178±33 minutes, and length of hospital stay was 1.4±1.1 days. Histologies included: endometrioid adenocarcinoma G1 (18.8%), G2 (45%), G3 (12.5%), and type II cancers (23.8%). The mean depth of invasion was 43.1±30.4%, and lymphovascular space invasion was present in 46.3% of cases. Mean pelvic and aortic lymph node yields were 26.6±16.4 and 12.7±6.4, respectively. Thirty-four (42.5%) patients had pelvic LN metastasis, and 33 had SLN metastasis. The sensitivity for detecting LN metastasis using SLN was 97%. Fifteen (18.8%) patients had aortic LN metastasis (2 IR, 8 IR+infra-mesenteric [IM], and 5 IM) and all had SLN metastasis. Conversely, 15/33 (45.5%) patients with SLN metastasis had aortic metastasis; 6/33 (18.2%) with SLN metastasis had isolated tumor cells by IHC and 2/6 (33%) of these cases had IR metastasis compared with 8/27 (30%) of cases with H&E SLN metastasis. There were no cases with isolated IR or inframesenteric LN metastasis.

Conclusions: These findings suggested that SLN metastasis, whether identified by H&E or isolated tumor cells with IHC, poses a risk for IR aortic LN metastasis. The phenomenon of “isolated infra-renal metastasis” in patients with EC appears uncommon in patients undergoing pelvic SLN mapping.

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Proteomics of endometrial carcinogenesis: identification of candidates underlying disease pathogenesis

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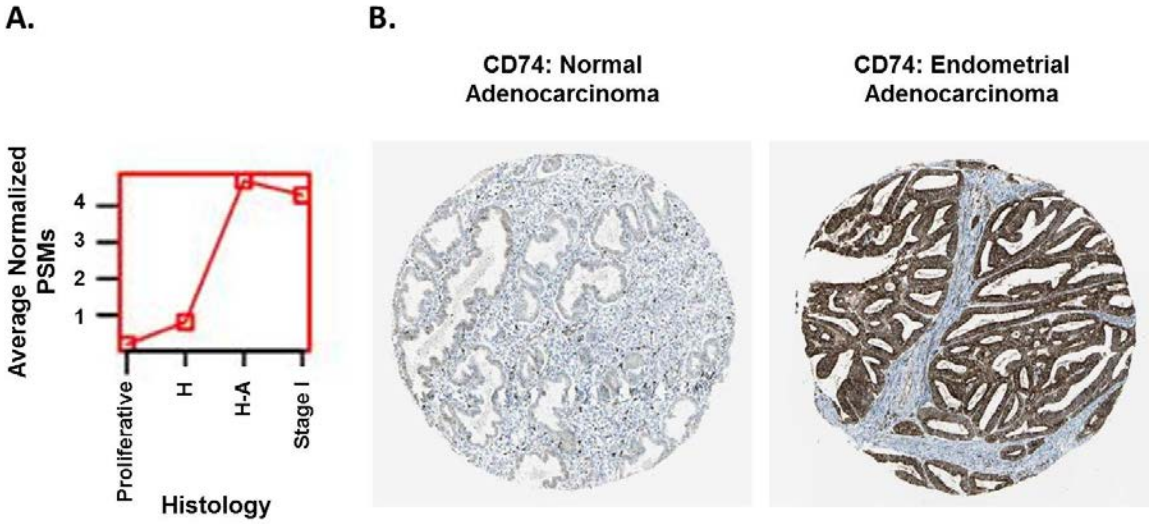
Objectives: Although considerable improvements in endometrial cancer (EC) patient treatment have been made, the precise carcinogenic mechanisms underlying the transformation from normal to malignancy remains unclear. We sought to identify proteins whose abundance changes correlate with carcinogenesis from representative tissue specimens from normal endometrium, endometrial hyperplasia without atypia (H), hyperplasia with atypia (H-A), and stage I endometrial cancer by mass spectrometry (MS)-based proteomics.

Methods: Epithelial cells from 75 paraffin uterine samples (15 proliferative endometrium; 13 endometrial hyperplasia; 16 congenital adrenal hyperplasia; and 31 stage I, G1,2 cancer) were obtained using laser microdissection and analyzed by MS. Wilcoxon ranked sum testing and ANOVA were used to identify differentially abundant candidates ($P<0.05$) that correlate with carcinogenesis.

Results: Forty-five proteins were identified with differential abundances that varied significantly among normal proliferative, H, H-A, and stage I endometrial cancer in a pattern consistent with carcinogenesis. Several were increased in H-A and stage I cancer relative to normal proliferative and H tissues, including annexin A6, plectin, and the human leukocyte antigen class II histocompatibility antigen gamma chain protein (CD74). CD74, which was increased fivefold in H-A and stage I cancer (Figure 1A), has recently been shown to be elevated in multiple cancers and affects the function of Scribble, a tumor/metastasis suppressor. Assessment of *CD74* abundance in normal vs EC tissues utilizing the Human Protein Atlas (HPA) resource revealed that *CD74* is frequently elevated in endometrial cancer (Figure 1B).

Conclusions: A panel of proteins stratifying normal proliferative/H endometrium from H-A and stage I endometrial cancer has been identified. Of these, *CD74* was significantly elevated in H-A and stage I cancer tissues, consistent with previous reports of this protein being increased with cancer progression and metastasis in multiple organ sites. These data support investigation of *CD74* as an etiological factor underlying EC pathogenesis.

Fig 1: A. Average peptide spectrum matches (PSM) for CD74 in Proliferative, H, H-A and Stage I endometrial cancer. B. CD74 abundance in representative normal endometrium vs endometrial cancer (images from HPA).



338 - Poster Session A

Large tumors in endometrial cancer: a change in perspective

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Objectives: In endometrial cancer, tumor size is generally thought to be a harbinger for other prognostic factors, including myometrial invasion and lymphovascular space invasion (LVSI). However, the data that have led to these conclusions have included a paucity of patients with large tumors (>6 cm). Our goal was to fully elucidate the rate of lymph node metastasis across the full spectrum of tumor sizes encountered in clinical practice.

Methods: Following institutional review board approval, a review was performed on patients who were evaluated for endometrial cancer at a single academic institution from 2000 to 2010. Data were obtained from an initial distribution of patients of all tumor sizes. A probability weighted stratified sample was used to obtain data from additional patients within the upper and lower extremes of tumor size. Predictive models for lymph node metastases were fitted using a generalized additive model.

Results: Data from 170 patients were used to determine the initial distribution. Data were subsequently added from an additional 135 patients within overrepresented extremes of tumor size for a total sample of 305 patients. Univariate analysis for association with lymph node metastasis demonstrated that tumor size was highly significant ($P<0.0001$). In multivariate analysis, the relationship between tumor size and lymph node metastasis was still significant after adjusting for myometrial invasion, LVSI, and histology ($P<0.0031$). The relationship was not monotonic and plateaued around 6 cm. Rates of lymph node metastasis for tumors >0, 1, 2, 3, 4, 5, 6, and >7 cm were 0%, 8%, 6%, 19%, 22%, 29%, 30%, and 45%, respectively.

Conclusions: Tumor size was an independent predictor of lymph node metastases when the entire clinical spectrum of tumor sizes was included. The very high rate of lymph node metastases (approximately 30% to 45%) remained consistently seen at tumor sizes >6 cm. Clinical decision-making or algorithms that determine the need for lymphadenectomy should not only include tumor size but should also consider the specific rate of lymph node metastasis for larger tumors.

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339 - Poster Session A

Who should treat complex atypical endometrial hyperplasia?

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Objectives: Due to the risk of finding carcinoma in hysterectomy specimens after surgery for complex atypical endometrial hyperplasia (CAH), it has been suggested that these patients be referred to gynecologic oncologists preoperatively for the potential need for lymphadenectomy. The objectives of this study were to evaluate the risk of uterine cancer and to model the risk of lymphatic spread in women with endometrial cancer found at hysterectomy after a preoperative diagnosis of CAH.

Methods: We performed a retrospective review of 155 patients with a preoperative diagnosis of CAH who subsequently underwent hysterectomy. Clinical characteristics and pathologic information were abstracted from the medical records. Risk of lymphatic spread based on Gynecologic Oncology Group (GOG)-33 criteria and categorization as high-intermediate risk based on GOG-99 criteria were subsequently applied.

Results: Fifty-five of the 155 patients (36.7%) had endometrial carcinoma in the hysterectomy specimen. One patient (0.6%) had a grade 3 endometrial carcinoma, 5 (3.2%) had lymphovascular space involvement, and 7 (4.5%) had deep (>50%) myometrial invasion. No patients had gross intraperitoneal disease. Using GOG-33 criteria for nodal spread, 39 patients (25.1%) were potential candidates for staging with 23 patients (14.8%) considered moderate risk with one risk factor, 14 patients (9.0%) had moderate risk with two risk factors, and 2 patients (1.3%) had high risk with deep myometrial invasion only. However, based on GOG-33 criteria, the risk of lymph node spread for a patient with a preoperative diagnosis of CAH was only 1.3% for pelvic nodes and 0.7% for para-aortic nodes. Nine patients (6.0%) met criteria for high-intermediate risk based on GOG-99.

Conclusions: Given the high rates of underlying endometrial cancer and potential need for lymphadenectomy, patients with a preoperative diagnosis of CAH desiring definitive management with hysterectomy should be referred to a gynecologic oncologist.

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340 - Poster Session A

Is observation reasonable in older patients with early-stage uterine papillary serous carcinoma and clear cell carcinoma?

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Objectives: Early-stage uterine papillary serous carcinoma (UPSC) and clear cell (CC) carcinoma have 5-year survival rates as low as 38%. The decision to use adjuvant therapy is influenced by patient and tumor characteristics. We sought to determine whether adjuvant therapy after primary surgery for the treatment of stage I-II UPSC and CC improved progression-free (PFS) and overall survival (OS).

Methods: A single-institution, retrospective cohort study of women diagnosed with stage I-II UPSC or CC endometrial cancer from January 2000 through December 2009 was performed. All patients underwent primary surgery followed by either observation (OBS) or adjuvant therapy that included radiation therapy (RT) or chemotherapy (CT). CT patients were treated with 4 to 6 cycles of paclitaxel and carboplatin. RT patients were treated with whole pelvic radiation therapy (WPRT), brachytherapy (BT), or both and were considered collectively. Statistical analysis included Fisher's exact and Student's t-test as appropriate. Kaplan-Meier analysis was used to evaluate PFS and OS.

Results: Of 118 patients who were identified, 74 were stage IA, 23 were stage IB, and 21 were stage II. Fifty-two patients underwent OBS and 66 received adjuvant treatment, with 49 patients (74%) receiving CT, 10 (15%) receiving RT, and 7 (11%) receiving both. Although the OBS group was older (70.2 vs 63.2 years, P=0.0009), the two groups were otherwise similar in demographics, tumor characteristics, and surgical management. Nine patients (17%) recurred in the OBS group compared to 17 (26%) in the adjuvant group (P=0.37). Two-year PFS was similar between adjuvant and OBS groups (82% vs 70%, P=0.82). While median OS favored adjuvant treatment (65.4 months [95% CI 33.2-97.6]) compared to OBS (41.6 months [95% CI 35.3-47.8]), this was not statistically significant (P=0.61).

Conclusions: In this cohort with early-stage UPSC and CC endometrial carcinoma, adjuvant therapy did not improve PFS or OS. Observation may be reasonable in a subset of older patients who may not tolerate adjuvant therapy.

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341 - Poster Session A

Association between endometrioid endometrial cancer (EC) risk classification and gene expression in The Cancer Genome Atlas (TCGA) dataset

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Objectives: To investigate if gene expression can differentiate EC risk classification based on Gynecologic Oncology Group (GOG) 99 in TCGA patients.

Methods: Gene expression was extracted from sequenced samples in TCGA data from 271 endometrioid type EC. Clinicopathologic parameters (grade, invasion, age, lymph node status) were evaluated in univariate, multivariate analysis. Patients were stratified to high risk (HR), high intermediate risk (HIR), and low/low intermediate risk (LR) based on clinicpathologic parameters from GOG 99. Cox proportional hazard ratio was used for survival analysis. BRB-ArrayTools were used (http://linus.nci.nih.gov/BRB-ArrayTools/) to construct a gene signature profile to classify patients among LR, HIR, and HR. Genes differentially expressed between the classes at a univariate significance level of P<0.001 were included in the predictor or gene signature. A cross-validated misclassification rate was used to evaluate the gene signature. The level of agreement between the predictor and the actual risk status was evaluated with accuracy and kappa test.

Results: There were 167 patients in the LR group, 81 patients in HIR group, and 23 patients in HR group in TCGA database with EC. GOG 99 risk classification and FIGO stage were independently significant for survival in the multivariate analysis (P<0.001). A total of 18,048 genes were included in the initial analysis, with 446 genes classified into HR, HIR, and LR-LIR subgroups individually (P=0.01), with 58% accuracy and a kappa coefficient of 0.32. When combining HR and HIR groups, the gene signature compared with LH patients included 608 genes (P=0.01), with 69%accuracy and a kappa coefficient of

0.36 (AUC 0.69), closer to the values of the gene signature that included only LH vs HR patients (accuracy 81%, kappa 0.33, AUC 0.74). Also, the expression of these 608 genes was separated into two different clusters by consensus clustering.

Conclusions: Gene expression analysis could differentiate risk groups in endometrioid EC. The gene signature grouping HIR and HR vs LR seems to be more accurate than using all three risk groups. This gene signature may help to identify higher risk patients with EC prior to surgery.

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342 - Poster Session A

Does the order of surgery and radiation therapy matter in the treatment of stage II endometrial cancer?

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Objectives: To determine whether the order of surgery and radiation therapy in the treatment of patients with endometrial cancer (EC) with gross cervical involvement affects overall survival (OS).

Methods: A total of 2,079 patients with EC involving the cervix were identified from the National Cancer Data Base (NCDB). All patients included in this study had gross cervical involvement of the tumor. OS was compared between four groups of patients: those who underwent radiation therapy followed by extirpative surgery (RT-Surg), those who underwent primary extirpative surgery followed by radiation (Surg-RT), those who underwent radiation as definitive treatment (RT), and those who underwent radical hysterectomy without radiation therapy as definitive treatment (RAH). OS was calculated for each group using Kaplan-Meier methods.

Results: Of the 2,079 patients identified, 161, 985, 189, and 744 patients were included in the RT-Surg, Surg-RT, RT, and RAH groups, respectively. Mean OS was 95, 113, 108, and 19 months for the RT-Surg, Surg-RT, RT, and RAH groups, respectively. When accounting for those patients with only node-negative disease, OS was 99 months, 113 months, 140 months, and 32 months for the RT-Surg, Surg-RT, RT, and RAH groups, respectively. For those patients with node-negative stage II EC with gross cervical involvement, OS was statistically significantly longer for those undergoing Surg-RT than for those undergoing RT-Surg by log-rank test (P=0.008).

Conclusions: The optimal timing of radiation therapy in relationship to surgery for patients with EC with gross cervical involvement has yet to be determined. For patients with node-negative clinical stage II EC, primary surgery followed by radiation therapy seems to convey a survival advantage when compared to radiation therapy followed by surgery.

Poster Session B
Sunday, March 23, 2014
Exhibit Hall

343 - Poster Session B

Impact of guideline adherence on patient outcomes in early-stage epithelial ovarian cancer

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Objectives: To evaluate the effects of adherence to National Comprehensive Cancer Network (NCCN) guidelines on survival outcomes in patients with early-stage epithelial ovarian cancer.

Methods: We retrospectively reviewed data on 266 patients with stage I epithelial ovarian cancer from our institutional cancer registry to determine compliance with treatment guidelines for surgery and adjuvant treatment. Patients were categorized according to adherence or nonadherence. The primary endpoints were recurrence-free survival and disease-specific survival. HRs for survival were estimated with a Cox proportional hazards model.

Results: Of the 266 patients, 71 (26.7%) underwent adequate surgical staging in accordance with the guidelines. The guidelines for adjuvant chemotherapy were followed adequately in all 71 patients with adherence to surgical staging and in 163 of the 195 patients with nonadherence to surgical staging (83.6%). Multivariate analysis, adjusted for prognostic factors, identified higher recurrence-free survival (HR 0.36, 95% CI 0.15–0.88) and disease-specific survival (HR 0.42, 95% CI 0.16–

1.12) among patients whose treatment adhered to both surgical and chemotherapy guidelines, although the difference in disease-specific survival was not statistically significant. When excluding clear cell histology from the cohort, the guideline-adherent group had significantly better disease-specific survival than the nonadherent group (HR 0.13, 95% CI 0.02–0.94).

Conclusions: The results of this study suggested that adherence to NCCN guidelines may improve survival outcomes in patients with early-stage epithelial ovarian cancer, particularly in cases other than clear cell histology.

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Availability and scope of integrated screening for patients with Lynch syndrome

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Objectives: Despite the documented benefits of screening and prophylactic interventions in familial cancer syndromes, these strategies have not been fully integrated into the care of patients with Lynch syndrome. Our objective was to evaluate the availability and scope of integrated centers for the medical care of Lynch syndrome patients in the United States.

Methods: The 60 National Cancer Institute (NCI)-designated cancer centers were contacted and asked a uniform set of questions according to an institutional review board-approved script. The questions focused on the care provided to Lynch syndrome patients, including recommended screening interventions, medical specialties involved in patient care, designation of a team leader, and methods employed to encourage cancer surveillance.

Results: Thirty-three (55%) of the NCI-designated centers agreed to participate in this study. All centers routinely recommended colonoscopy for Lynch patients. The other recommended screening modalities were endoscopy (82%), urinalysis (70%), endometrial sampling (64%), dermatologic examination (58%), pelvic ultrasonography (55%), serum CA-125 (42%), urine cytology (42%), and imaging with CT scan and/or MRI (3%). Eighty-eight percent of centers recommended risk-reducing hysterectomy and oophorectomy at completion of child-bearing. While each center had a multidisciplinary team for Lynch syndrome patients, the composition of this team varied (100% included gynecology, gastroenterology, and genetics; 82% included general surgery; 70% included dermatology; 55% included psychiatry; and 64% included social work). A team leader was designated at 64% of centers, most commonly a geneticist (48%) or gastroenterologist (29%). Only 46% of centers had an established system for communicating follow-up with patients and encouraging surveillance; the remainder left this task to the patient.

Conclusions: The institutions surveyed have developed multidisciplinary teams to care for Lynch syndrome patients. It is not surprising that there is a lack of consensus on practice patterns across institutions because evidence in the literature on the utility of most screening modalities is limited. One area in need of further development is methods communicating with patients and encouraging cancer surveillance.

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Socioeconomic status and health insurance as predictors of access to high-volume hospital care for women with early-stage ovarian cancer

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Objectives: To investigate the impact of sociodemographic, clinical, and health care system variables on access to high-volume ovarian cancer providers among women with stage I/II disease.

Methods: Consecutive patients diagnosed with stage I/II epithelial ovarian cancer between January 1, 1999, and December 31, 2006, were identified from the California Cancer Registry. Multivariate logistic regression analyses were used to evaluate for differences in access to high-volume hospitals (HVH) (≥20 cases/year) and high-volume physicians (HVP) (≥10 cases/year) according to race, health insurance payer, increasing composite selected exempt service (SES) quintile (SES-1 to SES-5), and clinical characteristics. Kaplan-Meier analysis was used to assess disease-specific survival. A Cox proportional hazards model was fitted to evaluate the independent effect on survival of demographic, disease-related, and provider volume predictors.

Results: A total of 5,445 patients were identified. The median age at diagnosis was 54.0 years (range, 18-99 years); 72.5% of patients had stage I disease and 27.5% had stage II disease. Overall, 977 patients (17.9%) were cared for at HVHs, and 869 patients (16.0%) were treated by HVPs. African Americans were less likely to receive care at LVHs (odds ratio [OR] 0.68, 95% CI 0.48-0.97). SES and payer status were significantly correlated with access to HVHs. Compared to the highest SES category (SES-5), patients with lower SES were significantly more likely to receive care at a LVH, with the lowest SES group (SES-1) having the highest risk (OR 1.74, 95% CI 1.32-2.30). Compared to managed care insurance (HMO/PPO), private/military/county-funded insurance (OR 1.61, 95% CI 1.29-1.99) and not insured status (OR 1.88, 95%CI 1.20-2.95) were independent predictors of LVH care. On multivariate analysis, LVH was associated with inferior ovarian cancer-specific survival compared to HVH (HR 1.24, 95% CI 1.02-1.49).

Conclusions: Among patients with early-stage ovarian cancer, treatment at an HVH is an independent predictor of superior ovarian cancer-specific survival, but access to HVHs is limited. Barriers to high-volume care for early-stage ovarian cancer are more pronounced for patients with low SES and non-managed care insurance.

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346 - Poster Session B

Cost comparison among robotic, laparoscopic, and laparoendoscopic single-site surgery in gynecologic oncology

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Objectives: Minimally invasive surgical (MIS) techniques have become standard practice in the management of patients in gynecologic oncology. In the era of the Affordable Care Act and with increased requirements for savings, it is important to evaluate the cost-effectiveness of different surgical approaches with similar outcomes. We sought to compare the operative, professional, and overall costs as well as complication rates among laparoscopy, robotic, and laparoendoscopic single-site surgery (LESS) in the management of patients with gynecologic malignancies.

Methods: Using retrospective chart review, 60 patients who underwent MIS within our institution were divided equally into three groups based upon the choice of surgical approach. Cost data were obtained from the hospital billing records and included professional fees, operating room costs, instrument costs, nursing costs, hospital charges, and total costs. Statistical analysis was performed using ANOVA and Chi-square tests, while Wilcoxon rank sum tests was used to compare costs across all groups.

Results: There was no difference in demographics, body mass index, preoperative diagnosis, comorbidities, procedure performed, or operative complication rates among the three groups. Median surgeon fees were highest for laparoscopy ($4,997 vs $3,890 vs $3,890, respectively, P=0.0003) when compared to robotic and LESS, and this relationship remained significant after adjusting for operative time (P=0.008). Median operative room costs were highest for the robotic group when compared to the laparoscopy and LESS groups ($26,854 vs $22,403 vs $22,152, respectively, P=0.001), also independent of operative time (P<0.0001). Disposable instrument costs were highest for the LESS group compared to the robotic and laparoscopic groups ($3,475 vs $2,121 vs $1,754, respectively, P=0.004). Total costs were higher for robotic surgery, followed by laparoscopic surgery and then by LESS ($37,926 vs $35,238 vs $32,231, P=0.0135).

Conclusions: Robotic surgery costs are significantly higher than both laparoscopic and LESS costs in our cohort of patients undergoing gynecologic oncologic surgery. We expect that with improvement in operative times and better choice of instrumentation, LESS will become the most cost-effective surgical approach for our patients.

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Use of a perioperative anticoagulation protocol in gynecologic oncology patients receiving continuous epidural analgesia

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Objectives: Nearly all gynecologic oncology patients have risk factors for venous thromboembolism (VTE). Our institution recently observed a significantly higher rate of VTE among patients receiving continuous epidural analgesia (CEA) and responded with new guidelines for perioperative anticoagulant use. We undertook this study to determine if the change in guidelines affected VTE rate.

Methods: In July 2012, a multidisciplinary team refined anticoagulation guidelines by requiring a prophylactic dose of anticoagulant within 1 hour after CEA catheter placement or before skin incision regardless of anesthesia type. Institutional review board approval was obtained and retrospective data collected for women having laparotomy between July 1, 2011, and June 30, 2013. Those having surgery in the year prior to the new protocol were used for comparison. Data included demographic and 30-day perioperative outcomes. Those with VTE identified preoperatively were excluded. The primary outcome was rate of VTE. The secondary outcome was protocol compliance. Chi-square and logistic regression were performed.

Results: There were 194 women treated under the new protocol (NP) and 237 historical cases (HC). More NP patients had cancer (68% vs 58%, P=0.038), pulmonary disease (24% vs 14%, P=0.013), and nonhypertensive cardiovascular disease (10% vs 2%, P<0.001). Other comorbidities, operative duration, estimated blood loss, and length of stay did not vary. Use of CEA increased over time (24% HC vs 34% NP, P=0.023). Compliance improved in CEA cases (12.5% HC vs 41.5% NP, P<0.001) but remained significantly below that in non-CEA (41.5% NP [CEA] vs 91% NP [non-CEA], P<0.001). When all cases were combined, CEA showed an association with VTE (P=0.003), but the rate of VTE differed in HC (1.7% non-CEA vs 8.9% CEA, P=0.008) compared with NP cases (0.8% non-CEA vs 4.6% CEA, P=0.076). The change in rate of VTE with CEA was not significant under the new guidelines (P=0.34). The overall rate of VTE, independent of anesthesia type, was stable (3.4% HC vs 2.1% NP, P=0.41).

Conclusions: CEA is associated with a significantly increased risk of VTE, but this could be a reflection of underlying noncompliance with perioperative anticoagulation recommendations. Compliance levels >40% are likely required before an effect, if any, can be demonstrated.

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Body mass index (BMI), postoperative complications, and perioperative resource utilization by hysterectomy approach for patients in a national cohort with endometrial cancer or complex atypical hyperplasia

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Objectives: The appropriate role for laparotomy and laparoscopy in the treatment of obese patients with endometrial cancer (EC) or complex atypical hyperplasia (CAH) has been debated in published research and clinical practice. The objective of this study was to compare postoperative complications and perioperative resource utilization between laparotomy and laparoscopy staging stratified by BMI among a national cohort with EC or CAH.

Methods: Women with the diagnosis of EC or CAH undergoing hysterectomy in the American College of Surgeons National Surgical Quality Improvement Program from 2005 to 2011 were identified. A composite index of major postoperative complications occurring within 30 days of surgery, total operative time, anesthesia time (time in operating room that is not operative time), and hospital stay were calculated. Patients' BMIs were grouped as: <30 (Group 1), 30-40 (Group 2), 40-50 (Group 3), and >50 (Group 4). The rates of complications and resource utilization in laparotomy and laparoscopy approaches were compared, stratified by BMI groups. Statistical significance was assessed using Fisher's exact, Chi-squared, and Student's t-tests.

Results: A total of 1,396 patients met inclusion criteria. Laparoscopy was associated with fewer composite postoperative complications in comparison to laparotomy in BMI Groups 1 (4.8% vs 12.3%) and 2 (6.4% vs 14.3%) but not Groups 3 (10.7% vs 17.4%) and 4 (10.2% vs 23.9%) (P values 0.002, 0.005, 0.125, 0.056, respectively) (Table). Median operative times were longer in all BMI groups by 25% to 60% (36 to 63 minutes) for laparoscopy. Median anesthesia times were longer in all BMI groups by 10% to 26% (5 to 12 minutes) for laparoscopy. Hospital stays were shorter for all BMI groups by an average of 1.9 to 4.3 days with laparoscopy.

Conclusions: Women with BMIs <40 undergoing laparoscopic EC and CAH staging had fewer postoperative complications, longer operative times, longer anesthesia time, and shorter hospital stays. For women with BMIs >40, laparoscopy still offered improved hospital stay durations, with a statistical trend toward fewer postoperative complications, while still requiring more operative and anesthesia time.

Table: Postoperative morbidity of laparotomy (Open) and laparoscopy (MIS) stratified by body mass index (BMI)

	BMI group for laparotomy and laparoscopy							
	BMI < 30		BMI 30-40		BMI 40-50		BMI >50	
	Open	MIS	Open	MIS	Open	MIS	Open	MIS
Number of cases	227	288	252	234	161	112	71	49
Morbidity type								
Vascular	0.44%	0%	0.40%	0%	0%	0%	0%	0%
Wound / Incision	4.41%	1.74%	6.75%	0.85%	13.66%	4.46%	16.90%	0%
Pulmonary	1.76%	0.60%	0.40%	0%	1.86%	0.86%	1.41%	0%
Renal	0.44%	0%	0.40%	0%	0%	0.89%	0%	0%
Blood Transfusion	6.17%	0.69%	1.59%	0.85%	1.86%	1.79%	4.23%	2.04%
Venous thromboembolism	0.88%	0%	2.38%	2.14%	1.24%	1.79%	0%	0%
Infectious	0.88%	0.35%	4.76%	2.99%	3.73%	4.46	4.23%	8.16%
Composite Morbidity	12.30%	4.80%	14.30%	6.40%	17.40%	10.70%	23.90%	10.20%
P-value for composite morbidity	0.002		0.005		0.125		0.056	

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Use of Lean and Six Sigma methodology to improve clinic efficiency in a high-volume tertiary care gynecologic oncology clinic

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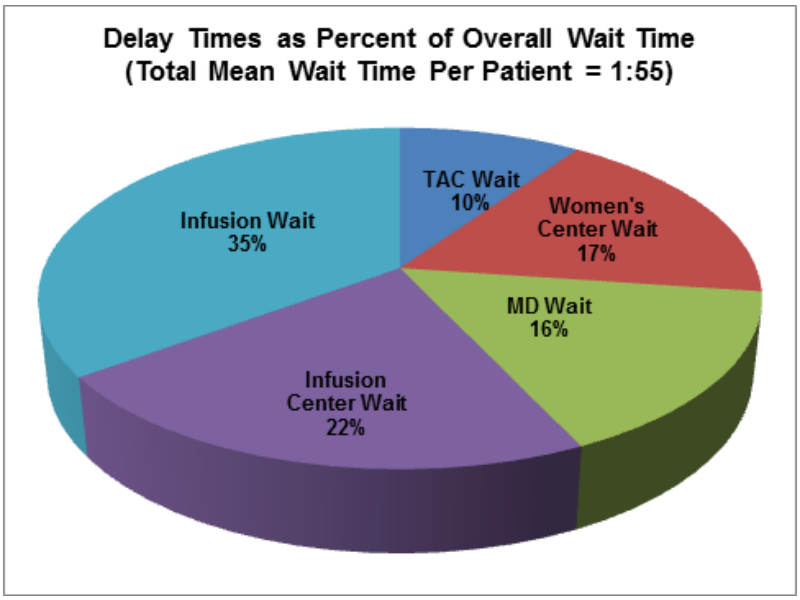
Objectives: Gynecologic oncology patients undergoing chemotherapy require frequent visits to the cancer center. Each care visit often involves appointments at multiple locations within the cancer center (laboratory, physician, infusion unit). This physical discontinuity can lead to considerable variability in patient flow, decreased care efficiency, and a less positive patient experience. The purpose of this study was to use Six Sigma/Lean methodology to identify variability in patient flow to guide solutions for improvement.

Methods: We used patient surveys and clinical timestamps to identify which visit components were frequently contributing to delays and to identify process variability. Women recorded the details of their appointments and wait times using a standardized tool, and this information was corroborated with electronically recorded timestamps.

Results: Twenty-one women participated in the initial phase of the study. While women experienced relatively short wait times (mean, 11 minutes; range, 0-22 minutes) for the first appointment, the average wait time between appointments gradually increased, with a peak mean wait time of 65 minutes (range, 26 minutes to 1 hour and 57 minutes) just prior to drug infusion. The total mean wait time, inclusive of all appointments, totaled 1 hour and 55 minutes (range, 50 minutes to 2 hours and 49 minutes), indicating the excess amount of time per day spent in the cancer center. Although a portion of patients did arrive late to appointments, the number whose visits started later than the scheduled time far exceeded this quantity. This trend was especially apparent in the gynecologic oncology clinic and infusion unit.

Conclusions: Analyzing patient flow through the cancer center can elucidate inefficiencies and guide improvements. Next steps toward manageable interventions include confirming the points of greatest process variability through value stream mapping and enlisting change management techniques to direct adjustments.



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An economic analysis of cisplatin alone versus cisplatin doublets in the treatment of women with advanced or recurrent cervical cancer

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Objectives: Randomized trials have demonstrated improvements in overall survival when using platinum doublets compared to single-agent platinum in the treatment of women with advanced or recurrent cervical cancer. We sought to evaluate the cost-effectiveness of these regimens.

Methods: Gynecologic Oncology Group (GOG) protocols 169 and 204 were analyzed using a decision model. Cisplatin alone was compared to cisplatin/paclitaxel (CP), cisplatin/topotecan (CT), cisplatin/gemcitabine (GC), and cisplatin/vinorelbine (CV). Parameters included overall survival (OS), cost, and complications. One-way sensitivity analyses were performed.

Results: The incremental cost-effectiveness ratio (ICER) for C vs CP was $12,409/quality-adjusted life-year (QALY) gained. In the cost-effective analysis, CT, GC, and VC were all dominated by CP. Sensitivity analyses demonstrated that even if the CT, GC, and VC were given without cost, CP would still be the regimen of choice.

Conclusions: CP is an acceptable alternative to cisplatin alone for the treatment of patients with advanced or recurrent cervical cancer, with an increase in cost of only $12,049/QALY. Given that GOG 204 also showed statistically significantly improved survival for CP, CP should be considered the regimen of choice.

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351 - Poster Session B

Safety and cost savings of omitting cardiac surveillance during treatment with pegylated liposomal doxorubicin in gynecologic oncology survivors

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Objectives: The manufacturers of pegylated liposomal doxorubicin (PLD) recommend careful monitoring of cardiac function in patients undergoing PLD treatment. However, a recent retrospective report suggests that routine surveillance of cardiac function may not be necessary in gynecologic oncology patients receiving PLD treatment. Our objective was to examine the safety and cost savings of omitting cardiac surveillance during treatment with PLD.

Methods: In this retrospective, single-institution review, we examined consecutively treated patients from 2002-2013 who received PLD alone, or in combination, for the treatment of a gynecologic malignancy. Over the last decade, we have employed a selective cardiac surveillance strategy in this setting, with echocardiography (ECHO) performed only in patients at high risk for congestive heart failure (CHF) or who develop symptoms during treatment. Clinical records were reviewed for adverse effects and outcomes. Cost analyses were performed utilizing published Medicare professional and technical fee rates for ECHO (cost: $341.29 per test).

Results: Ninety-three patients received PLD during the study period; their mean age was 61.8 years. The majority of patients were treated for ovarian, tubal, or peritoneal carcinoma (78%). Median cumulative administered dose of PLD was 240 mg/m^2, with 12 patients receiving ≥530 mg/m^2. Nine patients (9.6%) underwent pre-, peri-, or post-treatment ECHO. Of these, eight had at least one cardiovascular risk factor. Two of these patients developed shortness of breath during treatment that was ultimately unrelated to chemotherapy. No patients experienced peri/posttreatment CHF or any other cardiac toxicity during a mean follow-up of 19.2 months. Selective, instead of routine, use of ECHO in the study population resulted in a cost savings of $57,336.72.

Conclusions: In our analysis, there was no clinical evidence of PLD-induced CHF, suggesting that there is little need to perform cardiac surveillance in patients without significant cardiovascular risk factors. Omission of cardiac surveillance resulted in significant cost savings without adversely affecting clinical outcomes.

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Cost-effectiveness analysis of treatment modalities for women with high-intermediate risk endometrial carcinoma: should Gynecologic Oncology Group (GOG) 249 have included a chemotherapy-only arm?

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Objectives: GOG 249 was developed to determine if the combination of vaginal brachytherapy (BT) and three cycles of paclitaxel and carboplatin (PC) are superior to whole pelvic radiation therapy (WPRT) in terms of disease-free survival for high-intermediate risk (H-IR) endometrial cancer (EMCA) patients. Accordingly, we estimated the costs and outcomes of four treatment modalities used for the management of H-IR EMCA.

Methods: A decision analysis model compared four treatment strategies for the management of H-IR EMCA following robotic hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. Patients were classified as H-IR using GOG 99 criteria: grade 2 or 3 histology, deep myometrial invasion, and lymphovascular space invasion. The four strategies were: 1) observation, 2) WPRT, 3) adjuvant chemotherapy with three cycles of PC plus BT, and 4) adjuvant chemotherapy with six cycles of PC. Five-year disease-free survival was estimated from published data. 2013 Medicare reimbursement rates were used to estimate costs for surgery, chemotherapy, and radiation therapy. Cost-effectiveness ratios and incremental cost-effectiveness ratios (ICERs) were determined for each strategy. Sensitivity analyses were performed on pertinent uncertainties.

Results: For the estimated 8,000 women diagnosed annually with H-IR EMCA in the United States, the estimated annual cost of observation is $15.7 million (M), with 5,712 5-year disease-free survivors. Three cycles of PC and BT cost $35.7 M and resulted in an additional 1,088 5-year disease-free survivors compared to observation. WPRT was the most expensive strategy at $97.0 M and had 1,248 more 5-year disease-free survivors than observation. Six cycles of PC was the most cost-effective strategy at a cost of $23.6 M and resulted in 7,008 5-year disease-free survivors. The ICER of each additional 5-year disease-free survivor in the chemotherapy-alone strategy compared to observation was $6,130.

Conclusions: Although outcomes from GOG 249 will ultimately help to define adjuvant therapy decisions in H-IR EMCA, our data demonstrate that adjuvant chemotherapy is a cost-effective strategy. Radiation strategies increase the number of disease-free survivors, but substantial costs of radiation therapy affect the cost-effectiveness of these strategies.

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353 - Poster Session B

A novel clinical trial recruitment strategy for women's cancers

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Objectives: National clinical trial enrollment in cancer studies remains <4%. To address the impediments to trial participation, we developed a novel online registry of women interested in clinical research as well as a clinical trial matching mechanism. We sought to improve clinical trial accrual at a single institution using this strategy to match potentially eligible women with open studies.

Methods: Using a secure online verification platform (Docusign) for informed consent, we designed a web-based registry for women >18 years who expressed interest in clinical research. Women could enroll and provide brief clinical and demographic information remotely to aid in determining if they were eligible for an open study at our institution. The registry was approved by the institutional review board, and the registry website was linked to other portals, including the hospital's and several women's cancers support organizations' websites, as well as posted to several social media outlets.

Results: In the first 5.5 months, 225 participants enrolled online for an average of 41 participants per month, almost eight times the rate of accrual compared to an older paper-based system. In addition, since the implementation, 184 participants have been identified as qualifying for at least one research study available at our institution, with 41 of these qualifying for more than one study. Seven women (4%) have consented thus far, and study staff are in the process of working with 20 other participants (total of 14.6%) to set up face-to-face consenting for appropriate studies.

Conclusions: Clinical trial enrollment was significantly improved by implementation of an online registry to aid matching of relevant studies with interested patients. In the first 6 months since launching the web-based portal, a fourfold improvement was seen over our previous enrollment.

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Out with the old and in with the neoadjuvant: changes and influences in ovarian cancer practice patterns among Society of Gynecologic Oncology (SGO) members

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Objectives: To identify current practice patterns among members of SGO in prescribing neoadjuvant chemotherapy (NACT) and to determine the threshold for changing practice patterns.

Methods: A survey was emailed to current SGO members practicing in the United States (n=872). An internet survey database was used to administer the survey and collect data. Frequencies and distributions were calculated for all survey questions.

Results: Twenty-seven percent of members with valid email addresses responded (n=155). The majority of physicians still perform up-front cytoreductive surgery (97% administer neoadjuvant chemotherapy <50% of the time), but 50% of physicians reported changing their practice patterns in administration of NACT since the recent Vergote et al publication. Most participants (78%) still use <1 cm of residual disease as the standard of optimal cytoreduction; 21% employ a definition of no gross residual disease. In deciding whether to attempt up-front surgery, a patient's performance status most strongly affected the physician's decision of whether to proceed (39%), followed by medical comorbidities (28%), and CT findings (21%). When asked specifically if a test could predict whether a patient could be optimally cytoreduced to no gross residual disease, most felt that that a specific test would have to be >90% accurate in predicting suboptimal cytoreduction in order for them to administer NACT. Interestingly, 25% of practitioners stated that they would proceed with surgery despite a >90% test accuracy if they still thought they could optimally cytoreduce a patient to no residual disease.

Conclusions: The majority of gynecologic oncologists still proceed with up-front cytoreductive surgery, but more physicians are administering NACT. Most survey participants feel that there is not an adequate predictor for suboptimal cytoreduction and place more emphasis on patient factors such as health and performance status rather than CT or physical examination findings when deciding whether to provide NACT.

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355 - Poster Session B

National Comprehensive Cancer Network (NCCN) guidelines for gynecologic malignancies: where's the beef?

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Objectives: To evaluate the level of scientific evidence behind the NCCN guidelines for ovarian, uterine, and cervical cancers with regard to evaluation, staging, therapy, and surveillance.

Methods: The references in the NCCN guidelines were evaluated based on category and level of evidence. Category 1 is high-level evidence with uniform consensus, 2A is lower-level evidence with uniform consensus, 2B is lower-level evidence with nonuniform consensus about the panel, and Category 3 is any level with major disagreement about the panel. Level I evidence refers to a properly designed randomized, controlled trial (RCT); Level II evidence is from well-designed non-RCTs, cohort, or case-control studies; and Level III consists of expert opinion, descriptive studies, or clinical experience.

Results: A total of 338 recommendations were evaluated for cervical, uterine, and ovarian neoplasms. Most recommendations were Category 2A (73.3%); Category 1 recommendations comprised only 6.8% and the remaining 19.9% were composed of categories with nonuniform consensus (2B and 3). In uterine neoplasms, only 3/154 recommendations (1.9%) were Category 1, 81.8% were Category 2A, and 16.3% were nonuniform consensus. Of these, only 26.6% were based on Level I evidence. Guidelines for ovarian cancer contained 124 recommendations, the majority of which were category 2A (71%). The recommendations were based mostly on Level II evidence (74.2%); only 24.2% of the cited work was based on RCTs. Sixty recommendations were made for cervical neoplasms, 11.7% of which were Category 1. Thirty-four (56.7%) were Category 2A, and nonuniform consensus (2B and 3) comprised nearly one-third (31.3%) of the recommendations. Most recommendations were based on Level II evidence (61.7%). Level I evidence was cited in 31.7% of recommendations, and Level III evidence was cited in 6.7%.

Conclusions: With health care reform in progress, the need for generalizable consensus recommendations and quality scientific evidence is greater than ever. Nearly one third of the NCCN guidelines have nonuniform panel consensus and are largely based on Level II and III evidence. These data highlight a marked lack of consensus among participating institutions, with a preponderance of non-Level 1 data.

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356 - Poster Session B

Clinical utility and cost-effectiveness of preoperative CT in endometrial cancer patients

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Objectives: To determine the clinical value of the routine use of preoperative CT in endometrial cancer (EC).

Methods: Data for 1,393 consecutive patients treated for EC between 1999 and 2008 were reviewed. A total of 225 (16%) patients with both preoperative endometrial sampling and abdominal CT scans available were included in the study. Based on preoperative diagnosis, we dichotomized patients in low (grades 1 and 2 endometrioid) and high (grade 3 endometrioid and type II) risk and evaluated the clinical utility (capability of detecting gross intra-abdominal disease [GID], enlarged nodes [>1 cm], and/or relevant incidental findings [IF]) and cost-effectiveness of CT.

Results: The low-risk group included 138 (61%) women, and 87 (39%) women were included in the high-risk group. GID was detected in 4 (2%) and 14 (16%) patients in the low- and high-risk groups, respectively (P<.001). The rate of true positive pelvic/aortic nodes on CT examination was 67%/71% and 67%/78% for low- and high-risk EC, respectively (P>0.05). Surgical plans changed in 16 (7%) patients, based on IF detected by CT. The potential role of CT to reduce the rate of conversion from minimally invasive to open surgery (i.e., patients with GID not clinically evident at physical examination) was estimated at 1:35 and 1:8 in low-risk and high risk-groups, respectively (P=.005). Costs to identify one “positive” patient were $28,048 for low-risk EC vs $8,536 for high-risk EC. The role of CT in detecting findings not evident at a minimally invasive pelvic procedure (i.e., gross positive aortic nodes and upper abdominal/retroperitoneal IF) was 1:13 ($10,199) and 1:5 ($4,160) in low- compared to high-risk EC (P=0.007).

Conclusions: In high-risk patients, CT may help in formulating operative plan, thus reducing the need for conversion following minimally invasive exploration. Also, CT may help to identify significant extrapelvic findings not apparent during minimally invasive procedures confined to the pelvis.

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Improving outcomes in patients with suspected ovarian cancer: a quality improvement program

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Objectives: Although primary surgical debulking is the cornerstone of ovarian cancer treatment, it can be associated with significant morbidity. Neoadjuvant chemotherapy (NACT) followed by interval cytoreduction (IC) has been adopted as an alternative to primary debulking for select patients with suspected ovarian cancer. We initiated a quality improvement (QI) project that incorporated NACT for those patients who were deemed unlikely to undergo optimal primary surgical debulking.

Methods: From January 1, 2013 to July 31, 2013, patients with suspected ovarian cancer deemed by their surgeons to have a low likelihood of optimal debulking were triaged to NACT followed by IC. A decision for surgery was based on a comprehensive review of clinical data, performance status, and radiographic assessment. Demographics, surgical data, postoperative complications, and 60-day mortality were collected. The University Health System Consortium (UHC) mortality risk adjustment evaluated the observed/expected mortality (OEM) on all hospitalized gynecologic oncology patients. The OEM for the first 6 months of the QI project was compared to the OEM from the 12 months before o initiating the QI project.

Results: Of 89 enrolled patients, 75 were eligible, and 49 (65%) underwent primary debulking with an 86% optimal debulking rate. Seven patients had 13 postoperative complications. There was a 16% 30-day readmission rate and a 2% mortality rate. Twenty-six patients (35%) underwent NACT. One patient had a complication after laparoscopic biopsy and two patients (8%) died before receiving NACT. Twenty-two patients have undergone IC, with an 86% optimal debulking rate. Two patients had three postoperative complications. There was a 9% 30-day readmission rate and 5% mortality rate after IC. There was a 33% reduction in the average OEM for the gynecologic oncology service for January to June 2013 compared to January to December 2012 (0.56 [range, 0-1.1] vs 0.839 [range, 0-2.46]).

Conclusions: Although it is difficult to predict which patients are most likely to undergo optimal primary surgical debulking, surgical morbidity and mortality can be decreased by using NACT in select patients. The initiation of a QI project has contributed to a substantial decrease in mortality at our institution.

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Cost comparison between in hospital death and discharge to hospice among gynecologic cancer patients

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Objectives: To calculate the difference in inpatient cost between death in hospital and discharge to hospice among patients with gynecologic cancers.

Methods: The University Health System Consortium (UHC) database is a compilation of data from >110 academic medical centers and nearly 250 affiliate hospitals. Total cost and discharge data were queried using the ICD-9 codes for cervical, endometrial, and ovarian cancer during October 2009 to July 2013. Race was stratified as African American (AA), Asian (A), and Caucasian (C). Discharge status was based on patients diagnosed with a gynecologic malignancy who either died in the hospital or were discharged to hospice care. Mean direct costs associated with in-hospital death without hospice intervention and discharge to hospice were compared.

Results: The mean direct cost for patients who died in the hospital was significantly higher than for those who were discharged to hospice ($20,934, 95% CI $19,486-$22,022 vs $11,726, 95% CI $11,323-$12,130, $P<0.05$). Discharge to hospice was associated with a 44% cost reduction. When stratified according to race, the mean cost for AA ($10,444) admitted to hospice was significantly lower than for A ($14,311) and C ($12,137, $P<0.0001$).

Conclusions: Hospice enrollment for appropriate patients is a National Quality Forum-endorsed measure and has been included as an American Society of Clinical Oncology Quality Oncology Practice Initiative (QOPI) indicator. We found that discharge to hospice is associated with significant cost reduction compared to death in hospital among gynecologic oncology patients. AA had the lowest associated costs among racial groups when admitted to hospice. Future research can focus on minimizing this health disparity and further elucidating the role of palliative care in gynecology oncology. The 2014

Affordable Care Act emphasizes improving quality while controlling cost; we conclude that the timely offering of hospice care to suitable gynecology oncology patients achieves both of these aims.

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Preoperative imaging of uterine malignancy

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Objectives: To characterize the utility of preoperative imaging studies in surgical treatment of uterine malignancy at a single academic medical center.

Methods: Retrospective chart review was undertaken of all patients undergoing surgery for uterine cancer at a single institution from 2009 to 2012. Among patients who received CT or MRI scans, radiologist reports were abstracted for evidence of deep myoinvasion, evidence of pelvic or paraaortic lymphadenopathy, extracorporeal disease, or incidental findings. Patients referred due to a pelvic mass were excluded from the analysis.

Results: Of 458 patients undergoing hysterectomy for uterine cancer, 208 (45%) received preoperative CT or MRI. Preoperative CT/MRI scans were ordered equally by referring clinicians and gynecologic oncologists (47%/53%). Preoperative CT/MRI was most common among patients referred with grade 3 endometrioid or nonendometrioid histology (84%), but 80 of 253 patients (32%) with grade 1 endometrioid cancer underwent CT/MRI scans. Of 11 scans suggesting nodal metastases, all 11 patients had uterine indications for comprehensive staging by modified Mayo criteria, and 6/11 (55%) had nodal disease on final pathology. Patients who underwent preoperative imaging and had no evidence of deep myoinvasion or extrauterine disease (a negative test result) were less likely to have received minimally invasive surgery (MIS) than patients who did not have preoperative CT/MRI (P=0.02). Medicare reimbursement for abdominopelvic CT scan in 2012 was $581.

Conclusions: In our series, preoperative CT/MRI imaging did not affect the surgical planning with respect to the use of MIS. A negative scan did not seem to influence the choice of surgical approach and also did not make the patient more likely to undergo MIS rather than laparotomy. As experience with MIS evolves to include resection of extrauterine disease in many cases, preoperative CT/MRI imaging should be used less frequently. Although a subset of patients may be best managed nonoperatively if they require treatment of extensive metastatic extrauterine disease, in practice, 45% of patients with uterine malignancy undergo costly preoperative imaging of a disease primarily managed surgically.

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Fighting cancer together: shared medical appointments - a feasibility survey

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Objectives: Shared medical appointments (SMA) are a novel approach to health-care delivery. In lieu of the traditional single provider and patient visit, a physician engages of group of patients in an extended visit that allows more time for education and discussion. This model has now been applied in various medical conditions but has not been attempted in gynecologic oncology. Our objective was to assess the perceived feasibility of and interest in SMA among gynecologic cancer patients and providers.

Methods: A qualitative study interviewing health-care providers and patients at a comprehensive cancer hospital was performed. Individual interviews were conducted, transcribed, and coded and themes were identified.

Results: A total of 26 health-care providers and 24 patients were interviewed. The median age of patients was 60 years (range, 34-85 years). The majority were white (75%) and had ovarian cancer (63%). All patients reported a history of surgery, chemotherapy, or both, with 36% actively receiving treatment. The majority of providers interviewed were physicians (65%). The remainder of providers included clinical pharmacists, advanced practice nurses, registered nurses, and a psychologist. Thirty-five percent of providers, but no patients, had previous knowledge of SMA. After a brief description of the model, 92% of providers and 58% of patients stated they would be interested or would consider participating in a group. Of the seven patients not interested in SMA, all cited privacy concerns as a reason for disinterest. Overall patients would like

to see more information about treatment during their appointments. When patients were asked about advantages of SMA, the two most common answers were support (63%) and education (38%). The most prevalent concerns about a group approach were difficulty with group dynamics (29%); privacy concerns (29%); and increased anxiety, fear, and concern about bad news (21%). Both providers and patients rated prechemotherapy and survivorship as optimal settings to initiate SMA.

Conclusions: In an era of rising health-care costs and increasing demands on providers, SMA offer an innovative approach to improve efficiency and quality of care consistent with published aims of the Institute of Medicine. Our data suggest that there is enough provider and patient interest to consider integration of SMA into comprehensive care of the cancer patient.

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Breast cancer following ovarian cancer in *BRCA* mutation carriers: what is the cost of surveillance?

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Objectives: Women with *BRCA* mutations have an elevated risk of developing breast cancer and epithelial ovarian cancer (EOC) (ovary, fallopian tube, and peritoneal carcinomas). We compared the costs of breast cancer surveillance between *BRCA* mutation carriers and women without mutations (WT) following a diagnosis of EOC.

Methods: The institutional review board approved a retrospective review of 360 women with EOC identified by the Women's Cancer Registry from 1998-2012 who had *BRCA* genetic testing and subsequent care at our institution.

Results: A total of 134 (37%) EOC patients were found to carry a germline *BRCA*1 or *BRCA*2 mutation. Fifteen women subsequently developed breast cancer: 12 (9%) *BRCA* patients and 3 (2%) WT patients. *BRCA* mutation carriers had significantly more annual mammograms (MMG) than WT patients (78% vs 38%, $P<0.0001$). The frequency of breast cancer surveillance in *BRCA* mutation carriers was unaffected by stage of disease (87% early-stage vs 81% late-stage). In contrast, WT patients with advanced-stage disease had less breast cancer surveillance than early-stage patients (32% vs 76%, $P<0.001$). Other breast cancer surveillance and risk-reducing strategies were only used in *BRCA* mutation carriers: annual breast MRI in 60 patients (45%), >1 breast surgeon consultation in 53 patients (39%), and tamoxifen or aromatase inhibitors in 25 (19%) of patients for an average of 12 months. Fifteen *BRCA* mutation carriers underwent a prophylactic mastectomy. Seventy-five percent of breast cancers were detected by either MMG or breast exams, and all patients were diagnosed with early breast cancer (Table 1). MRI did not detect any breast cancers. Surveillance was significantly more costly in *BRCA* mutation carriers than in WT patients at $512 vs $261 to detect 1 cancer/year ($P=0.0007$).

