sarcomatoid carcinoma; 1 lymphoepithelioma-like carcinoma and 1 adenoid cystic carcinoma. Immunohistochemical profile for the UCa was CK7, CK5/6, CK903, p63, Thrombomodulin positive; CK20, CDX2 negative. P16 was positive in 67% (12/18) of UCas; GATA-3 was negative in 78% (14/18) of UCas. The 4 UCs were all positive for GATA-3 and two were positive for p16. Adenocarcinomas (8) have different immunohistochemical profiles: CK7 positive in all 8 cases; CK20 in 6; CDX2 in 5 and thrombomodulin in 2 cases. CK5/6 and p63 were negative in all 8 cases. All patients underwent surgical excision. 22 patients had lymph node metastases (17 UCa; 5 adenocarcinoma). 15 patients had distant metastases (12 UCa and 3 adenocarcinoma), with lung as the most common site. In addition to surgery, 22 patients had chemotherapy, 8 had radiation and 12 had chemoradiation. 114 patients had clinical outcome data, with follow-up of 0.03 to 236.8 months (median: 19.7 months). 24 patients were alive with no disease (median: 17 months); 35 patients were alive with disease (median: 20 months); 28 patients died of disease (median survival: 11 months); 2 patients died of other causes; 25 patients died of unknown causes.

Conclusions: Primary urethra carcinomas are rare, a majority having overlapping morphological features and immunohistochemical profiles of UC and SCC. We propose these should be called Urethral Carcinoma, rather than UC or SCC. PUC may behave aggressively with lymph node and distant metastases with a short median survival time.

1080 Detecting Additional Chromosomal Translocations in TFE3 Translocation Renal Cell RCC By RNA-Seq

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Background: *TFE3* translocation renal cell carcinoma (RCC), officially accepted as distinct subtype by 2004 WHO classification, is characterized by chromosomal translocations involving *TFE3* gene (Xp11). As such, *TFE3* translocation RCC has worse prognosis than other RCC subtypes. However, little is known about other chromosomal translocations or fusions in this particular RCC subtype. Therefore, it was investigated if any other recurrent chromosomal translocations or fusions are associated with *TFE3* translocation RCC.

Design: RNA-seq has been performed on *TFE3* translocation RCC cell lines: UOK109 and UOK145 for unbiased detection of chromosomal translocations including *TFE3*. All potential translocations were detected with SOAPf------use [1] fusion detection pipeline (Version 1.26) plus several layers of additional filters. More *TFE3* translocation RCC samples in TCGA (The Cancer Genome Atlas) RNA-seq database have been analyzed for additional translocations/fusions by the same method.

Results: *PSF-TFE3* and *NONO-TFE3* translocations have been detected in UOK 145 and UOK109 cell lines, respectively. Onaverage, 1-2 translocations/fusions have been identified in the cell lines and 7 cases from TCGA RNA-seq database. Among these translocations/fusions, none of them are recurrent except *TFE3* related translocations/fusions.

Conclusions: There are on average 1-2 translocations in *TFE3* translocation RCC. However, except *TFE3* related translocations, none of them are recurrent. These translocations may be more likely to be secondary/passenger events during the carcinogenesis. This study further elucidates the important carcinogenic role of *TFE3* in this subtype RCC.

[1]. Jia W, Qiu K, He M, Song P, Zhou Q, Zhou F, Yu Y, Zhu D, Nickerson ML, Wan S, Liao X, Zhu X, Peng S, Li Y, Wang J, Guo G: SOAPfuse: an algorithm for identifying fusion transcripts from paired-end RNA-Seq data. Genome biology 2013, 14:R12.

1081 Distinguish Sarcomatoid Urothelial Carcinoma and Inflammatory Myofibroblastic Tumor By TERT Promoter Mutations

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Background: Inflammatory myofibroblastic tumor (IMT) of the urinary bladder is an unusual spindle cell lesion that exhibits cytologic atypia, infiltrative growth, and mitotic activity mimicking malignant tumors, such as sarcomatoid urothelial carcinoma (UC). Most IMT are positive for cytokeratin. ALK reactivity was seen in 56% of cases. In addition, Absent ALK expression was associated with a higher age overall, subtle histologic differences, and death from disease or distant metastases (in a younger subset). Recently, *TERT* promoter mutations appear as marker of urothelial carcinoma. Therefore, it was investigated if *TERT* promoter mutations could be used to distinguish sarcomatoid UC from IMT.

Design: Cases of sarcomatoid UC and IMTs were collected. Slides were reviewed and selected to make sure that the lesion is at least >20% of all tissue. Macro-dissection was performed in some of cases. gDNA was extracted from those tissue. *TERT* promoter mutations were detected by standard PCR-sequencing.

Results: 20 cases of sarcomatoid UC were collected for this study. Sarcomatoid component were 5-90% of whole tumor. Most of tumors were predominantly located at bladder (with few from kidney and ureter). Other diversion components were squamous, glandular differentiation and small cell carcinoma. 17 cases (85%) were found to have *TERT* promoter mutations. In 9 cases of IMTs were collected for this study, 3 of them come from bladder; the others come from different body sits including Liver, lung and soft tissue. Most of the IMTs were positive for cytokeratin, negative for ALK. However, None of IMT was positive for *TERT* promoter mutation.

Conclusions: *TERT* promoter mutation could be a biomarker for sarcomatoid UC to distinguish from IMT. This assay can be potentially useful in some clinical setting, such as small biopsy specimen.

1082 Spatial-Temporal Analysis of Urothelial Carcinoma for TERT Promoter Mutations

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Background: Urothelial carcinomas (UC) are well known for multifocality and recurrence. Recent studies suggest that *TERT* promoter mutations could be a biomarker for the diagnosis or follow up urothelial carcinoma in urine. Therefore, the *TERT* promoter mutation status in those recurrent and multifocal urothelial carcinoma are important information for the utility of *TERT* promoter mutations as urothelial carcinoma biomarker.

Design: For recurrent UC, we collected cases from 10 patients, 23 specimens. For multifocal UC, we collected cases from another 10 patients, 25 different tumor sits. All slides were reviewed and selected to make sure that at least 20% of UC components are present. Macro-dissection was performed in some of cases. gDNA was extracted from those tissue. *TERT* promoter mutations were detected by standard PCR-sequencing.

Results: For recurrent UC, specimens from 8/10 patients were positive for *TERT* promoter mutations, the rest of 2 were negative for the mutations. Importantly, the mutation status were maintained in the recurrent UC. For multifocal UC, specimens from 7/10 patients were positive for *TERT* promoter mutations, the rest of 3 were negative for the mutations. Again, the mutation status were maintained in theses multifocal UCs, too.

Conclusions: We found that *TERT* promoter mutations status keeps consistently in recurrent and multifocal UC of the same individual. This indicates that carcinogenesis of recurrent and multifocal UC from the same individual are probably the same. Importantly, *TERT* promoter mutation would be a good biomarker for the patient whose previous UC were positive for the mutations.

1083 Interobserver Reproducibility in Grading "Poorly Formed Glands" as Gleason Pattern 4 Prostate Cancer Among Urologic Pathologists

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Background: Gleason pattern 4 (GP4) prostate cancer (PCa) in needle biopsy is critical for patient management and prognostication. The 2005 ISUP modified Gleason grading system regards "poorly formed glands" as GP4. The diagnostic reproducibility is unknown.

Design: Digital images of 8 PCas representing a spectrum of well to poorly formed glands were used to query 17 urologic pathologists for the definition of "poorly formed glands". They were then asked to grade additional 23 PCa cases with poorly formed glands as GP4 or not. These cases were classified into 9 sub-groups based on the number of poorly formed glands (<5, 5-10, >10 in each focus) and location (immediately adjacent to, between and away from other well formed PCa glands) by two study authors before the study. A consensus diagnosis was defined as agreement by 75% participants.

Results: Of 8 images queried for the definition of "poorly formed" glands, 5 attained consensus. Small cancer glands with rigid but well-formed lumens were not considered "poorly formed". Small glands with no discernible lumens, elongated glands with compressed lumen and elongated small nests/cords with no discernible lumen were considered "poorly formed glands". The interobserver agreement for the definition of "poorly formed glands" is fair (kappa=0.35). The diagnostic agreement in 23 ases was fair (kappa=0.34) with 16 (70%) attained consensus. Focus with < 5 poorly formed glands regardless of their locations attained a consensus diagnosis of "not GP4" with a sensitivity, specificity and accuracy of 67% (4/6), 100% (10/10) and 88%, respectively. Focus with >10 poorly formed glands that are not immediately adjacent to other well-formed glands attained a consensus diagnosis of GP4 with a sensitivity, specificity and accuracy of 60% (6/10), 100% (6/6) and 75% (12/16), respectively. The last 3 cases did not achieve a consensus as the poorly formed glands were at the edge of the biopsy specimens. Majority of participants (15/17) would grade poorly formed glands as GP4 only when they retained poorly formed morphology in at least 2 levels.

Conclusions: The agreement for grading "poorly formed" PCa glands as GP4 is only fair among urologic pathologists. More studies are needed to better define "poorly formed" PCa glands. Focus with < 5 poorly formed glands regardless of their locations is not diagnostic of GP 4. Focus with >10 poorly formed glands that are not immediately adjacent to other well-formed glands are diagnostic of GP4.

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1084 Application of Standardised Tumour Regression Scoring Systems To Post-Neoadjuvant Serous Ovarian Carcinoma

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Background: There is no standardised method for assessment of chemotherapeutic response in epithelial ovarian cancer (EOC). EOC is increasingly treated with neo-adjuvant chemotherapy (NAC), with interval debulking. The presence of more viable disease is a negative prognostic factor in advanced EOC post- NAC and there is a need for a reproducible method for the assessment of treatment response.

Design: The archive at UCHG was searched for cases of serous adenocarcinoma of ovarian/primary peritoneal origin resected from 2009 - 2013. 21 post-NAC resections were identified. Histology was reviewed and two well-established tumour regression grade (TRG) systems, usually applied to Gastrointestinal malignancies, were applied;- Mandard TRG and Dworak TRG,

Mandard TRG		Dworak TRG	
Score	Histological findings	Score	Histological findings
1	Complete regression (=fibrosis without detectable tumour)	0	No regression
2	Fibrosis with scattered tumour cells	1	Predominantly tumour with significant fibrosis and/or vasculopathy
3	Fibrosis and tumour cells with preponderance of fibrosis	2	Predominantly fibrosis with scattered tumour cells(slightly recognisable histologically)
4	Fibrosis and tumour cells with preponderance of tumour cells	3	Only scattered tumour cells in the space of fibrosis with/without acellular mucin
5	Tissue of tumour without changes of regression	4	No vital tumour cells detectable

Treatment response was assessed in all sections and both systems were applied by two independent pathologists.

Results: Twenty cases showed partial pathological response; 1 showed complete pathological response. Chemotherapeutic effect was characterised by fibrosis, foamy macrophages and nuclear enlargement. “Free” psammoma bodies were a feature, specific to post-NAC serous carcinoma , analogous to the presence of acellular mucin in post-NAC rectal tumours.

Mandard TRG showed interobserver agreement in 18 of 21 cases (85.7%); for Dworak TRG there was agreement in 17 of 21 cases (80.9%).

18 cases with extra-ovarian deposits demonstrated a better treatment response in extra-ovarian deposits in comparison to the ovary, 9/18 cases (50%).

Conclusions: Mandard TRG was developed for oesophageal carcinoma but is already widely applied to assess to lower GI Adenocarcinomas and occasionally breast cancers. In this study, Mandard TRG was applicable and reproducible in ovarian serous adenocarcinomas .

1085 Recurrent Granulosa Cell Tumors: Clinicopathological and Molecular Markers

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Background: GCT comprise 2-5% of ovarian neoplasms, with unpredictable patterns of recurrence. The HER family, GATA4 and SMAD3 genes are reportedly involved in granulosa cell proliferation and apoptosis and may serve as new predictors of recurrence. The aim of this study was to evaluate the determinants of recurrence in GCT from a large single institution cohort.

Design: 137 patients diagnosed with GCT (1975-2014) were identified. Clinicopathological variables were obtained from EMR and pathologic records. Immunohistochemical staining (IHC) for calretinin, inhibin, HER 2, CD56, SMAD3, GATA4 was done on tumor tissue microarray for 88 GCT cases. Each marker was scored for % and intensity and H-score was established combining both.

Results: Of 137 GCT cases, 124 (90.5%) were Adult (AGCT) and 13 (9.5%) were Juvenile (JGCT). 12/137 (8.8%) patients had recurrence. AGCT recurred in 10/124 (8.0%) vs. 2/13 (15.3%) JGCT. Recurrence was significantly more frequent in Stage III and Caucasian (CA) patients. Recurrence was more frequent in tumor size ≥ 5cm and mitoses > 2/10hpf. Significantly increased expression of HER-2, SMAD3 and CD56 was seen in the recurrent cases. No significant differences were noted in the expression of Calretinin and Inhibin and VEGF.

Table 1: Clinicopathological features of recurrent compared to non-recurrent GCT

	N (%)	P value
RACE	10	
CA	7(70)	
AA	3(30)	
TUMOR SIZE (cm)	10	0.727
≤ 5	4(40)	
>5	6(60)	
MITOTIC ACTIVITY	12	0.126
≤ 2/10HPF	2(16.7)	
>2/10 HPF	10(83.3)	
FIGO STAGE	12	
I	2(16.7)	
II	2(16.7)	
III	3(25)	
Unstaged	5(41.7)	

Table 2: IHC markers in recurrent and non-recurrent GCT

	Recurrent (%)	Non-recurrent (%)	P value
Her-2			
H-score	20	0	0.011
SMAD3			
H-score	70	9	0.0001
CD56			
H-score	80	25	0.004
GATA4			
H-score	20	5	0.29

Conclusions: Recurrence is significantly higher in CA and stage III patients. JGCT show a higher tendency to recur, suggesting an aggressive course. CD56 may prove to be a prognostic marker for recurrent GCT. Expression of HER-2 and SMAD3 may present potential targets for novel therapy.

1086 Prognostic Factors for Pelvic Lymph Node (LN) Metastasis and Relapse in Pattern C Endocervical Adenocarcinomas (EAC): A Multi-Institutional Study

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Background: A new proposed pattern-based method (NM) (Int J Gyn Path 2013;32:592-601) has shown that classifying EAC by pattern correlates better with LN metastasis than using depth of invasion (DOI). Pattern A and most pattern B cases have not LN metastasis. While, patients with pattern C are more likely to have pathologic features found at the time of radical hysterectomy that might require adjuvant therapy.

The aim of this study was to assess the prognostic significance of local tumor factor in predicting LN metastasis and/or recurrence in patients with pattern C EAC.

Design: According to the NM, pattern C EAC is a tumor with extensive destructive stromal invasion. 180 cases originally diagnosed as pattern C EAC were re-review to assess the following architectural patterns of growth (APG): diffuse destructive (DD), confluent (CON), focal/linear destructive (FLD) and with a band-like lymphocytic infiltrate (BLL), solid component (SC) or micropapillary (MP) features. The most prominent portion of the tumor was selected for this study.

Data regarding tumor size, lower uterine segment extension (LUE) and number of lymphovascular spaces (LVS) with invasion, were defined.

Cox regression model was used in multivariate analysis.

Results: Ages ranged from 23 to 82 years (mean:47.2) the median follow-up was 39.5 months. The APG were assessed as DD in combination with CON (DD+CON) in 48%, DD in 14%, CON 10%, FLD 15%, BLL in 4%, SC in 5% and MP in 4% patients. The tumors ranged in size from 9 to 51 mm in maximum dimension (mean:22 mm). A total of 47 (26%) patients had LN metastasis, and 52% of them had tumors with DD+CON pattern. In comparison none of the 26 patients with tumors with a FLD pattern, had positive LN ($p<0.001$). All tumors with a MP component had LN metastasis (p:0.005). The number of LVS with invasion was significantly higher in patients with relapse (≥ 20 LVS). Sites of recurrence included retroperitoneum, vagina, lung, liver and pelvis. DOI was not found to be an independent factor (p:0.42).

Conclusions: Not all pattern C EAC behave aggressively. Most patients who have LN metastasis had tumors with DD+CON pattern. In contrast, none of the patients with tumors with a FLD pattern had LN metastasis or recurrence. In this study, all patients with metastatic disease or recurrence had > 20 LVS with involvement, suggesting that the number of LVS with involvement rather than DOI is the most important prognostic factor.

1087 Expression of Protease Activated Receptor-2 Is Related To Advanced Clinical Stage and Adverse Prognosis in Ovarian Clear Cell Adenocarcinoma

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Background: Protease activated receptor-2 (PAR-2) is G-protein-coupled receptors that is activated by protease such as trypsin. Recent studies demonstrate that PAR-2 activity correlates with cell proliferation and tumor growth in various tissue, and PAR-2 modulators is expected to valuable new thrapeutic agents. But the expression and role of PAR-2 in ovarian clear cell adenocarcinoma (OCCC) has not been investigated. Meanwhile, oxidative stress arising from endometriosis has been considered as cause of carcinogenesis in OCCC. We have previously demonstrated that oxidative stress upregulate PAR2 expression. Therefore this study is carried out to investigate the expression level of PAR-2 and its relation to clinicopathological factors and oxidative stress in OCCC.

Design: Immunohistochemical (IHC) evaluation of PAR-2 was performed on 95 cases of OCCC (FIGO stage I: 69, stage II: 2, stage III: 18, stage IV: 6). Strong expression was classified as positive PAR-2 expression (positive cells, >1%). In IHC evaluation of oxidative stress markers (COX2, iNOS, 8-OHdG), 31 cases of ovarian endometrioid adenocarcinoma (OEC) were also examined to compare with OCCC. These IHC stain was scored using Allred score (positive: $PS3^3$and IS^32). In addition, the clinicopathological findings including prognosis of 94 cases of OCCC were evaluated in detail.

Results: Fourteen cases of 71 in early FIGO stage (I-II) (20%) and 14 cases of 24 in advanced FIGO stage (III-IV)(58%) showed positive PAR-2 expression. Increased expression of PAR-2 was significantly correlated with advanced FIGO stage (p=0.0007). Advanced FIGO stage (p<.0001), LN metastasis (p<.0001) and increased expression of PAR-2 (p=0.011) were associated with shorter overall survival. There was no significant difference in COX2 and iNOS between OCCC and OEC. On the other hand, 59 cases (62%) of OCCC showed positive 8-OHdG expression, whereas all OEC showed negative them. We found no correlations between the expression of PAR-2 and the markers of oxidative stress. The presence of endometriosis did not affect the expression of these markers and prognosis.
Conclusions: 1) Our results suggest that PAR-2 plays an important role in the progression of OCCC. Therefore PAR-2 modulators may be a candidate of molecular target drug against to OCCC. 2) The expression of 8-OHdG is characteristic finding of OCCC in endometriosis-related ovarian carcinoma. The injury of DNA by oxidative stress may be involved in the carcinogenesis of OCCC.

1088 PTEN and ARID1A Mutations Are Favorably Prognostic of Survival in Endometrial Cancers Across Disease Stage and Tumor Histologic Grade

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Background: Mutations in the *PTEN* and *ARID1A* genes are known to be important in the pathogenesis of endometrial carcinoma (EC) and correlate with EC molecular subtypes (Nature, 2013 PMID: 23636398). *PTEN* mutations have further been associated with favorable pathological, clinical, and molecular features, but not survival outcomes per se. To our knowledge, *ARID1A* mutations have not been associated with favorable features or survival outcomes. Here we investigate the prognostic impact of *PTEN* and *ARID1A* mutations in EC.
Design: All available clinicopathological and mutation data for the 248 fully sequenced EC in The Cancer Genome Atlas Uterine Corpus EC database were downloaded and compiled. For each tumor, mutation data were discretized into either being mutated or not; *PTEN* and *ARID1A* mutation data was then analyzed for prognostic value using Cox proportional hazards regressions and Kaplan-Meier survival plots. All statistical analyses were conducted using the R 3.1.1 statistical software package.
Results: Mutations in *PTEN* and *ARID1A* independently were found to be highly favorably prognostic of overall survival (*PTEN*, death Hazard Ratio [HR] = 0.366, p-value = 0.018; *ARID1A*, HR = 0.177, p-value = 0.019) across all EC. A composite measure of having a mutation in *PTEN* and/or *ARID1A* was additionally favorably prognostic of overall survival (death HR = 0.276, p-value = 0.0025), and was robust even after controlling for tumor stage and histologic grade (recurrence HR = 0.434, p-value = 0.045, disease-free survival). Within an important group of aggressive EC, those with *TP53* mutations, the composite measure (*PTEN* and/or *ARID1A* mutation) was found to mirror these greater findings, although the result did not reach statistical significance (recurrence HR 0.352, p-value = 0.17, disease-free survival).
Conclusions: *PTEN* and *ARID1A* mutations are highly favorably prognostic of survival in EC. A composite measure of the two remains statistically significantly even after controlling for disease stage and tumor histologic grade, and may be prognostic in aggressive EC with *TP53* mutations as well. Mutational analysis of these two genes at the time of EC diagnosis could provide important prognostic information for patients beyond stage and grade alone.

1089 Pelvic Carcinosarcomas Are Frequently Associated With Serous Tubal Intraepithelial Carcinoma

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Background: It is widely accepted that serous tubal intraepitelial carcinoma (STIC) is the precursor of ovarian and "primary peritoneal" high-grade serous carcinoma (HGSC), while endometrioid (EC) and clear cell carcinomas (CCC) derive from malignant transformation of endometriosis. Pelvic carcinosarcomas (PCS)(ovarian, tubal and primary peritoneal) are rare and very aggressive malignancies, whose pathogenesis and molecular profile are poorly investigated. The goal of the study is to identify putative precursor lesions of PCS.
Design: A total of 16 PCS were collected retrospectively from the archive of the Department of Pathology, Spedali Civili di Brescia. Tumor slides were reviewed in order to assess primary tumoral site, carcinomatous (CC) and sarcomatous component (SC) and presence of STIC. Immunostaining of p53 was performed on FFPE primary tumor tissues sections and STICs and scored as: null (0%), weak (<75%, weak) and overexpressed (>75%, strong).
Results: Primary tumor sites were the fallopian tube (2 cases) and the ovary (13 cases). One patient with ovarian HGSC and carcinosarcomatous pelvic metastasis was also included in the study. CC was represented by high grade serous in 13 cases, endometrioid in 2 cases and undifferentiated in 1 case. The SC contained heterologous elements in 9/16 cases. All cases showed a concordant p53 immunostaining pattern in both tumor components (CC and SC) and it was classified as null in 3 cases, weak in 2 cases and overexpressed in 11 cases. The presence of STIC was identified in 9/16 cases. STIC p53 staining pattern was identical to that observed in the corresponding primary tumor.
Conclusions: The majority of PCS display morphological features similar to HGSC and show p53 immunostaining pattern indicative of TP53 gene mutations (null or overexpressed). They are frequently associated with STIC which shows an identical p53 immunostaining pattern. This may suggest an involvement of STIC and TP53 mutations in the pathogenesis of pelvic carcinosarcomas, as it has been demonstrated for pelvic HGSC.

1090 Cathepsin-k Expression in Gynecologic PEComas and Uterine Leiomyomas

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Background: Gynecologic perivascular epithelioid cell tumors (PEComas) are rare entities. Distinguishing these tumors from typical uterine leiomyomas, an important differential diagnostic consideration, can sometimes be easily made on the basis of morphology alone but overlap can exist. Leiomyomas can have an epitheliod morphology and express HMB-45, features usually seen in PEComas. For these reasons, distinguishing uterine leiomyomas and PEComas can be sometimes challenging. Recently, studies have shown that tumors of the PEComa family are strongly immunoreactive for cathepsin-k, a cysteine protease in the papain family that plays a role in osteoclast functioning. Here, we evaluate the expression of cathepsin-k in gynecologic PEComas compared to uterine leiomyomas.
Design: Cases of gynecologic PEComas diagnosed at our institution were retrieved from our files (1990-2014) and reviewed by a gynecologic pathologist. Tumors met diagnostic criteria for PEComas as defined by WHO: epitheliod or spindle cell neoplasms with myomelanocytic differentiation by IHC. They labeled for at least 2 melanocytic markers (Melan-A, HMB-45 and MITF-1). Selected cases were stained with cathepsin-k (clone 3F9, Abcam) and staining results were graded and compared to that of 10 histologically different uterine leiomyomas.
Results: A total of 5 (n=5) gynecologic PEComa cases were identified. Sites included the uterus and broad ligament, with one case diagnosed as a high grade sarcoma with PEComa features. Cathepsin-k expression was diffusely strongly positive (3+ cytoplasmic) in 4/5 PEComas. Most leiomyomas were negative for cathepsin-k (n=7/10) or showed focal and weak staining (1+ cytoplasmic) (n=3/10). The one PEComa case that was not strongly cathepsin-k positive had a staining pattern similar to leiomyomas and had only focal HMB-45 positivity in the same areas. Based on cathepsin-k expression patterns, this case was most likely a true leiomyoma. Finally, the high grade sarcoma case is most likely a malignant PEComa, as it had a 3+ cathepsin-k staining pattern.
Conclusions: Our study showed that gynecologic PEComas are diffuse and strongly immunoreactive for cathepsin-k compared to uterine leiomyomas and this stain serves as a useful adjunct in distinguishing the two entities.

1091 Histomorphologic Changes at the Fimbrial Ends of Primary Epithelial Ovarian Tumors; Is It the Site of Primary Ovarian Tumors More Than Expected?

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Background: In this study we evaluated histomorphologic changes at the fimbrial end of both serous and non serous ovarian cancers to evaluate origin of both type and we also used immunohistochemistry to determine tumor differentiation.
Design: 40 primary epithelial ovarian tumors and 40 control cases were included in the study. SEE-FIM protocol was used to sample fimbrial ends of all cases. Precursor lesions at the fimbrial ends were evaluated and p53 staining was applied for detecting p53 signature. For each tumor case PAX8, WT-1 and Calretinin were applied to determine mesothelial or Mullerian differentiation and to compare the staining pattern of tumors located in the ovary and fimbrial end.
Results: 70% of tumors were serous and 61% of them were high grade. The presence of tumor at the fimbrial end was statistically significant (p=0.02) in serous cancers compared to non-serous ones. There was no significant statistical difference between tumor grade with presence of tumor and STIC (serous tubal intraepithelial carcinoma) at the fimbrial end within serous cancers (p>0.05). STIC with tumor was seen in 6 of 28 cases, p53 signature in 11 of 28 and, tumor with p53 signature in 8 of 11 serous cancers. p53 signature was statistically significant in serous cancers (p=0.04) compared to control group and non serous cancers. All serous tumors at the fimbrial end and ovary showed tubal staining pattern. Tumor at the fimbrial end was seen in 33% of non serous cancers and 50% of them were borderline. STIC was seen in one case and p53 signature was seen in 5 of 12. Except mucinous carcinomas all non-serous cancers showed tubal staining pattern.
Conclusions: The results of our study suggest that in serous carcinoma, both invasive tumor and in situ carcinomas are not limited only in high grade tumors, but can be seen equally in low grade tumors. We showed that fimbrial ends can be a site of origins for non serous tumors also; but future studies with more cases are needed.

1092 CCNE1 Amplification and Overexpression Characterizes Ovarian Clear Cell Carcinoma But Not Ovarian Endometrioid Carcinoma

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Background: Ovarian clear cell and endometrioid carcinomas are believed to arise from a common precursor -ovarian endometrioma- and share certain molecular genetic alterations including *ARID1A* inactivating mutation. However, they have distinctive clinicopathological features, suggesting different molecular pathways involved in their development. Based on our previous genome-wide study disclosing *CCNE1* amplification in ovarian clear cell carcinoma in a discovery set, we analyzed *CCNE1* amplification and compared its expression between ovarian clear cell and endometrioid carcinomas. *CCNE1* encodes cyclin E1 and promotes cell cycle progression and genomic instability that are associated with tumor development.
Design: The expression levels of cyclin E1 were determined by immunohistochemistry in 89 ovarian clear cell carcinomas and 49 ovarian endometrioid carcinomas. DNA copy

number changes of *CCNE1* was assessed by two-color fluorescence in situ hybridization (FISH) in the tumors showing cyclin E1 overexpression. ARID1A loss and *TERT* (telomerase reverse transcriptase) mutation data were also available for comparison.
Results: Cyclin E1 overexpression occurred in 22 (25.3%) of 89 ovarian clear cell carcinomas but none in endometrioid carcinomas. *CCNE1* FISH in clear cell carcinomas revealed that 16.2% had an increased *CCNE1* copy number. All cases with *CCNE1* amplification demonstrated an intense immunoreactivity of cyclin E1. *CCNE1* amplification positively correlated with *TERT* promoter mutation (p= 0.015) which was thought to be one of the molecular mechanisms to increase TERT expression and maintain telomere length in cancer cells. There was no correlation between *CCNE1* amplification and loss of ARID1A protein, a characteristic feature of ovarian clear cell carcinoma.
Conclusions: Gene amplification and upregulation of *CCNE1* occur in ovarian clear cell carcinoma but not in ovarian endometrioid carcinoma, suggesting both types of ovarian cancer develop through distinct molecular pathways. CCNE mutations along with TERT promoter mutations occurring in progression may be responsible for clear cell carcinoma aggressiveness.

1093 Increased Proliferation in "Atypical Hyperplasia/Endometrioid Intraepithelial Neoplasia" of Endometrium With Concurrent Inactivation of ARID1A and PTEN Tumor Suppressors

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Background: Uterine endometrioid carcinoma is the most common neoplastic disease in female reproductive organs and develops from a precursor lesion, atypical hyperplasia/endometrioid intraepithelial neoplasia (AH/EIN). Although the genomic landscape of endometrioid carcinoma has been recently revealed, the molecular alterations that contribute to tumor progression from AH/EIN to carcinoma remain to be elucidated.
Design: In this study, we used immunohistochemistry to determine if loss of expression of two of the most commonly mutated tumor suppressors in endometrioid carcinoma, *PTEN* and *ARID1A*, was associated with increased proliferation in AH/EIN.
Results: We found that 78 (70%) of 112 cases exhibited decreased or undetectable PTEN and 15 (13%) of 112 cases had loss of ARID1A staining. ARID1A loss was focal, while PTEN loss was diffuse, and all specimens with ARID1A loss had concurrent PTEN loss (p=0.0003). Mapping the distribution of PTEN and ARID1A staining in the same specimens demonstrated that all AH/EIN areas with ARID1A loss were geographically nested within the areas of PTEN loss. A significant increase in the proliferative activity was observed in areas of AH/EIN with concurrent loss of PTEN and ARID1A compared to immediately adjacent AH/EIN areas showing only PTEN loss. In a cell culture system, co-silencing ARID1A and PTEN in human endometrial epithelial cells increased cellular proliferation to a greater degree than silencing either ARID1A or PTEN alone.
Conclusions: These results suggest an essential gatekeeper role of ARID1A that prevents PTEN inactivation from promoting cellular proliferation in the transition of pre-cancerous lesions to uterine endometrioid carcinoma.

1094 CXCL12 and CXCL3 Expression in Young Women With Endometrial Cancer

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Background: Endometrial carcinoma is the commonest gynaecological malignancy with endometroid (Type1) tumours contributing 80% of the burden. Pre-menopausal endometrial tumours are not common and can be associated with Lynch syndrome in 30% of cases. Monocyte infiltration and chemokine ligands including CXCL3 and CXCL12 have been associated in the development and metastatic potential of a number of cancers.
Design: Fifty patients, diagnosed with type1 endometrial cancer under the age of forty one from fifteen centres across England were included. Tissue cores in a tissue micro-array were immune-stained for PGM1, CXCL12, CXCL3, MLH1, MSH2, MSH6, PMS2, Ki67 and P53. Slides were scored under light microscopy using a composite of stain area and intensity. We retrospectively reviewed patient notes for clinicopathological data.
Results: Eighty percent of patients had at least 1 MMR protein unexpressed. MMR protein expression was not significantly associated with CXCL12 (P=0.92) but was associated with CXCL3 (P=0.05) for all MMR proteins and PGM1 for MSH6 (P=0.01). CXCL12 expression was significantly higher in tumours with myometrial invasion (P=0.01) and higher stage (P=0.01). CXCL3 expression was not significantly associated with any prognostic markers. PGM1 expression was significantly higher in earlier stage MMR positive tumours (P=0.03) and synchronous tumour development (P=0.04). Ki67 and P53 expression was significantly lower in MMR protein negative tumours compared to those with positive MMR protein expression (P=0.01) but associated with higher grade tumours (P=0.01 and P=0.02 respectively). Ki67 was significantly associated with lymphovascular invasion (P=0.02) and P53 inversely with myometrial invasion (P=0.00).
Conclusions: Our results suggest a role of PGM1, CXCL3 and the CXCL12-CXCR4 axis in the proliferation and metastatic potential of endometrial cancer in young women. The feasibility of using Ki67 and P53 as biomarkers of more advanced disease is also suggested in this patient population.

1095 Lymphocyte Populations in Endometrial Cancer of Young Women: An Immunohistochemical Study on TMA

Abdul Badran, Patricia Ellis, Roberto Dina. Imperial College, London, United Kingdom; Royal Surrey Hospital, Guildford, United Kingdom.
Background: Considerable evidence implicates a role for an inflammatory response in the development and propagation of endometrial cancer. Pre-menopausal endometrial tumours are not common and can be associated with Lynch syndrome in 30% of cases. Lymphocytic infiltration affects tumour behaviours and response to chemotherapy. Discussions on the role of T lymphocytes in endometrial cancer are inconclusive and have not been studied in endometrial tumours occurring in young women <40 years.
Design: We investigated the association of lymphocyte infiltration markers with the development and outcomes of endometrial cancer in young women. Fifty patients, diagnosed with type1 endometrial cancer under the age of forty one from fifteen different NHS trusts across England were included. One hundred and seventy one tissue cores were used to construct 4 tissue microarrays and subjected to immunohistochemical staining for FoxP3, CD3, CD20, CD56, CD4, CD8, MLH1, MSH2, MSH6, PMS2. TMA slides were then scored under light microscopy. We retrospectively reviewed patient notes for clinicopathological data.
Results: Eighty per cent of patients had at least 1 MMR protein unexpressed. CD3 and CD20 expression was significantly higher in MMR negative tumours (P=0.01 and P=0.05 respectively). Conversely Fox P3 was significantly less expressed in patients with negative MMR protein expression (P=0.05) and in association with myometrial invasion (P=.0.04). CD56 and CD4 expression were significantly lower in higher stage tumours (P=0.05 for both) and in patients developing synchronous tumours for CD56 (P=0.01). CD3, CD20 and CD8 were expressed less in tumours associated with poor prognostic factors but did not reach statistical significance.
Conclusions: FoxP3, CD56 and CD4 expression negatively correlated with poor prognostic markers. Higher lymphocyte tumour infiltration seems to be associated with tumours not expressing MMR protein.

1096 HER2 Amplification in Uterine Serous Carcinoma and Endometrial Intraepithelial Carcinoma

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Background: A subset of uterine serous carcinoma (USC) overexpress Her2, and clinical trials with Her2 targeted therapy are underway. However, the Her2 scoring criteria for USC are not well established, and the HER2 status of the precursor lesion endometrial intraepithelial carcinoma (EIC) is not known. Here, we compare the breast and gastric carcinoma (GI) scoring criteria for Her2 immunohistochemistry (IHC) to the results of fluorescence in situ hybridization (FISH) for Her2 amplification in EIC and USC.
Design: Her2 IHC (Dako HercepTest) and dual probe FISH (Abbott Molecular PathVysion Kit) were performed on whole sections of surgically resected tissues from 85 cases (35 EIC, 47 primary USC, 3 metastatic USC). 2013 ASCO/CAP guidelines for Her2 IHC and FISH interpretation in breast carcinoma and Dako HercepTest Her2 GI IHC scoring guidelines were used.
Results: **Comparison of Her2 Status in EIC and USC by IHC and FISH**

Her2 Amplification Status	By Breast IHC Score	By GI IHC Score	By FISH
Positive	5%	5%	15%
Equivocal	31%	35%	6%
Negative	65%	60%	79%

More cases of EIC and USC are classified as Her2 positive by FISH than by IHC. There was no statistical difference in the correlation between the IHC status and FISH status when using the breast or GI scoring criteria. Applying the breast and GI scoring criteria, 8-9% IHC negative cases were FISH amplified; 23% IHC equivocal cases were FISH amplified; 50% IHC positive cases were FISH amplified. FISH positivity was seen equally in EIC (11%) and primary USC (19%). When comparing the Her2 status between EIC and USC within the same tumor (n=15), 47% cases demonstrated discordance in the IHC (n=3), FISH (n=3) or both IHC and FISH (n=1). Among the FISH discrepant cases, 2 had Her2+ EIC and Her2- USC, while 2 had Her2- EIC and Her2+ USC.
Conclusions: There is poor correlation between Her2 IHC and FISH in USC. As compared to IHC, FISH was better able to discriminate between positive and negative cases as only 5 cases were equivocal. The breast and GI scoring criteria perform equally, and use of the breast scoring method is appropriate. Areas of EIC and USC in the same patient show substantial discordance, raising the question of tumor evolution and possibly guiding treatment strategies when limited samples are available for testing. Further trials are needed to evaluate if the tumors of the patients who respond to Her2 directed therapy have Her2 amplification by IHC or FISH.

1097 Utility of Cytokeratin 17 in the Diagnosis of Invasive Squamous Lesions of the Vulva

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Background: The diagnosis of early stromal invasion in the setting of vulvar intraepithelial neoplasia (VIN) can be challenging both in small biopsies and excisional specimens. Cytokeratin 17 (CK17), an acidic keratin mostly found in the basal cells of complex epithelia, has been recently proposed as a useful marker of stromal invasion in squamous neoplastic lesions of the anus. We investigated the utility of CK17 in determining stromal invasion in squamous neoplastic lesions of the vulva.
Design: A total of 108 vulvar specimens received from 2009 to 2013 were reviewed, including 52 cases of VIN, 20 superficially invasive squamous cell carcinoma (SISCC), 16 invasive squamous cell carcinomas (ISCC), 8 lichen sclerosus, 3 fibroepithelial

polyps, 2 chronic vulvitis, 4 pseudoepitheliomatous hyperplasia and 3 extramammary Paget's disease. The pattern of immunohistochemical expression of CK17 was evaluated. In intraepithelial lesions, positive staining for CK17 was considered as either peripheral staining (basal or outer third) or as diffuse staining while cases were considered negative if they displayed complete absence of CK17 expression, showed staining limited to the surface (suprabasal or inner two thirds), or if expression was present in <10% of basal cells. For invasive carcinomas, expression of CK17 was evaluated in the invasive component. Statistical analysis was performed using Fisher's exact test. Statistical significance was defined as p value <0.05.

Results: Three of 52 cases of VIN (5.8%), 2 of 17 non-neoplastic (NN) cases (11.7%) and 25 of 36 cases of squamous cell carcinoma (SCC) (69.4%) showed positive staining for CK17. There was a statistically significant difference between NN and SCC ($p<0.05$) and between VIN and SCC cases ($p<0.05$). Twelve of 20 (60%) cases of SISCC and 13 of 16 cases (81.2%) of ISCC showed positive staining for CK17 in the invasive component. There was no statistically significant difference between SISCC and ISCC ($p=0.27$). In 10 of 12 SISCC cases, CK17 positivity was confined to the invasive component while the overlying VIN was negative for CK17. Additionally, cases of extramammary Paget's disease showed negative staining of the neoplastic cells for CK17 while the surrounding keratinocytes revealed diffuse positivity with this marker.

Conclusions: In concordance to what has been reported in anal squamous lesions, CK17 may be an useful adjunct for the diagnosis of squamous cell carcinoma of the vulva, especially in the setting of early stromal invasion.

1098 Primary Versus Metastatic Ovarian Tumors: Challenging the Validity of Common Diagnostic Features

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Background: Distinguishing primary ovarian from metastatic carcinoma to the ovary is sometimes challenging to clinicians and pathologists and is important for selecting appropriate surgery, therapeutic options and prognostication. We re-examined the features traditionally used to assist pathologists in this differential diagnosis in a single, tertiary care practice.

Design: We reviewed the pathology of ovarian cancer specimens between 2000 and 2013, removed by at least a cystectomy procedure. Age, size, laterality, external surface involvement, CA-125 and past history were compared between primary ovarian serous carcinomas (OSC), non-serous carcinomas (NSC) and metastatic tumors (MT) to the ovary. c2 test, t-test and Mann-Whitney tests were used in the analyses.

Results: After exclusion of cases with neoadjuvant chemotherapy, we identified 205 OSC, 161 NSC and 136 MT. In the MT group, 137 extra-ovarian sites of origin were identified, including colon (52, 38.2%), endometrium (31, 22.8%), appendix (13, 9.5 %), stomach (12, 8.8%), breast (11, 8.1%), cervix (6, 4.4%), upper GIT (4, 2.9%), lung (2, 1.5%) and other (6, 4.4%). The results are summarized in Table 1. Compared with NSC, MT were significantly smaller ($p = 0.002$), more likely bilateral ($p < 0.001$) and showed external surface involvement ($p < 0.001$) but CA125 levels ($p = 0.36$) and age ($P = 0.76$) were comparable. Compared with OSC, MT had lower CA125 levels ($p < 0.001$). The difference in mean age, size, bilaterality and external surface involvement was not significant ($p > 0.5$).

Table 1

	OSCN=205	NSCN=161	MTN=136
Age (mean ± SD)	58.6 ± 12.9	56.6 ± 14.9	56 ± 12.1
Size (CM, mean ± SD)	11 ± 6.3	14.7 ± 7.9	11.8 ± 7.9
Bilaterality (%)	62	16.15	54.4
External surface (%)	76.6	35.4	66.2
CA 125: elevated/testedmean ± SD	131/1371351.1 ± 2671.67	93/106608.6 ± 1417.3	68/84373.45 ± 895
Previous cancer (%)	22 (10.7)	11 (6.8)	81 (59.6)

Conclusions: Traditional features used to guide pathologists in differentiating primary from metastatic tumors frequently overlap and are valid only in tumors with non-serous histology. CA125 levels and history of previous cancer are helpful when serous histology is considered. Our findings underscore the value of close communication between pathologists and gynecologists in evaluating ovarian masses, especially during frozen section, when ancillary tests are limited.