Conclusions: Breast cancer is more common in *BRCA* mutation carriers than WT patients following EOC, although the incidence is low. MMG detected most breast cancers at an early stage. Multimodality breast cancer surveillance used in *BRCA* mutation carriers was twice the cost of annual MMG in WT patients. Multimodality breast cancer surveillance should be reconsidered in *BRCA* mutation carriers after EOC, given the significant additional cost and low rates of detection.

	BRCA-associated breast cancer N=12	BRCA wild type breast cancer N=3
Initial detection		
Clinical breast exam	2 (17%)	2 (67%)
Mammogram	7 (58%)	1 (33%)
Prophylactic mastectomy	3 (25%)	0
Stage breast cancer		
DCIS	4	0
Stage 1	6	0
Stage 2	2	3

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Robotic versus abdominal radical hysterectomy for early cervical cancer: a single-center experience

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Objectives: To compare pathologic, intraoperative, and postoperative outcomes of robotic radical hysterectomy (RRH) to abdominal radical hysterectomy (ARH) in patients with early-stage cervical carcinoma, some of whom were treated after neoadjuvant chemotherapy.

Methods: A retrospective analysis of women who underwent RRH and ARH from January 2006 to December 2012 was performed. The data analyzed included patient demographics, histology, clinical stage, surgical margins, and lymph node and disease status. Comparison was made to a group of historical open radical hysterectomies. Statistical analysis was performed using STATA10.

Results: A total of 150 women underwent RRH and 150 patients had ARH during the study period. Squamous was the most common histology for both groups (48% and 45%, respectively), followed by adenocarcinoma (34% and 36%, respectively). There was a statistically significant difference in age (45 vs 48 years), tumor diameter (mean 22 vs 30 mm), number of removed lymph nodes (22 vs 26), and mean positive pelvic lymph node count (0.3 vs 1.2), and no statistical difference in lymphovascular space involvement. We observed no statistical differences in operative time (289 vs 216 min) or statistical differences in estimated blood loss (95 vs 239 mL) or hospital stay (3.9 vs 5.7 days) in favor of RRH. None of the robotic procedures required conversion to laparotomy. The differences in major operative and postoperative complications between the two groups were not significant. Adjuvant treatment was administrated in 30% of patient after RRH and in 55% after ARH. Recurrence rates were not statistically different for the two groups.

Conclusions: RRH is safe and feasible and has been shown to be associated with improved operative outcomes. Longer follow-up is needed, but early data are supportive of at least equivalent oncologic outcomes compared with other surgical modalities.

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Trends in robotic surgery in uterine cancer: a nationwide study of 13,719 patients

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Objectives: To analyze the trends and associated charges in the use of robotic surgery in endometrial cancer.

Methods: Data were obtained from the National Inpatient Survey for the years 2008 to 2010. We divided the study into three study periods: Q4-2008 to Q2-2009, Q3-2009 to Q1-2010, and Q2-2010 to Q4-2010. Costs were adjusted to the fourth quarter of 2010 using the hospital Producer Price Index. Chi-square, t-test, ANOVA test, and binomial logistic regression methods were used to adjust for confounding variables.

Results: Of 13,719 patients, 67% had open surgery (OS), 13% laparoscopic surgery (LS), and 20% robotic surgery (RS). The median age was 62 years (range, 20-99 years). The majority of patients were white (79%). Most patients were covered by either private insurance (49%) or Medicare (41%); the remainder were covered by either Medicaid (6%) or were uninsured (4%). Over the three time periods, the proportion of patients receiving RS increased from 14% to 20% to 26%, with a corresponding decrease in LS (35% to 31% to 34%) and OS (36% to 34% to 29%) ($P<0.01$). We found the mean age of patients receiving RS increased (62 to 62 to 63 years, $P=0.02$). In a subset analysis of patients receiving RS, we found an increase in the use of RS among those of lower socioeconomic class (37% to 41% to 44%, $P=0.01$). Additionally, we found an increase in the proportion of patients undergoing RS who were covered either by Medicare or Medicaid or who were uninsured (37% to 40% to 46%, 3% to 4% to 4%, and 1% to 2% to 2%, $P<0.01$). In a subset analysis of patients receiving RS, there was also an increase in the morbidly obese (14% to 14% to 19%, $P<0.01$). We found an increase in overall charges for hospitalization from $31,012 to $32,348 to $33,916 over the three study periods ($P<0.01$). More specifically, the median charge for RS vs LS was $36,046 vs $31,363 ($P<0.01$). However, we were unable to show a significant change in charges for RS over the study period ($37,683 to $36,866 to $34,301, $P=0.08$). After adjusting for race, type of insurance, income, and obesity, there was significant increase in numbers of patients receiving RS over each time period (HR 1.69, 95% CI 1.59-1.81, $P<0.01$).

Conclusions: In this nationwide study, we found an increase in the use of RS for endometrial cancer without a variation in associated hospital charges.

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Is paclitaxel a more cost-effective choice for maintenance therapy than bevacizumab in the primary treatment of advanced ovarian cancer?

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Objectives: To determine whether the addition of maintenance therapy with bevacizumab or paclitaxel for the primary treatment of ovarian cancer is cost-effective in the state of Maryland.

Methods: A cost-effectiveness analysis was performed comparing adjuvant therapy and adjuvant therapy plus maintenance therapy. The data for bevacizumab maintenance therapy was obtained from Gynecologic Oncology Group (GOG) 218, which compared 6 cycles of paclitaxel and carboplatin (PC) to 6 cycles of paclitaxel, carboplatin, and bevacizumab followed by 16 cycles of bevacizumab (PCB). The data for paclitaxel maintenance therapy were obtained from GOG 178, which compared 6 cycles of paclitaxel and carboplatin plus 3 months of paclitaxel (PC+3P) to 6 cycles of paclitaxel and carboplatin plus 12 months of paclitaxel (PC+12P). Actual costs of treatment plus potential costs of complications were established for each strategy. Progression-free survival (PFS), overall survival (OS), and bowel perforation rates were taken from the respective manuscripts. A strategy is considered cost-effective if its incremental cost-effectiveness ratio (ICER) is <$50,000 per life-year saved.

Results: Total cost per treatment group of the evaluated regimens were as follows: PC $10,794 vs PCB $268,574 and PC+3P $16,047 vs PC+12P $31,806. Estimated terminal cost per treatment group of the evaluated regimens was as follows: PC $11,805 vs PCB $ 261,738 and PC+3P $15,614 vs PC+12P $31,969. These costs led to ICER-PFS PC REFERENCE vs PCB $65,772 and PC+3P REFERENCE vs PC+12P $2,044. In addition, the costs led to an ICER-OS PC REFERENCE vs PCB $624,831 and PC+3P REFERENCE vs PC+12P $3,270.

Conclusions: Our investigation confirms previous literature indicating that maintenance paclitaxel is more cost-effective than bevacizumab. In contrast to prior studies, our investigation separately compared each maintenance arm to its matched control arm. Using a threshold of $50,000 per life-year saved, maintenance bevacizumab was not cost-effective from a PFS or OS standpoint. Maintenance paclitaxel is cost-effective from both a PFS and OS standpoint. However, the improvement in OS associated with maintenance paclitaxel in GOG 178 was not significant.

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Multiple lines of chemotherapy in recurrent epithelial ovarian cancer, are more lines better? A decision analytic model

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Objectives: Recurrent epithelial ovarian cancer (EOC) is commonly treated with multiple lines of chemotherapy, but data regarding its effectiveness are limited. This study sought to model the effectiveness of multiple lines of chemotherapy in recurrent EOC.

Methods: A decision analytic Markov model was constructed using TreeAge software. Platinum-sensitive recurrent EOC patients who were not candidates for secondary surgical cytoreduction were treated at the time of first recurrence. Six strategies were analyzed, each beginning with carboplatin and gemcitabine and followed by successive lines of chemotherapy: 1) carboplatin and gemcitabine only, 2) two lines, 3) three lines, 4) four lines, 5) five lines, or 6) six lines of recurrent therapy. Primary outcome was expected life-years (LY) gained per person for each strategy. Probabilities and response rates were derived from published peer-reviewed studies. Sensitivity analyses on pertinent model parameters were performed. Cost and utility analyses are ongoing.

Results: The number of LY gained increased with increasing lines of chemotherapy. Treatment with carboplatin and gemcitabine alone provided a gain of 1.79 LY, while those receiving 6 lines of chemotherapy gained an expected 3.43 LY. The incremental gain in LY with each additional line of chemotherapy increased until the fourth line of chemotherapy, peaking at

almost 8 months. However, after the fourth line of therapy, the incremental LY gained decreased, with <3 months gained between lines 4 and 5 and <1 month from 5 to 6 lines of chemotherapy.

Conclusions: This decision analytic model provides additional information about the effectiveness of multiple lines of chemotherapy in recurrent EOC. Beyond the fourth line of chemotherapy, the model shows diminishing returns on life expectancy gained, with <3 months for each additional line of chemotherapy. This is notably shorter than time spent receiving a single standard line of chemotherapy. Thus, more lines of chemotherapy merit careful consideration to balance expected benefits with goals of care and treatment-associated toxicities.

Table.

Lines of Chemotherapy in REOC	LY Gained/Person	Incremental LY Gained/Person
1	1.79	0
2	2.12	0.32
3	2.49	0.37
4	3.13	0.64
5	3.35	0.23
6	3.43	0.08

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Is the survival advantage gained by the addition of bevacizumab to chemotherapy for the treatment of recurrent, persistent, or advanced cervical cancer worth the additional cost? A cost-effectiveness analysis

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Objectives: To determine whether the addition of bevacizumab to standard chemotherapy in the treatment of patients with stage IVB, persistent, or recurrent cervical cancer is cost-effective.

Methods: Tree age Pro 2009 software was used to construct a cost-effectiveness model to compare treatment with chemotherapy (CTX) to treatment with chemotherapy with the addition of bevacizumab (B). The model was based on data abstracted from available results of Gynecologic Oncology Group (GOG) 240. The two chemotherapy backbones from the trial were combined for this analysis, resulting in two groups: chemotherapy (CTX) and chemotherapy + bevacizumab (CTX+B). Overall survival (OS) was the primary outcome used to compare the two treatments. Number of cycles was based on median time to progression from the trial. Costs were abstracted from Medicare data and the medical literature. Cost of CTX was estimated as the cost of cisplatin and paclitaxel. Costs of drugs were varied over a range for sensitivity analysis. Adverse events listed in the abstract for GOG 240 were added to the costs of the two regimens and varied for the sensitivity analysis. Cost-effectiveness ratios (CERs) were calculated for each treatment arm and then expressed as incremental cost effectiveness ratios (ICERs). Health utility was assumed to be equal between the two regimens.

Results: The cost of treating one patient with 6 cycles of CTX was $2,100 and resulted in a median overall survival of 13.3 months, with a CER of $158. The cost of receiving 8 cycles of CTX+B was $88,550 and was associated with a median OS of 17 months. This resulted in a CER of $5,209 and an ICER of $23,365 per additional month of survival or $280,380 per life-year saved. When the additional cost of the increased number of grade 3/4 toxicities was added to the cost of CTX+B, the ICER increased to $295,000.

Conclusions: The addition of bevacizumab to standard chemotherapy for the treatment of persistent, recurrent, or stage IVB cervical cancer in this model was not cost-effective. The model was most sensitive to cost of bevacizumab but did not achieve an ICER of <$100,000 per life-year saved until the cost was decreased by 60% of its full price.

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Analysis of patients referred to an academic gynecologic oncology clinic with an OVA1 test

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Objectives: Patients with ovarian cancer (OVCA) who are managed by a physician with expertise in gynecologic cancer have improved survival. Validated tools can guide referral of patients to a gynecologic cancer specialist, including risk of malignancy index (RMI), CA-125 and ultrasound (US), HE4, and OVA1. We sought to examine the use of OVA1 in referrals to an academic gynecologic oncology clinic.

Methods: We conducted a retrospective review of records for patients referred to an academic gynecologic oncology clinic with an adnexal mass and OVA1 from 2010 to 2012.

Results: Forty-two consecutive patients were identified with a median age of 59 years. More than one major medical comorbidity was documented in 59.5%, and the median number of prior abdominal surgeries was 1 (range, 0-6). All patients had a pelvic mass found by physical examination and/or imaging, of which 31.0% were palpable, 57.1% were nonpalpable, and 11.8% did not have a physical examination before referral. Referral imaging was similarly divided between US (54.8%) and CT (42.9%). Fourteen patients were premenopausal (PRM) (33.3%) and 28 were postmenopausal (POM) (66.6%). Among PRM patients, 78.6% (n=11) had abnormal OVA1, with median CA-125 of 34 U/mL. Average mass size was 6.0 cm, 28.6% were <4 cm, and 20.4% were simple cystic. When evaluating other algorithms for referral, 64.3% of patients (n=9) met referral criteria by either SGO-ACOG or RMI. Seven of the 11 PRM pts underwent surgery; 14.2% had minimally invasive disease and no epithelial OVCA was found. Among POM patients, 92.9% (n=26) had abnormal OVA1, with median CA-125 of 15 U/mL. Average mass size was 6.4 cm, 35.7% were <4 cm, and 35.7% were simple cystic. According to other algorithms, 57.1% (n=16) met referral criteria by either SGO-ACOG or RMI. Sixteen of the 28 POM patients underwent surgery; 56.3% had minimally invasive disease and no epithelial OVCA was found. For all patients, the most common pathology was serous cystadenoma and fibroma, followed by endometrioma. Three borderline tumors were found. After a median follow-up of 1 year, patients who did not undergo surgery were alive and well, with the exception of two who died of other causes.

Conclusions: No epithelial OVCA was found in this study. There is a lack of appropriate utilization of validated referral tools, in particular OVA1. Decreased adherence was most pronounced in POM women; they were referred with lower CA-125 values, more simple cysts, and smaller size masses. Conscientious use of algorithms and screening tests will help to accurately refer patients to a specialist and decrease health-care costs.

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Risk of breast cancer following ovarian cancer and the impact on overall survival

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Objectives: *BRCA* mutation carriers are at increased risk of breast cancer and epithelial ovarian cancer (EOC), including ovary, fallopian tube, and peritoneal cancers. Cancer surveillance guidelines for these high-risk women exist, although the risk and rationale for breast cancer surveillance after EOC in *BRCA* mutation carriers is not well established. We sought to determine the risk and outcome of breast cancer after a diagnosis of EOC.

Methods: Institutional review board-approved retrospective review of Women's Cancer Registries identified 360 women with EOC from 1998 to 2012 who had *BRCA* genetic testing and subsequent care at our institution.

Results: A total of 134 patients (37%) had a *BRCA* mutation: 100 *BRCA*1, 33 *BRCA*2, and 1 *BRCA*1 and *BRCA*2 mutation. *BRCA* mutation carriers were younger than wild-type patients (WT) at EOC diagnosis (52 vs 62 years, $P<0.001$). Most patients had advanced-stage disease: 90% *BRCA*, 80% WT. *BRCA* mutation carriers were more likely to receive chemotherapy than WT patients (99% vs 93%, $P=0.004$). They were more likely to develop breast cancer than WT patients after adjusting for age (HR 10.6, $P=0.0026$); 15 patients (12 *BRCA*, 3 WT) developed breast cancer at a median of 3 years after EOC diagnosis. All breast cancers were early-stage: 4 ductal carcinoma in situ, 6 stage I, and 5 stage II. Six women received chemotherapy for their breast cancer. Patients with *BRCA*-associated EOC had a lower risk of death than WT EOC, with a median survival of 10 vs 5 years (HR 0.6, $P=0.001$). EOC-specific survival between *BRCA* mutation carriers and WT was 73% and 50% at 5 years and 50% and 27% at 10 years, respectively. There were 185 deaths, with 96% due to EOC in both *BRCA* mutation carriers and WT patients. There was one death in a WT EOC patient due to breast cancer. There was no difference in overall survival rates between cases with breast cancer and without after covarying for age and stage of EOC at time of diagnosis and *BRCA* status ($P=0.1$).

Conclusions: Women with *BRCA*-associated EOC have a better outcome and a higher risk of subsequent breast cancer than WT EOC patients. Overall survival was dominated by EOC-related mortality. Breast cancer surveillance recommendations in women with *BRCA*-associated EOC should be balanced by the minimal impact of breast cancer on survival. There is limited utility for breast cancer surveillance in WT patients following a diagnosis of late-stage EOC.

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Outcomes of pelvic exenteration: does surgeon experience matter?

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Objectives: To determine the influence of surgeon experience on intraoperative, postoperative, and long-term outcomes among patients undergoing pelvic exenteration for gynecologic cancer.

Methods: A logistic regression model, stratified by surgeon, was used to model the relationship between events of interest and surgeon experience. Surgeon experience was measured as the total number of prior cases for a given surgeon at the time of a given exenteration, enabling us to account for differences in surgeon experience over time. Spearman's rank correlation was used to estimate the relationship between individual surgeon experience and estimated blood loss (EBL), duration of surgery (DOS), intraoperative transfusion, and length of hospital stay (LOS). Cox proportional hazards regression, stratified by surgeon, was used to model overall survival (OS) and recurrence-free survival (RFS) as a function of surgeon experience.

Results: A total of 141 exenterations were performed by 19 surgeons from 1993 to present for the following disease sites: cervical (53.2%), vulvar (7.1%), vaginal (26.2%), and uterine (12.8%) cancer. Median surgeon experience over the study period was 476 cases (range, 5-1,805). The majority of patients underwent total pelvic exenteration (73.1%), incontinent urinary diversion (58.9%), and vertical rectus abdominis musculocutaneous reconstruction (39.7%). At the time of analysis, 70 patients had recurred (49.6%), with the majority of recurrences being distant (64.3%), and 38.3% of patients had died of disease. The readmission rate was 50%. EBL ($P<0.01$), DOS ($P<0.01$), and administration of intraoperative blood products ($P=0.02$) were inversely associated with surgeon experience. Surgeon experience was not associated with OS (HR 1.06, 95% CI 0.96-1.18, $P=0.24$) but was associated with RFS (1.14, 95% CI 1.03-1.26, $P=0.01$). Postoperatively, 95% of patients experienced a complication. There was no significant difference in postoperative complication rates based on surgeon experience.

Conclusions: Intraoperative outcomes among patients undergoing pelvic exenteration appear to improve with increasing surgeon experience. The rate of postoperative complications among all patients is high and does not appear to be influenced by surgeon experience. Long-term survival outcomes are not significantly associated with surgeon experience.

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Trends in the use of robotic surgery for the treatment of cervical cancer

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Objectives: To describe trends in the adoption of robotic surgery for the treatment of cervical cancer and the associated impact of these trends on cost of treatment.

Methods: University HealthSystem Consortium keeps an administrative database with contributions from 118 academic medical centers and 299 affiliate hospitals, representing >90% of United States nonprofit academic medical centers. This database was queried to identify all patients with cervical cancer (ICD-9 180.x) undergoing radical hysterectomy (ICD-9 686.x, 687.x) from the fourth quarter of 2008 through the third quarter of 2013. Trends in frequency, cost, and clinical outcomes were compared by surgical approach, including open (OH), robotic (RH), and laparoscopic (LH) surgeries.

Results: We compared the frequencies of OH, RH, and LH in 2009 and 2012, as these were the earliest and most recent full calendar years for which data were available. In 2009, there were 69% OH, 23% RH, and 8% LH; in 2012, there were 57% OH, 32% RH, and 11% LH. Since the fourth quarter of 2008, the fraction of RH has increased linearly ($R^2=0.83$), largely at the expense of OH, which has decreased linearly ($R^2=0.93$). The mean direct cost of hospitalization for radical hysterectomy per patient has increased linearly by $649 per year ($R^2=0.98$). In 2013, OH was associated with a 2.4-fold longer length of hospital stay and 3-fold higher intensive care unit (ICU) admission rate. Despite this, there was no difference in mean direct cost of hospitalization between OH and RH ($P=0.32$). This may be attributable to the cost of surgical services, which was >$2,450 higher per patient undergoing RH compared to OH. The trend in complication rates may also be a contributing factor because the rate of complications increased from 2.8% to 5.3% for RH and decreased from 8.3% to 5.9% for OH since 2009.

Conclusions: RH for the surgical management of cervical cancer is increasing and is associated with shorter hospital stays and fewer ICU admissions compared to OH. However, RH complication rates are rising, and there was no difference in cost between RH and OH. A better understanding of the underlying factors associated with complications and cost, such as patient selection or surgeon expertise, may help to reduce complications and control costs without compromising quality of care.

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An economic analysis of bevacizumab in treatment of cervical cancer

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Objectives: Despite significant improvements in overall survival for women with advanced cancer with platinum-based agents, more patients are receiving platinum upfront with radiation therapy. Therefore, newer combinations with and without platinum are being studied. We sought to evaluate the cost-effectiveness of such therapies.

Methods: The Gynecologic Oncology Group (GOG) 240 schema was used to design a cost-effectiveness decision model. In analysis, all regimens consisted of 6 cycles. Regimen 1 was cisplatin/paclitaxel (CP). Regimen 2 was CP with bevacizumab (CP+B). Regimen 3 was paclitaxel/topotecan (PT). Regimen 4 was PT with bevacizumab (PT+B). Parameters included overall survival (OS), cost, and complications. Sensitivity analyses were performed.

Results: The average cost for 6 cycles of each regimen was: CP, $21,760; CP+B, $97,606; PT, $51,770; and PT+B, $74,281. Sensitivity analysis revealed that to achieve an incremental cost-effectiveness ratio (ICER) for CP+B:CP of <$50,000/quality-adjusted life-year (QALY) gained, the average OS of these patients would have to increase from 1.1 years with CP to 2.5 years with CP+B. To achieve an ICER <$50,000/QALY would require an survival of 5.5 years for PT and 3.1 years for PT+B.

Conclusions: Unless the newer regimens tested against CP increase survival by more than two times, CP will be the most cost-effective regimen. Even a 12-month increase in OS will not make the newer regimens cost-effective.

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Evaluation of a universal surgical risk calculator for quality improvement on a gynecologic oncology service

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Objectives: The National Surgical Quality Improvement Program (NSQIP) sponsored by the American College of Surgeons (ACS) is aimed at preventing perioperative morbidity and mortality. An online calculator was recently published by the ACS, but the primary studies used did not include actual data from gynecologic surgeries. Thus, the objective of this study was to evaluate the performance of the ACS NSQIP Universal Surgical Risk Calculator on the patients of a gynecologic oncology service.

Methods: We reviewed 185 consecutive surgical cases performed by the gynecologic oncology service between February and June 2012. The demographic data required for the calculator were collected as well as diagnosis and cancer stage. Charts were also reviewed to determine actual perioperative outcomes in the first 30 days after surgery. Specific complications were: death, pneumonia, cardiac complications, surgical site (SSI) or urinary tract infections (UTI), renal failure (RF), or thromboemboli (VTE). These data were compared with the modeled outcomes and a Brier score (where scores approaching zero are better) was calculated for individual outcomes and the whole model. Significance was calculated based on $P<0.05$.

Results: For our population, the model accurately predicated death ($P=0.16$), VTE ($P=0.15$), UTI ($P=0.08$), and RF ($P=0.06$). Predicted risk was twofold greater than experienced for cardiac complications; the experienced SSI and pneumonia rates were twofold and fourfold greater than predicted, respectively. For the entire model, the Brier score of 199 was significantly different from 0 ($P<0.001$), indicating poor performance of the model. The Brier scores for death, VTE, UTI, and RF were 53, 55, 111, and 107, respectively, and the 95% CIs crossed 0.

Conclusions: Overall, the NSQIP Universal Risk Calculator accurately predicted some individual outcomes, but clinically significant differences were present in predicted cardiac complications, SSI, and pneumonia. The problem with a Universal

Surgical Risk Calculator is that applicability across multiple subspecialties necessitates that complications are not accurately estimated in some areas. Our data support this statement and show that before this model can achieve global acceptance, some risks reported by the calculator may need to be interpreted with reservation.

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373 - Poster Session B

Is pharmacologic prophylaxis indicated for prevention of thromboembolic disease after robotic and laparoscopic hysterectomy in a gynecologic oncology practice? Analysis of morbidity and cost in 1,335 cases

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Objectives: To report the incidence of deep venous thrombosis (DVT) and pulmonary embolus (PE) from minimally invasive hysterectomy among gynecologic oncology patients and evaluate the benefit of pharmacologic prophylaxis.

Methods: We conducted a retrospective evaluation of all patients who underwent robotic (RH) or laparoscopic hysterectomy LH for benign and malignant conditions. We evaluated the demographic, intraoperative, and postoperative factors that increased the risk of DVT/PE. Most of the patients (95%) did not receive pharmacologic prophylaxis.

Results: The mean age of the groups was 53±13 years for RH and 51±12 years for LH. The body mass index average was 29 for RH and 29 for LH. The average number of comorbidities for both groups were not significantly different (RH=2 and LH=1). The percent of patients who suffered hypertension was 29% in RH and 34% in LH. The risk of DVT in both groups was minimal, with only 1/1,054 in the RH group and 1/281 in the LH group, with no significant difference between the groups. The risk of developing PE was the same as that of developing DVT in both groups. No postoperative deaths were reported.

Conclusions: The risk of thromboembolic disease without the use of pharmacologic prophylaxis among RH or LH cases is close to zero. According to Epocrates Pharmacologic Guide, the cost of enoxaparin for a 40 mg/0.4 mL vial is $207.57. The adult thromboembolism prophylaxis dose is 40 mg/day. This would result in a cost of $207.57 to $415/day, which would have totaled >$277,000 for cost that was unnecessary. In addition, the risk of bleeding complications and transfusion is unwarranted. The national mandate for pharmacologic prophylaxis is expensive and increases the risk of morbidity with no benefit.

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374 - Poster Session B

Cross-sectional study on the impact of a natural disaster on delivery of gynecologic oncology care

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-**Objectives:** Hurricane Sandy (HS) had a profound economic impact in the Northeast, with an estimated $50 billion in damages. The health care system in New York City was shaken, with hospital closures and the evacuation of thousands of patients. This study compared access to gynecologic oncologic care across a private (Pv) and a city hospital (C), both of which were closed due to the storm.

Methods: Medical records of all active gynecologic oncology chemotherapy (CT), radiotherapy (RT), and surgical patients were reviewed from October 29 2012, the eve of the storm, to February 7 2012, the date that C reopened. Pv facilities were closed for up to 35 days, and C facilities closed for up to 98 days. New referrals to each hospital during this time period were excluded. Delays in chemotherapy infusion, radiation therapy, and surgical scheduling were compared. Statistical analysis included Student's t-test and Fisher's-exact test, using R.

Results: A total of 113 active patients were identified during the time HS hit and its aftermath; 59 (52.2%) were Pv and 54 (47.8%) C patients. At Pv, 33/59 (55.9%) were receiving CT, 1/59 (1.7%) were receiving RT, and 28/59 (47.5%) had planned surgery. At C, 40/54 (74.1%) were receiving CT, 7/54 (12.3%) were receiving RT, and 18/54 (33.3%) had planned surgery. A statistically significant difference was found in the mean delay in CT at Pv (7.6 days) compared to C (21.7 days) (P =0.0004). See Table for additional details of CT. The mean delay in scheduled surgery at Pv (14.2 days) was not significantly different compared to C (22.7 days) (P =0.3979). The rate of surgical cancellations was also not significantly different between the two hospitals: 5/28 (1.8%) at Pv and 7/18 (3.9%) at C (*P*=0.1703). There was no delay in RT at Pv.

All C patients receiving RT had care temporarily transferred to Pv, with a mean delay of 25.0 days. There were 4/7 (57.1%) newly diagnosed C patients receiving RT, with a mean delay of 62.3 days from diagnosis to initiation of RT. There was high retention rate at each hospital, with only 3/59 (5.1%) Pv patients and 3/54 (5.6%) C patients lost to follow-up during HS.

Conclusions: In the wake of a devastating natural disaster, gynecologic oncology care was maintained at both Pv and C despite temporary closure and relocation of outpatient, inpatient, and surgical services. The disparities in care revealed were in access to CT and RT.

Table 1: Characteristics of Patients Actively Receiving Chemotherapy During HS:

Patient Characteristics	Private Hospital (Pv) n/total n (%)	City Hospital (C) n/total n (%)	P value
Primary CT	6/33 (18.2%)	15/40 (37.5%)	0.118
Recurrent Disease	24/33 (72.7%)	20/40 (50%)	0.0828
Neoadjuvant CT	3/33 (9.1%)	5/40 (12.5%)	0.7218
2^{nd} Line Recurrence	7/33 (21.2%)	12/40 (30%)	0.434
3^{rd} Line Recurrence	17/33 (52%)	8/40 (20%)	0.0199

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Significant delay in the treatment of endometrial cancer based on race and insurance status

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Objectives: Although white women are more likely to be diagnosed with endometrial cancer compared to African American women, the rate of mortality is higher for African Americans. The cause of this disparity is unknown. We analyzed the time interval from diagnosis of endometrial cancer to treatment as it pertains to race and socioeconomic factors and its possible impact on survival.

Methods: This was a retrospective, single-institution chart review using our cancer registry database. We identified 889 patients who were diagnosed with endometrial cancer between January 2005 and June 2012. Clinicopathologic characteristics, demographics, insurance status, distance from medical center, body mass index (BMI), dates of diagnosis, and treatment were obtained from the medical records. Survival and association was determined by a one-way ANOVA test.

Results: At the time of the study 699 patients were alive and 190 were dead. The average age was 62 years (range, 24-91 years). Stages I, II, III, and IV disease accounted for 69%, 6%, 15%, and 10% of patients, respectively. White race accounted for 64%, African Americans for 24%, and Hispanics for 7% of our study population. The majority of patients were privately insured (n=441), followed by Medicare (n=375). The mean interval time from diagnosis to treatment was 47.5 days (range, 0-363 days). A statistically significant difference was noted for this time interval with regard to both race and insurance status: white and African Americans (42.6 vs 57.3 days, P=0.048), privately insured and Medicare (38.4 vs 54.1 days, P<0.001). There was a significant association with increased risk of death with a longer delay (43.3 vs 64.8 days, P<0.001). No statistically significance difference was noted for distance from medical center or BMI.

Conclusions: A significant increase in interval of time from diagnosis to treatment of endometrial cancer was seen for both race and insurance status. A longer interval from diagnosis to treatment was associated with increased mortality. The causes of these delays are likely multifactorial but need further investigation.

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Patterns of care of women with low-grade cervical cytologic abnormalities

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Objectives: The most common abnormal cervical cytology diagnoses are atypical squamous cells of unknown significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL). When these diagnoses are made on specimens collected in the absence of any prior cervical cytology during the previous year, it is recommended to repeat the sampling 6months later. Those patients exhibiting abnormal cytology 6 months after the diagnosis of ASCUS or LSIL should proceed to colposcopy, whereas those with normal cytology 6 months later may return to screening.

Methods: Reports of cervical cytology are contained in a database of health-care provision in a jurisdiction serving 10 million people, deterministically linkable to all other health services databases, including physician reimbursement claims for colposcopy. We identified all women who had abnormal cytology reports of ASCUS or LSIL during 2008 and 2009, preceded by an interval of at least 1 year without a cervical cytology report. We searched for additional cytology reports and for colposcopy billing claims during the 24 months following the date of the first abnormal report. We linked the postal code of each woman to an aggregate measure of socioeconomic status.

Results: We identified 74,770 women with ASCUS or LSIL cytology ≥12 months since any prior cytology during the study period. Among women with ASCUS, 69.7% underwent repeat cytology as did 60.3% of women with LSIL. Repeat cytology following ASCUS disclosed normal (68.2%), ASCUS (19.3%), LSIL (10.6%), and HSIL (1.4%); following LSIL, the corresponding percentages were 48.3%, 18.0%, 30.8%, and 2.6%. Among women with ASCUS, 16.2% went directly to colposcopy, and 14.0% did not repeat cytology or go to colposcopy. Among women with LSIL, 26.4% went directly to colposcopy, but 13.4% went nowhere.

Conclusions: We have demonstrated substantial improvement in cervical cytology 6 months after ASCUS and LSIL, highlighting unnecessary referrals of many women with ASCUS and LSIL directly to colposcopy without repeat cytology, and lack of follow-up for one sixth of women with low-grade cytology.

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Utilizing peer teen advocates and social media to increase human papillomavirus (HPV) vaccination awareness in urban settings

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Objectives: HPV vaccination has demonstrated efficacy in reducing HPV prevalence. Lack of knowledge about HPV is consistently noted as a barrier to HPV vaccination. The vaccination rate in Milwaukee is <30%. The Medical College of Wisconsin, The City of Milwaukee Health Department, and The Boys & Girls Clubs of Greater Milwaukee initiated a community-based research pilot aimed at increasing teens' HPV knowledge with a multimedia campaign designed for their peers. Our goal was to determine the feasibility of incorporating teens into development of HPV-related health messages using social media and conventional media and learn whether their culturally relevant materials would resonate with other teens.

Methods: Six youth leaders recruited from select Boys & Girls Clubs formed the core peer educators. These educators recruited 30 youths, who received age- and culturally-appropriate HPV education. The youths met with community mentors and developed an HPV "brand," logo, and website. The core educators and their recruits formed six teams who designed relevant brochures, billboards, and/or public service announcements (PSAs).

Results: Our website www.itsjust3HPV.org promoted the project, displayed the teen-developed materials and encouraged the community to vote for their favorites over a 2-week period. Winners were announced at the 2nd Annual Spread the Word PSA premiere held on May 9, 2013, in Milwaukee, a citywide teen health event. The winning billboards have been displayed locally, and the winning brochure is being disseminated in local health clinics. The website was launched in April 2013 and logged >3,000 views in first 5 months. August 2013 metrics indicate 29 views/day. The PSA videos, which remain viewable on YouTube, have been viewed >300 times.

Conclusions: Adolescents can and should be engaged in the development of culturally relevant health messaging. Our strategy represents one approach to developing materials that appeal to this demographic. In a relatively short period of time, the HPV health message has been successfully disseminated based on our current metrics. The ability to track metrics from the website should allow us to monitor continued dissemination. Ultimately, we would like to see if innovative campaigns result in increased HPV vaccination rates.

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Type I uterine cancer in United States (US)-born vs immigrants: a study of 4,834 patients

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Objectives: To determine the association of type I endometrioid uterine cancer in US-born vs immigrant Asians.

Methods: Data were obtained from the National Cancer Institute from 2001 to 2009. Chi-square, t-test, and binomial regression **Methods** were used for statistical analyses.

Results: Of 4,834 Asians with uterine cancer in our study, 62% were US-born and 38% were immigrants. Of all patients, 2,972 (61%) had type I (grade 1 or 2, endometrioid histology) uterine cancer. Compared to type II disease (grade 3, clear cell and serous histology), type I patients were younger (55 vs 59 years, $P<0.01$) and had lower-stage disease (90% vs 71%, $P<0.01$). Immigrants had a significantly lower proportion of type I uterine cancers compared to their US-born counterparts (56% vs 65%, $P<0.01$). Of the immigrants, Japanese (48% vs 68%, $P<0.01$) had a lower proportion of type I cancers compared to Chinese (52% vs 63%, $P<0.01$) and Filipino (58% vs 66%, $P<0.01$). The 5-year disease-specific survivals of immigrant vs US-born Asians with type I cancer was 92%.

Conclusions: US-born Asians are more likely to be diagnosed with type I uterine cancer compared to immigrant Asians. Among all ethnic groups, Japanese immigrants had the lowest proportion of type I cancers.

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The use of a geographic information system to identify advanced cervical cancer patients in California

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Objectives: Novel biologic therapy has been shown to have activity in advanced and recurrent cervical cancer patients. Geographic information system (GIS) analysis integrates geospatial data with population-based reporting summaries. We propose to use GIS to target cervical cancer patients who may benefit from this treatment.

Methods: Geographic, demographic, socioeconomic, and outcomes data were obtained from the 2012 United States Census and National Cancer Institute Databases from 2001 to 2009. Chi-square and t-test methods were used for statistical analyses.

Results: Of 11,561 patients in California, 1,330 (14%) had advanced stage IV disease. The median age was 51 years (range, 20-98 years). White, Hispanic, Asian, and black comprised 46%, 34%, 12%, and 8% of the population, respectively. The overall 5-year survival was 39%, with worsened survival in counties with higher poverty rates (21%, $P=0.03$). The survival of these advanced cancers based on race was 16% for whites, 24% for Hispanics, 23% for Asians, and 12% for blacks ($P<0.01$). To evaluate trends, we divided the study into three time periods: 2001-2003, 2004-2006, and 2007-2009. The percentage of advanced-stage disease increased from 13% to 14% to 16% according to time period ($P<0.01$). Using GIS to target these patients, we found that >56% of advanced cervical cancer patients resided in southern California. More specifically, 433 (33%) in Los Angeles, 86 (6%) in San Diego, 79 (6%) in Orange, 73 (5%) in San Bernardino, and 68 (5%) in Riverside county with corresponding survivals of 20%, 24%, 18%, 7%, and 5% ($P<0.01$). Using United States census data to define poverty as 15% of the population, 53% of advanced cervical cancer patients resided in counties with higher poverty.

Conclusions: The proportion of advanced cervical cancer patients in California has increased over our study period. GIS targeted the women who may benefit from novel biologic agents, with most cases being diagnosed in Los Angeles and San

Diego counties. Because the majority of these women reside in lower-resource settings, these regions may require additional resources from state or federal insurance agencies.

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Sarcopenia: preoperative assessment of muscle mass to predict surgical complications and prognosis in patients with endometrial cancer

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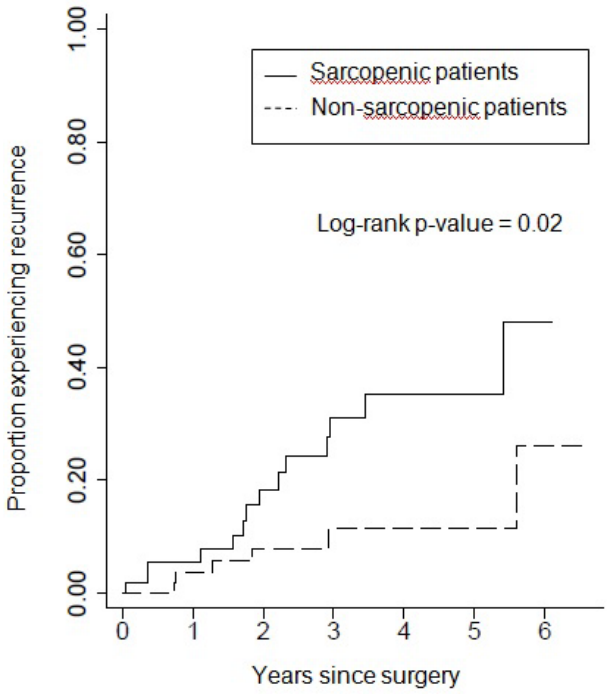
Objectives: To examine the impact of sarcopenia (low skeletal muscle mass) on surgical complications and prognosis in patients with endometrial cancer.

Methods: We performed a retrospective review of 122 endometrial cancer patients who underwent surgery between 2005 and 2009. Sarcopenia was assessed on preoperative CT scan by measuring the lumbar psoas muscle cross-sectional area and was defined as any value below the median (<4.38 cm^2). Sarcopenic obesity was defined as sarcopenia plus body mass index (BMI) of ≥30. Microsatellite instability (MSI) was analyzed using the National Cancer Institute consensus markers and tumor from hysterectomy specimens. Outcome variables included postoperative complications, length of hospital stay, 90-day readmission rate, recurrence-free survival (RFS), and overall survival (OS). The Kaplan-Meier method was used to establish the estimate survival curves, and distributions were compared using the log-rank test. Variables known to affect survival were entered into a multivariable Cox proportional hazards model.

Results: Of the 122 patients, 30 (25%) met criteria for sarcopenic obesity. Sarcopenic patients were typically older (mean age, 69.7 vs 62.1 years, $P<0.001$), had lower BMIs (31.1 vs 39.4, $P<0.001$), and had more comorbidities ($P=0.048$). MSI was not associated with sarcopenia (61% sarcopenic vs 72% nonsarcopenic patients, $P=0.25$). Overall sarcopenia was not associated with such clinical outcomes as hospital stay, 90-day readmission rate, or early/late complications. Compared to nonsarcopenic patients, those with sarcopenia had a shorter time to recurrence (log-rank $P=0.02$) (Figure 1), but there was no difference in OS (log-rank $P=0.20$). After adjusting for race and BMI, sarcopenia was associated with more rapid recurrence (HR_{adj} 3.55; 95% CI 1.25, 10.1). It did not predict OS in crude or after adjustment for race, BMI, and clear cell tumor (HR_{adj} 1.89; 95% CI 0.78, 4.57).

Conclusions: Sarcopenia is linked to RFS but does appear to negatively impact surgical outcomes or OS in endometrial cancer patients. Sarcopenic obesity may have more clinical implications in this population and warrants further investigation.

Figure 1. Recurrence-free survival by Kaplan Meier analysis between patients with sarcopenia and those with no sarcopenia.



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Human papillomavirus (HPV) genotype prevalence in invasive vaginal cancers from a registry-based United States population

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Objectives: To describe the HPV genotype distribution in invasive vaginal cancers diagnosed before introduction of the HPV vaccine.

Methods: Four population-based registries and three residual tissue repositories provided formalin-fixed, paraffin-embedded (FFPE) tissue from eligible cases diagnosed between 1994 and 2005 that were tested with the linear array (LA) HPV genotyping test. Samples with negative or inadequate LA results were retested with the INNO-LiPA HPV genotyping assay. Clinical, demographic, and all-cause survival data were assessed by HPV status.

Results: Sixty cases of invasive vaginal cancer were identified. Among the patients, 75% were positive for any HPV. The most frequently detected was HPV16 (55%, 33/60), followed by HPV33 (18.3%, 11/60). Only one case was positive for HPV18 (1.7%). Multiple types were detected in 15% of patients. Those who were <60 years old were more likely than those who were ≥60 years to be HPV16- or HPV18-positive (HPV16/18): 77.3% vs 44.7% (P=0.038). The median age at diagnosis was younger in the HPV16/18 group (59 years) vs other HPV-positive (68 years) and no HPV (77 years) (P=0.003). The HPV distribution was not significantly different between race/ethnicity and place of residence. The 5-year unadjusted all-cause survival was 57.4% among vaginal cancers that were HPV-positive vs 35.4% among HPV-negative vaginal cancers. The unadjusted HR comparing HPV-positive to HPV-negative was 0.62 (95% CI 0.28–1.39). However, after adjusting for age, the HR was 1.57 (95% CI 0.63- 3.91).

Conclusions: In the largest United States case series of invasive vaginal cancer to date, HPV16 and HPV33 and not HPV18 were the most common genotypes observed in cases diagnosed before introduction of the HPV vaccines. Younger women with vaginal cancer were more likely to be HPV-positive. Further studies are needed to clearly elucidate the prognostic effect of HPV in vaginal cancer after controlling for age.

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Body mass index and lymph node metastases in endometrial cancer: can we omit lymphadenectomy in the morbidly obese?

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Objectives: Pelvic and para-aortic lymphadenectomy is more technically difficult in morbidly obese patients with endometrial cancer. Obese women are more likely to have less aggressive (type I) endometrial cancers. Many specialists, thus, operate under the assumption that these patients have tumors with a lower chance of lymph node metastasis and omit complete lymph node dissection. However, the relationship between obesity and risk of lymph node metastasis has never been fully elucidated. We investigated the impact of body mass index (BMI) on rate of lymph node metastasis in these patients.

Methods: Following institutional board review approval, a retrospective chart review was performed on patients who underwent surgical staging of endometrial cancer at a comprehensive cancer center from 2000 to 2010. Data were first obtained from a representative distribution of patients. Based on the initial findings, quintiles were determined, and the lowest and highest quintiles of BMI were overrepresented in the remaining patients using a probability-weighted stratified sample. Predictive models for lymph node metastases were fitted using a generalized additive model. Significance defined as P<0.05.

Results: A total of 1,750 patients were evaluated during the study period. Data were abstracted from a total of 305 patients (170 most recent patients to determine initial distribution and an additional 135 patients in overrepresented quintiles of BMI). In univariate analysis, BMI was not correlated with an increased risk of lymph node metastasis (P=0.24). Age, tumor size, myometrial invasion, and lymphovascular space invasion were all correlated with an increased rate of lymph node metastasis. Endometrioid histology was correlated with a decreased rate of lymph node metastasis. In multivariate analyses, BMI did not show any association with rate of lymph node metastasis after controlling for age, tumor size, lymphovascular space invasion, myometrial invasion, and histology (P=0.63).

Conclusions: BMI was not correlated with the rate of lymph node metastasis. Although it is tempting to omit lymph node dissection in the morbidly obese patient (due to technical difficulty and a perceived nonaggressive nature of these tumors), BMI should not be used as a criterion to triage patients with endometrial cancer for lymph node dissection.

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383 - Poster Session B

Socioeconomic status as a predictor of adherence to treatment guidelines for early-stage ovarian cancer

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Objectives: To investigate the impact of socioeconomic status (SES) and other demographic variables on adherence to National Comprehensive Cancer Center (NCCN) ovarian cancer treatment guidelines among patients with stage I/II disease.

Methods: Consecutive patients diagnosed with stage I/II epithelial ovarian cancer between January 1, 1999 and December 31, 2006 were identified from the California Cancer Registry. Univariate analysis and multivariate logistic regression models were used to evaluate for differences in surgical procedures, chemotherapy treatment, and overall care adherence to NCCN guideline care according increasing SES quintile (SES-1 to SES-5), other demographic variables, tumor characteristics, and hospital/physician annual case volume.

Results: A total of 5,445 patients were identified. The median age at diagnosis was 54.0 years (range, 18-99 years); 72.5% of patients had stage I disease and 27.5% had stage II disease. With a median follow-up time of 4.9 years, the 5-year ovarian cancer-specific survival for all patients was 82.7% (SE=0.6). Overall, 23.7% of patients received care that was adherent to NCCN guidelines. Compared to patients in SES-5, patients in SES-1 were significantly less likely to receive proper surgery (27.3% vs 47.9%, $P<0.001$) and indicated chemotherapy (42.4% vs 53.6%, $P<0.001$). There was a linear relationship between increasing SES and the likelihood of overall treatment plan adherence to NCCN guidelines: SES-1=16.4%, SES-2=19.0%, SES-3=22.4%, SES-4=24.2%, SES-5=31.6% ($P<0.001$). Binary logistic regression analysis revealed that compared to SES-5, decreasing SES was independently predictive of a higher risk of nonadherent care: SES-4, OR 1.51, 95% CI 1.26-1.81; SES-3, OR 1.55, 95% CI 1.28-1.87; SES-2, OR 1.78, 95% CI, 1.44-2.20; SES-1, OR 2.01, 95% CI 1.55-2.62. Medicaid payer status (OR 1.30, 95% CI 1.04-1.62), low-volume hospitals (OR 1.58, 95% CI 1.35-1.86), and low-volume physicians (OR 1.24, 95% CI 1.04-1.48) were also independently associated with an increased risk of overall treatment nonadherence to NCCN guidelines.

Conclusions: Among patients with early-stage ovarian cancer, low SES and low provider case volume are significant and independent predictors of deviation from NCCN guidelines for surgery, chemotherapy, and overall treatment.

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384 - Poster Session B

The increase in type I uterine cancer in 9,217 Hispanic women: a 20-year study

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Objectives: To evaluate the trends of type I uterine cancer in Hispanic women in the United States.

Methods: Data were obtained from the National Cancer Institute from 1990 to 2010. Trends were divided into three time periods: 1990-1996, 1997-2003, and 2004-2010. Chi-square, t-test, and binomial regression methods were implemented for statistical analyses. Survival analysis was done using Kaplan-Meier and Cox regression methods.

Results: Of 9,217 Hispanic uterine cancer patients, 5,210 (57%) had type I (grade 1 or 2, endometrioid histology) uterine cancer; the remainder had type II disease. Compared to type II disease (grade 3, clear cell and serous histology), type I patients were younger (56% vs 60%, $P<0.01$) and had lower-stage disease (90% vs 60%, $P<0.01$). Based on migratory status, 53% were United States (US)-born and 47% were immigrants. Of all patients, US-born Hispanics had a significantly higher proportion of type I uterine cancers compared to their immigrant counterparts (55% vs 50%, $P<0.01$). The survival of US-born Hispanics was significantly lower compared with the immigrants (83% vs 88%, $P<0.01$). Over the three time periods, the proportion of type I uterine cancer increased from 31% to 56% to 60% ($P<0.01$). The US-born Hispanic women had an increase of type I uterine cancer from 31% to 56% to 58% ($P<0.01$) and the immigrant Hispanics had an increase from 31% to 49% to 52% ($P<0.01$). This trend was evident after adjusting for age, stage, and immigration status (HR 1.08,

95% CI 1.07-1.10, *P*<0.01). Over the three time periods, the overall 5-year survival did not significantly change (87% to 88% to 89%, *P*=0.24).

Conclusions: US-born Hispanics are more likely to be diagnosed with type I uterine cancer compared to immigrant Hispanics. Over time, both groups showed an increasing trend in proportion of type I cancers.

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385 - Poster Session B

Diabetes mellitus and ovarian cancer: more complex than increasing risk

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Objectives: Diabetes mellitus is a known risk factor for several malignancies, including endometrial and colorectal cancers. It is also associated with poorer outcomes in breast and prostate cancers. This association is less clear in ovarian cancer. We sought to examine the effect of diabetes on progression-free survival (PFS) and overall survival (OS) in women with ovarian cancer.

Methods: A retrospective cohort study of epithelial ovarian cancer patients diagnosed between 2004 and 2009 at a single institution was performed. Demographic and pathologic data, diagnosis of diabetes, and antihyperglycemic medication use were abstracted. Pearson Chi-square test and t test were used to compare variables. The Kaplan-Meier method and the log rank test were used to compare PFS and OS between women with and without diabetes.

Results: Of 367 patients who met inclusion criteria, 62 (17%) had a recorded diagnosis of diabetes. There was no difference in age, histology, debulking status, or administration of intraperitoneal chemotherapy between nondiabetic (ND) and diabetic (DM) patients. Body mass index (BMI) was significantly different between the two groups (ND vs DM, 27.5 vs 30.7, *P*<0.001). There were more stage I and stage IV patients in the ND group (*P*=0.04). Although there was no difference in PFS or OS based on BMI <30 vs ≥30 (16.5 vs 12.6 months, *P*=0.072 and 41.0 vs 33.1 months, *P*=0.4, respectively), DM patients had poorer PFS (24.0 vs 35.5 months, *P*=0.024) and OS (35.5 vs 50.8 months, *P*=0.005) compared to ND patients. Metformin use among diabetic patients did not appear to affect PFS or OS.

Conclusions: Ovarian cancer patients with diabetes have poorer PFS and OS than patients without diabetes; this association is independent of obesity. In this cohort, metformin use did not affect outcomes. The pathophysiology of this observation requires more inquiry.

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386 - Poster Session B

Borderline ovarian tumor in the elderly: impact on recurrence and survival

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Objectives: Borderline ovarian tumor (BOT) is uncommon in elderly women. We investigated the characteristics and treatment outcomes of elderly women with BOT.

Methods: A hospital-based tumor registry was used to identify patients with BOT who were treated between 1996 and 2011. Patients were divided into two cohorts: <65 years and ≥65 years. Recurrence and survival were examined using the Kaplan-Meier method. Multivariate Cox proportional hazards model was used to estimate HRs with 95% CI.

Results: In total, 364 patients were identified, including 326 patients aged <65 years and 38 patients aged ≥65 years. The elderly patients had more comorbidities (*P*<0.001), larger tumor size at diagnosis (*P*=0.001), more perioperative complications (*P*=0.001), and longer postoperative hospital stay (*P*<0.001). In a multivariate model, the HRs for recurrence and disease-related death in patients aged ≥65 years were 2.53 (95% CI 1.03-6.23) and 7.66 (95% CI 1.09-53.95), respectively.

Conclusions: Characteristics and survival of elderly patients with BOTs differ distinctly from those of younger patients. Old age was an independent poor prognostic factor for recurrence and disease-related death.