1099 The Role of the TLR4 Pathway and the Spindle Assembly Checkpoint in Ovarian Cancer Prognosis

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Background: The TLR4 pathway and the spindle assembly checkpoint have been implicated in numerous cancers including ovarian cancer. Two surrogate markers of these pathways, MyD88 and MAD2, have been extensively investigated by our group and have shown to have significant impact on patient prognosis including reduced PFS, OS and the development of chemoresistance to the front-line anticancer drug paclitaxel. The aim of this study was to assess whether these two potential prognostic biomarkers act via dependent or independent mechanisms. The relationship between MAD2 and MyD88 was investigated through alteration of MyD88/TLR4 expression in two ovarian cancer cells lines, a MyD88 negative cell line A2780 and a MyD88 positive cell line SKOV-3. Additionally two TLR4/MyD88 regulatory microRNAs Mir-146a and Mir-21 were also assessed in this study.

Design: Alteration of TLR4/MyD88 expression in these two cell lines was achieved through the use of an MyD88 overexpression plasmid vector and through the use of siRNA targeting TLR4 or MyD88. Following transfection, MyD88, TLR4 and MAD2 expression was assessed through qPCR and western blot analysis. The expression of the two TLR4/MyD88 regulatory microRNAs, Mir-21 and Mir-146a was also assessed following confirmation of knockdown or overexpression. The effect on chemoresponse following knockdown of MyD88/TLR4 was also assessed in SKOV-3 cells using the CCK-8 assay.

Results: It was found that knockdown or overexpression of MyD88 in SKOV-3 or A2780 cells respectively had no effect on MAD2 expression or the expression of Mir-21 and Mir-146a. Additionally knockdown of TLR4 in both cell models was also shown to have no effect on MAD2. Interestingly, knockdown of TLR4 in SKOV-3 cells was shown to restore chemosensitivity to paclitaxel.

Conclusions: The results of this study suggest that MAD2 and MyD88 are independent biomarkers in ovarian cancer. By using these two markers it may be possible to triage women into chemoresistant/chemosensitive groups prior to the onset of chemotherapy, with the ultimate aim of improving ovarian cancer patient prognosis.

1100 High Grade Serous Carcinoma Arising in Low Grade Serous Carcinoma

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Background: Low and high grade ovarian serous carcinomas are now considered two distinct diseases with different clinicopathologic features and molecular alterations, and yet a small number of cases of high grade serous carcinoma arising in low grade serous carcinomas have been reported. The aim of this study was to examine the spectrum of atypia in a series of low grade serous carcinomas.

Design: The slides from 246 serous carcinomas from the ovarian tumor repository were reviewed revealing 23 tumors with a low grade serous carcinoma component by the MD Anderson grading criteria. The histologic slides were examined for areas of nuclear pleomorphism greater than seen in low grade carcinoma but less than diagnostic of high grade carcinoma, foci that qualified as high grade serous carcinoma, and the mitotic rate. The clinicopathologic features and follow-up data were analyzed.

Results: Of the 23 cases, 16 were pure low grade serous carcinomas, 3 were low grade with areas of increased nuclear pleomorphism, and four contained areas of high grade serous carcinoma.

Clinicopathologic Features of Low Grade Serous Carcinoma Groups

	Uniform Low Grade N=16 (70 %)	Focal Pleomorphism N=3 (13 %)	High Grade in Low Grade N=4 (17 %)
Age (mean)	62	51	48
FIGO Stage			
I	3 (19)	1 (33)	0
II	0	0	1 (33)
III	12 (75)	2 (67)	3 (75)
IV	1 (6)	0	0
Mitotic rate	16 (100)	3 (100)	1 (25)
Follow-up median	7.8 yrs	4.8 yrs	5.0 yrs
Recurred	6 (37)	1 (33)	2 (50)
Died of disease	3 (19)	2 (67)	1 (25)

Conclusions: This study confirms the findings of others that low grade serous carcinomas are usually high stage at presentation, have a low mitotic rate and that a substantial number of patients will suffer recurrences or death from tumor over time. This study demonstrates that a spectrum of atypia exists in up to 30% of low grade serous carcinomas; focal "higher" grade nuclear pleomorphism may be present and some tumors may contain overt high grade serous carcinoma with a high mitotic rate. These latter tumors are similarly high stage with recurrences and death from disease. Extensive sampling of low grade serous carcinomas is warranted to detect these focally high grade tumors.

1101 Prognosis of Ovarian Low Grade Serous Carcinoma: An Assessment of Multiple Grading Systems

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Background: It is now widely accepted that high and low grade ovarian serous carcinomas as defined in 2014 WHO Classification of Tumours of the Ovary and the two-tiered MD Anderson grading system are distinct disease entities with different clinicopathologic and molecular features. It is also widely assumed that low grade serous carcinomas have a better prognosis than high grade carcinomas, although several studies have questioned this conclusion. This study was undertaken to delineate the survival of low and high grade ovarian serous carcinomas utilizing all of the current grading systems in a large series of tumors treated at a single institution.

Design: The slides of 346 of 990 patients entered in the Ovarian Cancer SPORE tumor repository with "serous" in the diagnosis field since 1990 were reviewed by two of the authors without survival information. 100 cases were deleted after histologic review because of borderline or mixed histology or the absence of slides from the files. The remaining cases were assessed for the following histologic parameters: two-tiered

MD Anderson grade (WHO low or high grade), FIGO grade, Shimizu grade, original grade, mitotic rate. Survival was compared utilizing the Kaplan-Meier method along with logrank tests.

Results: Utilizing the MD Anderson two-tiered grading system, 16 cases were pure low grade, seven cases with classic low grade carcinoma had high or higher grade foci (these 7 cases were eliminated from the statistical analysis of low vs high grade), and 223 were high grade throughout. Analysis revealed a difference in survival that approached statistical significance for both overall survival (p=0.079) and recurrence-free survival (p=0.087) using the MD Anderson two-tiered system. Dichotomizing the FIGO grade into low (FIGO 1) vs high (FIGO 2 and 3) revealed a trend toward a better recurrence-free survival (p=0.065), but no difference in overall survival (p=0.124). The other grading systems showed no differences in recurrence-free or overall survival.

Conclusions: The two-tiered classification system reveals a trend towards better overall and recurrence-free survival among low grade cases that may become clearer as analysis of the remaining cases in the tumor repository increases the number of low grade carcinomas in the study. The presence of high grade carcinoma arising in low grade carcinomas warrants extensive sampling of low grade carcinomas to exclude a higher grade tumor.

1102 Leiomyoma With Bizarre Nuclei: Correlation Between Morphology and Fumarate Hydratase/S-(2-Succino)-Cysteine Expression

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Background: Tumors associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome are characterized by cells with prominent eosinophilic nucleoli and perinucleolar halos. These features have also been observed in a subset of leiomyomas with bizarre nuclei (LMBN). While HLRCC is defined by germline mutations in fumarate hydratase (FH), resulting in formation of S-(2-succino)-cysteine (2SC), it is unknown if LMBN show a similar aberration. In this study, we evaluate LMBN morphology and its correlation with FH/2SC expression.

Design: 28 LMBN were reviewed for cellularity (compared to adjacent myometrium), "alveolar pattern" of edema, staghorn vessels, distribution of bizarre nuclei, cytoplasmic hyaline globules, and eosinophilic nucleoli with perinucleolar halos. Immunohistochemistry for FH/2SC was performed. Data was analyzed by Fisher exact test with Bonferroni adjustment.

Results: The patients ranged from 26 to 69 (mean 46.6) years and none had a history of renal or cutaneous tumors (unknown in 5). The morphologic features are highlighted in Table 1. There was loss of FH staining with diffuse 2SC expression in 50% of cases. The presence of an alveolar pattern of edema showed a statistically significant association (p=0.0044) with aberrant FH/2SC expression. Weaker associations were detected for the presence of staghorn vessels, hyaline globules, and nucleoli/halos (p<0.05).

	Cellularity	"Alveolar" Edema	Staghorn Vessels	Bizarre Nuclei (Diffuse)	Hyaline Globules	Nucleoli/ Halos (Diffuse)
All cases (n=28)	86%	36%	68%	57%	82%	68%
FH-/2SC+ (n=14)	86%	64%	93%	57%	100%	93%
FH+/2SC- (n=14)	86%	7%	43%	57%	64%	43%

Table 1: Morphologic Features

Conclusions: Previously described morphologic features of HLRCC tumors and aberrant FH/2SC staining are not specific to this syndrome as both can be seen in an important subset of LMBN. For LMBN, the greater the number of associated morphologic features observed, the higher the likelihood FH/2SC will be aberrantly expressed (Table 2). FH mutational analysis is in progress to further define FH negative LMBN.

# of Features	# FH+/2SC-	# FH-/2SC+	% FH-/2SC+
0	2	0	0
1	3	0	0
2	8	1	11
3	1	5	83
4	0	8	100

Table 2: Estimated Probability of Aberrant FH/2SC

1103 Mismatch Repair Protein Defects in Clear Cell Carcinoma of the Ovary: Incidence and Morphologic Associations in 57 Cases

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Background: Lynch Syndrome (LS) is defined by defects in one or more mismatch repair (MMR) proteins. Several morphologic features have been predictive of MMR loss in both LS-associated endometrial and colon carcinomas; however, no correlation has been identified for ovarian tumors. In this study we evaluate a series of ovarian clear cell carcinomas (O-CCC) to determine the incidence of MMR defects and potential association with specific histologic features.

Design: 57 O-CCC were reviewed for predominant histological pattern (papillary, tubulocystic, solid, mixed), peritumoral lymphoid aggregates, inflammatory infiltrate, and nuclear pleomorphism. Immunohistochemistry for the 4 MMR proteins was performed and data was analyzed using the Fisher exact test.

Results: Patients ranged from 31 to 82 (mean 55.6) years. Abnormal MMR expression was identified in 5% (3/57) of O-CCC and included MSH2/MSH6, MLH1/PMS2, and PMS2 loss. These patients were diagnosed at 31 to 40 (mean 37) years, were stage I (2) and stage III (1) at presentation, and none had a concurrent endometrial or colon carcinoma. Tumors with a diffuse inflammatory infiltrate and marked nuclear pleomorphism were more frequently associated with MMR defects (p=0.0041 and p=0.0455, respectively). All 3 O-CCC with MMR loss exhibited both features, but were found in only 7% (4/54) of tumors with MMR expression. The patient with loss of MSH2/MSH6 was confirmed to have a MSH2 germline mutation and testing is in progress for the others. Two patients (stage I and stage III) are alive without any evidence of LS-associated disease at 7 and 8 years, whereas the third was lost to follow-up.

Conclusions: In this study, the frequency of abnormal MMR expression among unselected O-CCC patients was 5%, which although is slightly higher than LS-associated colorectal and endometrial carcinoma, is more striking given that O-CCC is much less common. Previous studies have been unable to identify a relationship between histology and MMR loss, but this study identified a correlation with a diffuse inflammatory infiltrate and marked nuclear pleomorphism. Potentially, O-CCC with these histologic characteristics can be selected for MMR analysis. Furthermore, given that stage III O-CCC typically has an unfavorable prognosis, perhaps association with LS potends a more favorable outcome.

1104 Primary Extranodal Marginal Zone Lymphoma (MALT)-Like Lymphoid Proliferations of the Endometrium

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Background: Primary lymphoma of the endometrium is exceptionally rare. Some recurring morphological and immunophenotypic features are described in case reports of low-grade endometrial B-cell lymphoma, but these have not been well characterized and their malignant potential is unknown. In this study, we define the morphological, immunohistochemical, and molecular spectrum of these atypical endometrial lymphoid proliferations.

Design: 8 hysterectomies with a diagnosis of primary endometrial lymphoma/atypical lymphoid proliferation were identified from institutional archives. Histology was reviewed and lymphoid infiltrates were evaluated for expression of CD3, CD20, CD43, CD5, CD10, BCL2, CD21, CD23, kappa/lambda, IgG, IgM, IgD. FISH for IGH@ and MALT1 and PCR for clonal IGH@ gene rearrangements were performed.

Results: Patients ranged from 50 to 87 (median 62) years. Lymphoid proliferations were primarily confined to the endometrium (6/8), nodular (7/8), and composed of a monomorphic population of small lymphocytes (8/8). In some cases, there was coalescence of nodules (3/8) or infiltration of myometrium (2/8). One case showed diffuse growth with extensive involvement of the endomyometrium, left ovary and fallopian tube, and regional lymph nodes. Pertinent immunophenotype and clonality results are shown in Table 1. All cases were negative for IGH@ and MALT1 rearrangements by FISH. All patients with follow-up (6/8) are alive, and only one (with diffuse infiltrate) has persistent disease after resection alone (mean 3.3 years, range 4.1 months–8.7 years).

Case	CD20	CD10	CD5	CD43	Heavy Chains	Clonality (PCR/ISH)
1	+	-	-	+	-	Clonal (PCR)
2	+	-	Dim	+	IgM	Clonal (PCR)
3	+	-	Dim	+	IgM	Insufficient
4	+	-	-	+	IgM	Clonal (PCR, kappa)
5	+	-	-	+	N/A	Clonal (PCR, kappa)
6	+	-	-	+	-	Clonal (PCR)
7	+	-	Dim	+	IgM	N/A
8	+	-	-	-	IgG	Clonal (PCR, lambda)

Conclusions: Herein we describe and characterize the largest cohort of primary MALT-like lymphoid proliferations of the uterus. Proliferations consist of CD20+CD10-CD5-(rarely+)CD43+ small B cells. While these nodular proliferations are clonal and morphologically atypical, they are universally indolent, and in the absence of diffuse growth, do not warrant a diagnosis of lymphoma. On this basis, we propose the term "endometrial MALT-like lymphoproliferative disorder" for this unique pathologic entity.

1105 Comparison of Gene Methylation Patterns Between Atypical Leiomyoma and Leiomyosarcoma

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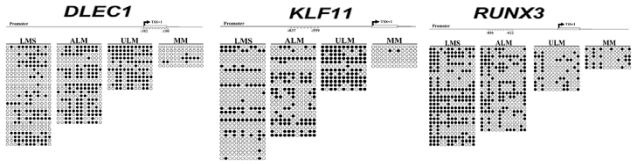
Background: The relationship between leiomyosarcoma (LMS) and atypical leiomyoma (ALM) remains unclear, therefore, identification and characterization of the molecular relationship of ALM to LMS is highly relevant to understanding the genetic basis of these tumors. Based on previous global methylation profiling analysis, two ER and PR modulators, *DLEC1* and *KLF11*, are highly methylated in usual leiomyoma (ULM). In contrast, *RUNX3,* a tumor suppressor, is frequently inactivated by DNA hypermethylation. *RUNX3* regulates several cancer related pathways, including P53, Akt, Notch, and Wnt pathways, which are often linked to leiomyosarcoma. In this study, we investigated the methylation patterns of these three genes in ULM, ALM and LMS.

Design: Formalin fixed paraffin embedded tissue from 12 ULM, 30 ALM, and 24 LMS was retrospectively collected and all cases were reviewed to confirm the diagnosis based on WHO and Stanford scheme. Six normal myometrium were used as control. Methylation analysis was performed using Sequenom MassArray. DNA from each case was extracted with QIAamp EpiTect Bisulfite kits and PCR amplification incorporating the T7 promoter sequence was performed and separated based on methylated versus nonmethylated CpG sites. Data was analyzed using Mass Spectrometry and biostatistical analysis was performed. EpiTect Control DNA and Control DNA Set were used as control DNA.

Results: *DLEC1* and *KLF11* were highly methylated in ULM in comparison to normal myometrium ($p<0.001$) and to LMS ($p<0.05$). The levels of *KLF11* promoter methylation in ALM and LMS were very low and were significantly different from ULM ($p<0.001$) and comparable to methylation levels in myometrium. Similar findings were observed for *DLEC1* promoter methylation in ALM and LMS. In contrast, the levels of *RUNX3* methylation in LMS and ALM were significantly higher than that of ULM and myometrium ($P<0.05$ and <0.01 respectively).



Conclusions: Data from chip-based methylation analysis of smooth muscle tumor related genes, *DLEC1*, *KLF11*, and *RUNX3*, show ALM has similar methylation patterns to LMS which are significantly different from ULM. Findings provide another layer of evidence of molecular similarity between ALM and LMS and our study suggests that methylation analysis can be a valuable tool in tumor classification.

1106 Papillary Squamous Cell Carcinoma of the Uterine Cervix – Removing the "Aggressive" Label

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Background: Papillary squamous cell carcinoma (PSCC) is a rare variant of cervical carcinoma that histologically resembles transitional cell carcinoma of the urinary bladder. PSCCs are considered clinically aggressive, despite limited literature that predates the chemoradiation regimens currently used to manage cervical cancer.

Design: Twenty cases of PSCC were identified over a 10 year period. Clinicopathologic variables were abstracted. The H&E slides of all PSCCs including diagnostic biopsies and specimens obtained at radical hysterectomy (RH) were reviewed as well as a retrospective cohort of IB1 conventional squamous cell cervical cancers (cSCC). Two-tailed T-test and McNemar's test were used to assess statistical significance.

Results: All PSCCs displayed papillary architecture with either squamous (n=13) or squamotransitional (n=7) morphology and included FIGO IA1 (n=1), IB1 (n=6), IB2 (n= 4), IIA (n=2), IIB (n=3), IIIB (n=2) and IVB (n=2) disease. Mean patient age was 47 ± 12.2 years (range: 26 to 76 years). All but one woman with ≤IB1 disease were treated with surgery, whereas all patients with ≥IB2 disease received chemoradiation. Histologic evaluation of RH specimens demonstrated that IB1 PSCCs (n=5) invaded less deeply into the cervical stroma and showed significantly less lymph-vascular invasion (LVI) than IB1 cSCCs (n=36), despite equivalent mean tumor diameters.

Stage IB1 tumors	PSCC (n=5)	cSCC (n=36)	p-value
Tumor size (cm)	2.1 ± 0.7	2.4 ± 0.8	0.50
DOI (cm)	0.3 ± 0.1	1.0 ± 0.5	
LVI	1/5 (20%)	17/36 (47.2%)	

Mean duration of follow up was 26 ± 25 months (range: 3 to 102 months). At last contact, 14 patients were alive without disease. Three patients (IIB and IIIB – non-compliant with therapy; IB2 – positive pelvic lymph nodes) were alive with residual disease. One patient with IB1 disease died of unknown causes. Both patients with IVB disease were lost to follow-up shortly after diagnosis.

Conclusions: PSCC appears to be associated with a good outcome following current standard of care, with stage-specific therapy. Given that PSCCs demonstrate less stromal and lymph-vascular invasion than stage and size-matched cSCCs, it may be possible to consider surgical management for a subset of women diagnosed with IB2 and/or IIA disease that would be otherwise triaged to chemoradiation on the basis of tumor size alone.

1107 Trop2 Is Significantly Overexpressed in Cervical Squamous and Adenocarcinomas

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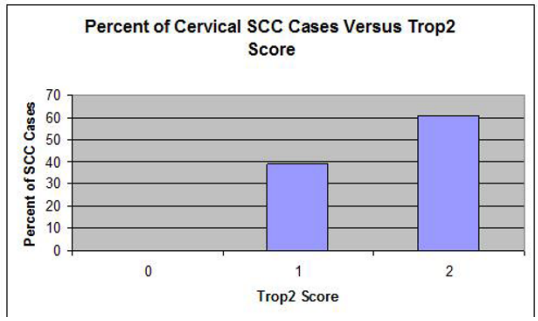
Background: Trop-2 (human-trophoblast-cell-surface-marker) is a cell surface glycoprotein of unknown function that is up-regulated relative to corresponding non-neoplastic tissue in a variety of tumors. Trop-2 expression has been shown to be associated with poorer prognosis in oral squamous cell, gastric, colorectal, and pancreatic carcinomas. Previous studies have demonstrated strong Trop-2 expression in cervical cancer cell lines and sensitivity to immunotherapy with a trop-2 antibody, hRS7.

Design: We assessed Trop2 expression by immunohistochemistry in cervical carcinomas of various histologic types using a tissue microarray approach. Trop2 expression was scored semiquantitatively as 0, 1, or 2, corresponding to absence of staining, weak/focal staining, and strong/diffuse staining, respectively.

Results: A total of 123 squamous cell carcinomas, 20 endocervical adenocarcinomas of usual type, 6 adenosquamous carcinomas, 1 clear cell carcinoma, and 1 large cell neuroendocrine carcinoma were studied. All squamous cell carcinomas showed Trop2 expression with 75 of 123 (61%) displaying strong, diffuse membranous staining. Among adenocarcinomas and adenosquamous carcinomas, 24 of 26 (92%) cases were Trop-2 positive, 11 of which (42%) displayed strong, diffuse staining. The large cell neuroendocrine carcinoma was also strongly Trop-2 positive. The clear cell carcinoma case did not show any Trop2 expression. No correlation of Trop2 staining was observed with tumor grade, lymphovascular invasion, or stage in any of the tumor types.



Conclusions: Trop2 is ubiquitously expressed in squamous cell carcinomas and adenocarcinomas of the uterine cervix, indicating that Trop-2 is a promising therapeutic target for hRS7 immunotherapy against these common cervical cancers.

1108 Differential Expression of Phosphorylated γH2AX in the Stroma of Type I and II Endometrial Carcinomas

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Background: Phosphorylation of histone H2AX is a mechanism in reaction to DNA double-strand breaks in the cell's response to DNA damage, resulting in generation of γ-H2AX. γ-H2AX is rapidly formed after damage and triggers the accumulation of many components involved in DNA repair, including proteins playing a role in cell cycle checkpoint activation. Endometrial cancers are classified in two categories. Type 1 tumors may arise from atypical hyperplasia or endometrial intraepithelial neoplasia by unopposed estrogen stimulation. Type II carcinomas are associated with atrophic endometria and p53 mutations. This study investigates whether these cancer types display different patterns of γ-H2AX in their adjacent stromal cells.

Design: γ-H2AX immunoexpression was evaluated in the stromal cells of formalin-fixed, paraffin-embedded archival endometrial specimens from 100 patients consisting of 82 endometrioid type I and 18 type II cancers (serous papillary, N=16; clear cell, N=2). A standard immunohistochemical technique was performed using a Ventana BenchMark XT immunostainer with a rabbit polyclonal affinity-purified antibody to human phospho-Histone H2AX (γH2AX, R&D Systems, Minneapolis, MN USA) at a dilution of 1:900. Scoring was done semiquantitatively as follows: (0), 0% immunoreactive cells, (1+), <5% immunoreactive cells, (2+), 5% to 50% immunoreactive cells, (3+), >50% immunoreactive cells.

Results: Immunostaining for γ-H2AX was seen in nuclear and nucleo- cytoplasmic patterns. For type I cancers, there were no cases of score 0 (0%), score 1+ was assigned in 14%, score 2+ in 24%, and score 3+ in 62% of cases. In contrast, in type II cancers score 0 was determined in 61%, score 1+ in 22%, score 2+ in 11%, and score 3+ in 6% of the specimens. Scoring was significantly higher in type I tumors compared with type II cancers ($P<0.0001$, chi-square test), and in grade 1/2 versus grade 3 tumors ($P<0.0001$, Fisher´s exact test). There was no statistical difference between type I grade 3 and type II lesions ($P=0.058$). Tumor recurrences were more frequently observed in low score cancers ($P=0.0036$).

Conclusions: γ-H2AX immunoexpression in the tumor surrounding stroma is significantly different in type I and II endometrial carcinomas, with relation to grade and recurrences. Low levels of expression of γ-H2AX in the microenvironment may contribute to aggressive tumor features, may facilitate spread in high grade endometrial cancers and point towards a contribution of epigenetic changes in stromal cells to endometrial cancer progression.

1109 Recurrence in Low-Risk Endometrial Adenocarcinoma (ECA): A Clinicopathologic Analysis in a Community Hospital Setting

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Background: Pathologic risk factors of recurrence in ECA include high tumor grade, myometrial invasion (MI) > 50%, and lymphovascular invasion (LVI). Patients without these risk factors, or patients <70 with less than 2 of the risk factors are considered low-risk ECA (LR-ECA). While vaginal recurrences can occur, distant disease is uncommon. There is limited literature evaluating this clinicopathologic scenario and the aim of this study was to evaluate pathologic and clinical findings in LR-ECA with local or distant recurrences.

Design: LR-ECA cases were retrieved in which follow-up demonstrated recurrences. Pathologic findings (tumor grade, size, depth of MI, LVI, cervical and lower-uterine segment involvement), clinical findings and follow-up were reviewed.

Results: There were 15 cases with an age range of 26-81 years (mean 62) and BMI range of 23.9-39.3 (mean 31). 8 patients had laparotomy and 7 robotic/ laparoscopic surgery. There were 12 cases of FIGO I and 3 FIGO II ECA. MI depth ranged from 10%-40% and in 5 patients there was no MI. The endometrial tumor size ranged from 0.8 to 7.5

cm (mean 3.5 cm). Lymph node dissection (LND) was performed in 3 cases and all were negative. Post operatively 1 patient received pelvic RT and 1 brachytherapy. There were 10 patients with vaginal recurrence (5 without MI), 1 of which had synchronous port site metastasis. 5 had distant/multiple recurrences (peritoneum, lung, chest wall, liver, abdominal LN & axilla). Based on final pathology, uterine risk factors fulfilled the Mayo Clinic criteria for LND in 9 patients, but only 1 underwent LND. Of these 9 vaginal recurrences, 1 developed peritoneal metastasis. There were no identifiable intrauterine risk factors except for tumor size > 2cm (3 patients). All histologic recurrences were well-differentiated ECA with 9 cases ER+ and 7 PR+. Follow-up of the 10 patients with vaginal recurrence showed 7 with no evidence of disease, 2 alive with disease, 1 status unknown.

Conclusions: While this is a small series, patients with vaginal recurrence in LR-ECA seem to do well, with 70-80% salvage rate following RT. Since 1/3 of these patients had no MI on pathologic examination, the etiology of vaginal recurrence may be related to the large tumor size. Therefore tumors more than 2 cm in size involving the lower uterine segment are at risk for vaginal recurrence and this patient population might be considered for brachytherapy.

1110 The Complexity of Ovarian Cancer Resistance Mechanisms: A Novel, Clinically Relevant, In-Vitro Investigation

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Background: Ovarian cancer (OC) is the leading cause of death from a gynaecological malignancy. Standard carboplatin/taxol chemotherapy often fails and patients relapse with chemoresistant disease. Novel carboplatin and taxol resistant cell lines were developed from UPN251 OC cells in a clinically relevant selection strategy, in order to better understand resistant mechanisms in OC. UPN251-7C models carboplatin resistance and UPN251-7T models taxol resistance. UPN251-6CALT and UPN251-6TALT were exposed to alternating treatments of both agents during development.

Design: Affymetrix mRNA/miRNA arrays were used to characterise gene/miRNA signatures linked with the development of chemoresistance in OC cell lines UPN251-7C (carboplatin) and UPN251-7T (taxol). Bioconductor software (RankProb), DAVID v6.7 and miRNA-target interactions (MTIs) analysis was carried out to identify de-regulated genes/miRNAs, gene pathways and gene/miRNA interactions involved in resistance.

Results: All UPN251 sublines developed using taxol were significantly resistant to taxol, vinblastine and olaparib (P-gp substrates), and reversible with elacridar (P-gp inhibitor) treatment. Significant up-regulation of the ABCB1 gene was seen in UPN251-7T which was reflected at the protein level by western blotting. SRPX2 is highly up-regulated in UPN251-7T taxol resistnt cells. GLI3 and CCL20 identified by DAVID are up/down regulated respectively in carboplatin resistant cells UPN251-7C with GLI3 having a validated interaction with miR-205 down regulated in UPN251-7C. LIN28B is highly up-regulated in carboplatin and down regulated in taxol resistant cells and has validated interaction with let-7i which is down-regulated in carboplatin resistant cells.

Conclusions: Results indicate that P-gp over-expression is a dominant mechanism for taxol resistance in our cell lines. Mechanisms for carboplatin resistance are more complicated. The top deregulated genes are involved in numerous pathways including apoptosis, tissue differentiation, cellular transformation, signal transduction, inflammation and cell migration. Bioinformatics analysis and literature investigation identify LIN28B, GLI3, CCL20 and SRPX2 and miRNAs let-7i and miR-205 as strong potential biomarkers for carboplatin/taxol resistance in OC from the cell lines UPN251-7C and UPN251-7T, warranting their investigation in clinical samples.

1111 Morphologic Changes in the Gynecologic Tract in Response To Fibristal

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Background: Ulipristal acetate (Fibristal, UPA) is a Selective Progesterone Receptor Modulator recently approved in Canada for treatment of symptomatic uterine leiomyomas and menorrhagia. Previous studies have described novel histological changes in the endometrium in response to UPA, called "progesterone receptor modulator-associated endometrial changes", or PAEC. However, there are no published data on the effects of UPA on other areas of the gynecologic tract.

Design: We evaluated pathology specimens resulting from various surgeries in patients who had received UPA prior to surgery. This included myomectomies and hysterectomies +/- salpingo-oophorectomies. Cases were reviewed to identify novel histologic changes (including PAEC) in all tissue types.

Results: A total of 60 patients had surgical procedures. No novel histologic changes were identified in leiomyomas or ovaries. Within the endometrial tissues, 22 (50%) patients had changes of PAEC (Table 1). In the Fallopian tubes, 12 patients (39%) showed foci of variable epithelial atypia. Architecturally, cells were crowded and stratified, with loss of polarity. Mild to marked nuclear atypia was seen, with multinucleation. Cilia were maintained. Immunohistochemical staining for p53 and Ki-67 were normal in these areas.

Conclusions: UPA/Fibristal causes reproducible unique changes in both endometrium and within the Fallopian tube epithelium. Awareness of these changes is necessary to prevent over-diagnosis of endometrial hyperplasia and/or tubal intraepithelial neoplasia in these patients.

	Number	Number with Novel Histologic Changes	Novel Histologic Changes
Leiomyomas	58	0	None
Endometrium	44	22	PAEC
Fallopian Tubes	31	12	UPA-Associated Tubal Atypia
Ovaries	14	0	None

1112 Corded and Hyalinized Endometrioid Carcinoma: A Clinicopathologic and Immunohistochemical Report of 8 Cases

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Background: Corded and hyalinized endometrioid carcinoma (CHEC) is a variant of endometrial adenocarcinoma that includes a component of epithelioid and spindle cells arranged in cords and clusters set within hyalinized extracellular material. CHEC often contains abundant keratinized squamous metaplasia and sometimes osteoid. This unusual combination of morphologies imparts a biphasic appearance which can mimic uterine carcinosarcoma.

Since its thorough characterization in 2005, few studies have investigated CHEC, although one study has shown these tumors to feature beta-catenin mutations. Moreover, as CHEC may present in young women, any association with mismatch repair (MMR) protein abnormalities is unknown. We present the clinicopathological and immunophenotypical features of 8 cases of CHEC focusing on MMR protein expression.

Design: We searched our institutional and consultative archives for cases of CHEC. All available H&E-stained sections were re-examined and relevant clinicopathological data was recorded. Immunohistochemistry for MMR protein expression, p53, beta-catenin, ER, PR, and Ki-67 was performed when possible. Additional mutation profiling studies are pending.

Results: Our search yielded tumors from 8 patients (mean age 42; range 32-53). In 7 patients with available history, 5 were FIGO stage IA and all are alive without disease (mean follow-up 162 weeks; range 15-917).

All tumors showed characteristic epithelioid/spindled corded and hyalinized cells ("CHEC cells") often capped by keratinizing squamous metaplasia. Osteoid was present in 5 cases and was often focal. The glandular component was endometrioid in all cases (5 FIGO 1; 2 FIGO 2; 1 FIGO 3). When performed, CHEC cells from all cases showed nuclear beta-catenin expression (6/6), wild-type p53 staining (6/6), and intact MMR expression (6/6). CHEC cells typically showed a low (5%) Ki-67 index (4/5). In one case, the Ki-67 index was higher than the glandular component. ER/PR expression in CHEC cells was less robust than the glandular component. Endometrioid ovarian tumors were present in 2 cases, 1 of which was histologically CHEC.

Conclusions: Abnormal nuclear accumulation of beta-catenin and intact expression of MMR proteins are common in CHEC, features consistent with sporadic endometrioid tumors. The clinical presentation and characteristic morphology of CHEC support the hypothesis of an unusual metaplastic endometrioid carcinoma. In diagnostically challenging cases, immunohistochemistry for beta-catenin, p53, and Ki-67 can potentially help distinguish CHEC from carcinosarcoma.

1113 FOXO1 Expression in CAH/Grade 1 Endometrioid Carcinoma Treated With Progestins

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Background: NuclearFOXO1 expression is absent in the majority of Grade I uterine endometrioid carcinomas (UEC) and complex atypical hyperplasia (CAH). FOXO1 is a transcription factor that regulates apoptosis, cell cycle and metabolism. Nuclear FOXO1 expression is present in secretory glands, but is absent in proliferative glands. Inactivation of PTEN causes loss of nuclear FOXO1 expression and it has been shown that progesterone regulates FOXO1 expression in the endometrium. The purpose of this study was to determine if progestin treatment of CAH/Grade 1 UEC results in increased nuclear expression.

Design: 7 cases of CAH/Grade 1 UEC before and after treatment with progestin were identified from our files. Slides were reviewed and histological features confirmed. The cases were scored for intensity and percent of nuclear and cytoplasmic staining in glands and stroma of lesional and normal tissue. The intensity of staining was scored as weak (0), moderate (1) and strong (3). In addition, human endometrial cell lines RL95 and PTEN deleted Hec1A clone 16 were evaluated for nuclear expression of FOXO1 by Western blot before and after treatment with progestin.

Results: 5/7 of the pretreatment lesions showed a range of staining in the glands (weak to moderate cytoplasmic) and the stroma (predominately nuclear). Of these cases only 2 showed expression in normal tissue with a similar staining pattern. After treatment a range of staining was also seen, but 3/5 cases lacked glandular staining and 4/5 had reduced stromal staining. Only 2 cases showed an increase in the stroma: one showed an increase in nuclear staining (10% to 20%) and in the other staining was confined to the cytoplasm. Finally, 2 cases that completely lacked staining in the pretreatment lesions did not have residual disease on post-treatment sampling. The treatment of cell lines with progesterone did not result in the expression of FOXO1 in the nucleus.

Conclusions: Previous studies have shown a lack of FOXO1 expression in CAH/Grade 1 UEC and we have shown that inactivation of PTEN results in loss of nuclear FOXO1 expression. In both primary human tissue samples and endometrial carcinoma cell lines progestin treatment did not result in increased epithelial nuclear or cytoplasmic expression of FOXO1. Although the number of cases examined was small the concordance with the *in vitro* studies strongly suggests that the regression of lesions in response to progestin does not involve FOXO1 expression in either the glands or the stroma.

1114 Ductal Carcinoma of the Breast Metastatic To the Ovary

Ai-Ying Chuang, Robert Young, Melinda Lerwill. Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan; Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Background: The recent literature on ductal carcinoma metastatic to the ovary is limited. We evaluated our experience with particular attention to morphologic features that overlap with those of primary ovarian tumors.

Design: 106 cases were identified from routine hospital and consultation material. Clinical data was reviewed, and the following pathologic features were evaluated: size, laterality, growth patterns, and cytologic features.

Results: The median age of patients at the time of detection of ovarian metastasis was 47 years (range, 17-79). The breast cancer was diagnosed before the ovarian metastasis in 94 cases (interval: 0.14 to 312 months, mean 54.3); the tumors were discovered synchronously in 6; and in 6 the breast cancer was discovered after identification of the ovarian metastasis (interval: 0.5-6 months, mean 2). The size of grossly recognizable tumors (64 cases) ranged from 0.6 to 23 cm (mean 8). Bilateral tumors were grossly identified in 46 cases. The sectioned surfaces were typically solid, with cysts in 13 cases that also had a solid component. Microscopic examination disclosed bilateral ovarian metastases in 63 cases, ovarian surface involvement in 37 and lymphatic invasion in 43. Multinodular growth was seen in 61 cases. Necrosis was seen in 36 cases. There was typically a heterogeneous microscopic appearance with 91% of the tumors having more than one pattern. Discrete nests were the predominant pattern in 53%, followed by diffuse growth (25%), glands and small acini (16%), papillae (2%), single cells (2%), and colloid pattern (1%). A prominent, usually collagenous, stroma was seen in 64 cases, in 43 of which it was dominant. The varied epithelial formations and often prominent stroma resulted in mimicry of many other neoplasms. A nested pattern caused confusion with carcinoid and granulosa cell tumor. Tubules lined by clear cells raised the differential of Sertoli cell tumor. Tubuloglandular patterns with associated prominent stroma suggested diagnoses ranging from adenofibroma to endometrioid and serous adenocarcinoma. Diffuse growth overlapped with the appearance of primary undifferentiated carcinoma.

Conclusions: Our experience highlights the great diversity of morphology of metastatic ductal carcinoma in the ovary, including mimicry of surface epithelial tumors. Awareness of this is crucial in prompting appropriate clinical and immunohistochemical evaluation.

1115 Lobular Carcinoma of the Breast Metastatic To the Ovary

Ai-Ying Chuang, Robert Young, Melinda Lerwill. Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan; Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Background: Lobular carcinoma has a greater propensity to present in the ovary, compared to ductal carcinoma, and poses a different spectrum of differential diagnosis. We reviewed our experience with metastatic lobular carcinoma to evaluate both clinical and pathologic issues that cause diagnostic difficulty.

Design: 38 cases were identified from routine hospital and consultation material. Clinical data was reviewed, and the following pathologic features were evaluated: size, laterality, growth patterns, and cytologic features.

Results: The median age of patients at the time of detection of ovarian metastasis was 51 years (39-91). A diagnosis of breast cancer was made before the ovarian tumor was discovered in 31 cases (0.8-211 months, mean 58); the tumors were discovered synchronously in 2 cases; and in 5 cases the breast cancer was not identified until after oophorectomy (2-59 months, mean 35). The tumors were grossly bilateral in 21 cases. The size of grossly recognizable tumors ranged from 0.5 to 18 cm (mean 5.9). The sectioned surfaces were typically solid, with cysts in only 1 case that also had a solid component. Microscopic examination disclosed bilateral ovarian metastases in 30 cases, ovarian surface involvement in 15 and lymphatic invasion in 9. Multinodular growth was seen in 26. Necrosis was present in 4, and in all of them it was limited (<5%). Diffuse growth of cells with little or no intervening stroma was the predominant pattern in 22 cases, delicate cords in 9, and single cells or small clusters in 7. Signet ring cells were present in 9 but accounted for ³10% of the tumor in only 3. Pleomorphic nuclei were present in 4 cases. 3 patients had coincidental surface epithelial neoplasia in the background, and 1 had a fibrothecoma. The primary neoplasm most closely mimicked was adult granulosa cell tumor because of similar diffuse growth and relatively uniform nuclei.

Conclusions: In 13% of patients with ovarian involvement by lobular carcinoma, the primary breast cancer was identified only after recognition of the metastasis, a higher percentage than for ductal carcinoma (6%). Lobular carcinomas in the ovary are of slightly smaller size and show a narrower morphologic spectrum than metastatic ductal carcinomas. The growth pattern is distinct from that of primary surface epithelial neoplasia and lacks the characteristic patterns of sex cord stromal tumors in the differential.

1116 Clinical Utility of Sentinel Lymph Nodes in Endometrial Cancer

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Background: Patients with low grade endometrial cancer undergo pelvic lymphadenectomy if the depth of myometrial invasion (DMI) is >50% by intraoperative evaluation; DMI is often inaccurate at frozen section. Sentinel lymph nodes (SLNs) are the first step in tumor drainage, and negative SLNs spare further lymphadenectomy, but application in endometrial cancer remains controversial.

Design: This is a retrospective study of patients with endometrial cancer and SLN biopsy from 2012-14. Our surgeons perform SLN biopsy and non-sentinel lymph node (NSLN) dissection, thus we assessed negative predictive value (NPV) and false negatives. Chi square was used to calculate significance.

Results: We reviewed 138 cases with 1153 nodes; 363 SLNs and 790 NSLNs, with procurement rates of 97% (Table 1). Metastatic disease was detected in 13% of cases; 6% of SLNs contained tumor versus 3% of NSLNs ($p<.05$). There was no relationship between size of metastasis and histologic grade, DMI, or lymph-vascular invasion (LVI). 98% of patients had concordant results; the false negative cases were serous cancer and adenosarcoma. Endometrioid histology was the most common (86%), with a NPV of 100%. Grade 1 endometrioid cases with positive SLNs had significantly more LVI and DMI>50% (Table 2). 14% of these patients with <50% DMI had positive SLNs (micrometastases), thus requiring further lymphadenectomy. Furthermore, 21% of patients with negative SLNs had DMI>50%. These patients underwent unncessary pelvic lymph node dissection after frozen section assessment.

Table 1. SLN and NSLN Information

Total number of nodes	1153
SLN	363
NSLN	790
Patients with metastatic nodes	18 (13%)
Macrometastases (>2mm)	8 (44%)
Micrometastases (>.2mm)	5 (28%)
Isolated tumor cells (	5 (28%)
Histologic grade, endometrioid	
G1	78 (66%)
G2	21 (18%)
G3	19 (16%)
NPV	97%

Table 2. LVI & DMI for Grade 1 Endometrioid Carcinoma

	SLN+	SLN-	
LVI	71%	6%	p
DMI=none	0%	56%	p
DMI	14%	21%	ns
DMI>50%	86%	21%	p

Conclusions: We found an excellent NPV, especially for endometrioid histology. Low grade endometrial cancers with positive SLNs correlated with higher tumor stage. However, our study showed that DMI overall was a poor predictor of SLN status. Therefore, intraoperative evaluation of SLNs may be more useful to assess disease extent, and to determine the need for complete pelvic lymph node dissection.