387 - Poster Session B

Management and outcomes for elderly women with vulvar cancer over time

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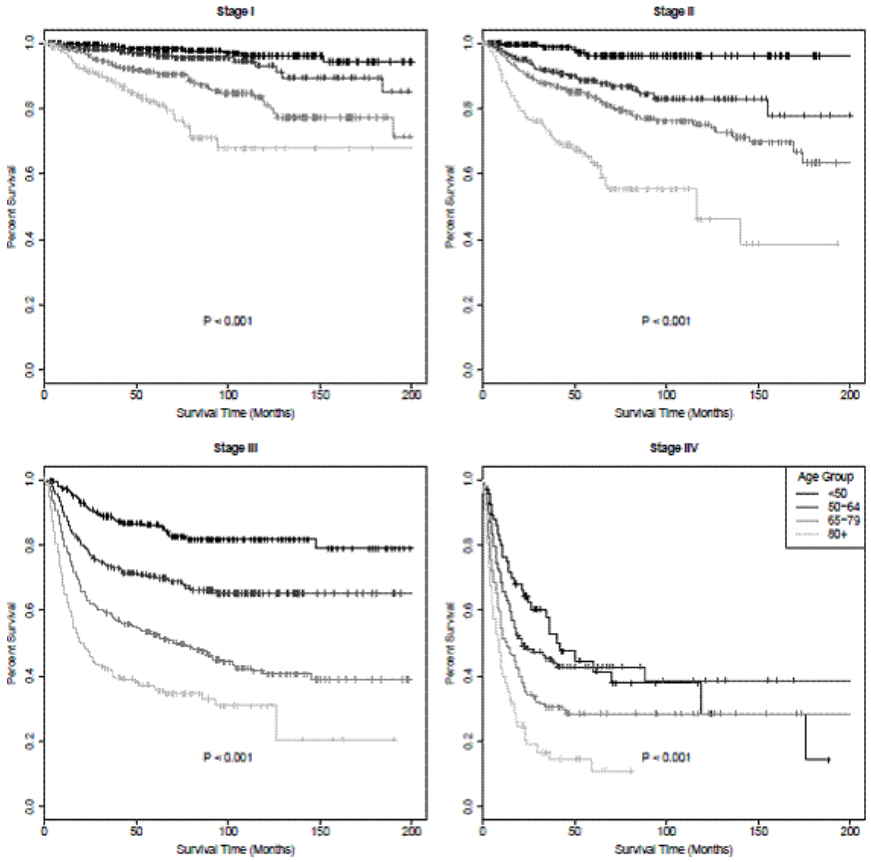
Objectives: To examine changes over time in survival and treatment patterns for women diagnosed with vulvar squamous cell carcinoma included in the Surveillance, Epidemiology, and End Results (SEER) Program.

Methods: Data from the SEER Program for 1988 - 2009 were used for this analysis. Women were stratified by age into the following groups: <50 years, 50-64 years, 65-79 years, and >80 years old. Differences in survival and treatment patterns were analyzed between age groups. Multivariate logistic regression models were constructed to examine treatment while adjusting for other confounders. Kaplan–Meier and Cox proportional hazards survival methods were used to assess differences in survival.

Results: The final study group consisted of 8,553 women: 1,806 (21.12%) <50 years, 2,141 (25.03%) 50-64 years, 2,585 (30.22%) 65-79 years, and 2,021 (23.63%) >80 years old. After adjusting for patient and tumor characteristics, older women were less likely to have surgery and more likely to receive radiotherapy. Over the entire study period, after adjusting for race, SEER registry, marital status, stage, age, treatment, grade, and history of subsequent secondary cancer, compared to women <50 years, women 50-64 had an almost twofold higher risk of disease-specific mortality (HR 1.91, 95% CI 1.55-2.34); those 65-79 years had a fourfold higher risk (HR 4.01, 95% CI 3.32-4.82), and those >80 years had a sevenfold higher risk (HR 6.98, 95% CI 5.77-8.46). After adjusting for the same variables, these trends stayed relatively constant over the time periods studied. After adjusting for the same variables, older women showed a higher risk of vulvar cancer-specific mortality in all stages (I-IV), and the risk increased with age. The largest difference was observed in stage II disease, with women >80 years having an HR of vulvar cancer-specific mortality of 19.43 (95% CI 7.88-47.89) compared to women <50 years old. We found the smallest difference in stage IV disease, in which patients >80 years had an HR of vulvar cancer-specific mortality of 3.03 (95% CI 2.01-4.56) compared to women <50 years old.

Conclusions: Women >50 years are at a higher risk of vulvar cancer-specific mortality, which increases with age. This association remained even after adjusting for treatment and other confounders and remained constant over time.



388 - Poster Session B

CGRRF1 as a novel biomarker of tissue response to metformin in the context of obesity

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Objectives: Obesity-associated hyperestrogenism and hyperinsulinemia contribute significantly to the pathogenesis of endometrial cancer. We recently demonstrated that metformin, a drug long used for the treatment of type 2 diabetes, attenuates both insulin and estrogen-mediated proliferative signaling in the obese rat endometrium. In this study, we sought to identify tissue biomarkers that may prove clinically useful to predict endometrial sensitivity and response to this systemic therapy. We identified CGRRF1 as a metformin-responsive gene and characterized its possible role in endometrial cancer prevention.

Methods: CGRRF1 was identified by cDNA microarray analysis as an upregulated gene in the endometrium of obese rats following treatment with the insulin-sensitizing drug TZD. CGRRF1 mRNA expression was evaluated by real-time quantitative polymerase chain reaction in the endometrium of obese and lean rats, treated and untreated with metformin, as well as in normal and malignant human endometrium. CGRRF1 levels were genetically manipulated in Ishikawa and ECC-1 cells, and its effects on proliferation and apoptosis were evaluated by MTT and Western blot.

Results: CGRRF1 was significantly and reliably induced by metformin treatment in the endometrial tissue of obese rats (n=4-9/group). In vitro studies demonstrated that overexpression of CGRRF1 inhibits endometrial cancer cell proliferation and upregulates caspase-3 expression, suggesting its role in the induction of apoptosis. Analysis of human endometrial tumors revealed that CGRRF1 expression is significantly lower in hyperplasia (n=6), Grade 1 (n=20), Grade 2 (n=72), Grade 3 (n=31), malignant mixed Müllerian tumor (n=9), and uterine papillary serous carcinoma (n=7) endometrial tumors compared to normal human endometrium (n=81, $P<0.05$), suggesting that loss of CGRRF1 correlates with disease progression.

Conclusions: CGRRF1 represents a reproducible tissue marker of metformin response in the obese endometrium. Furthermore, our preliminary data suggest that upregulation of CGRRF1 expression may prove clinically useful in the prevention or treatment of endometrial cancer.

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389 - Poster Session B

Patterns of care, predictors, and outcomes of chemotherapy in elderly women with early-stage uterine carcinosarcoma: a population-based analysis

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Objectives: Chemotherapy is recommended as a treatment option by the National Comprehensive Cancer Network (NCCN) guidelines for early-stage uterine carcinosarcoma (stages I-II). The objective of the current study was to examine the patterns of care, predictors, and impact of chemotherapy on survival in elderly women diagnosed with early-stage uterine carcinosarcoma.

Methods: The Surveillance, Epidemiology, and End Results (SEER)-Medicare database was used to identify women aged ≥65 years who were diagnosed with stage I-II uterine carcinosarcomas from 1991 through 2007. Only patients who had undergone a hysterectomy were included. Statistical analysis used multivariable logistic regression and Cox-proportional hazards models.

Results: A total of 462 women met the eligibility criteria; 374 had stage I and 88 had stage II uterine carcinosarcoma. Adjuvant chemotherapy was administered to 76 patients (16%). Of these, 40 received a platinum agent, either alone or in combination with other chemotherapeutic drugs. In examining the temporal trends, no appreciable difference was noted over time with regard to the administration of chemotherapy in either stage I (13.0% in 1991-1995, 13.3% in 1996-2000, and 17.4% in 2001-2007, $P=0.53$) or stage II uterine carcinosarcoma (20.8% in 1991-1995, 21.1% in 1996-2000, and 20.0% in 2001-2007, $P=0.99$). On multivariable analysis, the factors positively associated with the receipt of chemotherapy were

younger age at diagnosis, higher disease stage, residence in the eastern part of the United States, and lack of administration of external beam radiation ($P<0.05$). In the adjusted Cox-proportional hazards regression models, administration of three or more cycles of chemotherapy did not reduce the risk of death in stage I patients (HR 1.45, 95% CI 0.83-2.39), but it was associated with a nonsignificant trend toward decreased mortality in stage II patients (HR 0.83, 95% CI 0.32-1.95).

Conclusions: Approximately 13% to 20% of elderly patients diagnosed with early-stage uterine carcinosarcoma are treated with chemotherapy. This trend has remained stable over time. Treatment with chemotherapy was not associated with a significant survival benefit in either stage I or stage II uterine carcinosarcoma in this analysis.

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390 - Poster Session B (withdrawn at author's request)

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391 - Poster Session B

Transversus abdominis plane block in patients undergoing robotic surgery for gynecologic cancers: A randomized controlled trial

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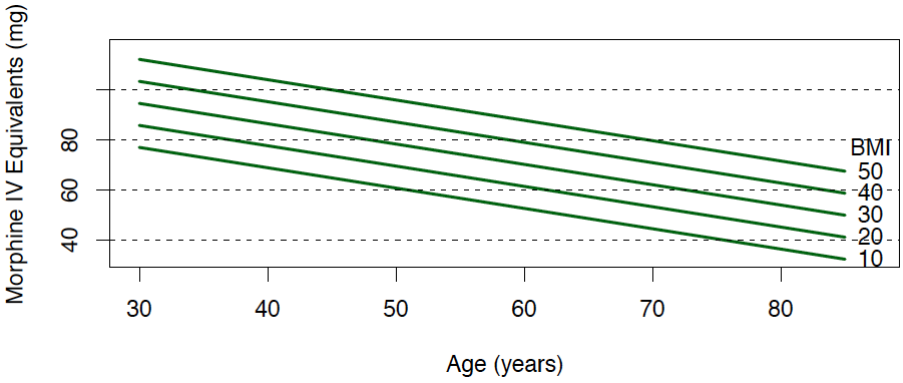
Objectives: Laparoscopy is presumed to be nearly "pain-free." However, patients routinely complain of port site pain, particularly at large port sites with fascial closure. The transversus abdominis plan (TAP) block is a peripheral nerve block for treatment of anterior abdominal wall pain. Our goal was to determine whether preoperative TAP block decreases opiate requirements following robotic surgery for gynecologic cancer.

Methods: We performed a randomized, double-blinded, placebo-controlled trial comparing preoperative TAP block placement with saline injection in women undergoing robotic surgery. Blocks were placed in a standardized fashion using ultrasound guidance. The primary outcome was total 24-hour opiate use. Secondary endpoints included postoperative pain scores, length of hospital stay, and safety. Opiate use was converted to intravenous morphine equivalents and compared using a two-sample T-test. Pain was measured using a Brief Pain Inventory (BPI), Visual Analog Scale (VAS), and outpatient pain diary. Secondary outcomes were analyzed using Chi-square and regression analysis.

Results: Among the 64 subjects, total 24-hour opiate use did not differ significantly between the treatment and control groups (64.9 mg vs 69.3 mg, $P=0.52$). There was no difference in average postoperative pain scores as assessed by BPI (6.44 vs 6.97, $P=0.37$) or VAS (3.12 vs 3.61, $P=0.30$). There was no difference in average pain diary scores or outpatient opiate use between groups. TAP block was safely placed in 63 of 64 patients, with body mass indexes (BMIs) ranging from 18.3 to 66.6. The control group was significantly younger (55.2 vs 62.1 years, $P=0.028$). After correction for age, the difference in total opiate use approached significance ($P=0.085$). Total opiate use showed a strong positive correlation with BMI ($P=0.0012$) and negative correlation with age ($P=0.0008$).

Conclusions: In this population, TAP block was feasible, even in the morbidly obese. However, block placement did not decrease total opiate use or pain scores. The random age imbalance between groups may have masked effectiveness of the block. Further analysis revealed a quantifiable correlation between BMI, age, and total opiate use. These novel data can be organized into a nomogram to assist clinicians in appropriate and safe dosing of postoperative opiate analgesics (Figure).



392 - Poster Session B

Impact of race, socioeconomic status, and the health care system on the treatment of advanced-stage ovarian cancer in California

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Objectives: To investigate the impact of race, socioeconomic status (SES), and health care system characteristics on receipt of National Comprehensive Cancer Network (NCCN) guideline care for stage IIIC/IV ovarian cancer.

Methods: Consecutive patients diagnosed with stage IIIC/IV epithelial ovarian cancer between January 1, 1999 and December 31, 2006 were identified from the California Cancer Registry. Multivariate logistic regression analyses evaluated differences in surgery, chemotherapy, treatment sequence, and NCCN guideline adherence according to race, increasing SES (SES-1 to SES-5), and provider annual case volume.

Results: A total of 11,865 patients were identified. Median age at diagnosis was 65.0 years. Overall median cancer-specific survival was 28.2 months. Black patients received NCCN guideline care in 34.6% of cases, while whites, Hispanics, and Asian/Pacific Islanders received guideline care in 46.2%, 44.6%, and 45.8% of cases, respectively ($P<0.0001$). Higher SES was associated with increased likelihood of receiving NCCN guideline care, which ranged from 39.0% for SES-1 to 50.9% for SES-5. After controlling for other factors, black race (odds ratio [OR] 1.57, 95% CI 1.28-1.93), SES-1 (OR 1.33, 95% CI 1.14-1.55), low-volume hospitals (OR 1.86, 95% CI 1.67-2.07), and low-volume physicians (OR 1.13, 95% CI 1.05-1.38) were associated with a statistically significant increase in receipt of non-NCCN guideline adherent care. Black race (OR 2.04, 95% CI 1.45, 2.87) and care by a low-volume physician predicted an increased risk of not undergoing surgery. Patients with SES-1 (OR 0.71, 95% CI 0.60-0.85) and those treated at low-volume hospitals (OR 0.88, 95% CI 0.77-0.99) or by low-volume physicians (OR 0.80, 95% CI 0.70-0.92) were less likely to undergo debulking surgery. Black race (OR 1.55, 95% CI 1.24-1.93) and SES-1 (OR 1.80, 95% CI 1.35-2.39) were significant predictors of not receiving chemotherapy.

Conclusions: Among patients with advanced-stage ovarian cancer, black race, low SES, and treatment by low-volume providers are significant and independent predictors of receiving no surgery, no debulking surgery, no chemotherapy, and non-NCCN guideline care. Additional research is needed to define the reasons for deviation from recommendations and develop appropriate risk-adjusted measurement models.

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393 - Poster Session B

Risk of complications after robotic hysterectomy for endometrial cancer in obese patients with preoperative comorbidities

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Objectives: To identify complications of robotic hysterectomy for endometrial cancer in obese patients compared by varying degrees of obesity.

Methods: A retrospective chart review was conducted on obese women who underwent a robotic staging surgery for endometrial cancer from 2006 to 2012. Basic demographics and pre-and postoperative complications were extracted from the medical records. Obesity was divided into three categories: moderately obese (BMI 30-35), severely obese (BMI 35-40), and morbidly obese (BMI >40). Complications were specified and a composite outcome (number of complications) was generated.

Results: The cohort included 382 obese patients: 30% moderately obese, 23% severely obese, and 47% morbidly obese, with BMIs ranging from 30 to 70. Postoperative complications occurred in 77 (20%) patients. The majority (13% of the cohort) had one postoperative complication; the total number of complications ranged from none to eight. Among morbidly obese patients, 19% had a postoperative complication compared with 25% of severely obese patients and 19% of moderately obese patients. There was no significant difference in the rate of complications across obesity categories ($P=0.4559$). Mean BMI was similar in patients with and without complications (BMI 40.94 and 42.16, respectively). The most common complications were readmission, ileus, fever, and wound infection.

Conclusions: Degree of obesity does not increase the risk of postoperative complications following robotic hysterectomy for endometrial cancer.

394 - Poster Session B

Type II endometrial cancer in Hispanic women: tumor characteristics, treatment and survival compared to non-Hispanic white women

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Objectives: To study the tumor characteristics, treatment, and outcome in Hispanic white women with type II endometrial adenocarcinoma (EC) compared to non-Hispanic white women.

Methods: Patients diagnosed with serous, clear cell, or grade 3 endometrioid EC were identified from the Surveillance, Epidemiology, and End Results (SEER) program from 1988 to 2009 and were divided into Hispanic white (HW) and non-Hispanic white women (NHW). HW women were further subdivided into natives and immigrants. Chi-square test, Welch t-test, Kaplan–Meier survival methods, and Cox regression proportional hazards were used.

Results: Of the 14,434 women who the inclusion criteria, 13,012 (90.2%) were NHW and 1,422 (9.8%) were HW. Among HW women, 390 (27%) were natives and 1,032 (73%) were immigrants. HW women were younger at presentation than NHW women, with a mean age of 63 vs 68 years (P<0.001). A higher proportion of HW women presented with late-stage disease compared to NHW women (43.8% vs 36.6%, P=0.04). Performing lymphadenectomy was not significantly different, but the proportion of patients who had positive lymph nodes was significantly higher among HW women compared to NWH women (27.6% vs 23.1%, P=0.02). On the other hand, the proportion of HW women (39.5% vs 42.3%, P=0.04) who received radiation therapy was significantly lower compared to NHW women. No difference in clinicopathologic characteristics was found between HW natives and immigrants. In multivariate Cox regression proportional hazards models adjusting for age, stage, histology, surgical treatment, extent of lymphadenectomy and radiation therapy, no difference in overall survival (OS) (HR 1.06, 95% CI 0.97-1.16, P=0.19) and cancer-specific survival (HR 1.02, 95% CI 0.91-1.14, P=0.75) was found between HW and NHW women. Interestingly, HW immigrants had better OS (HR 0.74, 95% CI 0.62-0.89, P<0.001) and cancer-specific survival (HR 0.72, 95% CI 0.58-0.90, P=0.003) than HW women born in the United States.

Conclusions: Although they were more likely to present with advanced-stage and positive nodal disease, no difference in outcome was noted between HW and NHW women with type II EC. Interestingly, HW immigrants had more favorable outcome compared to HW women born in the United States. With the heterogeneity of the HW group, additional studies of the individual groups may further elucidate factors that would explain this difference.

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395 - Poster Session B

The impact of obesity on 30-day morbidity and mortality after surgery for endometrial cancer

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Objectives: To examine the effect of body mass index (BMI) on surgical 30-day morbidity and mortality in patients undergoing surgery for endometrial cancer.

Methods: Patients diagnosed with endometrial cancer from 2005-2011 were identified from the American College of Surgeons National Surgical Quality Improvement Program participant use files. Patients were divided into three groups: non-obese (BMI <30) (NO), obese (BMI 30-<40) (O), and morbidly obese (BMI >40) (MO). Multivariable logistic regression models were used to assess the association between BMI groups and 30-day postoperative complications as well as 30-day mortality.

Results: Of 3,969 subjects, 1,530 (38.5%) were NO, 1,496 (37.7%) were O, and 943 (23.8%) were MO. The surgical approach was split between laparoscopy (48%) and laparotomy (52%). Overall 30-day morbidity and mortality were 13% and 0.7%, respectively. MO patients were more likely to develop postoperative complications compared to NO and O patients (16% vs 13% vs 11%, P=0.001). MO patients were more likely to develop surgical (14% vs 11% vs 9%, P<0.001) and septic complications (2.4% vs 2% vs 0.9%, P=0.01) compared to NO and O patients. No differences were noted in the rates of renal, cardiac, or pulmonary complications. In the laparotomy group, MO had a higher rate of any complication (NO 21%, O 18%, MO 25%, P=0.002) as well as surgical (NO 18%, O 14%, MO 22%, P=0.002) and septic (NO 2%, O 2%, MO 4%, P=0.048) complications. In the laparoscopy group, this difference between BMI groups disappeared. The 30-day mortality was not significantly different by BMI (NO 0.7%, O 0.7%, MO 0.3%, P=0.21). MO patients who underwent laparotomy were more likely to undergo surgical re-exploration (4% vs 2% vs 2%, P=0.043), but there was no difference in mean length of

hospital stay (3.6 vs 3.4 vs 3.0 days, *P*=0.14). After adjusting for confounders, O and MO were not independent predictors of 30-day morbidity or mortality.

Conclusions: MO patients with endometrial cancer were more likely to have postoperative complications following surgery, especially surgical and infectious complications. This difference was more prominent among women who underwent laparotomy but was not observed in the laparoscopy group, favoring minimally invasive surgery as the preferred surgical approach for such patient populations.

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396 - Poster Session B

Levonorgestrel intrauterine device (IUD) treatment of complex atypical hyperplasia and grade 1 endometrioid endometrial cancer in postmenopausal women

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Objectives: A large amount of retrospective data suggests a high conversion rate to benign endometrium following progesterone treatment, either intrauterine or systemic, in premenopausal women with complex atypical hyperplasia (CAH) and grade 1 endometrioid endometrial carcinoma (EMC) who wish to preserve fertility. Data in postmenopausal women are scant and suggest a far lower response rate. Unfortunately, surgery is not a feasible option for some morbidly obese and/or medically ill patients. We undertook this review of our experience with the levonorgesterol IUD to assess the endometrial response rates in postmenopausal women who are not surgical candidates.

Methods: Chart review was undertaken for all patients who underwent IUD insertion by a gynecologic oncologist at our institution from 2002 to 2013. Postmenopausal patients with CAH or grade 1 EMC were identified for further review. Complete response was defined as benign endometrium without hyperplasia on subsequent biopsy. Partial response was defined as nonatypical hyperplasia following treatment of CAH or nonatypical hyperplasia or CAH following treatment of EMC on subsequent biopsy.

Results: Of 26 postmenopausal patients who underwent IUD insertion, only 15 (57%) had follow-up sufficient to assess response. All had medical contraindications to surgical management. Mean body mass index was 45 (range, 17-72) and 9/15 (60%) had history of heart failure or myocardial infarction. A complete response was documented in 9 of 15 patients (60%), a partial response in 1 patient (7%), no response in 3 patients (20%), and progression of disease from CAH to grade 1 EMC in 1 patient (7%).

Conclusions: The majority of postmenopausal women with CAH or grade 1 EMC treated with levonorgesterol IUD due to medical contraindications to hysterectomy had complete responses. This rate is much higher than documented in the literature for postmenopausal women. Although the complete response rate was lower in postmenopausal women than rates reported in series of young women desiring to retain fertility, levonorgesterol IUD is a viable treatment option for women who are poor candidates for surgical management.

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397 - Poster Session B

Obesity and oncologic gynecologic surgery

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Objectives: In our center, 28% of the women treated for gynecologic cancer are obese. We investigated the impact of obesity on surgery.

Methods: A review on patients who underwent surgery for a gynecologic cancer was performed. We compared obese women (body mass index [BMI] ≥30) with normal-weight women. Data about the pathology, the surgical procedures, and the complications were collected.

Results: A total of 572 patients (292 obese and 280 normal weight) were enrolled from 1997 to 2013. Treatment was for endometrial cancer (n=289), cervical cancer (n=193), preventive salpingo-oophorectomy (n=39), and ovarian cancer (n=51). There were no significant differences between the groups with regard to patients and cancer characteristics, surgical

approach, and rate of conversion to laparotomy. In the obese group, there was less mini-invasive surgery (69% vs 81% in the normal-weight group), but this tendency was not significant (P=0.07). Conversion to laparotomy was necessary in 9% and 5% of the groups, respectively (P=0.34). The rate of complete procedures was not significantly different at 87% and 88% of the cases, respectively (P=0.63), even according to surgical approach (P=0.70). The groups were comparable regarding pelvic lymph node count (17.5±10 vs 17±11, P=0.84), para-aortic lymph node count (22±11 vs 18±8, P=0.12), intraoperative complications (3% vs 2%, P=0.48), early postoperative complications (8% vs 7%, P=0.81), and late complications (10% vs 7%, P=0.47).

Conclusions: Obesity among women with gynecologic cancer does not change surgical route and operative morbidity. Obesity should not influence surgical strategy.

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Perceptions of obesity and cancer risk in female bariatric surgery candidates: highlighting the need for physician action for unsuspectingly obese and high-risk patients

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Objectives: Obesity markedly increases cancer risk, but little is known about perceptions of risk and cancer screening in obese women. The study objectives were to determine: 1) whether obese women perceive themselves to be obese or at high-risk for malignancy, 2) the perceived impact of obesity on cancer risk, 3) compliance with cancer screening, and 4) rates of menstrual dysfunction in this high-risk group.

Methods: Institutional review board approval was obtained for this survey that was administered to female patients presenting for bariatric weight loss surgery. Demographic data, menstrual/gynecologic history, perception of cancer risk, and screening history were collected/analyzed. Women were also categorized as obese (body mass index [BMI] 30-39), morbidly obese (BMI 40-49), or super obese (BMI ≥50) and compared.

Results: Of the 93 women who completed the survey, the mean age was 44.9 years and mean BMI was 48.7; 14% were obese, 52% were morbidly obese, and 33% were super obese. A total of 45.7% of patients felt they were in "good," "very good," or "excellent" health, despite high rates of medical comorbidities. One third of the women had had a prior hysterectomy (bleeding was the most common indication). Menstrual irregularities were common. As BMI category increased, women were more likely to accurately self-assess their weight category as obese (23% obese vs 77% morbidly obese vs 85% super obese, P<0.001), but there were no significant differences in comorbidities/menstrual dysfunction. Two thirds of the women correctly identified obesity as a risk factor for uterine cancer, yet almost half (48%) of the 63 women who retained a uterus still perceived that it was "not likely" or “not possible” for them to develop uterine cancer. Participation in cancer screening was relatively robust, with 97% compliance with Pap tests, 86% compliance with mammography (for women ≥40 years), and 68% with colonoscopy (for women ≥50 years).

Conclusions: Morbidly obese women presenting for bariatric surgery have high rates of menstrual dysfunction, and although they correctly perceive that obesity increases the risk of uterine cancer, they often do not perceive themselves to be at higher risk. This disconnect may stem from the fact that 29.3% failed to recognize their own obesity. As obesity continues to become the norm in United States society, this lack of perception will likely only worsen.

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Metformin use is associated with improved survival in women with endometrial cancer

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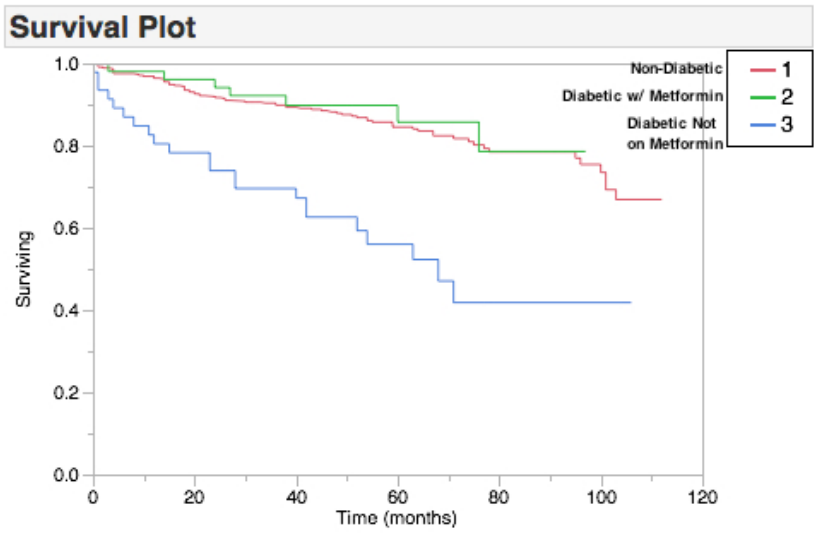
Objectives: Epidemiologic studies have indicated that patients who use metformin have decreased cancer incidence and increased cancer survival. This study investigated the relationship between metformin exposure and survival in women with endometrial cancer.

Methods: Patients with stage I-IV endometrial cancer diagnosed between 2004 and 2010 were identified from a single-institution tumor registry. Patient demographics, cancer characteristics, and the use of metformin and other diabetic

medications were determined from the retrospective medical record review. The primary outcomes analyzed were progression-free survival (PFS) and overall endometrial cancer survival (OS) using Kaplan-Meier survival curves.

Results: The cohort consisted of 542 women. OS and PFS were compared among women without diabetes (n=445), diabetic women exposed to metformin (n=51), and diabetic women without metformin use (n=46). The OS at 3 years was 90% for nondiabetics, 92% for diabetics on metformin, and 67% for diabetics not using metformin (P<0.001). Similarly, the PFS at 3 years was 83%, 86%, and 58%, respectively (P<0.001). The 5-year data were also calculated for those patients in whom 5 years had passed since diagnosis of endometrial cancer (n=234). The OS was 78% for nondiabetics, 74% for diabetics on metformin, and 48% for diabetics not using metformin (P<0.001). The respective PFS was 73%, 65%, and 34% (P<0.001).

Conclusions: Significant association between metformin exposure and increased OS and PFS were seen as compared to nonusers of metformin in women with endometrial cancer.



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400 - Poster Session B

Association between women's breast cancer incidence and smoking rates in Japan by graphical cohort analysis

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Objectives: Breast cancer constitutes approximately 40% of all cancers in women aged 40-49 years and has been the most prevalent cancer in Japanese women since the 1990s. In addition, the link between breast cancer and smoking is well known. In this study, we employed graphical cohort analysis to investigate the association between breast cancer incidence rate and smoking rate by age group.

Methods: The annual incidence rates of breast cancer between 1989 and 2008 were obtained from the Population-based Cancer Registries for the Monitoring of Cancer Incidence in Japan. The annual smoking rates in Japanese women between 1969 and 2009 were extracted from the records of the National Health and Nutrition Survey. Breast cancer incidence rates and smoking rates by age group were visually presented to examine their changes in these time periods. Birth cohort analysis was then performed and the results were graphically displayed.

Results: The breast cancer incidence rate was highest in those aged 45-49 years, followed in order by those aged 50-54 years and 60-64 years in every year examined. Cohort analysis showed that the incidence rate was highest in the 1940-1949 birth cohort, followed by the 1920-1929 birth cohort. The incidence rate in the 1950-1959 birth cohort has become high since 1999. Similarly, the incidence rate in the 1960-1969 birth cohort has increased rapidly since 1999, with the incidence rate in 2008 being approximately 5.6 times higher than that in 1999. In addition, graphical cohort analysis revealed the highest smoking rate was in the 1960-1969 birth cohort since 1989.

Conclusions: The breast cancer incidence rate was highest in women in their forties when the statistics were presented simply by age, and the incidence rates were equally high in the 1940-1949 and 1950-1959 cohorts (64-73 years old and 54-63 years old as of 2013, respectively). The incidence rate in the 1960-1969 birth cohort has increased rapidly since 1999. Although the graphical representation of data did not clarify which components (period, age, and birth cohort) influence the changes in breast cancer incidence rate, it did show that smoking cessation should be urgently promoted in the 1960-1969 birth cohort. Further in-depth analysis by period, age, and cohort is warranted. This work was supported by Health Labour Sciences Research Grant (Sobue Study group).

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401 - Poster Session B

Insulin receptor isoform expression in ovarian cancer in African American women

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Objectives: Two insulin receptor (INSR) isoforms, (INSR-B) and a splice variant that signals for cell proliferation and survival (INSR-A), are expressed in ovarian cancer (OC) cell lines. Obesity and type 2 diabetes are more common in the African American (AA) population, but little is known about OC INSR isoform expression in this group of patients. We hypothesized that differential expression of INSR-A in OC from AA women could represent a therapeutic target in this population.

Methods: Formalin-fixed, paraffin-embedded OC tissue was obtained through biospecimen repositories at both participating institutions. A total of 189 tumor samples were obtained: 93 samples from AA women and 96 from white (W) women matched for age, stage, and histology. Validated quantitative polymerase chain reaction-based assays for INSR-A and INSR-B were performed. INSR isoform expression as well as the expression ratio between groups was compared using Wilcoxon rank-sum tests.

Results: INSR-A expression was similar in AA (median expression=48,228 copies/mcg RNA, range=4,444-2,915,758) and W samples (median expression=57,848, range=3370-1,259,293) (P=0.35). INSR-B expression was slightly lower in AA (median expression=3,038, range=121-72,803) than W samples (median expression=4,634, range=214-803,401) (P=0.039). Ratio of A:B was significantly higher in the AA samples (median 17.7, range 1.8-262.2) than in the W sample set (median 12.4, range 0.1-205.5) (P=0.0009).

Conclusions: INSR-A and INSR-B are expressed on OC tissue from both races. INSR-A is the predominant isoform in both sample sets, but the isoform ratio (INSR-A:INSR-B) was higher in the AA group. This is the first study to investigate the expression level of the INSR in OC samples in the AA population and suggests that INSR-A signaling is a potential target in the AA population. Further analyses of proteins in the insulin-like growth factor pathway are currently underway.

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402 - Poster Session B

Bariatric surgery of a means to decrease mortality in women with type I endometrial cancer: an intriguing option in a population at risk for dying of complications of metabolic syndrome

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Objectives: To estimate the cost of bariatric surgery as a means to reduce death from complications of metabolic syndrome in obese women with endometrial cancer (EC).

Methods: A decision model was designed to compare the costs and effectiveness of routine care vs bariatric surgery referral for women with low-risk, stage I endometrioid EC, age <70 years, and a mean body mass index (BMI) of 40. A modified Markov state transition model with a time horizon of 15 years was used to simulate the overall survival (OS) of 96,232 women treated from 1988-2010 from Surveillance, Epidemiology, and End Results (SEER)*Stat data. To simulate the effects of bariatric surgery on OS, an HR 0.76 (95% CI 0.59-0.99) representing the OS improvement achieved in a prospective trial was modeled. Rates and costs of significant postoperative events (perioperative death 0.3%, reoperation 0.75%, major adverse events 1.9%, minor adverse events 3.2%) were derived from large published studies and modeled as distributions to account for uncertainty. We assumed that 90% of women undergoing bariatric procedures would experience a reduction in BMI, with two thirds achieving a BMI of 35 and one third a BMI of 30. We assumed that 5% of women not undergoing bariatric surgery would achieve a BMI of 35. Costs of treatment for obesity-related chronic diseases were modeled from

published data based on BMI cohorts. Quality of life (QOL)-related utility scores before and after bariatric surgery were modeled from a published prospective study; we assumed a slow regression back to baseline QOL over the 15 years of follow-up.

Results: The mean cost and effectiveness for each strategy were $38,660 and 8.07 quality-adjusted life-years (QALYs) for routine care vs $66,614 and 9.26 QALYs for bariatric surgery. Bariatric surgery had an incremental cost-effectiveness ratio (ICER) of $23,498 compared to routine care. At a willingness-to-pay threshold of $50,000/QALY, bariatric surgery was the strategy of choice in 100% of simulations. Assumption of no QOL benefit from bariatric surgery resulted in an ICER of $72,568/QALY.

Conclusions: Bariatric surgery is a potentially cost-effective intervention in reducing mortality from complications of metabolic syndrome in women with endometrial cancer. Continued investigation of bariatric surgery and a clinical trial in women with endometrial cancer should be strongly considered.

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403 - Poster Session B

A population-based comparison of human papillomavirus (HPV) distribution and cervical lesions in China

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Objectives: To compare HPV genotype distribution, prevalence, and rates/risk factors for cervical dysplasia between two different ethnic populations in China: the Uygur and Han.

Methods: Data for this study were extracted from the Shanxi Province Cervical Cancer Screening Study III. Women were included from two of the sites in the study: the Xinjiang (Uygur) and Henan (Han) provinces in China. This resulted in data from a total of 883 Uygur and 881 Han women. Demographic and risk factor information was obtained by questionnaire. Information on HPV status was obtained via testing for high-risk (HR)-HPV with hybrid capture 2 and cervical cytology. Unaided visual inspection of the cervix with acetic acid was also done. If an abnormality on any of these tests was noted, colposcopy with multiple cervical biopsies was performed. All data were analyzed by SPSS 15.0.

Results: The prevalence of HR-HPV was higher in the Han population than the Uygur population (12.26% vs 7.25%), but the prevalence of cervical intraepithelial neoplasia (CIN)2+ in the populations was similar (1.13% vs 1.95%). However, HPV-infected Uygur women were more likely to develop CIN2+ (26.56% vs 9.26%, *P*=0.004). Also, Uygur women with CIN2+ were more likely to be infected with HPV16 than Han women with an odds ratio of 9.75 (97% CI: 1.38-68.78). On multivariate analysis, the only demographic factor associated with increased risk of HPV infection was genital inflammation, which was higher in the Uygur population.

Conclusions: Tissue studies in China have previously shown that the rates of cervical cancer are higher in the Uygur population, but population studies have not addressed the reasons for this difference. The increased likelihood of developing CIN2+ after HPV infection in Uygur women compared to Han women may be impacted by many factors. These include not only geographic/population features, which limit access to care, but also cultural practices in this population. The Uygur women have an unusual practice of using sand to cleanse the vagina, which is likely a source of micro-tears and increased acquisition of HPV. Likely more significant is the finding that HR-HPV-positive Uygur women were more likely to be infected with HPV16. Possible targets for intervention in the Uygur population include not only improving access to care, but also providing education about hygiene practices.

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404 - Poster Session B

Prospective wound protocol to decrease the incidence of wound complications in obese gynecologic oncology patients

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Objectives: Obese women have a high incidence of wound separation after gynecologic oncology surgery. We explored the effect of a prospective care pathway for closure of vertical abdominal wounds on wound separation and infection.

Methods: Women aged 18-89 years with a body mass index (BMI) >30 undergoing a gynecologic procedure via a vertical abdominal incision were eligible. The surgical protocol included: use of cutting current or scalpel to open the skin, subcutaneous tissue, and fascia; running mass closure with two #1 loop Polydioxanone (PDS) sutures; placement of a subcutaneous closed-suction 7-mm drain; approximation of the subcutaneous tissues with 3-0 plain gut; and closure of the skin with staples. Wound complication was defined as the presence of either a wound infection or any separation. Demographic and perioperative data were analyzed using contingency tables. Chi-square tests were used to analyze predictors of wound complications.

Results: A total of 105 women were enrolled, with BMIs ranging from 30.0 to 76.4. The average BMI was 39.7±8.0. Overall, 39 patients (37%) had a wound complication: 33 (31%) had a wound separation and 22 (21%) had a wound infection. Women with a BMI of 30 to 39.9 had a significantly lower risk of wound complication compared to those with a BMI >40 (23% vs 58.5%, $P<0.001$). Among women with a BMI <40, 11 (17%) had wound separations and 7 (11%) required wound packing compared with 24 (59%) separations and 18 (44%) wounds requiring packing among women with BMIs >40 ($P<0.001$ for both). This was a significantly improved complication rate compared to our historical cohort: 40% for women with BMI 30 to 39.9 ($P=0.02$) and 60% for women with BMIs >40 ($P=0.49$).

Conclusions: This wound protocol appears to decrease the rate of wound complications among women with BMIs of 30 to 39.9. Only a small percentage of those with a BMI <40 required wound packing. Future clinical trials are needed to validate these findings and lessen the morbidity of open laparotomy in obese women.

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405 - Poster Session B

Durable responses to sequential Megace in recurrent endometrial cancer

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Objectives: Hormonal therapy in patients with recurrent endometrial cancer has been grossly underutilized. In recurrent endometrial cancer, most cytotoxic chemotherapy agents yield minimal improvement in survival. We propose that the use of hormonal therapy with sequential Megace (3 weeks on, 3 weeks off) can provide prolonged disease-free intervals for patients with minimal adverse effects.

Methods: After institutional review board approval, patients were retrospectively identified with endometrial cancer between 1999 and 2009 at a single institution. Clinical information was abstracted, including age of diagnosis, body mass index, histologic type, grade, stage, surgeries, progression-free survival, overall survival, chemotherapy, radiation, Megace administration, and complications.

Results: Twenty-five recurrent endometrial cancer patients were identified who received adjuvant Megace therapy. The median age of diagnosis was 57 years and median follow-up was 48 months (range, 12 to 144 months). All 25 patients underwent staging procedures, 17 patients received radiation therapy, 15 patients received pelvic radiation, 2 received cuff-only radiation therapy, and 20 received adjuvant chemotherapy. After recurrence, 23 patients were treated with sequential Megace, while 2 were treated with continuous Megace therapy. Median time on Megace therapy was 24 months, and the median time to progression was 24 months (range, 6 to 96 months). Thirty-six percent (9/25) of patients are alive with no evidence of disease, 16% (4/25) are alive with evidence of disease, 44% (11/25) are dead of disease, and 4% (1/25) are dead of other causes. Of the patients alive with no evidence of disease, median duration of therapy was 31.5 months (range, 14 to 96 months). Of the patients who died of disease, median duration of therapy was 17 months (range, 6 to 70 months). Two complications with venous thrombotic event were observed while on Megace therapy, including pulmonary embolus and deep venous thrombosis. No significant weight gain was noted; most patients lost weight while on Megace therapy.

Conclusions: The use of sequential Megace therapy, possibly due to incomplete down-regulation of receptors, may provide a benefit in longer-term disease-free survival. The low cost and minimal adverse effects warrant consideration of Megace as an alternative therapy in patients with recurrent endometrial cancer who have failed frontline therapy.

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406 - Poster Session B

Quantifying obesity-related increases in cost for the surgical management of uterine cancer

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Objectives: To quantify the added cost associated with obesity for the surgical treatment of uterine malignancy (UM).

Methods: The University HealthSystem Consortium (UHC) database, containing data representing >90% of United States nonprofit academic medical centers, was queried to identify all women with a diagnosis of UM (ICD-9 182.x and 179), with and without the comorbidity of obesity, who underwent open, laparoscopic, or robotic hysterectomy during the study period (2009 to 2013). Mean direct hospital costs were compared by method of hysterectomy between obese and nonobese cohorts. Continuous variables were compared with ANOVA and Student's t-tests; categorical variables were compared with Chi-square tests.

Results: A total of 25,263 patients were included and 8,407 (33%) were coded as obese. Of the hysterectomies performed on obese women, 55% were open, 9% were laparoscopic, and 36% were robotic. Of the hysterectomies performed on nonobese women, 52% were open, 15% were laparoscopic, and 33% were robotic. Frequencies of hysterectomy methods were significantly different ($P<0.0001$) between the obese and nonobese groups. Mean direct hospital costs were significantly greater for obese compared with nonobese women regardless of method of hysterectomy: open 17% higher ($12,021 vs $10,249, $P<0.0001$), laparoscopic 17% higher ($8,532 vs $7,290, $P<0.0001$), and robotic 15% higher ($10,180 vs $8,868, $P<0.0001$). In both obese and nonobese patients, minimally invasive approaches were less costly than open surgery ($P<0.05$). Although some obese patients may not have been coded as such, their inclusion in the nonobese cohort will reduce any observed cost differences. Therefore, these results represent a conservative estimate.

Conclusions: Obesity is associated with higher costs of surgical treatment of UM, regardless of method of hysterectomy. Our findings suggest that there are potentially significant economic benefits related to UM treatment that may be achieved by reducing obesity. In addition, the uniformly lower cost of minimally invasive approaches argues for their use when feasible. With the advent of novel payment models, including bundled payments, cost control is of major concern. Weight management and minimally invasive surgery may become increasingly important components of strategies for cost-effective management of UM.

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Barriers to cervical cancer screening in victims of intimate partner violence: a Gynecologic Oncology Fellows Research Network study

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Objectives: Intimate partner violence (IPV) is a preventable public health problem affecting millions of United States women. This term describes physical, sexual, or psychological harm by a current or former partner or spouse. Prior research suggests that women with a history of IPV have an increased incidence of cervical cancer and lower likelihood of being screened for cervical cancer. The objective of this study was to determine the key factors and most important barriers associated with a decreased likelihood of cervical cancer screening and follow-up among women who have experienced IPV.

Methods: Based on the health belief model and social cognitive theory, a survey was designed to address cervical cancer screening status, access to care, and barriers related to a history of IPV. Survey items used a 5-point Likert scale (1=strongly agree); summary scores were computed. Domestic violence shelters were contacted, and women within each participating shelter were asked to voluntarily complete an anonymous survey. Descriptive statistics, Chi-square and t-tests were performed.

Results: Interim analysis of 104 women who completed this survey revealed a mean age of 37 years, 51% who identified as non-white, 90% who earned <$20,000 in 2012, and 22% with no health insurance (53% had Medicaid only). Twenty-seven percent of women reported not having had a Pap smear within 3 years and were classified as not up-to-date. When compared to up-to-date women, they were more likely to report both inaccessibility to screening (mean scores 2.3 vs 1.8, $P=0.003$) and barriers related to a history of IPV (mean scores 2.7 vs 2.2, $P=0.018$). Women who were not up-to-date were as likely to report that they would follow-up on an abnormal test result as women who were up-to-date (mean score 1.7 vs 1.6, $P=0.583$). There was no statistically significant difference in responses between women who experienced sexual vs other forms of IPV. Sixty-one percent of women reported that a self-sampling screening test would be acceptable, but only 12% thought they would favor this method of screening.

Conclusions: For women who have experienced IPV, both inaccessibility to screening and concerns related to their history of IPV play significant roles in Pap smear screening. While self-sampling would be well accepted among the majority of women in this population, it may not significantly increase rates of screening.

408 - Poster Session B

A prospective, randomized trial on the impact of patient navigation in women with abnormal cervical cytology

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Objectives: The National Cancer Institute-sponsored Patient Navigation Research Program (PRNP) was established to assess the effectiveness of patient navigation (PN) programs to reduce the time to diagnostic resolution among patients with abnormal cancer screening. The PNRP defined PN as support and guidance to vulnerable persons with abnormal cancer screening, with the goal of overcoming barriers to timely quality of care. The purpose of this prospective trial was to determine if the use of PN increased the proportion of patients receiving timely and correct management following abnormal cervical cytology.

Methods: A total of 305 patients with abnormal cervical cytology were enrolled in this study between 2007 and 2010. The clinics were randomized to PN vs standard of care follow-up for patients. Eleven patients were excluded for pregnancy, age <18 years, or lost to follow-up. Appropriateness of care was determined by the 2006 American Society for Colposcopy and Cervical Pathology guidelines. Timeliness of care was defined as completion of a physician recommendation within 6 weeks of the scheduled follow-up. Patients were divided into three groups: 1) appropriate recommendation regardless of timeliness of care, 2) timely care regardless of recommendation, and 3) appropriate recommendation and timely care.

Results: Of 294 eligible patients, only 120 (40.8%) received appropriate recommendations for management of their abnormal cytology, with no difference between the study arms (odds ratio [OR] 1.004, 95% CI 0.42-2.39, *P*=0.992). There were 171 (58.2%) patients who received timely care, again with no significant difference between the two arms (OR 1.567, 95% CI 0.8-3.07, *P*=0.174). Only 56 patients (19%) received appropriate recommendations with timely care, with no benefit attributable to PN (OR 1.76, 95% CI 0.70-4.47, *P*=0.212). Even in 122 patients at higher risk for cervical intraepithelial neoplasia (low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion [HSIL], or atypical squamous cells-cannot exclude HSIL), there was neither more timely (OR 1.93, 95% CI 0.86-4.37, *P*=0.105) nor more appropriate care (OR 0.994, 95% CI 0.46-2.16, *P*=0.986) in the PN arm.

Conclusions: There was no benefit to PN in patients with abnormal cervical cytology in regard to appropriateness or timeliness of care, even in those patients at the greatest risk for having cervical dysplasia or cancer. Continued investigation of the opportunities for improving the low rate of timely and appropriate triage of abnormal cytology seen in this study is critical.

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409 - Poster Session B

Black race independently predicts worse survival in uterine carcinosarcoma

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Objectives: Uterine carcinosarcomas are rare and aggressive malignancies. Gynecologic Oncology Group (GOG) 150 suggested that black women had worse survival compared to non-black women. Our objective was to compare treatment and survival outcome between black and white women at a comprehensive cancer center serving a diverse racial population.

Methods: An institutional review board-approved institutional retrospective cohort study of uterine carcinosarcoma patients diagnosed between 2000-2012 was performed. Demographics, tumor characteristics, treatment methods, and survival were abstracted. Survival was compared by race and also stratified by stage (early vs advanced). Median progression-free and overall survival (PFS and OS) were calculated using Kaplan-Meier estimates and compared with the log-rank test. Multivariate survival analysis was performed with Cox proportional hazards model.

Results: Of the 158 women included in the cohort, 93 (59%) were black and 65 (41%) were white. Further, 95 (60%) had early-stage disease and 63 (40%) had advanced-stage disease. Age, body mass index (BMI), stage, residual disease, adjuvant treatment, histologic subtypes, and lymphadenectomy rates were similar between races. Black women recurred sooner (PFS 7.9 vs 14.2 months, *P*<0.001) and died earlier (OS 13.4 vs 30.8 months, *P*<0.001). There was no difference in survival between black and white women with advanced-stage disease (OS 8.5 vs 11.8 months, *P*=0.18). However, despite similar rates of adjuvant treatment and surgical staging, PFS and OS were worse in black women compared to white women

with early-stage disease (PFS 13.6 vs 77.4 months, *P*=0.001), (OS 25.4 vs 94.7 months, *P*=0.003). On multivariate analysis accounting for age, stage, BMI, and adjuvant treatment, black race remained independently associated with risk of death (HR 2.0, 95% CI 1.25-3.23).

Conclusions: Black women with uterine carcinosarcoma have worse survival compared to white women despite similar patient, surgical, and treatment characteristics. This difference is largely due to differences in survival in early-stage disease.

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410 - Poster Session B

Management of advanced epithelial ovarian cancer in the elderly

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Objectives: Ovarian cancer is the leading cause of mortality from gynecologic malignancies in the United States. Age alone has been shown to be an independent risk factor for diagnosis of ovarian cancer and has been identified as an independent risk factor for disease progression and death. The objective of this study was to evaluate the clinical outcomes of elderly women (>65 years) undergoing surgery for advanced ovarian cancer.

Methods: Patients >65 years undergoing surgery for advanced epithelial ovarian, fallopian, or primary peritoneal cancer were retrospectively identified using the Massachusetts General Hospital Tumor Registry. Demographic, pathologic, and clinical data were abstracted from the medical record. Survival estimates were calculated using the Kaplan-Meier method.

Results: Between December 1991 and February 2013, we identified 333 patients who underwent primary debulking surgery (PDS) or neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS). Median age was 72 years (range, 65-94 years); 75% (n=248) were diagnosed with stage III disease and 25% (n=85) with stage IV disease. A total of 260 patients (78%) underwent PDS and 73 patients (22%) underwent NACT-IDS.

Rates of cytoreduction were as follows:

	Type of Surgery	
Rate of Cytoreduction	PDS	NACT-IDS
Optimal (overall)	71%	83.6%
Optimal, no evidence of disease	70 (27%)	27 (37%)
Optimal, <5 mm	70 (27%)	21 (29%)
Optimal, <1 cm	45 (17%)	13 (18%)
Suboptimal, <2 cm	10 (3.8%)	2 (3%)
Suboptimal, >2 cm	65 (25%)	10 (14%)

Patients receiving NACT-IDS were more likely to undergo an optimal cytoreductive surgery compared to women receiving PDS (83.6% vs 71%, *P*=0.033). A significant improvement in overall survival was observed in women who underwent an optimal vs a suboptimal debulking surgery (*P*<0.005). Type of surgery (PDS vs NACT-IDS) did not affect overall survival. Of note, there was no difference in overall survival between the suboptimal 1-2 cm or >2 cm groups.

Conclusions: Optimal cytoreductive surgery is feasible in an elderly population (age >65 years). NACT may improve rates of cytoreduction in elderly patients. Optimal cytoreductive surgery, regardless of the approach employed (PDS or NACT-IDS), results in a significant improvement in overall survival.

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411 - Poster Session B

Biguanides inhibit proliferation and decrease estrogen receptor expression in ovarian granulosa cell tumors

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Objectives: Obesity and diabetes are associated with increased risk and worse outcomes for ovarian granulosa cell tumors. The antidiabetic drugs metformin and phenformin are biguanides with promising antitumorigenic effects. We examined the effects of metformin and phenformin on proliferation and apoptosis in ovarian granulosa tumor cells.

Methods: The KGN ovarian granulosa tumor cell line was treated with metformin and phenformin. Cell growth was determined by MTT assay. Cell cycle progression was assessed by Cellometer. Apoptosis was evaluated by Annexin V-FITC assay using Cellometer. Estrogen receptor-alpha (ERα), progesterone receptor (PR), AMPK, S6, cyclin D, CDK4, CDK6, p21, and p27 expression were documented by Western blotting. The effects of metformin and phenformin on ERα and PR mRNA expression was determined by real-time polymerase chain reaction.

Results: Metformin and phenformin inhibited cell proliferation in a dose-dependent manner in the KGN cell line within 48 to 72 hours of exposure (median inhibition concentration 2.5 mM for both agents, P=0.0001). Treatment with metformin and phenformin resulted in G2 and G1 cell cycle arrest, respectively. Both metformin and phenformin induced apoptosis in the KGN cells (P=0.0007-0.044). Western blot analysis demonstrated that metformin and phenformin increased phosphorylation of AMPK; decreased phosphorylation of S6; increased cyclin D1 expression; and decreased CDK4, CDK6, p21, and p27 expression within 24 hours of exposure. Treatment with metformin and phenformin decreased ERα mRNA and protein expression but had no effect on PR expression.