1117 The Rate of p16 Immunopositivity of Low-Grade Squamous Intraepithelial Lesions Appears to Correlate With Immunocompromised Status

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Background: The CAP/ASCCP Lower Anogential Squamous Terminology Guidelines recommend the use of p16 immunopositivity to categorize borderline cases as LSIL or HSIL. However, the reported rates of p16 immunopositivity among LSIL cases have been heterogenous, ranging from 0% to 47%. Additionally, the definition of immunopositivity varies among these studies from full-thickness to focal staining with few studies defining positivity as full thickness. We set out to determine the performance of p16 in LSIL cases within our patient population; characterized by high rates of immunosuppression secondary to HIV or organ transplantation.

Design: We identified retrospectively 26 cervical biopsies or loop electrosurgical excision procedures (LEEP) with a diagnosis of LSIL from 2011-2014, excluding condylomas. Of the 26, 17 had sufficient lesional tissue and immunostaining using CINtec® p16INK4a was subsequently performed. Positive staining was defined as full-thickness nuclear and cytoplasmic positivity and was evaluated by 2 pathologists blinded to the patient's clinical history. The patient's history of HSIL, clinical history and HPV positivity were additionally recorded.

Results: 13 of 17 patients (76%) were immunocompromised (12 HIV positive, 1 heart transplant). All 17 patients were positive for high risk HPV DNA prior to biopsy. 10 of 17 cases (59%) showed full-thickness immunopositivity for p16. HSIL was present on concurrent (1 within 4 months) LEEP in 6 of 17 (35%). LSIL p16 immunopositivity had a positive correlation with immunosuppression (p-value = 0.0241), whereas LSIL p16 immunopositivity did not appear to correlate with concurrent HSIL diagnosis (p-value = 0.37). The sensitivity of p16 positivity for concurrent HSIL was 71.4% (29.3%-95.5%) and the specificity was 50% (18.9%-81.1%).

Conclusions: In this patient population with high levels of immunocompromise mostly due to HIV, the p16 positivity rate in LSIL is quite high, even using a conservative definition for positivity. Moreover, there appears to be a significant correlation between p16 immunopositivity and the presence of immunosuppression. This finding merits further study in a larger number of patients to determine whether recommendations for p16 usage should be modified in certain patient populations and whether p16 expression in LSIL has any implications for future risk of developing cervical cancer and precancers. In the meantime, this finding supports the opinion that p16 should be used only in cases truly concerning for HSIL to avoid overtreatment.

1118 Endocervical Gastric-Type Adenocarcinoma: A Detailed Description of the Morphologic Heterogeneity of a Rare Entity Highlighting the Importance of Adequate Tumor Sampling

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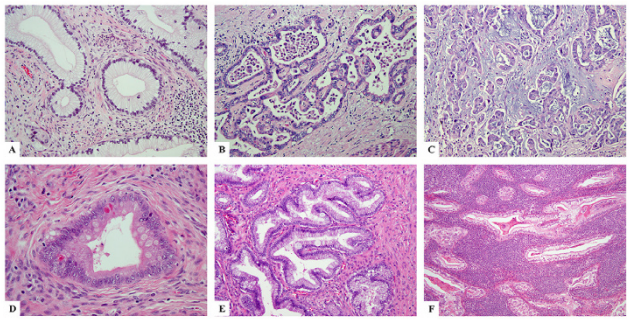
Background: Endocervical gastric-type adenocarcinoma (EGA) is a rare, aggressive non- human papillomavirus (HPV)-related cervical carcinoma. While the recognition of this rare tumor variant is essential, most studies have emphasized only the classic morphological features of EGA. Consequently, the histologic spectrum seen in these tumors has been underrecognized. This study describes the range of histologic features of EGA, emphasizing the marked intratumoral heterogeneity that can be present.

Design: 29 patients with EGA were identified from institutional databases and personal consult files. All available slides from the primary tumor & any metastatic foci were reviewed by 2 gynecologic pathologists. Detailed morphologic review was undertaken in each case, including p16 immunohistochemistry (IHC) were available.

Results: While the classic EGA features of voluminous, clear-to-pink cytoplasm and well-defined cell borders were present at least focally in all cases, there was extensive intratumoral heterogeneity. Most cases demonstrated a spectrum of morphologies, including variation in the proportion of glands which were well-formed and mucin-containing, cytoplasmic volume and quality, nuclear grade, presence of tumor buds or single invasive cells and extent of stromal reaction to invasion [fig 1A-C]. The most consistent finding overall was the rarity of mitotic and apoptotic figures in all cases, even in poorly differentiated areas. Unusual features noted in rare tumors included: dense pink intracytoplasmic globules (n=4), neurosecretory-like granules (n=2) and goblet cells (n=4) [fig 1D-E]. Metastatic sites included lymph nodes [fig 1F] and ovary. All cases tested (n=11) lacked the diffuse, strong p16 IHC staining associated with HPV-driven UEA.

Conclusions: While the classic histologic features of EGA are diagnostically helpful, they may constitute a minority of total tumor morphology. The relative absence of mitotic & apoptotic figures within an endocervical adenocarcinoma may aid recognition of EGA when the morphology is not entirely clear. In light of this morphologic heterogeneity, extensive tumor sampling plays a key role in the recognition of this rare entity.



1119 Endometrial Serous Carcinoma in Younger Women: Evidence of Frequent Derivation From an Endometrioid Substrate

Niamh Conlon, Robert Soslow, Deborah DeLair. Memorial Sloan Kettering Cancer Center, NY.

Background: High grade endometrial carcinoma (EC) remains a challenge for pathologists in terms of accurate and reproducible histologic subclassification. In recent years, there has been greater recognition of the heterogenous nature of this tumor category, in terms of both histology and molecular biology. The classic clinical picture associated with endometrial serous carcinoma (ESC) involves a non-obese, postmenopausal older woman, and ESC in women aged less than 60 years is relatively rare. We hypothesized that a cohort of younger women originally diagnosed with either pure ESC or mixed EC with a serous element would not fit the clinical stereotype and would rather demonstrate a mixed phenotype, with composite clinical, histologic and molecular features of both endometrioid endometrial carcinoma (EEC) and ESC.

Design: We identified 34 patients aged less than 60 years when diagnosed with ESC (N=25) or mixed EC with serous component (N=9) at our institution in 2006-2012. Epidemiologic and clinical data was reviewed. Histologic review of all cases was undertaken, and immunohistochemistry (IHC) for p53, PTEN, ARID1A, MSH6 and PMS2 was performed.

Results: On histologic review, 76% (26/34) of all cases had at least focal endometrioid morphology, including 68% of those initially diagnosed as pure ESC (17/25). 62% (21/34) had a least one histologic or IHC finding considered a discriminatory "endometrioid" feature (squamous metaplasia, background hyperplasia, PTEN or ARID1A or MMR loss). Mean body mass index (BMI) in the cohort was 30, and 80% (27/34) were overweight or obese. 78%(25/32) of patients were postmenopausal at diagnosis. 81% of the whole cohort had aberrant p53 staining, 48% showed PTEN loss (complete loss in 12 patients, focal in 3), 6% had ARID1A loss and 6% had MMR abnormalities. 13 of 15 (87%) patients with PTEN loss also had aberrant p53 staining.

Conclusions: Clinical, histologic and immunohistochemical results suggest that ESC in younger women frequently demonstrates many features traditionally considered "endometrioid" in nature, suggesting that at least a proportion of these carcinomas may derive from an endometrioid tumor substrate. The strong association between the presence of PTEN loss and aberrant p53 staining on IHC in this cohort may signify a form of "tumor progression" with early PTEN loss, followed by a change to more markedly high grade "serous-like" morphology with acquisition of a p53 mutation.

1120 Genomic Profile Analysis of Uterine Smooth Muscle Tumors By Comparative Genomic Hybridization. A Useful Diagnostic Tool in Challenging Lesions

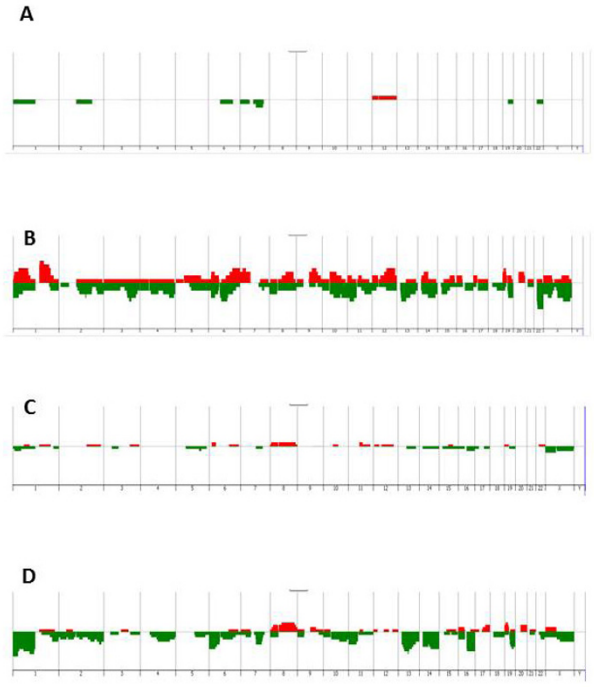
Sabrina Croce, Agnes Ribeiro, Celine Brulard, Jean-Christophe Noel, Frederic Amant, Mojgan Devouassoux-Shisheborah, Laurent Arnould, Gaetan MacGrogan, Frederic Chibon. Bergonie, Bordeaux, France; Erasme Hospital, Bruxelles, Belgium; University Hospital of Leuven, Leuven, Belgium; Hospital Croix Rousse, Lyon, France; JF Leclerc, Dijon, France.

Background: The diagnosis and management of uterine smooth muscle tumors with uncertain malignant potential (STUMP) is challenging and genomic data of these lesions as well as of uterine smooth muscle lesions in general are limited. We tested the hypothesis that genomic profile determination by array-CGH could split STUMP in 2 groups: one with scarce chromosomal alterations akin to leiomyoma (LM) and one with high chromosomal instability akin to leiomyosarcoma (LMS).

Design: Array-CGH analysis was conducted on 29 FFPE STUMPs. A group of 10 LM and 10 LMS served as controls. The Genomic Index (GI) was calculated for each profile as follows: $GI=A^2/C$, where A is the total number of alterations (segmental gains and losses) and C is the number of involved chromosomes.

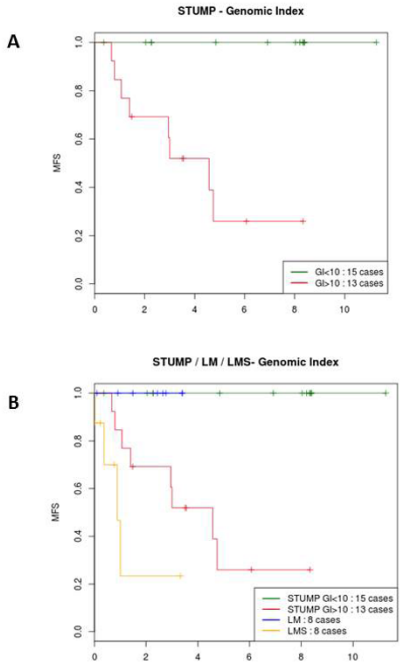
Results: Mean age was 50 years (24 to 85). Follow-up ranged from 12 to 156 months (average 70 months).The LM group showed a flat genomic profile with no or only sporadic alterations and the LMS group a rearranged chromosome profile with numerous intrachromosomal breaks. STUMP genomic profiles showed scarce to many chromosomal alterations.

Figure 1.
Penetrance plots.
Genomic profiles of the LM (A) LMS (B), STUMP with GI < 10 (C) and STUMP with GI > 10 (D)



At first by comparing GI in LM and LMS a threshold of 10 was assessed. Then this threshold was applied to STUMP below which non-recurring STUMPs were found akin to LM and over which STUMPs with recurrences and unfavorable outcomes akin to LMS were recorded.

Figure 2
Kaplan-Meier analysis of metastasis-free survival for STUMP (A) and for STUMP, LM and LMS (B) according to genomic index (GI).



Conclusions: Array-CGH analysis is an innovative diagnostic tool for problematic smooth muscle uterine lesions, complementary to the morphological evaluation approach. We provide an improved classification method for distinguishing malignant tumors from benign lesions within the category of STUMP, definitely in cases with equivocal morphological features.

1121 Leiomyoma With Bizarre Nuclei: Genomic Analysis By Comparative Genomic Hybridization

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Background: Leiomyoma with bizarre nuclei (LM-BN) is a rare LM variant that not infrequently is misdiagnosed as leiomyosarcoma even more when the BN density is high. The discrepancy between "cytologic atypia" and favorable outcome raises the question on the intrinsic nature of this neoplasm: a benign variant of LM with ischemic-reactive changes of degenerative nature or potentially a precursor of leiomyosarcoma. The goal of this study was to investigate the genomic profile of these tumors.

Design: We collected 24 FFPE LM-BN from our consultation practices. Genomic profiles were analyzed by Array-CGH (a-CGH), MED12 mutation status was also investigated. FH (IHC) was performed. Ten uterine LM and 10 LMS served as control.

Results: In 20/24 LM-BN the a-CGH could be analyzed. According to genomic profiles tumors were separated into 4 groups. One group was characterized by FH (ch1q42) deletion(6/20; homozygous 4/6), one group by RB-1 (ch13q14) loss (9/20; homozygous 4/9), another by RB-1 and TP53(ch17p13) losses (3/20) and the last group showed no deletions and rare chromosomal alterations (2/20). All LM-BN but 2 (in group 4) showed moderate chromosomal instability, that differ from LM (very flat profile) and LMS (with high level of instability). TP53 losses were heterozygous, and all associated with RB-1 deletions. In 6 LM-BN the usual component was analyzed and showed the same genomic profile as seen in areas with BN with some additional chromosomal events in the BN component. PCR for MED12 was feasible in 18/20 cases and was only mutated in 1. FH IHC was concordant with genomic status in 18/20 tumors with preserved FH expression in normal or heterozygous cases and 2 showing heterozygous deletion and negative IHC suggesting a mutation or an epigenetic event in the non-deleted allele. Other less frequent genomic events were deletions of MED4 (ch13q14) (10/20), CAMTA1 (ch1p36)(8/20), ARID1A (ch1p35) (7/20), PTEN (ch10q23) (2/20) genes.

Conclusions: LM-BN is a heterogeneous group of tumors with distinct genomic profiles with loss of 13q, 17p, 1p and 1q being recurrent genomic events and MED12 mutations being rare. These findings differ from those reported in conventional LM and LMS.

1122 Tumor heterogeneity in Uterine Serous Carcinoma assessed By Multiple Ligase Probe Amplification

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Background: Solid tumors show intra-tumor heterogeneity, which may be a challenge for evaluating the role of drugs in targeted therapies, since abnormalities in target genes can be heterogeneously distributed among different subpopulations of an individual tumor. The extent and prevalence of intra-tumor heterogeneity has not been fully evaluated in uterine serous carcinoma (USC).

Design: Three independent frozen samples were obtained from 12 different USC. These 36 samples were subjected to MLPA analysis for 106 different chromosomal loci using four different Multiple Ligation Probe Amplification (MLPA) kits from MRC Holland (SALSA MLPA KIT P171-A2 Gain-1, SALSA MLPA KIT P172-B1 Gain-2, SALSA MLPA KIT P173-A2 Gain-3 and SALSA MLPA KIT P294-A1 Tumour-loss), and assessed by capillary electrophoresis. Analysis of chromosomal gains and losses was performed in each sample. Comparative analysis of the three samples from each tumors was also performed.

Results: Chromosomal losses were observed in 22 of the 36 samples (61%), while chromosomal gains were seen in 35 of the samples (97%). The genes most frequently lost were FGFR1 (33%), BIRC1/NAIP (33%), BIRC4 (23%) and ERBB4 (16%), and the most frequently gained were CCNE1 (55%), EV11 (44%), PIK3CA (41%), UCKL4 (41%), AURKA (36%), NTRK1 (33%) and PTPN1 (33%). Concordance in chromosomal gain and loses between the three samples of each tumor was seen in 31 of the 106 chromosomal loci (i.e. 29%), while there was discordance in 47 (44%) of them. Overall 6 of the 12 cases exhibited significant heterogeneity (more than 3 discordant genes). The most frequently heterogeneous abnormal genes were ERBB2 (33%), UCKL4 (33%), BIRC4 (25%), BCAS1 (25%), TERT (25%), BCL6 (25%), NTRK1 (25%), SMARCB1 (25%) and tp53 (25%).

Conclusions: MLPA results show a high frequency of chromosomal gains and losses, confirming the frequent presence of chromosomal instability in USC. Significant heterogeneity was seen in 50% of the cases; sometimes involving genes which may be targeted by molecular therapy.

1123 Evaluation of CIN1 Loop Electrosurgical Excision Procedure (LEEP) Specimens Following an Initial Colposcopic Biopsy Diagnosis of CIN 2: Retrospective p16 Immunostaining on the Initial Colposcopic Biopsies

Agata Czapla, Jan Silverman, Uma Krishnamurti. Allegheny General Hospital, Pittsburgh, PA.

Background: According to the guidelines of the American Society of Colposcopy and Cervical Pathology (ASCCP), women with cervical biopsy-confirmed cervical intraepithelial neoplasia (CIN) 2/3 should undergo an excision to remove precancerous lesions in the cervical transformation zone. Although these treatments are efficacious in eliminating cervical precancerous lesions and thus in preventing cancer, they have also been associated with pregnancy complications, such as cervical stenosis or incompetence, especially in young women. Therefore, it is critical to ensure the accuracy of cervical biopsy diagnosis to avoid unnecessary treatment. The diagnostic reliability of cervical biopsies can be low due to intraobserver variability and poor reproducibility. The aim of the study is to evaluate the diagnostic utility of p16 immunostaining on cervical biopsies diagnosed as CIN 2 with subsequent loop electrosurgical excision procedures diagnosed as CIN 1.

Design: The Allegheny General Hospital and Western Pennsylvania Hospital Pathology database was searched from January 2004 to August 2014 for LEEP surgical specimens with a diagnosis of CIN 1 in which there was a previous colposcopic biopsy diagnosis of CIN 2. Immunohistochemical stain (IHC) for p16 was performed on the initial cervical biopsies and the results graded based on the LAST project guidelines.

Results: During a ten year period, 48 patients had colposcopic biopsy interpretations of CIN2 who subsequently underwent a loop electrosurgical excision procedure (LEEP) with a final diagnosis of only CIN1. Of these 48 biopsy specimens, only 10 (20.8%) recent cases had p16 performed at the time of initial diagnosis. On the 38 cases analyzed before the LAST guidelines, p16 was performed retrospectively with 23/38 (60.5%) having positive diffuse staining. 15/38 (39.5%) had negative staining with 9/15 (60%) showing only a few scattered positive cells, 3/15 (20%) showing focal less than 1/3 staining, and 3/15 (20%) showing completely negative staining.

Conclusions: 1. 68.7% of cervical biopsies diagnosed as CIN 2 were confirmed as CIN 2/3 by p16 immunostaining.
2. 31.3% of CIN 2 biopsies would have been downgraded to CIN 1 based on current LAST p16 immunostaining guidelines, potentially avoiding a LEEP.
3. The study supports that using the LAST p16 guidelines can decrease unnecessary LEEP procedures, thereby avoiding potential complications.

1124 Prevalence of HPV Types in Patients With Abnormal Cytology and Follow-Up Cervical Biopsies in Southern Spain

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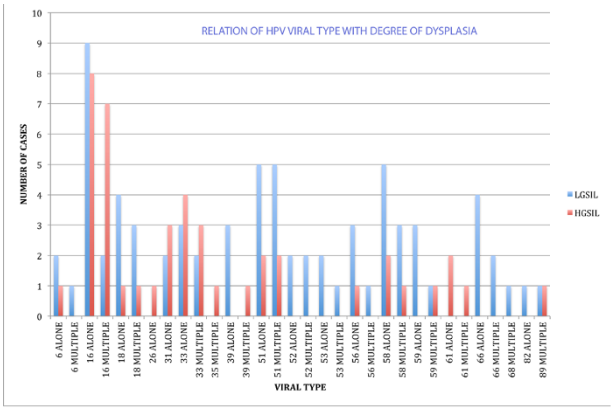
Background: HPV testing has become an important tool in the screening, diagnosis and prevention of cervical intraepithelial neoplasm and cervical cancer. In this study using two different types of HPV Test we evaluate frequency of HPV viral types in patients seen in a hospital setting in Seville, Spain.

Design: 110 cases were selected from a group of patients seen at the Viamed Hospital in Sevilla, with abnormal pap smear results. Every case had a diagnostic cervical biopsy and HPV studies performed with the Digene HC HPV DNA test and with a commercially available FHPV typing kit from Genomed (Switzerland) that allows for the detection

of Intermediate and High Risk HPV types. The frequency of involvement of each type was compared in patients with Low and High Grade Squamous Intraepitelial Lesions (LGSIL, HGSIL). The p-value statistic was calculated with chi-squared test.

Results: Of the 110 cases 3 had negative biopsies, 68 were LGSIL and 39 were HGSIL. HPV 16 was the only virus present in 17 cases but was also co-present with other viruses in 9 additional cases. Of cases with presence only of HPV 16, 9 were LGSIL and 8 were HGSIL. On the other hand, of the 9 cases where HPV 16 was co-infecting with additional viruses, 2 were LGSIL and 7 were HGSIL. HPV 16 and/or 18 were present in 34 of 107 cases with dysplasia. HPV 16 was present in 15 of 39 cases with HGSIL and HPV 18 only in one case. Figure 1 shows frequency o all viral types.



Conclusions: 1) Although most efforts in diagnosis and vaccination are geared to High Risk HPV viruses 16 and 18, the most common viruses associated with HGSIL, more than half of the cases with HGSIL seen in our practice are infected with other HPV viruses. 2) The percentage of HPV 16 cases co-infected with other HPV viruses associated with HGSIL is higher, although not statistically significant (p-value of 0.13), than the percentage of cases infected with only HPV 16. 3) Although HPV vaccination is playing an important role in preventing cervical carcinoma, other preventive measures need to remain in place. Other HPV type viruses can also be linked to Cervical dysplasia and presumably cervical cancer. These viruses may take over HPV 16 after universal vaccination.

1125 Molecular Analysis of Endometrial Clear Cell Carcinoma By Next Generation Sequencing: A Study of 34 Cases

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Background: Endometrial clear cell carcinoma (ECC) is a rare disease which may show aggressive clinical behavior. While endometrioid (EEC) and serous (ESC) endometrial carcinomas have been characterized at the molecular level, the molecular underpinning of ECCs is largely unknown, in part due the rarity of accurately classified *bona fide* tumors. Here we sought to define the somatic genetic alterations of ECCs by targeted next generation sequencing.

Design: Only confirmed ECCs which were rigorously reviewed by two gynecologic pathologists experienced in clear cell morphology were included. DNA extracted from 34 ECCs and matched normal tissue was subjected to massively parallel sequencing targeting the coding regions of 300 actionable cancer-related genes. Somatic single nucleotide variants, insertions and deletions, and copy number alterations were detected by MuTect and VarScan2, respectively.

Results: ECCsfrequently showed an EEC or ESC mutational profile. EEC abnormalities included a hypermutator phenotype, and/or the presence of somatic mutations in *ARID1A, PTEN, PIK3R1*, or *RAS*. ESC abnormalities included *TP53, PPP2R1A*, and *FBXW7* mutations and amplification of *ERBB2*. Ten (29%) and 7 (21%) tumors showed ESC and EEC type profiles respectively, while 10 (29%) showed "hybrid" mutational profiles with both EEC and ESC type abnormalities. The remaining 7 (21%) tumors showed changes not specific to either type. The frequencies of the somatic genetic alterations are shown below.

Gene	All cases (n=34)	Non-hypermutated (n=31)	Hypermutated (n=3)
TP53	44% (15)	39% (12)	100% (3)
PIK3CA	38% (13)	29% (10)	100% (3)
PIK3R1	32% (11)	26% (8)	100% (3)
ARID1A	32% (11)	26% (8)	100% (3)
PPP2R1A	32% (11)	32% (10)	33% (1)
FBXW7	21% (7)	19% (6)	33% (1)
KRAS	15% (5)	16% (5)	0
NRAS	6% (2)	6% (2)	0
HRAS	6% (2)	3% (1)	33% (1)
SPOP	15% (5)	16% (5)	0
ERBB2 (mutation)	6% (2)	3% (1)	33% (1)
ERBB2 (amplification)	9% (3)	10% (3)	0
SMARCA4	18% (6)	10% (3)	100% (3)
NF1	6% (2)	10% (3)	100% (3)
MSH6	9% (3)	0	100% (3)
MSH2	3% (1)	0	33% (1)
MLH1	6% (2)	3% (1)	33% (1)
PMS2	3% (1)	3% (1)	0

Conclusions: ECC is a molecularly heterogeneous group of tumors that show serous and endometrioid like profiles as well as a subset with "hybrid" features. As a group, alterations in targetable cancer related genes are highly prevalent.

1126 The Impact of Intraoperative Tumor Fragmentation or Morcellation in Patients With Early-Stage Uterine Leiomyosarcoma

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Background: Uterine leiomyosarcoma is a rare soft tissue sarcoma originating in the uterine corpus. Unfortunately, this disease entity is often confused with benign leiomyomas and occasionally morcellated at time of operative management, thus potentially spreading and seeding disease throughout the abdomino-pelvic cavity. We aimed to examine the impact of intraoperative tumor fragmentation or morcellation on the outcomes of patients (pts) with stage I high-grade uterine leiomyosarcoma (uLMS).

Design: We searched our institutional database for pts diagnosed with uterine confined stage I uLMS diagnosed between 2000-2014. We excluded pts who presented with recurrent disease. All operative notes were reviewed. Intraoperative tumor fragmentation was defined as mechanical morcellation of a specimen, gross rupture of tumor through uterine serosa or tumor capsule, or when tumor was cut through at the time of myomectomy or supracervical hysterectomy with corroborating pathologic data (positive surgical margins).

Results: We identified 136 pts with stage I high-grade uLMS. Intraoperative tumor fragmentation was noted in 32 (23.5%) cases; of these 15 (46.9%) underwent morcellation. The majority (n=29; 91%) of patients with intraoperative tumor fragmentation or morcellation presented to our institution after initial surgery at outside hospitals. Intraoperative tumor fragmentation or morcellation was associated with younger age (P<0.0001) and larger tumor size (P=0.001), respectively.

Median follow-up for all surviving pts was 47.2 mos (range, 5.3-172.8). Median OS was 45.3 (39.1-51.6) mos in pts with intraoperative tumor fragmentation or morcellation versus 105.2 mos (78.3-132.1) in the control group (P=0.02). Age, tumor size, and mitotic index did not significantly impact OS in this cohort.

Of the 12 pts who had a second-look operation or completion surgery after initial intraoperative tumor fragmentation or morcellation, 6 (50%) were found to have early progressive disease.

Conclusions: In this stage I high-grade uLMS population, poor tissue handling with intraoperative tumor fragmentation, intraoperative tumor rupture, and morcellation were the only prognostic factor significantly associated with OS. In cases where uterine malignancy is suspected, proper tissue handling to avoid intraperitoneal tumor fragmentation is paramount.

1127 Immunohistochemistry Panel To Differentiate Uterine Endometrial Stromal Sarcoma From Leiomyosarcoma; Something Old and Something New

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Background: Endometrial sarcomas are divided into endometrial stromal sarcoma (ESS) and leiomyosarcoma (LMS), each graded as low or high grade. Distinguishing ESS from LMS can be very challenging, especially on biopsies or small samples. The aim of this study is to evaluate well-known as well as new immunomarkers to differentiate between ESS and LMS and between low grade (LG) uterine sarcomas and leiomyoma (LM).

Design: 94 cases [28 ESS (19 LG, 9 undifferentiated/HG); 41 LMS (28 LG, 13 HG), 25 LM (6 atypical, 4 cellular)] were retrieved and arrayed. 10 immunomarkers (ER, PR, CD10, SMA, desmin, caldesmon, transgelin, ASC1, GEM [GTP binding protein

overexpressed in skeletal muscle], stathmin1) were used. The cores were evaluated by 2 pathologists for intensity (1+, 2+, 3+) and percentage (0%, <10, 11-50, 51-75, >75). The score (intensity x %) was used for final evaluation. A score of 8 was the cutoff value for analysis. In an order from largest to smallest significant variables, a predictive model was constructed and examined by receiver-operator-characteristics analysis to determine area-under-curve (AUC).

Results: The IHC panel of $ER^+/PR^+/CD10^+/GEM^+/$ $caldesmon^-/transgelin^-/SMA^-$ can predict any grade ESS vs. any grade LMS with high predictive value of AUC 0.903 (95% CI; OR 0.832-0.973, p<0.0001). The combination of $ER^+/PR^+/CD10^+/caldesmon^-/transgelin^-$ can predict LG-ESS from LG-LMS with high predictive value of AUC 0.914 (95% CI; OR 0.832-0.9995, p< 0.0001). Finally, cases with positive stahmin1 expression are 36 times greater to be LG-uterine sarcoma than LM. All 10 atypical and cellular leiomyomas were $stathmin1^-$. ASC1 failed to show any predictive value in our analysis.

Conclusions: 1- Adding novel antibodies such as GEM and transgelin to the routinely used panel of immunomarkers proved to have more predictive power to distinguish ESS from LMS when compared to the old panel. 2- Cases with positive expressions of ER/PR/CD10/caldesmon/trangelin are more likely to be LG-ESS than LG-LMS, which is a vital distinction for any pathologist to make due to the indolent course and hormone therapy for the former and the more aggressive behavior and radiation therapy for the later. 3- Stahmin1 expression could be a useful immunomarker in conjunction with morphology to differentiate LM from uterine sarcoma, especially the atypical LM which sometimes creates a major diagnostic challenge.

1128 Incidental Findings of Tubal Intraepithelial Neoplastic Changes in Women With Gynecologic Surgical Intervention for Non-Malignant Conditions

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Background: The association of Serous Tubal Intraepithelial Carcinoma (S-TIC) with advanced stage high grade serous carcinoma involving pelvic organs, peritoneum and omentum is reflected in recent new paradigm for the pathogenesis of ovarian cancer and parallels the implementation of the SEE-FIM protocol. In addition BRCA+ patients demonstrate higher frequency of STIC in fallopian tubes at the time of risk reducing salpingo-oophorectomies (RRSO). We have implemented the protocol since 2007 and were interested in determining the frequency of TIC in patients with surgical intervention for non-malignant gynecologic conditions.

Design: The search was restricted to patients with salpingo-oophorectomies with or without hysterectomy. Specimens were selected from patients with clinical or radiologic findings of either an ovarian/pelvic cyst. In addition, clinically symptomatic patients with abnormal vaginal bleeding, prolapse or pelvic pain were also included. BRCA positive patient undergoing RRSO were excluded.

Results: A total of 11 cases of incidental tubal neoplastic changes were identified between early 2007 and September 2014. Patients' age range 39-78 (mean ~66.2). Two patients were with p53 signatures and 9 with TIC. Two of the nine were also associated with 0.2 cm and 0.3 cm invasive high grade serous carcinoma, in the submucosa. Lymphovascular invasion was not present. Eight of eleven had negative companion pelvic wash; remainder 3 did not have pelvic wash cytology.

Incidental TIC and p53 signature were found in 2 patients due to preoperative findings of simple and complex endometrial hyperplasia, 2 -ovarian cysts, 1 - ovarian teratoma, 1- pelvic cyst/mass, 1-prolapse, 1- pelvic pain and 3- unknown.

Conclusions: The presence of STIC in BRCA positive asymptomatic patients is equated to an early detection of this lethal disease, and is due to methodical examination of the fimbria per SEE-FIM protocol following RRSO. Our results support that all fallopian tubes should be evaluated thoroughly, implementing SEE-FIM protocol, regardless of cancer risk.

1129 Comprehensive Genomic Profiling (CGP) of Cervical Adenocarcinoma Correlates With the Presence or Absence of High-Risk Human Papillomavirus (HPV) 16 or 18

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Background: High-risk HPV, particularly HPV-16 and HPV-18, are oncogenic drivers of cervical adenocarcinoma (cACA). However, a distinct subset of cACA arise independent of HPV infection. We employed CGP of 58 cACA to elucidate differences in genomic alterations (GA) and therapeutic targets between HPV-16 or HPV-18 positive, and HPV-16/18 negative tumors.

Design: Hybridization captured libraries for 236 cancer-related genes and 19 genes commonly rearranged in cancer was applied to ≥ 50ng of DNA extracted from 58 cACA FFPE specimens (22 primary, 36 mets) and sequenced to high, uniform coverage. HPV-16 and HPV-18 viral sequences, but not other hrHPV subtypes, were assayed. GA, which include: base substitutions, small insertions/deletions, rearrangements, and copy number alterations, were determined and reported for these patient samples.

Results: cACA were predominantly advanced stage (III/IV 77%, I/II 16%) despite varied histologic grade (G1 34%, G2 26%, G3 40%) in these young women (avg. 45.4y). 38/58 (65%) cACA had detectable HPV-16 (n=16) or HPV-18 (n=22) sequences, and 35% were HPV-16/18 negative (HPVN). 202 total GA were identified in the 58 cACA (3.48 GA per tumor) of which 111 clinically relevant GA (CRGA) (1.91 per tumor) involving 36 different genes with 51/58 (88%) of cACA featuring at least 1 CRGA. HPV-18 positive cases had the fewest GA (HPV-18 2.9; HPV-16 3.13; HPV-Neg 4.4) and CRGA per tumor (HPV-18 1.6; HPV-16 2.1; HPVNeg 2.2). HPV-16 tumors had a significantly higher rate of PIK3CA activating mutations compared to HPV-18 tumors (53% vs. 9%, p<0.01). HPV-16/18 negative tumors had higher rates of TP53 loss of function (55% vs. 8%, p<0.001), and CDKN2A/B loss and MYC amplification (each 20% vs. 0%, p=0.016) compared to HPV-16/18 positive tumors. Additional CRGA included *AKT1 (5.3%), ERBB2 (15.8%), GNAS (15.8%), KRAS (19.3%), STK11 (17.5%), and RICTOR (12.3%).* One HPV-16 positive cACA with a late recurrence in the lung harbored an *FGFR3-TACC3* gene fusion and showed a partial response to an FGFR3 inhibitor.

Conclusions: Frequent CRGA characterize HPV-16/18 positive and negative cACA. HPV-16/18 positive subtype correlates with the mutational mechanism of signaling pathway activation, while tumor suppressor loss is common HPV-16/18 negative cACA. Novel targets were identified at a high frequency in both HPV-16/18-positive and negative cACA providing rationale for CGP-directed therapeutic decision-making.

1130 Ultrastaging of Sentinel Lymph Nodes in Endometrial Carcinoma: A Tale of Two Protocols

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Background: Sentinel Lymph Node (SLN) sampling may provide valuable staging information without exposing patients (pt) to risks of lymph node dissection. There is no consensus protocol for optimal pathologic handling of these specimens. This study compares two ultrastaging protocols of SLN in endometrial carcinoma (EC).

Design: All SLN were serially sectioned perpendicular to the long axis in 2mm intervals and entirely submitted for routine H&E processing. SLN negative by routine processing had ultrastaging by one of the following: Method1 (M1), 5 H&E levels at 250µm intervals with 2 unstained slides at each level; pankeratin immunohistochemistry (IHC) performed on level 1 in cases with negative H&E levels or Method 2 (M2), 1 H&E level + 2 unstained slides cut 250µm into the tissue block; pankeratin IHC performed in cases with negative H&E. Histologic subtype, numbers of SLN, positive SLN, nonSLN, positive nonSLN and metastasis size were recorded.

Results: 114 pts had 356 SLN (1-16, median 2) sampled during hysterectomy for the following EC histotypes: endometrioid FIGO grade 1/2 , 79 (69%); endometrioid FIGO grade 3, 10 (9%); serous, 12 (10.5%); carcinosarcoma, 6 (5%); undifferentiated, 3 (3%); clear cell, 4 (3.5%). 111 had ultrastaging: M1, 53 pts; M2, 58 pts. 21 (18%) pts had 39 positive SLN detected as follows: routine processing, 3 pts; M1, 9 pts; M2, 9 pts. 3 pts with negative SLN had a positive nonSLN (false negative rate, 12.5%). Mean/median metastasis size was 2.9 mm (±3.5)/0.5 mm for M1 and 1.8 mm (±3.2)/0.5 mm for M2. 12/39 positive SLN were detected by ultrastaging that would otherwise have been negative representing a 30.8% increase in metastasis detection. This represents 8 additional patients (38% increase). Of these additional SLN, 3 were detected by IHC. In 4 pts, metastatic deposits in SLN were low volume disease (size £0.2 mm). Statistical analysis comparing M1 (5 lev ±IHC) and M2 (1 lev ±IHC) detected no statistically significant differences with respect to number of positive SLN detected, size of metastasis or false negative rate. The methods performed similarly for both low and high grade EC.

Conclusions: A more comprehensive US protocol had no significant advantages over a single wide interval and IHC in this study population. A pankeratin IHC stain enhances metastasis detection. Additional studies are required to further test this limited protocol as well as to evaluate the clinical significance of the low volume disease detected by ultrastaging.

1131 Comparative Analysis of Rb, P16 and ER Expression in Ovarian Cancers: An Immunohistochemical Study of 177 Tumors

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Background: Deregulation of CDK4/6, cyclin D/p16 and retinoblastoma (Rb) pathways are known aberrations in cancers. There has been a recent interest in exploring the combination of letrozole and CDK4/6 inhibitors in recurrent ER+ ovarian cancers. This study aimed to determine the frequency, patterns and clinicopathologic significance of Rb, p16 and ER in a large cohort of ovarian tumors (OVTs).

Design: Expression of Rb, P16 and ER was assessed by IHC on a tissue microarray of 177 OVTs. Nuclear staining for Rb was scored: negative (neg), (1+) and (2+) positive. Strong and diffuse p16 was considered positive. The H-scoring (H) system was used to evaluate ER. For the purpose of analysis, Rb1+ and ER of H£25 were considered neg.

Results: Table 1 summarizes the frequency of the markers in OVTs. Rb was neg in 100% GCTs (56% specificity p<0.001) and 79% of GCTs were neg for all 3 markers (85% specificity p<0.001). Co-expression of all three markers was 96% & 93% specific for HGSC and LGSC (15% and 13% sensitivity p<0.001). Rb was positive in 67% grade (G) 1/2 vs. 43% G3 tumors (p<0.05). P16 was positive in 31% G1/2 vs. 68% G3 tumors (p<0.001). There was no significant difference in the pattern of the markers with tumor size, lymph node and metastasis.

Tumor type	Rb+ (#, %)	P16+	ER H>25	Rb+, ER>25
High grade serous [HGSC] (n=46)	27 (59)	30 (65)	27 (59)	14 (30)
Low grade serous [LGSC] (n=8)	5 (63)	3 (38)	6 (75)	4 (50)
Endometrioid (n=34)	16 (47)	21 (62)	17 (50)	5 (15)
Mucinous carcinoma (n=19)	11 (58)	2 (11)	3 (16)	1 (5)
Granulosa cell tumor [GCT] (n=14)	0	2 (14)	1 (7)	0
Metastatic carcinoma (n=13)	9 (69)	4 (31)	2 (15)	2 (15)
Adenocarcinoma, NOS (n=12)	3 (25)	8 (67)	3 (25)	0
Dysgerminoma (n=9)	6 (67)	1 (11)	0	0
Yolk sac (n=7)	4 (57)	1 (14)	0	0
Others (n=15)	12 (80)	7 (47)	1 (7)	0
Total (n=177)	93 (53)	79 (45)	60 (34)	26 (15)

Conclusions: Neg/1+ staining for Rb is highly sensitive for GCT, and coordinate neg for Rb, P16 and ER may support its diagnosis. Positive staining for the 3 markers is specific for HGSC and LGSC. Rb and p16 show inverse expression pattern by tumor grade with more frequent Rb in low grade vs. more frequent p16 in G3 tumors. These data provide a rational basis for clinical trials that aim to target these proteins.

1132 The Impact of P16 Immunostain on the Diagnostic Agreement of Cervical Biopsies Using the New WHO Terminology

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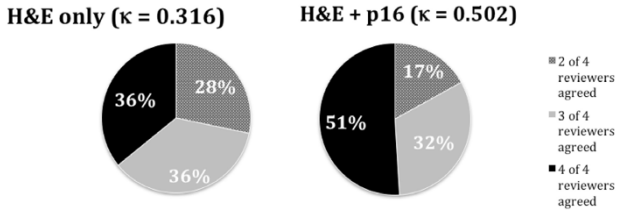
Background: P16 immunostain is recommended by the CAP/ASCCP Lower Anogential Squamous Terminology Project (LAST) as a routine adjunct to H&E morphologic assessement of cases in which the differential diagnosis is between precancer (CIN2, CIN3) and a mimic of precancer. The new (2014) WHO terminology for cervical intraepithelial lesions recommends a two-tier system of low- and high-grade squamous intraepithelial lesions (LSIL, HSIL). This study evaluated the impact of p16 immunostain on the inter-observer agreement using the new WHO classification.

Design: A total of 53 diagnostically challenging cervical biopsies from a 2-year period with available p16 immunostain were retrieved from our departmental archives. Four surgical pathologists with various level of experience in gynecologic pathology separately reviewed all cases, blinded to the original diagnosis and patient characteristics. An initial diagnosis of LSIL, HSIL, or No SIL was rendered by each pathologist based solely on the H&E stains. Pathologists also noted if they would order a p16 stain for each case. A second reading was done days later for each case using both H&E and p16 immunostained slides. Interobserver agreement was calculated using Fleiss' kappa.