Conclusions: Metformin and phenformin potently inhibited cell growth via G1 or G2 arrest and induced apoptosis in ovarian granulosa tumor cells via AMPK activation and mTOR pathway inhibition. In addition, metformin and phenformin decreased ERα expression, and this could be advantageous in ovarian granulosa cell tumors, which are known to secrete estradiol and respond to antiestrogen hormonal therapies. Thus, this work suggests that metformin may be a novel chemotherapeutic agent for ovarian granulosa cell tumors, a disease affected by obesity and diabetes.

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412 - Poster Session B

A centrosome clustering suspect, HSET, is a potential biomarker for breast cancer aggressiveness in triple-negative breast cancer (TNBC) patients

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Objectives: One widely accepted distinction between cancer and normal cells is the number of cellular organelles, called centrosomes. While normal cells have two centrosomes during mitosis, cancer cells have many centrosomes. Although extra centrosomes enable "optimal" chromosome missegregation to allow tumor-promoting aneuploidy, the inevitable spindle multipolarity that ensues with extra centrosomes is incompatible with cell survival. To resolve this conundrum, cancer cells have evolved mechanisms to cluster these extra centrosomes to assemble a pseudo-bipolar spindle during cell division. HSET, a nonessential minus end-directed motor of the kinesin-14 family, is a centrosome-clustering molecule essential for viability of extra centrosome-bearing cancer cells. Given that ~80% of breast cancers exhibit centrosome amplification, we examined whether HSET is selectively overexpressed in human breast tumors and differentially overexpressed among TNBC vs non-TNBC patients.

Methods: We interrogated human breast tissue microarrays from publically available Gene Expression Omnibus (GEO) and Cancer Genome Atlas (TCGA) databases. Specifically, one-channel data were from GEO and 599 two-channel data were from TCGA database, totaling to 3,166 patients. We evaluated differences in HSET gene expression for TNBC and non-TNBC groups using validated statistical methods. Immunohistochemical staining in paraffin-embedded breast tumor samples was performed using an anti-HSET rabbit polyclonal antibody.

Results: Our in silico data indicated higher HSET gene expression in TNBC (n=214) compared to non-TNBC (n=2,952) patients. Interestingly, irrespective of tumor grade, HSET gene expression was ~10% higher in TNBC (n=75) vs non-TNBC (n=105) patients (P<0.001). TCGA data-mining revealed ~35% higher HSET expression for TNBC (n=89) vs non-TNBC (n=425) (P<0.001) patients matched for tumor stage and lymph node status. Immunohistochemical staining yielded higher nuclear HSET expression in grade-matched TNBC (n=96) vs non-TNBC (n=64) women.

Conclusions: Taken together, HSET overexpression may serve as a novel biomarker of breast cancer aggressiveness.

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413 - Poster Session B

Comparative surgical outcomes in endometrial cancer patients staged with robotics or laparotomy 65 years and older

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Objectives: Older age is a risk factor associated with adverse outcomes in major surgery. We compared the outcomes in women ≥65 years undergoing surgical staging for endometrial cancer with laparotomy and robotic approaches.

Methods: Demographics, medical history, intraoperative, and hospital data were collected from staged endometrial cancer patients since initiating a robotics program at our institution. Outcomes included vital organ injury, venous thromboembolism, ileus, bowel obstruction, and urinary tract infection as well as wound, cardiac, central nervous system, and respiratory complications. The validated Charlson Comorbidity Index (CCI) was used to calculate scores for preoperative comorbidities. Standard statistical analysis was used.

Results: Of the 228 patients identified, 73 (32%) patients were ≥65 years. In the older cohort, robotic approach was used in 26 (36%) patients and laparotomy in 47 (64%) patients. Among robotic patients, women ≥65 years had a higher mean CCI score (7.6 vs 4.9, $P<0.01$) and were more likely to undergo lymphadenectomy (73% vs 47%, $P=0.02$). Elderly patients were also more likely to have FIGO grade 2/3 tumors (60% vs 45%, $P=0.04$). When the older and younger robotic cohorts were compared, there was no difference in intraoperative and postoperative complications, with the exception of increased urinary retention in the older group (15% vs 2%, $P=0.02$). Older patients had significantly longer hospital stays compared to younger patients (2.2 vs 1.3 days, $P<0.01$), but there was no difference in the rate of return to home at discharge ($P=0.09$). In the older cohort, when robotic and laparotomy approaches were compared, robotics was associated with decreased blood loss (130 vs 235 mL, $P=0.03$), rate of ileus (0 vs 15%, $P=0.04$), and length of stay (2.2 vs 4.4 days, $P<0.01$). The robotic approach was associated with a 96% return to home rather than medical facility discharge compared with 83% in the laparotomy group ($P=0.11$).

Conclusions: Women ≥65 year undergoing robotic surgical staging for endometrial cancer have more medical comorbidities and higher tumor grade compared to younger patients. Despite these differences, there was no significant increase in intraoperative and perioperative complications, with the exception of increased urinary retention. Robotic surgery appears to be safe in this at-risk population.

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414 - Poster Session B

Understanding barriers and facilitators to healthy lifestyle change in African American endometrial cancer survivors and their social network

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Objectives: This qualitative study sought to understand attitudes, barriers, and facilitators to lifestyle change among African American (AA) endometrial cancer survivors and their self-identified support network

Methods: AA endometrial cancer survivors and women in their social networks were recruited. Three focus groups (n=21) using a semistructured topic guide were conducted. Inclusion criteria included female gender, AA race, age ≥35 years, and obesity (body mass index [BMI] >25). Sessions were recorded and transcribed verbatim. Data were analyzed to identify salient themes.

Results: Participant age ranged from 35 to 75 years (median 64 years). Mean BMI was 38 (median 35). A diverse range of household incomes was represented, with 75% retired or not working. In addition, 35% had a college or graduate degree and 85% were identified as single. Comorbidities included: diabetes (35%), hypertension or cardiovascular disease (65%), and high cholesterol (35%). Several themes emerged: 1) weight fluctuation struggles; 2) psychosocial barriers, including motivation and gaps between knowledge and action; and 3) economic and resource limitations for food choice and exercise. External and internal barriers to lifestyle change included: 1) perceived cost of healthy food, exercise resources, or participation in formal weight loss programs; 2) lack of dietary knowledge; 3) poor food choices available at social events; 4) physical limitations (pain or mobility); 5) prior developed habits; 6) depression/other stressors; and 7) poor eating habits due to social isolation and boredom. Participants identified factors to facilitate change, including 1) having friends/family with similar goals, 2) receiving information from their physicians about diet and exercise, 3) linkage to community resources, and 4) reinforcement of goals by peers or medical staff. Participants demonstrated limited awareness of the association of endometrial cancer risk and obesity.

Conclusions: Endometrial cancer patients face poor health outcomes related to obesity. A cancer diagnosis can be a teachable moment to influence health behaviors in patients and their extended social network. This study identifies concrete economic, educational, and psychosocial barriers that can be addressed in a multidisciplinary approach to lifestyle change as a critical part of survivorship for this high-risk group.

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415 - Poster Session B

Body mass index (BMI) associations, including mismatch repair protein expression, in 1,051 endometrial carcinomas

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Objectives: Links between obesity, with its attendant estrogen abnormalities, and the endometrial carcinoma (EC) DNA Mismatch Repair Protein (MMR) system have recently been proposed. We investigated relationships between BMI and clinicopathological correlates, including MMR expression in a large single-institution EC cohort.

Methods: Clinical and pathological databases from 2007 to 2012 were used to identify consecutive hysterectomy specimens with EC. Univariate and multivariate analyses were used to explore relationships among BMI; age; stage; tumor type; and immunohistochemical results for MLH1, PMS2, MSH2, and MSH6.

Results: A total of 1,051 EC cases were identified. Overall, BMI was higher among women with normal MMR (P=0.002), and the lowest rate of protein loss (20.3%) was seen in the obese group (n=750) (P=0.003). However, when stratified by age and specific MMR, statistically significant differences localized exclusively to women <50 years old with loss of MSH2 and/or MSH6 (P=0.003 and P=0.005, respectively). Higher BMI correlated with endometrioid FIGO 1 and 2 tumors (P<0.001) and with stage IA (P<0.001). Conversely, MMR abnormalities did not show significant associations with stage (P=0.359) or histologic grade (P=0.107).

Conclusions: BMI showed statistically significant associations with MMR expression, tumor grade, and stage among 1,051 consecutive EC cases. Obesity correlated with lower-grade and -stage EC. A link between BMI and maintenance of the MMR system is not supported by our data because the only statistically significant association occurred in women <50 years old with MSH2 and/or MSH6 abnormalities, where Lynch syndrome-related cases are expected to cluster.

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416 - Poster Session B

Increasing minority participation in gynecologic oncology clinical trials through patient navigation

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Objectives: African American patients are less likely to enroll in clinical trials than other racial groups. The project “Increasing Minority Participation in Clinical Trials” (IMPaCT) aims to enhance the recruitment and retention of African Americans in therapeutic cancer clinical trials through patient navigation. The objective of this study was to assess the effect of the IMPaCT program on enrollment into gynecologic oncology clinical trials in a racially and socioeconomically diverse National Comprehensive Cancer Network cancer center.

Methods: Community health advisors were trained to serve as patient navigators (PNs) to help African American cancer patients overcome barriers to participation in clinical trials. The PNs educated patients about therapeutic trials, assisted with their recruitment into trials, and helped retain them by linking them to institutional services and community resources. Data were collected regarding number of patients referred to IMPaCT as well as the number of patients who declined, were ineligible, or were ultimately enrolled.

Results: Since 2006, 54 African American patients with gynecologic malignancies were referred to the IMPaCT program, and 28 (51.9%) were enrolled into clinical trials. Between 2006 and 2010, an average of 4.8 gynecologic oncology patients per year were referred and 1.8 patients per year were enrolled. Since 2011, an average of 10.0 patients per year were referred and 6.3 patients per year were enrolled. This translated to an improvement in the proportion of enrolled to referred from 0.38 to 0.63 in this time period.

Conclusions: Through an intensive institutional effort, the IMPaCT program has successfully recruited and enrolled African American women into gynecologic oncology clinical trials. As barriers to enrollment have been better identified, rates of referral and subsequent enrollment have improved.

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417 - Poster Session B

Weight-based chemotherapy dosing does not increase chemotherapy-related toxicity in obese gynecologic cancer patients

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Objectives: American Society of Clinical Oncology recommends the use of full weight-based (WB) doses of chemotherapy to treat obese patients with cancer. Many clinicians cap chemotherapy doses at a body surface area (BSA) of 2 m^2. The objective of this study was to determine how chemotherapy-related toxicities compare between groups of patients that varied with respect to BSA and dosing regimen. We hypothesized that obese patients receiving WB dosing would not have significantly higher chemotherapy-related toxicities than controls.

Methods: We performed a retrospective review of patients with BSA ≥2 m^2 who received WB chemotherapy for a gynecologic cancer between January and August 2013. Subjects were matched with two controls: patients with BSA <2 m^2 who received WB dosing and patients with BSA ≥2 m^2 who received capped dosing at BSA=2 m^2. The groups were matched for medical comorbidities and prior cancer treatment. Agents included paclitaxel, gemcitabine, and liposomal doxorubicin. A subanalysis was performed for patients receiving carboplatin and paclitaxel (CT) for primary therapy. Demographic and clinical information were extracted and analyzed via ANOVA and Fisher's exact test.

Results: A total of 75 patients were included. The three groups were similar in their medical comorbidities and prior cancer treatment. When comparing the pre- and posttreatment laboratory values for each cycle between the groups, there were no differences in white blood cell count (WBC), absolute neutrophil count (ANC) or platelet count. There was no difference between groups with regard to treatment delays, unplanned admissions, transfusions, or dose reductions for toxicity (all P values NS). This same association was consistent within the subanalysis of patients (n=50) receiving CT. Additionally, patients in each group who had received prior radiation therapy for gynecologic cancer experienced no added toxicity.

Conclusions: At our institution, gynecologic cancer patients with BSA ≥2 m^2 treated with WB chemotherapy had no increase in chemotherapy-related toxicities or dose reductions as compared to controls. A subanalysis of obese patients receiving WB doses of paclitaxel demonstrated similar results. Based on these data, consideration should be given to using WB dosing in obese patients. Further investigation is required to determine the effect of WB dosing on progression-free and overall survival.

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418 - Poster Session B

Minority participation in Gynecologic Oncology Group (GOG) studies

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Objectives: National Cancer Institute Strategic Plan for Leading the Nation, Objective #8 calls for overcoming cancer health disparities. As such, participation of minority populations in clinical trials is paramount to understanding and overcoming cancer racial disparities. The goal of this project was to evaluate minority participation in GOG clinical trials.

Methods: GOG publications from years 1985 to 2013 were reviewed. Data abstracted included racial breakdown, tumor type, study type, and year published. Minority enrollment was stratified by tumor site (ovarian, endometrial, cervical, and sarcoma), type of study (phase I, II, III, translational, and observational/quality-of-life studies) and year published. Based on Centers for Disease Control and Prevention (CDC) age-adjusted incidence for race, expected and observed ratios of racial participation were calculated.

Results: A total of 311 GOG publications involving 57,016 patients were reviewed. Racial breakdown was provided in 169 studies (54%) for a total of 44,820 patients: 83% white (n=37,321), 8% African American (AA) (n=3,574), and 9% other (n=3,925). The majority of studies were ovarian (n=150) and phase II (n=187). When evaluating the proportion of AA patients that were enrolled by quartile of publication year, a steady decline in proportion of AA patients were seen. Compared

to years 1985-1999, a 3.2-fold lower proportion of AA was noted in years 2010-2013 (21% and 6.7%, respectively, $P<0.01$). Additionally, “other” races exceeded AA enrollment in 67 of 169 trials that listed race (40%). Using a CDC age-adjusted incidence, observed enrollment of AA patients onto GOG clinical trials was significantly less than expected if accrual rates were equal across all races. Observed AA enrollment was 15-fold lower than expected for ovarian trials, 10-fold lower for endometrial, 4.5-fold lower for cervical, and 5.2-fold lower for sarcoma (each $P<0.001$). Additionally, observed AA enrollment was significantly lower for each study type ($P<0.001$). Individually, none of the GOG studies met expected enrollment for AA patients by these methods.

Conclusions: Enrollment of minority populations is vital for adequately describing the true racial disparity in gynecologic malignancies. Based on this study, significant attention should be directed toward strategies to enhance minority enrollment onto clinical trials.

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419 - Poster Session B

Positive margins on cervical excision in a high-risk population: are our best practices good enough?

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Objectives: Multiple studies show racial disparities for the survival of cervical cancer, which is predominant in women of African American (AA) descent. These at-risk populations may be spared this survival disadvantage with proper screening and treatment. Our aim was to look at margin status for patients treated with cervical excisional procedures at an inner city, university-based academic teaching center.

Methods: All patients treated at a referral colposcopy clinic at a single inner city academic teaching facility from March of 2011 to June of 2012 were retrospectively reviewed. All demographic, pathologic, and surgical data were collected. Patients with a diagnosis of cervical intraepithelial neoplasia (CIN) 2 or greater were recommended for excisional biopsy. Generalists within the department of obstetrics/gynecology who were members of the faculty teaching practice performed or supervised all aspects of patient care. Statistical analysis was performed with Chi-square analysis with a 95% CI.

Results: During this study period, 416 patients were referred to the colposcopy clinic, with 95 patients having CIN 2 (22.8%) or greater on biopsy. All patients received recommended procedures, with 73 having a loop electrosurgical excision procedure (39 operating room and 34 office-based) and 22 undergoing cold knife cone (CKC). There were six providers in this study, and the median procedures performed was 16 (range, 12-21). Patients were predominately AA (93%). Of the 95 patients, six (6.3%) had a diagnosis of adenocarcinoma in situ or invasive cervical cancer. In the remaining 89 patients, 34 (38.2%) had positive margins of at least CIN 1, and 26 of the 34 (76.5%) positive margins were CIN 2 or greater. No difference in margin status was noted for patients <30 years of age compared to those ≥30 years (38.9% vs 37.7%, $P=0.913$) or for parity of G0 or G1 when compared to G2 or greater (43.8% vs 35.1%, $P=0.562$). No one provider was noted to have a statistically significant higher positive margin status. Unfortunately, 22 positive margin patients (64.7%) were lost to follow-up.

Conclusions: Successful excision of high-grade lesions is necessary to prevent at-risk patients from developing cervical cancer. Because an experienced high-volume provider would better treat these patients and may prevent high rates of positive margins, consideration should be given to referral of affected patients to a gynecologic oncologist.

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420 - Poster Session B

Geographic disparities in cancer care: is optimizing the distribution of the gynecologic oncology workforce the answer? A Gynecologic Oncology Fellows Research Network study

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Objectives: A recent American Society of Clinical Oncology workforce study projected a significant shortage of medical and gynecologic oncologists (GOs) in the United States (US) by 2020, especially in rural/underserved (R/US) areas. This study

aim was to determine the patterns of distribution of United States GOs and to identify provider-based attitudes and barriers that may prevent more GOs from practicing in R/US regions.

Methods: US GO/SGO members (n=743) were electronically solicited to participate in an online survey regarding geographic distribution and participation in outreach care. Responses were analyzed using the Pearson Chi-square test.

Results: A total of 308 GOs (42%) responded; median age range was 35-45 years (43%), 58% were male, 82% were white, and 43% worked 60 to 80 hours weekly. Most had practiced ≥20 years (29%) in an urban setting (72%) at a university hospital (43%). Only 13% of GOs practiced in an area with a population <50,000, and 44% practiced within 50 miles of ≥10 other GOs. While 28% practiced in the same city where they attended fellowship, family/spouse (41%) and desire to remain in academics (43%) were the factors most influencing practice location. Approximately 50% believed geographic disparities exist in GO workforce distribution that may pose access barriers to care, but 39% "strongly agreed" that cancer patients who live in R/US regions should travel to urban cancer centers to receive care. Most respondents did not perform outreach care (57%). Those who did perform outreach traveled ≤50 miles, 1 to 2 days/month (90%). GOs who practiced within 50 miles of 0 to 5 other GOs were more likely to provide outreach compared to those practicing within 50 miles of ≥10 GOs (50% vs 34%, $P<0.0001$). Most (39%) believed the major barriers to providing cancer care in R/US areas were volume- and systems-based (i.e., lack of ancillary, treatment, pathology, and supportive services).

Conclusions: Among GOs, there are perceived geographic disparities in the distribution of the US GO workforce. A saturation of GOs in densely populated urban areas exists, with few providers positioned in R/US areas. There are significant barriers to providing advanced cancer care in R/US practice environments. Various factors may affect these attitudes, including personal factors as well as a shifting economic and political landscape in which oncologists care for people with cancer.

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421 - Poster Session B

Elderly patients and customized narcotic dosing after gynecologic cancer surgery

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Objectives: Systemic narcotic use in elderly patients is associated with adverse health outcomes. We examined narcotic consumption by age in postoperative gynecologic cancer patients to determine the appropriate dosage in the first 24 hours after surgery and in the 24 hours prior to discharge.

Methods: Data from a prospective trial of 64 robotic surgeries were analyzed along with a retrospective collection of 256 laparotomies from October 2011 to February 2013. Descriptive statistics were generated for each surgical modality. Age and narcotic use for both the first 24 hours after surgery and the 24 hours prior to discharge were analyzed using linear regression.

Results: Increasing age was correlated with decreasing narcotic requirements in the first 24 hours following robotic surgery ($P=0.0016$) and laparotomy with and without epidural ($P<0.0001$). Mean narcotic use (intravenous hydromorphone equivalents) was 6.7 mg in the robotic group. Epidurals decreased mean narcotic use in the first 24 hours from 11.3 mg to 6.1 mg ($P<0.0001$) in the laparotomy cohort. On multivariate regression, age remained a significant predictor, with a 1.3-mg decrease in use per decade of age ($P<0.0001$). Narcotic requirement in the first 24 hours with an epidural was 7.7 mg for a 45-year-old (1.3 mg q 4 hours) vs 4.0 mg for a 75-year-old (0.7 mg q 4 hours). Increasing age was also correlated with decreasing narcotic requirement in the 24 hours prior to discharge for the laparotomy with and without epidural cohorts ($P<0.0001$). Interestingly, mean narcotic use in the 24 hours prior to discharge (oxycodone equivalents) was higher for patients who received an epidural than for patients who did not (38.8 mg vs 25.7 mg, $P=0.005$). In a multivariate regression model for laparotomy patients, age remained a significant predictor for decreased narcotic use ($P<0.0001$). The oral oxycodone requirement in the 24 hours prior to discharge was 50.1 mg for a 45-year-old (8 mg q 4 hours) vs 24 mg for a 75-year-old (4 mg q 4 hours).

Conclusions: Elderly patients require a much lower dose of narcotics after gynecologic oncology surgery. Immediately after surgery and upon discharge, elderly patients use doses as low as one half of that of younger patients. Adjusted narcotic dosing by year of life can be calculated from these data and may enhance safety. These findings may have important consequences on unscheduled clinic/emergency department visits, quality-of-care indicators, and patient satisfaction.

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422 - Poster Session B

Contribution of human papillomavirus (HPV) genotypes to persistently abnormal cervical cytology in a high-risk Latino population

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Objectives: To determine HPV genotypes that contribute to persistently abnormal cytology following initial diagnosis of low-grade squamous intraepithelial lesion (LSIL) in a high-risk Latino population.

Methods: Between December 2009 and April 2011, 167 cervical cytology specimens with LSIL were tested with DNA microarrays against 40 HPV genotypes. Genotypes were subdivided into high-risk (HR), intermediate-risk (IR), and low-risk (LR) based on current classification. A retrospective chart review was performed to follow cytologic progression. We correlated associations of persistent abnormal cytology with HPV genotypes using Fisher exact test. $P<0.05$ was considered significant.

Results: Of 167 cases, 70 were excluded due to lack of follow-up data. Of the study group (n=97), 69% had persistently abnormal cytology (PAC) while 31% had normal cytology (NC). The PAC group had a significantly higher rate of infection with HR-HPV than the NC group (81% vs 57%, $P=0.02$). HPV16 was detected significantly more frequently in the PAC group than in the NC group (21% vs 0%, $P=0.004$). In addition, HPV56 was also detected more often in PAC group than in the NC group (21% vs 3%, $P=0.033$). There was no significant difference in the incidence of HPV18, LR-HPV, IR-HPV, or the average number of coinfecting genotypes between the two groups.

Conclusions: In this high-risk population, HPV16 and HPV56 appear to play important roles in the persistence of abnormal cervical cytology. Triaging patients with LSIL by HPV genotyping may identify those at greater risk for high-grade dysplasia and, therefore, guide surveillance and treatment.

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423 - Poster Session B

The characterization of morbidly obese ovarian cancer patients in the United States: a study of demographic and socioeconomic status

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Objectives: To analyze the demographics and socioeconomic status of the morbidly obese ovarian cancer patients in the United States.

Methods: Data were extracted on all ovarian cancer patients from the National Inpatient Survey in 2010. Morbidly obese women were identified using the ICD-9 diagnostic codes. Chi-square, t-test, and ANOVA tests were used in statistical analyses.

Results: Among the 5,401 ovarian cancer patients, the median age was 61 years (range, 18 to 101 years) and the majority were white (77%). Most of the women were insured by Medicare or private insurance (41% and 46%, respectively); the remainder had Medicaid or were uninsured (9% and 5%, respectively). A total of 211 women (4%) were identified as being morbidly obese. Morbidly obese patients were younger than the non-morbidly obese (median 56 years vs 61 years, $P<0.01$). Additionally, Native Americans, blacks, and Hispanics were more likely to be morbidly obese compared to whites and Asians (10%, 7%, and 4% vs 2% and 1%, respectively, $P<0.01$). Morbidly obese patients were more likely to be insured by Medicaid than by private insurance, Medicare, or were uninsured (7% vs 4%, 3%, and 2%, respectively, $P<0.01$). Moreover, morbidly obese patients were more likely to have a lower income (5% vs 3%, $P<0.01$). The morbidly obese had the same average length of stay as the non-morbidly obese (8 days vs 8 days, $P=0.26$). There were no significant differences between the morbidly obese and non-morbidly obese based on hospital volume, region of the United States, and academic vs community institution.

Conclusions: Morbidly obese ovarian cancer patients were more likely to be younger, of lower socioeconomic class, and have Medicaid insurance. Characterizing the morbidly obese patients with ovarian cancer may allow for focused preventive strategies and better allocation of resources to care for these vulnerable patients.

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424 - Poster Session B

Impact of obesity on secondary cytoreductive surgery and overall survival in women with recurrent ovarian cancer

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Objectives: Obesity may negatively influence tumor biology in women with epithelial ovarian cancers. To date, only body mass index (BMI) determined at the time of diagnosis has correlated with clinical outcome. We hypothesized that obesity negatively affects survival throughout the disease course and sought to determine the prognostic role of BMI at the time of secondary cytoreductive surgery (SCS) for recurrent ovarian cancer.

Methods: We performed a retrospective institutional review board-approved review of patients undergoing SCS for recurrent epithelial ovarian or peritoneal cancer between 1997 and 2012. We abstracted data that included patient height, weight at SCS, age, and clinical outcome. Statistical analyses included Fisher's exact test, Kaplan-Meier survival, and Cox regression analysis.

Results: We identified 104 patients; 2% were underweight (BMI <18.5), 45% were of ideal body weight (BMI ≥18.5 to <25), 30% were overweight (BMI ≥25 to <30), and 23% were obese (BMI ≥30). There were no differences in age or incidence of hypertension, diabetes, coronary artery disease, or venous thromboembolism among the BMI strata. Overall, 90 (87%) of all patients underwent optimal resection at SCS. BMI did not correlate with ability to perform optimal SCS (P=0.25). When examining patients in the four BMI strata (underweight, ideal, overweight, and obese), we observed a statistical trend between increasing BMI and poor outcome, with median survival not yet reached, 46 months, 38 months, and 34 months, respectively (P= 0.04). We further studied BMI in a multivariate analysis with disease-free interval (DFI) from initial surgery, optimal SCS, initial stage, and age at SCS. We identified BMI as an independent predictor of survival (P=0.02) along with DFI (P=0.04) and optimal resection (P=0.001).

Conclusions: In this cohort of women undergoing SCS for recurrent ovarian cancer, BMI significantly and independently correlated with overall survival. This observation suggests an effect of excess weight on tumor biology and/or response to treatment that is prevalent throughout the disease course. Further studies are underway to elucidate the mechanisms underlying these clinical observations.

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425 - Poster Session B

Weight loss in preparation for robotic-assisted surgery in the management of low-grade stage I uterine carcinoma: clinical outcomes

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Objectives: To evaluate the feasibility of weight loss through office counseling regarding diet and exercise and megesterol acetate for control of endometrial cancer (EC) before definitive hysterectomy.

Methods: Among 477 patients with EC who were evaluated (May 2009 to May 2013) by two attending surgeons, 24 (5%) elected to delay surgery for attempted weight loss. MRI was obtained to ascertain tumor size, myometrial invasion, and lymphatic status. Patients considering weight loss had grade 1-2 endometrioid histology, a reassuring MRI with no myometrial invasion, and no mass identified at hysteroscopy. Patients took megesterol 80 mg bid and were counseled regarding weight loss, low-carbohydrate diets, and exercise. Pelvic ultrasonography and endometrial biopsies were performed every 3 months.

Results: Mean age was 57±11.3 years and 20 (83%) women were postmenopausal. Twenty (83%) women underwent hysterectomy and four remain on megesterol with negative biopsies. Mean time for megesterol treatment was 6.7±5.9 months (range, 0-24 months). One patient underwent gastric bypass. Eighteen (75%) patients lost >10 lb. Mean weight loss was 24±27 lb (range, 0-95 lb) and mean body mass index decreased from 49 to 43 before surgery. Procedures included 19 robotic and 1 open hysterectomy/bilateral salpingo-oophorectomy ± pelvic-aortic lymphadenectomy. No major postoperative complications occurred, including deep venous thrombosis or wound complications. Pretreatment diagnoses included: complex atypical hyperplasia (n=1), grade 1 endometrioid (n=14), and grade 2 endometrioid carcinoma (n=4). Final pathology following hysterectomy was stage IA/grade 1 (n=10), IA/grade 2 (n=3), IIIC1 EC (n=2, sentinel lymph node micro-positive), and no residual cancer (n=5). Seventeen (85%) patients maintained their weight loss and 3 (15%) lost more weight. All women remain disease-free at a mean follow-up of 18±6 months.

Conclusions: Through simple counseling, diet, and exercise, morbidly obese patients were able to lose weight while taking low-dose megesterol before definitive surgery for EC. Robotic-assisted surgery was possible for 95% of these patients, who are at high-risk for surgical complications.

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426 - Poster Session B

The effect of age on completion of prescribed chemoradiation among patients with cervix cancer

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Objectives: Although cervical cancer (CXCA) is uncommon in the United States and is thought of as a cancer of young women, incidence rates across age are very similar, with 10.8 and 9.6 cases/100,000 women age 65-74 years and >74 years, respectively vs 9.6 and 11.1/100,000 women age 20-49 years and 50-64 years, respectively, in 2010. Despite similar incidence, knowledge of treatment tolerance and outcomes among elderly women with CXCA is limited. This study sought to explore these issues among women treated with chemo/radiation (CRT).

Methods: An institutional review board-approved chart review was undertaken of patients diagnosed with CXCA who received CRT. Primary outcome was completion of CRT within 56 days and secondary outcome was progression-free survival (PFS) and overall survival (OS) of patients by age. Statistical analysis was performed with SAS version 9.2.

Results: Of 465 patient charts were abstracted, 240 had CRT. Age distribution was 76% (n=182) <60 years and 24% (n=58) >60 years. There was no statistical significance between stage among the two groups. In addition, 48% of patients in the <60 age group were smokers vs 27% of those age >60 years (P=0.01). The >60 years group had a higher Charlson score (5 vs 6, P=0.0001). Patients <60 years were more likely to be treated on a clinical trial (38% vs 16%, P=0.002). This is reflected in the finding that fewer patients <60 years were treated with single-agent cisplatin (66% vs 88%) and more were treated with weekly cisplatin + additional agent (34% vs 12%, P=0.002). Rates for completion of therapy within 56 days were 55% for patients <60 years and 47% for patients >60 years (P=0.43). The recurrence rates were 36% (n=65) for patients <60 years vs 22% (n=13) for those in the >60 years group (P=0.56). Median OS was 6.6 years for the <60 years group vs 4.6 years for the >60 years group (P<0.37).

Conclusions: Despite anticipated frailty of our elderly population, there were no significant differences in ability to complete therapy by the 56-day benchmark, completion of prescribed chemotherapy, or outcome. Both age groups display low completion rates, which may be due to limited access to care or higher complication rates, warranting further investigation. One major difference identified was that elderly patients were less likely to be treated on a clinical trial than their younger counterparts. More in-depth study is required to further evaluate the reason and resulting outcomes of this difference because tolerance does not appear related to age.

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427 - Poster Session B

Redefining the role of obesity, race and diabetes in Type I and Type II endometrial cancers: Potential targets for treatment beyond cancer itself

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Objectives: Traditionally endometrial cancer (EC) had been dichotomized into phenotypically different type I and II disease. We sought to examine the distribution of obesity, diabetes mellitus (DM), and race between these subtypes and their association to clinical outcomes.

Methods: A multi-institutional institutional review board-approved retrospective analysis of all type I and II EC cases at two academic institutions from January 2005-December 2010 was conducted. Type I (endometrioid), type II (serous and clear cell), and high-grade (HG) (grade 3 endometrioid, serous, clear cell) cohorts were compared. Univariate and multivariate methods (adjusted for age, race, body mass index [BMI], stage, grade, adjuvant treatment) were used to determine time-to-recurrence (TTR), recurrence-free survival (RFS), and overall survival (OS).

Results: The distribution of the 1,411 cases was: 1144 type I, 267 type II, and 439 HG. Comparing type I and II EC, 66% of patients were obese and 25% had DM vs 51% and 23% ($P<0.0001$, $P=0.69$). Eighteen percent of patients were African American (AA) and 75% were white. The AA patients had higher median BMIs than whites in both type I ($P<0.001$) and II ($P<0.001$) EC and were twice as likely to have DM ($P<0.001$). In type I EC, DM was associated with worse RFS and OS in both the unadjusted and adjusted models (RFS HR 1.38, 95% CI 1.01-1.89; OS HR 1.86, 95% CI 1.30-2.67), but not with TTR. In contrast, there was no association between DM and outcomes in women with type II EC or HG. Although increased BMI was associated with improved TTR, RFS, and OS in type I EC, only TTR remained significant in the adjusted analysis (HR 0.98, 95% CI 0.95-1.0). Increased BMI was not associated with outcomes in the adjusted analysis for type II or HG EC. AA race was associated with worse RFS and OS in all EC cohorts, although these effects were not significant in all adjusted analyses (Table 1).

Conclusions: Obesity and DM are both highly prevalent in type I and II EC, especially among AA women. DM was associated with worse RFS and OS in women with type I EC. Increased BMI paradoxically may be protective in type I EC (TTR). Neither BMI, DM, nor AA race was associated with EC outcomes in type II or HG EC when applying adjusted models. Further studies are needed to elucidate this complex triad within each subtype of EC and its effect on non-cancer- and cancer-related outcomes.

Table 1. Diabetes, BMI and Race upon Endometrial Cancer Outcomes

	Unadjusted P-value			Adjusted P-Value		
	TTR	RFS	OS	TTR	RFS	OS
Type I						
Diabetes	0.61	0.04	<0.001	0.76	**0.02**	**0.0002**
BMI	0.002	<0.001	0.004	**0.05**	0.06	0.24
Race	0.21	0.03	0.002	0.52	0.26	0.14
Type II						
Diabetes	0.17	0.21	0.27	0.27	0.28	0.34
BMI	0.50	0.03	0.07	0.55	0.46	0.29
Race	0.09	0.01	0.01	0.38	0.13	0.36
High Grade						
Diabetes	0.62	0.56	0.28	0.53	0.91	0.71
BMI	0.68	0.42	0.47	0.91	0.96	0.73
Race	0.02	0.001	0.001	0.12	0.06	0.20

Table 1. Analysis of diabetes, BMI and race upon endometrial cancer outcomes within Type I, Type II and High Grade EC. Levels of significance (p-values) are provided for the unadjusted and adjusted analyses. TTR=Time to Recurrence. RFS=Recurrence Free Survival. OS=Overall Survival.

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428 - Poster Session B

The influence of obesity upon the survival of cervical cancer patients undergoing nonsurgical therapy

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Objectives: Increased body mass index (BMI) has been associated with increased death rates from all cancers. Obese patients may be less likely to be offered surgical treatment due to habitus and comorbidities. The objective of our study was to compare pathologic findings, cancer recurrence, and overall survival (OS) in normal-weight, overweight, obese, and morbidly obese patients undergoing primary treatment with chemotherapy and radiation for cervical cancer.

Methods: A retrospective, single-institution chart review was performed on 738 patients who underwent initial evaluation for cervical cancer between July 2000 and March 2013. BMI was calculated as an ordinal variable, and groups were subdivided into normal (BMI <25), overweight (BMI 25-30), obese I (BMI 30-35), obese II (BMI 35-40), and morbidly obese (BMI ≥40). Primary outcomes were OS and recurrence-free survival (RFS) from time of histopathologic diagnosis. Univariate Cox regression models were used to obtain BMI hazard ratios with 95% CI. All reported P values are 2-tailed.

Results: In total, 376 patients with cervical cancer were primarily treated with either chemotherapy and radiation (n=361) or radiation alone (n=15). Among these 376 patients, OS was worse with more advanced-stage cervical cancers (HR 1.31,

95% CI 1.21-1.41, *P*<0.0001) and greater age at presentation (HR 1.02, 95% CI 1.01-1.03, *P*=0.002). OS was not affected by race (HR 1.04, 95% CI 0.91–1.21, *P*=0.54) or histopathologic grade (HR 1.02, 95% CI 0.93-1.11, *P*=0.70). OS was not significantly affected by obesity (HR 0.78, 95% CI 0.53-1.15, *P*=0.21) or higher BMI (HR 0.92, 95% 0.80-1.03) at the time of initial therapy. No significant difference in RFS was seen in obese (HR 0.98, 95% CI 0.62-1.54, *P*=0.92) or higher BMI category (HR 0.95, 95% CI 0.85-1.07, *P*=0.42) patients undergoing primary nonsurgical therapy for cervical cancer.

Conclusions: While obesity is associated with multiple health risks and has been associated with increased cancer death rates, BMI does not appear to significantly affect OS or RFS in patients undergoing initial treatment for cervical cancer with chemotherapy and radiation. If surgery is precluded in these patients, the obese and morbidly obese have similar outcomes compared to those with lower BMIs.

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429 - Poster Session B

Cervical cancer screening history in elderly patients in a rural population

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Objectives: Cervical cancer screening is an important part of routine preventive care for women. Current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines recommend cessation of Pap smear screening after age 65 years for women who have had three consecutive negative cytology tests or two consecutive negative co-tests within the prior 5 years. Our aim was to evaluate screening history, histology, and treatment of elderly patients with a new diagnosis of cervical cancer after the age of 65.

Methods: A retrospective chart review of patients with a new diagnosis of cervical cancer after the age of 65 treated or followed at a medical center serving a rural population was performed (IRB 2013-0382). The electronic medical record and paper charts were reviewed to obtain information pertaining to age at diagnosis, screening history, histology, stage, treatment, disease status, and vital status.

Results: Eighty-three patients were identified with a new diagnosis of cervical cancer after the age of 65 years: 37% between ages 66 and 69, 43% between ages 70 and 79, and 18% between ages 80 and 95. Seventy percent of patients had squamous cell carcinoma, 20% had endocervical adenocarcinoma, and 10% had "other." Fifty-seven percent (n=48) presented with early-stage (stage I or II) disease and 42% (n=35) with late-stage disease. The majority of patients (83%) received combination chemo/radiation therapy (RT) or RT alone. Screening history was not documented for 35% of these patients. However, for those with a documented screening history, only 11% were appropriately screened. Of the remaining 45 patients, 53% had never been screened and 45% had some documented screening but at inadequate intervals.

Conclusions: Cervical cancer continues to be a concern in the elderly population. Failure to follow current ASCCP guidelines does not seem to account for the diagnosis of cervical cancer in women >65 years of age. Rather, these data suggest that health-care resources should focus on ensuring that all women have routine surveillance whether through their gynecologists or primary care providers.

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430 - Poster Session B

The use of metformin in obese women with endometrial cancer may reduce the risk of cancer recurrence: a retrospective review

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Objectives: Recent evidence suggests that hyperinsulinemia associated with obesity may be a significant risk factor for the development of endometrial cancer. Metformin is used in type 2 diabetes to lower circulating insulin levels. We sought to examine obese patients with endometrial cancer who were receiving metformin to determine if there was any impact on their cancer course.

Methods: A retrospective review of all women with the diagnosis of endometrial cancer and a body mass index (BMI) >30 over a 6-year period (2005-2011) at our institution was conducted. Records were reviewed for standard demographic data,

use of metformin, cancer characteristics, treatment, and cancer follow-up. All women had a minimum of a hysterectomy and bilateral salpingo-oophorectomy. Sarcomas were excluded from this analysis.

Results: Of 351 women who were identified as obese and diagnosed with endometrial cancer, 64 were on metformin (M+) at the time of diagnosis of endometrial cancer. The M+ women had a significantly higher mean BMI (44.0 vs 41.3, $P<0.05$) compared to those not on metformin (M-). Age was similar for M+ and M- women. Among the M+ women, 31.2% had a high-grade cancer vs 38.7% of M- women (ns). Among the 251 women had surgical staging that included lymphadenectomy, 16.7% of the M+ women had lymph node metastasis vs 12.9% for M- women (ns). A total of 125 (35.6%) of women received adjuvant therapy with either radiation, chemotherapy, or both, and the use of adjuvant therapy did not differ between the two groups. Recurrence occurred in 15.3% of the M- women vs only 3.1% of the M+ women who remained on the drug ($P=0.009$). With a minimum of 18 months follow-up, 89.1% of M+ women were alive and free of disease compared to 83.9% of M- women (ns).

Conclusions: Obese women who developed endometrial cancer while on metformin did not appear to have different pathologic risk factors from those not on metformin. However, the metformin patients were less likely to recur than those not on the drug. These findings suggest that a prospective trial of metformin at the time of diagnosis of endometrial cancer in the obese population may be warranted.

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431 - Poster Session B

Measurements of adiposity as predictive biomarkers for response to first-line bevacizumab-based chemotherapy in epithelial ovarian cancer (EOC)

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Objectives: Results of phase III trials have raised questions regarding patient selection, optimal dose, and schedule for antiangiogenic therapy in advanced EOC, of which the most widely used is bevacizumab (bev). There is a lack of reliable indicators to predict which patients will benefit most. Recognizing that obesity is associated with increased levels of vascular endothelial growth factor (VEGF), the primary target of bev, we sought to assess whether adiposity, measured in terms of body mass index (BMI), subcutaneous fat area (SFA), and visceral fat area (VFA), could predict response. We also sought to correlate results with angiogenic cytokines.

Methods: We retrospectively reviewed medical records of 46 patients with advanced EOC who received primary treatment with bev-based standard chemotherapy (chemo) (n=21) or chemo alone (n=25) for whom complete medical records, a CT scan prior to the first cycle of chemo, and banked serum were available. CT scan was used to measure SFA and VFA by radiologists blinded to patient outcomes. Enzyme-linked immunosorbent assay was used to measure serum levels of VEFG and angiopeitin-2 in the bev group.

Results: BMI, SFA, and VFA were dichotomized using the median and categorized as either “high” or “low”. In the bev group, progression-free survival (PFS) was shorter for patients with high BMI (10.0 vs 20.9 months), while in the chemo alone group, PFS was similar between high and low BMI (17.9 vs 12.1 months). In the bev group, patients with a high BMI had higher mean levels of VEGF and angiopoeitin-2 (254.5 vs 429.9 pg/mL and 23.85 vs 76.67 pg/mL, respectively). On multivariate analysis, neither BMI, SFA, nor VFA was predictive of PFS or overall survival (OS) in the chemo group. However, in the bev group, BMI was significantly associated with PFS ($P=0.02$). After accounting for age, stage, and residual disease, the adjusted HR for high vs low BMI was 5.16 (95% CI 1.31-20.24). Additionally, SFA was significantly associated with OS ($P=0.03$) in the bev group. After accounting for age, stage, and residual disease, the adjusted HR for high vs low SFA was 3.58 (95% CI 1.12-11.43).

Conclusions: To the best of our knowledge, these results provide the first evidence in EOC that patients with high levels of body fatness may not derive benefit from bev and that measurements of adiposity before starting bev-based treatment is likely to be a useful predictive biomarker. Which measurement of adiposity (BMI, SFA, or VFA) is most predictive warrants further investigation.

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432 - Poster Session B

Impact of obesity on the survival of cervical cancer patients

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Objectives: Obese patients may delay seeking medical treatment and may be less likely to be offered surgical treatment due to habitus and comorbidities. Additionally, increased body mass index (BMI) has been associated with increased death rates for many cancers. The objective of our study was to compare pathologic findings, cancer recurrence, and overall survival in normal-weight, overweight, obese, and morbidly obese patients diagnosed with cervical cancer.

Methods: A retrospective, single-institution chart review was performed on 738 patients who underwent initial evaluation for cervical cancer between July 2000 and March 2013. BMI was calculated, and groups were subdivided into normal (BMI <24.9), overweight (BMI 25-29.9), obese I (BMI 30-34.9), obese II (BMI 35-39.9), and morbidly obese (BMI ≥40). Primary outcomes were overall survival (OS) and recurrence-free survival (RFS) from time of histopathologic diagnosis. Cox regression models were used to obtain BMI HRs with 95% CIs. Jonckheere-Terpstra tests were used to look for associations between BMI categories and other variables of interest. All reported P values are 2-tailed.

Results: In the cohort, 245 patients were normal weight, 178 patients were overweight, 139 patients were obese I, 62 were obese II, and 70 were morbidly obese. Early-stage disease was present in 48.9% normal weight, 47.7% overweight, 56.1% obese I, 37.1% obese II, and 44.3% morbidly obese patients (P=0.72). Based on BMI category, high-grade cancers were in 87.4%, 89.9%, 26.4%, 88.8%, and 91.5% of patients, respectively (P=0.13). No significant difference in RFS was seen for all obese patients (P=0.29) or for morbidly obese patients (P=0.80) at the time of presentation, but when BMI was examined as a continuous variable, a significant difference was seen in RFS (P=0.007). OS was not significantly affected by BMI as a continuous variable (P=0.089), obesity (P=0.34), or morbid obesity (P=0.42) at the time of presentation.

Conclusions: Increasing BMI is associated with worse RFS in patients with cervical cancer. While obesity has been associated with increased cancer death rates, BMI does not appear to significantly affect OS in cervical cancer.

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433 - Poster Session B

Definitive therapy for clinical stage I endometrial cancer in the elderly: a National Cancer Database study

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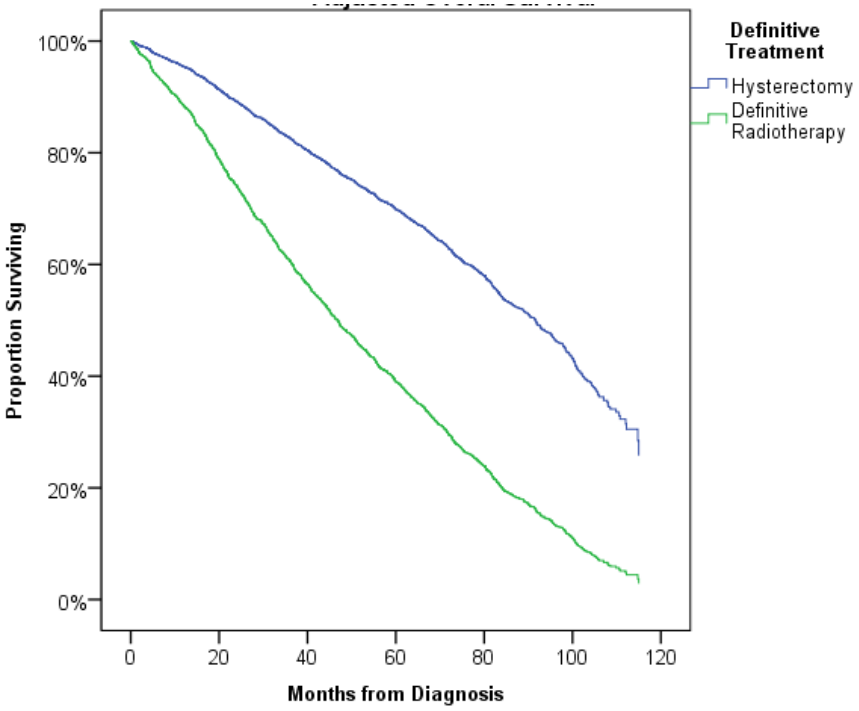
Objectives: Both radiotherapy and surgery can be definitive treatments for early-stage endometrial cancer. The aim of this study was to compare radiation incorporating brachytherapy (DRT) to definitive surgery (DS) in the elderly population in terms of surgical and survival outcomes.

Methods: We identified patients ≥75 years of age diagnosed with clinical stage I endometrial cancer between January 1998 and December 2011. Overall survival was estimated using the Kaplan-Meier method. Univariate and multivariable analyses using Chi-square, log-rank test, binary logistic regression, and Cox proportional hazards modeling were used to determine factors that affect treatment modality and outcomes.

Results: A total of 21,880 patients were identified with a median age of 80 years, of whom 51.4% had a Charlson-Deyo Comorbidity Score (morbidity) of 0. A total of 18,329 patients underwent DS that consisted of hysterectomy alone (43%) or full staging (57%), in which 5% of patients were upstaged to stage III or IV. The surgery group had a median surgical stay of 3 days, 3.7% unplanned readmission rate, and 1.3% 30-day mortality rate. Postoperative radiotherapy was given to 22% of patients. There were 1,585 patients who received radiation; of these, 511 had DRT. On multivariable analysis, older age and African American race were associated with increased likelihood of receiving DRT, while patients with insurance, type II histology, and treated outside of the northeast and midwest were more likely to undergo DS. Overall survival at 5 years is 66% and 29% for the DS and DRT groups, respectively. When age, morbidity, grade, and histology are controlled for, DRT conferred a 2.63-fold (range, 2.14-3.22) increase in mortality risk over DS.

Conclusions: This study suggests that definitive surgery for the elderly with early-stage endometrial cancer is superior to definitive radiotherapy with regard to 5-year survival rates when age and comorbidities are taken into account.



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434 - Poster Session B

Obesity and operating room efficiency by phase of robotic surgery: results from a prospective trial in gynecologic oncology

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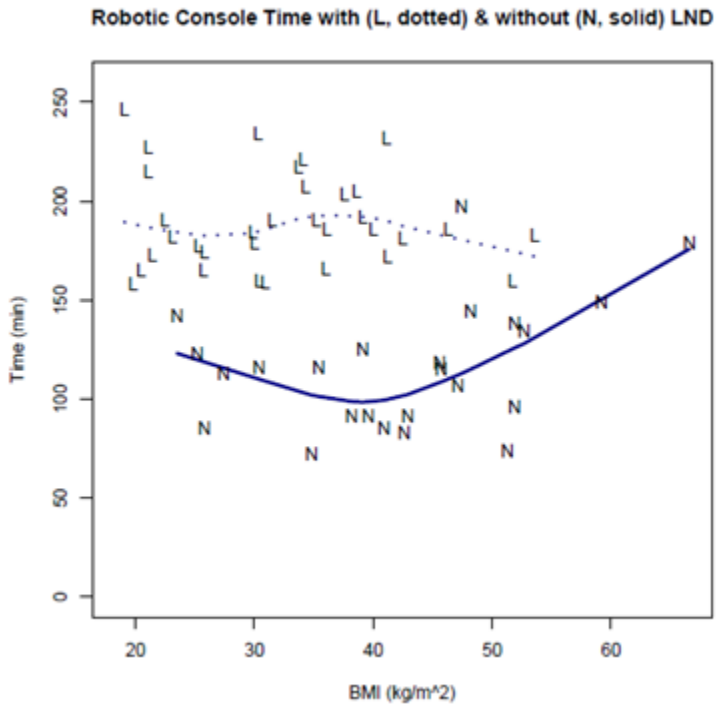
Objectives: To determine the impact of obesity on operating room (OR) efficiency during specific phases of robotic surgery. The five phases of interest were the intervals between OR entry, incision, robotic console start, robotic console end, procedure end, and time out of the OR. We hypothesized that there would be a direct correlation with increasing obesity and time to complete each surgical phase.

Methods: Prospective data from a randomized, phase III trial were used to correlate body mass index (BMI) and time needed to complete the surgical phases. The time intervals were correlated to BMI and fit with regression lines using the LOWESS method. Line slopes (representing additional minutes per BMI point) and P values were generated. Nodal counts were also compared against BMI.

Results: Data from 61 subjects were available for analysis. All subjects underwent hysterectomy and salpingo-oophorectomy. Lymph node dissection (LND) was performed in 33 patients and not performed in 28. Median BMI was 35.2. The times required to complete the following phases were similar regardless of BMI: OR entry to incision (P=0.21), incision to console start (P=0.61), console end to procedure end (P=0.19), and procedure end to out of the OR (P=0.61). Robot console time was significantly longer if LND was added (186 vs 116 min, P<0.0001). The correlation of robot console time with BMI was not significant with LND (P=0.65) or without LND (P=0.083), but some non-LND patients with BMIs >50 required longer console times. Although patients with lower BMIs were more likely to have LND, the total number of lymph nodes removed was the same across the range of BMIs (19.1-53.6, P=0.73). These findings were consistent for pelvic and para-aortic LND. Mean number of lymph nodes removed was 24.9±10.6 (total), 18.1±7.9 (pelvic), and 7.3±3.5 (para-aortic).

Conclusions: The degree of obesity does not harm OR efficiency in any phase of robotic surgery in gynecologic oncology. Centers that are unable to achieve equivalent efficiency across the spectrum of BMI should identify targets for system-level improvement. Surprisingly, similar and appropriate nodal counts can be obtained without an increase in operative time regardless of BMI. Future work should focus on patients with BMIs >50, who represent a population for which surgical efficiency may be diminished.



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435 - Poster Session B

Adherence to follow-up after treatment for high-grade dysplasia in underserved women

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Objectives: To determine adequacy of short-term and long-term follow-up following loop electrosurgical excision procedure (LEEP) or cold knife cone biopsy (CKC) for high-grade cervical dysplasia among low-income and minority women treated in an inner city safety net hospital.

Methods: Retrospective chart review was conducted on all women who underwent either LEEP or CKC for high-grade cervical dysplasia between January 1, 2007 and December 31, 2008 to determine the adequacy of follow-up through December 31, 2012. Adequate short-term follow up defined as two Pap tests or one Pap/human papillomavirus (HPV) co-test within 1 year following treatment. Adequate long-term follow-up was defined as annual screening beginning at 1 year after the date of LEEP/CKC if the patient had adequate negative short-term follow-up.