Results: Diagnostic agreement by at least three of four pathologists was observed in 72% of the cases on the initial (H&E only) reading, and 83% of the cases on the second reading (H&E + p16). Between the first and second readings, the interobserver agreement improved from kappa 0.316 to 0.502. After the initial (H&E) reading the study pathologists indicated that they would have ordered p16 immunostain in 19-38% of cases (mean 31%). Change in diagnosis was observed between the two readings in 28.5% of cases on average (range 8-40%).



Conclusions: Application of the LAST recommendation to use p16 immunostain as an adjunct, combined with the new WHO two-tiered grading system resulted in improved interobserver agreement. However, even with the addition of p16, the interobserver agreement remains suboptimal in diagnostically challenging cervical biopsies.

1133 Differentiated Cells Secrete Factors That Can Proliferate-Arrest and Force Differentiate Pluripotent Embryonal Carcinoma Stem Cells

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Background: Cancer stem cell (CSC) theory proposes that tumours are composed of a heterogeneous mixture of undifferentiated CSCs and their differentiated progeny. While undifferentiated CSCs and differentiated counterparts have been studied in isolation, little is known of their interaction *in vivo*. The aim of this study was to assess whether undifferentiated CSCs and the differentiated cells they produce interact when grown together.

Design: Co-culture experiments involved undifferentiated Pluripotent NTera2 human Embryonal Carcinoma cells and NTera2 cells differentiated by retinoic acid treatment for 7 days. Conditioned-media experiments involved incubation of NTera2 cells in undifferentiated ('undiff-conn') or differentiated ('diff-conn') conditioned media for 7 days. Differentiation status was confirmed by loss of expression of SSEA4 (flow cytometry) and Oct4-Sox2-Nanog (qPCR).

Results: Undifferentiated and differentiated cells were co-cultured in a 1:9 ratio, which arrested the growth of undifferentiated cells after only 7 days. Flow cytometry (SSEA4) indicated that NTera2 cells had not differentiated but had stopped proliferating. This data led us to hypothesise that differentiated cells secrete factors into their environment that can regulate the growth of undifferentiated CSCs. Confirming this, treatment with undiff-conn media increased the expression of SSEA4, suggesting an enhancement of the undifferentiated state. Furthermore, treatment with diff-conn media forced all cells to differentiate. A further validation, qPCR analysis showed that Oct4-Sox2-Nanog levels were increased in undiff-conn treated cells and dramatically lost in diff-conn treated cells.

Conclusions: Our data indicate that undifferentiated CSCs secrete factors to promote their undifferentiated state. In parallel, differentiated cells secrete factors that can arrest CSC proliferation in co-culture and force-differentiate CSCs in conditioned media conditions. These effects are achieved through a standard Oct4-Sox2-Nanog mechanism. These results are striking when it is noted that forcing differentiation upon CSCs removes their tumorigenic potential. As such, if the factors secreted by differentiated NTera2 cells can be identified in future work, they may be useful as a potential anti-cancer force-differentiation treatment.

1134 Genotype 16 HPV Vaccination Significantly Reduces Infection in Just Five Years

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Background: The identification of the human papillomavirus (HPV) as the main reason of the development of cervical cancer and other lesions has permitted the generation of various preventive measures among which are vaccines. Vaccine against 16 and 18 HPV genotypes (*Cervarix* ®) have been administrated to women among 14 years old since 2008 in Cantabria (SPAIN). Our aim in this study is to determine whether the introduction of the vaccine has changed the distribution of HPV.

Design: We conducted a retrospective study from 2003 to determine the annual distribution of each genotype of HPV. A total of 22615 patients were included in the trial. CLART® HPV2 kit (Genomics) was used for the determination of virus.

Results: Thirty nine percent of the cases presents at least one HPV infection, mainly because the study was performed on patients with high-risk biopsies. Data analysis shown a significant reduction (p=0,0022) of the presence of 16 HPV genotype when compared pre and post vaccination groups (by years before and after 2008, figure 1a). Genotype 18 was not altered, mainly because of its low incidence in Spain. Other genotypes such as 31 or 53, presents no decrease (figure 1b and c).

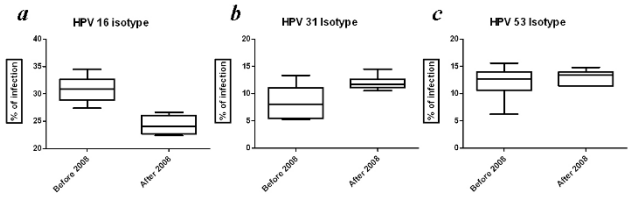

Figure 1: HPV infection of different genotypes before and after vaccine administration in 2008

Conclusions: Our data suggested that vaccination against HPV genotype is significantly reducing the presence of cervical cancer high risk HPV genotype (16), even without having been a long time since its introduction.

This work could not have been done without the invaluable assistance of our technicians Yolanda, Montse, Marilo, Estíbaliz, Montse and Emilia.

1135 Atypical Polypoid Adenomyoma (APA) of the Uterus: A Clinicopathologic Study of 71 Cases

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Background: APA has been regarded as a benign tumor; however, it is often associated with endometrioid adenocarcinoma, and its histologic diagnosis and biologic potential have been controversial.

Design: Clinicopathologic features, morphology, and the effects of hormonal (medroxyprogesterone acetate) therapy and biologic behavior were studied in 71 APA cases.

Results: The patients' ages ranged from 22 to 66 (mean: 30) years. All but three of the patients were premenopausal. Histologically, the lesions were composed of a biphasic proliferation of architecturally complex and cytologically atypical endometrial glands with a myomatous or myofibromatous stroma. Squamous metaplasia or morules were observed in 58 cases. Twenty-two had evidence of background endometrial hyperplasia and 17 had endometrioid carcinoma (14 in APA and 3 in the adjacent endometrium). All 6 patients who were initially treated with curettage or polypectomy followed by hormonal therapy had residual or recurrent APA. One treated by hormonal therapy became pregnant. Patients treated with hormonal therapy exhibited a decreased N/C ratio of epithelial cells, persistent atypical glandular structures, and a markedly edematous stroma. Hysterectomy was performed in 14 patients because a definite diagnosis could not be made preoperatively, the curettages raised the possibility of adenocarcinoma, or because there was a high possibility of residual or recurrent lesions. All showed residual or recurrent APA in hysterectomy specimens. Two showed superficial myometrial invasion, and three showed APA in a focus of adenomyosis. The overall residual or recurrent lesion rate was high (23 /70, 33%). All patients were alive and well at 1 to 202 months (mean, 39.6 months).

Conclusions: The rate of recurrent or residual APA was high, and the effects of hormonal therapy were limited. The risk of endometrial carcinoma in women with APA is also high. This study suggests that APA should be carefully evaluated, and cannot be regarded as a completely benign entity. The findings indicate a continued risk for the development of endometrial adenocarcinoma in patients in whom complete excision of APA can not be guaranteed. If a definite diagnosis of APA has been made on curettage or polypectomy, hysterectomy is the treatment of choice. However, treatment by complete curettage or polypectomy may be undertaken, thereby, preserving the reproductive function, providing there is subsequent close follow-up.

1136 Twin Placenta With Complete Hydatidiform Mole in the First Trimester: Histologic Diagnosis and Immunohistochemistry for the Imprint Gene Products P57 (Kip2) and TSSC3

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Background: Twin pregnancies with a normal placenta and complete mole (CM) are very rare, and they may pose a diagnostic challenge. This type of CM has higher risk of persistent trophoblastic disease than conventional CM. Microscopically, they resemble partial mole. The differential diagnosis is very important for patient management. p57 (Kip2) (p57) and TSSC3 are products of paternally imprinted, maternally expressed genes.

Design: Seven cases of morphologically twin pregnancies with CM in the first trimester were retrieved and studied by the immunostaining of p57 and TSSC3. DNA ploidy in three cases was also analyzed by flow cytometry, and all of them were diploid. One case was chromosomally analyzed.

Results: Patient ages ranged from 20- 38 years (mean, 28 years) and gestation weeks ranged from eight to 12 weeks (mean, 8 weeks). Clinically, partial mole was suspected in five cases, and hydatidiform mole and blighted ovum was considered in one case each. The initial pathologic diagnosis was partial mole in all cases. On review, the seven cases were histologically diagnosed as CM with twin (twin pregnancy with a coexisting normal placenta and CM). The admixture of large hydropic villi with circumscribed trophoblastic hyperplasia and smaller, normally appearing villi without trophoblastic hyperplasia was observed in all cases. The cytotrophoblasts and stromal cells in larger villi were negative for p57 (androgenic) and TSCC3, whereas these cells were positive in the smaller villi (biparental) in six cases. In the remaining case, in which larger villi showed 46XX and normally appearing villi showed 46 XY, cytotrophoblasts in larger villi diffusely expressed TSCC3. Normally appearing villi exhibited p57 and PSSC3 expression in a mosaic pattern. No patients developed persistent trophoblastic diseases.

Conclusions: The findings support the hypothesis that misexpression of p57 and TSSC3 is involved in the abnormal development of androgenic CMs. Immunohistochemical analysis is a useful tool for the differential diagnosis of twin placenta with CM and morphologically challenging CM cases.

The single case of twins with CM was considered to probably be due to androgenic/biparental chimera or a mosaic in molar and normally appearing villi, although molecular cytogenetic analysis was not done. Immunohistochemistry for the imprint gene products p57 and TSSC3 may be a useful screening tool for cytogenetic analyses.

1137 Morphologic and Genetic Heterogeneity in Mixed Endometrial Carcinomas

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Background: Mixed endometrial carcinomas (MECs) comprise a heterogeneous group of tumors characterized by an admixture of two or more distinct histologic subtypes of endometrial carcinoma. The genetic underpinning of MECs has yet to be fully established. We investigated the repertoire of somatic genetic alterations in 4 MECs by targeted capture sequencing of 341 cancer-related genes in each of their distinct histologic components.

Design: Six gynecologic pathologists reviewed slides from 13 tumors originally diagnosed as MECs; four tumors were unanimously diagnosed as *bona fide* MECs. Representative sections from each case were cut and subjected to microdissection, either laser-assisted or with a needle under a stereo-microscope. DNA was extracted from each tumor component and matched normal tissue and subjected to massively parallel sequencing using the MSK-IMPACT platform that targets the coding regions of 341 actionable cancer-related genes. Somatic single nucleotide variants were detected by MuTect; insertions and deletions were detected by VarScan2 and Strelka; copy number alterations were defined using VarScan2. Private mutations in each component were confirmed by Sanger sequencing.

Results: The 4 tumors were classified as mixed serous and high-grade endometrioid carcinoma, mixed serous and low-grade endometrioid carcinoma (SC/ELG), mixed low- and high-grade endometrioid carcinoma, and mixed high-grade endometrioid and undifferentiated carcinoma (EHG/U). In all cases, both components were found to be clonally related based on the presence of identical somatic genetic alterations. The number of mutations in common between the two components varied from case to case (median 10, range 1 to 217). A *POLE* hotspot mutation was found in both components of the SC/ELG, which showed an extraordinarily high number of somatic mutations, consistent with the ultramutator phenotype. In each case, morphologically distinct components harbored private genetic alterations (median 5, range 1 to 100), including mutations in *TOP1*, *SMARCA4, PDL1* and *JAK3*.

Conclusions: The histologically distinct components of MECs are composed of distinct clonal populations of neoplastic cells sharing the same initiating genetic lesions (i.e. founder somatic mutations), however each component displays private genetic events. Our findings have potential therapeutic implications, as mutations affecting targetable cancer genes may vary according to the histologic component of MECs.

1138 Stathmin-1 Distinguishes High-Grade From Low-Grade Cervical Intraepithelial Neoplasm

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Background: Stathmin-1 (STMN) is an important cytoplasmic microtubule-destabilizing protein and has been reported to be diagnostically useful in identifying cervical high grade squamous intraepithelial lesion (HGSIL). The objective of this study is to establish the diagnositc threshold of STMN by stratifying the staining grade at different layers, and to determine the sensitivity, specificity, and positive predictive value of STMN in cervical dysplasia by comparing to p16.

Design: Cervical biopsy specimens (including 28 cases of low grade squamous intraepithelial lesion (LGSIL/CIN1), 55 cases of HGSIL (CIN2 and CIN3), and 5 benign cases) were selected for STMN and p16 immunohistochemical staining. At least two independent blinded reviews were performed for each biopsy. For STMN, the staining is evaluated as either negative (no staining above the basal layer) or positive (cytoplasmic staining above basal layer). Further grading system for STMN above the basal layer is delineated as 0 (< 5%), 1 (5-25%), 2 (26-75%), and 3 (>75%) at different layers. Of p16 staining, only band like nuclear staining of p16 is considered positive. Sensitivity (SS), specificity (SP), and positive predictive value (PPV) are calculated.

Results: The staining results for STMN and p16 are summerized in [table1].

	con-trol	CIN1	CIN2	CIN3	SS_ CIN2	SS_ CIN3	SP_ CIN2	SP_ CIN3	PPV for HGSIL
STMN	0/5	0/25	23/27	28/28	85%	100%	88%	100%	100%
p16	0/5	3/25	25/27	26/28	91%	93%	87%	87%	94%
Either STMN or p16	0/5	3/25	26/27	28/28	96%	100%	96%	96%	100%
Parabasal layer			1.85± 0.19	2.96± 0.04					
Intermediate layer			0.85± 0.14	2.14± 0.16					
Superficial layer			0.07± 0.05	0.68± 0.15					

STMN had 100% SS and SP for CIN3 and 85% SS and 88% SP for CIN2 , and had 100% PPV for HGSIL. STMN complemented with p16 increased the sensitivity to detect HGSIL especially CIN2 from 91% to 96%. Of note, the STMN staining is more extensive in intermediate and superficial layers in CIN3 compared to CIN2.

Conclusions: Cytoplasmic staining of STMN above basal layer in cervical mucosa is a highly specific marker for HGSIL. By combining with p16, STMN can increase the specificity and sensitivity for CIN2, and could be used to distinguish from LGSIL and reactive/metaplastic cervical lesions. It might be interesting to set up a large study to follow up cervical lesions for their risk levels by combining histological diagnosis and biomarkers including STMN and p16.

1139 Fibroepithelial Polyps of the Vagina – A Clinical and Pathologic Study of 70 Cases

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Background: Fibroepithelial polyps of the vagina are relatively common lesions. However, their morphologic spectrum, although described in previous reports, has not been yet clearly characterized in a large series. Our objective was to assess the clinical and pathologic features of a series of vaginal fibroepithelial polyps.

Design: Pathology Department databases were reviewed from 2003 to 2013. Slides of vaginal fibroepithelial polyps were examined. Size, stromal hypercellularity, multinucleation, cytological atypia, mitosis and associated epithelial changes were recorded. Clinical charts were consulted, recording patients' age, fertile status and associated gynecological pathology. Twenty cases of normal vaginal samples were used as controls. Statistical analysis was performed with GraphPad Prism® software.

Results: We identified 70 cases of vaginal fibroepithelial polyps, corresponding to 65 patients (mean age: 54,8 years; range: 12-85 years). Four patients had multiple polyps, no patient was pregnant and 3 patients had previous radiation therapy for cervical or vulvar neoplasia. Thirty-six patients (51,4%) were post-menopausal. Fibroepithelial polyps had a mean size of 13,03 mm (range: 2-45 mm). Stromal hypercellularity (70% of cases) and stromal cellular multinucleation (92,9%) were significantly different between cases and controls ($p<0,0001$); all polyps larger than 12,5 mm were hypercellular and displayed multinucleated cells ($p<0,01$). Stromal cellular atypia was noted in 5,7% of cases; there was a tendency of atypical polyps to be larger than non-atypical (20,5 mm +-6,1 vs 13,8 mm +-9,8, $p=0,07$). Several kinds of stromal general features were noted, mainly: angiomatoid (24,3%), fibrotic (24,3%) and myxoid (5,7%). No mitotic figures were found in stromal cells. Epithelial changes were noted, such as acanthosis, papillomatosis and reactive changes (38,6%), but no conclusive evidence of HPV-cytopathic change was observed.

Conclusions: Stromal hypercellularity and multinucleation are common features in vaginal fibroepithelial polyps and are related with the size of the polyp. Stromal cell atypia, despite of being an unusual finding, has a tendency to be also related with the size of the polyp. Epithelial reactive changes are frequent but nonspecific features.

1140 Fimbria and Ampulla Tubal Epithelium Have Similar Transcriptome Profiles

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Background: Recently described precursors of High Grade Serous Carcinoma, the p53 signature, a latent precursor, and Serous Tubal Intraepithelial Carcinoma, a pre-malignant precursor, occur most frequently at the distal and fimbriated end of the fallopian tube (FTE). We recently demonstrated that the FTE of BRCA1 mutation carriers, at genetic risk of HGSC, have altered signaling pathways compared to controls. A key question is whether the gene expression differences identified at the ampulla between BRCA1 and non- mutation carriers is similar to differences at the fimbria. This study determines the transcriptome profiles of normal fimbrial FTE and normal ampulla FTE which may lead to an understanding of why the distal end of the fallopian tube is preferentially predisposed to malignant transformation.

Design: Snap-frozen matched fimbria and ampulla tissues were controlled for age and ovarian cycle status at surgery. Cases included 12 luteal phase and 12 follicular phase women at no known risk for ovarian cancer. Laser capture microscopy was used to microdissect FTE cells, using 7-10 sections per case. Total RNA was isolated, RNA extracted and cDNA amplified. The expression profiles were generated using Affymetrix Human Genome HTA-2.0 Array.

Results: Using gene level differential expression analysis with Affymetrix Expression Console software, we performed unsupervised hierarchical clustering analysis with all 24 samples. We used a fold change of < -2 or > 2 and ANOVA p-value < 0.05 as a cut-off criteria for selecting genes. The cases clustered predominantly by ovarian cycle status rather than by their differences in anatomical origin or their matched pair. There were 427 genes differentially expressed amongst the 4 groups – Fim-Luteal, Fim-Follicular, Amp-Luteal and Amp-Follicular. Independent of ovarian cycle status, very few differences (35 genes – SALL1, SERPINA3, ANXA13, PDK4, ME1, GSTA1, GSTA2 – genes involved in metabolic pathways) were observed between the ampulla and fimbria FTE.

Conclusions: The epithelia of the anatomically high-risk fallopian tube – the fimbria, show few differences in gene expression profiles compared to the lower risk portion – the ampulla. Expression differences predominantly are in response to the hormonal mileu, i.e. the secretory and proliferative phases of the ovarian cycle. The increased anatomic risk of the fimbria is likely due to effects of the microenvironment, such as repeated exposure to follicular fluid at ovulation, rather than intrinsic differences of the FTE in the two sites.

1141 Next Generation Sequencing for High Grade Neuroendocrine Carcinomas of the Cervix

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Background: Cervical neuroendocrine carcinoma is a rare but aggressive malignancy with limited data regarding its molecular genetics. Identification of clinically actionable mutations in this tumor type may help to direct targeted therapies. The purpose of this study was to compare the molecular changes in neuroendocrine carcinoma of the cervix to those of the more conventional cervical carcinoma histologies, squamous cell carcinoma and adenocarcinoma.

Design: We retrospectively analyzed next generation sequencing data based on a 46/50 gene platform consisting of mutational hotspots in a series of patients with advanced stage cervical carcinoma from 2012-2014. The formalin-fixed, paraffin-embedded tissue from 52 tumors, 17 neuroendocrine carcinomas and 35 squamous cell carcinomas/adenocarcinomas (conventional histology), was analyzed.

Results: Nine/17 (53%) of the neuroendocrine carcinomas and 20/35 (57%) of the conventional histology carcinomas demonstrated at least one mutation from the panel. Among the neuroendocrine carcinomas, mutations were identified in *TP53* (4/17, 24%), *KRAS* (3/17, 18%), *PIK3CA* (1/17, 6%) and *GNAS* mutation (1/17, 6%). For the conventional histology tumors, mutations were identified in *TP53* (2/35, 6%), *KRAS* (4/35, 11%), *PIK3CA* (7/35, 20%) and *GNAS* mutation (3/35, 9%).

Conclusions: Mutation in *PIK3CA* has been previously identified to be a relatively common and targetable aberration in cervical carcinomas with conventional histologies. However, high grade neuroendocrine carcinomas only rarely have mutation in *PIK3CA*. The mutation pattern found in small cell lung carcinomas is distinct from that seen in the neuroendocrine carcinomas of the cervix, suggesting that they may require a different treatment strategy. For example, small cell carcinoma of the lung frequently has *RB1* mutation; this was not observed in our patient cohort. Given the paucity of mutations identified in clinically actionable genes, patients with high grade neuroendocrine carcinomas should be considered for more extensive molecular diagnostics testing platforms.

1142 Specific Patterns of Invasion in Endometrial Carcinoma Are Associated With Isolated Carcinoma Cells in Lymph Nodes

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Background: The most important factor in determining prognosis in endometrial carcinoma is the presence of metastasis, including lymph node (LN) metastasis. Previous work has demonstrated that the presence of microcystic, elongated and fragmented glands (MELF) and single cell/cell-cluster invasion (SCI) is predictive of LN metastasis in low stage/well-differentiated endometrial carcinoma. One study commented on the presence of subtle lymph node metastasis in cases with MELF; indeed, we have observed that cases with MELF/SCI often have occult LN metastasis present as single carcinoma cells in sub-capsular sinuses or scattered in the LN. We undertook a retrospective review of endometrial carcinoma cases to determine whether the presence of MELF or SCI predicts the presence of occult LN metastasis.

Design: 82 cases of endometrioid endometrial carcinoma with pelvic and/or para aortic LN metastasis were reviewed and scored for presence or absence of MELF and SCI along with standard grading and staging parameters. LN metastasis were classified by nodal group (pelvic or para aortic) and categorized into three categories: isolated carcinoma cells (ICC), defined as isolated cells scattered throughout the node or forming a cluster <0.05 cm, micrometastasis (0.05-0.2 cm) or macrometastasis (> 0.2 cm). Comparisons were made between cases with MELF and/or SCI patterns and presence of ICC, micrometastasis, and macrometastasis in pelvic and para aortic nodes using chi squared analysis.

Results: In our cohort, 45% of cases had both MELF and SCI, 3.7% had MELF alone, 15.9% had SCI alone and 35.4% of cases had neither. There is a statistically significant association between the presence of MELF, SCI or both and the presence of ICC in the pelvic and/or para-aortic lymph nodes (p<0.005 for all comparisons).

	Number of Cases	Cases with ICC	Cases with Micrometastasis	Cases with Macrometastasis
MELF+ SCI-	37	21	16	19
MELF+ SCI-	3	1	2	1
MELF- SCI+	13	6	6	8
MELF- SCI-	29	3	13	22
Total	82	31	37	50

Conclusions: In cases of endometrial carcinoma with MELF or SCI, there is an increased incidence of isolated carcinoma cells in lymph nodes. Therefore, high-power scrutiny of LN is warranted as the presence of LN metastasis greatly affects therapy and prognosis. In cases where there is an increased likelihood of LN ICC due to the presence of MELF and/or SCI, cytokeratin immunohistochemistry could be considered to further aid in detecting ICC.

1143 Cytokeratin 17 (CK17) Is a Sensitive Marker of Differentiated Vulvar Intraepithelial Neoplasia (dVIN)

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Background: Diagnosis of dVIN is one of the greatest challenges in gynecologic pathology. We have previously shown that staining for CK17 can highlight the cells of dVIN, with positive staining of lesional cells and absence of staining in adjacent benign epithelium. We sought to validate this finding in an independent set of cases.

Design: 28 cases of dVIN were identified and a single representative block chosen for immunostaining. CK17 and p53 immunostaining was performed in each case. CK17 staining was assessed based on distribution (focal versus diffuse) and intensity (weak, moderate or strong), while p53 immunostaining was recorded as abnormal (either complete absence of staining, or stronger nuclear staining of significantly more basal squamous cells that was present in adjacent benign/reactive squamous epithelium) or normal (weak to moderately intense staining of some basal cells, similar to what was present in benign squamous epithelium).

Results: CK17 positivity was seen in 26 of 28 (93 %) cases of dVIN. In 24 cases CK17 immunoreactivity was strong and diffuse, while in 2 cases the staining was more focal and of intermediate to strong intensity. The transition from neoplastic to non-neoplastic epithelium was marked by an abrupt change from immunoreactivity to negative CK17 staining. p53 staining could be evaluated in 26 cases and was abnormal in 21 (complete loss of p53 staining in 10 cases and more intense p53 immunoreactivity in 11 cases).

Conclusions: CK17 immunostaining can serve as adjunct in the diagnosis of dVIN, or in helping to assess extent of disease by recognizing the boundary between the neoplastic and benign squamous epithelium.

1144 Tubo-Ovarian Cancer Histotypes in Patients With Germline BRCA1 or BRCA2 Mutations

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Background: Germline mutations in BRCA1/BRCA2 are associated with a markedly increased risk of developing tubo-ovarian cancer. Most cancers seen in these patients are known to be high-grade serous carcinomas, but a detailed assessment of cancer histotypes in these patients, based on modern diagnostic criteria, has not been done.

Design: 117 cases of tubo-ovarian cancer were identified in patients with known germline BRCA1 or BRCA2 mutations, and all slides from these tumors were reviewed by a gynecological pathologist.

Results: Of 117 tumors, 106 (91%) were high-grade serous carcinomas. The non-high-grade serous carcinomas included 4 low-grade serous carcinomas, one with admixed serous borderline tumor, 1 serous borderline tumor, 2 endometrioid carcinomas (one of fallopian tube origin and one arising in an endometriotic cyst), 2 clear cell carcinomas, 1 carcinosarcoma, and 1 dysgerminoma. All cases of low-grade serous carcinoma and endometrioid carcinoma tested to date showed "wild-type" p53 expression pattern. Further molecular analyses are in progress.

Conclusions: : A large majority of tubo-ovarian cancers arising in patients with BRCA1 or BRCA2 germline mutations are high-grade serous carcinomas, but a range of other cancer histotypes are occasionally encountered. Although some non high-grade serous cases may be coincidental, and unrelated to the underlying BRCA1 or BRCA2 mutation, there does appear to be an increased risk of low-grade serous carcinoma in these patients.

1145 Meconium-Associated Vascular Necrosis Is a Significant Placental Lesion Underdiagnosed By General Surgical Pathologists

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Background: The clinical utility of placental examination is to help explain adverse pregnancy outcomes. The general surgical pathologists (GSP) often perform this exam; however, studies have shown that they do not always recognize clinically important placental lesions that lead to poor outcomes. One such lesion is meconium-associated vascular necrosis (MAVN) that we had observed at our institution to have a very low diagnostic rate (<0.1%) compared to that reported in the literature (0.9-1.7%). The current study investigates this underdiagnosis and aims to identify the most useful histological criteria for the diagnosis.

Design: A 4-year retrospective review of all placentas with meconium was undertaken after identification from a computerized database using the key words "meconium" or "green." Two independent GSP were blinded to the clinical history and original diagnoses and a histologic exam of the umbilical cord for MAVN was performed. The critera included 1) rounding of the peripheral smooth muscle cells, 2) eosinophilic cytoplasm, 3) condensation and fragmentation of the nuclei, and 4) discohesion of the smooth muscle cells in the absence of inflammation. Cases were classified as "yes", "maybe", or "no" for MAVN. All cases classified as "yes" and "maybe" were re-reviewed by all the authors for a consensus diagnosis. The maternal and fetal history was reviewed for all these new MAVN cases.

Results: 313 placentas with meconium were found. 3 cases of MAVN previously identified were excluded. One GSP identified 5 cases as "yes" and 19 cases as "maybe" and the second GSP identified 7 cases as "yes" and 9 cases as "maybe". The GSP results were concordant for "yes" in 4 cases and as "maybe" in 3 cases. Consensus review finally classified 19 cases as MAVN with 68.4% associated with intrauterine fetal demise (IUFD). In the remaining cases, birth history indicated good outcomes. The most useful diagnostic feature was the presence of bright eosinophilic cytoplasm, visible at lower magnification, to aid in distinction from histologic mimics.

Conclusions: MAVN is underdiagnosed by the GSP and it is a significant lesion strongly associated with IUFD. With education and adherence to criteria, we were able to identify a significant number of new MAVN cases in retrospective review.

1146 Microcystic, Elongated, and Fragmented (MELF) Pattern Invasion in Ovarian Endometrioid Adenocarcinoma

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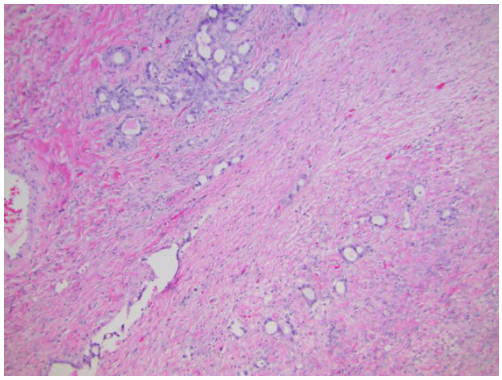
Background: Microcystic, elongated, and fragmented (MELF) is a well-recognized pattern of uterine endometrioid carcinoma (UEC), known to be associated with lymphovascular space invasion and occult lymph node metastasis. Currently, there is no literature evaluating MELF in ovarian endometrioid carcinoma (OEC) and its possible pathologic associations or prognostic implications. In this study, we retrospectively evaluated cases of OEC for MELF, associated pathologic features, and associated surgical staging information.

Design: Forty consecutive cases of OEC without concurrent UEC from our institution (1996-2014) were reviewed by two pathologists for MELF, histologic subtype, tumor grade, incidence of bilateral disease, presence of lymphovascular invasion, evidence of extranodal metastasis at surgical staging, and presence of lymph node metastasis. Data were analyzed using the Barnard exact test analysis.

Results: MELF pattern invasion, see figure 1, is identified in 28% of the cases reviewed. No cases show concurrent endometriosis or lymphovascular invasion, compared to OEC without MELF pattern invasion, of which 24% show endometriosis (p= 0.002) and 17% show lymphovascular invasion (p= 0.014). In patients with complete pelvic staging, pelvic lymph node metastasis is in 50% of patients with MELF invasion compared to 17% of patients without MELF. No association between MELF pattern invasion and bilaterality of disease, extranodal metastasis, or high grade features, such as clear cell, mucinous, or serous is found.

MELF Invasion in Ovary



Conclusions: MELF occurs in OEC at a similar or higher frequency than in UEC. MELF should be kept in mind when assessing OEC, as the pattern may be confused with endometriosis or endosalpingiosis. Although MELF is not associated with endometriosis or lymphovascular invasion, it is associated with positive lymph nodes in patients with full pelvic staging. This suggests the possibility that MELF tumors are under-sampled, and should prompt further evaluation.

Further studies of MELF will focus on immunohistochemical and molecular markers, as well as clinical outcomes associated with MELF in OEC.

1147 Differential Expression Patterns of GATA-3 in Usual and Differentiated Types of Vulvar Intraepithelial Neoplasia: Potential Diagnostic Implications

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Background: The two types of high-grade vulvar intraepithelial neoplasia (VIN), usual and differentiated types, have distinctive etiology, pathogenesis, and natural history. Little is known regarding the expression of GATA binding protein 3 (GATA-3) in VIN. The aim of this study was to determine whether these two types of VIN show any differences in the expression of GATA-3.

Design: Thirty-three cases of differentiated VIN were retrieved from archives. 15 of these were associated with invasive squamous cell carcinoma. 29 cases of usual type VIN and 20 cases of lichen sclerosus (with no prior history of VIN or carcinoma) were also obtained. Immunohistochemical staining for GATA-3 was performed on representative sections. Nuclear staining was considered positive. Staining patterns were recorded in terms of: intensity as weak (1+), moderate (2+) or strong (3+), percentage of cells as 0-25%, 26-50%, 51-75%, >75% and pattern of epithelial distribution.

Results: The benign non-neoplastic epidermis (identifiable in 45 cases) showed strong (3+) and diffuse (>75%) GATA-3 staining from basal to spinous layer. All cases of usual type VIN (28/28, 100%) and of lichen sclerosus (20/20, 100%) had a staining pattern identical to the benign epidermis. The pattern of GATA-3 expression was distinct in differentiated type VIN. Partial or complete loss of GATA-3 expression was seen in the basal cell layer of the neoplastic epithelium in 29/33 cases (88%) - > 75% basal cells with 0-1+ staining in 25 cases, 26-50% basal cells with 0-1+ staining in 4 cases. 15 of these were accompanied with to 0 to 1+ staining of the parabasal cells, 2 cases showed loss of GATA-3 in the spinous layer as well. The remaining 4 (12%) cases revealed intact GATA-3 expression similar to the benign epidermis. All invasive carcinomas (15/15, 100%) associated with differentiated VIN showed loss of GATA-3 expression – loss in > 75% tumor cells in 12/15 (80%) cases, loss in 26-50% tumor cells in 3/15 (20%) cases.

Conclusions: Our study provides new insight into the pathways of development of the two types of VIN. Down-regulation of GATA3 appears to be associated with differentiated VIN and not with usual type VIN. The progressive loss of GATA-3 from differentiated VIN to invasive carcinoma indicates that the down-regulation of GATA-3 occurs in the early stage of vulvar carcinogenesis. The pattern of GATA-3 expression in differentiated VIN is distinct from the non-neoplastic epidermis and that of usual type VIN and can serve as a useful tool in facilitating its diagnosis.

1148 GATA-3 Expression in Ovarian Tumors

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Background: There are few studies that have looked at GATA-3 expression in ovarian tumors. This study evaluates the GATA-3 expression in a varied panel of ovarian tumors.

Design: GATA-3 expression was evaluated by immunohistochemistry in 40 ovarian tumors on full tissue sections. Benign, borderline, and malignant neoplasms were all included in the analysis. GATA-3 expression was assessed as focal vs. diffuse and staining intensity was scored on a 0 to 3+ scale.

Results: Of the 40 tumors, the majority were high grade serous carcinomas (22 cases), in addition, there were 4 endometrioid, 2 clear cell, 2 mucinous, 1 mixed clear cell and mucinous, 1 low grade serous, and 2 high grade carcinomas, unclassified. There were 5 borderline tumors and 1 Brenner tumor. Of the 40 neoplasms, 12 demonstrated at least 1+ focal GATA-3 reactivity by immunohistochemistry (30%). These included 8 high grade serous carcinomas, 1 endometrioid carcinoma, 1 clear cell carcinoma, 1 high grade carcinoma, and 1 Brenner tumor. Only 2 neoplasms demonstrated diffuse and intense (3+) staining for GATA-3 (5%).

Conclusions: Strong GATA-3 expression is seen in a minority of ovarian neoplasms. The findings support prior studies and suggest that GATA-3 may be a useful marker in the setting of high grade tumors, especially in two clinical scenarios: within the estrogen receptor positive (ER+) tumor group for determining carcinomas of breast vs. Mullerian origin, and in distinguishing high grade gynecological vs. urothelial neoplasms.

1149 Nuclear Localization of β-Catenin Highlights EMT-Like Changes in Aggressive Cases of Vulvar Squamous Cell Carcinoma

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Background: β-catenin is an mediator of cell-cell interactions and adhesion in epithelium. Dysregulation of β-catenin signaling enables this protein to alternatively function as a nuclear transcription activator resulting in loss of cell adhesion, increased cellular proliferation, and phenotypic changes. Collectively, these changes characterize the epithelial-mesenchymal transition (EMT), which is associated with tumor progression in a number of malignancies. Vulvar squamous cell carcinoma (vSCC) is an understudied and highly morbid gynecologic malignancy. Studies have shown that vSCC with an infiltrative pattern of invasion is associated with worse outcomes, namely recurrence and lymph node metastasis, compared to those with nested/pushing patterns of invasion. We propose that infiltrative vulvar carcinoma may acquire increased aggressiveness through EMT-like changes reflected by aberrant nuclear localization of β-catenin.

Design: Immunohistochemical staining patterns of β-catenin were analyzed in 30 cases of vSCC. Ten cases contained a purely infiltrative pattern of invasion, 10 displayed a purely nested/pushing pattern and 10 displayed a mixed pattern with components of both infiltrative and nested/pushing invasion. Stained tumor sections were analyzed for nuclear localization or membranous staining of β-catenin. A staining pattern was defined as predominant when present in >75% of tumor cells.

Results: Predominant nuclear localization of β-catenin in tumor cells was observed in 8 (80%) tumors with a purely infiltrative pattern of invasion, compared to 3 (30%) in the purely pushing/nested tumors. In contrast, membranous staining for β-catenin predominated in 5 (50%) of the purely nested/pushing tumors compared to 1 (10%)

of the purely infiltrative tumors. Both membranous staining and nuclear localization of β-catenin was observed in 7 (70%) of the tumors with mixed invasive patterns. Importantly, in 6 of these 7 mixed tumors (85%), β-catenin showed membranous staining in the pushing regions and nuclear localization in the infiltrative regions.
Conclusions: Our results show that nuclear localization of β-catenin is highly associated with an infiltrative pattern of invasion in vSCC, suggesting that EMT-like changes may drive the more aggressive behavior in this subset of tumors. The application of β-catenin to the evaluation of vSCC can help to identify a subset of tumors with a greater propensity for recurrence and nodal metastasis, and therefore could lead to more precise treatment planning and use of adjuvant therapy.

1150 Perineural Invasion as an Indicator of Clinical Outcome in Vulvar Carcinoma

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Background: Vulvar squamous cell carcinoma (vSCC) is a disfiguring gynecologic malignancy affecting nearly 4500 new patients in the U.S. each year. Current criteria for treatment planning provide inadequate assessment of aggressive vSCC cases, resulting in insufficient use of adjuvant treatments and high rates of vSCC recurrence. Perineural invasion (PNI) is a pathologic feature inconsistantly included in the assessment and reporting of vSCC because its relevance to clinical outcomes in these women is not well defined. The purpose of this study was to determine the association between PNI and relevant clinical parameters and outcomes such as cancer recurrence and stromal response patterns.
Design: 103 cases of vSCC were evaluated for PNI using pathology report review, H&E morphology, and IHC dual-chromogen staining for S-100 & AE1/3. Medical records were reviewed for clinical and follow-up data. Statistical analysis was performed using Fisher's exact test for categorical data and t-test calculations for continuous data (significance at $p<0.05$).
Results: Patients whose tumors contained PNI had greater depth of invasion (*p=0.0015*) and a 2.6-fold higher risk of cancer recurrence than those whose tumors did not show PNI (*p=0.0290*). However, our data showed no significant correlation between the presence of PNI and nodal involvement, stage, or lymphovascular invasion (LVI), which suggests that PNI is an independent prognostic indicator of cancer recurrence. With respect to stromal response patterns, PNI was found in 69% of tumors with a fibromyxoid stromal response, compared to only 38% of tumors without a fibromyxoid stromal response (*p=0.0029*). Likewise, tumors with an infiltrative pattern of invasion were 3.5-times more likely to contain PNI than non-infiltrative tumors (*p=0.0028*).
Conclusions: Perineural invasion is a significant indicator of risk for recurrence in vulvar squamous cell carcinoma. Furthermore, PNI is closely associated with tumors displaying an infiltrative pattern of invasion and those with a fibromyxoid stromal response, histologic features which have recently been associated with worse outcomes in vSCC. The association of PNI with these aggressive tumor features and increased risk for recurrence, independent of LVI, nodal involvement, or stage, should encourage practicing pathologists to thoroughly search for and report the presence of PNI in vSCC.

1151 Papillary Immature Metaplasia of the Uterine Cervix – A Histopathological Revisit and Consideration for Cell of Origin

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Background: Papillary immature metaplasia (PIM) of uterine cervix is characterized by filiform papillary growth and partial loss of maturation. It has been considered as a variant of LSIL because of frequent association with HPV 6 and 11, but is frequently misdiagnosed as papillary squamous cell carcinoma, condylomatous carcinoma, or HSIL. Since there are only a few literature describing this entity, its clinical and histopathologic features are not well recognized. We had a few questions abut PIM, including HPV status, clinicopathological differences between PIM and conventional LSIL and HSIL, and the cell of origin.
Design: To answer the questions, we reviewed clinical and histopathologic findings of 21 PIMs, and compared the results of histochemical and immunohistochemical expressions to those of normal and abnormal cervical epithelial lesions. HPV status were analyzed by HPV DNA chips, which was designed to detect 40 HPV subtypes, and negative cases were confirmed by PCR.
Results: Histologically, most cases formed exophytic papillary lesions (81%), but a few cases showed flat topped plaque with downward epithelial proliferation (19%). The cells were composed of variable proportion of basaloid and squamoid cells in all cases, and all contained variable amount of mucin secreting epithelium within the lesion. 52% showed localized koilocytosis. Seven were associated with HSIL; two in the previous conization, and five in the adjacent mucosa. P16 immunostaining showed non-block positivity in all cases, except in the associated HSIL. They were associated with HPV 6 (n=3), 11 (n=7), 16 (n=1), 16/18 (n=1), but nine were HPV negative on HPV DNA chips, which were confirmed by PCR. All the cases showed basal or parabasal expression of CK17 (reserve cel marker) in contrast to uniform negativity in LSIL. 91 % showed top heavy expression pattern (91%) for CK 7 in contrast to the negativity (94%) in LSIL.
Conclusions: PIM is basically derived from columnar cells having metaplastic potential in the squamocolumnar junction, which was differentiated into reserve cells, and then toward immature and mature squamous epithelium. In contrast, LSIL appears to be a cellular change occurring in mature squamous epithelium. Cellular proliferation of PIM could be induced by HPV infection of both low and high risk HPV, but it is not necessarily associated with concurrent HPV infection. Association of HSIL in adjacent mucosa of PIM in some cases suggested a potential to progress from PIM to HSIL.