Results: A total of 104 women underwent LEEP/CKC during the study period. Their mean age was 32 years; 59% were black, 13% white, 14% Hispanic, and 2% Asian. Most women were insured (78% Medicaid, 13% other, 9% uninsured) and English-speaking (76%). Ninety percent of women (n=94) had at least one Pap test following treatment, 74% (n=77) had at least two Pap tests, and 56% (n=58) had at least three Pap tests. The median time from LEEP/CKC to first Pap test was 202 days. Only 16% of the total sample had adequate follow-up within 1 year of treatment, and 7% had adequate long-term follow-up. Among first Pap tests following LEEP/CKC, 76% (72/94) had normal results. Seven women (6% of the total) had positive margins for cervical intraepithelial neoplasia (CIN)3 following LEEP/CKC, none of whom followed-up within the subsequent 6 months. The median time to follow up in this group was 237 days.

Conclusions: Although most low-income and minority women received their first Pap test after LEEP/CKC, rates of subsequent follow-up declined rapidly. New guidelines recommending Pap and HPV co-testing as primary follow-up may be especially advantageous in high-risk populations because co-testing is more sensitive for detecting women at risk for recurrent disease, although longer recommended intervals could result in a further decrease in follow-up. Future studies should address methods to improve follow-up after treatment for high-grade dysplasia among vulnerable women to address cancer disparities related to inadequate follow-up.

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436 - Poster Session B

Role of chemosensitization in elderly vaginal cancer patients: a National Cancer Data Base (NCDB) study

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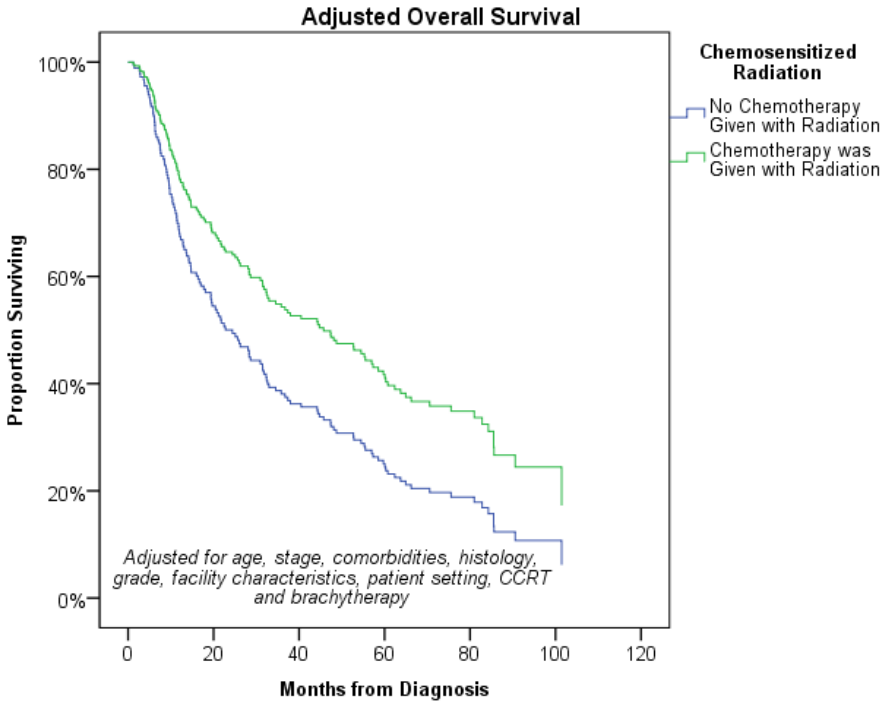
Objectives: Due to its rarity and similar pathologic and anatomic characteristics, vaginal cancer therapy recommendations mirror those of cervical cancer, including a multimodal approach with concurrent chemosensitizing radiation (CCRT), although patient demographics differ. The goal of this study was to evaluate the therapeutic benefit of CCRT in elderly vaginal cancer patients using the National Cancer Data Base (NCDB).

Methods: We identified patients ≥75 years of age in the NCDB who were diagnosed with vaginal cancer without distant metastatic disease and received radiotherapy from January 1998 to December 2011. Overall survival was estimated by the Kaplan-Meier method. Binary logistic regression was used to identify factors associated with use of CCRT. Univariate exploratory analysis was performed using log-rank test with Bonferroni correction. Cox proportional hazard modeling was used to identify factors that independently affect survival. Stratified log-rank analysis was also performed to identify specific cohorts in which CCRT confers a benefit. Point estimates with 95% CI are reported.

Results: We identified 2,573 patients, and CCRT was used in 718 (27.9%). Factors independently associated with decreased use of CCRT included increasing age (odds ratio [OR] 0.83; 95% CI 0.79,0.88) and comorbidities (OR 0.59; 95% CI 0.40,0.87). On multivariable analysis for survival, older age (OR 1.05; 95% CI 1.01,1.09) and higher disease stage (OR 1.31; 95% CI 1.07,1.61) independently predicted worse survival ,while CCRT was associated with improved survival (OR 0.63; 95% CI 0.43,0.94). On exploratory stratified log-rank analysis, stage II and III patients and those with Charlson-Deyo comorbidity scores (CDCS) of 0 demonstrated improved survival with CCRT ($P<0.005$). Within this cohort, CCRT was used in 34.1% of those with CDCS of 0 and 34.1% and 43.1% of patients with stage II and III disease, respectively.

Conclusions: CCRT use in elderly vaginal cancer patients is associated with improved survival but appears to be underutilized, even in patients with no comorbidities. This study suggests that CCRT should be strongly considered in elderly patients with locally advanced vaginal cancer and that age should not be used as a discriminant in the use of CCRT.



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437 - Poster Session B

The impact of obesity on pathologic features and survival with endometrial cancer: a Gynecologic Oncology Group (GOG) LAP2 ancillary data study

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Objectives: To determine the effect of body mass index (BMI) on surgicopathologic findings and survival in women enrolled on the GOG LAP2 trial, a randomized comparison of laparoscopic vs open surgical staging in clinically early-stage endometrial cancer (EC).

Methods: An ancillary data analysis of the LAP2 data was performed. Descriptive statistics were used for demographic, clinical, and surgicopathologic characteristics according to BMI category. Wilcoxon, Pearson, and Kruskal-Wallis tests were used for univariate and multivariate analysis. Log rank tests were used to compare survival lengths.

Results: The 2,596 women included in the analysis were stratified by BMI: <25 (29.5%), 25-30 (28.2%), 30-35 (21%), 35-40 (10.9%), and ≥40 (10.4%). Stage, grade, and histology differed by BMI, with 81% of women with BMI ≥40 having stage IA disease compared with 67% with BMI <25 (P=0.021), 26% with BMI ≥40 having grade 1 tumors compared with 18% with BMI <25 (P<.001), and 88% of patients with BMI ≥40 having endometrioid tumors compared with 76% with BMI <25 (P=0.005). Furthermore, obese women were less likely to have high-risk (HR) disease (+ lymph nodes, ovaries, cytology) or tumor features that met GOG 99 high-intermediate risk (HIR) criteria: 41% of BMI ≥40 were HR or HIR vs 58% of BMI <25 (P<.001). Adjuvant therapies (P=0.151) and recurrence (P=0.46) did not vary by weight. BMI (P=0.016), age (P<0.0001), race (P=0.033), and risk group (P<0.0001) predicted all-cause mortality. BMI was not predictive of disease-specific survival (P=0.79); only age (P=0.032) and risk group (P<.0001) remained significant factors.

Conclusions: This study demonstrated that obese women inherently have lower-risk disease but suggested that EC in low BMI women may be higher risk than previously thought. BMI was associated with all-cause but not disease-specific mortality, again suggesting the detrimental effect of obesity independent of EC. Given the obesity epidemic, these findings suggest that weight management should be a consideration in risk stratification of EC.

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438 - Poster Session B

Endometrial cancer complications and survival in morbidly obese African American and white women

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Objectives: The prevalence of morbid obesity, defined as a body mass index (BMI) ≥40, is increasing at twice the rate of obesity (BMI ≥30) in the United States. Obesity is the strongest modifiable exposure for endometrial cancer and is at least partially responsible for the increase in type I endometrial cancers. The aim of our study was to assess obesity as a risk factor in endometrial cancer.

Methods: From our database of 800 endometrial cancer patients, we examined 89 African American (AA) and 97 white women with endometrial cancer who received a hysterectomy at our institution to determine whether the racial disparities seen in tumor characteristics and survival persisted in a morbidly obese population. All slides were reviewed by a gynecologic pathologist. The clinical data was retrieved from medical charts. Chi-square tests, Kaplan-Meier curves, and Cox regression models were used for statistical analysis.

Results: The mean age at diagnosis was similar for whites (56.8 years) and AAs (56.9 years). The mean BMI in this morbidly obese population was slightly higher for AA women (mean BMI, 49.2) than for white women (mean BMI, 47.0) (P=0.09). AA women were more likely to have a type II tumor than white women (33.7% vs 15.5%, P=0.003) and to have higher-grade tumors (P<0.001). On average, AA women had longer hospital stays after surgery (mean, 5.4 days) compared to white women (mean, 3.5 days) (P=0.03). Other clinical variables, including FIGO stage, depth of invasion, lymph node involvement, myometrium involvement, postsurgical complications, and overall endometrial cancer-specific survival, were similar.

Conclusions: Morbidly obese AA women had relatively high rates of type II cancers, suggesting that obesity may play a stronger role in type II tumors than previously reported. In addition, despite longer hospital stays in AA women, other comparable clinical characteristics, postsurgical complications, and survival did not differ by race.

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439 - Poster Session B

Predicting everolimus/letrozole treatment efficacy in patients with advanced or recurrent endometrial cancer: a biomarker study

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Objectives: A phase II study using everolimus/letrozole demonstrated a high response rate for patients with advanced or recurrent endometrial cancer with a clinical benefit rate of 49% and objective response rate of 31%. The objective of this study is to determine whether various tumor biomarkers involved in the PI3K/mTOR and estrogen receptor (ER) signaling pathways can predict tumor response to the treatment. In our previous single agent everolimus trial, KRAS mutation was associated with non-response.

Methods: Formalin fixed, paraffin-embedded (FFPE) primary tumor tissue from patients was used for biomarker studies via mutational analysis and immunohistochemistry (IHC). Hot spot mutations of KRAS, CTNNB1, and PIK3CA were performed using Sanger sequencing. IHC was used to access the expression level of biomarkers ER, progesterone receptor (PR), 4EBP1, phosphorylated (p-) 4EBP1, S6RP, p-S6RP, p-mTOR, PTEN, p-AKT, PI3K, LKB1 and p-ERK1/2.

Results: 20 out of 35 patients had FFPE tissue available for DNA testing and 16 had tissue available for IHC study. One out of 20 (5.0%) patients was found to carry a KRAS mutation. Of interest, this patient was a complete responder. Four out of 18 (22.2%) patients were found to carry CTNNB1 mutations, among which three were responders and one was a non-responder. Five out of 19 patients (26.3%) were found to carry PIK3CA mutations and there was no association between PIK3CA mutations and clinical outcome, which differs from the previous reports that PIK3CA mutations may be associated with better treatment response. In the IHC study, only combined ER/PR level was associated with clinical benefit ($P<0.05$).

Conclusions: Combined ER/PR level was significantly higher in responders, and CTNNB1 mutations were observed more frequently in responders than non-responders. A KRAS mutation was identified in one of the complete responders. Of interest, this patient was also on metformin, which we have demonstrated to act as an anti-Kras therapeutic agent in preclinical studies. A phase II study of everolimus/letrozole/metformin has recently been initiated and biomarker analysis will be integrated.

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440 - Poster Session B

Evaluation of slide storage and detection of molecular markers by immunohistochemistry (IHC) in formalin-fixed, paraffin embedded endometrial cancer tissues from a clinical trial: a GOG study

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Objectives: To compare IHC staining for topoisomerase II alpha (TOP2A) on years old stored unstained slides with staining on freshly cut slides from stored blocks of tumor specimens on a clinical trial.

Methods: Sections and tissue blocks from 234 patients enrolled on GOG protocol 0177 were collected during 1999-2000 and stored centrally at room temperature. During 2004-2011 specimens were stored at 4°C at another location. Matched pairs of stored and freshly cut (3-12 weeks old) primary tumor tissues were prepared from 15 patients in 2012. TOP2A (KiS1), Ki67 (MIB1) and HER2 (Herceptest) were analyzed without knowledge of pairing or slide age. All IHC procedures were performed using a standardized antigen retrieval protocol and appropriate controls. Staining intensity and percentage of cells staining positive were recorded. The kappa statistic for marker expression concordance and signed rank test for differences in percentage cells staining positive in old-cut versus fresh-cut slides were applied.

Results: H-score for TOP2A expression was concordant in 12 of 15 (80%) pairs of stored and freshly cut tissues. A kappa value of 0.57 (95% CI: 0.14, 0.99) was in the intermediate range (0.4-0.75). Two of three discordant cases showed lower or no expression of TOP2A in the older slide, but high expression in the newer slide. In the third case the opposite was observed: high expression in the older slide and low expression in the newer slide. The proportion of cells with TOP2A

staining was lower on average by 12% in the older sections (P=.03); differences ranged between 50% lower and 10% higher. Categorization of Ki67 using a cut-off of 10% to define low expression was associated with moderate agreement between old and new cut slides (kappa =0.60; 95% CI: 0.24, 0.97). The expression of Ki67 was consistently lower in stored slides on average by 10% (P<.01); differences ranged between 0 and 35% lower in old slides. No difference in HER2 staining was observed between stored and freshly cut slides.

Conclusions: The IHC results were consistent with a moderate level of protein degradation associated with stored slides for some antigens. Use of stored slides may underestimate the expression of some IHC markers in endometrial cancer.

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441 - Poster Session B

A phase 0 study of dasatinib in endometrial cancer

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Objectives: Dasatinib is a potent, oral inhibitor of the Src family kinases, which are implicated in the formation and maintenance of various cancers. Direct measurement of a dasatinib biologic effect in solid tumor has not been reported. We designed a Phase 0-type clinical trial of dasatinib in women with endometrial cancer. Our goal was to demonstrate inhibition of Src activity in tissue and blood, with the hypothesis that activity in blood would serve as a surrogate for activity in tissue. We also planned to correlate Src activity with blood and tissue PK levels of dasatinib and levels of ER in the tissue pre and post treatment.

Methods: Patients were treated with dasatinib PO at 32 and 8 hours preoperatively. For PK analysis blood was drawn 2, 4 and 8 hours following the second dose. Tissue and blood were collected prior to treatment and at surgery. Two dose levels were planned: 100 and 200 mg x 2 doses. Extracts prepared from tissue and white blood cells were analyzed by Western blot for active Src (pY419) and total Src protein to assess inhibition of Src activity.

Results: Five patients were treated at the first dose level. There were no serious adverse events. The most frequent AEs were postoperative hyperglycemia and hypocalcemia and preoperative headache. Two patients had grade 1 QTc prolongation.

Preliminary scientific results are provocative. In 4 patients a reduction of >50% of Src tyrosine kinase activity was observed in tumor obtained at surgery vs tissue obtained prior to dasatinib. When levels of the Src protein found in both biopsy and surgical tumor specimens were considered, 2 of 5 specimens had >50% reduction in Src specific activity. There was substantial measurement variability. Analysis of white blood cell pSrc/Src and comparison with tissue levels are ongoing. PK levels for dasatinib were demonstrated in blood and in tumor at 9 hours, with an average ratio of tumor vs normal endometrium of 2.05.

Conclusions: In this first cohort, treated with a sub-therapeutic dose of dasatinib, we showed support of inhibition of Src activity in tumor: the first time that Src activity in solid tumor has been reported. We also demonstrated dasatinib PK levels in tumor tissue 9 hours after the second dose, with an average of twice the level of dasatinib in tumor tissue as compared to normal tissue. We are now moving to the second dose level.

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442 - Poster Session B

Hyperthermic intraperitoneal chemotherapy (HIPEC) in gynecologic malignancies

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Objectives: Peritoneal metastasis often is a sign of advanced carcinoma of the ovary and fallopian tube as well as primary peritoneal carcinomas. In the past, surgical approaches to peritoneal metastasis were palliative. However, the prognosis has been significantly improved with cytoreductive surgery. If it is possible to achieve a complete tumor-free result, HIPEC should further improve the prognosis.

Methods: Patients with peritoneal malignancies underwent cytoreductive surgery. HIPEC was performed in those in whom an optimal tumor resection was achieved. Peri- and postoperative courses were observed after HIPEC. Adverse events were recorded via the Clavien-Dindo classification, and grade III and IV complications were evaluated.

Results: We achieved optimal cytoreduction in 40 patients, who became candidates for HIPEC. The HIPEC procedure involved instillation of cisplatin solution (50 mg/m^2) at 41°C. The mean age of the patients was 59.8 years and the Peritoneal Cancer Index was 3-18. We performed >20 anastomoses. A total of 13 adverse events were documented in 8 patients, none involving insufficiencies of the anastomoses.

Conclusions: The current goal for surgical treatment of peritoneal carcinomatosis of ovarian cancer is complete cytoreduction. Multiple surgical procedures might be necessary to have no visible tumor remaining. HIPEC appears to have an additional positive effect on the median survival of patients with peritoneal metastasis. Because of minimal adverse effects, we believe that HIPEC is another important component of the treatment of peritoneal malignancy.

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443 - Poster Session B

Salvage therapy of intensively pretreated patients with epithelial ovarian cancer and other Müllerian tract carcinomas with treosulfan and gemcitabine

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Objectives: The prognosis of intensively pretreated patients (pts) with epithelial ovarian carcinoma (EOC) and related malignancies having failed multiple chemotherapy (CTx) regimens is poor, irrespectively of the individual platinum-resistance status. In preceding studies, the combination of treosulfan and prolonged low-dose gemcitabine (GeT) has shown promising activity in pretreated, mainly platinum-resistant EOC. This retrospective study has been set up in order yield more detailed information about the clinical value of GeT administered under routine conditions.

Methods: A total of 59 pts with recurrent EOC (n=54), fallopian tube cancer (FTC; n=2), peritoneal papillary-serous carcinoma (PPSC; n=2), and type II endometrial carcinoma (EC-II; n=1) who did not qualify for recruitment into a controlled clinical trial were included. Pts had failed a median of 3 (range 1-11) prior Ctx, 37 (62.7%) were platinum-resistant (group R) and 22 were sensitive (group S) according to the Markman criteria. GeT was administered for 1-11 q2w courses with treosulfan at 1 g/m² PO on days 1-4 and gemcitabine at 450 mg/m² IV (3 hour infusion) on day 1. Adverse effects were scored according to CTCAE 4.0, responses were classified according to RECIST 1.0. PFS and OS were calculated from the start of therapy until progression or death from any reason or loss to follow up, respectively.

Results: GeT was generally well tolerated. Hematological side-effects were frequent but manageable with G3-4 neutropenia seen in 6, G3-4 anemia in 8, G3 fever in 3, and G4 infection in 1 pt. Non-hematological toxicities rarely exceeded G2. In 1 pt, GeT was prematurely finished due to allergic exanthema. ORR was 44.8% (9 CR, 17 PR, 16 SD, 16 PD), PFS was 17.3 weeks (wks) and OS was 67.6 wks with no significant differences between group R and S in regard to ORR (40.5 vs 54.5%), PFS (17.0 vs 18.4 wks), and OS (63.0 vs 72.6 wks).

Conclusions: GeT given in a routine setting is feasible in pts with relapsed EOC and other Müllerian tract cancers. Facing the intensive pretreatment of the study population, GeT produced a meaningful response rate and survival which was not adversely influenced by clinical platinum-resistance. GeT should thus be further evaluated in large-scaled prospective trials in pts with platinum-resistant EOC and related malignancies.

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444 - Poster Session B

Prospective phase II trial of adjuvant pelvic radiation “sandwiched” between combination paclitaxel/carboplatin chemotherapy in women with uterine papillary serous carcinoma (UPSC)

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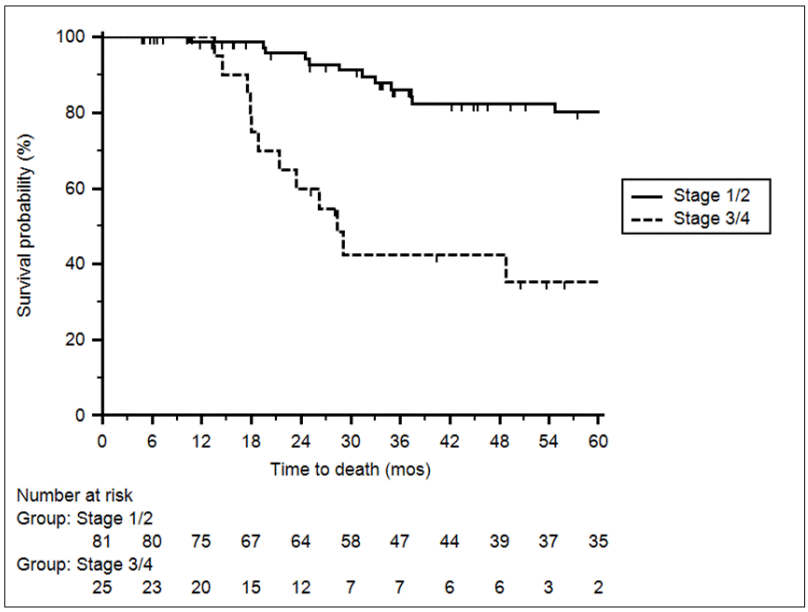
Objectives: To prospectively evaluate the safety, tolerability, and survival in women treated with adjuvant pelvic radiation "sandwiched" between six cycles of paclitaxel(T) and carboplatin(C) with completely resected UPSC (clinicaltrials.gov#: NCT00231868). These data represent the updated Phase II trial from a prior report.

Methods: Surgically staged pts with UPSC with no visible residual disease were enrolled. Treatment involved T (175 mg/m2) and C (AUC=6-7.5) every 21 days×3 doses, followed by radiation therapy (RT), including brachytherapy (BT), EBRT, or EBRT+BT, followed by an additional 3 cycles of T and C (AUC=5-6). Fields were extended for N2+ pelvic or para-aortic nodes. Toxicity was graded by NCI CTCv4.0. ITT survival analysis was done with KM methods.

Results: 113 eligible pts initiated treatment at a single institution with this regimen between 1999 and 2013. 106 pts completed at least 3 cycles of the prescribed chemotherapy and RT. Median age was 68 years (range: 37-83 years). 86/113 (76%) had disease confined to the uterus (stage 1&2) and 27/116 (24%) had completely resected extra-uterine disease (stage 3&4). 74/ 85 pts completed all 6 cycles of chemotherapy with RT; 6/85 (7.1%) completed EBRT alone and 5/85 (5.8%) completed BT alone. In the 106 pts who had at least 3 cycles of chemo and any RT mean PFS and OS for combined stage 1/2 pts is 50.5 ±1.9 months and 102.7 ±5.1 months, respectively. PFS and OS for stage 3&4 pts is 22.8 ±2.2 and 32.8 ±3.4 months, respectively. Five-year overall survival probability for stage 1/2 pts was 80.1% (95%CI:67.4-88.3) and stage 3/4 pts was 35.4%(95%CI:14.5-57.1). See Figure. Of the 604 chemo cycles administered, there were 119 (19.7%) G3 hematologic toxicities and 71 (11.8%) G4 heme toxicities, most commonly between cycles 4 and 5, after RT and most were self-limiting. There were 32(5.3%) G3/4 non-hematologic toxicities, including infection (5), neuropathy (5), and DVT(6). There were 32(5.3%) cycles with dose reductions and 53 (8.7%) with delays. There were no treatment-related deaths.

Conclusions: In this prospective registered trial, RT "sandwiched" between T/P chemotherapy is well-tolerated and highly efficacious in women with all stages of completely resected UPSC. This regimen should be considered as an arm for future phase III clinical trials in patients with UPSC.

Figure: 5 year Overall Survival (OS) by Stage



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445 - Poster Session B

T cells prepared for adoptive transfer therapy have enhanced homing ability to ovarian cancer microenvironment

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Objectives: Recent early stage clinical trials evaluating the adoptive transfer of ex vivo expanded peripheral T-cells have shown promising results in the treatment of recurrent ovarian cancer. Our goal was to evaluate whether lymphocytes prepared for adoptive transfer contain tumor specific effector T cells and whether the expanded T cells have the ability for engraftment to ovarian cancer.

Methods: Five HLA-A2 patients with recurrent ovarian cancer, who previously received prime-boost vaccination with autologous DC vaccine enrolled in a phase I clinical trial to determine the immune and clinical effects of ex vivo CD3/CD28 co-stimulated peripheral blood T cells. Harvested vaccine-primed peripheral T lymphocytes were expanded using beads coated with anti-CD3/anti-CD28 antibodies and IL-2. All T cells were identified by CD45, CD3, CD4 and CD8 expression and were stained for 10 chemokine receptors that are important for homing to ovarian cancer. Tumor-specific T cells were identified by a HER2/neu pentamer staining. Chemotaxis assays were performed to assess the functionality of these receptors.

Results: The use of CD3/CD28 beads resulted in preferential expansion of CD4+ cells compared to the apheresis samples. The 2 most commonly expressed chemokine receptors on the expanded cells were CXCR3 and CXCR4 (receptors for CXCL10 and CXCL12, which were highly expressed by ovarian cancer). At the end of the expansion, 70% of CD4+ and CD8+ cells expressed CXCR3 and CXCR4, compared to 20% of the peripheral T cells. The higher expression of CXCR3 and CXCR4 in the adoptive T cells resulted significantly increased chemotaxis toward CXCL10 and CXCL12, suggesting better homing ability to tumor microenvironment. The combination of additional chemokines did not enhance further migration. HER2/neu-specific T cells were detected in the expanded T cell population and showed migration toward CXCL10 and CXCL12.

Conclusions: The success of adoptive transfer of T cells depends on the large expansion of tumor-specific effector T cells that are capable of tumor engraftment. Our data confirm that cells prepared for adoptive transfer through CD3/CD28 bead expansion encompass tumor-specific T cells, which upregulate appropriate chemokine receptors and show enhanced migration towards chemokines highly expressed by ovarian cancer.

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446 - Poster Session B

Trial in progress: a randomized double-blind phase 3 trial comparing vintafolide + pegylated liposomal doxorubicin (PLD) versus PLD + placebo in patients with platinum-resistant ovarian cancer (PROCEED)

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Objectives: Folate receptor (FR) is expressed on the majority of epithelial ovarian cancers and FR expression appears to be a negative prognostic factor in this setting. Vintafolide (EC145) is a small-molecule drug-conjugate of folate designed to selectively deliver its cytotoxic payload, desacetylvinblastine monohydrazide (DAVLBH), to FR-expressing cells. ^{99m}Tc-Etarfolatide (EC20) is a small-molecular-weight folate-targeted companion imaging agent that can be used for the non-invasive, real-time assessment of functionally active FRs. In a phase 2 study comparing vintafolide + PLD with PLD alone, the combination demonstrated a statistically and clinically significant delay in PFS (5.0 months) compared with PLD alone (2.7 months) in women with platinum-resistant ovarian cancer. Data also indicated that ^{99m}Tc-etarfolatide may have utility for selecting patients most likely to benefit from vintafolide therapy.

Methods: This is an international, randomized, double-blind, placebo-controlled phase 3 study of PLD with or without vintafolide therapy in patients with primary or secondary platinum-resistant ovarian cancer (NCT01170650). Key eligibility criteria include: ≥18 years, pathology-confirmed epithelial ovarian, fallopian tube or primary peritoneal carcinoma, prior platinum-based chemotherapy, a RECIST v1.1 measureable lesion, and ECOG performance status 0 or 1. At baseline, patients undergo ^{99m}Tc-Etarfolatide imaging to identify FR-positive lesions and are subsequently randomized to the vintafolide ± PLD. PLD (50 mg/m^2) adjusted for Ideal Body weight is administered on day 1 of a 4-week cycle and treatment continues until the maximum allowable cumulative dose (550 mg/m^2) is reached or until disease progression or intolerable toxicity. Vintafolide (2.5 mg) or placebo is administered on days 1, 3, 5, 15, 17, and 19 of a 4-week cycle and treatment can continue for up to 20 cycles or until unacceptable toxicity or disease progression. The primary objective is to assess PFS based on investigator assessment (RECIST v1.1) in FR positive patients. Secondary objectives include OS, safety/tolerability, overall response rate, and disease control rate. Enrollment to the study is currently ongoing.

Results: Enrollment is currently ongoing.

Conclusions: Enrollment is currently ongoing.

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Economic impact among family caregivers of advanced ovarian cancer patients

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Objectives: The life of a family changes in many ways when cancer is diagnosed. These changes regard also financial costs. To the authors' knowledge, little work has been done to estimate the costs associated with care giving for cancer patients, during the first line treatment, including surgery and 6 chemotherapy cycles.

Methods: Between June 2009 and December 2012, advanced ovarian cancer patients' primary family caregivers were recruited from to the Division of Gynecologic Oncology of the University Campus Bio-Medico of Rome within 4 weeks of the patient's new diagnosis. Caregivers (N=90) reported demographic, medical information and economic cost, such as traveling to and from medical appointments, waiting with patients for appointments, missing work, attending to patients who are hospitalized.

Results: Between June 2009 to December 2012, 90 advanced ovarian cancer patients' primary family caregivers were enrolled in the study. The mean age of the study cohort was 52.3 years. They reported a 3% of missing work days. The mean cost for all caregivers was 988.529 € per year. So the mean cost of each caregiver was 10.981 € annually.

Conclusions: This economic analysis of caregiving in advanced ovarian cancer patients reports the significant burden that cancer treatment places on both families and society. These findings underscore the importance, when appropriate, of including valid estimates of the cost of informal caregiving when evaluating the cost-effectiveness of cancer treatments.

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CA-125 as a response marker for vintafolide+pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in platinum-resistant ovarian cancer: the PRECEDENT trial

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Objectives: Vintafolide (EC145), a folic acid/desacetylvinblastine conjugate, binds with high affinity to the folate receptor expressed on most epithelial ovarian cancers. In the randomized, open-label PRECEDENT trial, subjects with platinum-resistant ovarian cancer received vintafolide+pegylated liposomal doxorubicin (PLD) or PLD alone. Statistical significance of the primary objective (progression-free survival based on investigator assessment using RECIST v1.0 and prespecified clinical events) was achieved in the ITT population: median 21.7 weeks—vintafolide+PLD (n=100) vs 11.7 weeks—PLD alone (n=49) (HR 0.63; 95% CI 0.41-0.96; *P*=.031). An efficacy assessment based on CA-125 response is reported here and compared with overall response rate (ORR; complete response [CR]+partial response [PR]) based on RECIST criteria.

Methods: Women ≥18 years old with ECOG status 0-2 and exposure to ≤2 prior systemic cytotoxic regimens were randomized 2:1 to vintafolide (2.5 mg IV tiw, weeks 1 and 3, q 28 days)+PLD (50 mg/m^{2}IV day 1, q 28 days) or PLD alone (same dose/schedule). Best overall CA-125 response was assessed in a subset of the ITT population with a baseline CA-125 ≥2× ULN and ≥1 follow-up CA-125 evaluation. CA-125 CR was defined as a return to normal CA-125 levels (≤35 U/mL); PR was defined as a CA-125 decrease to ≤50% of baseline that was still above the ULN.

Results: 60 (vintafolide+PLD) and 26 (PLD alone) subjects were evaluable for CA-125 response. A higher confirmed CA-125 ORR was seen for vintafolide+PLD (21.7%) vs PLD alone (11.5%), as was a higher unconfirmed CA-125 ORR (38.3% vs 19.2%, respectively). CA-125 CR (confirmed and unconfirmed) occurred in 8.3% and 15.0% of vintafolide+PLD subjects, respectively, with no CA-125 CR in the PLD alone arm. In the same population, RECIST-confirmed ORR was 18.7% for vintafolide+PLD vs 12.2% for PLD alone, and RECIST-unconfirmed ORRs were 28.0% and 16.3%, respectively. One confirmed and 1 unconfirmed RECIST CR were noted in the vintafolide+PLD arm and 1 confirmed and 1 unconfirmed RECIST CR were observed in the PLD alone arm.

Conclusions: CA-125 level changes correlated with RECIST changes in subjects with platinum-resistant ovarian cancer and elevated CA-125 treated with vintafolide and PLD. CA-125 may overestimate CR compared with RECIST in the same population.

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Adverse event profile by folate receptor status for vintafolide+pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in platinum-resistant ovarian cancer

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Objectives: Vintafolide (EC145, MK-8109), a folic acid/desacetylvinblastine conjugate, binds with high affinity to folate receptors (FRs) expressed in cancers. This exploratory analysis evaluated adverse events (AEs) by FR status in the PRECEDENT trial (NCT00722592), a randomized open-label study of subjects with platinum-resistant ovarian cancer receiving vintafolide+pegylated liposomal doxorubicin (PLD) or PLD alone.

Methods: Women ≥18 years old with ECOG status 0-2 and exposure to ≤2 prior systemic cytotoxic regimens were randomized 2:1 to vintafolide (2.5 mg IV tiw, weeks 1 and 3, q28 days)+PLD (50 mg/m^2 IV day 1, q28 days) or PLD alone (same dose+schedule). Patients at centers with ^{99m}Tc nuclear imaging capability underwent SPECT imaging with etarfolatide to identify functionally active FRs. AEs in the safety population (received at least 1 dose of study drug) were evaluated by FR status (FR [100%, all target lesions positive]; FR [0%, all lesions negative]).

Results: 37 patients were FR (100%) (22, vintafolide+PLD; 15, PLD alone), and 19 were FR (0%) (13 vintafolide+PLD; 6, PLD alone). The number of patients reporting at least 1 drug-related AE was generally similar regardless of FR status or treatment arm. For the FR (100%) vs FR (0%) groups, the most common drug-related AEs (≥30% of patients in either group) in the vintafolide+PLD arm were fatigue (54.5% vs 46.2%), constipation (50.0% vs 46.2%), hand-foot syndrome (HFS) (40.9% vs 30.8%), anemia (40.9% vs 30.8%), nausea (36.4% vs 53.8%), stomatitis (36.4% vs 61.5%), rash (36.4% vs 15.4%), peripheral sensory neuropathy (31.8% vs 0%), neutropenia (27.3% vs 30.8%), vomiting (22.7% vs 38.5%), and asthenia (13.6% vs 38.5%). For the FR (100%) vs FR (0%) groups, the most common drug-related AEs (≥30% of patients in any group) in the PLD alone arm were HFS (53.3% vs 50%), nausea (33.3% vs 33.3%), stomatitis (33.3% vs 50.0%), fatigue (33.3% vs 33.3%), anemia (20.0% vs 50%), neutropenia (27.3% vs 50.0%), and leukopenia (13.6% vs 33.3%).

Conclusions: This exploratory analysis suggests that the AE profile appears numerically similar regardless of FR status for the vintafolide+PLD and PLD alone groups; however, the small sample size precludes a statistical analysis. Future analyses in larger patient populations are needed to confirm these findings.

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Model prediction of mean PFS and OS time from a phase II trial comparing vintafolide plus pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant ovarian cancer patients with 100% folate receptor–positive target

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Objectives: The randomized phase II trial PRECEDENT (NCT00722592) has shown that vintafolide (V) plus pegylated liposomal doxorubicin (PLD) showed a statistically significant improvement in progression-free survival (PFS) compared with PLD for platinum-resistant ovarian cancer (PROC). Observed efficacy was greatest in patients with 100% folate receptor (FR)-positive tumors, identified by ^{99m}Tc etarfolatide. Median PFS was 24.0 vs 6.6 weeks for FR (100%) patients treated with V+PLD vs PLD (HR 0.381; *P*=0.018). Notably, FR (100%) patients represent a subpopulation in PROC with a worse prognosis when treated with PLD. Additionally, post-PFS and overall survival (OS) values are meaningful. The objective of this study is to predict mean PFS, post-PFS, and OS for FR (100%) patients treated with V+PLD vs PLD.

Methods: Parametric Weibull survival models are estimated for FR (100%) subpopulation (n=37) using PRECEDENT data, adjusted for the following prespecified baseline factors: age (≥65 vs <65 years), platinum failure (primary vs secondary), CA-125 level (≥200 vs <200 U/mL), geography (North America vs Europe), log of the sum of the longest diameters of target lesions, log of months since last platinum treatment, and ECOG PS (1 or 2 vs 0). Models provide survival probabilities for each patient given the baseline covariates for a given treatment. The mean of each individual's survival probabilities at any time point across all times yields the population survival curve for the treatment. Area under the curve is the mean survival time over a time period. Variance of the mean is estimated using bootstrapping.

Results: Model predictions based on patients' assigned treatment in the trial are very close to actual mean times calculated from the Kaplan-Meier curves. The models further predict mean times for a given treatment across all trial patients over 2 years:

Mean time (months)	PFS	95% CI		Post-PFS	95% CI		OS	95% CI	
PLD	2.6	1.4	5.7	6.7	2.5	12.4	9.3	5.3	15.4
V+PLD	6.8	3.9	10.9	7.6	2.8	11.5	14.3	11.0	17.6
Diff	4.1	-0.8	8.3	0.9	-7.4	7.4	5.0	-2.9	10.1

Conclusions: Results suggest large benefit for mean PFS and OS associated with V+PLD. Results will be further evaluated after the ongoing phase III trial (PROCEED). These data may be used for future evaluation of the cost/benefit of V+PLD vs PLD for decision makers.

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Adoptive transfer of CD3/CD28 co-stimulated T cells improves clinical outcome in patient with recurrent ovarian cancer

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Objectives: The prognosis for patients with recurrent ovarian cancer remains dismal. To obtain high frequency tumor-reactive T cells to specifically kill cancer cells and to achieve long lasting immune memory, we performed a phase-I trial of adoptive transfer of vaccine-primed CD3/CD28-costimulated autologous T cells combined with vaccine boost and bevacizumab in patients with recurrent ovarian cancer who were previously vaccinated with autologous dendritic cells pulsed with autologous oxidized whole tumor lysate (OC-DC).

Methods: Patients with recurrent ovarian cancer, who have previously been vaccinated with OC-DC and have undergone collection of vaccine primed T cells by apheresis post vaccination were enrolled in a T cell dose escalation study where they underwent outpatient non-myeloablating lymphodepleting chemotherapy with intravenous cyclophosphamide (300 mg/m^2/day) and fludarabine (30 mg/m^2/day) on day (−3 to −5) followed by infusion of autologous ex vivo CD3/CD28-co-stimulated T-cells on day 0; vaccination boost with OC-DC on day 2 and OC-DC and bevacizumab every 4 weeks until end of study. Safety, feasibility and immune related clinical efficacy were assessed at the end of the study.

Results: Eight patients have completed vaccination and T cell transfer to date. Our study demonstrates the feasibility of ex vivo T-cell expansion in a heavily pretreated patient population, and the tolerability of outpatient lymphodepletion followed by T-cell transfer. The hematologic recovery was rapid and resulted in two important changes in circulating T cells: (1) it reduced the relative frequency of Tregs over the total CD4+ cells, and (2) it decreased the CD4+ to CD8+ ratio. Clinical benefit was observed in five (63%) patients at end of study. The remaining three patients (37%) experienced disease progression.

Conclusions: Our results suggest the combination of cellular immunotherapy comprising of vaccination with autologous dendritic cells pulsed with oxidized whole tumor lysate followed by the adoptive transfer of vaccine primed T cells is a safe and promising approach for the treatment of recurrent ovarian cancer and warrants further optimization.

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Para-aortic lymph node (PAN) assessment and its surgical indication in patients with stage IB-IIA cervical cancer

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Objectives: To investigate the frequency of PAN involvement in stage IB-IIA cervical carcinoma and to determine the feasibility and indication of para-aortic lymphadenectomy.

Methods: We conducted a retrospective review of a prospectively maintained database of 561 patients with Stages IB-IIA cervical carcinoma who underwent radical hysterectomy and systematic pelvic and PAN dissection from January 2007 to December 2009. PAN dissection was performed to the level of IMA (inferior mesenteric artery), or to the level of renal vein if

there were enlarged nodes above IMA. Multiple logistic regression analysis was employed to determine the high-risk factors for PAN metastasis.

Results: Median age was 44 years (range, 20–78). The last follow-up was February 2013. Twenty-three patients didn't responded and the follow-up rate was 95.9%. The median follow-up of 50 months (range, 3–73 months). Histology included 44 (7.8%) with adenocarcinoma, 491 (87.5%) with squamous carcinoma, 15 (2.7%) with adenosquamous carcinoma and 11 (2%) with neuroendocrine cancer. FIGO stage for the group were IB1=167(29.8%); IB2=81(14.4%); IIA=313(55.8%). Median number of nodes evaluated was 27(range, 12–63) ; The frequency of PAN involvement was 9.8% (55 patients) for all and was 4.8%□A7.4% and 13.1% in FIGO stage IB1□AIB2 and IIA, respectively. 146(26%) patients had pelvic lymph node (PLN) metastases and 67(11.9%) had common iliac lymph node (CILN) metastases. In a multivariate analysis, FIGO Stage, tumor size, lymphvascular space invasion and pelvic nodal involvement were independent risk factors for PAN metastasis. By using a receiver operating characteristic curve, we found the optimal cut off point of tumor size to predict PAN metastasis was 3cm (sensitivity,96.4%; specificity, 46.2%). The mean operating time for para-aortic lymphadenectomy was 30 min (range, 20–60 min) and the median blood loss during the overall surgical procedure was 300 ml (range 100–1150 ml). Forty-nine (8.7%) patients had perioperational complications, but no surgery-related death occurred.

Conclusions: PAN dissection is safe and feasible for cervical cancer patients. It is recommended that paraaortic lymphadenectomy should be routinely done for stage IB-IIA cervical cancer patients whose tumor size is no less than 3cm.

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Laparoscopic treatment of early-stage ovarian cancer: surgical technique and outcome

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Objectives: To describe our experience in the laparoscopic treatment of early-stage ovarian cancer at the Oncology Unit of the Gynecology Department, Hospital Italiano Buenos Aires, Argentina.

Methods: Twenty-one cases with early-stage ovarian cancer, treated between January 2007 and December 2011, were retrospectively analyzed. These patients underwent complete staging surgery, considering hysterectomy with adnexectomy, pelvic and lumboaortic lymphadenectomy (up to renal veins), omentectomy and multiple peritoneal biopsies were performed. Both patients´ characteristics and perioperative outcomes (surgical time, blood transfusions, number of lymph nodes removed and complications) were analyzed.

Results: Twenty-one surgeries were performed during the above mentioned period. All patients underwent surgical treatment; in twenty of them the surgery performed was a complete staging. Mean age was 51 years old (r, 39 -78) and BMI, 26 (r, 20-42). No conversion to laparotomy was necessary. Three complications occurred: a popliteal compartment syndrome and ureteral obstruction in the same patient and pelvic lymphocele in another one. Mean number of pelvic and lumboaortic lymph nodes removed was 21 (r, 9-32) and 12 (r, 4-19), respectively. Mean surgical time, 210 minutes (r, 160-360); mean hospital stay, 31 hour (r, 24-72). No recurrences were reported in a mean 19-month follow-up period (r, 3 - 48 months).

Conclusions: Laparoscopic surgery is an excellent alternative to perform surgical staging in patients with ovarian cancer presumed to be in its early stage. It is a feasible and safe procedure that should be performed by trained gynecologic oncologists.

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Trends in the pathological diagnosis of serous fallopian tube, peritoneal, and ovarian cancer in the US

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Objectives: To identify the trends in the pathological diagnosis of serous fallopian tube vs peritoneal vs ovarian epithelial cancers.

Methods: Data was obtained from National Cancer Institute for the years between 2001 and 2009. Chi squared and t-test were used for statistical analyses.

Results: The median age of the overall group was 63 (range: 18 to 102). Whites, Blacks and Asians comprised of 88%, 6%, and 6% of all patients. Of 23,997 women diagnosed with epithelial cancers, 1,014 (4%), 2,810 (12%), and 20,173 (84%) were fallopian tube, peritoneal, and ovarian cancers. We divided the study group into 3 time periods from 2001 to 2003, 2004 to 2006, and 2007 to 2009. Over the study periods, the proportion of fallopian tube cancers increased with a subsequent decrease in ovarian cancer cases (3% to 4% to 8%; $P<0.01$; 86 to 84 to 82%; $P<0.01$). However, the proportion of peritoneal cancers did not change (11% to 12% to 12%; $P=0.12$). The 5-year survival of those with fallopian tube, peritoneal and ovarian cancers was 53% to 38% to 27%, respectively ($P<0.01$). Of those with advanced stage disease, the survival was 48%, 31%, and 27% ($P<0.01$).

Conclusions: Over time, the proportion of serous fallopian tube cancer diagnosis increased nearly threefold with a corresponding decrease in ovarian cancer diagnosis. The survival of fallopian cancer patients is higher than that of ovarian or peritoneal cancers. The shift in the diagnosis of the serous pelvic cancers suggests the need for standardized diagnostic criteria.

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Polyphyllin D, a Chinese herb, potentiates cisplatin-induced death in ovarian cancer cell lines

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Objectives: Polyphyllin D (PD), a major component of the Chinese herb, Paris polyphylla, has been reported to have anti-neoplastic activity. In this study, we 1) assessed the activity of PD alone and in combination with cisplatin on ovarian cancer (OVCA) cell survival and 2) explored the molecular determinants of PD-response.

Methods: Twenty OVCA cell lines were subjected to PD treatment alone and in combination with cisplatin, and in parallel, Affymetrix expression analysis (HuRSTA genechip). OVCA cell sensitivity to PD +/- cisplatin was quantified using MTS proliferation assays. Pearson's correlation was calculated for gene expression and PD IC50 values. Genes associated with PD sensitivity were evaluated for associations with survival in 5 clinico-genomic datasets encompassing 969 patients, including 1) Moffitt (MCC) (U133Plus, n=142); 2) Total Cancer Care (TCC) (HuRSTA, n=57); 3) The Cancer Genome Atlas (TCGA) (U133A, n=497); 4) MD Anderson (MDA) (U133Plus, n=53); and 5) Australian (AUS, n=220).

Results: PD exhibited anti-proliferative effects against all tested OVCA cell lines, with IC_{50} values ranging from 0.2 to 1.4 µM. Furthermore, in all cell lines, PD treatment significantly decreased cisplatin IC_{50} (mean IC_{50} reduction of 2.1 µM; $P<0.02$). Pearson's correlation test identified 25 probe sets, representing 18 unique genes to be associated with PD sensitivity (FDR=0). Three of these genes were associated with survival from OVCA: CLDN4 (MCC, $P=0.001$), PSD4 (MCC, $P=0.003$, and TCGA, $P=0.003$), and TTC22 (MCC, $P<0.001$).

Conclusions: Our findings highlight the value of PD as a natural product with potential anti-cancer properties, which may also enhance the activity of existing therapeutic agents.

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Epidemiologic characteristics of cervical cancer in Korean women

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Objectives: To evaluate the epidemiologic characteristics of cervical cancer in Korean women and to emphasize the significance of screening test in cervical cancer

Methods: The basic data for incidence rate, rate of cervical cancer screening, stage distribution and 5-year survival rates were obtained from the database of the Korea Central Cancer Registry.

Results: A total of 49,503 women were diagnosed with cervical cancer from 1999 to 2010. Since the peak of 4,572 cases in 2001, the annual number of cervical cancer cases has been steadily declining, and reached 3,857 in 2010. The age-standardized incidence rate (ASR) of cervical cancer also decreased from 18.6 per 100,000 women in 1999 to 12.3 per

100,000 women in 2010. Compared with the ASR of 2002, all areas showed a reduced ASR in 2010. However, the ASRs of other areas were higher than that of Seoul. To review the relationship between the rate of cervical cancer screening and the incidence rate of cervical cancer, we examined the overall rate of participation in the cervical cancer screening arm of the National Cancer Screening Program, whose target population includes Medical Aid Program recipients and the lower income bracket of National Health Insurance beneficiaries, and the screening rate of cervical cancer based on recommendation including individual screening as well as organized screening. Although the former has been increasing steadily since 2004, it does not reach 20% even in 2010. The latter has also increased from 58.3% in 2004 to 62.4% in 2011. In the analysis of stage distribution, stage Ib1 was the most common stage at 26.6%, followed by stage Ia1 at 20.8%. However, about 50% of patients were diagnosed at a loco-regionally advanced stage ≥ Ib2. Five-year survival rate from 1993 to 1995 was 77.5%. After that, 5-year survival rate improved slightly more than 80%. However, 5-year survival rate seems to be stagnant between 80.0% and 81.2% over the last 15 years.

Conclusions: Cervical screening tests such as the Pap smear should be the gold standard strategy to decrease the incidence and to improve the survival outcomes of cervical cancer. In addition, screening programs for cervical cancer should be designed, organized and directed within the context of a nationwide program for cancer control.

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The malignant potential of endometrial polyps can be determined by incorporating the Endometrial Intraepithelial Neoplasia (EIN) classification

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Objectives: The reported frequency of malignant or pre malignant changes confined to endometrial polyp is 0.5-6%. The management of Atypical Endometrial Hyperplasia (AEH) confined to endometrial polyp (EP) is not yet established. Recently, an alternative pathological nomenclature has emerged, using the term Endometrial Intraepithelial Neoplasia (EIN) instead of terms of atypia. The objective of this study was to evaluate the safety of conservative hysteroscopic resection of endometrial polyps with AEH or EIN.

Methods: Retrospective cohort study of all cases of hysteroscopic endometrial polyp resections performed at a single center between the years 2000-2011. Inclusion criteria were a pathologic evidence of AEH in a polyp, additional pathologic assessment of endometrial curetting and a final pathologic report of a hysterectomy specimen. A pathologist revision was made according to the EIN classification.

Results: Of 32 patients with AEH in a polyp, 25 had normal endometrial curetting. Even with AEH confined to polyp, AEH or carcinoma were present in the hysterectomy specimen in 12 cases (48%). EIN in polyp (14 cases) was correlated with 57% of diagnosis of EIN/carcinoma in the uterus, whereas in the absence of EIN in polyp only 1 of 9 cases showed EIN in the final pathologic specimen (PPV of 57% and NPV of 94%).

Conclusions: The diagnosis of EIN in endometrial polyp may be better predictor than AEH regarding endometrial involvement by malignant or pre-malignant states. The safety of conservative hysteroscopic resection of endometrial polyp with AEH/ EIN is questioned.

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Conjugation to SMAC mimetic potentiates sigma-2 ligand induced tumor cell death in ovarian cancer

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Objectives: Drug resistance is a significant problem in the treatment of ovarian cancer and can be caused by multiple mechanisms. Inhibition of apoptosis by the inhibitor of apoptosis proteins (IAPs) represents one such mechanism, and can be overcome by a mitochondrial protein called SMAC (Second Mitochondria-derived Activator of Caspases). We have previously shown that the ligands of sigma-2 receptors effectively induce tumor cell death. Additionally, because sigma-2 receptors are preferentially expressed in tumor cells, their ligands provide an effective mechanism for selective anti-cancer therapy. In the current work we have improved upon the previously described sigma-2 ligand, SW43, by conjugating it to a pro-apoptotic

small molecule SMAC mimetic compound, SW52, thus generating a novel compound SW-IV-134. The objective of this study was to perform the in-vitro characterization of SW-IV-134 and explore its effectiveness in preclinical models of ovarian cancer.

Methods: A panel of ovarian cancer cell lines (SKOV3, HEYA8, HEYA8 MDR, and OVCAR3) was treated with SW-IV-134. Cell viability and mechanism of cell death was determined using CellTiter-Glo Assay, Quantitative RT-PCR, ELISA, and immunoblotting. In-vivo therapeutic efficacy of SW-IV-134 was assessed in an intraperitoneal mouse model using tumor cell line xenografts.

Results: SW-IV-134 retained adequate sigma-2 receptor binding affinity in the context of the conjugate and potently induced cell death in ovarian cancer cells. The cell death induced by SW-IV-134 was significantly greater than that observed with SW43, SW52, and SW43 plus SW52. Furthermore, the intra-peritoneal administration of SW-IV-134 significantly reduced tumor burden and improved overall survival in a mouse xenograft model of ovarian cancer without causing significant toxicity to normal tissues. Mechanistically, SW-IV-134 induced degradation of CIAP-1 and CIAP-2 leading to NF-κB activation and TNF-α dependent cell death.

Conclusions: In conclusion, our findings suggest that coupling sigma-2 ligands to SMAC mimetics enhances their effectiveness while maintaining the cancer selectivity. This encouraging proof-of-principle data support further development of similar compounds for future clinical application.

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Quantitative assessment of immunofluorescence-based biomarkers in ovarian cancer with respect to clinical outcome

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Objectives: Ovarian cancer is the fifth leading cause of cancer related deaths among women with the majority of cases diagnosed at an advanced stage where therapeutic options are limited to surgical debulking and adjuvant platinum-based chemotherapy regimens. Given the paucity of reliable tissue biomarkers to predict response to therapy, we quantified the ovarian biomarkers using a validated quantitative multiplex immunofluorescent (QMIF) platform on formalin-fixed, paraffin-embedded (FFPE) ovarian tissues to access biomarker expression patterns with respect to clinical outcome.