1152 Comprehensive Analysis of PAX8 Expression in Malignant Tumors of Uterine Cervix

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Background: Immunohistochemistry for transcription factor PAX8 (paired box gene 8) has recently emerged as a powerful tool in the differential diagnosis of gynecologic malignancies, especially when encountered at a metastatic site. Previous studies have shown PAX8 expression in majority of ovarian and endometrial carcinomas, however, data regarding PAX8 expression in cervical tumors are scarce.
Design: Tissue microarray slides with duplicate samples were prepared containing cervical tumors of various histologic subtypes retrieved from our departmental archives. H&E stain and PAX8 immunohistochemical stain were performed, and nuclear expression of PAX8 was examined by 2 reviewers.
Results: A total of 148 cases were included in the study. PAX8 immunohistochemistry was positive in 65% (13/20) of usual type endocervical adenocarcinomas, in 83% (5/6) of endometrioid endocervical adenocarcinomas, 43% (3/7) of adenosquamous carcinomas, and only 6% (6/109) of squamous cell carcinomas. One clear cell carcinoma and one serous carcinoma case also showed PAX8 immunoreactivity, while one basosquamous carcinoma, one large cell neuroendocrine carcinoma and two botryoid rhabdomyosarcomas were negative for PAX8. In addition to tumor type, histologic grade may also affect PAX8 expression. PAX8 showed higher sensitivity for well and moderately differentiated adenocarcinomas (67% and 78%, respectively) than poorly differentiated adenocarcinomas (25%). Poorly differentiated squamous cell carcinoma on the other hand appeared more likely to express PAX8 (9%) than well and moderately differentiated squamous cell carcinomas (0% and 2%).

Tumor Types	Total No. Cases	No. of positive (%)
Adenoca, usual type	20	13 (65%)
well-diff	6	4 (67%)
mod-diff	9	7 (78%)
poorly-diff	4	1 (25%)
Endometrioid adenoca	6	5 (83%)
Adenosquamous ca	7	3 (43%)
Squamous ca	109	6 (6%)
well-diff	2	0 (0%)
mod-diff	46	1 (2%)
poorly-diff	44	4 (9%)

Conclusions: PAX8 is expressed in over 60% of endocervical adenocarcinomas, a much lower rate compared with previously reported high sensitivity (over 90%) for other Mullerian - ovarian non-mucinous and endometrial - adenocarcinomas. PAX8 immunostain should be interpreted with caution in a metastatic lesion, when the possible primary sites include uterine cervix as a significant proportion of endocervical adenocarcinomas and vast majority of cervical squamous cell carcinomas lack immunoreactivity for this marker.

1153 Cyclin D1 Overexpression as a Common Denominator for the Development of Uterine Leiomyosarcoma and Smooth Muscle Tumor of Uncertain Malignant Potential

Wei Hong, Serena Wong, Natalia Buza, Pei Hui. Yale University New Haven Hospital, New Haven, CT.
Background: The pathogenesis of uterine leiomyosarcoma (LMS) is poorly understood. Smooth muscle tumor of uncertain malignant potential (STUMP) has been proposed as a possible precursor, as a result of its borderline malignant morphology and recent molecular data. We investigated cyclin D1 expression among other cell cycle regulators in uterine benign leiomyoma (LM), STUMP and LMS.
Design: Cases with a diagnosis of STUMP or LMS during a 31-year period were retrieved from our departmental files. All H&E slides were reviewed and re-classified according to the current (2014) WHO criteria as LM, STUMP and LMS, followed by tissue microarray (TMA) construction. Clinical and follow-up data were collected. Immunostains for cyclin D1, p53 and p16 were performed on sections of the TMA.
Results: A total of68 cases were included in this study: 10 LM, 12 STUMP and 46 LMS. Follow up was available for 55 cases (mean: 81 months, range: 1-359 months). Patients with LM and STUMP presented at a younger age (mean: 39 and 41 years, respectively) compared with LMS (mean: 58 years). LM and STUMP showed no tumor recurrence while LMS had a 55% recurrence rate with a mean time to recurrence of 26 months (1-105 months). LM and STUMP had a lower mitotic rate compared with LMS (mean: 5, 6, and 19/10 high power field, respectively). Over 50% of STUMP and LMS stained positive for p53, p16 and cyclin D1, while all LM cases were negative for p53 and only 20% of LM showed positivity for p16 and cyclin D1. No significant difference was found between STUMP and LMS for the expression of these markers.

	LM	STUMP	LMS
Number of cases	10	12	46
Patient age (year), mean (range)	39 (25-46)	41 (28-55)	58 (30-95)
Follow up (month), mean (range)	202 (112-334)	124 (10-359)	51(1-194)
Tumor size (cm), mean (range)	7.3 (2.5-12)	9.2 (4-37)	9.8 (1.6-30)
Mitosis/10HPF, mean (range)	5 (0-8)	6 (1-12)	18 (0-80)
p53 positivity, n (%)	0 (0%)	6 (50%)	23 (50%)
p16 positivity, n (%)	2 (20%)	11 (92%)	37 (80%)
Cyclin D1 positivity, n (%)	2 (20%)	7 (58%)	23 (50%)

Conclusions: Uterine STUMP and LMS share common alterations of cell cycle regulators including cyclin D1, p53 and P16. Our data also indicate that cyclin D1 expression may not be limited to high-grade endometrial stromal sarcoma, as previously suggested. Abnormal expression of cyclin D1 combined with p53 and p16 may be useful markers in separating STUMP from benign LM.

1154 Cytogenetic Abnormalities in Mullerian Adenosarcoma

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Background: Mullerian adenosarcoma (MA) is an uncommon biphasic neoplasm of the female genital tract, composed of malignant stroma and benign epithelium. Little is known about the molecular and cytogenetic aberrations in MA pathogenesis, including transformation into sarcomatous overgrowth (SO). Herein we report all karyotypes obtained on MA cases at our institution.

Design: All cases of MA with fresh tissue submitted for cytogenetic analysis (n=20) were included in this IRB-approved study. Karyotypes, when obtained, were reviewed by a cytogeneticist and the reported findings were confirmed. H&E slides of the tumor, when available, were also reviewed for assessment of SO.

Results: Samples included 14 primary MA (7 without SO, 7 with SO), and six metastatic MA (sarcomatous component). Karyotypes were successfully obtained in 13/20 (65%) cases. Five karyotypes were normal (46,XX) and corresponded to two primary MA without SO, two MA with SO, and one metastatic sarcoma. Eight (40%) karyotypes obtained had cytogenetic aberrations. Two of these (one primary MA with SO and one metastatic sarcoma) were markedly complex, displaying extreme aneuploidy with numerous rearrangements. Six (two each of primary MA without SO, primary MA with SO, and metastatic sarcoma) demonstrated non-complex clonal aberrations in one or more chromosomes, of which four (66%) included an abnormality involving chromosome 8 (2 with rearrangements at 8q13 and 2 have extra copies that include the 8q13 band).

Conclusions: MA grows slowly in culture and thus karyotypes are difficult to obtain. In the five cases with normal karyotype, it is possible that non-neoplastic tissue was submitted or grew in culture. Six of eight cases with abnormal karyotypes showed alterations of chromosome 8, including both extra copies as well as rearrangements. Molecular genetic aberrations in MA have recently been described, including amplification of *MYBL1,* which is located on 8q13. Further study is warranted to explore the genetic mechanism by which 8q13 abnormalities contribute to MA tumorigenesis.

1155 Expression of a Therapeutic Target (PD-L1) in HPV+ and HPV- Vulvar Squamous Cell Carcinoma

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Background: Some tumors express programmed death ligand 1 (PD-L1) which has the unique capacity to engage PD-1 on T cells and block anti-tumor immunity. In clinical trials, blockade of PD-1 signaling with therapeutic anti-PD-L1 or anti-PD-1 antibodies has produced durable clinical responses in patients with lung adenocarcinoma, renal cell carcinoma, and melanoma. Because PD-L1 is upregulated in many EBV+ and HHV8+ lymphomas, some have proposed that that viral-driven tumors are particularly adept at co-opting the PD-1 signaling axis for immune evasion. In this study, we applied this model to vulvar squamous cell carcinomas (SCC), many of which are HPV positive and all of which are extremely difficult to manage once nodal spread has occurred. The goal was to determine whether PD-L1 expression occurs in these tumors, in which case patients with these tumors could be potential candidates for immunotherapy.

Design: Whole tissue sections from 50 vulvar SCCs (14 HPV+; 36 HPV-) were immunostained using a monoclonal antibody for PD-L1 (clone 405.9A11). Semi-quantitative scoring was performed for intensity (0=negative, 1=weak, 2=moderate, 3=strong) and the percentage of tumors cell positive (0= <10%, 1=10-50%, and 2=>50%). For statistical analysis, cases with >50% positivity were considered "strong positive" cases and a fisher's exact test was used.

Results: 12 SCC (24%; 5 HPV+, 7 HPV-) showed <10% positivity, 24 SCC (48%; 9 HPV+, 15 HPV-) showed 10-50% positivity, and 14 (28%; 0 HPV+, 14 HPV-) showed >50% positivity for PD-L1. There was a highly significant association between strong positive cases (>50% tumor cells expressing PD-L1) and HPV negative tumors (p=0.005). However, in all, 76% of all tumors showed ≥ 10% immunopositivity for PD-L1.

Conclusions: This is the first study to show significant expression of PD-L1 -a potential therapeutic target- in vulvar SCC and suggests the majority of patients with this tumor could be rational candidates for a trial of anti-PD-L1 or anti-PD-1 immunotherapy. Because PD-L1 expression in vulvar SCC was inversely correlated with HPV status, HPV likely employs alternate mechanisms for immune evasion.

1156 Depth of Invasion: A Reliable Predictor of Lymphadenectomy in FIGO Grade II Endometrial Carcinoma Patients

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Background: FIGO system has been standarized for endometrioid carcinoma grading and depth of invasion for tumor staging. It is generally accepted that FIGO grade I endometrioid carcinoma patients do not need, but grade III do need lymphadenectomy. However, it remains unclear whether to perform lymphadenectomy in grade II carcinoma patients.

Design: To assess if depth of invasion could be employed to evaluate the need of lymphadenectomy in FIGO grade II endometrial carcinoma patients, we retrospectively reviewed the hysterectomy cases during 2007-2013. Lymph node (LN) status, lymphovascular invasion (LVI), depth of invasion and FIGO grading in hysterectomy cases were addressed. LN status was categorized as positive and negative groups, and depth of invasion were defined by two-tier and four-tier structures. The correlation of LN staging and depth of invasion was calculated using Chi-square analysis.

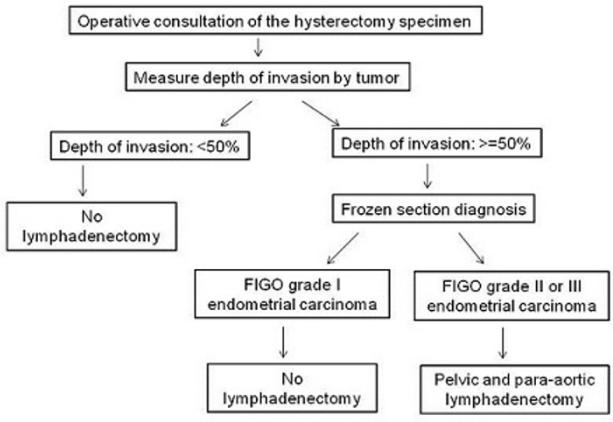
Results: Of 499 radical hysterectomy cases (age: 61.2 ± 11.9 yrs), 155 patients had FIGO grade II endometrial carcinoma (36.0%), 231 grade I (53.7%), and 45 grade III (10.5 %). Five of these grade II tumors had positive LNs, and depth of invasion ≥50%.

	Depth of invasion	Cases of positive pelvic LNs	Cases of positive paraaortic LNs	Cases of negative LNs
Two-tier structure		0 (0/96)	0 (0/96)	70 (70/96)
	≥50%	3 (3/50)	2 (2/50)	31 (31/50)
Four-tier structure	0-25%	0 (0/56)	0 (0/56)	41 (41/56)
	25-50%	0 (0/34)	0 (0/34)	25 (25/34)
	50-75%	1 (1/27)	1 (1/27)	19 (19/27)
	>75%	2 (2/23)	1 (1/23)	13 (13/23)

Positive LN status was significantly associated with the depth of invasion (p<0.01). Of all grade I tumor with ≥ 50% depth of tumor invasion, no positive LNs were identified (n=14). In addition, the status of LVI was consistent with LN staging, and related to the depth of invasion.

Conclusions: Depth of invasion is important to decide if the FIGO grade II endometrial carcinoma patient needs lymphadenectomy during hysterectomy. Thus, we propose a protocol when to perform lymph node dissection in endometrial carcinoma patients.

Figure 1 A Protocol for Lymph Node Dissection in FIGO Grade II Endometrial Carcinoma Patient



1157 Predictive Value of Krt7 and p16 Biomarkers in Cervical Low Grade Squamous Intraepithelial Lesions

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Background: Recent studies have demonstrated that most high-grade squamous intraepithelial lesions (HSILs) express cervical squamocolumnar junction (SCJ)-specific markers (such as Krt7) as well as positive (or block) staining for p16. In one study, LSILs lacking SCJ marker staining were more likely to regress over follow-up. The objective of this study is to evaluate the relationship of Krt7 and p16 staining to LSIL outcome.

Design: An institutional retrospective review of all cervical biopsies from 2008-2011 by Pathology Laboratory Information System identified 120 cases of LSILs with at least one year follow-up data (pap smears, high-risk HPV status, biopsies and excisions). All cases were tested for Krt7 and p16 immunostains. Staining patterns and clinical

follow-up outcome were analyzed. Clinical follow-up is defined as follows: Regression = negative follow-up (including negative high risk HPV), persistence = follow-up with high-risk HPV or LSIL, progression = follow-up with ASC-H or ≥HSIL.
Results: In all, 120 LSIL cases were studied; 82.5% (n=99) were SCJ- while 17.5% (n=21) were SCJ+. In the SCJ- population, majority of cases were p16- (68.7%, n=68). In contrast, in the SCJ+ population, almost half of LSILs are p16+ (47.6%, n=10). When the clinical follow-up was reviewed, for the SCJ- cases, 82.8% (n=82) regressed while the remaining cases (17.2%, n=17) either persisted (11.1%, n=11) or progressed (6.1%, n=6). However, for the SCJ+ cases, nearly half of the cases (42.9%, n=9) persisted (19.1%, n=4) or progressed (23.8%, n=5), a difference that was highly significant (p = 0.004, Fisher's exact test). p16 staining did not add benefit in predicting future behavior of LSILs (p = 1, Fisher's exact test).
Conclusions: This study demonstrates that SCJ marker-positive LSILs have a significantly higher risk of persistence or progression, supporting the concept that the location of the LSIL (in SCJ vs mature metaplastic or ectocervical epithelium) influences outcome. While p16 highlights a higher percentage of SCJ+ LSILs, it does not appear to predict clinical outcome in this population of SIL. The concept of two different types of LSIL with distinctly different risks of progression based on SCJ biomarker staining merits further study.

1158 Simultaneous Detection, Typing, and Quantification of Viral Load of All 15 High-Risk HPV Subtypes in High-Grade SIL and Squamous Cell Carcinoma Involving Multiple Anatomic Sites of the Female Lower Genital Tract – A Multiplex Real-Time PCR-Based Study

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Background: Type-specific detection of high-risk HR-HPV allows detection of co-infection, monitoring recurrent infection, determination of viral load & provide clue to which subtype predominates in future because of HPV16/18 vaccination program. This study will identify HR-HPV subtypes associated with high-grade dysplasia (HSIL) and Squamous cell carcinomas (SqCa) involving multiple anatomic sites in the female genital tract, estimate and compare the viral loads of each subtypes & anatomic sites.
Design: Twenty two samples, including HSIL of uterine cervix (CIN), vagina (VAIN), vulva (VIN), & vulvar SqCa with nodal metastasis (Met SqCa) from 7 patients were retrieved. Representative lesional tissues were dissected & DNA extracted by using QIAam DNA FFPE Kit. Multiplex PCR was run to identify all 15 high-risk HPV subtypes along with known positive control. Viral load and cell numbers were calculated retrospectively.
Results: Of the total, 5 cases were CIN-3, 3 VAIN-3, 11 VIN-3, 1 VIN-3 with superficial invasion, 1 vulvar SqCa, and 1 met SqCa in inguinal lymph node. Fig. 1 shows the distribution of subtypes & patterns of co-infection.

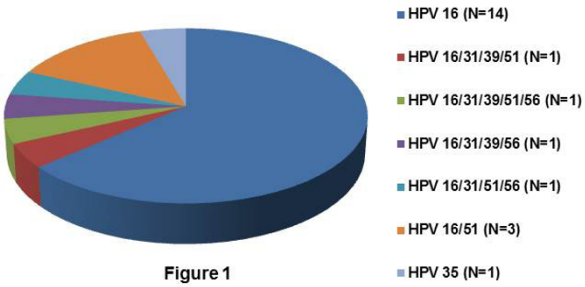

Figure 1

The viral load data is presented in Table 1.

HPV Subtypes	N	Virues per 100 cells		
		Mean	Range	Median
HPV 16	21	161970	1-784000	7036
HPV 31	4	183	2-271	5
HPV 35	1	3965	-	-
HPV 39	3	85	-	-
HPV 51	5	207	1-646	92
HPV 56	3	1	1-2	1

Conclusions: Multi-viral HPV subtypes infection is common in HSIL & SqCa involving multiple anatomic sites. As many as 5 subtypes are found in one case; the vaginal lesion has subtypes found in both cervix and vulva. HPV 51 is found to be the next most frequent subtype after HPV 16. Viral load in recurrent lesion was higher than the initial VIN-3 when it recurred after 4 years. Gradual diminishing of viral load was observed from primary in-situ lesion to invasive carcinoma to metastatic site.

1159 Clinicopathologic Characteristics of Endometrial Carcinomas With POLE Mutations

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Background: Recent molecular-based analyses of endometrial cancers have identified a subset of ultra-mutated endometrial carcinomas that are characterized by mutations in the DNA polymerase epsilon (POLE) gene resulting in transcriptional errors and increased mutation frequency. These cases reportedly have a favorable prognosis and higher grade although the histologic features of these tumors have not been well described. We report our findings in a diverse population of endometrial cancers from a single institution.
Design: DNA was extracted from paraffin blocks from 104 archival cases of endometrial carcinoma (86 endometrioid [E]; 14 serous [S]; 4 clear cell[C]), amplified using PCR primers directed at the exons 9, 10,13,14 of the POLE gene and sequenced in both directions using Sanger sequencing to detect POLE mutations. The histologic slides were reviewed and immunoperoxidase stains for p53, p16, ER and PR were performed on those cases showing POLE mutations. The data were analyzed by cross-sectional analysis and Kaplan Meier survival analysis.
Results: 19 of 104 (18.2%) cases tested showed POLE mutations in exon 9 (n= 5); exon 10 (n=9); exon 13 (n=3) and exon 14 (n=4), including 6 cases with two mutations and 1 case with four. These mutations were all localized within the exonuclease domain of POLE and may affect proofreading. Histologic category of POLE mutated cases included 17 E (15 G1-2; 1 G3; and 1 dedifferentiated), 1 case each S and C. Immunohistochemistry results were typical for each cell type including wild type p53, mottled p16 and positive ER and PR for the E cases. Only the S tumor showed mutated p53 and diffuse p16 and the C tumor was negative for the 4 markers. POLE mutated cases presented at stage 1A-4B and 6 (31.6%) died of endometrial cancer appropriate for stage and cell type. Cross-sectional analyses showed no significant difference between POLE mutated and wild type for mean age, stage, depth of myometrial invasion and lymph node status. Kaplan-Meier survival analysis showed no significant difference in survival between women with POLE mutated and POLE wild type cancers. Median survival was 81.7 months for POLE wild type patients compared with 65.6 months for mutated POLE (log rank p=.65).
Conclusions: We found a higher rate of POLE mutations in endometrial cancers than previously reported and many unreported new mutation sites. The cases with POLE mutations were histologically more diverse than has been previously reported. Similarly, there was no survival advantage for our patients with POLE mutations.

1160 Immunohistochemical Analysis of Endometrial Carcinomas Harboring POLE Exonuclease Domain Mutation

Yaser Hussein, Cheng-Han Lee, Martin Kobel, Britta Weigelt, Douglas Levine, Robert Soslow. Memorial Sloan Kettering Cancer Center, New York, NY; University of Alberta, Edmonton, Canada; University of Calgary, Calgary, Canada.
Background: POLE exonuclease domain mutations have been identified in a subset of endometrial carcinomas. A recent histopathologic review found that endometrial carcinomas harboring POLE exonuclease domain mutation (EC-POLE) are commonly high grade and frequently show morphologic ambiguity, intratumoral heterogeneity, and components that may morphologically mimic serous carcinoma (SC). However, in contrast to SC, patients with EC-POLE have favorable outcomes. The aim of this study was to define the immunohistochemical (IHC) characteristics of EC-POLE.
Design: 13 cases of EC-POLE from 2 academic institutions were included in this study; the clinicopathologic features of which were recently reported (Modern Pathology; in press). IHC for PTEN, ARID1A, p53, p16, PR, PMS2 and MSH6 was performed and slides were reviewed by 2 gynecologic pathologists.
Results: 8 cases were purely and ambiguously endometrioid carcinoma (EMC); 7/8 were FIGO grade III. 3 additional tumors demonstrated defining morphologic features of EMC, at least focally, but also showed components suggestive of mixed EMC & SC, while 2 more cases were difficult to subclassify (ambiguous). All EC-POLE showed loss of PTEN and/or ARID1A. PTEN and ARID1A loss was observed in 10/13 and 6/13 cases, respectively. Diffuse P53 overexpression was seen in 2/13 cases, while P16 overexpression was found in only 1 case. 9/13 tumors were positive for PR. PMS2 or MSH6 loss was seen in 1 and 5 cases, respectively. The immunoprofile of the morphologically "mixed" carcinomas and ambiguous tumors is illustrated below.

Histology	PTEN	ARID1A	P53	P16	PR	PMS2	MSH6
"Mixed"	-	-	-	-	+	+	-
"Mixed"	-	+	-	-	-	+	+
"Mixed"	-	+	+	+	+	+	-
Ambiguous	-	+	-	-	-	+	+
Ambiguous	-	-	-	-	-	+	+

Conclusions: Our study shows that IHC may be a useful adjunct tool in histotyping EC-POLE. Although ECs-POLE are commonly high grade and frequently show morphologic ambiguity and components raising the possibility of SC, our IHC findings support the presence of endometrioid differentiation in every tumor. Furthermore, homogenously aberrant p53 immunoexpression may be occasionally seen in EC-POLE. As these tumors have favorable prognosis, it is important not to miscalssfiy EC-POLE as SC. Interestingly, ~1/2 of EC-POLE shows abnormal DNA mismatch repair protein expression; the mechanism of which is still unknown.

1161 PlGF/Nrp1/VEGFR1 Axis Is Upregulated In Gestational Trophoblastic Disease

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Background: Gestational trophoblastic disease (GTD) encompasses an array of pregnancy-related trophoblastic lesions in which hysterectomy remains first-line treatment of chemoresistant disease in patients who are often of child-bearing age. Placental growth factor (PlGF), neuropilin 1 (Nrp1) and vascular endothelial growth factor receptor 1 (VEGFR1) are members of the VEGF family involved in angiogenesis and may play a role in GTD pathogenesis. Anti-PlGF and anti-Nrp1 antibodies have been successfully tested in human Phase I clinical trials with favorable side effect profiles. We sought to investigate immunoexpression of PlGF and its receptors, Nrp1 and VEGFR1, as potential therapeutic targets in GTD.

Design: 20 primary GTD, including 6 invasive complete hydatidiform moles (CHM), 2 persistent partial hydatidiform moles (PHM), 2 epithelioid trophoblastic tumors (ETT), 5 placental site trophoblastic tumors (PSTT) and 5 choriocarcinomas (CCA), diagnosed from 1996-2014 were retrieved from departmental archives. Immunohistochemical stains for PlGF, Nrp1 and VEGFR1 were performed on whole tissue sections. Third-trimester placenta was used as a positive control. Intensity was scored as 1+ (weak), 2+ (moderate) and 3+ (strong).

Results: All GTD showed diffuse cytoplasmic PlGF, Nrp1 and/or VEGFR1 staining in all trophoblastic cells. PlGF expression was 2+ and 1+ in 5 (1 PSTT, 2 CCA and 2 CHM) and 15 (4 PSTT, 3 CCA, 2 ETT, 4 CHM and 2 PHM) cases, respectively. Nrp1 was 3+ in 8 (6 CHM, 1 CCA and 1 PSTT) cases and 1+ in 3 CCA, while negative in only a single ETT. Nrp1 was 2+ in 8 (4 PSTT, 1 CCA, 2 PHM and 1 ETT) cases in which 7 also showed focal 3+ staining. VEGFR1 expression was 3+ in all GTD except a single CCA with 1+ staining.

Conclusions: The PlGF/Nrp1/VEGFR1 pathway is upregulated across all types of GTD and may represent a novel avenue for targeted therapy in patients with chemoresistant GTD and those who desire fertility.

1162 Immunoexpression of p16 in Uterine Leiomyomas With Infarct Type Necrosis

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Background: The cell cycle marker p16 has been shown to be overexpressed in uterine leiomyosarcomas and theoretically useful for distinguishing between benign and malignant smooth muscle tumors. Its use is limited in routine practice because it has been noted to show variable expression in benign histological variants, specifically, leiomyoma with bizarre nuclei, a tumor that is difficult to distinguish from leiomyosarcoma. The expression of p16 in other benign variants, particularly those with problematic histological features, has seldom been studied.

Design: p16 expression pattern in 35 benign uterine leiomyomas with infarct type necrosis were studied. Any staining in the nucleus and/or cytoplasm was considered positive. The extent of positive staining surrounding the infarct was classified as none, <33%, 33-66% and >66%. The extent of staining in areas away from the infarct was classified as none, scattered/isolated, <33%, 33-66% and >66%. Clinical and drug histories and follow-up were also obtained.

Results: Age of patients was 23-55 years (median, 43.6), and presentations were menorrhagia, pain, mass, or combinations thereof. 25 were treated with hysterectomy and the remainder with myomectomy. Preoperative drugs (oral contraceptives/GnRH-a/tranexamic acid) were prescribed in 18. One was pregnant. Tumor sizes ranged from 1.5-24 cm (mean, 7.8). All tumors had absent-to-mild atypia except for one case in which the atypia was mild-to-moderate. The mean mitotic count was 1.4/10HPFs (ranged 0-16). All had unequivocal infarct-type necrosis. The extent of p16 positivity in areas surrounding the infarct was 0 in 3 cases (8.6%); <33% in 25 cases (71.4%); 33-66% in 4 cases (11.4%) and >66% in 3 cases (8.6%). The extent of p16 positivity in areas away from the infarct was 0 in 4 cases (11.4%); scattered/isolated in 21 cases (60%); <33% in 8 cases (22.9%); 33-66% in 1 case (2.9%) and >66% in 1 case (2.9%). None of the patients, including those with tumors that showed >66% p16 positivity, developed recurrence after a mean follow-up of 41.4 months (range 1-126).

Conclusions: p16 expression in benign uterine leiomyomas with infarct type necrosis is common, particularly concentrated in tumor cells surrounding an infarct. Its utility in leiomyomas with uncertain type of necrosis may be limited. [Equal contributions from authors 1&2].

1163 Microsatelite Instability in Endometrial Carcinoma With Mucinous Differentiation Associated With KRAS Mutation

Cynthia Jackson, Mai He, Margaret Steinhoff, Virginia Breese, Michelle Xiong, W Dwayne Lawrence, Jinjun Xiong. Rhode Island Hospita, Providence, RI; Women & Infants Hospital of Rhode Island, Providence, RI; Brown University Alpert Medical School, Providence, RI.

Background: Endometrial carcinoma is associated with numeric and structural chromosomal abnormalities, microsatellite instability (MSI), and alterations that activate oncogenes and inactivate tumor suppressor genes. Our previous studies showed that endometrial carcinomas with significant mucinous differentiation (ECMD, >10% of tumor cells contain intracytoplasmic mucin) are associated with significantly higher frequency of *KRAS* mutations. The current study investigated the association of MSI and *KRAS* mutations in endometrial carcinoma of the uterus.

Design: With IRB approval, a total of 46 cases were identified from the archival files of the Department of Pathology, W&I Hospital. 14 endometrioid carcinoma (EC), 24 ECMD and 8 serous carcinoma (SC) were selected for this study. Genomic DNA was extracted from formalin-fixed paraffin-embedded tissue sections that were macro-dissected to ensure greater than 80% of tumor cells in the selected region. PNA-PCR amplification of *KRAS* codons 12 and 13 was performed (RIH, RI), followed by sequencing using capillary electrophoresis. MSI status was evaluated using Promega's MSI Analysis System, which uses fluorescent multiplexed PCR followed by fragment length analysis to compare the sizing patterns of five mononucleotide repeat markers and two pentanucleotide repeat markers between tumor and matched normal DNA.

Results: 3 of 14 (21.4%) of EC and 5 of 24 (20.8%) ECMD tumors were MSI positive. *KRAS* codons 12 and 13 mutations were detected in 4 of 14 (28.6%) EC and 16 of 24 (66.7%) ECMD (P=0.04). In ECMD, MSI positive tumors were more frequently associated with *KRAS* mutations (4/5, 80%) than *KRAS* wild type (1/5, 20%). In EC, MSI positive tumors showed 1 of 3 (33%) with *KRAS* mutation and 2 of 3 (67%) with KRAS wild type. No MSI or *KRAS* mutations were identified in SC.

Conclusions: MSI positive tumors were almost evenly distributed in EC and ECMD tumors. Interestingly, MSI-positive tumors are associated with *KRAS* mutant more frequently than *KRAS* wild type in ECMD tumors. These results indicate a close correlation between KRAS mutations and a morphology of mucinous differentiation, and close association between MSI and *KRAS* mutations in ECMD. Further study of the mechanism for this close association in ECMD to understand tumorgenesis appears warranted.

1164 Genotype-Phenotype Correlation in Complete Hydatidiform Moles: Can Morphologic Features Separate Heterozygous and Homozygous Complete Moles?

Joshua Jeanty, Natalia Buza, Pei Hui. Yale University New Haven Hospital, New Haven, CT.

Background: Complete Hydatidiform Mole (CHM) is non-neoplastic proliferative disorder of the villous trophoblast with unique paternal-only genome that has a predilection for developing persistent gestational trophoblastic disease (pGTD) in approximately 15-29% of the cases. Previous studies have suggested, that the risk of pGTD may be higher for heterozygous (dispermic) than for homozygous (monospermic) CHM. Our study aimed at assessing the detailed morphologic features in correlation with the genotype in this group of lesions.

Design: A total of 33 cases of CHM – including 13 heterozygous and 20 homozygous cases – were retrieved from our departmental archives. All cases have been subjected to DNA genotyping using AmpFISTR Identifiler. All H&E slides were reviewed blinded to the genotype by three pathologists and the following morphologic features were assessed: trophoblast proliferation, maximum villous size, cistern formation, necrosis, karyorrhexis, atypia, mitotic count and Ki 67 proliferation index. Patient characteristics and gestational age were collected form electronic medical records.

Results: Homozygous complete moles have a statistically significant higher rate of trophoblastic proliferations, atypia and necrosis when compared to heterozygous ones (p values, 0.008139, 0.0242, and 0.01536 respectively), with PPV of 69%, 67% and 76%, respectively. Karyorrhexis and cistern formation did not show a statistically significant difference between both groups. The average mitotic count and Ki 67 proliferation index were statistically higher in homozygous moles (19.6 versus 14.5/10 high power field, respectively; p value 0.0008611, Ki 67 p value 0.0434). The homozygous complete moles had a slightly larger maximum villous size with an average of 5.8 mm vs. 5.3 mm (p value 0.6309).

Conclusions: Our results indicate that homozygous complete moles tend to have a greater degree of trophoblastic proliferations, atypia and necrosis and higher mitotic count and Ki 67 proliferation index when compared to heterozygous CHM. The morphologic phenotype of heterozygous complete moles appears to be in contrast with the more aggressive clinical behavior described in prior studies. This observation could possibly be attributed to the time of evacuation and diagnosis and highlights that CHM can show a range of morphologic changes. Studies of clinical parameters including patient follow-up remain necessary to further stratify the genetic differences for risk prediction of pGTD.

1165 Fibromyxoid Stroma in Vulvar Squamous Cell Carcinoma Predicts Lymph Node Metastasis and Extracapsular Extension

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Background: Lymph node involvement and extracapsular extension (ECE) in vulvar squamous cell carcinoma (vSCC) are reportable pathologic features because they are associated with poor outcome and require increased dosage of adjuvant radiation. The aims of this study were to characterize lymph node (LN) metastases in vSCC and to identify histopathologic features of the primary tumor that may predict lymph node involvement and ECE.

Design: Consecutive vSCC resections and associated lymph node samples from 1997-2013 were reviewed by two gynecologic pathologists. For the primary tumor, growth pattern (infiltrative, non-infiltrative), stromal response (fibromyxoid (FMX) stroma present/absent) and depth of invasion (DOI) were recorded. For the metastasis, ECE (present/absent), size, focality (single or multifocal), location (subcapsular, central, diffuse/obliterative), growth pattern (infiltrative, non-infiltrative) and stromal response (FMX stroma present/absent) were documented. Statistical analysis was performed using Fisher's exact test for categorical data and t-test calculations for continuous data.

Results: 143 vSCC had 93 LN samplings and 30 (32%) contained metastatic disease. An infiltrative growth pattern was highly associated with a FMX stromal response in both primary tumors (p< 0.0001) and metastases (p=0.0022). Tumor growth pattern and stromal response in the metastases matched the primary tumor in 90% (27/30) and 83% (25/30) of cases, respectively. Seventeen cases (57%) showed ECE. FMX stroma

was the only characteristics of the primary tumor that was associated with both positive LN status (p=0.0749) and ECE (p=0.0227). Nodal characteristics associated with ECE are summarized in Table 1

ECE (n)	Diffuse/Obliterative	Size (mean, mm)	FMX stroma	Infiltrative growth
Yes (17)	13	16.29	15	13
No (13)	3	11.46	3	3
p value	0.0086	0.0374	0.0005	0.0086

Conclusions: 1. FMX stroma in the primary tumor is significantly associated with nodal metastasis and ECE. Therefore, the presence of FMX stroma in a biopsy may be of value for surgical planning.
2. Nodal characteristics predictive of ECE are increasing size of the metastasis, diffuse/obliterative involvement, and presence of infiltrative growth pattern and FMX stroma.
3. Interestingly, tumor growth pattern / stromal response are predominantly recapitulated in nodal metastases, a finding which may provide insight into the mechanism of vSCC metastasis.

1166 Tumor Growth Pattern Can Predict Nodal Metastasis: A Study of 130 Cases of Endocervical Adenocarcinoma

Susanne Jeffus, Charles Quick, Simona Stolnicu, Irene Aguilera-Barrantes, Cherie Paquette, Kristen Atkins, Raquel Valencia-Cedillo, Isabel Alvarado-Cabrero. University of Arkansas for Medical Sciences, Little Rock, AR; University of Medicine, Targu Mures, Romania; Medical College of Wisconsin, Milwaukee, WI; Virginia Health Systems, Charlottesville, VA; Mexican Oncology Hospital, IMSS, Mexico, Mexico.
Background: According to FIGO classification, 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 features but also LN; however, > 95% of LN resections in EAC are negative. Therefore, we investigated pathologic parameters that may better identify patients at risk of developing LN metastasis.
Design: 130 cases collected from 5 International Institutions were analyzed, including patient age, tumor size, grade of differentiation, DOI, presence of lymphovascular invasion (LVI) and presence of LN metastasis, The cases were classified using a new proposed method (Int J Gynecol Pathol 2013; 32: 595-601).
Results: A total of 130 women aged 27 to 82 years (mean 48) were identified with EAC. All patients were staged between IA1 and IV, with DOI ranging from 2 to 25mm; LVI was documented in 73(56%) cases. To compare the standard staging method using DOI criteria and the suggested new method with patterns, we created

	Patients	Patients withPos LN	Total LN	LVI	# Pos LN	Stage I	Stage II-IV
Standard Method	130	26(20%)	2372	73(56%)	42(32%)	104(80%)	26(20%)
Pattern A	16(12%)	0(0%)	237	0(0%)	0(0%)	16(100%)	0(0%)
Pattern B	22(17%)	2(9%)	410	7(32%)	2(0.48%)	20(91%)	2(9%)
Pattern C	92(71%)	24(26%)	1725	66(72%)	40(2.3%)	68(74%)	24(26%)

Conclusions: No pattern A patients demonstrated lymph node metastasis, therefore, these patients need not undergo LN resection during their initial therapy.
Patients with Pattern B tumors are candidates for lymphadenectomy as 9% demonstrated LN involvement.
Patients with a pattern C tumor demonstrate markedly increased incidence of positive LNs and should be treated aggressively. Pattern C tumors are also associated with higher stage disease.

1167 Insulin-Like Growth Factor 1 Receptor Expression Increases With Body Mass Index in 894 Endometrial Carcinomas

Amy Joehlin-Price, Julie Stephens, Floor Backes, David Cohn, Adrian Suarez. Ohio State University, Columbus, OH.
Background: Obesity-related abnormalities in the insulin-like growth factor pathway are suspected to mediate a high risk for endometrial carcinoma (EC). Drugs targeting insulin-like growth factor 1 receptor (IGF1R) are available but a relationship between obesity and EC IGF1R expression has not been established.
Design: A tissue microarray with 1882 cores representing 894 consecutive hysterectomies with EC was stained with a monoclonal IGF-1R antibody. EC were scored according to percentage of positive staining (0-5%=0, 6-25%=1, 26-50%=2, ≥51%=3) and for staining intensity (0-3+). Immunoreactivity scores (IRS) of 0-9 were obtained by multiplying those two values. IRS were classified in two groups (0-3 and 4-9) and risk factor logistic regression was used to assess the association with BMI adjusting for age, FIGO grade, stage, and lymphovascular invasion (LVI).
Results: Median BMI was 35.3 (range 14.7-85.0) kg/m^2. 61% of patients had IRS scores from 4-9 and 39% from 0-3. Overall there was a significant difference in the IRS distribution between BMI categories (<30 kg/m^2, 31-39 kg/m^2 and ≥40 kg/m^2) with the proportion of patients with IRS 4-9 increasing as BMI increased (p=0.002). The unadjusted odds of having an IRS score in the 4-9 range was 1.51 (95% CI: 1.08-2.10, p=0.015) for patients with BMI 31-39 kg/m^2 compared to those with BMI <30 kg/m^2 (reference group) and 1.79 (95% CI: 1.29-2.50, p=0.001) for patients with BMI ≥40 kg/m^2 compared to those with BMI of <30 kg/m^2. The odds ratios remained significant (OR 1.42, CI 1.01-2.00, p=0.043 and OR 1.53, CI: 1.08-2.17, p=0.017, respectively) after adjusting for stage, LVI, age and FIGO grade.
Examined separately, endometrioid FIGO 1 tumors (n=513) demonstrated unadjusted odds ratios of having an IRS score in the 4-9 range comparing patients with BMI 31-39 kg/m^2 and BMI ≥40 kg/m^2 to those with a BMI of <30 kg/m^2 of 2.16 (CI: 1.33-3.52, p=0.002) and 2.07 (CI: 1.31-3.25, p=0.002) respectively. There was little change in the odds ratio after adjusting for stage, LVI and age (odds ratio 2.19, CI: 1.33-3.61, p=0.002 and 1.96, CI: 1.23-3.11, p=0.004, respectively) .
Conclusions: There is a significant direct association between tumor IGF1R expression and BMI in this large cohort of women with EC. Increased IGF1R tumor expression may be key in the development and maintenance of EC of different grades and histologic types.

1168 Microcystic, Elongated, and Fragmented Pattern of Invasion in 472 Single-Institution Consecutive FIGO-1 Endometrioid Endometrial Carcinoma Correlates With Positive Lymph Node Status

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Background: Most endometrioid endometrial carcinomas (EEC) represent low grade disease that is cured with surgery. Because lymph node involvement is very uncommon lymphadenectomies are not universally performed. However, a minority of EEC cases demonstrates more aggressive behavior and may have positive nodes at presentation. Microcystic, elongated, and fragmented (MELF) invasive glands may be a histologic clue to this behavior.
Design: Consecutive FIGO1 EEC hysterectomy specimens with lymph node dissections from 2007-2012 were reviewed for the presence of MELF. Additional data were pulled from the original pathology reports, including lymph node status and presence or absence of lymphovascular invasion (LVI). Proportions were compared using Fisher's Exact test. A p-value of 0.05 was considered significant.
Results: 472 consecutive FIGO1 EEC cases with lymph node dissections were identified. Of these, 72 cases (15.3%) demonstrated MELF invasion, 30 cases demonstrated LVI (6.4%), and 16 cases (3.4%) were reported as N1 or N2 (lymph node positive). 1.0% (n=4) of MELF-negative cases and 16.7% (n=12) of MELF-positive cases had positive lymph nodes, p<0.001. Conversely, MELF was significantly more frequent in node positive patients (n=12, 75%) than in node negative patients (n=60, 13.2%), p<0.001. LVI was also significantly associated with N1 or N2 node status, with 0.7% (n=3) of LVI-negative cases and 43.3% (n=13) of LVI-positive cases demonstrating positive lymph nodes, p<0.001. However, logistic regression models to describe the relationship between positive lymph node status and LVI and MELF could not be explored due to the small numbers (n=3 and n=4) in some of these groups.
Conclusions: In a large single-institution cohort of consecutive FIGO1 EEC with lymph node dissections, MELF invasion patterns were noted 15.3% of the time and were significantly associated with positive lymph nodes. Despite the large number of cases in this series, the difficulty of studying node-positive FIGO1 EEC is highlighted, in that our multivariable model was not possible due to small n values in some of the groups. Further evaluation of MELF invasion patterns and their influence on LVI and lymph node metastases is warranted.

1169 Dissecting Gonadoblastoma of Scully: A Morphologic Variant That Mimics Germinoma

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Background: Dr. Robert E. Scully, who recognized and defined gonadoblastoma (GB), used the term "dissecting gonadoblastoma" (DGB) to describe a variant morphology having the same cellular components as GB but with a diffuse or pseudoinvasive pattern instead of the classic nested arrangement. We investigated this pattern and its relationship to classic GB.
Design: 48 cases of GBs were identified and evaluated for the presence and morphologic features of DGB, patient age, karyotype, and associated invasive germ cell tumor. Immunohistochemical (IHC) stains for OCT4, inhibin, calretinin, FOXL2, SOX9, SF1, and WT1 were performed.
Results: 36 (75%) DGBs were identified. Clinical information was available in 30 patients: age was 3-32 years old (median, 16); 29 were phenotypic females and 1 male; 21 were known to have only 1 X chromosome (16 of which had confirmed Y chromosomes), while 2 others were 46XX. The DGBs consisted of large coalescent nests (solid/expansile pattern), which were often interrupted by fibrovascular septa (92%), of mostly germ cells with minor sex cord cells. Other variant morphologies were small anastomosing nests (anastomosing pattern) and cord-like arrangements (corded pattern) of germ cells with inconspicuous sex cord cells that were irregularly distributed in the stroma. Mixed patterns were seen in 23 DGBs, with solid/expansile usually being predominant. The germ cells ranged from resembling spermatogonia to IGCNU-like; OCT4 was variably positive, staining only the latter type (7/7). The sex cord cells were small with dense, oval or angulated nuclei with inconspicuous nucleoli and positivity for inhibin (9/9, strong), calretinin (3/3, variable), FOXL2 (9/9, strong), SOX9 (9/9, weak and focal), SF1 (8/9, strong), and WT1 (4/7, variable). 21 had invasive germinoma (3 of which with embryonal carcinoma, yolk sac tumor, and choriocarcinoma, respectively); 1 had an epidermoid cyst. Granulomas were present in 25 of 29 invasive germinomas, 5 DGBs, and 4 classic GBs. Fibrovascular septa were also seen in 20 invasive germinomas and 9 classic GBs.
Conclusions: DGB is commonly seen in association with classic GB and displays identical IHC features, supporting it as a morphologic variant of GB. DGB often mimics invasive germinoma; the presence of sex cord cells (identification aided by IHC for sex cord markers) and heterogenous germ cells are useful differential features. The lack of a granulomatous reaction also favors DGB over germinoma, and may be especially helpful in the corded pattern of DGB.

1170 Assessing the Accuracy of Histomorphology in Distinguishing Between HPV-Positive and HPV-Negative Vulvar Squamous Cell Carcinomas

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Background: Vulvar squamous cell carcinoma (VSCC) is two molecularly distinct diseases separable by etiology, i.e. human papilloma virus (HPV)-positive and HPV-negative VSCC. They differ with respect to precursor lesions (usual vulvar intraepithelial neoplasia, uVIN, and differentiated VIN, dVIN) and possibly clinical outcomes, with evidence suggesting HPV-negative VSCC has a worse prognosis. The ability to study different clinical outcomes requires accurate distinction between the two cancer types which can be difficult by morphology alone. This study compares the accuracy of histomorphology in the diagnosis of HPV-positive vs. HPV-negative VSCC, using p16 immunohistochemistry (IHC) as a surrogate for high risk HPV infection.

Design: Vancouver General Hospital Pathology records were searched for cases of invasive VSCC with slides and blocks available for analysis from 1985-2005 (n=193). Representative H&E sections were examined by two pathologists (ANK and CBG), and tumours were designated as HPV-positive or HPV-negative based on morphologic assessment of both invasive carcinoma and, where present, VIN. For example, well-differentiated keratinizing pattern or dVIN was considered evidence of non-HPV etiology, while basaloid pattern of VSCC or uVIN was considered evidence of HPV-related VSCC. Whole slide IHC for p16 was performed using Ventana CINtec antibody E6H4. HPV-positive staining was defined as "block" p16 positivity of the basal cells, with variable extension into the mid or superficial layers. Patchy positivity was not considered true p16 positivity.

Results: By morphologic criteria, 47/193 tumours (24%) were designated HPV-positive, and 146 (76%) were designated HPV-negative. p16 IHC revealed 77 (40%) HPV-positive and 116 (60%) HPV-negative tumours. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value of an HPV-positive morphologic designation were 0.56, 0.97, 0.91 and 0.77. For an HPV-negative morphologic designation, these values were 0.97, 0.56, 0.77 and 0.91.

Conclusions: The use of morphologic criteria alone does not accurately classify VSCC according to etiology, in particular because of the low sensitivity for detecting HPV-positive tumours and the only moderate PPV of an HPV-negative tumour designation. If information about HPV status of VSCC is important for research or treatment, it is necessary to routinely use adjunct diagnostic techniques.

1171 Bizzare Cell Dysplasia of the Cervix

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Background: A proportion of cervical squamous intraepithelial lesions encountered in surgical pathology practice contain high grade dysplastic epithelium HSIL (CIN III) with enlarged cells containing bizarre nuclei - so called bizarre cell dysplasia (BCD) that are outside of the current classification criteria. To elucidate the nature of these lesions we studied 19 cervical cone biopsy cases containing BCD.

Design: BCD cells were defined as 1) Presence of large cells comparable in size to superficial cells of squamous epithelium in normal ectocervix. 2) Presence of cells with abnormal, large pleomorphic nuclei with bizarre shapes resulting from massive nuclear enlargement or fusion of several dysplastic nuclei within a single cell. This results in 3) very high N/C ratio. 4) Bizarre cells scattered throughout the whole thickness of dysplastic squamous epithelium. Multi-target PCR and ISH HPV detection was performed on all BCD cases identified in one year routine practise of the authors with special anti-cross-contamination precautions implemented.

Results: BCD lesions arise within the conventional high grade squamous dysplasia HSIL (CIN III). Epithelium with BCD is prone to exhibiting biological features of endocervical crypt glandular extension. Surprisingly, all BCD-lesions were HPV type 16 related. This finding is statistically significant ($p < 0.01$) in comparison to HPV type distribution in general Czech population as well as in comparison to control group of 50 consecutive CIN III lesions in cone biopsies examined in our laboratory. One case was identified at the stage of invasive carcinoma.

Conclusions: Cytologically BCD displays characteristic morphologic changes which are recognizable, but poses a significant risk of misdiagnoses as LSIL due to the enlargement of dysplastic cells and multinucleation. This pitfall is of clinical importance since histological verification of the lesion might be delayed. BCD represents an unrecognized and potentially clinically significant subgroup of cervical intraepithelial lesions. Based on the unique histological, cytological and biological features of BCD together with its exclusive association with HPV 16 infection, we believe that BCD presents a specific variant of HSIL (CIN III).

1172 Inter- and Intraobserver Variability in Predicting Endometrial Polyp Using the Established Histologic Criteria

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Background: The diagnostic of endometrial polyp (EP) on endometrial biopsies can be challenging and it is subject to inter- and intraobserver variability. The aims of this study are to evaluate the inter- and intraobserver variability in diagnosing EP, and to determine which of the combined histologic features best predict EP.

Design: A retrospective of 104 patients that underwent hysteroscopy or sonohysterography following endometrial biopsy. Histology slides were reviewed by three blinded pathologists to identify the following histologic parameters: (1) thick-walled blood vessels; (2) irregularly shaped and positioned glands; and (3) increased stromal fibrosis. Each specimen was reviewed at least twice and then the discrepant cases by all 3 pathologists to determine intraobserver and interobserver variability. The final diagnosis was compared to the sonohysterographic/hysteroscopic finding which is clinically used to diagnose EP. Sensitivity and specificity as well as positive predictive value (PPV) and negative predictive value (NPV) were calculated using Fleiss's kappa statistics and Kendall's coefficient of concordance.

Results: Based on the initial histology report, 57 patients had polyp and 47 patients had other diagnosis, and 38 had lesions on imaging compared to 66 with no lesions. Of those diagnosed with polyp, 19 had lesions on imaging and 38 had no lesions on imaging, for 50.0% [95% CI: 33.4-66.6] sensitivity and 42.4% [95% CI: 30.3-55.2] sensitivity. Intraobserver reliability of repeat evaluations by the same pathologist to identify polyp (if 2 of the 3 criteria were met) was moderate for each of the three pathologists (Fleiss' Kappa 0.49 to 0.66), and agreement among the three pathologists using the first evaluation from each pathologist was significant [Kendall's coefficient of concordance=0.74, p-value < 0.0001]. When the consensus among all pathologists was that at least 2 criteria had been met, the PPV and NPV improved to 43.7% and 66.7%, respectively.

Conclusions: The diagnosis of EP on endometrial biopsy is highly subject to inter- and intraobserver variability. Consensus on these cases and the use of at least 2 out of 3 criteria could improve the positive and negative predictive value of diagnosis of EP. This recommendation could prevent the overdiagnosis resulting to unnecessary operative procedures for polyp removal or underdiganosis of EP leading to more physician visits for continued bleeding and more biopsies performed.

1173 Brenner Tumor Lack TERT Promoter Mutations That Are Common in Urothelial Carcinoma

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Background: Brenner tumors are uncommon ovarian neoplasms, which have overlapping features with urothelial neoplasms, both morphologically and immunophenotypically. Recently, TERT promoter mutation appears as a biomarker for urothelial carcinoma. However, TERT promoter mutation status has never been investigated in Brenner's tumor.

Design: Cases of Brenner tumor were collected. Slides were reviewed and selected to make sure the lesion is at least >20% of all tissue. Macro-dissection was performed in some of cases. Genomic deoxyribonucleic acid (gDNA) was extracted from those tissues. TERT promoter mutations were detected by standard PCR-sequencing. P63, GATA3 and PAX8 immunohistochemical (IHC) stains were also performed.

Results: 15 cases of Brenner tumor were collected for this study. The mean age of patient at diagnosis is 45 years (ranging from: 38-76 years). The mean size of tumor is 4 cm (ranging from 0.5-30 cm). All of Brenner's tumors had identical immunophenotype of urothelial carcinoma: positive for P63 and GATA3; negative for PAX8. However, none of Brenner's tumor was positive for TERT promoter mutation.

Conclusions: Brenner tumors are immunophenotypically identical with urothelial carcinoma. However, Brenner's tumor lack TERT promoter mutations which are detected in approximately ~70% of urothelial carcinoma. This indicates that carcinogenesis of Brenner's tumor may be different from those of urothelial carcinoma.

1174 The Familial Ovarian Tumor Study: A Morphological and Immunohistochemical Review

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Background: High grade serous carcinoma (HGSC) is associated with germline mutations of BRCA1/2 in approximately 15% of cases. The aim was to determine the accuracy of diagnostic classification of ovarian carcinoma and to determine if morphological and immunohistochemical (IHC) features distinguish HGSC with germline mutations from sporadic HGSC.

Design: Mutation screening and family pedigrees were obtained in 1414 women diagnosed from 1995 to 1999 and from 2002 to 2004. Representative tumor blocks were available for 645 cases. Tissue microarrays were stained for p53, WT-1, CK7, CK20, CDX2, HNF-1, and PTEN. Reviewers were blinded to original diagnosis and to germline mutation status. Included in this study are 65 patients with documented BRCA mutations and a control group of HGSC patients (n=54) with both negative family history and negative germline testing results.

Results: A significant number of cases received a revised diagnosis after a review of morphology and IHC (n=128/645, 20%). The most frequently changed original diagnoses were endometrioid carcinoma (n=46/128, 36%), and adenocarcinoma NOS (n=19/128, 15%) - 89% were reclassified as HGSC. 15/128 (12%) cases originally diagnosed as invasive adenocarcinoma were revised to borderline tumor. Metastatic adenocarcinoma from the gastrointestinal tract was misclassified as a primary ovarian endometrioid or mucinous adenocarcinoma (n=5/128, 4%). Cases from community hospitals were more likely to have their diagnosis changed compared to those from academic centres (p=0.002). All patients with BRCA germline mutations had High Grade Serous Carcinoma. A morphological review showed that tumor infiltrating lymphocytes (TILs) were more prominent in the tumours of patients with BRCA mutations (p=0.02) compared to the Control group of sporadic HGSC. However, there was no significant difference in tumor grade, architecture, atypia, mitotic count, frequency of giant bizarre nuclei, presence of geographic necrosis, or IHC staining between HGSC patients with and without BRCA germline mutations.

Conclusions: IHC studies and review by an experienced gynecological pathologist are critical to correctly classify ovarian malignancies. Diagnoses are more likely to be revised in cases from community hospitals. The quantity of TILs is the only morphological feature that significantly differentiates BRCA germline mutation HGSC from sporadic HGSC. Biomarkers currently commonly used do not differentiate BRCA associated HGSC.

1175 L1CAM: Promising Prognostic Factor in FIGO Stage I, Type I Endometrial Adenocarcinomas

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Background: FIGO stage I, type I endometrial carcinomas have an excellent prognosis with 5-yr survival rates of >90%. However, a small subgroup of patients will experience tumor relapse, often with fatal progression. Recently L1CAM was shown to be a prognostic marker that showed clear superiority over the currently used multifactor risk score including histological type, grade and stage. The aim of this study was to evaluate the prognostic significance of L1CAM in a large single center patient cohort study.

Design: Patients treated for endometrial carcinoma at University Womens' Hospital in Tuebingen, Germany between 2003-2013 were identified. Histological slides and paraffin material were retrieved, and appropriate tumor blocks were selected for immunohistochemistry after central pathology review. Immunohistochemistry was performed using primary L1CAM antibodies (clone L1-14.10). Cases were rated L1CAM positive if more than 10% of epithelial tumor cells showed positive immunostaining. The Kaplan-Meier method was used for survival analysis.

Results: A total of 343 cases of FIGO stage I, endometrioid adenocarcinoma was available for immunohistochemistry. L1CAM staining was found to be positive in 41/343 (12%) cases. 35/41 (85%) only showed focal staining, in the remaining 6/41 (15%) cases, diffuse staining was observed. For all FIGO stage I, type I carcinomas, 5-yr survival rates were 57% for patients with L1CAM-positive carcinomas and 89% for patients with L1CAM-negative carcinomas ($p<0.002$). In the G1 subgroup, 5-yr survival rates were 57% for patients with L1CAM-positive tumors and 91% for patients with L1CAM-negative tumors ($p=0.002$).

Conclusions: Our study confirmed recent findings of L1CAM being a highly relevant prognosticator in low risk endometrial carcinoma patients. L1CAM might help identify a subset of patients, for whom adjuvant treatment strategies currently reserved for high-risk patients only, might be beneficial.

1176 Occult Endometrioid Cancer and Occult Serous Cancer of the Fallopian Tubes in Patients With Pure Endometrioid Adenocarcinoma of the Endometrium: A Study of 429 Cases With Complete Examination of the Tubes

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Background: The value of complete examination of the fallopian tubes, rather than a representative section, in patients with clinically low stage, pure endometrioid adenocarcinoma of the endometrium is not well known. This study defined the incidence of occult tubal endometrioid cancer and occult tubal serous cancer in these patients and the effect on assignment of site of origin; tumor staging; and behavior.

Design: Fallopian tubes in all patients with endometrial adenocarcinoma were thinly sliced and completely examined (SEE-FIM protocol). This study analyzed only patients with pure endometrioid adenocarcinoma and excluded tumors mixed with serous carcinoma, clear cell carcinoma or carcinosarcoma. The anatomic sites of tubal involvement by endometrioid adenocarcinoma, serous tubal intraepithelial carcinoma (STIC), and mucosal atypia that fell short of STIC (serous tubal intraepithelial lesion (STIL) were evaluated, as well as endometriosis in the mucosa, serosa and/or muscularis. The original assignment of primary origin for the tubal tumor and the FIGO stage that was used for clinical management was also used in this study. Adjuvant treatment and patient outcome was recorded.

Results: Among 429 cases, 15 (3.5%) had endometrioid adenocarcinoma in the tubes (10 in mucosa with or without tumor in serosa/muscularis; 5 in serosa/muscularis but not mucosa). 11 of these 15 were grossly occult. Only 3/15 had adjacent tubal endometriosis to suggest primary tubal origin and the rest were originally classified as spread of the endometrial tumor for clinical management purposes. 7 cases (1.6% of all 429) (mostly grade 1) would have been assigned a lower FIGO stage for the endometrial cancer without recognition of the grossly occult tubal tumor. 3 of these 7 had chemotherapy; none of the 7 had recurrence (median 1 year follow up, range 0 to 6 yrs). Detached intraluminal tumor (presumed artifact due to uterine manipulator use and excluded from FIGO up-staging) was seen in 48 cases (11%). STIC was present in 1/429 cases and STIL in 6/429 cases. No recurrence was observed in patients with STIC or STIL.

Conclusions: Complete examination of grossly normal fallopian tubes in otherwise low stage endometrial endometrioid cancer identifies rare cases of occult tubal endometrioid adenocarcinoma and STIC. The clinical significance requires larger scale long term follow up and so the appropriate assignment of primary origin of tubal endometrioid tumor (tubal versus endometrial) and overall FIGO stage remains controversial.

1177 An Infiltrative Growth Pattern Is Able To Predict Poor Outcome in Stage I Type I Endometrial Carcinomas

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Background: FIGO grading is a prognosticator for type I endometrial carcinoma at stage I, but the assessment of the amount of solid growth and of nuclear atypia may be problematic. Alternative approaches for prognostic factors included the pattern of invasion in a binary grading system and the microcystic, elongated, fragmented glands (MELF) pattern. Recently, the pattern of invasion was shown to be of predictive value for lymph node metastases in cervical adenocarcinoma. The aim of this analysis was to test the prognostic value of the pattern of invasion and the MELF pattern in stage I endometrial carcinoma in comparison to FIGO grading.

Design: 392 endometrial carcinomas from a single institution were reviewed jointly by two pathologists without clinical information on a multi-headed microscope. Histological type, FIGO grade, depth of myometrial invasion, the presence of any LVSI and MELF structures were assessed. In addition, the type of invasion was classified into expansile and infiltrative based on the arrangement of the tumor glands and nests, the tumor borders and the degree of desmoplastic stromal reaction. For statistical analysis the chi squared test and Kaplan Meier survival curves were performed ($p<0.05$= statistically significant).

Results: 363 carcinomas were classified as type I (all endometrioid of usual or special type), of which 295 were G 1, 51 G 2 and 17 G 3 according to FIGO. Median follow up was 3.8 years. An infiltrative pattern was found in 20% of G 1, 38% of G2 and 59% of G3 carcinomas, whereas a MELF pattern was found in 10% of G1, 19% of G2 and 18% of G3 carcinomas. Both FIGO grading and invasion pattern were significant for survival ($p=0.001$ and $p=0.01$, respectively) but neither MELF nor LVSI. No significant difference for survival was found between FIGO G1 and G2 carcinomas. Among low-grade (G1 and G2) carcinomas the infiltrate pattern showed a trend for adverse prognosis but without statistical significance.

Conclusions: An infiltrative pattern of invasion but not the presence of MELF and LVSI are able to predict poor prognosis in type I endometrial carcinomas. Due to the similar outcome of FIGO G1 and G2 carcinomas a binary FIGO grading (low=G1/2 versus high=G3) should be considered for clinical practice.

1178 Can CA IX Be Used To Distinguish Between Gynecologic, Pancreatic and Cholangiocarcinoma? A Tissue Microarray Study of 757 Tumors

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Background: Immunohistochemistry (IHC) for CA IX is mainly used to differentiate clear cell from other types of renal cell carcinoma. Recent studies have evaluated CA IX expression in other carcinomas and have reported reactivity in intrahepatic cholangiocarcinoma. This has led to the hypothesis that CA IX may have utility in determining site of origin when a patient presents with intra-abdominal carcinomatosis, not infrequently seen with ovarian and other gynecologic carcinomas. Although PAX-8 is a specific marker of gynecologic tumors, a proportion of gynecologic cancers (~15%) are negative for PAX-8. We examined CA IX expression in gynecologic carcinomas, pancreatic carcinomas and cholangiocarcinomas to evaluate for potential diagnostic utility.

Design: CA IX expression was evaluated by IHC on 246 gynecologic tumors (29 endocervical, 53 endometrial, 164 ovarian epithelial tumors from 3 datasets [dataset 1: predominantly clear cell carcinomas, dataset 2: predominantly high grade serous carcinoma, dataset 3: early stage tumors, predominantly borderline]), 289 pancreatic tumors and 222 cholangiocarcinomas on tissue microarrays. CA IX expression was semiquantitatively scored using an H-score method, with score greater than 1 considered positive.

Results: Pancreatic and cholangiocarcinomas showed expression of CA IX (mean H-scores of 165 and 157, respectively), with the difference in H-score not statistically significant. Gynecologic tumors showed a high percentage of CA IX staining. When compared to pancreatobiliary tumors, the differences in mean H-scores, with the exception of endocervical carcinomas, were statistically significant ($P<0.0001$).

		H-Score (Positive Cases)			P Value (H-Score Comparison)	
Primary Site of Carcinoma	Total No. (%) of Cases Positive	Mean	Median	Range	Pancreatic Carcinomas	Cholangio-carcinoma
Endocervix	26/29 (90%)	158	144	20-300	0.1231	0.1835
Endometrium	50/52 (96%)	103	107	1-270		
Ovarian-dataset 1	49/51 (96%)	115	120	3-268		
Ovarian-dataset 2	53/53 (100%)	116	107	6-252		
Ovarian-dataset 3	58/60 (97%)	112	97	2-297		

Conclusions: CA IX expression is seen in both pancreatobiliary and gynecologic carcinomas. While the differences in mean H-score between the two groups are statistically significant, the presence of staining in gynecologic tumors limits the utility of CA IX to distinguish the origin of intra-abdominal carcinomatosis.

1179 Utility of a Two Antibody Panel for Mismatch Repair Deficiency Screening in Female Genital Tract Carcinomas

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Background: Tumours are reported as having an abnormal expression pattern for DNA mismatch repair (MMR) proteins that may be associated with Lynch syndrome, if immunohistochemical stains for any one of the MMR proteins MLH1, PMS2, MSH2 and MSH6 are negative. Hall *et al* [Pathology 2010;42(5):409-413] previously demonstrated that a two antibody panel immunohistochemical test comprising PMS2 and MSH6 could be utilised for MMR deficiency screening in colorectal adenocarcinomas without loss of sensitivity when compared with the traditional four marker panel. We proposed that staining for PMS2 and MSH6 alone should also be sufficient to detect all cases of mismatch repair deficiency in primary female genital tract carcinomas.

Design: The electronic database of the Department of Anatomical Pathology at Austin Health (Melbourne, Australia) was searched for all primary female genital tract carcinomas on which a four antibody immunohistochemistry panel for MMR proteins had been performed, and an audit of the slides for loss of MMR staining was conducted.
Results: 117 cases of primary female genital tract carcinoma that had been tested with a four antibody MMR protein panel were identified. 40 cases displayed loss of at least one mismatch repair protein. All cases of MLH1 or MSH2 loss were associated with loss of PMS2 or MSH6 respectively. In instances where there was loss of only a single MMR protein, the protein was always MSH6.
Conclusions: A two antibody panel test comprising PMS2 and MSH6 can be safely utilised in place of the four antibody panel protocol in primary female genital tract carcinomas, without loss of sensitivity.

1180 Sox2 Is Expressed in Gliomatosis Peritonei: A Clinicopathologic and Immunohistochemical Study of 21 Cases

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Background: Gliomatosis peritonei is characterized by mature glial tissue in the peritoneum, a rare condition associated with ovarian immature teratoma. Presence of gliomatosis peritonei, regardless of the extent has not been associated with adverse outcome and is considered grade 0, in the grading system used for immature teratomas, hence does not require further treatment. This study presents one of the largest reported series of such tumors.
Design: 21 cases of gliomatosis peritonei with available clinical data were identified in our pathology files from 1988 to 2014. Patients' chart, pathology reports and available H&E slides were reviewed. Tissue blocks and/or unstained slides were used for immunohistochemical study.
Results: Patients' ages rangedfrom 5 to 42 years old (median 19). In addition to gliomatosis peritonei, the patients were diagnosed with immature teratoma (n=14), mixed germ cell tumor with immature teratoma component (n=6), and mature teratoma with carcinoid tumor (n=1). Gliomatosis peritonei was diagnosed at the same time of ovarian neoplasm in 16 patients, at second-look surgeries in 5 patients (ranging from 4 months to 16 years after the original surgery). High grade glioma arising from gliomatosis peritonei and characterized by increased nuclear atypia, mitotic activity and vascular proliferation was identified in one patient. Immunohistochemical staining for Sox2 was diffusely positive in both immature teratoma (n=4) and gliomatosis peritonei (n=8). Immunohistochemical staining for Oct4 was focally positive (n=2) or negative (n=1) in immature teratoma and negative in gliomatosis peritonei (n=7).

Pt	Age	Ovarian Neoplasm	Interval*	Teratoma Component		Gliomatosis Peritonei		Follow-up
				Sox2	Oct4	Sox2	Oct4	
1	18	Immature teratoma, low grade	Concurrent	NA	NA	NA	NA	ANED, 19 months
2	29	Immature teratoma, low grade	Concurrent	NA	NA	NA	NA	ANED, 2 months
3	14	Immature teratoma, high grade	2 years	Positive	Scant material	Positive	Negative	ANED, 67 months
4	15	Immature teratoma, low grade	Concurrent	NA	NA	Positive	NA	NA
5	19	Immature teratoma, high grade	Concurrent	Positive	Negative	Positive	Negative	ANED, 58 months
6	13	Mixed germ cell tumor	Concurrent	Positive	Focal positive	Positive	Negative	ANED, 1 month
7	36	Mixed germ cell tumor	Concurrent	NA	NA	NA	NA	ANED, 1 month
8	15	Immature teratoma, high grade	Concurrent	Positive	Focal positive	Positive	Negative	ANED, 28 months
9	33	Immature teratoma, low grade	16 years	NA	NA	NA	NA	ANED, 193 months
10	19	Mixed germ cell tumor	10 months	NA	NA	Positive	Negative	ANED, 21 months
11	22	Immature teratoma, high grade	4 months	NA	NA	NA	NA	ANED, 8 months
12	40	Mixed germ cell tumor	4 months	NA	NA	Positive	Negative	ANED, 17 months
13	42	Mixed germ cell tumor	Concurrent	NA	NA	Positive	Negative	ANED, 12 months
14	5	Mature cystic teratoma with carcinoid tumor	Concurrent	NA	NA	NA	NA	ANED, 3 months
15**	10	Immature teratoma, low grade	Concurrent	NA	NA	NA	NA	NA
16	10	Mixed germ cell tumor	Concurrent	NA	NA	NA	NA	NA
17	21	Immature teratoma, high grade	Concurrent	NA	NA	NA	NA	NA
18	21	Immature teratoma, high grade	Concurrent	NA	NA	NA	NA	NA
19	14	Immature teratoma, low grade	Concurrent	NA	NA	NA	NA	NA
20	22	Immature teratoma, high grade	Concurrent	NA	NA	NA	NA	ANED, 5 months
21	41	Immature teratoma, high grade	Concurrent	NA	NA	NA	NA	ANED, 229 months

Abbreviation: NA: unavailable; ANED: alive with no evidence of disease
*The interval is between initial diagnosis of immature teratoma and diagnosis of gliomatosis peritonei.
** Case 15, high grade glioma

Conclusions: Our data showed that the majority of cases gliomatosis peritonei were associated with immature teratoma or mixed germ cell tumor. Even though gliomatosis peritonei is composed of mature glial tissue, it is important to carefully exam the specimen to rule out associated immature teratoma, which could alter therapy, or very rarely malignant transformation to high grade glioma. Sox2 is expressed in gliomatosis peritonei, suggesting that these glial cells are not terminally differentiated and may have proliferative potential.

1181 Morphologic and Immunohistochemical Re-Evaluation of Tumors Initially Diagnosed as Ovarian Endometrioid Carcinoma

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Background: Most ovarian endometrioid carcinomas (OEC) are low-grade with characteristic morphologic features. High-grade OEC are uncommon but may mimic high-grade ovarian serous carcinomas (OSC) and undifferentiated carcinomas. We reviewed the histologic, immunophenotypic and clinical features of tumors initially diagnosed as OEC, re-classified them as OEC or non-OEC (NOEC), and sought to identify helpful histological features for separating OEC from NOEC, especially OSC.
Design: 109 cases originally diagnosed as OEC were reviewed and reclassified as OEC or NOEC using current World Health Organization (WHO) criteria. We also noted the presence of confirmatory endometrioid features (CEF): (1) squamous metaplasia, (2) endometriosis, (3) adenofibromatous background, (4) borderline endometroid component. A tissue microarray was constructed from 30 representative OEC and 11 NOEC and sections were stained for WT-1, p16, and p53.
Results: Seventy-five (69%) tumors demonstrated unequivocal histologic features of OEC (56 FIGO grade 1, 16 grade 2, 3 grade 3) while 34 (31%) were reclassified as NOEC (8 FIGO grade 2, 26 grade 3). Patients with OEC were younger (median 52 vs. 57 years, p=0.04) and presented with unilateral (84% vs. 63%, p=0.02) and larger tumors (median 10.6 vs. 7 cm, p=0.03) than those with NOEC. Sixty-three (84%) OEC showed ³1 CEF: squamous differentiation (68%); endometriosis (51%); adenofibromatous background (21%); borderline component (44%). Most NOEC demonstrated morphologic features of high-grade OSC. Only one CEF was seen in 5 NOEC (15%). Three of 29 (10%) OEC stained for WT-1, 6/29 (21%) demonstrated p53 overexpression and 7/30 (23%) showed diffuse p16 staining. All, except for 1, OEC with aberrant immunophenotype (88%), exhibited ³1 CEF. Nine of 11 (82%) NOEC demonstrated expression of ³1 immunomarker, and only 2 (18%) of these tumors showed CEF. Patients with OEC generally presented with low-stage (FIGO I/II) disease (89% vs. 35%, p<0.0001) and had a significantly better overall survival (p=0.003), than those with NOEC.
Conclusions: A significant proportion of high-grade OEC were reclassified as high-grade OSC on review. The use of CEFs allied with a small panel of immunomarkers enables distinction of OEC from OSC.

1182 Targeted Screening With Combined Age and Morphology Based Criteria Enriches Detection of Lynch Syndrome in Endometrial Cancer

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Background: Lynch syndrome is associated with endometrial cancer in approximately 2-5% of cases. In these patients, screening for Lynch syndrome may lead to prevention of a second cancer and incident cancers in family members via risk-reducing strategies. The goal of the study was to evaluate the detection rate of Lynch syndrome in endometrial cancer via a targeted screening approach.
Design: Beginning in June 2009, we incorporated targeted Lynch syndrome screening via immunohistochemistry for MMR proteins, MLH1, PMS2, MSH2 and MSH6, followed by MLH1 promoter hypermethylation, in select cases of endometrial carcinoma. Criteria for patient selection included: 1) Age: all patients <50 years; 2) Morphology: patients of any age with tumors showing morphologic features suggestive of microsatellite instability (i.e. LUS-centered tumors, hard to classify non-serous carcinomas, tumors with peritumoral or tumor infiltrating lymphocytes and tumors with synchronous ovarian carcinomas); 3) Clinician's request based on family or personal history; 4) Ad hoc retrospective testing of cases before 2009 based on the established criteria on patients discovered on follow-up visits.
Results: In a 4.5 year period, there were 328 new cases of non-serous endometrial cancers, of which 2 cases had known Lynch syndrome prior to the diagnosis. Seventy-five additional patients were selected for testing; 16 of 75 showed complete absence of at least one MMR protein by IHC. Of these, 11 of 75 (age 41-89, mean 63.6) exhibited loss of MLH1 and PMS2 and subsequent MLH1 promoter hypermethylation. In contrast, 4 additional cases exhibited evidence of germline mutation. 2 cases (ages 52 and 56, mean 54) showed loss of MSH6 by IHC and genetic analysis revealed germline mutation. In addition, 2 cases (ages 23 and 33, mean 28) had MLH1 loss by IHC without promoter hypermethylation (one case had a confirmed germline MLH1 mutation, while the other patient refused germline testing). The remaining abnormal case exhibited loss of PMS2, while sequencing revealed a wild-type gene. By using a targeted screening approach, approximately 1.8% of endometrial cancers (6 of 328) were associated with Lynch syndrome.
Conclusions: Targeted screening for Lynch syndrome with combined age and morphology based criteria effectively enriches detection of Lynch syndrome in endometrial cancer. However, the detection rate is still lower than published series that offer universal screening.

1183 Differentiating Primary and Extra-Genital Origin Metastasis Mucinous Ovarian Tumors: An Algorithm Combining PAX8 With Tumor Laterality

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Background: Differentiating Primary Ovarian mucinous tumors (POMTs) from metastatic mucinous carcinomas involving the ovary (MOMCs) is often challenging. Paired box gene-8 protein (PAX8) has been demonstrated to be a reliable marker in identifying tumors of ovarian origin. This article was to analyze the utility of the algorithm combining PAX8 with clinicopathologic characteristics in differentiating POMTs from extra-genital origin MOMCs.
Design: A total of 78 cases of POMTs, 18 extra-genital origin MOMCs, and 70 extra-genital origin primary mucinous carcinomas (PMCs) were reviewed along with clinical records and follow-up data. The expression pattern of PAX8 was investigated by immunohistochemistry using rabbit monoclonal antibody (rabbit mAb) and rabbit polyclonal antibody (rabbit pAb) respectively.
Results: Compared with PAX8 rabbit pAb, PAX8 rabbit mAb demonstrated superior specificity but unfavorable sensitivity in benign POMTs (67.7% vs. 90.3%), borderline POMTs (60.9% vs. 82.6%), primary ovarian mucinous carcinomas (POMCs) (45.8% vs. 75%), extra-genital origin MOMCs (0% vs. 16.7%) and extra-genital origin PMCs (0% vs. 31.4%). When they were evaluated independently in differentiating POMTs from extra-genital origin MOMCs, the accuracy of PAX8 (rabbit mAb) immunostaining status (67.7%), tumor size (69.8%) and laterality (89.6%) was not satisfactory. Once PAX8 (rabbit mAb) immunostaining status was combined with tumor laterality, the diagnostic accuracy was dramatically raised to 97.9% with significantly high sensitivity (97.4%) and perfect specificity (100%).
Conclusions: PAX8 (rabbit mAb) was a specific marker in differentiating POMTs from extra-genital origin MOMCs. As a simple, convenient and high performance-to-price ratio algorithm, combination of PAX8 (rabbit mAb) immunostaining with tumor laterality should be strongly recommended in our routine practice.

1184 Molecular Characteristics of Mixed Ovarian Carcinomas

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Background: Ovarian carcinoma exists as a group of 5 major histotypes: High grade serous (HGSC), Endometrioid (EC), Clear Cell (CCC), Mucinous (MC) and low grade serous (LGSC). Each has a broad morphological spectrum, with the ability to mimic features of other histotypes. Historically, this has lead to a relatively high frequency of mixed type carcinoma diagnoses (up to 11%). However, recent immunohistochemical (IHC) studies suggest a much lower incidence.

Design: In this study, we reviewed a population-based cohort of 871 cases of ovarian carcinoma and through international collaboration, established a cohort totaling 22 mixed ovarian carcinomas. Molecular differences between the distinct components of each mixed case were interrogated using IHC, NanoString-based gene expression, and Ion-Torrent cancer-gene hotspot sequencing analyses.

Results: Mixed ovarian carcinomas were found at a frequency of 1.7% in our cohort when modern diagnostic criteria were applied. EC/CCC mixed carcinomas were seen most frequently (6 cases), however EC/LGSC, CCC/MC and other mixes were also observed (4, 2 and 3 cases, respectively). Seven additional cases were also referred to our study from collaborating centres, including 3 EC/CCC, 3 HGSC/CCC and 1 EC/CCC/Seromucinous mix. Overall, IHC and molecular data support reclassification of at least 9 of the 22 cases as a single histotype with morphological heterogeneity. Of the remaining cases (2 EC/LGSC, 1 CCC/MC, 6 EC/CCC, 2 HGSC/CCC, and 2 other mixes), some appeared as classic "true" mixed cell type carcinomas while rare cases exhibited unique profiles of IHC, gene expression, and mutation that did not allow a conclusive histotype diagnosis.

Conclusions: Our data provide objective support to recent changes in ovarian cancer diagnostic criteria suggesting mixed-cell type carcinomas are not a major subgroup of patients. Immunohistochemical, gene expression, and sequencing data suggest "true" mixed-cell type carcinomas account for less than 1% of total epithelial ovarian cancers. A few commonly used immunohistochemical markers were typically sufficient for classification of diagnostically problematic cases.

1185 Association of Microscopic Findings of Ovarian High-Grade Serous Carcinoma (HGSC) and Status of BRCA Mutation

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Background: Recently there have been a few publications indicating that certain microscopic features of ovarian HGSC have a predictive value for the status of BRCA mutation; however, there are controversial findings in the literature as well as a lack of prospective studies. This study was performed to further evaluate this relationship as it may have an important impact on patient care. Considering many patients with advanced stage HGSC receive neo-adjuvant chemotherapy (NAC), we also examined if specific morphologic patterns may be associated with certain responses.

Design: A total of 80 ovarian HGSC cases were retrieved from a medium sized academic medical center over the last 4 years. Slides from each case were examined to assess morphologic pattern (solid, high-grade endometrioid, transitional, papillary and/or clear cell), mitotic index, tumor infiltrating lymphocytes, extensive tumor necrosis, psammoma bodies, tumor giant cells and serous tubal intraepithelial carcinoma (STIC). The patient's BRCA status was ascertained after pathology review. We compared BRCA1 positive cases (n=5), high risk patients with a personal history of breast cancer or a family history of ovarian cancer (n=18), and sporadic cancer cases (n=57).

Results: Using previously published algorithms, created in an attempt to correlate specific histologic features of HGSC and BRCA status, did not predict high risk patients or those with BRCA mutation in our data set. Solid, endometrioid and transitional patterns did not confer higher risk than patients with sporadic cancers. In addition, we did not find an association between mitotic index, tumor infiltrating lymphocytes and necrosis in high risk or BRCA positive patients. Of the 29 patients who received NAC, 8 had residual STIC (28%), in contrast to the 51 patients without NAC who had STIC in 19 cases (37%). Notably, there were increased clear cell features, necrosis, tumor giant cells and psammoma bodies in specimens after NAC.

Conclusions: These findings indicate there are no definitive patterns or algorithms to predict BRCA association. Additional studies with larger sample size may help elucidate the relationship between histologic patterns and BRCA status. Extensive tumor necrosis, clear cell features, tumor giant cells and psammoma bodies are characteristic findings after NAC, although the biologic meaning of tumor giant cells remains to be clarified.

1186 GHRH Receptor Expression in Malignant Mixed Müllerian Tumor: A Potentially Targetable Biopredictor

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Background: Malignant Mixed Mullerian Tumors (MMMT) are aggressive malignant neoplasms with high recurrence rates and poor prognosis. Despite advances in imaging and adjuvant therapies in recent years, the prognosis of these tumors has not improved. In fact, there are currently no consensus treatment guidelines for the management of these rare neoplasms. Growth hormone releasing hormone (GHRH) is produced by a variety of malignant tumors and acts as a growth factor in an autocrine/paracrine manner. It requires the presence of its receptor, GHRH-R, to exert its effect on neoplastic cells. In this study we evaluated the expression of GHRH-R in a group of MMMTs.

Design: Thirty-one examples of MMMT (uterus 25, ovary 3, uterine tube 2, and pelvic epithelium 1) were retrieved from the files of Department of Pathology at the University of Miami, Jackson Memorial Hospital. Immunohistochemistry was performed on paraffin sections using polyclonal anti-GHRH-R antibody (Abcam, Cambridge, MA) and a polymer detection system. The staining results were evaluated in both epithelial and mesenchymal components of each tumor and recorded as negative, focal or diffuse. The presence of GHRH-R RNA and that of its biologically active splice variant (SV1) were evaluated by RT-PCR in six tumors.

Results: Positive reactions for GHRH-R were detected in 30 tumors (96%). The epithelial components were diffusely positive in 23 (74%) and focally positive in 6 tumors (19%). The sarcomatous elements were diffusely positive in 19 (58%) and focally positive in 11 tumors (36%). One uterine MMMT was negative for GHRH-R in both components. RT-PCR was positive for GHRH-R RNA and its splice variant in all six tumors.

Conclusions: We conclude that GHRH-R is expressed by the majority of MMMTs in both epithelial and mesenchymal components. This finding could potentially serve as a basis for therapeutic approaches using peptide receptor antagonists that have shown significant efficacy in experimental models with minimal pharmacologic side effects (*Bellyei S, et al. Cancer Letters: 2010; 293: 31–40*).

1187 Ovarian Mucinous Borderline Neoplasms: Is Complete Surgical Staging Warranted?

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Background: Complete surgical staging for early epithelial ovarian cancer and borderline tumors is recommended as up to 35% of patients are upstaged from stage I to II after microscopic evaluation. However, based on our current knowledge, the vast majority of mucinous neoplasms are confined to the ovary with overall good prognosis, including mucinous carcinomas which make up 3-4% of ovarian cancers when GI metastasis is excluded. The purpose of this study is to determine if complete surgical staging, particularly at the time of frozen section diagnosis, is warranted for a diagnosis of mucinous borderline neoplasm (MBN).