Methods: Eighty-nine patients were evaluated using tissue microarrays consisting of three 0.6mm tumor cores per diagnostic specimen; fallopian tubes and five different ovarian cell lines were included as pos/neg controls. Four biomarkers CK7, VEGF, PERK1/2 and TP53 were evaluated with QMIF, with individual and combined antibody features constructed utilizing intensity and area values. Kaplan-Meier with log-rank test along with multivariate Cox proportional hazards model were employed to determine biomarker association with respect to overall (OS) and progression free survival (PFS).

Results: Mean age 59yrs, 80% serous, 88% Grade 3 and 85% >/= Stage IIIC. Median follow-up 32 months; 5-year OS 51% and platinum resistance 54%. In multivariate analysis CK7+TP53+ was an independent prognostic marker for both PFS and OS (p-value <0.001 and 0.04), i.e., greater amounts associated with decreased survival. By contrast, increased levels of PERK1/2 were associated with a decreased tumor recurrence and increased platinum sensitivity (P=0.020 and 0.006) while increasing amounts of VEGF were associated with greater tumor recurrence (P=0.004) as well as platinum sensitivity (P=0.03).

Conclusions: Quantitative assessment of TP53, PERK1/2 and VEGF provides valuable information with respect to chemoresponse and tumor recurrence. The application of QMIF to biomarker investigation will provide another level of complexity to tumor profile which is currently not available using standard IHC assays.

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460 - Poster Session B

Antisense oligonucleotide suppression of human IGF-1R inhibits the growth and survival of epithelial ovarian cancer cells

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Objectives: Preclinical evaluation of the anti-neoplastic activity of antisense oligonucleotide (AS) suppression of human insulin-like growth factor I receptor (IGF-IR) in human epithelial ovarian cancer (EOC).

Methods: Ovarian cancer cells from 36 patients with EOC were investigated under serum-free tissue culture conditions. IGF-I production was evaluated by standard ELISA. IGF-IR and phosphorylated IRS-1, AKT, and MAP kinase expression and protein levels were evaluated by immunohistochemistry and Western blotting. Cancer cell growth and proliferation assays were performed in triplicates using MTT assay. Apoptosis was evaluated by TUNNEL assay.

Results: All ovarian cancer tissue samples tested produced IGF-I and expressed IGF-IR, supporting the existence of an autocrine loop. Treatment of primary ovarian cancer cell lines with an IGF-1R AS inhibited growth and proliferation and decreased clonogenicity in soft agar assay. AS treatment was demonstrated to inhibit the expression of IGF-1R and decrease the concentration of phosphorylated IRS-1, AKT, and MAP kinase signaling protein downstream of the IGF-IR. We also observed that the IGF-1R AS sensitized cancer cell lines to cisplatin in vitro through the PI3K pathway.

Conclusions: IGF-IR enhances the proliferation and tumorigenicity of human ovarian cancer cells and inhibition of IGF-IR by AS oligonucleotide treatment potentiates the activity of cisplatin in vitro. Therefore, IGF-1R is a potential molecular target in ovarian cancer.

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461 - Poster Session B

The distribution of high-risk human papillomavirus genotype in high-grade cervical intraepithelial neoplasia of Korean women

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Objectives: The aim of this study was to assess the distribution of HPV genotypes in high-grade cervical intraepithelial neoplasia (CIN) in Korea.

Methods: This prospective study included consecutive 1009 patients who referred for cervical biopsy due to abnormal cytology. HPV genotyping was performed on the cervical smear using PCR-based DNA chip test for 21 high-risk HPV types.

Results: Histologic diagnosis was chronic cervicitis (CC), CIN 1, CIN 2, CIN3, and invasive carcinoma (IC) in 332 (32.9 %), 143 (14.1 %), 104 (10.3 %), 351 (34.7 %), and 79 (7.8 %) patients, respectively. High-risk HPV DNA was detected in 591 (58.7 %) patients and multiple HPV types were identified in 181 (17.9 %) patients. High-risk HPV DNA was detected in 41.5 %, 50.3 %, 63.4 %, 72.3 %, and 77.2% of patients with CC, CIN 1, CIN 2, CIN 3, and IC, respectively. The leading HPV types were HPV 16 (31.0 %), HPV 58 (12.9 %), HPV 18 (8.9 %), HPV 52 (7.4 %), HPV 31 (5.6 %), and HPV 33 (5.2%) for patients with high-grade lesions (CIN 2/3 and IC). The overall positivity rate of HPV 16 (odds ratio [OR], 6.83; 95 % confidence interval [CI], 4.54-10.29; $P<0.001$), HPV 18 (OR, 2.04; 95% CI, 1.20-3.45; $P=0.008$), HPV 31 (OR, 5.09; 95 % CI, 2.22-11.71; $P=0.001$), HPV 33 (OR, 3.19; 95% CI, 1.53-6.64; $P=0.002$), HPV 52 (OR, 2.56; 95% CI, 1.46-4.50; $P=0.001$), and HPV 58 (OR, 2.16; 95% CI, 1.65-4.13; $P<0.001$) was significantly higher in high-grade lesions than in low-grade lesions. HPV 30, 35, and 45 were overrepresented in high-grade lesions than in low-grade lesions, but the differences were not statistically significant.

Conclusions: HPV 16, 58, 18, 52, 31, and 33 were the most common genotypes which are represented in high-grade CIN and these were significantly associated with development of high-grade CIN. The development of vaccines against these HPV types is required in Korea.

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462 - Poster Session B

Comparative study results of conventional cytology, cervical colposcopy and histopathology obtained by LEEP

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Objectives: Cervical cancer is the second most common cancer among women, with approximately 500,000 new cases per year in the world. There is a reduction of about 80% of mortality through adequate screening of women aged 25-65 years. Despite effective strategies for its prevention, cancer of the cervix remains a major public health problem, especially in developing countries where the incidence is about two times higher. This study aims to compare the results obtained from these three diagnostic methods for cervical intraepithelial neoplasia. Two propaedeutic procedures were developed and are

now regarded as fundamental in the early diagnosis of these lesions: colposcopic examination and cytological smear. The LEEP, initially used in order to treat chronic cervicitis and cervical biopsies, modified the handler.

Methods: This retrospective cohort study was performed in the service of Lower Genital Tract Pathology of the Hospital Universitario Evangelico de Curitiba, in Curitiba, Paraná state, in the period January 2011 to July 2012. Patients included in the study were all those who had high-grade squamous intraepithelial lesion on cytology and / or underwent colposcopy and had histopathology cervical by LOOP procedure. The correlation of the results of cytology and colposcopy was performed in relation to histology because this is the gold standard for diagnosis. The study included 201 patients aged between 14 and 78 years, mean 36.3 years.

Results: When the three diagnostic methods were compared, there was correlation of 16.5% (34/206). When comparing cytology with histopathology, we observed a concordance of 31% (64/206) with colposcopy and histopathology in 19.5%. Thirty-six patients showed no correlation between the three methods (17.4%). The intention of our service by using the approach "See and Treat" was to avoid possible loss of follow-up among women with high-grade squamous intraepithelial lesion. The goal was achieved as the rate of noncompliance with follow-up was high, however the vast majority were already adequately treated.

Conclusions: The approach "See and Treat" should be considered more in public services where the low adherence of patients to follow-up is expected. In addition, efforts should be implemented to reduce losses.

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463 - Poster Session B

Secondary primary cancer after cervical cancer

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Objectives: To investigate the incidence and patterns of secondary cancer after cervical cancer.

Methods: Data from the Korea Central Cancer Registry was reviewed and analyzed between 1993 and 2010. Standardized incidence ratios (SIRs) of the secondary cancer among women with cervical cancer were analyzed.

Results: Total 72,805 women who were diagnosed of primarily invasive cervical cancer have been evaluated with mean follow up period of 7.3 years. Mean of initial diagnosis of cervical cancer was 51.4 year old. Peak age of cervical cancer was 40 to 59 years (49.8%). Four percent of the women (n=2913) had a secondary cancer: 0.18 % of the total 72,805 women had the third or more primary cancer (n=134). The overall SIR for a secondary cancer was 1.05 (95% CI, 1.01–1.09): esophagus (1.86), anus (2.42), respiratory system (2.05), lung (2.13), corpus uteri (1.91), urinary system (1.59), bladder (2.38), and bone and joints (2.70). The risk of secondary cancer at esophagus, anus, and bone and joints did not increase in subgroup with the interval less than 60 months. Interestingly, the decreasing overall SIR for a secondary cancer was breast (0.82) for all follow up period and rectum (0.66) for follow up period up to 59 months. This might be explained by ovarian ablation from treatment for cervical cancer and the shared radiotherapy field.

Conclusions: The secondary cancer was significantly identified in women after treatment of cervical cancer rather than general population. The incidence of breast and rectal cancer decreased after treatment of cervical cancer.

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STAT1 pathway promotes progression of serous papillary endometrial cancer

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Objectives: Serous papillary endometrial cancers (SPEC) are highly progressive with poor prognosis, and its oncogenic profile is known different from endometrioid endometrial cancers. It, however, still remains unclear that which pathway promotes tumor progression. In this study, we aimed to figure out SPEC-specific pathways through genome-wide analysis to reveal the mechanism promoting tumor growth and progression.

Methods: Gene expression microarray and immunohistochemical staining were conducted using 69 samples of endometrial cancer under protocols approved by the Institutional Review Board to investigate SPEC-specific pathways. Using SPAC-1L, a SPEC cell line, cellular proliferation, migration, and invasion were assessed with or without siRNAs for target genes. In vivotumorigenesis was also assessed with NOD-SCID mice.

Results: Genes expression microarray analysis revealed STAT1 pathway was highly activated in SPECs, and STAT1 expression was confirmed significantly higher in SPECs by immunohistochemical staining (P<0.001). Immunohistochemical staining also exhibited co-localization of ICAM-1 and PD-L1 at tumor frontier with prominent infiltration of CD8-T cells in SPECs (P<0.001). IFN-g induced gene expression of cMyc, ICAM-1 and PD-L1 (P<0.05) as well as STAT1 in SPAC-1L cells, and promoted cellular proliferation (P<0.05), adhesion (P<0.0001), and invasion (P=0.0002). In contrast, suppression of STAT1 attenuated induction of these genes (P<0.05), and inhibited invasion (P<0.05) and xenograft tumor growth on NOD-SCID mice (P<0.0001).

Conclusions: These results indicate that STAT1 pathway is specifically activated in SPECs to be associated with their aggressive features. Concerning immune-activity at tumor microenvironment, targeting STAT1 pathway with attenuation of tumor-immunity could be a potent candidate in the treatment of SPECs although further analysis is mandatory.

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465 - Poster Session B

Residual diseases after conization of women with stage IA-IB1 cervical carcinoma in region with high incidence

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Objectives: To determine rate of residual diseases, influencing factors after conization, and survival outcome of women with stage IA to IB1 cervical carcinoma in region with high incidence.

Methods: A retrospective study of 185 stage IA to IB1 cervical carcinoma patients who had undergone cervical conization followed by hysterectomy during 2006-2012. Patients' characteristics, histopathologic data and survival data were recorded. Independent factors correlated with residual lesions in the subsequent hysterectomy specimens were analyzed by descriptive statistics. Regression analysis was used for determined predicting factors for residual cancer. Survival function was analyzed by Kaplan-Meier method.

Results: The mean age of studied patients was 48.89 (range 25-78) years old. 74 women (40%) were menopause. The most common symptom is check-up, 141 patients (76.2%). The most abnormal cervical cytology was HSIL, 86 women (54.1%), the second was SCCA, 35 women (22%). Cone specimen was free margin in 28 women (15.9%). In case of having diseases at margin, we found SIL 32.7% and cancer 53.2%. The most common histologic type were SCCA (129 women, 69.7%), and adenocarcinoma (40 women, 21.6%). Pathology of hysterectomy specimens found residual cancer in 70 women (37.8%), CIN in 42 women (22.7%). 184 patients (99.5%) were complete response. 6 women had disease recurrence and 5 patients were cured after treatment for recurrent diseases. One patient was alive with disease progression. Postmenopause, having diseases and type of diseases at conization margins, depth of invasion of cone specimens and FIGO stage were significantly correlated with residual cancer in hysterectomy specimens. The mean progression free survival was 84.25 months (95% CI 80.76- 87.75).

Conclusions: Pathologic margin, depth of invasion in cone tissue, and postmenopause were independent risk factors for residual cancer in stage IA to IB1 cervical carcinoma after conization.

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466 - Poster Session B

A metabolomic approach to identifying platinum resistance in ovarian cancer

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Objectives: The "Warburg Effect" refers to the differences in metabolism between cancer and normal cells. Acquisition of metabolic alterations has been shown to be essential for the unremitting growth of cancer; the relation of such alterations to chemo-sensitivity has not been investigated. The objective of this study is to identify the metabolic alterations that are

specifically associated with platinum resistance, using a global metabolomics approach in two epithelial ovarian cancer cell lines.

Methods: A global metabolic analysis of the A2780 platinum-sensitive and its isogeneic platinum-resistant C200 ovarian cancer cell line was performed utilizing ultra-high performance Liquid Chromatography/Mass Spectroscopy and Gas Chromatography/Mass Spectroscopy. Per-metabolite comparisons were made between cell lines and an interpretive analysis was carried out using the KEGG (Kyoto Encyclopedia of Genes and Genomes) metabolic library and the Ingenuity exogenous molecule library.

Results: Of the 253 identified metabolites, 152 were found to be dissimilar ($P<0.05$) between A2780 and C200 cells. Of these, 57 had increased and 92 had decreased levels in C200. The top altered KEGG pathways based on significant difference or impact of alterations were: 1) cysteine and methionine; 2) D-arginine and ornithine; 3) starch and sucrose; 4) amino sugar and nucleotide; 5) pyrimidine and 6) glutathione pathways. The glutathione pathway has been implicated to play a key role in platinum resistance in ovarian cancer as well as other malignancies. An Ingenuity Pathway Analysis revealed networks of altered metabolites related to free radical scavenging, drug metabolism, and molecular transport. This novel finding can be explained by the known mechanism of action of cisplatin, and suggests that adaptations made by resistant cells occur in pathways involving free-radical attack on DNA which lead to apoptosis.

Conclusions: Our finding discloses that the chemo-resistant C200 has distinct metabolic alterations, some of which may be responsible for, or contribute towards its platinum resistance. This distinct metabolic signature of platinum resistance can be translated to biomarker(s) development for detection of chemo-resistant ovarian tumors and to potentially identify metabolism based lethal drug targets for chemo-resistant tumors.

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467 - Poster Session B

The inhibitory effects of metformin on ovarian cancer growth mimic those seen with caloric restriction

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Objectives: Calorie restriction (CR) has been demonstrated to restrict the growth of various cancers. Metformin, by activation of AMPK, may induce metabolic changes similar to those seen with CR. The aim of our study was to investigate the downstream effects of metformin on ovarian cancer growth and compare them to those seen with CR.

Methods: 6 week old female C57B6 mice were fed either regular diet (RD, n=30), high energy diet (HED, n=30) or were 30% calorie restricted (CRD, n=10) for 30 days and then injected with 5x106 ID8 mouse ovarian cancer cell lines. RD and HED mice were randomly divided into three subgroups (n=10): (1) M0: received metformin 200mg/kg in drinking water from day the diet was initiated, (2) MI: received metformin from the day of tumor injection and (3) control group had no metformin treatment. After 60 days, mice were sacrificed. Tumor nodules were assessed in different organs by gross as well as microscopic examination (H&E stains of tumor sections). Tumor scoring was developed that included number and size of nodules. IGF-1 and insulin levels were estimated by ELISA. Immunohistochemistry was performed of tumor sections for pACC to assess AMPK activation.

Results: Mice on a CRD had significantly smaller tumor burden and ascites volume compared to RD and HED mice ($P<0.001$). The use of metformin in RD and HED mice resulted in a significant reduction in tumor burden in the peritoneum ($P<0.05$), liver ($P<0.05$), kidney ($P<0.0001$), spleen ($P<0.0001$) and bowel ($P<0.05$). The same effect was seen irrespective of time of metformin initiation. Metformin-treatment resulted in activation of AMPK and decreased levels of IGF-1 and insulin in plasma and ascitic fluid, similar to the effects seen with CR alone.

Conclusions: Metformin seems to inhibit ovarian cancer growth irrespective of caloric intake. The use of metformin results in AMPK activation and reduction in blood levels of IGF-1 and insulin similar to the effects of CR. These results provide further evidence to support a potential role for this drug in the treatment of ovarian cancer.

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468 - Poster Session B

Effect of dietary modulation on ovarian cancer progression and metastasis

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Objectives: Calorie restriction (CR) has been shown to delay the growth of various cancer types; no information is available in ovarian cancer. The aim of our study is to investigate the effect of calorie restriction on ovarian cancer progression and metastasis in an isogeneic mouse model of epithelial ovarian cancer.

Methods: C57B6 mice were subjected to three types of diet: regular diet (RD, n=10), high-energy diet (HED, n=10) and calorie-restricted diet (CRD, n=10). Post 30 days of diet, 5x106 ID8 mouse ovarian cancer cells were injected in the intra-peritoneal cavity. After 60 days, mice were sacrificed; tumor nodules morphology and count were assessed in various organs by gross inspection and histologic exam. Growth factors (insulin, leptin, adiponectin, IGF) and cytokines (IL-6, VEGF, MCP-1) were measured using ELISA in blood and ascitic fluid. Immunohistochemistry staining (IHC) for Ki67, p-ACC, p-mTOR, p-Akt was performed.

Results: Compared to RD and CRD, HED fed mice showed the most extensive tumor nodule formation and the highest tumor score (diaphragm, peritoneum, bowel, liver, kidney, spleen) (P<0.01- 0.001). They had higher levels of insulin and leptin (P<0.001) in both ascites and serum compared to RD and CRD. IGF-1 was significantly higher (P<0.0001) in only the ascitic fluid. The cytokines, MCP-1, VEGF and IL-6, were also higher in the serum and ascites of HED mice. On the other hand, CRD fed mice exhibited a notably reduced tumor burden at every examined site compared to RD and HED mice. This was associated with a significant reduction in levels of insulin, IGF-1, leptin, MCP-1, VEGF and IL-6 both in serum and ascites, compared to RD or HED fed mice. IHC showed tumors from CRD mice to have an increased expression of p-ACC and a lower expression of p-mTOR and p-Akt, compared to RD and HED fed mice, indicating activation of the AMPK pathway.

Conclusions: Ovarian cancer growth and metastasis occur more aggressively under high-energy diet conditions, while they are significantly curtailed under calorie restriction. CRD is associated with decreased secretion of growth factors and cytokines and activation of AMPK pathway. Based on these findings, it is worthwhile to investigate the impact of diet modulation as adjunct to other anticancer therapies in the treatment of epithelial ovarian cancer.

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469 - Poster Session B

Metformin use is associated with earlier stage at diagnosis in ovarian cancer patients

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Objectives: Preclinical and clinical studies have shown a role of metformin use in inhibiting tumor progression in different types of cancer. The aim of the study is to evaluate the role of metformin use reported at the time of diagnosis on tumor characteristics and survival.

Methods: A retrospective cohort chart review of women with ovarian cancer at two institutions in Detroit. Inclusion criteria were FIGO stage I-IV epithelial ovarian, fallopian, or peritoneal cancer. Demographic, clinical and outcome data were abstracted for each patient including age, race, histology, FIGO stage, grade, as well as recurrence and survival. Prognostic variables and disease specific survival were compared using Chi-square tests, the Kaplan-Meier (log-rank) method, and Cox proportional hazards analysis.

Results: 220 women with ovarian cancer were included in the study, 120 with no diabetes and no history of metformin use (control), 55 with diabetes and metformin use (DM-Metformin), 45 diabetics with non-metformin treatment (DM non-metformin). Median age at diagnosis was 58 years for control, 59 years for DM-Metformin and 64 years for DM-non-metformin). We divided the patients to early stage (I-II) and advance stage (III-IV). DM-Metformin patients presented with earlier stage disease (55%) compared to control (34%) (p-value 0.008) and DM-non metformin (29%) (p-value 0.009). In Kaplan-Meier analyses, DM-Metformin group had a longer OS and PFS compared to DM non-metformin patients (p-values 0.0217 and 0.0252 respectively). In Cox proportional hazards analyses that included adjustment for demographic and clinical covariates there was a trend for a longer OS and PFS but it did not reach statistical significance.

Conclusions: Metformin use is associated with earlier stage disease at diagnosis compared to DM non-metformin patients and non-diabetic ovarian cancer patients. Although metformin use is associated with longer OS and PFS compared to non-metformin DM and control in univariate analyses, it did not reach statistical significance in the multivariate analyses.

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470 - Poster Session B

Ovarian high grade serous cancer xenografts as pre-clinical models of response to chemotherapy

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Objectives: Primary treatment for high-grade serous cancer (HGSC) patients consists of surgical debulking and platinum/taxol chemotherapy. This uniform approach to treating a highly heterogeneous disease is largely to blame for the virtually unchanged overall survival in the last 30 years. For successful new treatment strategies, pre-clinical in vivo models must be predictive of similar activity in humans. To date, no models of HGSC exist that recapitulate both inter- and intra-patient heterogeneity. HGSC patient-derived xenografts (PDX) could potentially resolve some of these issues, as these tumors have been shown to recapitulate the biological characteristics of the primary tumor. In this study, we tested the ability of a PDX model of HGSC to predict response to standard of care chemotherapeutics and thus examined its utility as a pre-clinical model.

Methods: We have established conditions to generate PDX from fresh tumor and ascites samples. The mammary fat pads of NOD/SCID/Il2rg$^{-/-}$ mice were injected with 10^6 cancer cells from platinum sensitive (n=3), platinum resistant/refractory (n=13) and prospectively identified (n=2) patients. Once tumors were palpable (~200mm^3), mice were treated with carboplatin (75 mg/kg IP q week x 2 doses) or vehicle (saline IP q week x 2 doses). Tumor size was assessed every 72 hours. At the end of treatment, tumor histology was assessed.

Results: PDX derived from sensitive patients showed a 77-90% reduction in tumor volume with platinum therapy. Platinum resistant PDX showed at most a 30% reduction in tumor volume or grew in spite of platinum therapy. Two samples obtained prospectively showed a 60-90% reduction in tumor volume and correspond to platinum sensitive patients. All PDX histology was confirmed to be HGSC.

Conclusions: Our results suggest that PDX recapitulate patient response to chemotherapy. Specifically, the xenografts derived from chemosensitive patients show a nearly complete response to platinum therapy; conversely, xenografts derived from chemoresistant patients show a minimal response. Impressively, we were able to prospectively identify chemosensitive patients. These data suggest that the PDX model allows for accurate identification of platinum sensitivity and resistance and may allow for assessment of the efficacy of novel chemotherapies.

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471 - Poster Session B

Practice intentions: cervical cancer screening among HPV-vaccinated women

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Objectives: The Centers for Disease Control Advisory Committee on Immunization Practices recommends HPV vaccination of all females aged 9 to 26 years. Current recommendations for cervical cancer screening do not vary by HPV vaccination status. The objective of this study is to investigate whether physicians intend to change their screening practices and beliefs based on HPV vaccination status and whether they use criteria to vaccinate.

Methods: A nationally representative sample of 2,101 U.S. physicians who perform cervical cancer screening from the 2007 to 2010 Cervical Cancer Screening Supplement to the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) was used. Data represented approximately 100,000 providers and were stratified by specialty: obstetrician/gynecologist (ob/gyn) vs other specialties (internal medicine, family/general medicine and midlevel providers) and by survey type.

Results: Over 92% of providers did not intend to change their cervical cancer screening practices and management for HPV vaccinated women. The majority believed that HPV vaccination will result in fewer abnormal Papanicolaou (Pap) tests and fewer referrals to colposcopy, with percentages ranging from 58.6% to 66.8% for the different physician and surveys types.

NAMCS office-based ob/gyn's were more likely than other specialties to rarely or never use number of sexual partners to determine who gets the HPV vaccine (66.7% vs 55.1%, $P<0.05$), more likely to recommend the vaccine to females with

history of abnormal Pap result (77.3% vs 62%, *P*<0.05) and to females with a history of HPV positive test result (73.9% vs 56.1, *P*<0.05).

Conclusions: Although the majority of providers believe that HPV vaccination will result in fewer abnormal Pap tests and colposcopies, they do not intend to change cervical cancer screening practices based on vaccination status. Ob/gyn's are more likely to recommend vaccination to females with abnormal test results who may benefit less from it than those with normal results while other specialties are more likely to use number of sexual partners to determine who should receive the vaccine, which is not recommended. Improving physician understanding of the HPV vaccine and appropriate vaccine targeting may lead to more efficient cervical cancer screening and prevention.

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472 - Poster Session B

Treatment of low-risk GTN with biweekly actinomycin-D

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Objectives: Biweekly "pulsed" actinomycin-D (act-D) for the treatment of low-risk gestational trophoblastic neoplasia (GTN) has been shown to be superior to weekly methotrexate in terms of achieving a complete response in a randomized controlled trial (RCT). However, results from RCTs do not always translate into the 'real-world' setting. We endeavored to evaluate the performance of act-D in our institution, and to document the rate of complete response in patients with WHO scores of 5-6 and in those with high pre-treatment bHCG levels.

Methods: All patients with low-risk GTN (WHO score 0-6) requiring chemotherapy and treated at our institution from 2000 to 2012 were identified from the chemotherapy database. Those patients who received first-line act-D, 1.25mg/m2 IV every 14 days were eligible, and cases were reviewed after receiving IRB approval. Demographics, such as age and FIGO score, treatment details, such as number of cycles of chemotherapy required to achieve a bHCG of zero and number of consolidation cycles, and outcomes, such as treatment failure and recurrence were extracted from the electronic medical record.

Results: Forty-four patients were eligible. Mean age of the cohort was 33 years (range 20-49 years) and mean pre-treatment bHCG level was 21,995 mIU/ml (range 12-172,045 mIU/ml). Six patients had a pre-treatment bHCG level of >50,000 mIU/ml. Median WHO score for the cohort was 3 (mean 2.6), and four patients had a WHO score of 5 or 6. The rate of complete response with act-D first-line therapy was 86.4% (38 of 44 patients). Six out of 44 patients (13.6%) experienced a treatment failure and were treated with second-line chemotherapy. The rate of treatment failure in patients with high bHCG levels (1/6, 16.7%) and in patients with WHO scores of 5-6 (0/4, 0%) was not significantly different from the rate in the cohort overall (*P*= 0.99, Fisher's exact test). At a median follow-up of 12 months, 2 of 44 patients (4.5%) experienced a relapse after achieving a bHCG of zero. One of these patients had an initial WHO score of 6 and bHCG of 261 mIU/ml; the other had a WHO score of 4 and bHCG of 21 mIU/ml. All patients were eventually cured.

Conclusions: Act-D performed well in our institution, including in patients with high bHCG level or WHO score of 5-6. Results were comparable to those published in an RCT.

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473 - Poster Session B (withdrawn at author's request)

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474 - Poster Session B

Cervical intraepithelial neoplasia 3+ (CIN3+) is not the right endpoint for evaluating screening algorithms, as it does not reflect cancer risk accurately

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Objectives: To assess the utility of measuring the changes over time in rates of diagnosis of Cervical Intraepithelial Neoplasia 3 (CIN3) and invasive cervical cancer, and the composite of those two measures, CIN3+, in members of a large health maintenance organization (HMO).

Methods: All cases of invasive squamous cervical cancer diagnosed of a large health maintenance organization for 2003-2012 were extracted the Northern California Cancer Registry (NCCN). Numbers of CIN3 diagnosed per year were measured from women from facilities served continuously by the Regional lab over the same time period. Concurrent changes in clinical practice, screening rates, and screening intervals are reported. There was approximately a 10% increase in membership during the study period.

Results:

Procedure Change	YEAR	HEDIS Screening Rates	CIN3	Squamous Cancer
CoTesting at 3 year intervals begins to replace annual cytology	2003		273	45
	2004	80.0	296	40
Optional Colposcopy and biopsy for PAP-HPV+ X2; Display of HPV result to cytotechs initiated	2005	79.0	258	48
Display of HPV result to cytotechs completed	2006	81.0	595	57
Rescreening of all HPV positive NILM slides instead of random QA	2007	82.0	766	62
	2008	85.2	870	62
Mandatory Colposcopy and Biopsy for PAP-HPV+ X2	2009	86.7	968	47
SurePath	2010	85.5	701	43
	2011	86.5	706	36
	2012	86.3	843	45

Results are not meaningfully changed if CIN3 and AIS are considered in place of CIN3 alone, or if squamous and glandular cancers are reported together.

Conclusions: Risk of CIN3+ has been widely used as a surrogate for cervical cancer risk in observational studies driving clinical practice guidelines, including the current national recommendations for management of women with abnormal screening tests. The fact that the detection of CIN3 (which we are not trying to prevent) increases as the detection of cancer (which we are trying to prevent) decreases, means that combining the two for statistical convenience is a potentially misleading compromise. Our experience is instructive: Risk of CIN3+ for our population in 2012 was approximately triple that of 2003, but squamous cancer risk is unchanged. Observational studies of large populations over time will be essential to obtain the risk of cancer as an outcome measure to guide clinical practice.

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475 - Poster Session B

Triage of HPV positive women with low grade squamous epithelial lesion (LSIL) cytology by p16/Ki-67

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Objectives: To investigate the sensitivity of p16/Ki-67 cytology for CIN3+ when used for triage of HPV positive women with LSIL age 30 and older.

Methods: Deidentified residual specimens of SurePath cytology medium were obtained following cotesting of 2400 women members of a large health maintenance organization (HMO) age 30 and older who were Hybrid Capture 2 positive. Cytology slides from the residual material were created, stained for p16/Ki-67, and interpreted at MTM Laboratories/Roche Molecular Diagnostics in Heidelberg, Germany. Slide evaluators had no knowledge of the histologic outcomes determined by HMO pathologists. Results did not influence clinical management. This study was approved by the HMO IRB and judged exempt by the NCI IRB.

Results: Colposcopic biopsy results were available for 451 women age 30+ with HPV positive LSIL. The p16/Ki-67 positivity in this population was 65%. The sensitivity of p16/Ki-67 for CIN3+ was 93% and the risk of CIN3+ among women negative for p16/Ki-67 was 1.2% (1-NPV), a level for which 1 year follow up is recommended in current national guidelines

		Sensitivity	Specificity	PPV	NPV	Referral
	CIN2+	94.03%	40.19%	20.13%	97.67%	
p16-ki67+, LSIL	N=67	(84.65-98.07)	(35.49-45.08)	(15.92-25.09)	(93.77-99.25)	64.54%
	CIN3+	92.86%	37.20%	8.31%	98.84%	
	N=28	(75.04-98.75)	(32.79-41.83)	(5.60-12.08)	(95.42-99.80)	

Conclusions: Sensitivity for CIN3+ of p16/Ki-67 from SurePath medium in women with HPV positive LSIL is sufficient that immediate colposcopy is not required for women who are p16/Ki-67 negative. Compared to current guidelines for LSIL cytology, p16/Ki-67 triage could reduce immediate referral to colposcopy by 35%. Unlike p16 alone, which requires morphologic assessment of p16-positive cells, p16/Ki-67 evaluation is based on staining alone and may be fully automated. Further studies are required to evaluate p16/Ki-67 for triage of HPV-positive women with NILM and ASC-US. If a negative predictive value of similar magnitude is observed for these women, a substantial and welcome decrement in the total number of colposcopies required will be possible without significant loss of sensitivity for the screening program.

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476 - Poster Session B

Development of serum multimarker assay for the differentiation diagnosis of ovarian cancer in patients with ovarian tumor

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Objectives: The objective of this study was to analyze the concentration of serum multivariate markers and find the optimized combination to diagnose ovarian cancer in patients with ovarian tumor.

Methods: We collected serum samples prospectively from patients treated with ovarian tumors. Total 412 samples, including malignant and benign ovarian tumor and normal controls, were analyzed for their ovarian cancer-related 23 proteins, including CA-125, HE4, Prolactin, PDGF-AA and IL8, by Luminex methods, which is a multiplexed immunoassay.

Results: More than half of the biomarkers tested were found to differ significantly between benign and malignant cases. Among them, as individual markers, CA-125 and HE4 provided the discrimination between benign and malignant cases. When the diverse combinations of these biomarkers were made from two to six, the four-biomarker panel provided a highest level of discriminatory power than either marker considered alone. We identified that these four-biomarker panels could discriminate ovarian cancers from benign cases with more than 95% sensitivity (SN) and 95% negative predictive value (NPV) at 75% specificity (SP). Especially, they showed 87% SN and 90% NPV at 75% SP in pre-menopausal women, and 84% SN and 93% NPV at 75% SP in early stage ovarian cancer. These four-biomarker panels showed the improved differentiation diagnosis in early stage cancer and pre-menopausal women comparing to the CA-125 alone.

Conclusions: We describe a blood-based assay using multimarkers that can distinguish women with ovarian cancer from those with benign conditions. Preliminary evaluation of the multimarker panels suggests it has the potential to improve the accuracy to diagnose ovarian cancers. While promising, the performance needs to be assessed in a blinded clinical validation study.

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477 - Poster Session B

Analysis and comparison of somatic mutations between primary and recurrent ovarian carcinomas: a study in serial samples

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Objectives: The objective of this study was to determine the frequency and types of point somatic mutations in epithelial ovarian cancer using a mutation detection protocol called OncoMap that employs mass spectrometric-based genotyping technology.

Methods: The ASAN Center for Cancer Genome Discovery (CCGD) Program, collaborated with the Dana-Farber Cancer Institute (DFCI), has adapted a high-throughput genotyping platform to determine the mutation status of a large panel of known cancer genes. The mutation detection protocol, termed OncoMap, detect a lot of somatic mutations in proven oncogenes in formalin-fixed paraffin-embedded (FFPE) tissue samples. We performed OncoMap v.4 on a set of 92 FFPE samples of epithelial ovarian cancer (EOC) which were matched paired samples of initially diagnosed and recurrent state of 46 patients. We isolated genomic DNA from these samples, and after a quality assurance tests, ran each of these samples on the OncoMap v.4 platform.

Results: In all samples, mutation was observed in 33.7% of samples. Among them, 29.3% of the samples had the single mutation, and the remaining 4.3% had two mutations. Among all 41 genes, 35 mutations have been found in 4 genes. The frequency of mutation is high in CDKN2A (2.2%), KRAS (6.5%), MLH1 (8.2%) and TP53 (20.7%). TP53 showed the most frequent mutations. However, there was no correlation between the presence of mutation in each gene and clinical prognosis. Actually, the number of patients may be insufficient to see the difference of prognosis. Also it is thought to be caused by heterogeneity of cell type and grade. Furthermore, somatic mutations were not different between primary and recurrent ovarian carcinomas. Every mutations presenting in recurrent samples were shown in matched primary samples.

Conclusions: In the OncoMap analysis with Korean samples, somatic mutations were rare comparing with well-known other cancers. The most common somatic mutations were found in CDKN2A, KRAS, MLH1, and TP53. No obvious differences between primary and recurrent samples suggest that the recurrence of EOC should be thought as a serial progress of the pathogenesis of primary cancer.

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478 - Poster Session B

Primary care providers' knowledge of Hereditary Breast and Ovarian Cancer (HBOC) syndrome

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Objectives: To assess basic knowledge of HBOC and application of genetic principles in risk assessment among primary care providers (PCPs) in Georgia

Methods: A 34-question survey was administered to a sample of 1,000 PCPs in Georgia selected randomly from a list of licensed providers. The initial response rate to the survey (both paper-based and online) was 37.8%. The final sample size included 275 providers: 26.9% obstetrician/gynecologists (ob/gyns), 18.5% internal medicine physicians (IM), 32.4% family practice physicians (FP), and 22.2% midlevel providers (ML). Questions included identification of the inheritance pattern of HBOC and recognition of family histories that conferred the greatest risk for a *BRCA* mutation.

Results: While 53.4% of respondents identified autosomal dominant inheritance of *BRCA* mutations, 19% did not recognize paternal inheritance. Of respondents, 39% correctly identified the combined personal and family history that conveyed the greatest risk of HBOC. However, 73.9% failed to recognize that a 1st-degree relative with a known *BRCA* mutation implies the greatest risk for a healthy woman. Only 3.9% of respondents identified a personal/family history of ovarian cancer as a strong predictor of a *BRCA* mutation. In bivariate analysis, ob/gyns demonstrated the greatest knowledge of HBOC inheritance (64.3% ob/gyns, 45.1% FP, 60.8% IM, 45.6% ML, P=0.04). Ob/gyns were also more likely to recognize the cancer histories that conveyed the highest risk for a *BRCA* mutation (54.4% ob/gyns, 37.8% FP, 35.3% IM 25.9% ML, P=0.01). These differences were confirmed in multivariate analyses.

Conclusions: Among PCPs practicing in Georgia, important HBOC knowledge gaps were identified. In general PCPs were more likely to understand the inheritance of *BRCA* mutations, than be able to identify the highest risk individuals and

families. Although ob/gyns demonstrated the most clinically applicable knowledge when compared to other PCPs, important deficits remain. Further educational efforts directed toward PCPs will be critical to ensure patients at greatest risk for HBOC are identified and referred for genetic counseling.

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479 - Poster Session B

Preclinical assessment of donor PBMCs in a humanized mouse model of ovarian cancer

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Objectives: Many unknowns remain in the development of immune strategies against chemoresistant ovarian cancer, including the identification of biomarkers and clinically relevant endpoints for monitoring immune response. Thus, the focus of this study is to track cytotoxic immune cells and overall anti-tumor response using a translationally applicable "humanized" mouse model of ovarian cancer.

Methods: NOD scid gamma (NSG) immunodeficient mice were i.p. injected with 0.5 x 10^6 human SKOV3-AF2 tumor cells, followed by treatment administered by i.p. injection 3-7 days later with healthy donor derived 1 x 10^6 PBMCs and i.p. with 1000U IL-2 three times weekly. Tumor growth was monitored with CA125 ELISA and immune cells were tracked by flow cytometry in serially collected blood. At necropsy, tumor progression and ascites were documented; also, peritoneal wash was collected, as well as blood and bone marrow. Tumor nodules or tissue samples were fixed/paraffin embedded for IHC. Peritoneal washes with PBS were assessed for ex vivo cell cytotoxicity against ovarian tumor cells.

Results: Tumor growth was rapid and diffuse in untreated NSG mice, which typically developed ~2 mL of ascites and succumbed to death in ~3-4 weeks. In contrast, at the same time point there was no detectable tumor or ascites in mice treated i.p. with healthy donor PBMCs + IL-2. Rapid increase in T-lymphocytes and NK cells was observed in peripheral blood at 7 days post PBMC injection and beyond. The greatest number of T cells and NK cells were found in the peritoneal washes of PBMC treated mice, followed by peripheral blood and small numbers in bone marrow. To determine the potential correlation between immune cell cytotoxicity and tumor burden, ongoing experiments include the evaluation of CA125 as a clinically relevant marker to monitor progression-free survival in the PBMC-treated mice.

Conclusions: Collectively, immune cells from healthy donors can be optimized for effective in vivo anti-tumor cytotoxicity to inhibit ovarian tumor growth and improve progression-free survival. Significant translational impact is expected to be derived from understanding the anti-tumor immune response through tracking of immune cell biomarkers, measuring anti-tumor cytotoxicity elicited by lymphocytes and surrogate endpoints of tumor response

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480 - Poster Session B

Forgotten appointments equals missed opportunities: exploring the reasons for low HPV vaccine series completion rates

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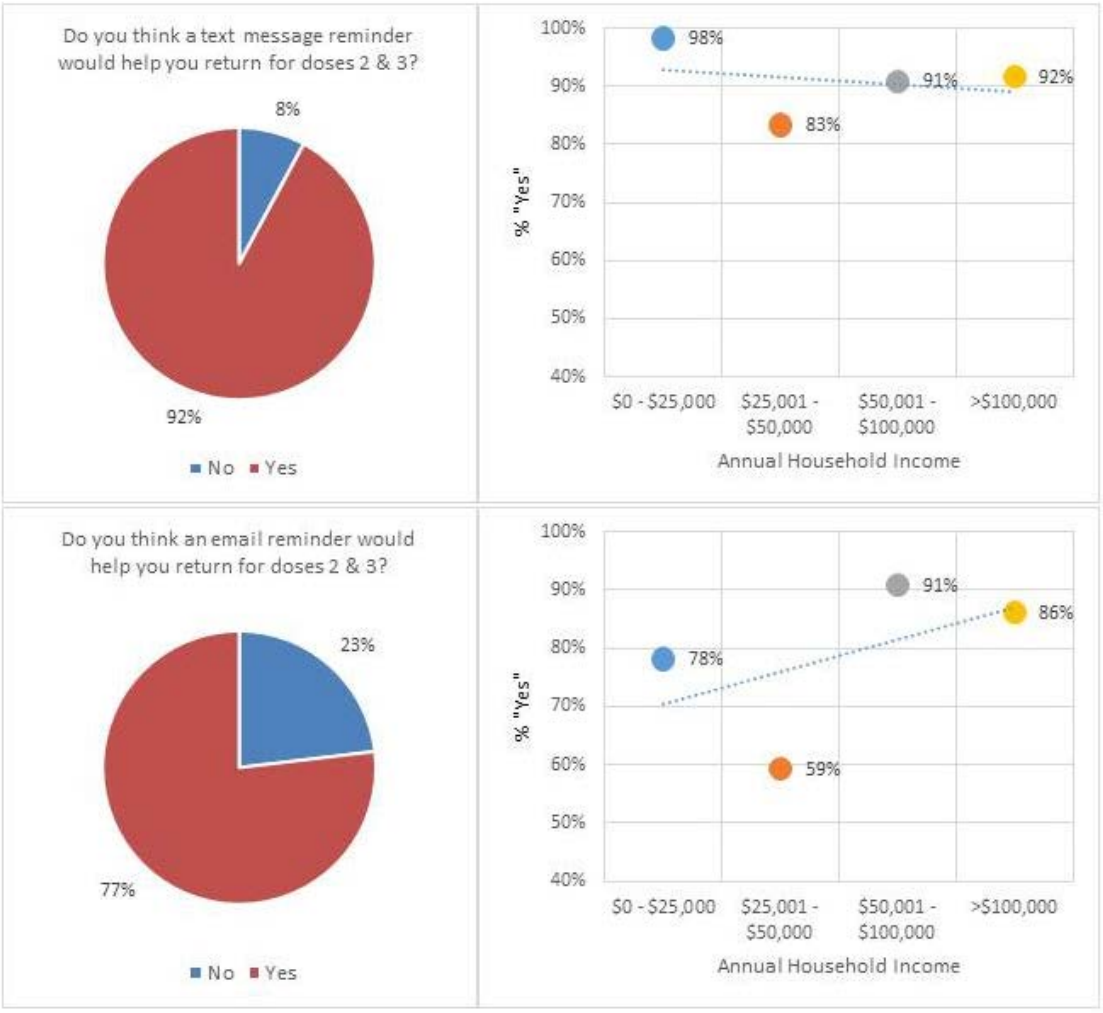
Objectives: HPV vaccine series completion rates continue to lag far below initiation rates. As part of a quality improvement initiative, we aimed to explore the reasons why patients do not complete the 3-dose vaccine series.

Methods: IRB approval was obtained. Surveys in English or Spanish were administered to parents of boys and girls of vaccine-eligible ages at an urban, academic pediatrics practice. Descriptive statistics and Fisher Exact was calculated using VassarStats clinical research calculator.

Results: 193 surveys were returned. Median age of reference child was 14 (range 9-26), with 52% female and 48% male children. The most commonly anticipated reason for failure to complete the vaccine series was forgotten appointments, endorsed by 64% of parents. 92% of parents felt that text message reminders for vaccine doses 2 and 3 would increase their child's chances of completing the series, and 77% felt that email reminders would help. Among those who wanted reminders, there was no difference in desire for text message reminders between parents of low vs high income (93% vs 91%, P=0.75), but low income was associated with a lower desire for email reminders (72% vs 88%, P=0.027) (Figure 1). There was no difference in desire for email reminders between African American vs Caucasian parents (83% vs 73%, P=0.15), but desire for text message reminders was higher among African American parents than Caucasians (100% vs 86%, P=0.005). Only

4% of parents preferred the current standard of phone call reminders. The second most frequent (48%) reported barrier was perceived difficulty taking time out of work/school for vaccine appointments, with half of those patients ranking it as 1 or 2 in importance. 47% of parents felt that extended clinic hours would help them return for completion.

Conclusions: Parents of all racial and socioeconomic groups cited forgotten appointments as the most likely reason for missing doses 2 and 3 of the HPV vaccine series, and there was strong interest in electronic appointment reminders across all groups. We are currently implementing an automated text and email reminder system specific for HPV vaccine visits at our institution in efforts to improve HPV vaccine series completion. Alternative sites or hours for vaccination may also be helpful.



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481 - Poster Session B

Can the need for adjuvant radiotherapy be predicted preoperatively in patients with early-stage cervical cancer?

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Objectives: To determine rate and preoperative predicting factors of postoperative adjuvant radiation therapy after hysterectomy in early-stage cervical carcinoma.

Methods: A retrospective study of 359 stage IA to IIA1 cervical carcinoma patients who had undergone hysterectomy during 2006-2012. Patients' characteristics, histopathologic data and survival data were recorded. Independent factors correlated with postoperative adjuvant radiation therapy were analyzed by descriptive statistics. Regression analysis was used for determination of predicting factors for the need of adjuvant irradiation.

Results: The mean age of studied patients was 49.6 (range 25-78) years old. The most common symptom is check-up, 200 patients (55.7%). The most diagnostic procedure was conization, 190 women (52.9%). The most common histologic type were SCCA (216 women, 60.1%), and adenocarcinoma (101 women, 28.1%). Most women were classified in stage IB1, 235 (65.5%). Hysterectomy was performed in class III of 266 women, class II of 14 women, class I of 71 women, and abandoned in 8 women. 13% of women were surgically treated by laparoscopic approach. Pelvic node metastasis was found in 23 women. Parametrium involvement was found in 14 women. 80 women needed adjuvant radiation because of high-risk factors in 40 women and intermediate-risk-factors in 40 women. 99.4% of patients achieved complete response after treatment. Tumor recurrence was found in 18 women; 10 had local at vaginal stump, 4 had pelvis, 4 had distant recurrence. At the end of follow-up period, 349 women were alive without disease, 10 women were alive with disease. Preoperative tumor grade 3 and FIGO stage ≥ IB1 were significantly correlated with higher rate of the need of postoperative radiation with $P<0.001$.

Conclusions: The rate of the need of adjuvant radiation after hysterectomy in early-stage cervical carcinoma was 22.3% and it can be predicted by grade 3 or FIGO stage ≥ 1B1.

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In vitro and in vivo evaluation of active hexose correlated compound (AHCC) for the eradication of HPV

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Objectives: Evaluate if Active Hexose Correlated Compound (AHCC) will eradicate HPV expression in vitro and in vivocervical cancer models. Define the mechanism of AHCC eradication of HPV infections.

Methods: Cervical cancer cells, SiHa (HPV16/18+) and C-33A (HPV-, were treated with AHCC 0.42mg/mL x 1 dose and incubated for 72 hours with sampling every 24 hours. Study was then repeated with AHCC 0.42mg/mL once daily x 7 days then observed x 7 days. Samples were collected every 24 hours for 14 days. A confirmatory study in cervical cancer orthotopic mouse models, SiHa (HPV+) and C-33A (HPV-), was conducted with 10 mice per arm: AHCC 50 mg/kg/d, vehicle control and no treatment. Tumors were measured 3 times a week and blood samples collected at baseline and bi-weekly until end of the study. After 30 days of treatment, there were 30 days of observation to evaluate the potential recurrence of HPV infections. Tumors were then extracted and PCR was used to evaluate the HPV expression. ELISA assays were performed to evaluate three interferon (IFN) alpha (α), beta (β), and gamma (γ) expression and immunoglobulin G1 (IgG1).

Results: There was in vitro suppression of HPV expression after a single dose at 24 hours, but suppression was not sustained; HPV was detected again at 48 hours. With dosing every 24 hours for 7 days followed by 7 days of no treatment, HPV eradication was achieved. In the in vivo confirmatory animal studies, HPV expression was eradicated with once daily AHCC dosing for 90 days and sustained after 30-day observation. Immune modulation (increase) of IFNα ($P<0.03$), IFNβ ($P<0.03$), and IFNγ ($P<0.03$) and IgG1 ($P<0.05$) was observed in AHCC treated mice compared to untreated controls. In the C33a (HPV-) and SiHa (HPV16/18+) mouse orthotopic models a statistically significant decrease was observed in the rate of tumor growth in the AHCC (50 mg/kg/d) groups compared to untreated ($P<0.001$).

Conclusions: The demonstrated immune modulation is particularly relevant because E6/E7 oncogenic activity in HPV infection is believed to be related to suppression of IFN expression/signaling. These data suggest AHCC will eradicate HPV 16/18 infections attributed to the modulation of the expression and signaling of IFNα/β/γ and may have a role in the prevention of HPV-related cervical cancer. A confirmatory pilot study in HPV+ women is underway.

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483 - Poster Session B

The clinical relevance of a chemo response assay for treatment of epithelial ovarian cancer

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Objectives: In the United States epithelial ovarian cancer (EOC) is the leading cause of mortality from gynecologic cancers. Platinum-based combination chemotherapy is currently the recommended first line chemotherapy for advanced stage cancer in combination with a Taxane agent. However, it is estimated that ~20% of patients are platinum resistant and 30% are

partially sensitive, which is associated with a worse progression-free survival and overall survival. In this study we analyzed the sensitivity and specificity of the Precision Therapeutics ChemoFx response assay in predicting platinum sensitivity.

Methods: This was a retrospective, single institution observational study of predictive chemosensitivity assays using the Precision Therapeutic ChemoFx assay. We identified 37 patients who were diagnosed with EOC between January 1, 2008 and July 31, 2012. Chemotherapy response was determined by CA 125 levels, and/or CT imaging. Sensitivity and specificity of the Precision Therapeutics ChemoFx sensitivity test was determined. Pearson Chi square test was performed to determine test of independence for the two variables

Results: For the 37 patients analyzed, serous carcinoma accounted for 73%, mucinous adenocarcinoma 8.1%, carcinosarcoma 10.8%, clear cell, endometrioid and mixed endometrioid/clear cell 2.7% each. The majority of patients were diagnosed with stage III (46%) and Stage IV (24.3%). The majority (78.4%) were initially treated with carboplatin and paclitaxel x 6 cycles. Our actual results to front line chemotherapy with a platinum and taxane agent showed that 66.7% were clinically platinum sensitive (CPS), 21.2% were platinum resistant, and 12.1% were platinum refractory. However, the ChemoFx chemosensitivity assay showed 36.4% to be platinum responsive, 33.3% platinum intermediate responsive, and 30.3% to be platinum non-responsive. Therefore, the correlation between our Clinical Platinum Sensitive (CPS) group and the Predicted platinum sensitive (PPS) group using the ChemoFx assay was 66.7% (P=1.178), while 80% of the Non-Response group in the ChemoFx assay were found to actually be platinum sensitive to a first line platinum and taxane agent.

Conclusions: The Precision Therapeutics ChemoFx assay results did not correlate with actual chemotherapy response rate within our patient group.

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484 - Poster Session B

Disparity of cervical cancer care delivery in low-middle income countries

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Objectives: To compare the cervical cancer treatment programs in three low-resource settings: Honduras, Paraguay, and Vietnam and to learn the key successes, limitations and lessons learned from these country experiences.

Methods: We performed an analysis of the cervical cancer treatment programs in three low-middle income countries: Honduras, Paraguay, and Central Vietnam in 2013. The populations, cervical cancer incidence, health care providers, pathology support, and availability of chemotherapy and radiation therapy were evaluated. Standard statistical methods for analysis of the data were used.

Results: The three primary public cancer centers in Honduras, Paraguay, and Central Vietnam serve 8.3 million, 6.6 million, and 1 million populations, respectively. The age standardized incidence and mortality were 37.8 and 19.7 cases per 100,000 women in Honduras, 35 and 16.6 cases per 100,000 women in Paraguay, and lower rates of 11.4 cases and 5.7 cases per 100,000 women in Central Vietnam (P<0.01). In each of the three regions, only one public cancer hospital is available to serve the entire region. In Honduras, cancer hospital has 12 surgical/medical/radiation oncologists; the cancer hospital in Paraguay and Central Vietnam has 20 and 40 full-time oncologists. Nine, 25, and 40 trainees are being trained respectively in Honduras, Paraguay, and Central Vietnam. Frozen section is not available in Honduras and the average time for the final pathology to be signed out is >4 weeks. Pathology supports in Paraguay and Vietnam are similar to that in the United States. Basic chemotherapy drugs are limited in Honduras. In Honduras, radiation oncology department has only one Cobalt machine and does not have brachytherapy. Chemotherapy and some targeted therapies are available in both Paraguay and Central Vietnam. The GDP per capita is $2,264, $6,100, and $3,500 for Honduras, Paraguay, and Vietnam, respectively, with Honduras spending the least per capita on health care. Economy and the lack of governmental support in cancer care contributed to the disparity in cervical cancer care delivery in low-resource settings.

Conclusions: There is a disparity in cervical cancer delivery among low-middle income countries. Improved economy and dedication to cancer care is needed to improve the outcome of cervical cancer treatments.

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Type I interferons modulate methotrexate resistance in gestational trophoblastic neoplasia

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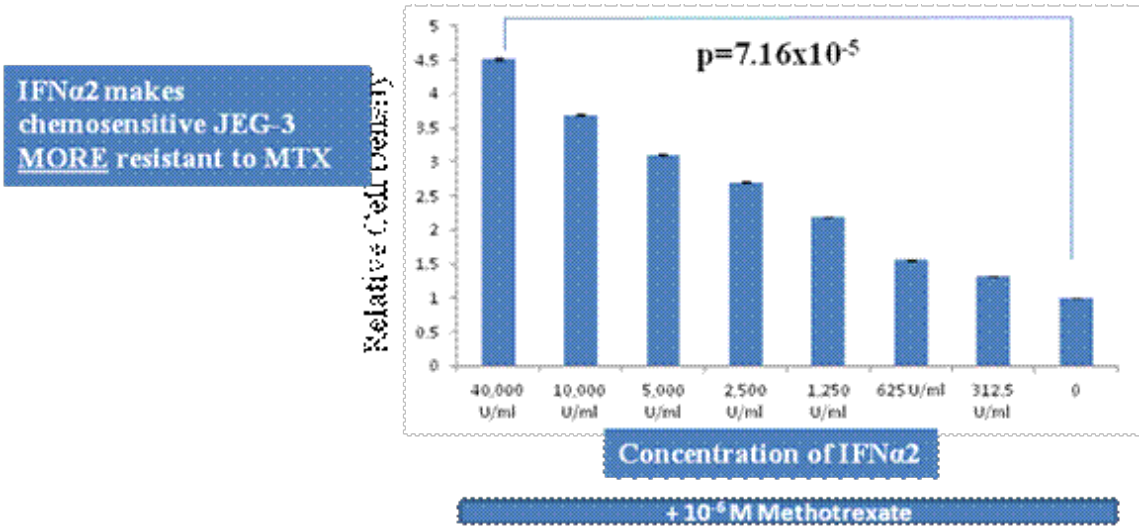
Objectives: To explore a role for Type I interferons in an in vitro model of methotrexate resistant gestational trophoblastic neoplasia.

Methods: An in vitro model for methotrexate resistant gestational trophoblastic neoplasia neoplasia was created using serial passage of an immortalized normal placenta cell line and the choriocarcinoma cell line JEG-3 in increasingly higher concentrations of methotrexate. Differentially expressed genes between the sensitive and resistant cell lines were compared using Affymetrix 2.0 plus arrays and validated using qRT-PCR and Western blot. Pathway modeling revealed a possible role for Type I interferon signaling in methotrexate resistance. A functional role for Type I interferons in methotrexate resistance was assessed using cell proliferation assays.

Results: Gene expression profiling identified the interferon response genes IFI27 and OAS1 as the most highly overexpressed genes in methotrexate resistant compared to methotrexate sensitive cell lines. Additional analysis identified upregulation of 10 additional interferon response genes. Pathway modeling linked all these targets to Type I interferon signaling. By real time PCR, methotrexate resistant cell lines upregulated Type I interferon expression, with a significantly greater upregulation in IFNA2 compared to IFNB1. Using recombinant cytokines, exogenous interferon alpha 2 had the ability to partially reverse methotrexate sensitivity, whereas exogenous interferon beta 1 had the ability to partially reverse methotrexate resistance. Anti-interferon alpha antibody also had the ability to partially reverse methotrexate resistance.

Conclusions: Type I interferons induce opposing effects on neoplastic trophoblast growth. Interferon alpha 2 increases cell proliferation, whereas interferon beta 1 decreases cell proliferation. Methotrexate resistant trophoblasts appear to have the ability to control the ratio of Type I interferons in such a way as to encourage proliferation. Type I interferons or their downstream mediators may be useful targets for predicting or treating methotrexate resistant gestational trophoblastic neoplasia.



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486 - Poster Session B

Comparative costs of first-line chemotherapy for gestational trophoblastic neoplasia: a second look

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Objectives: Several single-agent therapies have been used for treatment of low-risk gestational trophoblastic neoplasia (LR GTN), with generally similar overall effectiveness. We estimated the relative costs of two commonly prescribed agents, pulsed actinomycin-D (ActD) and weekly methotrexate (MTX).

Methods: Using a Markov state transition model, we estimated costs and outcomes of Pulsed ActD and MTX. Probability estimates for failure, toxicity, need for additional treatments, and number of treatment cycles were derived from Gynecologic Oncology Group (GOG) 174. Costs for drugs, toxicity, potential wage losses, laboratory tests, and inpatients and outpatient

fees were obtained from 2012 CMS Medicare rates and the literature. The model was run as a stochastic microsimulation: 10,000 “patients” were run through the model 5,000 times, with the value for each parameter drawn from probability distributions during each run. We assumed all patients ultimately achieved a complete response (CR).

Results: Despite a significantly higher CR probability with initial therapy with ActD (71%) compared to MTX (53%), estimated mean costs of MTX were significantly less: $6,113 (95% CI $4,533-8,376) vs $26,046 (95% CI $23,266-29,894). The higher cost of ACT was attributable to higher drug costs, and higher incidences of nausea (24%, 95% CI 10-33% vs 10%, 95% CI 2-18%) and neutropenia (20%, 95% CI 8-28% vs 12%, 95% CI 5-18%). Mean number of treatment cycles were significantly lower with ActD (8.72, 95% CI 8.19-9.01) compared with MTX (9.58, 95% CI 9.01-10.03), but total mean time to CR was higher (16.36 weeks, 95% CI 15.4-16.9, vs 10.48 weeks, 95% CI 9.58-11.03).

Conclusions: Although ActD for initial therapy of LR GTN results in fewer cycles needed for CR, side effects, total time to CR, and costs are substantially higher compared to initial MTX. More data on patient preferences for relevant outcomes of GTN therapy are needed to estimate the relative cost-effectiveness of these two regimens.

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487 - Poster Session B

Risk factors for recurrent high grade vaginal intraepithelial neoplasia and progression to carcinoma

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Objectives: High grade vaginal intraepithelial neoplasia (VAIN) II-III has a variable clinical course, and due to its relative rarity, data on the efficacy of treatment and risk of recurrence and progression to carcinoma is limited. Our objective was to evaluate predictors of persistence of disease and describe the risk of progression to carcinoma in a cohort of women with high grade VAIN.

Methods: Under an IRB-approved protocol we retrospectively identified 44 patients with biopsy proven VAIN II-III from 1995 to 2013; 11 patients with VAIN II and 33 patients with VAIN III were identified who had adequate follow-up. Demographics, treatment, and clinical course were documented. Patients were followed with regular semi-annual colposcopy and biopsies at the discretion of the attending gynecologic oncology physician. Standard statistical analyses were applied.

Results: Median age of the cohort is 59 years old (range 20 – 86). Median follow up is 39 months. 34 patients (75%) had a prior diagnosis of cervical intraepithelial neoplasia (CIN), 16 patients (36%) had a prior hysterectomy due to early stage cervical cancer (n=5) or CIN III (n=11). 13 patients (30%) had a prior hysterectomy for benign indications. 4 patients (36%) with VAIN II and 14 patients (42%) with VAIN III recurred over treatment follow-up. Primary treatment with topical therapy, CO2 laser, and surgical excision, had similar rates of recurrence 50%, 40%, and 27% respectively. There were no statistically significant risk factors associated with recurrence. 4 patients (9%) progressed to invasive vaginal or vulvar cancer while 2 patients (5%) developed ano-rectal cancer during surveillance. Median time to progression to cancer was 64 months (range 30 to 101). There was no difference in median age at time of initial dysplasia diagnosis between those who progressed to malignancy and the remainder of patients.

Conclusions: In this small cohort, patients with high grade VAIN had a high risk of recurrence irrespective of type of treatment. There were no clear predictors of recurrence based on traditional risk factors for lower genital tract dysplasia or histopathologic criteria. VAIN can progress to invasive cancer of the lower genital tract, suggesting the need for ongoing evaluation with cytology and comprehensive colposcopy by a skilled specialist.

	Recurred	No Recurrence
Median Age	58 years old	59 years old
Smokers	83% (n=15)	76% (n=19)
HPV	7% (n=1)	9% (n=2)
Hx CIN	60% (n=6)	48% (n=10)
Multifocal lesion	6% (n=1)	8% (n=2)

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488 - Poster Session B

Patient, tumor, and health system factors affecting groin node dissection rates in vulvar carcinoma: results from a population-based analysis

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Objectives: To determine the rate of groin node dissection for vulvar carcinoma in a population-based cohort, and the patient, tumor, or health system factors associated with having this procedure.

Methods: This retrospective population-based cohort includes all cases of invasive squamous cell carcinoma identified in the provincial cancer registry from 1998-2007. Data collection was completed for all clinical and pathologic factors by chart abstraction. Analysis was descriptive and included Chi-squared analysis for proportions.

Results: Clinical and pathologic data were collected for 1109 patients. After removing those with fixed/inoperable groin nodes or microinvasive disease, 942 patients who were eligible for groin node dissection (GND) were included in this preliminary analysis. 654 patients (69.4%) had a GND as part of their primary management, while 288 patients (30.6%) did not. Upon exploration of the reasons for no GND, 53% had a reason provided in the chart, including age, obesity, advanced disease, or comorbidities. 25% of these patients refused GND. 47% of those without GND did not provide a reason as to why this was omitted. When comparing those who had GND (n=654) to those without GND (n=288), significant differences included age (65 years vs 72 years, $P<0.001$), comorbidities (3.8% vs 11.5%, $P<0.001$), advanced disease (28.1% vs 36.5%, $P=0.01$), and surgeon at the time of vulvar resection (among those with GND, 4.8% had their vulva resection by a non-gyn oncologist, vs those without GND, 22% had their vulva resection by a non-gyn oncologist, $P<0.001$).

Conclusions: This population-based cohort demonstrates 30.6% of invasive vulvar cancer patients did not have a GND as part of their primary management. Adequate knowledge and treatment of the groin nodes is critical to outcomes in vulvar carcinoma. Vulvar cancer patients should be carefully evaluated by clinicians with expertise in this rare disease to ensure GND is completed when feasible. Rate of GND is higher for patients who had a gynecologic oncologist involved in removal of the vulvar tumor.

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489 - Poster Session B

Frequency of missing data from vulvar carcinoma pathology reports: results from a population-based cohort

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Objectives: Pathology factors are critical for optimal decision-making in vulvar carcinoma. The objective of this study is to describe the completeness of pathology reporting for vulva cancer using a contemporary, population-based cohort.

Methods: This retrospective population-based cohort included all cases of invasive squamous cell carcinoma of the vulva identified in the provincial cancer registry from 1998-2007. Vulvar resections with specimen size >1.5 cm were included in this analysis. The pathology reports were abstracted for tumor size, grade, lymphovascular invasion (LVSI), depth of invasion, tumor thickness, peripheral and deep margins. Reports were considered complete if all of these factors were included. Additional variables included institution and type of pathologist (general vs gyn pathologist). Analysis was descriptive, and included Chi-squared analysis for proportions, and Cochran Armitage test for trends.

Results: The cohort included 1109 patients, with 1830 vulva specimen reports. After removing 819 specimens <1.5 cm in size, there were 1101 vulva resection specimens included in this preliminary analysis. Overall, 15% of reports over the 10-year period were considered complete. Completeness of reports improved over time, but to a peak value of only 25% ($P<0.0001$). In 2002, the rate of complete reports increased significantly ($P<0.0001$), largely due to one high-volume centre that developed a pathology checklist for reporting. Over the time period of the cohort, reporting of individual variables improved; reporting of depth of invasion increased from 30% to 80% ($P<0.0001$), LVSI improved from 70% to 82% ($P=0.0035$), and size improved from 68% to 85% ($P<0.0001$). Reporting of these variables was significantly higher by gyn pathologists vs general pathologists ($P<0.0001$).

Conclusions: Among this cohort, the rate of complete pathology reports was overall low (15%), with missing data important for clinical decision-making. Completeness of pathology reports improved significantly with a pathology checklist, highlighting the importance of synoptic reporting. Optimal reporting of tumor variables is critical for management of this rare tumor.

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490 - Poster Session B

The impact of concurrent chemoradiation on survival compared to adjuvant radiation therapy alone in patients with node-positive vulvar cancer

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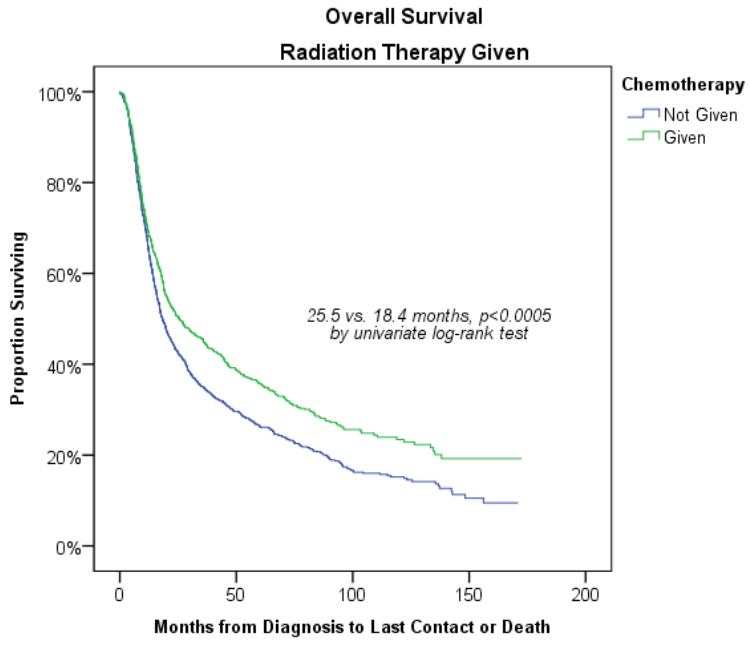
Objectives: Standard therapy for vulvar cancer with ≥2 positive inguinofemoral lymph nodes (LN) is adjuvant radiation therapy (RT). Concurrent chemoradiation (CCRT) demonstrated survival benefit over RT alone in cervical cancer, which led some to implement this treatment strategy in vulvar cancer patients with nodal involvement. Using the National Cancer Database (NCDB), we examined the impact of RT versus CCRT on overall survival (OS) in patients with vulvar cancer and ≥2 positive inguinofemoral LN.

Methods: Through the NCDB, we identified patients with FIGO stage IIIB-IVA vulvar cancer diagnosed from 1/1998 to 12/2011 who underwent unilateral or bilateral inguinofemoral lymphadenectomy (≥6 LN per side) and had ≥2 positive LN. Demographic, clinicopathologic, treatment and outcome data were collected. OS was determined using the Kaplan-Meier method. Univariate and multivariable analyses were used done to determine variables affecting survival.

Results: A total of 2,601 patients met inclusion criteria, of which, 800 (30.8%) patients received no adjuvant RT. Of the 1,801(69.2%) patients that received adjuvant RT, 762 (40.3%) were treated with concurrent chemotherapy. The OS for RT alone and CCRT were, 18.4 and 25.5 months, respectively (P<0.01). On multivariable analysis, increasing age [OR 1.04(1.03,1.05)], multiple comorbidities [OR 1.37(1.2,1.56)] and higher stage [OR 1.37(1.17,1.59) were independently predictive of worse survival; while adjuvant RT [OR 0.71(0.59,0.86)] was predictive of improved survival. Grade [OR 1.07(0.95,1.21)], tumor size [OR 1.02(1.00,1.04)], and CCRT [OR 1.03(0.85,1.26)] were not independent predictors of survival.

Conclusions: This study confirms the findings of Gynecologic Oncology Group 37 which documented survival benefit for adjuvant RT in vulvar cancer with ≥2 positive LNs. The use of CCRT resulted in a 7-month improvement in OS over RT alone on univariate analysis, but this benefit did not remain statistically significant on multivariable analysis. This study failed to show any additional benefit of CCRT for node-positive vulvar cancer, suggesting that unlike other gynecologic malignancies, RT alone may be sufficient for treatment of vulvar nodal metastases. Further prospective study is needed to clarify this important clinical question.



491 - Poster Session B

Outpatient laparoscopic radical hysterectomy

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Objectives: The goal of our study is to report on the first series of ambulatory laparoscopic radical hysterectomy in patients with early-stage cervical cancer.

Methods: We performed a retrospective review of all patients who underwent an outpatient laparoscopic radical hysterectomy at the Instituto de Cancerología — Las Americas in Medellin, Colombia, between January and September 2013. Inclusion criteria were: age <60 years old, informed consent, residence <1-hour distance from medical center, available caregiver at home during initial 48 hours, ECOG 0 and ASA 1, BMI <30.

Results: A total of 8 patients were included and all had stage IB1. The median age was 38 years (31-53) and the median body mass index was 24.1 (19.1-30). Histology was adenocarcinoma in 6 patients (75%) and squamous cell carcinoma in 2 patients (25%). No lymph node mapping was performed. The median operative time was 138 min (120–160) and the median estimated blood loss was 40 ml (30-150). No intraoperative or postoperative transfusions were given. There were no intraoperative or postoperative complications. All patients underwent a transversus abdominis plane block and 5 patients (62.5%) reported 0/10, two patients (25%) reported 1/10 and 1 patient (12.5%) reported 2/10 in the pain evaluation scale at discharge. All patients were able to void spontaneously and tolerate oral intake before discharge. There were no readmissions postoperatively either to our hospital or to their local hospitals. The median nodal count was 14 (8–30). All patients had negative margins and no parametrial involvement. One patient (12.5%) had positive lymph node. The median follow up was 2 months (0.3-7). Three patients (37.5%) underwent adjuvant chemoradiation.

Conclusions: Outpatient laparoscopic radical hysterectomy is feasible and can be performed safely in a developing country in well-selected patients.

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492 - Poster Session B

A randomized controlled trial of a proficiency-based, virtual-reality robotic simulation curriculum to teach robotic suturing

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Objectives: To determine if a proficiency-based, virtual-reality robotic suturing curriculum improves robotic suturing skill.

Methods: Residents and attending surgeons were randomized between two training methods over 5 weeks: 1) intervention with a proficiency-based robotic suturing curriculum using da Vinci® Skills Simulator in addition to usual clinical duties or 2) usual clinical duties alone. Curriculum included 6 tasks: Suture Sponge 1, 2, 3, Camera targeting 1, 2, and Horizontal Suturing Defect (HSD). Participants set their own training hours during 5 weeks with the goal of achieving two successes with the first 5 tasks and performing the HSD 10 times. Robotic suturing skill was evaluated before and after the training period using an inanimate vaginal cuff model which participants sutured using the da Vinci® Surgical System. Performances were videotaped using the robotic camera. Videos were graded independently by 3 robotic surgeons, blinded to participant identity, pre- or post-test status, and group, using a “GOALS+ score” consisting of the GOALS score for laparoscopy plus two metrics for robotics: precision and instrument/camera awareness. Participants also completed a survey to establish previous surgical experience and evaluate the training curriculum.

Results: None of the 27 randomized participants had prior experience as the primary console surgeon for an entire robotic surgery. 23 of the 27 completed both the pre- and post-test, including 6 attending surgeons and 17 residents. The average robotic simulator training time over the 5 weeks was 243 minutes for the 13 participants in the intervention group and 284 minutes for the subset of 5 participants who achieved all the training goals of the proficiency curriculum. The primary

outcome of the study, improvement in the GOALS+ score was significantly greater in the intervention group than in the control group (Wilcoxon rank sum test, *P*=0.036; independent samples t-test, *P*= 0.028).

Conclusions: Among trainees and surgeons with limited prior robotic surgery experience, participation in a proficiency-based, virtual-reality robotic surgery simulation curriculum results in significant improvement in ability to robotically suture an inanimate model of the vaginal cuff.

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493 - Poster Session B

Does removal of a positive sentinel node without lymphadenectomy impact pelvic sidewall control in endometrial cancer?

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Objectives: The aim of this study was to evaluate pelvic sidewall (PSW) control in endometrial cancer following removal of a positive pelvic sentinel lymph node (SLN) compared to SLN with pelvic lymph node dissection (SLN+LND).

Methods: All cases that underwent SLN mapping were identified. Only cases with a positive pelvic SLN were included in the current analyses. Tumor outside the uterus (adnexa, peritoneum) or positive paraaortic lymph nodes were exclusion criteria. PSW control was defined as absence of nodal recurrence in the iliac/obturator regions. Appropriate statistical tests were used.

Results: Forty-four cases with a positive pelvic SLN were identified. Among these 44 cases, a positive SLN was noted in 51 hemi-pelvises. A median of 1 SLN was removed (range, 1-8). In 25/51 (49%) hemi-pelvises with a positive SLN, a concurrent lymph node dissection was performed, with a median of 4 additional nodes removed (range, 1-21). The SLN and SLN+LND groups did not differ in pathological risk factors, adjuvant chemotherapy (85% [22/26] vs 84% [21/25], *P*=1.0), or median follow-up (26.5 vs 32.0 months, *P*=0.1). Adjuvant pelvic radiation (IVRT, WPRT, combined) was used less in the SLN group (18/26 [69%]) vsSLN+LND group (21/25 [84%], *P*=0.3). A pelvic recurrence developed in 2 of 26 (7.7%) SLN-only cases. A patient with carcinosarcoma developed a parametrial recurrence concurrent with lung metastases 24 months after diagnosis. Another patient with endometrioid cancer had a presacral recurrence 16 months after diagnosis. Both had received 6 cycles of carboplatin/paclitaxel and IVRT. There were no actual PSW recurrences in the typical nodal basins in any of the 51 hemi-pelvises with positive SLNs. The 2-year overall pelvic recurrence-free survival was 95% in the SLN vs 100% in the SLN+LND group (*P*=0.2).

Conclusions: Our preliminary findings suggest that removal of a positive SLN with adjuvant therapy does not adversely impact the risk of PSW recurrence. SLN and SLN+LND did not significantly differ with respect to pelvic recurrences. These data question the need for a full LND in cases with positive SLNs. Long-term follow-up and validation of these results are needed.

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494 - Poster Session B (withdrawn at author's request)

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495 - Poster Session B

Extraperitoneal para-aortic lymphadenectomy by robot-assisted laparoscopy in gynecologic oncology: the learning curve

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Objectives: We are reporting the preliminary experience of 2 cancer centers in extraperitoneal paraaortic lymphadenectomy by robot-assisted laparoscopy in gynecologic oncology.

Methods: Two teams from the cancer centers performed robot-assisted extraperitoneal paraaortic lymphadenectomy in 33 patients with gynecologic cancer. We divided the trial into 2 phases: the first 14 patients and subsequent patients.

Results: There were 14 patients in the first phase (cervical cancer only) and 19 in the second (16 cervical cancers, 2 endometrial cancers and 1 adnexal cancer). The skin-to-skin operative time, mean lymph node count and estimated blood loss were 215 min (+/-49.6), 14.1 (+/-5.4) and 81 ml (+/-84.1) respectively in the first phase vs 216.5 min (+/-66.6), 21.7 (+/-11.7) (*P*=0.02) and 131.8 ml (+/-163.2) in the second.
There was no conversion to laparotomy, one laparoscopic conversion for hemorrhage lateral to the inferior mesenteric artery and 1 use of hemostatic matrix for an injury to the left gonadal artery (2 non-transfused patients). 1 patient had lateral aortic hematoma not requiring a transfusion or return to the operating room. 33.3% of patients reported postoperative complications (11/33): 7 lymphocysts (0 in the first phase vs 7 in the second), 3 leg dysesthesia (left genitofemoral nerve) (1 in the first phase vs 2 in the second) and 1 leg lymphedema in the second phase.

Conclusions: Robot-assisted extraperitoneal paraaortic lymphadenectomy is feasible and efficient following a learning curve of 14 patients.

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496 - Poster Session B

Ultrasound-guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine for patients undergoing robotic-assisted hysterectomy: a retrospective cohort study

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Objectives: Robotic-assisted hysterectomy has been associated with decreased length of stay and decreased pain when compared to open surgery. However, patients who undergo robot-assisted procedures still experience postoperative pain. Recent studies have shown transversus abdominis plane or TAP blocks to be an effective method of pain control in open and laparoscopic hysterectomy but none has evaluated its use in robot-assisted hysterectomy patients. The purpose of this study is to determine the effect of a TAP block with liposomal bupivacaine on maximum pain scores in patients undergoing robotic assisted total hysterectomy.

Methods: 60 patients who underwent robotic-assisted total hysterectomy were retrospectively evaluated up to 24 hours post-injection. The patients were all ASA I-III. Median age was 59 (27-80). The cohort consisted of 30 patients who did not receive a TAP block (7/2012-9/2012) and 30 patients who received preoperative bilateral subcostal TAP blocks (11/2012-5/2013). Pain intensity was assessed by nursing staff via an 11-point VAS scale. Narcotic use was normalized to micrograms of fentanyl. Statistics were performed using GraphPad Prism v 6.0b.

Results: There was no difference between the 2 groups in age and ASA status. However, there was a significant difference between the 2 groups in weight (83 ± 25 kg vs 99 ± 31 kg *P*=0.03) and length of surgery (219 ± 46 minutes vs 251 ± 67 minutes *P*=0.03). Those patients who received a TAP block had decreased maximal pain scores over the first 24 hours post injection compared to those who did not (4.8 ± 2.7 vs 6.4 ± 2.2 *P*=0.02). Those with TAP block also had decreased narcotic use (124 ± 103 mcg vs 182 ± 113 mcg *P*= 0.04). 4 patients in the TAP group were opioid free after 24 hours. None in the control group was opioid free. 6 patients in the TAP group experienced postoperative nausea versus 16 in the control group *P*=0.04. There was a significant decrease in length of stay in those who received a TAP block compared to those who did not (11.5 ± 8.8 hours vs 34.3 ± 38 hours; *P*=0.02).

Conclusions: Preoperative placement of a subcostal TAP block with liposomal bupivacaine may decrease maximal pain scores, narcotic use, length of stay, and postoperative nausea in those patients undergoing a robotic assisted total hysterectomy.

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497 - Poster Session B

Postoperative pain scores and narcotic use in robotic-assisted versus laparoscopic hysterectomy for endometrial cancer

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Objectives: Uncertainty exists regarding the impact of the type of minimally invasive approach to hysterectomy on the perioperative outcomes of women with endometrial cancer (EC). We sought to compare pain scores and narcotic use in the first 24 hours following surgery in women who underwent laparoscopic (LS) versus robotic-assisted laparoscopic (RA) hysterectomy for EC.

Methods: A retrospective review was performed in consecutive patients who underwent LS or RA hysterectomy at a single institution between January 2008 and May 2012. Perioperative outcomes and analgesic use were compared. Conversions to laparotomy were excluded. Univariate and multivariate linear regression modeling evaluated predictors of opioid consumption in the post-anesthesia care unit (PACU).

Results: 335 consecutive cases (213 LS; 122 RA) were analyzed. Age, BMI, prior abdominal surgery, preoperative narcotic and anxiolytic use, tobacco use, menopausal status, mean number of lymph nodes removed, and specific comorbidities (hypertension, diabetes, cardiovascular disease) were not significantly different between surgical groups. Cases converted to open were excluded. Median duration of surgery was significantly longer (224 vs 184 min, $P<0.0001$) and median estimated blood loss was significantly lower (50 vs 75 ml, $P=0.03$) in the RA group. Median time to achieve PACU discharge eligibility was slightly shorter in the RA group (91 vs 99 min, $P=0.02$). Median pain scores at 6 and 12 hours were not significantly different between groups. Median IV narcotic use in PACU was 1.7 mg morphine equivalents for RA compared to 3.3 mg morphine equivalents for LS ($P<0.0001$); total 24 hr postoperative narcotic use was 5.8 mg versus 6.7 mg, respectively (P=ns). In univariate analysis, a LS approach ($P=0.005$), premenopausal status ($P=0.02$), and shorter surgical duration ($P=0.046$) were associated with higher PACU IV narcotic requirement. In multivariate analysis, LS approach ($P=0.007$) and menopausal status ($P=0.03$) were associated with higher IV narcotic requirement in PACU.

Conclusions: In this single-institution experience, despite longer surgical duration, robotic-assisted hysterectomy for endometrial cancer was associated with lower use of IV narcotics in PACU and slightly shorter PACU stays compared to laparoscopic procedures.

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498 - Poster Session B

Does minimally invasive surgery compromise the oncologic outcome of women with high-risk non-endometrioid endometrial carcinomas

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Objectives: To assess outcome in patients with high-risk non-endometrioid endometrial carcinomas undergoing minimally invasive surgical (MIS) approaches compared to laparotomy (LAP).

Methods: We identified all women with endometrial cancer surgically staged at our institution from January 2000 to December 2012. Only patients with serous, clear cell carcinosarcoma and undifferentiated carcinomas were included in our analysis. MIS included laparoscopy with or without robotic assistance not requiring conversion to laparotomy. Cases converted to laparotomy were included in the LAP cohort. Patients were excluded if they received neoadjuvant therapy, had a portion of surgery performed at an outside facility, or had another primary synchronous carcinoma. Appropriate statistical tests were performed.

Results: 607 (24%) patients met our inclusion criteria. The LAP cohort had more cases with advanced-stage disease and, therefore, we limited our current analyses to cases with stage I disease only. 388/607 (64%) cases were stage I. The median age, BMI, and ASA scores were not statistically different. Histologic subtypes were similarly distributed between the MIS and LAP cases ($P=0.5$). Adjuvant therapy of some form was given in 89% of cases in both groups ($P=1.0$). Chemotherapy +/- radiotherapy was used in 140/199 (70%) LAP compared to 122/157 (78%) MIS cases ($P=0.1$). The median follow-up was 39.6 months (range, 1-156 months) for LAP compared to 25.1 months (range, 0-146 months) for MIS ($P<0.001$); therefore, a 2-year disease-specific survival (DSS) was assessed. The 2-yr DSS for LAP was 81.7% (SE 2.9%) compared to 89.6% (SE 2.8%) for MIS ($P=0.04$).

Conclusions: MIS approaches seem to be safe and do not compromise survival in patients with stage I high-risk non-endometrioid endometrial carcinomas. Continued follow-up and assessment of outcome is needed.

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499 - Poster Session B

Hemostatic gelatin-thrombin matrix is associated with pelvic abscesses in patients undergoing surgery for gynecologic cancer

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Objectives: Hemorrhage and pelvic infection continue to be common complications of surgery for gynecologic cancer. The use of gelatin-thrombin matrix to avert bleeding has increased substantially. We sought to assess the association of the use of these products and the development of pelvic abscesses.

Methods: Data for all patients undergoing hysterectomy for gynecologic cancer and benign disease were abstracted from databases at a tertiary hospital. Open and minimally invasive hysterectomies were examined and vaginal hysterectomies were excluded. Blood loss, surgery type, comorbidities, abscess formation and use of thrombin sealants were examined. An abscess was defined as a walled-off fluid collection in the pelvis (as seen on CT scan) associated with fever (>38° C) and leukocytosis (>11,000/μL). Standard statistical models were employed.

Results: Of the 413 patients identified, 202 (49%) underwent surgery for malignancy. Gelatin-thrombin matrix was used in 166 patients (40%). While the rate of abscess was low (3%), 89% of patients who developed pelvic abscesses received gelatin-thrombin matrix for bleeding (*P*=0.009). In bivariate analyses, blood loss >500cc (OR= 3.9, 95% CI 1.1-12.9, *P*=.02), ascites (OR=6.5, 95% CI 1.6-26.1, *P*=.023), drain placement (OR=4.5, 95% CI 1.3-15.1, *P*=.009), and gelatin-thrombin matrix use (OR=7.0, 95% CI 1.5-32.9, *P*=.009) were significantly associated with abscess formation. Logistic regression revealed that only gel matrix thrombin use independently predicted the development of pelvic abscesses (HR=7.0, 95% CI 1.5-32.9, *P*=.013).

Conclusions: Gelatin-thrombin matrix use may be associated with an increased risk of the development of pelvic abscesses. While these products are important in the setting of intraoperative bleeding, this data suggest that their use could also be detrimental and when used, benefits should outweigh risks. The mechanisms underlying this finding are unknown and merit further study.

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500 - Poster Session B

Robotic surgery 6-year analysis of annual perioperative outcomes for patients with endometrial cancer

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Objectives: A robotic surgery program was initiated in mid-2006 and perioperative outcomes data has been continuously collected and analyzed. The objective of this study was to perform a 6-year annual comparison of perioperative outcomes for patients with endometrial cancer (EC) who underwent robotic-assisted laparoscopic hysterectomy (RALH) and lymphadenectomy (LN).

Methods: Retrospective analyses of clinical-pathologic factors and surgical outcomes from 735 serial patients with EC who underwent RALH with LN (7/06 to 6/12). 12 (1.6%) laparotomy conversions were excluded.

Results: 379 (51.6%) of RALH cases had comprehensive pelvic/aortic LN (PALN) and 356 (48.4%) had pelvic LN (PLN) only. 42, 79, 108, 162, 165, and 179 cases were performed in years 1, 2, 3, 4, 5, and 6, respectively. Between year 1 vs 6, mean age increased (57.4±10.7 vs 63.5±12.0; *P*<0.05), but hospital length-of-stay and EBL did not change significantly (0.98±0.41 vs 1.39±1.08 days, and 94±59 vs 96±54 mL, respectively). Mean BMI increased consistently (28.2±7.1 vs 33.2±8.3 kg/m^2, *P*<0.001). PLN operative time (OT) remained stable and PALN OT decreased (185±53 vs 172±40 min, *P*<0.05), PLN counts increased (12.5±8.3 vs 20.9±10.4, *P*<0.001) and aortic LN remained stable for years 1 vs 6. Total node counts increased from 19.1 to 27.1 (years 1 to 6; *P*<0.01). 105/735 (14.3%) cases had positive LN, with a significant increase in year-6 likely secondary to sentinel LN mapping. Only 6 (0.8%) cases had intraoperative complications and 91 (12.3%) postoperative complications, including 3 (0.4%) DVT/PE, and no deaths.

Conclusions: Performance of PALN decreased, PLN increased, and the percentage of metastatic LN increased during this analysis. PLN counts increased and OT for PALN decreased significantly while age and BMI increased annually. VTE and transfusion were rare, without the use of heparin prophylaxis.

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501 - Poster Session B

Incidence of port site hernias in robotic and laparoscopy assisted procedures in gynecologic oncology

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Objectives: The incidence of port site hernia and/or dehiscence using bladeless trocars is 0-1.2%. Robotic surgery uses additional port sites and increases manipulation of instruments, raising the concern for more complications. We sought to characterize the incidence of port site complications following robotic surgery when fascia was not routinely closed.

Methods: A retrospective analysis of all robotic- and laparoscopic-assisted hysterectomy performed in a gynecologic oncology practice between 1/2005 and 12/2012 were included. Bladeless 12mm and 8mm robotic trocars were used. Fascial closure was not routinely performed except after specimen removal through the port site. The decision to close the fascia remained at the discretion of the surgeon.

Results: A total of 1425 procedures were included. Mean patient age was 52.8 years. Mean Body Mass Index was 29.3 (±6.8) kg/m2. Final pathology confirmed malignancy in 28.3% of cases, primarily endometrial cancer. The total of hernia was 0.5%. In cancer patients the risk of port site hernia was 1.1%. The rate of hernia formation among the laparoscopic (0%) compared with the robotic group (0.7%) which was not statistically significant.

Conclusions: Port site hernias and dehiscences are rare in RA gynecologic oncology procedures. When bladeless dilating trocars are used, routine closure of even up to a 12mm port site is unnecessary, even in cases requiring removal of the specimen through the trocar sites.

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502 - Poster Session B

Do the skills of a gynecologic oncologist cross species?

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Objectives: Gynecologic oncologists are called upon frequently for the treatment of non-human primates. There is little data regarding the incidence and type of treatment being administered. Our study aims to assess the incidence of gynecologic surgery performed on great apes by gynecologic oncologists.

Methods: An email survey was sent to members of the Society of Gynecologic Oncology using the REDCap survey tool. The survey contained questions regarding frequency and types of consultations by a zoo, and physician knowledge and attitudes regarding such consultations. The survey focused on great apes. All responses were anonymous, and subjects provided consent by submitting the survey. The survey was approved by the Colorado Institutional Review Board and the Denver Zoo.

Results: A total of 1507 email surveys were distributed, with 141 responses, for a response rate of 9.36%. Of respondents, 18 (44.44%) gynecologic oncologists had been consulted by a zoo for the care of a great ape (2 OB, 4 medical gynecology, 16 surgical gynecology, 2 infertility, 5 imaging interpretations). Surgery was performed by 15 (83.33%) physicians. The main difficulties encountered during consultation included differences in anatomy (4, 22.22%), not enough diagnostic information (5, 27.78%), little room for error or complications (13, 72.22%), and limited surgical instruments (4, 22.22%). Of respondents who performed surgery, 15 (83.33%) felt that the anatomy of the great ape was similar enough to human anatomy to make them feel comfortable. Pathology included gynecologic cancers (3, 16.67%), infection (7, 38.89%), and benign uterine mass (5, 27.78%). Success was reported in 16 (88.89%) cases. Overall 15 (83.33%) gynecologic oncologists who performed a consult for a zoo had a positive experience. Of all survey respondents, 66 (46.81%) would make themselves available for future consult.

Conclusions: Our study shows the frequency and nature of consultations by zoo veterinarians, and treatment among responding gynecologic oncologists. It is likely that these consultations will continue to increase in number as relationships are established between our medical communities. A survey of other OB/GYN subspecialists is needed, and a consult guideline, is needed to better prepare and protect such physicians for great ape consultations.

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503 - Poster Session B

Comparison of perioperative outcomes and complication rates between conventional versus robotic-assisted laparoscopy in the evaluation and management of early, advanced stage and recurrent ovarian, fallopian tube and primary peritoneal cancer

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Objectives: To examine perioperative outcomes, including complication rates, of conventional laparoscopy (CL) versus robotic-assisted laparoscopy (RALS) in evaluation and management of early, advanced and recurrent ovarian, fallopian tube and peritoneal cancer.

Methods: This is a retrospective analysis of a prospectively maintained database of surgery performed 7/2008 to 12/2012. 63 women had 83 surgeries; 22 surgeries for early stage disease (FIGO stage I) and 61 for advanced and/or recurrent disease.

Results: Of the 22 for early, 10 were CL, 9 were RALS and 3 were laparoscopy converted to laparotomy (LP). There was no significant difference between CL and RALS in estimated blood loss (EBL P=0.27) or length of stay (LOS P=0.43); however, both had less EBL (P=0.03, 0.03, respectively) and LOS (P=0.03, 0.03) than LP. There was no difference in OR time (ORT) among groups (P=0.79). There was 1 (33%) intraoperative complication in LP. 1 (10%) postoperative complication in CL, 2(22%) in RALS and 1 (33%) in LP, no difference (P=0.61). Among the 42 patients with advanced/recurrent disease, 61 surgeries were performed; 14 diagnostic and 47 cytoreductive. Of the 47, there was no difference in ORT (P=0.10). There was no difference in EBL or LOS between CL and RALS (P=0.82, P=0.87); however, both were less in CL (P<0.001 and P=0.02) and RALS (P=0.01 and P=0.02) compared to LP. There were 5 (63%) intraoperative transfusions in LP and none in CL or RALS. Including all surgeries for advanced/recurrent disease, there was 1 (12%) intraoperative complication in LP. There was no difference in postoperative complications between groups (P=0.89); 8 (19%) had postoperative complications in CL, 2 (18%) in RALS and 2 (25%) in LP. There were no grade 4 or 5 complications and no perioperative or intraoperative deaths.

Conclusions: Perioperative and oncologic outcomes are comparable between CL and RALS in both early and advanced/recurrent disease and not inferior to laparotomy, making CL and RALS an acceptable approach in selected patients.

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504 - Poster Session B

Breaking bad news in gynecologic oncology: a national fellows' assessment pilot study

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Objectives: Effective communication is fundamental to the optimal treatment of women suffering from gynecologic malignancies. Breaking bad news is an unavoidable aspect of gynecologic oncology practice. The importance of breaking bad news appropriately is universally recognized; however, many physicians are not comfortable within this area. This study aims to determine the feasibility of objectively assessing gynecology oncology (GO) fellows in the domain of breaking bad news at a national level.

Methods: GO fellows' ability to break bad news was assessed as a component of an objective surgical assessment of a technical skills [OSATS] national pilot study. A simulated patient scenario was developed and the validated Breaking Bad News Assessment Score [BAS] was used.

Results: The participant group represented 50% of all GO fellows in Canada. The median BAS total score was 64/110. Candidates' management of the eliciting concerns domain was the lowest scoring, with the majority of candidates (n=6) awarded the minimum score of 3. The domain "Providing information" was addressed well by second-year fellows compared to first-year fellows (P=0.03). GO fellows' self-reported scores accurately predict their objective BAS.

Conclusions: Breaking bad news is a key skill for GO physicians as evidenced by its specific inclusion in GO curricula internationally. It is feasible to assess GO fellows' communication skills objectively at a national level. GO fellows have an understanding of the limitation of their skills. Eliciting concerns is the single most valued component for patients receiving bad news and the domain requiring most attention for GO physicians.

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505 - Poster Session B

Understanding patient learning styles in gynecologic oncology: a pilot study

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Objectives: Patients must understand the complex treatment options offered by clinicians. This study sought to prospectively determine patients' preferred modes of learning and assess the content most relevant to making major medical decisions.

Methods: An anonymous survey was designed and IRB approved. Women presenting between 6/1/13 and 7/31/13 were approached. Demographic data and treatment history were gathered. The primary outcome was preferred learning mode as assessed by a 5-level Likert method scaled over 13 choices. Secondarily, the value of specific types of information was evaluated. Response data was considered negative (0 or 1), neutral (2), or positive (3 or 4). Proportional odds modeling assessed each response level per factor of interest.

Results: The survey was offered 213 times to 163 women. 19 declined (9%) and 144 unique women participated (88%). Median age was 62 (range 17-85) and 84% were Caucasian. Over half had secondary or some higher education (63%), while 36% had at least some high school. Most were returning patients (96%) seen for ovarian (37%) or uterine cancer surveillance (22%) and had 1-3 (42%) or ≥4 visits in the past three months (27%). Almost all responded to questions assessing the primary outcome (median N=137, range 133-143). The most popular non-verbal learning mode was using pictures or diagrams (80%). Social media was preferred by only 10% with 75% disliking it. 59% felt positively and 30% felt negatively about the Internet. Older patients were 0.68 times (95% CI 0.54-0.86) less likely to prefer the Internet (P=0.001). 49% disliked patient support groups while 20% preferred them. Visit frequency ≥4 compared with no recent visits influenced preference for talking with a nurse (OR 5.1, 95% CI 1.9-13.4, P<0.001). When making a decision, 99% valued knowing the options, risks/benefits, expected outcome, and physician recommendations. Least important was impact on sexual functioning (43% negative, 18% neutral), particularly for older patients (OR 0.46, 95% CI 0.35-0.60, P<0.001).

Conclusions: Women are able to identify their learning styles and specify the scope of information needed for complex medical decision-making. Age and visit frequency influence selections. Emphasis should be given to the use of visual aids and teaching by nursing and licensed independent practitioners.

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506 - Poster Session B

Aggressive surgical debulking at time of primary and interval surgery at referral oncologic center: surgical and oncological outcomes

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Objectives: To investigate the oncologic and surgical outcomes in newly diagnosed advanced epithelial ovarian cancer patients FIGO stage IIIC-IV who underwent primary maximal debulking surgery (PDS) or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) at a referral cancer center.

Methods: A retrospective review of patients operated between January 2000 and December 2008 at European Institute of Oncology (IEO), Milan, Italy, was performed. All newly referred diagnosed and untreated patients with suspected advanced epithelial ovarian cancer underwent PDS unless severe comorbidities. On the other hand, patients who underwent NACT were referred by medical oncologists to our institution after initial chemotherapy.

Results: PDS and IDS were performed in 259 and 104 patients, respectively. Complete cytoreduction was obtained in 115 (44%) patients in PDS and in 70 (67.3%) patients in IDS group. Residual tumor between 1 and 10 mm was obtained in 83 (32.1%) patients in PDS and in 26 (25%) patients in IDS group. Overall major postoperative complications occurred in 13.8% in the PDS group versus 8.6% in the IDS (0.218). Minor complications occurred in 64.4% in the PDS group versus 59.6% in the IDS (0.402). The median (range) PFS for patients undergoing PDS and NACT-IDS was 19 months (16–21 months) and 22 months (17-26 months), respectively (P=0.548). The median (range) OS for patients undergoing PDS and NACT-IDS was 50 months (42–57 months) and 43 months (30-55 months), respectively (P=0.665).(Figure 1 A-B) The median PFS and OS in both groups was significantly higher in patients with complete cytoreduction. (Figure 2 A-B) (Figure 3 A-B)

Conclusions: Patients undergoing NACT-IDS performed at specialized centers by surgeons with extended formal training in cytoreductive techniques may experience a prolonged survival after aggressive debulking. Aggressive surgical debulking procedures have a similar morbidity in PDS and IDS patients.

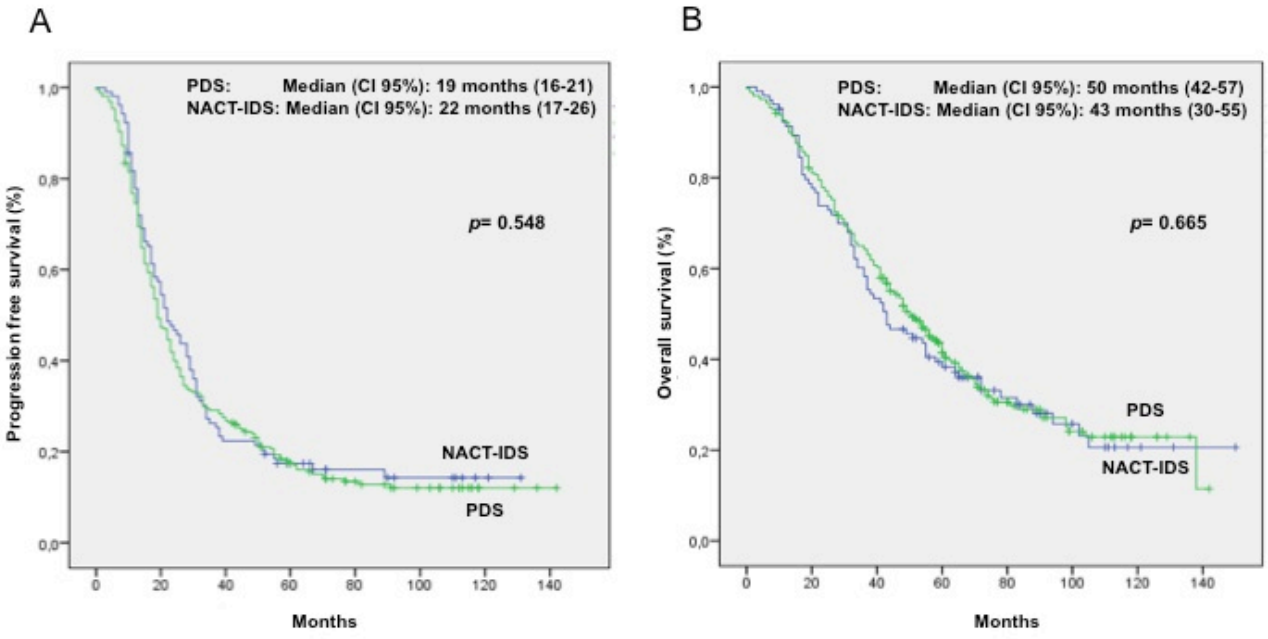

Figure 1: Progression Free Survival (A) and Overall Survival (B) in patients who underwent primary debulking surgery (PDS) or neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS).

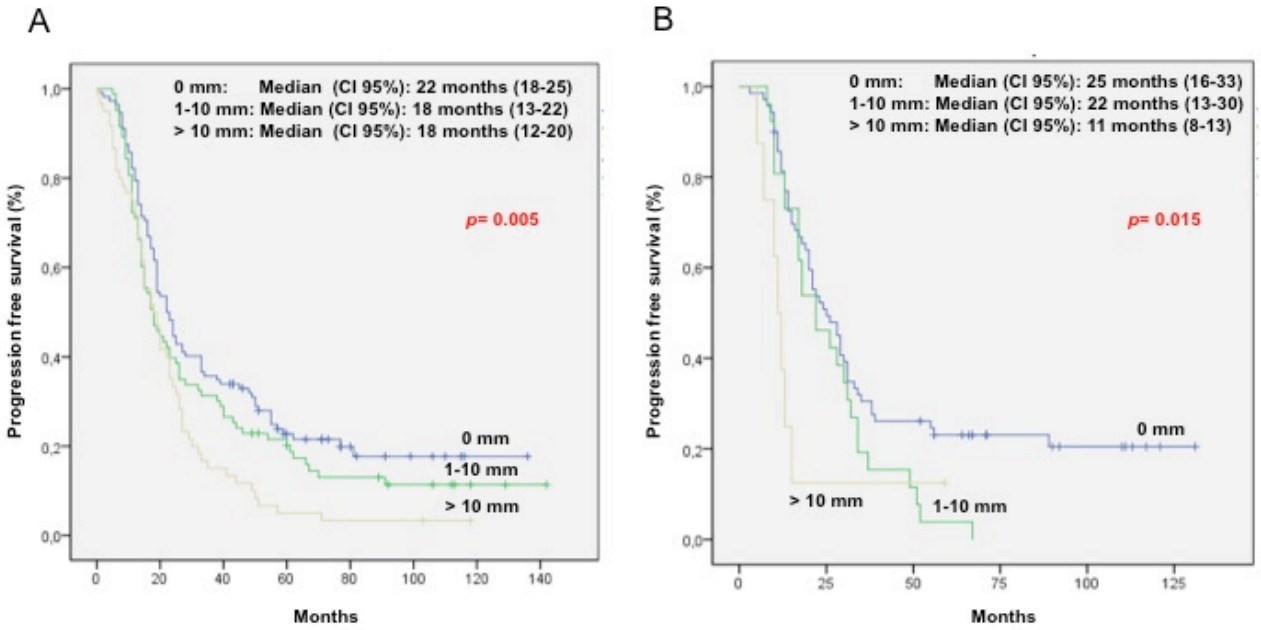

Figure 2: Progression free survival according to the size of residual disease (in mm) in patients who underwent Primary debuking surgery (A) and neoadjuvant chemotherapy followed by interval debulking surgery (B)

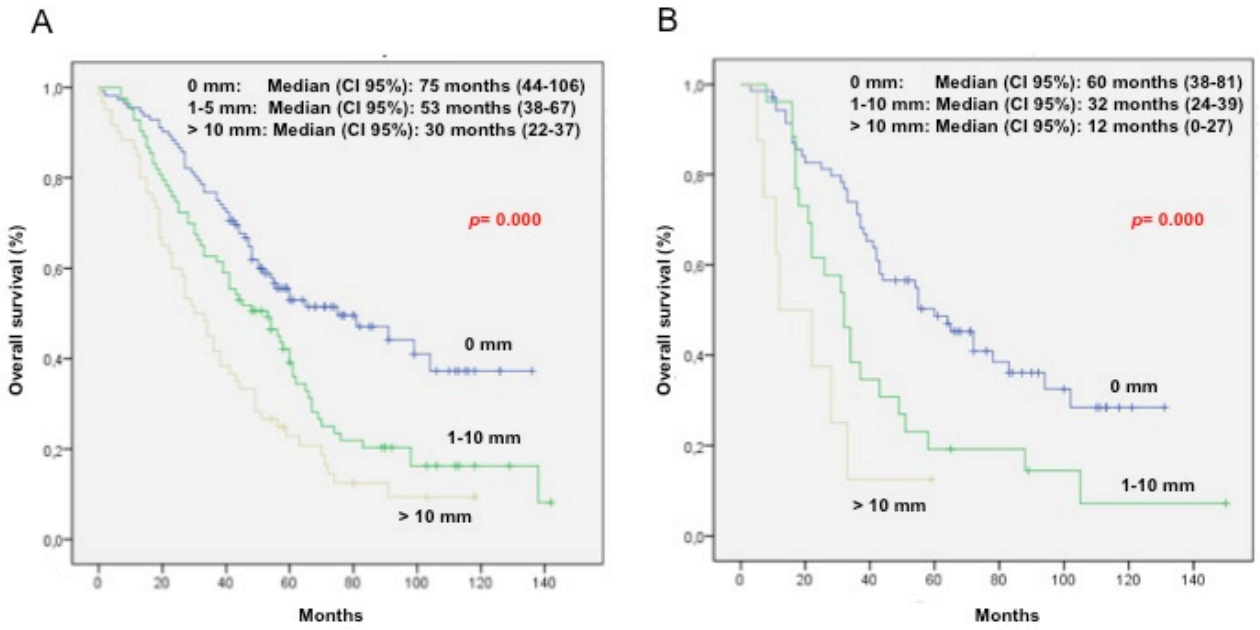

Figure 3: Overall survival (OS) according to size of residual disease (in mm) in patients who underwent Primary debuking surgery (A) and neoadjuvant chemotherapy followed by interval debulking surgery (B)

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507 - Poster Session B

A low-carbohydrate nutritional program improves weight, insulin, and estrogenic parameters in obese patients with estrogen receptor positive endometrial cancer

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Objectives: This feasibility study evaluated whether a low-carbohydrate, calorie-restricted dietary intervention could achieve decreased adiposity, weight loss, and measurable metabolic changes in endometrial cancer survivors.