Design: The pathology archives were searched for consecutive cases of mucinous neoplasms diagnosed on frozen section from 2005 to 2014. Frozen section diagnosis, final diagnosis and results of surgical staging were recorded. Cases where GI metastasis could not be ruled out and cases where the final diagnosis was not mucinous type were excluded.

Results: A total of 141 cases were identified. On frozen section, 90 cases (90/141; 64%) were mucinous cystadenoma, 39 cases (39/141; 28%) were MBN, and 12 cases (12/141; 9%) were invasive mucinous carcinoma. For cases of cystadenoma on frozen section, 80 cases (80/90; 89%) remained unchanged and 10 cases (10/90; 11%) were upgraded to MBN on final diagnosis. For cases of MBN on frozen section, 27 cases (27/39; 69%) remained unchanged, 3 cases (3/39; 8%) were downgraded to cystadenoma and 9 cases (9/39; 23%) were upgraded to carcinoma on final diagnosis. All cases of carcinoma on frozen section were unchanged on final diagnosis (12/12; 100%). Stage was determined for 51 cases where the final diagnosis was MBN or carcinoma and complete surgical staging took place. For MBN, zero cases (0/30) were upstaged. For carcinoma, 3 cases were upstaged to stage II (3/21; 14%).

Conclusions: Based on our current knowledge of mucinous ovarian tumors, MBN is essentially benign and mucinous carcinomas are rare. Our data show that upstaging did not occur with MBN, whereas 14% of carcinomas were upstaged after complete surgical staging. Intraoperative frozen section diagnosis of ovarian mucinous tumors can be challenging due to the large size of these specimens and limited sampling that occurs. We found that 23% of cases with a frozen section diagnosis of MBN were upgraded to carcinoma on the final. Overall, our data do not support complete surgical staging for a final diagnosis of MBN, however complete surgical staging for a frozen section diagnosis of MBN may still be warranted since up to a quarter of these cases were changed to carcinoma on final diagnosis.

1188 Utility of Claudin-18 and p16 Immunohistochemistry for distinguishing Gastric-Type Adenocarcinoma From Other Subtypes of Cervical Adenocarcinoma

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Background: Gastric-type adenocarcinoma (GA) is a recently established subtype of uterine cervical adenocarcinoma. Although the typical histological features of GA have been documented, distinguishing GA from other cervical adenocarcinomas is not always easy. Here, we performed comprehensive immunohistochemical analysis of cervical adenocarcinoma in order to establish the best panel of markers for distinguishing GA from other subtypes. Special attention was paid to the expression of Claudin-18 (CLDN18), a novel gastric marker that is expressed in lobular endocervical glandular hyperplasia.

Design: Immunohistochemistry for p16, CLDN18, MUC6, HIK1083, MUC5AC, ER, and CDX2 was performed in 63 patients who had cervical adenocarcinomas removed surgically. The case series included 37 usual-type adenocarcinomas (UA), nine non-gastric-type mucinous adenocarcinomas (NGMA), nine gastric-type adenocarcinomas (GA), four adenocarcinomas suspicious for the gastric phenotype, two clear cell carcinomas, one serous adenocarcinoma, and one neuroendocrine carcinoma. Background non-neoplastic endocervical glands were evaluated in 36 cases.

Results: CLDN18 is expressed in most GAs (89%), whereas its expression is rare (8%) and often focal in non-GAs. Diffuse expression of p16, which was observed in almost all UAs and NGMAs, was never seen in GAs.

	p16 + (≥80%)	CLDN18 + (≥10%)	MUC6 + (≥10%)	HIK1083 + (≥10%)	MUC5AC + (≥10%)	ER + (≥10%)	CDX2 + (≥10%)
UA	35/37 (95%)	2/37 (5%)	2/37 (5%)	0/37 (0%)	27/37 (73%)	15/37 (41%)	9/37 (24%)
NGMA	9/9 (100%)	2/9 (22%)	3/6 (33%)	1/9 (11%)	9/9 (100%)	0/9 (0%)	3/9 (33%)
GA	0/9 (0%)	8/9 (89%)	6/9 (67%)	4/9 (44%)	7/9 (78%)	0/9 (0%)	1/9 (11%)
Suspected GA	2/4 (50%)	2/4 (50%)	1/4 (25%)	2/4 (50%)	3/4 (75%)	0/4 (0%)	2/4 (50%)
Other adeno-carcinomas	4/4 (100%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	0/4 (0%)
Non-neoplastic endocervical glands	0/36 (0%)	0/36 (0%)	9/36 (25%)	0/36 (0%)	24/36 (67%)	36/36 (100%)	0/36 (0%)

Conclusions: GA of the uterine cervix is characterized by CLDN18-positivity and a non-diffuse pattern of p16 staining. A CLDN18/p16 immunohistochemistry panel is useful for distinguishing GAs from other subtypes. Using this panel, we were able to diagnose two of the four adenocarcinomas that were suspected of being the gastric phenotype on H&E sections as GAs.

1189 Atopic Dermatitis Is an Independent Risk Factor for Cervical Human Papillomavirus Infection

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Background: Cervical human papillomavirus (HPV) infection is more likely to persist and cause cancer in immunosuppressed women. Recent studies suggest atopic dermatitis, which is known to affect cell-mediated immunity, may be associated with recalcitrant warts; therefore, we hypothesized that women with atopic dermatitis may be more likely to be positive for high risk HPV infection and develop high grade cervical dysplasia (CIN2+).

Design: Retrospective cohort of 1200 women who were randomly selected from a series of more than 6000 index cervical pap smears that were either positive or negative for high risk HPV. Patient age, race, history of atopic dermatitis, allergic rhinitis, smoking, body mass index, socioeconomic status, marital status, hormone contraceptive use, and two-year clinical outcomes, including follow-up pap smears, HPV testing, and cervical biopsy results were recorded. All cases with an atopic dermatitis diagnoses (n=74) were confirmed by a dermatologist. Analysis was restricted to white females with documented clinical follow-up, which yielded 577 HPV positive and 583 HPV negative cases for comparison. Associations were tested by X^2 analysis and logistic regression modeling.

Results: Atopic dermatitis was more common in the HPV positive group (48/577, 8.3%) compared with the HPV negative cohort (26/583, 4.5%) (p=0.007). Logistic regression analysis revealed an adjusted odds ratio of 3.75 [1.3-10.9] (p=0.02) after controlling for potential confounding variables. Older married women were less likely to be positive for HPV (OR 0.55 [0.43-0.71]) (p<0.0001). Younger single women were more likely to show persistent HPV infection (p=0.03). Smoking history was not associated with an HPV positive index pap smear, but it was the only covariate that tended to be an indicator of progression to CIN2+ (OR 1.52 [0.90-2.58]) (p=0.12).

Conclusions: Atopic dermatitis may be an independent risk factor for high-risk HPV infection, even after controlling for a number of known covariates. However, it does not appear to increase the risk of persistent high risk HPV infection, or progression to high grade dysplasia.

1190 Role of p16 in Downgrading -IN 2 Diagnoses and Predicting Higher Grade Lesions

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Background: In 2012, the CAP and ASCCP published the "LAST" recommendations for standardization of reporting terminology for HPV-related squamous lesions of the lower anogenital tract, including the use of a two-tier nomenclature (LSIL/HSIL) to better represent the dichotomous biology of HPV (transient infection vs. preneoplasia). The use of biomarkers, specifically p16 immunohistochemistry, was recommended to distinguish precancer (HSIL) from low-grade (LSIL) and non-HPV-related changes. Our objectives were to determine the frequency with which -IN 2 diagnosis would be downgraded based on the use of p16, and if p16 status was predictive of subsequent higher grade lesions.

Design: All available cases from 2009 diagnosed as -IN 2 of the cervix, vagina, vulva, and anus were reviewed, with p16 staining (Biocare Medical, clone G175-405) performed in all cases with sufficient material. Slides were independently reviewed by two pathologists, with discrepant p16 interpretations adjudicated by a third pathologist. Medical records were reviewed for any subsequent documented pathology for each patient, and all available relevant surgical specimens reviewed. The proportions of p16-positive (diffuse, block reactivity) and negative (all other expression patterns) cases were determined, and the frequency of a subsequent diagnosis of -IN 3 was compared between the two groups using chi-squared analysis.

Results: 200 cases (from 194 patients) diagnosed as -IN 2 with available material were identified- 168 cervical, 28 anal/perianal, 2 vulvar, and 2 vaginal. Of these, 32% were negative for p16. 166 patients (86%) had subsequent pathology (with follow-up between 4 days and 67 months), of which 132 were excisional procedures. 18.3% of cases were associated with a subsequent diagnosis of -IN 3 on biopsy or excision, with a frequency of 24.5% in p16-positive cases vs. 4.3% in p16 negative cases (p=0.003).

Conclusions: Approximately one third of -IN 2 diagnoses would be downgraded to LSIL over one year in a busy academic practice based on adherence to the LAST recommendations. The finding that p16 expression is significantly associated with a higher risk for -IN 3 on a subsequent specimen (representing clarification of -IN 2 diagnostic uncertainty, progression of -IN 2, or an unsampled coexisting lesion) suggests that the use of p16 to adjudicate -IN 2 diagnosis as LSIL/HSIL would likely predict lesion potential more accurately and avoid unnecessary excisional procedures for LSIL and/or non-HPV-related changes.

1191 Universal Screening for Gynecologic and Colorectal Cancer: A Single Institution Experience

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Background: Routine screening of patients with colorectal cancer (CRC) for Lynch syndrome (LS) has become increasingly common, but routine screening for LS in women with endometrial cancer (EC) is rarely performed. In 2011, leading cancer institutions and public health agencies created the Lynch Syndrome Screening Network (LSSN) in order to promote routine LS screening on all newly diagnosed ECs as well as CRCs. To determine the utility of universal screening for gynecologic cancer patients, we report the results of a universal screening program for EC, CRC, and ovarian cancer (OC) covering a 36 month period at a single institution.

Design: All CRCs, ECs and OCs were studied for mismatch repair protein deficiency by immunohistochemistry (IHC) over a 36 month period. All cases with MLH1 deficiency underwent methylation analysis (EC, OC) or *BRAF* V600E mutation analysis (CRC). A subset also had microsatellite instability studies. Cases were classified as "likely LS-associated" if there was deficiency of MSH2 and/or MSH6, PMS2, or MLH1 in absence of methylation or *BRAF* mutation. Equivocal cases were classified separately as "requiring further study." All other cases were classified as "unlikely LS-associated."

Results: Of 686 CRCs screened, 10.8% had deficient MMR (dMMR) and 7.4% were "likely LS-associated," while 30.4% of 293 ECs were dMMR and 9.6% were "likely LS-associated." Only 3.8% of OC were "likely LS-associated;" all but one were clear cell or endometrioid histology.

Conclusions: Universal screening of EC identifies a similar, if not higher rate of likely LS-associated cases when compared to CRC (9.6% vs 7.4%). Universal screening for OC is not cost-effective as most cases that are likely to be LS-associated (3.8% overall) can be identified by screening criteria using age and/or histologic type. Sporadic methylation appears to be increased in EC compared to CRC. Universal screening of EC for LS is practical and cost-effective, especially if a 2-antibody screening protocol is used. Successful implementation requires collaboration among genetic counselors, gynecologic oncologists, and pathologists.

1192 Ovarian Cancer Histotype Diagnosis in the UK: A Review of Cases From 5 Hospitals From 2002-2008

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Background: Epithelial ovarian carcinomas (EOC) comprise 5 major distinct histotypes: high grade serous (HGSC), clear cell (CCC), endometrioid (EC), low grade serous (LGSC) and mucinous (MC), each with characteristic genetic and clinicopathological profiles. Growing evidence suggests significant variability in diagnosis, especially in historic cohorts. Using modern morphologic criteria and limited immunohistochemistry (IHC), reproducible histotype diagnosis is possible in routine practice.

Design: Expert review of 186 cases from 5 UK hospitals was carried out blinded to original diagnosis, aiming to assess concordance between original (2002-8) and review (2014) diagnosis, determine IHC use and identify areas of diagnostic difficulty.

Results: The concordance between the original diagnosis and expert review using current morphological criteria was 65% (120/186). The single most frequent misdiagnosis was HGSC diagnosed as EC (19/186, 10%). Of the 5 major histotypes, the lowest concordance was in diagnosis of MC and EC. A review diagnosis of borderline tumour was made in 5% (9/186) of cases originally diagnosed as EOC.

	2014 Review Diagnosis						
Original Diagnosis	HGSC	CCC	EC	LGSC	MC	OTHER	TOTAL (%concordance)
HGSC	67	6	4	4	-	1	82 (82%)
CCC	4	19	2	-	-	1	26 (73%)
EC	19	-	14	-	-	-	33 (42%)
LGSC	-	-	-	8	-	4	12 (67%)
MC	1	1	2	-	6	6	16 (38%)
OTHER	6	-	4	-	-	7	17
TOTAL	97	26	26	12	6	29	186

IHC was utilized in 51% of cases, most commonly CK7, CK20, CEA, CA125, WT1, ER and p53. Reviewers recommended IHC in 24% cases, most commonly WT1, p53 and ER.
Conclusions: Accurate histotype diagnosis of primary EOC is vital for correct patient management including genetic counselling . This study shows a significant level of discrepancy in recognition of all major histotypes. While these results are probably not representative of current diagnostic practice, specifically challenging areas are highlighted. Cost-effective IHC panels for specific diagnostic dilemmas will be proposed.

1193 Comparison of Different Histopathological Methods for the Evaluation of Inguinal Sentinel Lymph Node in Squamous Cell Carcinoma of the Vulva

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Background: The sentinel lymph node (SLN) biopsy has been increasingly implemented in the treatment of vulvar carcinoma. However, no standardized procedure for gross sectioning and histological evaluation has been established. In this study we aimed to compare different methods for the analysis of SLN in vulvar cancer.
Design: Thirty cases of vulvar squamous cell carcinoma, FIGO stage IB, with SNL biopsy (2000-2014) were included in the study. Conventional examination of one H&E longitudinal section was compared to detailed examination with multiple parallel cross sections, post lymph node re-inclusion, plus four level H&E 100mm apart.
Results: Vulvarsquamous cell carcinoma cases included unilateral (n=27) and central tumours (n=2), with a median size of 1.9cm. Median depth of stromal invasion was 4mm. Five had lymphovascular and 8 had perineural invasion. The number of SLNs excised per patient ranged from 1 to 6. All were submitted to frozen section evaluation. Occult metastases, not detected in conventional examination, were found in 3 of the cases (10%) by detail examination. They were located in the subcapsular region and measure 0.10mm, 0.42mm and 1.10 mm. Three patients were submitted to lymphadenectomy, and 4 were treated with radiotherapy. Median follow-up was 13.6 months (range 1-129). Two patients died of disease and two were alive with disease.
Conclusions: Detailed analysis of SLN in vulvar carcinoma allowed higher rate of metastases identification. Further studies are needed to establish the clinical significance of occult metastases detection both in terms of treatment and prognosis.

1194 Mullerian Adenosarcomas With Rhabdomyoblastic Differentiation Are Associated With an Aggressive Clinical Course

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Background: Adenosarcomas (AS) are biphasic, low grade neoplasms. Morphologic criteria that are associated with more aggressive behavior in AS include underlying myometrial invasion and sarcomatous overgrowth (SO). Although rhabdomyoblastic differentiation (RD) is commonly seen in AS, its relationship to clinical outcome is unclear.
Design: The surgical pathology files of The Johns Hopkins Hospital were searched for cases of AS. The final cohort consisted of 52 cases that had previously been evaluated with a myogenin immunohistochemical stain (Cell Marque, Rocklin, CA). All slides were reviewed, and the diagnoses confirmed. RD was based on a combination of morphologic and immunohistochemical criteria (positive myogenin staining), in order to avoid misclassification of embryonal rhabdomyosarcoma. Myometrial invasion was assessed on hysterectomy or large resection specimens. Clinical outcome including disease recurrence and death were recorded. Fisher's Exact test was used for statistical analysis, with a p-value <0.05 considered significant.
Results: A total of 52 cases were retrieved. The mean patient age was 48.5 years (range 17-86). Primary sites included: uterine corpus (36), cervix/vagina (15) and ovary (1). 26 cases were classified as usual AS and 26 as AS with SO. RD was detected in 28 (54%) cases, including 18 (64%) with SO. Hysterectomy and staging procedures were performed on 33 of the 52 cases. Myoinvasion was identified in 20 (70%) cases. Both RD and SO were independently associated with invasion ($p=0.0013$ *and* $p=0.0377$, respectively). Metastasis at the time of surgery or disease recurrence occurred in 12 (36%) cases, but these were not associated with either RD or SO ($p=0.2728$, $p=0.1451$, respectively). Clinical follow up was available in 32 cases including 13 cases with RD (40%). The mean follow up was 47.6 months (range 2-144). 8 (25%) total patients were dead of disease, including 6 from the RD group. The 5-year overall survival for all patients with RD was 54% and all those without RD was 84% ($p=0.0382$). All patients who died had invasion and metastatic or recurrent disease.
Conclusions: Rhabdomyoblastic differentiation is frequently seen in AS, and can be identified morphologically and with immunohistochemical stains. This finding is significantly associated with underlying myoinvasion and overall survival was lower in this group. Additionally, our series confirm that myoinvasion and SO, are markers of poor prognosis in AS.

1195 The Risk Stratification By p16 Immunostaining of CIN1: A Report From the qHPV Vaccine Program

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Background: The risk of precancer/cancer (HSIL+) is the concept driving guidelines for cervical neoplasia management. Given a LSIL/CIN1 biopsy there is risk for missed/unsampled HSIL/CIN2/3. We here question whether a CIN1 biopsy stratified by p16 immunohistochemistry (IHC) better estimates HSIL+ risk. Specifically, does a p16+ CIN1 signify coexistent or impending CIN2/3? Conversely, does a p16- CIN1 suggest that HPV infection will likely resolve? Short of a new prospective clinical trial to define the natural history of CIN1, one of the only datasets that avoids the limitations of published studies is in the placebo arm of the quadrivalent HPV (qHPV) vaccine program.
Design: The placebo arm of the qHPV trial database was searched for adjudicated diagnoses of CIN1 with HPV typing, cytology history, and tissue outcome pathology. Tissue blocks were conservatively sectioned and the first two sections stained with p16 IHC and H&E. p16 was scored using LAST criteria and H&Es were reviewed for concordance with the adjudicated diagnosis. These data were independently analyzed for factors previously shown to correlate with precancerous outcomes including antecedent high-grade (HG) cytology and the presence of HPV16.
Results: There were 524 patient biopsies with complete data. Median follow-up was 239 days (range: 24-982). 63 (12%) of patients had a follow-up diagnosis of HSIL+. 247 (47%) were p16-positive, 85 (16%) were HPV16-positive, and 64 (12%) had an antecedent HG Pap. p16 positivity achieved marginal statistical significance (p=0.06) for predicting future HSIL+. In contrast, HPV16 and prior HG Pap were significant risk factors at p=0.01 and 0.02, respectively. The associations with CIN2/3 (vs. not), expressed as odds ratios (95% CI), were 1.6 (0.91-2.8) for p16, 2.0(1.0-3.7) for HPV16, and 2.2 (1.1-2.4) for prior HG Pap. Logistic regression demonstrated that the range of risk for ≥CIN2 ranged from 7.6% to 36.3% among women with CIN1 with the highest risk if the patient had a prior HG Pap & was HPV16 & p16-positive.
Conclusions: p16 IHC does not risk stratify CIN1 patients in a manner that would alter recommended management for CIN1. This reinforces the LAST recommendations that p16 should only be used selectively for problematic cases, such as CIN2 and mimics of CIN3. Among CIN1+ young women, HPV16 and antecedent HG cytology are more predictive of risk of HSIL+ than p16 IHC. This underscores that biomarker utility for management of CIN1 is fundamentally limited by sampling error.

1196 Discovery of Human Papillomavirus in Normal-Appearing Cervical Squamo-Columnar Junction Cells

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Background: Recent studies suggest that cancer of the cervix originates from a unique population of residual embryonic cells at the squamo-columnar junction (SCJ). Markers of SCJ cells (cytokeratin 7; CK7) highlight most pre-invasive lesions (SIL) and malignancies arising near the SCJ. Two important questions are whether SCJ cells are targeted by initial infection and if they could be a reservoir of histologically latent HPV. Thus we examined SCJ cells that were histologically normal for evidence of HPV infection.
Design: 15 LEEP specimens from women with a prior history of SIL but no evidence of low (LSIL) or high (HSIL) grade SIL in the LEEP specimen were selected. SCJ cells were identified based on morphology and CK7 immunohistochemistry. CK7+ SCJ cells were immunostained with p16 and Ki-67 to determine if a candidate p16+/Ki67+ sub-population was present. p16+ SCJ cells were then analyzed for HPV by in-situ hybridization (ISH) and laser capture micro-dissection (LCM) assisted PCR-based HPV genotyping. Internal controls included adjacent normal-appearing squamous and endocervical epithelia.
Results: 5/15 (33%) contained SCJ cells. Median age was 41 y (range 25-55 y). Prior diagnoses included 2 biopsy proven HSIL, 1 HSIL and adenocarcinoma in-situ , 1 LSIL and one case with LSIL cytology. In 4/5, the SCJ region was preserved in serial sections and contained discrete foci of p16+/Ki67+SCJ cells. These cells were positive for HPV by ISH. HPV genotyping and microdissection-mRNA amplification-PCR for HPV16 E6 and E7 confirmed the presence of HPV16 nucleic acids in these cells. Control tissues were negative for p16 and HPV.
Conclusions: This is the first study to demonstrate that histologically normal SCJ cells can contain carcinogenic HPV in the absence of a contiguous CIN. It suggests that SCJ cells can be infected by HPV and that this infection can precede the onset of neoplasia. If SCJ cells are a reservoir for HPV that would have profound implications for our understanding of latent cervical HPV infection. These findings further support the hypothesis that targeted ablation of the SCJ region would significantly reduce the risk of cervical neoplasia.

1197 Lipoblastoma-Like Tumor of the Vulva: Analysis of 7 New Cases

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Background: Lipoblastoma-like tumor of the vulva (LLTV) is an exceptionally rare adipocytic mesenchymal tumor with only three cases previously reported in 2002 by Lae and colleagues. The aim of this study is to examine additional cases so as to better characterize this tumor type.
Design: Seven cases of LLTV were identified in the consult files of one of the authors (CDMF). Clinical data and follow-up information were obtained from the referring pathologists. H&E slides were reviewed for all cases. PLAG-1 and Rb1 immunohistochemistry was evaluated in all tumors for which materials were available. DDIT3 FISH was performed for cases with myxoid liposarcoma in the differential diagnosis.
Results: Detailed clinical information is available in 6 cases so far. Patient age ranged from 17 to 46 years (median 27). Lesions presented as a vulvar mass with variable growth rate, sometimes painful. Pre-op diagnosis was Bartholin gland cyst (3), inguinal hernia (1), lipoma/cyst (1) and unknown (1). The size of the mass ranged from 3.5 cm to 15 cm (median 8.8). The lesions were described as grossly myxoid or gelatinous (3), well defined (4), and lobulated (3); None of the lesions exhibited necrosis.Histologically,

LLTV were lobulated and composed of variable proportions of mature adipocytes, bland lipoblasts, and spindle cells with short stubby nuclei in a diffusely myxoid background with prominent branching vessels. Nuclear atypia was minimal. No necrosis or mitotic activity was identified. Only 1 of 6 tumors (in a 26 year old patient) was positive for PLAG-1 and Rb1. Rb1 was lost and PLAG-1 was not expressed in all other tumors. Tumors were negative for S100 (4/4), CD34 (3/4), and MDM2 and CDK4 (4/5; one with scattered cell positive for both antibodies). DDIT3 FISH was negative in 2/2 cases. The follow-up interval ranged from 4 months to 6 years (median 4 years). Only one patient developed local recurrence, two years following the excision of the primary tumor. None of the patients developed metastatic disease.
Conclusions: LLTV are indolent adipocytic mesenchymal tumors arising in adults. Lack of PLAG-1 expression in the majority of LLTV suggests that these lesions are distinct from "true" lipoblastoma. The loss of Rb-1 in the majority of cases suggests a possible role of 13q chromosomal alterations and a possible relationship with the spindle cell lipoma tumor family.

1198 The Histologic Spectrum of Adolescent Endometriosis

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Background: Endometriosis (ENDO), most commonly biopsied in adults, has an elusive pathogenesis. Classic clinical and histologic definitions refer to the presence of endometrial glands and stroma. Adolescent ENDO, not previously well characterized histologically, may provide insight into the disease's early stages and origin.
Design: Prospective case accrual was via an IRB-approved protocol from December, 2012-December, 2013. All patients with laparascopically evident ENDO underwent biopsy. H&E-stained slides from those under age 21 yr were reviewed.
Results: 123 samples from 91 patients, ages 11-20 yr (mean and median, 16 yr), were included. Intraoperatively, biopsied lesions most commonly appeared red and polypoid or clear-to-white and filamentous, sometimes pale tan-yellow or brown and sessile, and least commonly blue or black. Microscopically, red and clear/white lesions frequently consisted of numerous small thin-walled vessels in a delicate mesenchyme with overlying variably hyperplastic mesothelium. The delicate mesenchyme frequently contained eosinophils and mast cells and formed a morphologic continuum with samples showing a less highly vascularized "pseudodecidualized" stroma. Other red and clear/white lesions and tan-yellow to brown lesions had a range of histologic features, including reactive/hyperplastic surface mesothelium with or without fibrosis, psammomatous calcification, hemosiderin, gland-like epithelium, and cellular inflammation. When present, glands showed cuboidal, columnar, and/or tubal differentiation, often with apical cytoplasmic "snouts", and sometimes with underlying pseudodecidualized stroma and/or smooth muscle coat.
Conclusions: Our study shows that a substantial subset of pediatric lesions clinically determined to represent ENDO lack classic microscopic features. This suggests that standard histologic definitions of ENDO fail to encompass the full spectrum of adolescent ENDO and furthermore may conceptually limit understanding of the disease's origin. Marked variation in "early" pathology may reflect different types of pathogenesis and/or different stages of disease evolution, or in some cases a disease that is something other than "ENDO." We cannot rule out a role for hypervascular stroma with primitive mesenchymal cells serving as a source or recruiter for stem-like cells with the potential to induce epithelial differentiation in some instances of ENDO.

1199 Radiation-Associated Mucosal and Stromal Atypia of the Fallopian Tube: Morphologic Features in 52 Patients, Emphasizing Distinction From Serous Tubal Intraepithelial Carcinoma

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Background: Radiation-induced atypia of normal epithelium and stroma that can mimic neoplasia is reported in many organs, including the cervix, however it has not been studied in the fallopian tubes. To prevent misinterpretation as serous tubal intraepithelial carcinoma (STIC), it would be valuable to understand the range of mucosal and stromal alterations in fallopian tubes from women who received radiation for abdomino-pelvic cancer prior to undergoing a surgery that includes salpingectomy.
Design: 52 patients with abdomino-pelvic radiation therapy for cancer of the endometrium (21), cervix (16), colon (11), or ovary(2), or uterine leiomyosarcoma (2) prior to salpingectomy were included. Fallopian tubes were examined for morphologic features of STIC and of radiation atypia: epithelial atypia (nucleocytomegaly, variable nuclear shape/size, nucleoli, smudged chromatin), multinucleation, degeneration, mucosal atrophy, stromal atypia (nuclear enlargement, irregular nuclear contours), stromal fibrosis, and mucosal or stromal inflammation.
Results: Mucosal atypia with (7) or without (9) underlying edematous/myxoid reactive stroma was present in 31% (16/52) of patients. Atypia was mild (12/16) or moderate (4/16); mostly unilateral (10/16) but often multifocal (12/16), spanning no more than a few dozen cells in length. Most cases did not exhibit mucosal tufting, budding, or stratification. Atypia involved non-fimbriated tube only (12/16) or fimbriae plus non-fimbriated tube (4/16). Micro-foci of submucosal edematous/myxoid reactive stroma were also present beneath non-atypical degenerating, attenuated or denuded mucosa in 5/52 patients. The reactive stroma often contained chronic inflammation and neovascularization and resembled desmoplastic stroma. Extensive mucosal denudation and stromal edema of the fimbriae was present in 29% (15/52). Stromal atypia was present in 1/52 but none exhibited abnormal blood vessels. None of the cases exhibited severe nuclear atypia, mitoses, hyperchromasia, or increased nucleus to cytoplasm (N/C) ratio.
Conclusions: Although mild to moderate mucosal atypia, often accompanied by submucosal reactive stroma, can be seen in fallopian tubes following radiation therapy, the absence of severe atypia, mitoses, and increased N/C ratio distinguishes this alteration from STIC. The presence of multifocal submucosal reactive stroma should not be interpreted as desmoplastic stroma but as an additional feature of radiation-induced alteration of fallopian tubes.

1200 Defining Staining Patterns of Mismatch Repair Immunohistochemistry in Gynecologic Malignancies

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Background: Technical performance of mismatch repair immunohistochemical markers specifically in gynecologic tumour is understudied. Anecdotally, it has been suggested that equivocal or inadequate staining patterns are more commonly observed than in colorectal tumours.
In the literature, six staining patterns with MMR-IHC have been identified as problematic.
focal staining of tumor with weakened intensity
focal staining of tumor with unimpaired intensity
lack of positive control in negative stained tumor
cytoplasmic staining
Unpaired loss- ie MLH1/MSH6 or MSH2/PMS2
Diffuse Tumor staining present but weakened intensity compared to normal tissue.
Design: We derived a set of endometrial and ovarian tumors (100) with mismatch repair immunohistochemistry, microsatellite status and germline data even when the IHC was intact. The IHC was reviewed by observers (gynecologic and gastrointestinal pathologists) blinded to MSI and germline status. The staining patterns were classified according to the 6 patterns listed above.
Results: The best internal control was lymphocytes and benign glands. Endometrial stroma often did not stain and myometrium was often weak in staining intensity. Cases also tended to show a specific heterogenous staining pattern with loss of staining of the basal aspect of the tumor. Pattern 1 was most often seen in MLH1 and this pattern may be associated with miscorsatellite instability but with none of the cases showed germline alteration. Pattern 2 was most often seen with MSH6 This pattern was MSS and showed no germline alteration. We identified 4 cases with pattern 3, 2 of which were tested and showed germline mutation. Cases with pattern 6 when observed were all MSS and germline intact. We identified 2 cases of endometrial cancer in which there were islands of loss of tumor staining with retained expression in lymphocytes and other tumor regions showing staining. This was different form pattern 2 which was more patchy loss. Both of these were unstable and showed germline mutation. One ovarian case was intact despite a strong family history and the patient was found to have a germline mutation.
Conclusions: There does appear to be more heterogeneity in staining of gynecologic cancers compared to gastrointestinal tumors. Regional as opposed to patchy loss of staining in tumor should be considered highly suspicious. Intact staining does not fully exclude Lynch syndrome.

1201 A Comprehensive Analysis of Placental Insufficiency in Late-Onset Small for Gestational Age Births

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Background: Late-Onset Small for Gestational Age (LO-SGA) fetuses do not show ultrasound features of placental insufficiency but latent placental insuficiency can contribute to pathogenesis and prognosis.
Design: A series of placentas were evaluated from singleton pregnancies of SGA births (birth weight below the 10th percentile) delivered after 34 weeks with normal umbilical artery Doppler (pulsatility index below the 95th percentile), that were matched by gestational age with adequate-for-gestational age (AGA) controls. Middle cerebral and uterine arteries, umbilical vein blood flow and Placental Growth Factor (PlGF) levels in maternal blood were evaluated. Placental lesions were classified histologically according to Redline's classification as maternal underperfusion, fetal underperfusion or inflammation. Perinatal morbidity and neurodevelopmental outcomes at 24 months (age-corrected, applying the Bayley Scale to assess cognitive, language, and motor competencies) were evaluated. Results were compared with placental underperfusion (PUP) signs.
Results: A total of 284 placentas were evaluated (142 SGA and 142 AGA). Placentas were smaller and had more lesions, mainly reflecting maternal underperfusion in the SGA group. Among LO-SGA babies, those with PUP had higher perinatal morbidity, more alterations in prenatal ultrasound parameters (high uterine and middle cerebral arteries pulsatility indexes and low umbilical vein blood flow normalized for expected fetal weight) and lower PlGF. Neurodevelopmental outcomes were also significantly poorer.
Conclusions: In a substantial fraction of near-term SGA babies without Doppler evidence of placental insufficiency, histologic changes consistent with PUP are identifiable and can be prenatally predicted by a combination of parameters (high uterine artery pulsatility index and low umbilical vein blood flow). These infants are at greater risk of perinatal morbidity and abnormal neurodevelopmental outcomes at 2 years of age.

1202 CA-125-Expression in Conjunction With High Numbers of Infiltrating T-Cells Is Associated With Improved Survival in High-Grade Serous Ovarian Carcinoma

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Background: CA-125 is a well-known tumor marker used for monitoring the response to therapy and tumor recurrence. Immunohistochemistry demonstrates CA-125 expression in over 95% of high-grade serous ovarian carcinomas. Recently, we have shown that CA-125 is a potential target of tumor-infiltrating T-lymphocytes (TILs) in HLA-ligandome analysis of ovarian cancer. The aim of the current study is to correlate the CA-125 expression pattern with overrepresentation in the HLA ligandome, TIL density and outcome.

Design: HLA ligandome analysis was performed for 52 cases of high-grade serous ovarian carcinoma, revealing CA-125 as a major candidate. For validation a tissue microarray was constructed from paraffin embedded tissue of the same cases. We used immunohistochemistry to analyse the expression of CA-125 and number of CD3-positive TILs. In a second, independent analysis of 143 cases with up to 120 months follow-up, the prognostic effect of TILs and CA-125 was evaluated with Kaplan-Meier analysis.

Results: In our first case series we found a positive correlation between strong and diffuse expression of CA-125 and high-level presence in the HLA ligandome. In the retrospective series we saw a strong and diffuse circumferential staining pattern of CA-125 in 43 of 134 cases (32.0%), a moderate and non-circumferential staining in 76 cases (56.7%). Only 15 of 134 cases (11.1%) were either CA-125 negative or weakly positive. Survival was significantly better for cases with expression of CA-125 and high vs. low levels of intraepithelial TILs (> 7 per HPF). The 5-year overall survival was 67% vs.28% (p= 0.033, log rank).

Conclusions: Our data suggest that CA-125 is an effective target for TILs and a good candidate for multipeptide vaccination of ovarian cancer, based on its robust expression and representation in the HLA-ligandome. The improved prognosis of patients with CA-125 expression and high numbers of TILs suggest a role of CA-125 derived epitopes in the anti-tumor response.

1203 Ovarian Teratomas Associated With Anti-NMDAR Encephalitis Are Distinguished By Hypercellular Glial Tissue Associated With Germinal Center Formation

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Background: Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a rare but severe paraneoplastic limbic encephalitis that is often associated with ovarian teratoma in young women. Two features are thought to be suggestive of such teratomas: lymphoid infiltrates involving neural elements and dysplastic neurons. This study compared inflammatory infiltrates (including the FOXP3+ regulatory T cell population), neural tissue sub-populations, and the degree of glial atypia in teratomas with and without anti-NMDAR encephalitis.

Design: Lymphoid and neural populations were evaluated in 9 ovarian teratomas in women with anti-NMDAR encephalitis (average patient age 22) and in 51 ovarian teratomas in women without encephalitis (average age 28). The topographic distribution (neural versus non-neural elements), quantity of lymphoid infiltrates and aggregates (with versus without germinal centers), and the morphology and density of the neural tissue components were compared..

Results: The presence of lymphoid aggregates with germinal centers involving neural elements was higher among teratomas with (8/9) versus without encephalitis (3/51). However, there was no difference in lymphoid infiltrates/aggregates lacking germinal centers, density of CD3+ lymphocytes within neural elements, or the presence of regulatory T cells. CD20+ B cells did not infiltrate the neural tissue in either case, and were more prominent in lymphocytic aggregates with germinal centers. Teratomas with encephalitis exhibited fewer mature neurons in glial tissue (p=0.02) and a significantly more hypercellular astrocytic population (p=0.01). Atypical astrocyte features including increased nuclear size, chromatin clearing, and nuclear contour wrinkling were characteristic for teratomas with encephalitis.

Conclusions: Loss of mature neurons and an atypical astrocytic glial population are distinguishing features of teratomas associated with encephalitis. The topographically adjacent finding of lymphoid aggregates with germinal centers suggests a possible immune-mediated mechanism of injury to neural tissues in the teratoma, which may give rise to a paraneoplastic process.

1204 Napsin A Has Utility in the Diagnosis of Clear Cell Carcinoma in the Ovary But May Be Less Valuable in the Endometrium

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Background: Clear cell carcinoma (CCC) in the female genital tract can be a challenging diagnosis, given the significant morphologic overlap with other high grade carcinomas, but the distinction has important prognostic and therapeutic implications. Recent reports suggest that napsin A may be a sensitive and specific marker for ovarian and uterine CCC. We evaluated the utility of napsin A alone and in combination with HNF-1B, another putative marker for CCC, in the diagnosis of gynecologic CCC.

Design: Five tissue microarrays (TMA) were constructed from 600+ endometrial and ovarian neoplasms. Two 1-2 mm cores were included from each case. Each TMA was stained for napsin A and HNF-1B. Napsin A was scored based on granular cytoplasmic staining and classified as positive based on at least 1-10% staining. HNF-1B was considered positive with greater than 10% staining (weak or strong). Dual positivity was also assessed.

Results:

	Clear Cell Carcinoma		High Grade Serous Carcinoma	
	Ovary	Endometrium	Ovary	Endometrium
Napsin A	72% (34/47)	0% (0/1)	1% (3/250)	26% (5/19)
HNF-1B	72% (34/47)	100% (1/1)	7% (17/250)	53% (10/19)

Interestingly, a significant proportion (about one-third) of mucinous ovarian neoplasms showed positive staining for napsin A in a dot-like perinuclear pattern. The 2 ovarian yolk sac tumors were negative for napsin A.

Conclusions: Napsin A staining is not unique to CCC in the female genital tract. Napsin A stained a significant number of uterine serous carcinomas which limits utility in the diagnosis of uterine CCC. However, napsin A is potentially valuable for the diagnosis of ovarian CCC, as staining for this marker was only present in a small percentage of ovarian high-grade serous carcinomas. Further study is warranted to investigate the full spectrum of napsin A staining in mullerian tumors with clear cytoplasm, especially given the rate of positivity in mucinous neoplasms.

1205 Mutational Profile of Undifferentiated Endometrial Carcinoma Suggests Its Origin From Endometrioid Carcinoma

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Background: Undifferentiated endometrial carcinomas (UEC) are very aggressive high-grade endometrial carcinomas, which are frequently under-recognized. UEC associated with well differentiated endometrioid carcinomas (EEC) are called dedifferentiated carcinoma. The question of whether UEC without a well differentiated component arise de novo or not has not been yet answered. In this study, we analyzed if the most common molecular alterations found in EEC are also present in UEC using a commercial NGS cancer-specific panel.

Design: DNA was extracted from 26 UEC FFPE samples and enriched using HaloPlex Cancer Research Panel kit. This panel contains 1205 hotspots in 199 regions from 47 cancer-related genes, including most of those frequently mutated in EEC, such as PTEN, PIK3CA, PIK3R1, CNNTB1 (β-catenin gene), KRAS, and TP53. Sequencing was performed on chips 316 with IonTorrent technology. A specific bioinformatics analysis pipeline was developed to accomplish accurate variant identification and annotation. Functional annotation of the variants was performed using human database release 74 from ensembl.

Results: Fourteen UECC (54%) carried at least one mutation typical of EEC and 40% of the tumors carried more than one of these mutations. The most frequently mutated genes were PIK3R1, PIK3CA and PTEN (37%, 37% and 26% of the cases, respectively). TP53 mutations were found in 7 cases (26%), but in 5 cases they were associated with other typical EEC mutations. Interestingly, CNNTB1 was mutated in only one case (5.26%).

Conclusions: Taking into account that the coverage of PTEN mutations in this panel is only 50% of those reported by the TCGA consortium and that we did not analyze ARID1A, a frequently mutated gene in EEC, our results suggested that most UEC developed from EEC. In some cases, TP53 mutations might participate in cancer progression.

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1206 Cytokeratin 7 Immunohistochemical Stain Pattern Does Not Correlate With Future Dysplasia When Applied To Adjudicated Low-Grade Cervix Biopsies

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Background: Recently several investigators have proposed using markers of cervical squamocolumnar junctional cells (SCJ) including cytokeratin 7 (CK7) to highlight two groups within the CIN1 category with different risks of progression to high-grade disease. Using CK7 we aim to investigate this hypothesis using a prospectively collected dataset with adjudicated diagnoses and approximately 5-years of follow-up. Additionally we aim to further examine CK7 stain patterns in all grades of dysplasia.

Design: 326 cervix biopsies were stained with CK7 (100 each of CIN1, CIN2, and CIN3, 25 benign, and one invasive carcinoma). Six cases were cut-through. Cases were independently reviewed for CK7 pattern by two pathologists with discrepancies resolved by consensus. Positive staining was defined as either full-thickness squamous epithelium stain or partial thickness stain with diffuse rather than patchy pattern. Clinical followup was by laboratory chart review of all further cervix pathology.

Results: High-grade cervical biopsies were more likely to be CK7 positive (CIN1 59% positive, CIN2 69%, and CIN3 81%). CK7 significantly correlated with tissue diagnosis when comparing CIN1 vs. CIN2/3 (p=0.005) but was not significant for CIN1 vs. CIN2 (p=0.155). When limited to CIN1 cases with clinical follow-up (n=70), there was no significant association between CK7 positivity and future CIN2+/HSIL (OR 0.443 [95% CI 0.11-1.7886]) see Table 1. In comparison, index biopsy diagnosis of ≥CIN2 by H&E morphology predicted future CIN2+/HSIL (OR 0.0684 [95% CI 0.0349-0.1342]).