Methods: 8 early stage, ER+ endometrial cancer survivors, with a BMI >28 kg/m^2, were enrolled in the dietary intervention. Patients with an underlying inflammatory medical condition or diabetes on medical treatment were excluded. All patients underwent appropriate surgical management and adjuvant therapy. The mean age was 59.8 years (42 – 68), with a mean weight of 231.6 lbs (191.4 – 292.0) and mean BMI of 39.3 kg/m^2 (29.2 – 49.5). The dietary intervention provided 0.5 gm of protein/lb of actual body weight, less than 40 gm of carbohydrates and 800 – 1200 total calories per day. Weekly health coaching, protein meal substitutes and essential nutritional supplement were provided. Physical examinations and serum metabolic testing were obtained every 2 weeks for the first 12 weeks and monthly thereafter. The average weight loss period spanned for 23.5 weeks (15 – 35) due to the variance in weight loss goals, aimed at a BMI of ≤ 28 kg/m^2.

Results: Statistically significant declines in total body weight, estrogenic markers, and fasting insulin were observed. The mean weight loss was 18.0% after 15 weeks (P=6.45x10^{-7}), equivalent to 41.3 lbs per individual. The mean percentage of total body fat loss was 6.3%. Weight loss averaged 5.3 lbs/week in week 1 and 2.6 lbs/week in weeks 2 -15. Total serum estrogen, estrone and estradiol decreased by 22.8% (P=0.0185), 20.2% (P=0.0065) and 32.5% (P=0.1030), respectively, after 15 weeks. Declines in fasting insulin level were 51% (P=0.0044) and 61% (P=0.0055) after weeks 3 and 15. A corresponding 65.2% decline in C-peptide was also observed at 15 weeks (P=0.0021).

Conclusions: Our results support that a low carbohydrate dietary intervention can successfully achieve loss of adiposity and weight, improve hyperinsulinemia and decrease unopposed estrogenic drive. These metabolic changes have the potential to

positively impact endometrial cancer survival. Large-scale clinical trials are needed to delineate the long-term role of this intervention as a life style change.

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508 - Poster Session B

Prognostic factors associated with long-term survival in ovarian cancer

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Objectives: Population-based cancer registries have prolonged follow-up on ovarian cancer survivors. Our objective was to identify prognostic factors associated with long-term (LT) survival (>10 years).

Methods: The California Cancer Registry (CCR) contains demographic, diagnostic, treatment, and outcome information of California cancer patients, with nearly 100% follow-up. We identified epithelial ovarian cancer patients, diagnosed between 1994 and 2001, and followed through December 2011, with a minimum of 10 years follow-up for all surviving patients. Exclusions included: if diagnosed at autopsy or if missing information about their SES, race/ethnicity, stage, grade, treatment, or cause of death. Characteristics of (LT) survivors (>10 years) were compared to short-term (ST) survivors (2-5 years). Multivariate logistic regression and Cox proportional hazard modeling were used to identify significant predictors of LT survival.

Results: 12,927 women were diagnosed with epithelial ovarian cancer during this period. We identified 4,094 patients who were LT survivors, and compared this group to 2,722 patients who were ST survivors. Significant differences between LT and ST survival groups included: age <50 years (46% vs 22%), non-Caucasian (33% vs 24%), have grade 1 or 2 tumors (42% vs 20%), stage I cancer (52% vs 5%), and have mucinous, endometrioid, or clear cell histologies (13% vs 3%, 21% vs 8%, 9% vs 2%, respectively). 1,271 women with stage III/IV cancer were LT survivors. In multivariate analysis, young age remained a significant predictor of being a LT survivor, with all age groups having 2 - nearly 4 times better probability of surviving than those in the 75+ group. Stage was the strongest predictor, followed by non-serous histology, and then grade. Race, SES, insurance type, and hospital volumes were not independently significant. LT survival characteristics for stage IIIC cancers included: age <65, low grade, and non-serous histology; for stage IA only age <50 and grade were significant.

Conclusions: Almost one third of ovarian cancer patients survived more than 10 years, and 1,271 had advanced stage disease. These will be the focus for future studies. Most of the prognostic factors are non-modifiable, but are important for counseling.

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509 - Poster Session B

Clinical analysis of 13 cases of vulvar Paget's disease

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Objectives: Vulvar Paget's disease is a rare disease. It has a relatively high misdiagnosis rate and there are still controversies regarding its treatment. The objective of this study was to investigate its clinical features and summarize the experience of the management of this disease in order to gain a better understanding of this rare disease and improve its cure rate.

Methods: The clinical records of 13 cases of vulvar Paget's disease admitted in Cancer Center of Sun Yat-sen University and the Third Affiliated Hospital of Sun Yat-sen University from January 1964 to December 2006 were analyzed.

Results: The average age of 13 cases was 61 years and the mean time from the onset of the disease to diagnose was 2 years. Pathologically intraepithelial Paget's disease was the most common (10/13) followed by invasive Paget's disease (2/13) and Paget's disease with underlying adenocarcinoma (1/13). Three patients underwent simple vulvectomy. Three patients underwent wide local excision. Four patients underwent radical vulvectomy and three patients underwent radical vulvectomy with unilateral lymph node dissection. Eight patients remain free of disease and three had recurrence of Paget's disease. One died of disease and one died of other etiology.

Conclusions: Surgery is the first choice for patients with vulvar Paget's disease. Patients who are not suitable for long-term follow up have extensive lesions or are old aged are more preferable for radical vulvectomy and expectation of recurrence is lower.

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510 - Poster Session B

A survey of female cancer patients' awareness of and preferences for receiving sexual health interventions

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Objectives: To assess female cancer patients' awareness of sexual/vaginal health issues and their preferences for associated interventions.

Methods: Women with a history of gynecologic or breast cancer completed a one-time survey assessing their awareness of sexual/vaginal health issues, health promotion strategies, and their preferences for receiving sexual health interventions.

Results: Of 218 female cancer patients/survivors, 109 (50%) had gynecologic cancer and 109 (50%) had breast cancer. Median age was 49 years (range, 21-75), and 61% were married/cohabitating. Seventy percent (153) reported being somewhat to very concerned about sexual function/vaginal health. Fifty-five percent (120) reported vaginal dryness, 39% (84) vaginal pain, and 51% (112) loss of libido. Sexual/vaginal health issues existed before cancer and continued or worsened afterwards for 32% (69). Forty-two percent (91) had no problems before but problems became prevalent post-diagnosis. Only 16% (35) had no issues before or after cancer. Many heard of vaginal lubricants, moisturizers, and pelvic floor exercises (97%, 72%, 57%), but only 28% had used moisturizers and pelvic floor exercises, whereas 74% had used lubricants. Sixty-nine percent (150) thought it would be helpful to speak with a sexual health expert, and 43% (93) indicated a need for more information about sexual/vaginal health. Seventy-nine percent (173) were comfortable bringing up sexual health with the medical team, but only 48% (105) had done so; 70% (152) preferred the topic to be raised by the medical team. There were significant differences in intervention preference by age group. Written material would be well received by all, but delivery preference significantly varied; older women preferred to read materials on their own ($P<0.01$), whereas younger women wanted to discuss them with the medical team ($P<0.02$). Older women were not as interested in or comfortable with online interventions ($P<0.05$), despite 93% having email and 94% having computer access.

Conclusions: Our findings confirm that female cancer patients/survivors have unmet sexual/vaginal health needs, and preferences for receiving sexual health information may vary by age. Our cohort was not completely satisfied with sexual/vaginal health resources but did not communicate these concerns with the medical team.

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511 - Poster Session B

The impact of outpatient versus inpatient referrals to hospice

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Objectives: To evaluate the differences in outcomes between patients who have been referred to hospice from the inpatient (IN) versus outpatient (OUT) setting.

Methods: A retrospective analysis of all gynecologic oncology patients who were discharged from the hospital or clinic to hospice care from January 2009 – June 2012 was conducted. Clinical data included disease site and stage, hospice type chosen (home vs hospital based), treatment with chemotherapy, and number and type of invasive procedures performed. Demographic data included age, race, and dates of death, which were recovered from the Social Security Death Index. Fisher's exact tests and Wilcoxon two-group tests were used to compare outcomes between the IN and OUT groups.

Results: Eight-nine inpatients and 37 outpatients were identified that resulted in discharge to hospice care. The majority were Caucasian 93/126 (74%) or African American 27/126 (21%, $P=0.34$). Cancer types included 66 (52%) patients with ovarian, 32 (25%) with uterine, 21 (17%) with cervical, and 7 (6%) with vulvar or vaginal cancers, with no difference in stage distribution when comparing the IN vs OUT groups ($P=0.58$). Median age for IN patients was 63 (54-72) vs 72 in the OUT group (66-78, $P=0.0004$). Sixty-six percent (58/89) of the IN group had invasive procedures within 4 weeks of death

compared to 24% (9/37) of OUT patients ($P<0.0001$) and there was a significant difference between IN vs OUT patient groups with respect to palliative chemotherapy received within 6 weeks of death (63% vs 22% $P<0.0001$). The percentage of patients choosing home hospice care was higher in the OUT group (86% vs 78%, $P=0.33$). Median time from hospice referral to death was statistically significant between the IN vs OUT groups (16 d vs 38 d, $P=.0002$).

Conclusions: Patients who were referred to hospice from the outpatient setting spent more time under hospice care, underwent fewer invasive procedures within 4 weeks and less chemotherapy within 6 weeks of death, and trended towards higher rates of home hospice choice. This data should encourage physicians to capture patients during outpatient visits to optimize the use of hospice services and avoid inpatient hospital admission towards the end of life.

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512 - Poster Session B

Symptoms burden in subjects with cervical cancer and supportive care: preliminary result from a developing country

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Objectives: Cervical cancer is not only a leading gynecologic cancer in the developing countries but disproportionately accounts for the burden due to cancer. In spite of the need for holistic care of cervical cancer, little is known about the experience of the affected populations beyond their cancer treatment. This study aims to investigate the pattern and distribution of symptoms burden in subjects with cervical cancer in a developing context.

Methods: This cross sectional study was carried out among 61 consenting participants with cervical cancer using a designed questionnaire to elicit socio-demographic with clinical profile and symptoms burden. Subsequently, Centre for Epidemiological Studies Depression Scale Revised (CESD-R) was used to ascertain presence of depressive symptoms in participants. Data analyses were done using SPSS-15.

Results: The majority of the subjects, 25 (41.0%) and 34 (55.7%) were in their fifth decade of life and unmarried, respectively. 3 (4.9%) participants presented with early stage cancer, while close to two-thirds of the participants made up of 38 (62.3%) subjects had advanced stage cancer. The largest proportion, consisting of about 7 in every 10 participants had pain, 35 (57.4%) participants reported sexual dysfunction, and common sexual problems that were reported include loss of libido, dyspareunia and anorganism, among others. In addition, physical complications like ulcer, weight loss and multiple complaints were seen in 28 (45.9%) participants. Significant depressive symptoms based on CESD-R cut-off score of 16 and above was elicited among close to half of the participants, 29 (47.5%).

Conclusions: Late presentation and significant burden of diverse symptoms including pain, sexual, physical and depressive were prevalent among individuals with cervical cancer. Health education with proactive health interventions to promote early presentation and supportive care to ensure qualitative overall care are implied.

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513 - Poster Session B

Chemotherapy is a reasonable option for adjuvant therapy in the treatment of high-intermediate risk endometrial cancer

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Objectives: Gynecologic Oncology Group (GOG) 99 identified a group of high-intermediate risk (HIR) endometrial cancer patients that may benefit from adjuvant treatment; the ideal type of treatment is unknown. Our objective was to compare survival of HIR patients who had various treatments, including chemotherapy (CT), whole pelvic radiation therapy (WPRT) with or without brachytherapy (BT) and observation (OBS).

Methods: A retrospective cohort study of endometrial cancer patients diagnosed between 2000 and 2009 was performed. All patients had endometrioid histology and GOG 99 criteria for HIR, including grade 2 or 3, deep myometrial invasion and lymphovascular space invasion (LVSI). Clinical factors between various treatment cohorts were compared using Student's t-test and Chi-squared test. Survival was calculated using Kaplan-Meier estimates and compared with the log rank test.

Results: Two hundred thirty-four patients met inclusion criteria. One hundred nineteen (51%) were stage 1A, 86 (37%) were stage 1B, and 29 (12%) were stage II. Twenty patients (9%) received adjuvant platinum-based CT, 34 (14%) received WPRT +/- BT and 180 (77%) were observed. Observed patients were more likely to be older, have stage 1A disease, and less likely to have LVSI than patients who received adjuvant treatment. Median PFS did not differ between OBS (60.7 mos), WPRT+/- BT (30.4 mos) and CT (not yet reached) (P=0.14). There was a 15% recurrence rate in the CT group with a median follow-up of 29 mos. Clinical and demographic factors (age, BMI, stage, grade, LVSI) were similar between groups receiving CT and WPRT +/- BT. When comparing these 2 groups, survival analysis suggests an improvement in PFS for the CT group compared to the WPRT +/- BT group (P=0.051).

Conclusions: When compared to radiation therapy, chemotherapy for the adjuvant treatment of high-intermediate risk endometrial cancer represents a reasonable treatment option. Chemotherapy alone should be studied prospectively for endometrial cancer patients who have high risk for recurrence.

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514 - Poster Session B

A low-carbohydrate nutritional program improves adiposity, metabolic, and nutritional parameters in obese patients with estrogen receptor positive endometrial and breast cancer

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Objectives: This feasibility study evaluated whether a low-carbohydrate, calorie-restricted dietary intervention could achieve decreased adiposity, weight loss, and measurable metabolic changes in endometrial and breast cancer survivors.

Methods: Thirty-two early stage ER+ cancer survivors (8 endometrial and 24 breast) with a BMI >28 kg/m^2 were enrolled in a low-carbohydrate, calorie-restricted dietary intervention. Patients with an underlying inflammatory medical condition or diabetes on medical treatment were excluded. All patients underwent appropriate surgical management and adjuvant therapy. The mean age was 56.8 years (42 – 68), with a mean weight of 222.8 lbs (170.8 – 296.6) and mean BMI of 37.7 kg/m^2 (28.4 – 49.5). The dietary intervention provided 0.5 gm of protein/lb of actual body weight, less than 40 gm of carbohydrates, and 800 – 1200 total calories per day. Weekly health coaching, protein meal substitutes and essential nutritional supplements were provided. Physical examinations and serum metabolic testing were obtained at set periodic intervals. The average weight loss period spanned for 23 weeks (15 – 59) due to the variance in weight loss goals, aimed at a BMI of ≤28 kg/m^2.

Results: The mean weight loss was 20.8% of total body weight (P=8.75x10^{-13}), equivalent to 46 lbs per individual. The mean percentage of total body fat loss was 7.28%. Weight loss averaged 5.5 lbs/week in week 1 and 2.2 lbs/week in weeks 2 -19. Total serum estrogen, estrone and estradiol decreased by 29.1% (P=0.005), 24.1% (P=0.01) and 49.2% (P=0.003), respectively. Declines in fasting insulin levels were 41% (P=3.40x10^{-5}) after week 3 and 51% (P=6.30x10^{-7}) at the endpoint of dietary intervention. C-peptide levels also had a corresponding decline (32%; P=7.80x10^{-5}). CRP decreased significantly compared to baseline (40.2%; P=0.0006).

Conclusions: Our results support that a low-carbohydrate dietary intervention can successfully achieve loss of adiposity and weight, improve hyperinsulinemia, and decrease unopposed estrogenic drive. These metabolic changes have the potential to positively impact endometrial and breast cancer survival. Large-scale clinical trials are needed to delineate the long-term role of this intervention as a life style change.

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515 - Poster Session B

National trends in the place of death and the impact of unscheduled admissions in patients with gynecological cancer in England

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Objectives: The illness trajectory of gynecological cancers is relatively less well studied compared with other cancers. The purpose of this study is to determine trends in the place of death and predict the impact of unscheduled admissions in the last month of life on patients with gynecological cancer.

Methods: Data were extracted from a linked dataset of Office for National Statistics deaths data and Hospital Episode Statistics for 71,269 patients who died of gynecological cancer in England from January 2000 to July 2012. Multivariate regression analysis was used to develop a model to assess the impact on place of death. The model was validated with a different dataset of 2,808 women who died of gynecological cancer in the subsequent 6 months.

Results: Forty-three percent of all women diagnosed with gynecological cancer died in hospital over the study period. The variables that significantly predicted death in hospital were more recent year of death (OR 0.93, $P<0.001$), increasing age group (OR 1.17, $P<0.001$), increasing deprivation status (OR 1.06, $P<0.001$), and increasing frequency and length of elective and emergency admissions ($P<0.001$). Each subsequent emergency admission in the last month of life increased the odds of death in hospital by 2.4 times (OR 2.38, $P<0.001$). Hospital deaths were significantly lower in all other regions compared to London. The model correctly identified 73% of hospital deaths with a sensitivity of 75% and a specificity of 72%. When the model was applied to predict the effect on outcome of avoidable emergency admissions, assuming that if steps were taken to prevent one less emergency admission into hospital in the last month of life, 16% of deaths could be avoided in hospital.

Conclusions: Inequity in end-of-life care exists within gynecological cancers with elderly patients more likely to die in hospital. This suggests a greater focus on advance care planning for younger patients with less co-morbidity. Improved services are required in the community to prevent unscheduled admissions alongside better skills at identifying the dying phase for hospitalized patients.

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516 - Poster Session B

Outpatient rapid desensitization for gynecologic oncology patients with mild to moderate hypersensitivity reactions to platinums

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Objectives: Platinums (carboplatin and cisplatin) are associated with hypersensitivity reactions (HSR). While 50% of HSR to carboplatin are mild, re-challenge is often associated with earlier onset and more severe HSR. Most published desensitization protocols were implemented in the inpatient settings. The objective of study is to assess the safety and efficacy of outpatient rapid desensitization in gynecologic oncology patients with a history of mild to moderate HSR to platinums.

Methods: A retrospective chart review was performed in gynecologic oncology patients with mild to moderate HSR to platinums who received outpatient desensitization during the period from January 2011 to July 2013. Patients with severe reactions to platinums were excluded. Desensitization protocols involved premedications with antihistamines and steroids followed by 1-solution, 4-step titration of platinums (1.5 hours for carboplatin and 2.25 hours for cisplatin). The primary end point was the rate of successful administrations of each course of platinums in the outpatient clinic.

Results: Eighteen eligible patients were identified. Eight patients had initial mild HSR, and 10 patients had initial moderate HSR. Seventeen patients successfully completed 94/95 (98.9%) desensitization courses in the outpatient clinic. Of the 95 desensitization courses conducted, 65 (68.4%) induced no reactions, 18 (18.9%) induced mild reactions and 12 (12.6%) induced moderate reactions. No life-threatening reactions or hospital admissions required. All symptoms were managed successfully with antihistamines and steroid. Only 1 patient did not complete desensitization due to moderate/severe reactions and carboplatin was discontinued.

Conclusions: Patients with mild to moderate hypersensitivity reactions to platinums can be safely and effectively desensitized in the outpatient clinic through rapid 4-step desensitization. Severe breakthrough reactions are less common.

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517 - Poster Session B

Surveillance testing in women following a diagnosis of early-stage endometrial cancer

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Objectives: The majority of women with uterine cancer are diagnosed with early-stage disease and have a long life-expectancy. While guidelines recommend surveillance testing following treatment, these recommendations are not evidence based. We examined use of surveillance testing in elderly women with early-stage endometrial cancer.

Methods: We used the SEER-Medicare database to identify patients with stage I-II, endometrioid endometrial cancer who underwent hysterectomy from 1995 to 2007. Three surveillance periods (7-18, 19-30, 31-42 months) after diagnosis were identified. Use of vaginal cuff cytology and imaging were quantified for each period. Costs were determined based on published Medicare reimbursement schedules.

Results: Between 1995 and 2007, 10,782 patients were identified. During the first year of surveillance, use of cytology (66.9% in 1995 to 70.8% in 2007), chest CT (2.0% to 12.1%), abdominopelvic CT (13.8% to 26.6%) and PET (0% to 2.2%) increased, while use of chest radiography (42.6% to 35.9%) decreased over time ($P<0.05$ for all). The mean per-patient number of cytologic specimens increased from 1.2 in 1995 to 1.5 in 2007, while use of chest CT (0.02 to 0.2), abdominopelvic CT (0.2 to 0.4) and PET (0 to 0.02) also all increased from 1995 to 2007. In 2007, 50.1% of women underwent some type of radiologic surveillance 7-18 months after diagnosis while 14.6% underwent 2 or more radiologic assessments with cytology. The findings were similar for surveillance periods 2 and 3. Patients with higher socioeconomic status were significantly more likely to undergo high-intensity surveillance.

Conclusions: The use of costly diagnostic imaging and cytologic surveillance is increasing rapidly for patients with localized uterine cancer. The benefits of surveillance are uncertain; however, the testing is associated with substantial cost.

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518 - Poster Session B

Missed opportunities: patterns of medical care and hospice utilization among ovarian cancer patients

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Objectives: In order to fully utilize the limited health care dollars available, we must evaluate the benefits of aggressive measures taken at the end of life. The goal of our study was to assess patterns of medical care and hospice utilization among ovarian cancer (OVCA) patients (pts) to understand current practices at our institution.

Methods: Pts diagnosed with OVCA, fallopian tube, or primary peritoneal cancer treated at our institution during 2007-2011 were identified from the tumor registry. Statistical analyses included Wilcoxon Mann-Whitney and Chi square analysis.

Results: One thousand sixty-eight records were identified. Four hundred eighty pts only received treatment (tx) recommendations; 885 transferred care to another practice or were lost to follow-up. One hundred eighty-three pts had sufficient information regarding care during the last 6 months of life. Table 1 lists pertinent demographics. 93.4% of pts received adjuvant tx 6 months before death. The majority of pts visited the ER were admitted to the hospital, or underwent invasive procedures during the 6 months prior to death. See Table 1. Seventy-three and eight-tenths percent of pts enrolled in hospice before death. Pts who received provider recommendations to enroll in hospice were more likely to do so than those who did not (OR 27.1, $P=<0.001$), with a median hospice stay of 18 days prior to death. Caucasian pts and those with at least a college education had shorter hospice stays versus non-Caucasian pts and less educated pts ($P=0.009$ and 0.017). 22.4% of pts died in the hospital. Among those pts, 43.9% died in the palliative care unit, 39% died on the floor, and 17.4% died in the ICU. While pt age was not associated with likelihood of dying in the hospital, time from diagnosis was inversely associated with dying in the hospital (OR=0.72 per year since dx, $P=0.006$). Compared to married pts, unmarried pts were 2.95 times more likely to die in the hospital ($P=0.015$).

Conclusions: The vast majority of OVCA pts at our institution underwent procedures and tx for their disease in the 6 months preceding death. Although most pts ultimately enrolled in hospice, the interval between hospice enrollment and death was very short. As health care providers, we must not only accept the responsibility of initiating discussions with pts regarding their prognosis, but must also encourage timely hospice referral and appropriate utilization of hospice services.

Table 1.

Characteristic	N (%)
Age	
Median: 58	
Race/Ethnicity	
Caucasian	124 (67.8)
African American	24 (13.1)
Hispanic	24 (13.1)
Asian	10 (5.5)
Other	1 (0.5)
Cancer Type	
Ovarian	177 (96.7)
Fallopian Tube	5 (2.7)
Primary Peritoneal	1 (0.5)
Stage of Cancer	
Stage I	4 (2.2)
Stage II	8 (4.4)
Stage III	79 (43.2)
Stage IV	36 (19.7)
Unstaged/Neoadjuvant	42 (23.0)
Not documented	14 (7.7)
Marital Status	
Single	29 (15.8)
Married	114 (62.3)
Divorced	21 (11.5)
Widowed	19 (10.4)
Education	
Less than College	99 (54.1)
College & Beyond	61 (33.3)
Unknown	23 (12.6)
Type of Insurance	
Private	110 (60.1)
Medicare	58 (31.7)
Medicaid/Self-pay/Indigent	15 (8.2)
Treatment during the 6 months prior to death	
Chemotherapy	112 (61.2)
Radiation	4 (2.2)
Chemoradiation	2 (1.0)
Hormonal	11 (6.0)
Clinical Trial	42(23.0)
None	12 (6.6)
ER visits, admissions, and procedures during the 6 months prior to death	
At least one ER visit	160 (87.4)
At least one Hospital Admission	172 (94.0)
At least one ICU admission	26 (14.2)
At least one invasive procedure	151 (82.5)

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519 - Poster Session B

An afterthought: end-of-life care documentation among ovarian cancer patients

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Objectives: Current NCCN guidelines encourage early discussion of goals of care with patients (pts). Despite this, many cancer pts do not create documents outlining the end-of-life care they desire. The objective of our study was to evaluate patterns of end-of-life care documentation among ovarian cancer pts and describe timing of DNR order initiation at our institution.

Methods: Pts diagnosed with ovarian, fallopian tube, or primary peritoneal cancer treated at our institution during 2007-2011 were identified from the tumor registry. Demographic and clinical data were abstracted from the electronic medical record (EMR). Statistical analyses included Wilcoxon Mann-Whitney, Chi-square, and multivariate analysis.

Results: One thousand sixty-eight records were identified. Four hundred eight pts only received treatment recommendations, and 885 transferred their care to another practice or were lost to follow-up before death. One hundred eight-three pts met the qualifications for this study by having information regarding care during the last 6 months of life. Median age was 58. Table 1 lists pertinent demographics. Seventy-three and eight-tenths percent of pts had an in-hospital DNR order (IH-DNR) and 30.6% had an out-of-hospital DNR order (OH-DNR) in the EMR. These documents were created a

median of 15 and 11 days prior to death, respectively. Pts with DNR orders who went to hospice had an IH-DNR created a median of 6 days, and an OH-DNR created a median of 1 day prior to hospice enrollment. Caucasian pts were less likely to have both an IH-DNR (OR=0.44, *P*=0.04) & an OH-DNR (OR=0.51, *P*=0.04) when compared to non-Caucasian pts. 27.9% of pts had a Medical Power of Attorney in their EMR and 19.7% had a Living Will. These documents were created a median of 381 and 378 days prior to death, respectively.

Conclusions: Our data indicate that pts who create a Medical Power of Attorney and Living Wills do so far in advance of their death. DNR orders, on the other hand, appear to be initiated at a time when the patient is close to death. In order to help maximize alignment with pt desires regarding end-of-life care, discussions about advanced directives must be initiated prior to the time immediately preceding death.

Table 1.

Characteristic	N (%)
Race/Ethnicity	
Caucasian	124 (67.8)
African American	24 (13.1)
Hispanic	24 (13.1)
Asian	10 (5.5)
Other	1 (0.5)
Cancer Type	
Ovarian	177 (96.7)
Fallopian Tube	5 (2.7)
Primary Peritoneal	1 (0.5)
Stage of Cancer	
Stage I	4 (2.2)
Stage II	8 (4.4)
Stage III	79 (43.2)
Stage IV	36 (19.7)
Unstaged/Neoadjuvant	42 (23.0)
Not documented	14 (7.7)
Marital Status	
Single	29 (15.8)
Married	114 (62.3)
Divorced	21 (11.5)
Widowed	19 (10.4)
Education	
Less than College	99 (54.1)
College & Beyond	61 (33.3)
Unknown	23 (12.6)
Type of Insurance	
Private	110 (60.1)
Medicare	58 (31.7)
Medicaid/Self-pay/Indigent	15 (8.2)

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520 - Poster Session B

The effect of treatment modality and sequence on clinically significant chronic lymphedema in patients with vulvar carcinoma

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Objectives: To describe the rates of clinically significant chronic lymphedema (CL) after treatment for vulvar carcinoma by treatment modality and sequence.

Methods: Institutional review board approval was obtained. Patients with a primary diagnosis of squamous cell vulvar carcinoma were identified from January 2000 - December 2010. Patients who had an inguinal lymph node dissection (ILND) or groin radiation (RT) were selected for analysis. Records were reviewed for demographic, clinicopathologic, treatment, and outcome information retrospectively. Clinically significant CL was defined as patients who required treatment with compression stockings, wrapping, or physical therapy, and was recorded by laterality. Patients were divided by groin treated into the following groups: ILND without adjuvant RT, ILND followed by adjuvant RT, neoadjuvant chemoradiation (NCRT) without ILND, and NCRT followed by ILND. Pearson Chi-square or Fisher's exact tests were used for statistical analysis.

Results: There were 149 patients that resulted in 271 treated groins. See Table 1 for demographic and clinicopathologic data. With regards to the treatment groups of ILND without RT, ILND followed by RT, NCRT without ILND and NCRT followed by ILND, there were 111, 37, 94 and 29 groins respectively. The rates of CL in patients with single modality treatment (ILND and NCRT alone) were 11% and 6%, respectively. Multimodal therapy resulted in higher rates of CL, 14% in the ILND followed by RT (n=37) group and 17% in the NCRT followed by ILND (n=29), though this difference was not significant. Stage, inguinal wound complications, vulvar wound breakdown and vulvar infections were not associated with an increased risk of CL.

Conclusions: The rates of clinically significant CL were not impacted by single modality or multimodal treatment or sequence of therapy in this study. The low rate of CL in our study is likely because we included only patients with symptomatic lymphedema. Knowing the rates of CL in these various treatment groups will be helpful in the counseling of patients. No predictive factors for CL could be identified. A significant proportion of patients with multimodal treatment will go on to develop lymphedema and further investigation is needed to identify predictors.

Table 1:

Demographics	n=149(%)	p-value
Age (median, range)	69.5 (26-92)	
Race		
Caucasian	141(94.6)	
African American	8(5.4)	
Tobacco Use		
Never	83(55.7)	
Prior	25(16.7)	
Current	39(26.2)	
Unknown	2(1.3)	
Stage		
I	70(47)	
II	18(12.1)	
III	48(32.2)	
IV	6(4)	
Unknown	7(4.6)	
Grade		
1	57(38)	
2	46(30.7)	
3	28(18.7)	
unknown	19(12.7)	
Lymph Node Dissection		
None	20(13.4)	
Unilateral	70(47)	
Bilateral	39(26.1)	
Unknown	20(13.4)	
Treatment Modality by Groin	N=298	
ILND, no RT	111(37.2)	
ILND, adjuvant RT	37(12.4)	
Neoadjuvant CRT, no ILND	94(31.5)	
Neoadjuvant CRT, ILND	29(9.7)	
% Chronic Lymphedema by Variable		
Treatment Modality Sequence		p=0.14
ILND, no RT	11%	
ILND, adjuvant RT	14%	
Neoadjuvant CRT, no ILND	6%	
Neoadjuvant CRT, ILND	17%	
Stage		p=0.09
I	11%	
II	0%	
III	9%	
IV	0%	
Smoking	13%	p=0.07
Inguinal Wound Complication	6%	p=0.26
Vulvar Wound Breakdown	7%	p=.78
Vulvar Infection	9%	p=1

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521 - Poster Session B

Improved quality of life for early stage estrogen positive cancer survivors on a low-carbohydrate, calorie-restricted dietary intervention

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Objectives: This feasibility study evaluated quality of life measures in overweight endometrial and breast cancer survivors on a low-carbohydrate, calorie-restricted dietary intervention.

Methods: Overweight, estrogen-receptor positive postmenopausal endometrial and breast cancer survivors who completed appropriate surgical management and adjuvant therapy were eligible for the study. There were 35 women enrolled on the study, 31 completed the dietary intervention and surveys were used for analysis. The mean age was 57 years (42-68), with a mean weight of 220.5 lbs (170.8-296.6) and mean BMI of 37.5 kg/m^2 (28.4 – 49.5). The dietary intervention utilizes 0.5g protein/lb (actual body weight), less than 40 grams of carbohydrates, and 800-1200 calories per day. Patients utilized the dietary intervention for an average of 25.8 weeks (7-59) depending upon their weight loss goals, aimed at achieving a BMI of ≤28 kg/m^2. Quality of life was measured by a short-form health survey, SF-36, measuring functional status, wellbeing and overall evaluation of health (Brazier, 1992). Patients completed the quality of life questionnaire at baseline and every 2 months until the end of year 2. The Student's t-test was used to analyze mental and physical health scores at baseline and intervals thereafter, $P \leq 0.05$ was considered statistically significant.

Results: The mean total body weight reduction after dietary intervention was 21.9% ($P=4.4\times10^{-13}$), equivalent to 48.4 lb per individual at the diet termination. The improvement in the mean physical health scores of 19.7% from baseline to diet termination was statistically significant ($P=7.43\times10^{-8}$). While the majority of subjects had baseline scores above the population norm, mental health scores also improved by 7.2% when compared to diet termination ($P=0.0134$).

Conclusions: Overall physical and mental health quality of life scores were significantly improved as a result of the low-carbohydrate, calorie-restricted dietary intervention in overweight, estrogen-receptor positive postmenopausal endometrial and breast cancer survivors. Additional research with a larger sample size may confirm the quality of life improvement associated with weight loss through a low carbohydrate dietary intervention.

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522 - Poster Session B

Novel functions for LIN28A/B in ovarian cancer predisposition and tumorigenicity

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Objectives: The RNA binding proteins LIN28A and LIN28B function at a critical junction of pluripotency, metabolism and metastasis. Recent evidence implicates the LIN28 gene family as key determinants of ovarian cancer susceptibility. However, the clinical significance and the mechanisms by which the LIN28 genes contribute to ovarian cancer have not been explored.

Methods: We utilized multivariate logistic regression to test associations between LIN28A/B transcript, gene and microRNA expression and outcome demographics for the 581 ovarian cancers characterized by the Cancer Genome Atlas consortium (TCGA). LIN28A/B expression was targeted in established ovarian cancer cell lines (A2780, TOV112D) using siRNA and shRNA. Gene and microRNA expression was validated by qPCR and Western blot. Ovarian cancer spheroids were induced by culturing cells in serum-free media in ultralow-attachment plates.

Results: Our results indicate that LIN28A expression is associated with shorter disease-free interval in women with optimally debulked high grade serous ovarian cancers ($P<0.05$). Using serial logistic regression with L1 normalization (Lasso analysis), we discovered LIN28A levels correlated robustly with multiple genes rather than miRNAs: APOC3 (beta = 0.74), FGG (beta = 0.69), HBG1 (beta = 0.67) and HEMGN (beta = 0.67). Robust correlations between LIN28B and multiple miRNAs were detected: let-7b (beta = -0.47), let-7d (beta = -0.34), let-7i (beta = -0.31) as well as others [miR-222 (beta = -0.29), let-7e, miR-222, miR-324-5p] not previously known to be regulated by either LIN28 gene. Lastly, we found that expression of LIN28B but not LIN28A was induced by culturing A2780 and TOV112D ovarian cancer cells as spheroids. Knockdown of LIN28B expression confirms that LIN28B directly regulates the let-7 and other miRNAs identified by our analyses, promotes spheroid assembly and in vivo tumorigenicity of ovarian cancer cell lines.

Conclusions: Our data indicate that LIN28A primarily functions by regulating patterns of gene expression while LIN28B plays a key role in determining levels of let-7 and other microRNAs. These analyses identify novel pathways potentially important for determining not only ovarian cancer susceptibility but also the proliferation and metastasis of this disease.

523 - Poster Session B

Serine protease matriptase and CA-125 co-testing for ovarian cancer detection

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Objectives: To identify new biomarkers to assist in the detection and therapeutic intervention of epithelial ovarian cancer (EOC).

Methods: Candidate biomarkers to complement CA-125 in the detection of (EOC) were selected by micro-array expression. Quantitative real-time PCR was used to measure mRNA levels of candidate biomarkers in a sample set consisting of 7 specimens of benign ovarian epithelium, 13 benign ovarian masses, and 53 EOCs. Based on these results, 6 novel ELISA immunoassays were developed. The first ELSIA test selected for validation was designed to assay the serine protease matriptase in an IRB-approved serum bank of 85 EOC patients. High CA-125 and matriptase levels were defined as 2 standard deviations above the mean of the benign ovarian epithelium sample set.

Results: High CA-125 mRNA expression had a sensitivity of 68% and specificity of 86%, with a positive predictive value (PPV) of 97% and a negative predictive value (NPV) of 26%. High matriptase mRNA expression had a sensitivity of 77% and a specificity of 86%, with a PPV and NPV of 98% and 33%, respectively. Combined, the sensitivity and specificity of the 2 markers for detecting EOC was 92% and 86%, with a PPV of 98% and a NPV of 60%. The sensitivity of CA-125 and matriptase for early stage disease (stage I-II) was 60% and 68%, respectively. This improved to 92% when the 2 markers were combined. High CA-125 and matriptase levels were detected by ELISA in 72% and 39% of serum samples from EOC patients, respectively. Combined, the sensitivity of the 2 markers for detecting EOC improved to 87%. High levels of matriptase or CA-125 were found in 39% of serum samples from patients with early stage disease. However, matriptase and CA-125 co-testing identified 72% of patients with early stage disease. High serum CA-125 and matriptase levels were found in 85% and 43% of patients with advanced stage disease. Matriptase and CA-125 co-testing identified 94% of patients with advanced stage disease.

Conclusions: These data suggest that matriptase is a useful biomarker for ovarian cancer and improves the sensitivity of CA-125 for detecting both early and advanced stage disease. Based on finding high levels of tumor and serum matriptase expression in patients with ovarian cancer, matriptase enzymatic activity may be a novel therapeutic target.

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524 - Poster Session B

Prevalence of cognitive impairment, pain, depression, and neuropathy in women with gynecologic malignancies

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Objectives: Survivorship and quality of life for women with gynecologic malignancies is negatively impacted by cognitive deficits, pain, depression and neuropathy. The goal of our study was to determine prevalence of these symptoms in our ambulatory gynecologic oncology practice.

Methods: One hundred sixty-five women treated for gynecologic malignancies were identified and interviewed utilizing the Montreal Cognitive Assessment (MoCA), Patient Health Questionnaire 9 (PHQ-9) for depression, and Wong-Baker Pain Scale. Fisher's exact and Student's-t tests were performed using SPSS software.

Results: The mean MoCA score was 24.13 (range 13-30; SD 3.9) and 96 (60%) screened positive for CI as evidenced by MoCA scores less $\leq$26. Of these, 39 (24%) had scores <21. CI was associated with non-white race, low education level, and older age at diagnosis ($P<0.05$). Thirty-one (19%) patients reported clinically relevant pain (Wong-Baker score $\geq$6). Clinically relevant neuropathy was reported by 37 (22%) patients, and was associated with ovarian cancer, advanced stage, and prior treatment with chemotherapy ($P\leq0.05$). 32 (19%) and 20 (12%) screened positive for mild and moderate/severe depression respectively. Depression was associated with pain and neuropathy ($P<0.05$). 55 (33%) patients were interested in participating in clinical trials related to pain, neuropathy and cognitive function.

Conclusions: A high proportion of women with gynecologic malignancies in our patient population screened positive for CI, pain, neuropathy and depression that impacts their quality of life. Further research is needed to address these symptoms and assess the impact of CI on decision-making and adherence to complex treatment plans with associated side effects and sequelae.

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525 - Poster Session B

Correlation of survival-stratified proteomic and curated gene data reveal a three-protein biomarker panel that predicts long-term survival of patients with primary epithelial ovarian cancer

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Objectives: To address the current need for diagnostic tools that can predict disease prognosis in epithelial ovarian cancer (EOC) patients, we combined proteomic data generated from primary EOC patient tissues stratified by survivorship with survival-associated gene abundances identified from the Curated Ovarian Database (COD).

Methods: Paraffin tumor specimens from short- (n=15, <2 yr) and long-term (n=28, >7yr) ovarian cancer survivors were analyzed by mass spectrometry (MS)-based proteomics, and significant protein abundance differences were identified by Wilcoxon non-parametric testing ($P<0.05$). Differentially abundant proteins were correlated to a 191-gene transcript set compiled from Combat batch corrected COD data predictive of overall (n=1,138) and 10-yr (n=733) overall survival. ROC and Kaplan-Meier curves were generated for correlated candidates across the proteomic discovery patient cohort analyzed.

Results: Eighty-seven significantly, differentially abundant proteins were identified between long- and short-term ovarian cancer survivors ($P<0.05$). Correlation of these candidates with survival-associated COD genes revealed three proteins, namely, signal recognition particle receptor subunit beta (SRPRB), antigen peptide transporter 1 (TAP1) and serpin B1 (SERPINB1), that exhibited significantly decreased abundances ($P<0.05$) in short versus long-term survivors as well as hazard ratios (HR)<0.76 across COD data. Kaplan-Meier analyses revealed mean HR scores of 0.75 ± 0.02 and log rank p-values of 0.00042 ± 0.00041 across this candidate set. ROC and leave-one-out (LOO) statistics of these three candidates combined revealed an AUC of 0.774 and an LOO accuracy of 0.761 for predicting survival.

Conclusions: Mass spectrometry proteomics and utilization of the COD has revealed three proteins whose differential abundances correlate significantly with time of survival in EOC patients. Prospective assessment of these proteins should be performed to confirm their association with long-term survival. Identification of patients with long-term survival may allow for personalized care and restriction of patients with poor prognosis cancer to participate in investigational trials.

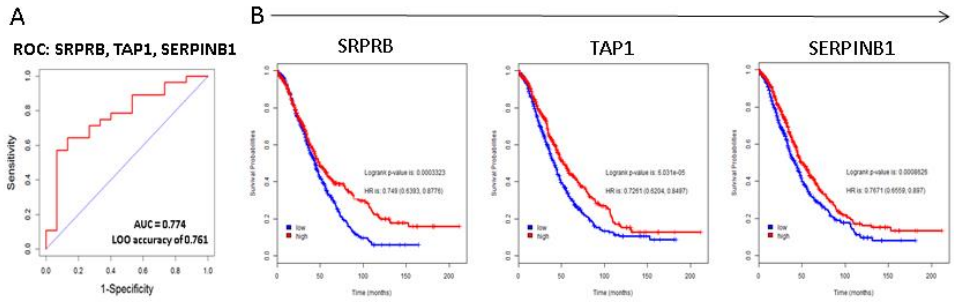

Figure 1A: ROC curve detailing accuracy of SRPRB, TAP1 and SERPINB1 combined in predicting survival across patient cohort analyzed (AUC = 0.774, LOO accuracy of 0.761). Figure 1B: Kaplan-Meier plots of SRPRB, TAP and SERPINB1 predicting survival across patient cohort.

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526 - Poster Session B

Diminished survival of separated, divorced, or widowed uterine cancer patients: a potential focus for survivorship programs

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Objectives: Relationship status has been associated with prognosis in multiple cancer types and the biopsychosocial impacts of relationship status likely play significant roles in the context of health and disease. We sought to define the effect of relationship status on disease-specific survival (DSS) in patients diagnosed with uterine cancer.

Methods: Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program from 1988-2006. Women were stratified by reported relationship status grouped as current (C) relationship (married, partnered, or common law relationship), single (S), former (F) relationship (separated, divorced, or widowed), or undeclared (U) and DSS was analyzed via the Kaplan-Meier method and by univariate and multivariate Cox regression modeling.

Results: There were 59,628 uterine cancer patients with DSS data. The distribution of cases by reported relationship status was 52% C, 14% S, 29% F, and 5% U. The DSS by relationship status was 87% for C (identified in previous studies to have the best outcome), 85% for S, 77% for F, and 86% for U. Differences in DSS were more exaggerated when stratified by historical stage and race. The unadjusted hazard ratio (HR) for DSS was 1.24 (95% CI 1.16-1.32) for S, 1.91 (95% CI 1.82-1.99) for F, and 1.21 (95% CI 1.09-1.35) for U, relative to DSS for C. Patient-reported relationship status was an independent prognostic variable even after adjusting for age, historical stage, race, and radiation treatment.

Conclusions: Women in a current relationship had the best DSS and those who are separated, divorced or widowed had the worst DSS. Single women had intermediate DSS. Patient-reported relationship status was an independent prognostic factor for uterine cancer DSS that merits prospective evaluation to determine mechanism (depression, anxiety, dysregulation of cortisol and inflammatory cytokines), and whether survivorship interventions can mitigate the impact of relationship status on DSS.

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527 - Poster Session B

Location of hospice referral and its impact on subsequent emergency department (ED) visits

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Objectives: It has previously been shown that referral to hospice can decrease inpatient admission rates, particularly from the outpatient setting. The objective of this study was to determine if outpatient or inpatient hospice referrals affect the ED visit rate of patients with gynecologic malignancies.

Methods: Gynecologic oncology patients with a hospice referral from the hospital or from clinic between January 2009 and June 2012 were identified and data was abstracted from their medical records under an IRB-approved protocol. Clinical information sought included emergency room visits and hospital admissions. Data was analyzed using a Fisher's exact test.

Results: There were 126 patients identified, with 89 (71%) of these patients referred from an inpatient setting and 37 (29%) as outpatient. The average age of women referred as an inpatient was 61.3 years while outpatient-referred women averaged 69.8 years. Cancer types in the outpatient referral group included 25 (68%) patients with ovarian, 9 (24%) with uterine, 2 (5%) with cervical, and 1 (3%) with vulvar or vaginal cancers. In the inpatient referral group, cancer types included 41 (46%) patients with ovarian, 23 (25%) with uterine, 19 (21%) with cervical, and 6 (6%) with vulvar or vaginal cancers. The difference in subsequent ED visits after referral between inpatient (4/89, 4%) vs outpatient referrals (1/37, 3%) was not significant (P=0.99). There was also no difference in hospice type (home hospice vs inpatient hospice) when selecting for patients that had an ED visit (P=0.58).

Conclusions: Whether referred to hospice from an inpatient vs outpatient setting, there was not a significant difference in the number of subsequent ED visits among the groups. Enrollment in hospice can decrease subsequent ER visits, thereby reducing health care cost, regardless of how they were referred, and whether they are at home or in inpatient hospice.

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528 - Poster Session B

BRCA mutation status is not associated with diminished ovarian reserve among women at high risk for ovarian cancer

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Objectives: Studies have suggested that women with *BRCA* mutations are more likely to experience diminished ovarian reserve, which may lead to premature menopause and/or infertility. Our objective was to compare ovarian reserve between

women who carry *BRCA* (*BRCA*1+ or *BRCA*2+) mutations and those who do not (*BRCA*-) by measuring Anti-Müllerian hormone (AMH), a serum marker used to predict response to ovarian stimulation.

Methods: Serum from premenopausal patients in a high-risk ovarian cancer-screening clinic was banked from 2006-2012. Women were defined as high risk if they had a known *BRCA* mutation or a strong family history of breast or ovarian cancer. Women who received chemotherapy and those with unknown *BRCA* status were excluded. Serum AMH was measured in triplicate with a commercially available ELISA kit. A regression model that included age, smoking status and hormone use was used to test the association of *BRCA* status and serum AMH.

Results: 41 *BRCA*1+ women, 47 *BRCA*2+ women and 13 *BRCA*- women, contributed a total of 101 samples. Only race differed between women with *BRCA* mutations and those who were *BRCA*- (P=0.019). All other demographic factors including age, tobacco use, breast cancer history, and obstetrical history were similar between groups (all P>0.05), though *BRCA*1+ and *BRCA*2+ patients were younger than *BRCA*- women (36.4 yrs vs 37.2 yrs vs 39.8 yrs, P=0.053). Overall, the mean serum AMH of *BRCA*1+ patients was 2.50 + 3.15 ng/mL, *BRCA*2+ patients was 2.14 + 2.49 ng/mL while the mean AMH of *BRCA*- patients was 1.98 + 2.20 ng/mL. When placed into the model, age was significantly associated with AMH, with log transformed AMH being 0.07 units lower with each year of increased age (P<0.001). Log transformed AMH was 0.23 units lower in *BRCA*1+ patients and 0.33 units lower in *BRCA*2+ patients compared to *BRCA*- patients, however, this was not statistically significant (P=0.438, P=0.271).

Conclusions: In women at high risk for ovarian cancer, serum AMH concentration was not significantly associated with *BRCA* mutation status, suggesting that *BRCA* mutation carriers do not have diminished ovarian reserve compared to women who do not have a *BRCA* mutation. These findings may have significant clinical implications as *BRCA* mutation carriers struggle to balance desire for fertility with the need for risk-reducing oophorectomy.

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529 - Poster Session B

Survival of women with microinvasive adenocarcinoma of the cervix is not improved by radical surgery

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Objectives: To evaluate if radical surgery impacts 5-year survival in patients with microinvasive adenocarcinoma (ACA) of the cervix.

Methods: The NCI's Surveillance, Epidemiology, and End Results (SEER) Program's 18 registries were queried from 1988 - 2007 to perform a retrospective cohort study of women with microinvasive (≤3 mm in depth and ≤7 mm in horizontal spread) FIGO stage IA1 cervical cancer. Overall 5-year survival by hysterectomy type (simple [SH] vs radical [RH]) and cell type (squamous cell cancer [SCC] vs ACA) was determined utilizing the Kaplan-Meier method and 95% confidence intervals were calculated. Lymph node status was also evaluated. Patients who received adjuvant radiation were excluded from analysis.

Results: Of the 1,401 patients with microinvasive cervical cancer, 1,111 (79.3%) had SCC and 290 (20.7%) had ACA. Among patients with ACA, the 5-year survival was 98.7% (95% CI= 94.9 to 99.7) for SH and 95.6% (95% CI= 90.4 to 98.0) for RH, with 47% undergoing RH. In this cohort, 0.8% had positive pelvic nodes, none had positive aortic nodes, and 91.2% had confirmed negative nodes (8% not reported). For comparison, survival and node involvement was calculated for patients with 1A1 SCC. Among these patients, 5-year survival was 96.6% (95% CI= 95.1 to 97.6) following SH and 98.2% (95% CI= 95.4 to 99.3) after RH, with 21% of patients receiving RH. The frequency of nodal involvement in stage IA1 SCC was 0.7% for pelvic nodes and 0.04% for aortic nodes, with 83.3% of patients having confirmed negative nodes (16% not reported).

Conclusions: Although our estimates are somewhat limited by a modest sample size, our findings suggest that survival of women with microinvasive ACA is not improved by radical surgery. The data suggest that choice of surgical approach (RH vs SH) should not be influenced by cell type. Regardless of histology, the frequency of nodal involvement was very low, supporting the fact that these patients do not benefit from lymphadenectomy. The final decision regarding class of hysterectomy should be individualized based on patient preference and clinical risk factors, but we submit this study as evidence that, ceteris paribus, treatment for stage 1A1 ACA can be the same as for 1A1 SCC.

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530 - Poster Session B

A pilot study of depression prevalence and progression in patients receiving chemotherapy for gynecologic malignancies using a validated tool

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Objectives: Research involving chemotherapy patients has been predominantly focused on the physical aspects of chemotherapy. We chose to begin to look at the psychological effects of chemotherapy by exploring the use of a validated depression scale, the Patient's Health Questionnaire 9 (PHQ-9) in patients initiating and undergoing primary chemotherapy for gynecologic malignancies.

Methods: After IRB approval 63 sequential patients who were beginning chemotherapy for gynecologic malignancies were asked to complete a baseline PHQ-9 survey and to complete a follow-up survey prior to each subsequent cycle of chemotherapy for a total of 6 separate responses. Per the survey instructions, the screen was scored from 0 to 23 with cutoffs at 10 for mild depression, 14 for moderate, 19 for moderately severe, and greater than 20 for severe depression. Score rates are presented as the sum of PHQ-9 scores with the denominator the number of patients measured. The score rate was used in order to reduce the effect of missing values and provide comparability between cycles.

Results: The score rates showed a decline over time from 5.9 to 4.0. The number of patients who completed the survey declined with each cycle especially after 3 cycles. Forty-one percent of all patients did not have a recorded score for the last cycle. Missing value analysis of the data showed a potential demarcation for missing values occurred after the 3rd cycle. Contingency table analysis of these data demonstrated that those patients who did not have a recorded score after the mid-point of treatment had more severe depression than those who continued to receive the depression screen ($P<.05$).

Conclusions: This pilot study showed that it is feasible for patients on chemotherapy with gynecologic malignancies to self-administer depression survey instruments. It also showed that scores appeared to decline over time. Further, patients who dropped out were not surprisingly more depressed than patients who continued chemotherapy. Future directions for this research include interventions to refine reasons for depression in this patient population, the influence of anxiety on depression in this group of patients, and refine the reasons for early stopping of chemo that may be related to psychological factors.