Follow up Diagnosis	Index biopsy CK7 (-)	Index biopsy CK7 (+)	Total
≤CIN1	23	34	57
≥CIN2	3	10	13
Total	26	44	70

Conclusions: In this study we confirm that HSIL lesions are more likely CK7 positive compared to LSIL/CIN1. In a subset analysis of CIN1, there was no significant association between CK7 and outcome. These findings are contrary to those of other researchers who have used a panel of SCJ stains and found higher risk of disease progression in CK7 positive CIN1 cases compared to CK7 negative. As it is possible that the prior studies may have used CIN1 cohorts contaminated with CIN2 cases, further studies of CK7 should use only well-characterized consensus cases given the recognized inter-observer variability regarding these diagnoses. Further, the utility of a biomarker on a single cervix biopsy will always be limited by sampling error as a higher-grade lesion can be present but not biopsied.

1207 Morphologic Pattern of Myometrial Invasion and Cancer-Stem Cell Markers in Endometrial Endometrioid Adenocarcinoma

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Background: In endometrial endometrioid adenocarcinoma (EEC), depth of invasion (DOI) is of critical importance in determining management. Identification of several morphologic patterns of myometrial invasion (MI) is to help to assess for DOI, tumor spread and LVI. Cancer stem cells (CSCs) are related to resistance of conventional therapies in various malignancies and may play a critical role in cancer progression. We evaluated the association between patterns of MI and immunohistochemical (IHC) profiles of CSC, and its clinicopathological significance in EEC.

Design: In total, 73 cases of EEC with MI were included. For each case, all H&E slides were scrutinized for the pattern of MI referred description by Cole et al.: infiltrating; expansile; adenomyosis (AM)-like; microcystic, elongated and fragmented (MELF) pattern. Representative whole sections were immunostained with CD44, CD133, Nanog1, Sall4, ER, PR, p16, and p53. Clinicopathologic features included age, DOI, patterns of MI, LVI, margin, lymph node metastasis, adjuvant treatment, disease progression or survival outcome. During the follow-up, five patients experienced disease progressions (3 peritoneal recurrences and 2 lymph node metastases of neck), but all patients were alive.

Results: Stages were grouped: 45 cases (61.7%) in stage I (40 stage IA and 5 IB); 2 in stage II (2.7%); 25 (34.2%) in stage III (2 IIIA, 2 IIIB, and 21 IIIC); one (1.4%) in stage IVA. FIGO grade was 39 cases (53.4%) of grade 1, 20 (27.4%) of grade 2, and 14 (19.2%) of grade 3. DOI was divided into less than half (n=50, 68.5%) versus exceeding half (n=23, 31.5%). MI showed infiltrating (n=36, 49.3%), AM-like (n=19, 26.0%), MELF (n=11, 15.1%), and expansile pattern (n=7, 9.6%). LVI in 28 patients (38.4%) and LN involvement in 22 (30.1%) were identified. Tumors with infiltrating pattern was associated with high FIGO grade (p=0.002), loss of ER/PR (p=0.014/p=0.026), Nanog1 expression (p=0.009), and disease progression (p=0.019). Tumors with MELF pattern showed frequent LN metastasis (p<0.001), LVI (p=0.011), ER loss (p=0.036), expression of CD44 (p=0.006) and CD133 (p=0.016). EECs showing AM-like/expansile patterns had lower DOI, better FIGO grade, lower LN metastasis, preserved hormonal receptors, and no expression of CSC markers.

Conclusions: EECs with infiltrating/MELF pattern of MI were associated with worse prognostic factors (higher FIGO grade, LN metastasis, LVI), loss of ER/PR, and expression for CD44, CD133 and/or Nanog1. Therefore, expression of CSC profiles may be an unfavorable indicator of EEC.

1208 Incidental Nodal Lymphangioleiomyomatosis Is Not a Harbinger of Pulmonary Lymphangioleiomyomatosis: A Clinicopathologic Study of 17 Cases With Evaluation of Diagnostic Immunohistochemistry

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Background: Lymphangioleiomyomatosis (LAM) is a condition characterized by a proliferation of perivascular epithelioid cells typically affecting the lung, but may also be found in lymph nodes and other organs. Some investigators propose LAM is a low grade, destructive neoplasm capable of metastasis and death while others counter that it is an uncontrolled proliferation of cells best regarded as a disease than a tumor. Regardless, LAM is sometimes seen as an incidental finding in lymph nodes in surgical specimens, particularly those obtained for gynecologic indications. A large study of 22 patients (Matsui et al, Hum Pathol) found that extrapulmonary LAM preceded development of pulmonary LAM by 1-2 years; however, these lesions were often several centimeters in size. To the best of our knowledge, no study has investigated the clinical significance of incidental nodal LAM and whether it is a harbinger of pulmonary LAM.

Design: Cases were retrieved with keywords "LAM" and "lymph node." All slides were reviewed and affected lymph node sites, quantity and size were recorded. Immunohistochemical stains for HMB45, melanA/A103 and beta-catenin were performed. Detailed clinical history and follow up were obtained for every case.

Results: All patients were women whose age ranged 35-71 years (median 59). None had a history of tuberous sclerosis. Sixteen of 17 cases were incidental findings from surgery related to gynecologic neoplasms. The remaining case was for management of only nodal LAM. Affected lymph nodes ranged 1 to 6 representing 2% to 100% of all sampled lymph nodes (total nodes sampled ranged 3 to 52). Mean size was 1 mm up to 22 mm (overall mean 4.6, median 3). Lymph node sites affected were regional abdominopelvic chains routinely sampled in staging operations. HMB45 showed strong, but variable staining, melanA/A103 was very focally expressed or negative whereas beta-catenin showed strong, diffuse cytoplasmic reactivity in every case. Follow up ranged 3 to 123 months (mean 38, median 29). No patient with incidental nodal LAM recurred or developed pulmonary LAM. The one patient treated for nodal LAM of 22 mm in size had local recurrence in her regional lymph nodes.

Conclusions: Incidental nodal LAM is not a precursor to development of pulmonary LAM. Nodal LAM of larger size (>20 mm) may show local recurrence. Cytoplasmic beta-catenin expression is a more reliable diagnostic marker than HMB45 or melanA/A103.

1209 Chorionic Villi Intrusion into Myometrial Lymphovascular Spaces and Deep Trophoblast Infiltration Are Common and Specific Findings in Placenta Creta: A Histopathologic Review of 56 Cases

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Background: Placenta creta (PC) is characterized by invasion of placental villi into the myometrium in the setting of a dysfunctional or absent decidua. Diagnosis of PC and its subclassification as placenta accreta (PA), increta (PI) and percreta (PP) is important, particularly in cases of hysterectomy due to unanticipated intractable postpartum hemorrhage. Previous studies have documented a significant increase in the amount of implantation site intermediate trophoblast (ISIT) and greater depth of ISIT extension into the myometrium. In addition, we have anecdotally observed chorionic villi in myometrial lymphovascular spaces in cases of PC. The aim of this study was to explore the prevalence and specificity of these features.

Design: 56 postpartum hysterectomies, 39 with PC and 17 without were reviewed. PC cases were designated as PA, PI and PP. Villous intrusion into lymphovascular spaces was recorded. Using immunohistochemistry for GATA3, the amount of ISIT (number of positive cells in 5 40X fields) and depth of myometrial infiltration by ISIT (% of myometrial wall thickness and distance of ISIT to closest serosal surface) were assessed.

Results: Median gestational ages of the PC group (34.6 weeks, range 19-39) and control group (36.4 weeks, range 17-42) were comparable. Presence of chorionic villi in myometrial lymphovascular spaces was frequent in PC: 23/39 vs 1/17 controls (52.6 vs 5.8%, p=0.0003). This finding was more common in PP (67%) and PI (74%) than in PA (20%, p=0.007). Mean total ISIT number per 5 HPFs was greater in PC (634) than in controls (371, p=0.006). Mean depth of ISIT myometrial invasion was greater in PC (49.1 %) than in controls (13.4%, p=0.002). Likewise, mean distance of deepest ISIT to serosa was shorter in PC (6.3mm) than in controls (21.4mm, p<0.0001). A myometrial depth ³25% was seen in 77.2% PC cases and none of the controls. ISIT distance to serosa £15 mm was seen in 86.3% PC and only 11% controls.

Conclusions: For the first time, we document the finding of chorionic villi intrusion into myometrial lymphovascular spaces, which is highly specific to PC and particularly common in PI and PP. In addition, assessment of ISIT amount and depth of myometrial invasion using GATA3 immunohistochemistry can assist in the diagnosis of PC. We hypothesize that placental invasion in PC is due, at least partially, to ISIT transformation of low resistance myometrial vessels leading to subsequent protrusion of villi into their lumens, in the context of absent decidua.

1210 Tumor Infiltrating Lymphocytes (TILs) as a Function of Histological Subtype and Genetic Background of Ovarian Epithelial Carcinomas

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Background: Ovarian epithelial carcinoma (OEC) comprises a large family of tumors with distinct clinicopathological, morphological, immunohistochemical, molecular, and genetic subtypes. Studies suggest that immune response and the presence of tumor infiltrating lymphocytes (TILs) are associated with longer disease free progression and survival. Furthermore, the presence of TILs can be correlated with the genetic background of the carcinoma, e.g. loss of BRCA1 or mismatch repair (MMR) gene expression. In this study, we sought to comprehensively examine a large set of various OECs for the presence of TILs as well as to determine any association with BRCA germline mutation status and loss of mismatch repair (MMR) protein expression.

Design: Formalin-fixed paraffin embedded tissues (n=678) from a wide variety of OECs were obtained as part of population-based familial ovarian cancer study. Known BRCA mutation carriers (n=65) and a control group of HGSC cases with negative family history and germline testing (n=54) were included in this study. Using automated image analysis and manual scoring of tissue microarrays, the number of CD3+, CD8+, Foxp3+, CD68+ cells were enumerated. MMR protein status was determined by manual scoring of MLH1, PMS2, MSH2, and MSH6 immunohistochemistry. Statistical analysis was performed using ANOVA (p<0.05) and Fisher's Exact Test p<0.05).

Results: The frequency of CD3+ and FoxP+ TILS did not statistically differ between different subtypes of OEC (p=0.66 to p=0.85). Morphologically, increased number of TILs was associated with loss of MMR protein expression in endometrioid OEC (p<0.02) as well as BRCA+ high grade serous carcinoma (HGSC) (p<0.005). Loss of MMR protein expression was found to be more frequent in endometrioid OEC and intact in all serous and mucinous borderline tumors. CD68+ macrophages were found more frequently in BRCA+ HGSC (p<0.045).

Conclusions: The frequency of TILS and CD68+ macrophages varies amongst different morphological subtypes of OEC and genetic background. This data may provide further insight into the interplay of morphological features, immune response, and genetic factors in determining clinical behavior and patient outcome.

1211 Unusual Variants of Invasive Squamous Cell Carcinoma of the Uterine Cervix

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Background: Squamous cell carcinoma it is the most common invasive neoplasia of the uterine cervix. They typically have nests, cords, or tongues of irregular borders, anastomosed with stromal reaction or even diffuse cell sheets. The cells show well-defined borders with or without keratin. The morphologic spectrum of these tumors and their variants such as condylomatous, lymphoepithelioma like, squamous transitional, sarcomatoid, verrucopapillary, ISCC with columnar differentiation and basaloid have been described, however, can be quite variable.

Design: All cases of invasive squamous cell carcinoma of the uterine cervix accessioned in the surgical pathology files at Instituto Nacional de Cancerologia treated with radical hysterectomy during the period from 2005 to the year 2013 were reviewed. Immunohistochemical stains for P63, P16 and CK5/6 were performed in all cases to confirm the diagnosis. Twenty-seven cases showed unusual cytological features or patterns of growth that could lead to misdiagnosis.

Results: During 8-year study period, 96 cases of primary invasive squamous cell carcinoma of uterine cervix were available for review. Twenty-seven cases showed unusual cytological features or patterns of growth that could lead to misdiagnosis. These unusual features included adenoid growth pattern (4), CIN 3 like growth pattern (4), insular (2), micropapillary pattern (1), lace pattern (3), paraganglioma like pattern (1), microcystic pattern (1), pilomatrixoma like pattern (3), acantholytic pattern (3). Unusual cytological features included tumors with clear cells (4), sebaceous like carcinoma (1). In several instances, these unusual morphologic features were initially suggestive of alternative possibilities in the differential diagnosis, including non-invasive lesions, immature metaplasia, adenocarcinoma, neuroendocrine carcinoma or metastatic lesions.

Conclusions: Unusual histologic patterns can be identified in up to 28% of invasive cervical neoplasms, therefore, it is important to distinguish these unusual morphologic variants of squamous cell carcinoma of the uterine cervix to avoid misdiagnosis that could lead to change the treatment and prognosis of patients.

1212 Clinicopathologic Analysis of Verruciform Proliferations of the External Genitalia and Perineum, Including So-Called "Giant Condyloma"

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Background: Verrucous and verrucopapillary lesions of the external genitalia and perineum comprise a spectrum whichis diagnostically challenging. These lesions are problematic because large condylomas can clinically mimic malignancy, and conversely, non-HPV related verruciform lesions can be bland yet have been associated with squamous cell carcinoma (SCC). Moreover, these two categories are often confused with one another. Our goal was to review a series of cases diagnosed as such and to identify parameters useful in their separation.

Design: Search of our database between the years of 2005-2014 for the keywords "giant condyloma" (GC) "verruciform", "verrucous", "verruco-papillary" and "verruciform LSC". All cases were reviewed and clinical followup was obtained. HPV analysis status was noted.

Results: 36 specimens (diagnostic or follow-up biopsies and/or partial/radical resections) from 22 patients were identified. Data with regard to recurrence or development of carcinoma was available in 15/22 (77%). HPV genotyping was available in four cases.

6 patients had GC. Mean age was 55 (median 60) yrs. The histologic features were marked verrucopapillary architecture, mild basal atypia, and minimal encroachment of stroma; of note, viral cytopathic effect was often absent and effacement of the epithelial-stromal interface with inflammation could be seen, and mimicked invasion. Low risk HPV was detected in 3 and absent in 1. Lesions from 2 elderly patients recurred; no subsequent carcinoma was documented.

16 patients had other types of verruciform proliferations, which included verruciform dVIN, verruciform LSC, verrucous hyperplasia and verrucous acanthosis with altered differentiation. Mean age was 71 (median 77) yrs. Despite the absence of atypia (VIN) in many, 10 (62.5%) had verrucous carcinoma or invasive SCC that preceded (by clinical report), coexisted or followed the diagnostic biopsy. HPV testing was negative in 2/2 patients.

Conclusions: GC and verruciform proliferations are distinct clinicopathologic entities that often occur in elderly patients and may be confused with one another, as either may lack basal atypia or cytopathic effect. A key distinguishing feature is a more verruciform as opposed to condylomatous growth pattern and abnormal keratinocyte maturation, if present, in the latter. Complete excision of lesions and close followup is advised in the latter as these lesions have a higher rate of associated malignancy. Condylomatous lesions also bear close followup due to the risk of recurrence.

1213 The Variable Spectrum of Tubal Intraepithelial Neoplasia in Women With High Grade Serous Carcinoma

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Background: The distal fallopian tube has emerged as an important pathogenic site for high grade serous carcinoma (HGSC), both in patients with and without genetic risk factors. Serous tubal intraepithelial carcinoma (STIC) is detected in 5% to 10% of women undergoing risk-reducing salpingo-oophorectomy for mutations in the *BRCA1* or *BRCA2* genes, and in 20-60% of consecutively examined HGSCs. There is a presumed carcinogenic sequence in the tube, ranging from the p53 signature to low (STIL) and high (STIC) grade tubal intraepithelial neoplasia (TIN). However, the frequency with which this sequence can be visualized in cases of HGSC is not clear.

Design: We searched our surgical pathology files for STICs diagnosed in a two-year period (2012-2014). The slides were reviewed by two pathologists (CC and AP) to evaluate the presence or absence of associated lower grade (TIL) lesions. These were defined as cytologic atypia in the tubal epithelium but with preserved cell polarity, lack of stratified growth and absence of cell exfoliation.

Results: A total of 36 cases were retrieved. Nearly one-half (47%) had a spectrum of epithelial atypia in keeping with a gradient of progression from low to high grade TIN. Four (11%) had foci of epithelial changes that would be reclassified as low grade TIN only (they did not fulfill criteria for classic STIC). Fifteen (42%) cases demonstrated the presence of STIC but no other lower grade lesions. The mean age of patients with pure STIC was 64, while the mean age of women with STICs and/or lower grade lesions was 58 ($p = 0.11$).

Conclusions: This study shows that tubal intraepithelial neoplasia in women with HGSC is a heterogeneous entity and implies that transit times from normal to malignancy could vary considerably across this spectrum. The two groups trend toward different mean ages, and these differences in STIC presentation could reflect different patterns of HGSC evolution.

1214 EWS16T Is a Useful Marker for the Detection of Microsatellite Instability in Endometrial Cancer

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Background: Microsatellite instability (MSI), the genome-wide accumulation of DNA replication errors, is the hallmark lesion of DNA mismatch repair (MMR)-deficient cancers. Identification of patients with MMR-deficiency is important given their personal and family risk for synchronous and metachronous tumors, in particular colorectal and endometrial carcinomas (EC). Recently, a new MSI target locus consisting of a mononucleotide (T) 16 tract located in the 3' untranslated region of the Ewing Sarcoma Break Point Region 1 (*EWSR1*) gene, named EWS16T, was identified as a sensitive and specific marker for MMR-deficiency in colorectal carcinoma patients. The current 'gold standard' for the detection of MMR deficiency in EC patients is immunohistochemical (IHC) analysis of the MMR proteins. We sought to benchmark ESW16T as a marker of MMR-deficient ECs through the analysis of EC cell lines with known MMR status, and to define the accuracy of this marker for the identification of MMR-deficient primary ECs.

Design: Twenty-five EC cell lines and 49 primary ECs, retrieved from the authors' institution, were subjected to IHC assessment of MMR protein status by two pathologists. DNA samples extracted from EC cell lines and microdissected primary ECs were PCR amplified using FAM-labeled primer pairs for the EWS16T locus and subjected to fragment analysis. Results were analyzed using Gene Mapper 4.0.

Results: Assessment of EWS16T tract length revealed that all MMR-deficient EC cell lines defined by IHC also displayed novel alleles in EWS16T poly-T tract (15/15), while of those classified as MMR-proficient only 3 showed instability (3/10), equating to an accuracy of 88%. In a cohort of 49 primary ECs, 29/35 MMR-deficient but 0/14 MMR-proficient cancers showed EWS16T tract instability, demonstrating an accuracy of 87.8%. Taken together, the analysis of the EWS16T tract in EC cell lines and primary ECs showed a sensitivity, specificity, positive predictive value and negative predictive value of 88%, 87.5%, 93.6% and 77.8%, respectively.

Conclusions: The EWS16T locus represents a novel, quasi-monomorphic MSI target locus that identifies MMR-deficient ECs with high sensitivity and specificity.

1215 Endometrial Neuroendocrine Carcinoma: A Clinicopathologic Study of 24 Cases

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Background: Neuroendocrine carcinoma (NECa) is an uncommon histologic subtype of endometrial (EM) carcinoma. Due to its rarity, reports of EM NECa have been limited to small case series of up to 16 patients. In this study we present the clinicopathologic features and behavior of 24 cases of EM NECa, the largest case series to date.

Design: 24 cases of EM NECa from 1999-2013 were retrieved. Clinical information was obtained from patients' (pts) charts or the treating phyisicians. The following parameters were recorded: age, clinical presentation, FIGO stage, treatment (tx), and follow up (f/up). In all cases, available slides were re-reviewed. The following parameters were recorded: morphologic features, lymph-vascular space invasion (LVSI), necrosis, mitotic rate, and immunohistochemical stain results.

Results: The pts' age ranged from 37 to 86yrs (mean, 61). Clinical presentations included vaginal bleeding, abnormal Pap smear, and symptoms related to metastases. Microscopically, the NE component showed large cell morphology (14), small cell morphology (4), or both (6). 9 tumors had pure NE morphology, while 15 tumors also had one or more other histotypes (14 endometrioid, 1 serous, 1 clear cell, and 1 undifferentiated). LVSI was present in 22 cases, and zonal necrosis in 20. Mitotic figures ranged from 17 to 128 per 10 HPFs (mean, 45). All tumors were positive for at least one NE marker (chromogranin, synaptophysin, CD56) with percentage of positive cells ranging from 10-100%. 13 of 16 cases were cyokeratin positive. Initial diagnoses included grade 3 endometrioid adenocarcinoma (6), undifferentiated carcinoma (5), carcinosarcoma (1), and PNET (1). All pts underwent hysterectomy and bilateral salpingo-oophorectomy. FIGO stage at diagnosis was IA in 3 cases, IB (3), II (2), IIIA (4), IIIB (4), IIIC (3), and IV (5). Tx and f/up information was available for 19 pts. 17 pts received adjuvant chemotherapy and/or radiation therapy. 11 pts died of disease (58%), with a mean survival of 14mos. 1 pt was alive with disease (5%), with

a f/up interval of 12mos. 7 pts were disease free (37%), with a f/up interval of 18mos to 11yrs. 2 patients had recurrences at 6mos and 2yrs, but responded to therapy and were disease free at last f/up.
Conclusions: EM NECa is a rare disease which affects patients with a wide age range. Most cases are large cell type, and mixed with an endometrioid adenocarcinoma. While EM NECa is an aggressive disease, a third of the patients had long term survival (mean 6.5yrs). There were no morphologic features or clinical parameters such as disease stage or treatment that predicted outcome.

1216 Characterization of Tumor Associated Macrophages in Endometrioid Endometrial Cancer

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Background: Stromal reaction seems to play an important role in the progression of endometrioid endometrial carcinomas (EEC). Tumor-associated macrophages (TAMs) are M2-like macrophages that can stimulate tumor progression. Their presence is associated with myometrial invasion but their phenotype is not well defined. Discovery of good markers for M2-like macrophage subsets could help in the diagnosis and prognosis of EEC.
Design: We collected peripheral blood samples from patients with EEC and healthy donors. Cell immunostaining with TAMs markers was conducted and data were acquired using a MacsQuant cytometer. Following EEC patient hysterectomy, tumor and their benign counterpart tissue was harvested. TAMs markers analysis on digested tissues was performed by flow cytometry. Phenotype comparison of healthy donor *versus* patient monocytes, and non-tumor *versus* tumor tissue macrophages was performed by MacsQuantify software.
Results: *Characterization of monocyte population on peripheral blood samples of EEC patients and healthy donors.*
In EEC patients, there is a significant increase in alternative monocyte population (p=0.0470). The expression of the integrin CD11b in classical monocytes of patients is significantly higher than that of healthy donors (p=0.0145).
Characterization of macrophage population on paired tissue samples from EEC patients.
The amount of T lymphocytes varies greatly in tumor stroma. There are two subgroups of patients in relation with the T helper cell population (CD4+). While some cases have similar number of T helper cells in both, the non-tumor and tumor stroma, others have higher percentages. There is a greater population of CD14+ cells in tumor stroma compared with non-tumor. The expression of some molecules related with M2-like polarization (CX3CR1, CD206) varies between non-tumor and tumor stroma macrophages.
Conclusions: T lymphocytes populations are similar in the peripheral blood of EEC patients and healthy donors. EEC patients have a greater number of alternative monocytes in peripheral blood. CD11b expression in classical monocytes is greater in EC patients than in healthy donors. T lymphocytes infiltration is increased in the tumor stroma. The expression of some M2-like markers (CX3CR1, CD206) differs between non-tumor and tumor stroma.

1217 Cervical Cytology Results Among Women Subsequently Diagnosed With Endometrial Cancer

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Background: With the recent FDA-approval of HPV primary cervical cancer screening for use in the US, concern has been raised that eliminating cervical cytology would have a deleterious impact on the detection of endometrial cancer in older women.
Design: The hospital records of 710 women with endometrial cancers diagnosed at our institution between 2002 and 2013 were reviewed. Extracted data included prior cytological screening results, histological type and grade, and FIGO stage at the time of hysterectomy.
Results: A total of 710 women with endometrial cancer were diagnosed during this time frame and of these, 392 (55%) had a prior satisfactory for evaluation cervical cytology result within 0.5 – 241 months of their diagnosis. 71 (18.1%) of the 392 prior cervical cytology specimens had a cytological abnormality that would have resulted in the evaluation of the patient. This includes 23 cases diagnosed as malignant, 34 as atypical glandular cells, 7 as endometrial cells in a woman >40 years, and 7 as squamous abnormalities greater than atypical squamous cells of undetermined significance. Among women with prior abnormal cytology, 21 (29.6%) had either uterine serous carcinoma (USC) or clear cell carcinoma (CCCA). For comparison, among 321 women with a prior negative or ASCUS cytology, 32 (9.9%) had USC/CCCA. Overall, a prior abnormal cytology was found in 23 (41.8%) of 55 women with USC/CCCA compared to only 42 (12.8%) of the 328 women with endometrioid adenocarcinomas. Among women with a prior abnormal cytology who underwent a hysterectomy and staging, 63.3% were FIGO Stage I, 55.0% were histological grade 3, and 13.3% had nodal involvement. Among women with a negative prior cytology, 81.8% were FIGO Stage I, 21.2% were histological grade 3, and 4.5% had nodal involvement. However, when restricted to women with endometrioid histology, there was little difference between women with and without abnormal cervical cytology with respect to tumor grade and nodal status.
Conclusions: Abnormal cervical cytology is an uncommon finding in endometrial cancer and when it does occur it is associated with poor prognostic features including USC/CCCA and higher FIGO stage in women with endometrioid carcinomas. Therefore, the omission of cervical cytology with HPV primary screening is unlikely to have an adverse impact on the detection of endometrial cancer.

1218 Recurrent Ovarian Mucinous Neoplasms With Expansile Invasion and Intraepithelial Carcinoma – Are There Any Predictive Morphologic Features?

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Background: Most ovarian mucinous borderline tumors (OMBT) reportedly have a "benign" behavior, even when associated with intraepithelial carcinoma (IEC) or expansile invasion (EI). The former is characterized by marked cytologic atypia confined to the epithelium and the latter by confluent gland pattern measuring >5mm, without evidence of infiltrative invasion. In our experience both patterns of OMBT can be associated with recurrence, albeit rare, and the clinical course is variable. We performed a review of these tumors with attention to identifying any morphologic features that may predict behavior.
Design: 37 cases of OMBT with IEC or EI that had slides and follow-up were retrieved (1987-2011). The parameters evaluated were-age, tumor size, laterality, type of OMBT (i.e. intestinal vs. endocervical), presence of microinvasion (MI), microinvasive carcinoma (MiCA), pseudomyxoma ovarii, pseudomyxoma peritonei, extraovarian disease, treatment, and follow up.
Results: Patients' age ranged from 16-86 yrs (mean-47.3). Tumor size ranged from 3.5 cm to 35 cm. Laterality: 21 right and 16 left. 34 were intestinal and 3 endocervical. The cases were composed of 11 OMBT with IEC and 26 OMBT with EI, and of these 14 had associated IEC. Two cases were associated with a mature cystic teratoma. 1 case had pseudomyxoma ovarii but none had pseudomyxoma peritonei at presentation. 7 cases had MI, of which 4 were associated with OMBT IEC, and 3 with OMBT EI. 4 cases of OMBT EI had MiCA. 9 patients received chemotherapy. Follow up ranged from 24-305 mos with a mean of 47 mos. 27 of 37 (73%) patients were alive with no evidence of disease (ANED), 4 (11%) died of disease (DOD), 5 (13%) died of other causes and 1 died of unknown causes (3%). Of the 4 patients who DOD, 3 had OMBT EI with moderate to severe nuclear atypia (2 also had MIC) and 1 had OMBT IEC. None of the patients who DOD had known extraovarian disease at presentation. 3 of 4 patients who DOD recurred within 2 yrs and 1 recurred after 5 yrs.
Conclusions: Most patients (73%) with OMBT with IEC or EI showed no recurrent disease. However, a subset of patients recurred and DOD (11%). Recurrences occured within 2 yrs in 3 of 4 patients. The histologic features associated with recurrence include moderate to severe nuclear atypia in the EI component, and MiICA. Though our case numbers are limited, the presence of moderate to severe atypia in OMBT may warrant a diagnosis of moderately differentiated mucinous carcinoma.

1219 Undifferentiated Carcinoma of the Endometrium – A Review of the Morphologic Spectrum and Variants in 50 Well-Characterized Cases

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Background: Endometrial undifferentiated carcinoma (UCA) is an aggressive, under recognized neoplasm that can be misdiagnosed as endometrioid adenocarcinoma (EC), FIGO grade 3, carcinosarcoma (CS), serous or neuroendocrine carcinoma. UCA can occur in the pure form or with EC, i.e. de-differentiation (DDC). Misdiagnosis particularly in the latter scenario is clinically significant as UCA, regardless of the extent, confers a much worse prognosis. The reason for under recognition of UCA is lack of familiarity with its morphologic spectrum. While some morphologic features have been previously reported, focused analysis of the various patterns of UCA is lacking. Typically UCA is composed of solid sheets of monotonous cells with lack of glands, frequent mitoses and necrosis. In our review of the largest cohort (50 cases) of endometrial UCA we recognized other morphologic features not yet described.
Design: 50 cases of endometrial UCA/recurrent tumors were retrieved from our pathology files (1988-present) and H&E slides reviewed on all cases. Parameters evaluated included subtype of UCA i.e. pure UCA vs. DDC, type of tumor associated with DDC, presence of UCA in extrauterine sites, morphologic features and clinical follow-up.
Results: 15 pure UCA and 35 DDC were identified. Of 50 cases, UCA was present only in the primary tumor in 12 (24%), in primary and metastases/recurrence in 25 (50%), only in the recurrence in 2 (4%) and was not known in 11 (22%). On histologic review 42 of 50 (84%) cases showed discohesive cells, 33 (66%) geographic necrosis, 14 (28%) rhabdoid morphology, 11 (22%) corded pattern (resembling sex cord tumors or lobular carcinoma), 10 (20%) nested pattern, 8 (16%) myxoid stroma, 7 (14%) spindle (with transition to UCA), 6 (12%) clear cytoplasm, 4 (8%) bizarre atypia, 1 (2%) case each of signet ring, marked acute inflammation, and adenoid cystic like (ACA). Follow up was available in 45 cases. 22/45 (49%) patients died of disease, and of these 17 died within 12 months (77%) of diagnosis. There was no correlation between morphology and overall survival.
Conclusions: The most common features of UCA include discohesive cells, geographic necrosis and rhabdoid pattern. Nested, myxoid, signet ring, clear cell and ACA patterns though less common should be included in the morphologic spectrum of UCA. UCA with spindle pattern can be mistaken for CS, but transition with UCA component should alert the pathologist to this variant pattern. We found that more than 75% of patients died of disease within a year of diagnosis, and late recurrences were uncommon (14%).

1220 Morphologic and Molecular Evaluation of Extra-Uterine Mullerian Carcinoma

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Background: Pelvic high grade serous carcinoma (HGSC) can display a variety of morphologic patterns that may correlate with biologic behavior. Tumors with papillary, micropapillary, and infiltrative architecture ("classic") differ from solid, pseudoEndometrioid, and Transitional ("SET") growth patterns; the latter associated with *BRCA* mutation, lower frequency of tubal intraepithelial carcinoma and younger age. Here we characterize the molecular alterations in extra-uterine HGSC and other Mullerian carcinomas, with particular attention to classic vs SET HGSC.

Design: DNA was isolated from 146 carcinomas of the fallopian tube, ovary, or peritoneum containing ³20% tumor. Targeted next generation sequencing (NGS) of the exonic DNA sequences of 275 cancer genes was performed on an Illumina HiSeq 2500 sequencer. Single nucleotide variants (SNV) identified were correlated with morphologic subtype of carcinoma.

Results: Morphologically tumors were classified as HGSC (109; 75%), endometrioid carcinoma (11; 8%), clear cell carcinoma (9; 6%), low grade serous carcinoma (5; 3%), mucinous adenocarcinoma (5; 3%), mixed Mullerian carcinoma (4; 3%), carcinosarcoma (2), and undifferentiated carcinoma (1). The majority of HGSC exhibited classic morphology (74, 68%), and a subset displayed SET features (12, 11%), while the remaining had mixed classic and SET morphology (23, 21%). Table 1 highlights SNVs identified by histologic subtype with *TP53* mutations occurring predominantly in HGSC, *ARID1A* and *PIK3CA* in both clear cell and endometrioid carcinomas, and *PTEN* and *CTNNB1* predominantly in endometrioid carcinomas. SET HGSC were more likely to harbor *BRCA1* mutations (58%) than classic HGSC (19%) (*p=0.007). No other significant differences in the mutational profiles between SET HGSC and classic HGSC were present.

	HGSC (%)			Clear Cell (%)	Endometrioid (%)
	All n=109	Classic n=74	SET n=12	n=9	n=11
TP53	91	91	92	11	0
ARID1A	8	7	25	67	64
PIK3CA	5	7	0	67	55
PTEN	4	3	0	0	45
CTNNB1	1	1	0	11	45
BRCA1	29	19*	58*	0	9
BRCA2	14	14	17	22	0
ATM	10	9	8	22	9

Conclusions: In this cohort of HGSCs, NGS confirms a powerful association between SET morphology and *BRCA1* mutations with 67% of SET tumors containing a mutation in either *BRCA1* or *BRCA2*. This underscores the importance of non-classic histology in HGSC and begs the question of whether SET histology reflects a unique target cell susceptibility or differentiation pathway in this population that is not reflected in the other molecular variables.

1221 FOXM1 Immunoexpression in Ovarian Carcinomas

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Background: Ovarian carcinoma is the most lethal gynecologic malignancy, accounting for about three percent of all cancers in women. Forkhead Box M1 (FOXM1) is a member of the Forkhead family of transcription factors and it is aberrantly overexpressed in many human cancers, including the malignant tumors of the ovary. FOXM1 protein has been identified as an indirect target of several widely used cancer drugs. Several *in vitro* and *in vivo* studies have demonstrated that FOXM1 expression levels in ovarian cancer cells increase with tumor grade, although no studies were performed in other histotypes beside high grade serous carcinoma. The purpose of this study was to evaluate FOXM1 immunoexpression in different histological types of epithelial ovarian cancer and to correlate it with clinical data.

Design: Immunohistochemical analysis for FOXM1 was performed in a total of 110 ovarian tissue specimens, and clinical data of all cases retrieved. We have evaluated nuclear expression of FOXM1 in 19 cystadenomas (cAd), 25 serous borderline tumors (SBT), 3 low grade serous carcinomas (LGSC), 49 high grade serous carcinomas (HGSC) and 14 clear cell carcinomas (CCC), using TMAs. Tests for association between immunohistochemical expression and clinical features were computed using Fisher's exact test.

Results: Expression of FOXM1 was observed in 12 cystadenomas, 23 SBT, 3 LGSC, 29 HGSC and 2 CCC.

FOXM1 Nuclear Immunoexpression	cAd	SBT	LGSC	HGSC	CCC
	n (%)	n (%)	n (%)	n (%)	n (%)
Positive	12 (63)	23 (92)	3 (100)	29 (59)	2 (14)
Negative	7 (37)	2 (8)	0 (0)	20 (41)	12 (86)
Total	19	25	3	49	14

A statistically significant difference regarding FOXM1 expression was detected among all tumor types, namely HGSC from CCC (p=0.0052), SBT and LGSC from CCC (p=0.0001), SBT and LGSC from HGSC (p=0.0015) as well as all serous types of tumors from clear cell carcinomas (p=0.001).

Clinical pathological data (stage and survival) showed no association with FOXM1 immunoexpression.

Conclusions: In our cohort, FOXM1 expression is not correlated with clinical findings. FOXM1 protein expression is associated with serous type but not with clear cell type ovarian tumors (p=0.001). This finding may have important implications in addressing new therapeutical management.

Regarding serous ovarian tumors, FOXM1 protein is present in all lesions of type I tumors, suggesting a role in serous low grade carcinogenic pathway.

1222 Vascular invasion in Uterine Sarcomas. Is It Always Real? A Multi-Institutional Study

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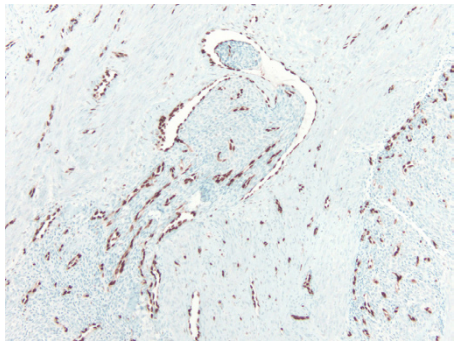
Background: Vascular invasion (VI) is common in both low and high grade uterine sarcomas. Although blood borne metastases are frequent in high grade sarcomas, they are rarely seen in low grade sarcomas, even in cases with VI.

Design: We reviewed 42 high grade sarcomas(HGS)(undifferentiated sarcoma and leiomyosarcoma) and 31 low-grade endometrial stromal sarcomas(ESS). All cases had VI

Immunostains were performed in all cases for vascular markers(CD31,ERG,D2-40). Follow-up:1 to 216 mo (mean 48 mo;median 36 mo).

Results: ESS contained tumor in vessels frequently attached to the vessel wall (56%), suggesting a polypoid intrusion into the vascular lumen; small vessels within tumor cell aggregates were present (40%), surrounded by a thin fibrous band at the most invasive leading intravascular front (31%). Immunostains showed endothelial cells lining the vessels and surrounding the intravascular tumor cell aggregates in 100% cases. Only 8 (25%) patients had pelvic(6) and/or lung metastasis(5);only one died of disease.



HGS contained tumor in vessels separated from the vessel wall (77%); with no associated stroma or small vessels within the clusters (67%), and surrounding fibrinous reaction around the tumor (16%). Immunostains showed endothelial cells lining the involved vessel but not surrounding the intravascular tumor cell clusters. 33(79%) patients showed pelvic recurrence(13) and/or lung metastasis(27); 21(50%) died of disease, 14(33%) were alive with disease and 7(17%) had no evidence of disease

Immunostains showed intravascular tumor foci in veins(72 cases) rather than lymphatics(11 cases).

Conclusions: 1. Histologic features including projection of the tumor inside the vascular lumen, tumor cluster containing stroma and/or small vessels and lined by a thin fibrous band of tissue would suggest pseudoinvasion

2. Immunostains for vascular markers would clearly distinguish VI from pseudoinvasion by demonstrating the embolus in reality is covered by endothelial cells that continued from the vessel endothelium

3. Pseudoinvasion(vascular intrusion) can be suspected on H&E, confirmed with immunostains, and can explain cases of "VI" in sarcomas with very low incidence of recurrence/metastasis.

1223 A Clinicopathologic Review of Ovarian Mucinous Carcinomas: Does an Aggressive Variant Exist and Is Morphology Predictive?

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Background: Distinguishing primary ovarian mucinous carcinomas from secondaries can be challenging. Although primary tumors present mainly as stage 1 disease, associated with expansile pattern of invasion and are known to be associated with a favorable outcome, there are some cases that have extraovarian involvement at the time of presentation, behave aggressively and despite extensive clinical work up, no extraovarian primary is identified.

Design: We retrieved all ovarian mucinous carcinomas from University Health Network pathology files between 2002 and 2014. The available hematoxylin & eosin stained slides were reviewed by two gynecological pathologists (MR and SM) and a gastrointestinal pathologist (RC) to record the clinicopathological parameters such as background of

borderline tumor, expansile pattern of invasion, papillary and villous architecture in areas of confluent growth, a multicystic, Swiss-cheese infiltrative/destructive pattern, appendiceal pathology and the presence of extraovarian tumor at presentation. Clinical data bases were searched for any history of extraovarian carcinoma, treatment, recurrence and clinical outcome.

Results: We identified 49 primary mucinous ovarian carcinomas and 47 metastatic carcinomas (13 colonic, 15 appendiceal, 8 gastric/upper GI, 3 gallbladder, 5 pancreas, 1 lung, 2 cervix). Primary ovarian tumors were divided into two groups based on histological patterns: i) papillary and villous architecture with a background of borderline mucinous (PVB) and, ii) a multicystic infiltrative pattern (MCI). Low-grade appendiceal mucinous neoplasms (LAMN) spreading to the ovaries showed morphologic features more akin to ovarian mucinous borderline tumors. Clinical follow-up was available for a period of 4 to 112 months. Table 1 summarizes our findings.

Histologic pattern	Age	Extraovarian involvement	Death	Median overall survival (months)
PVB	21-80 Mean: 50	4/28 (14%)	4/28 (14%)	43
MCI	36-82Mean: 58	4/11 (28%)	6/11 (54%)	12

Conclusions: Our preliminary data suggests that there is a small group of primary ovarian mucinous adenocarcinomas (approximately 20%) with a multicystic infiltrative pattern that are more often associated with extraovarian involvement at presentation, have different histological features and their clinical behavior is more aggressive than usual ovarian mucinous carcinomas.

1224 Usefulness of p16/Ki-67 Dual Staining in the Triage of Human Papillomavirus Positive Women With Minor Pap Test Abnormalities

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Background: Current guidelines of cervical cancer prevention are moving towards strategies based on human papillomavirus (HPV) testing as the primary test. Pap cytology has a role in these schemes either in the primary screening (co-testing) or in the triage of HPV+ women. One of the major concerns of these guidelines is that there is no satisfying clinical management algorithm for HPV+ women with minor or no abnormalities in the Pap test, i.e. low-grade squamous intraepithelial lesions (LSIL), atypical squamous cells (ASC) and negative result. The objective of this study is to assess the usefulness of p16/Ki-67 dual staining in the triage of HPV+ women with LSIL, ASC and negative Pap test results, to detect the subset of patients harboring high-grade squamous intraepithelial lesions (HSIL).

Design: From October 2009 to May 2014, 797 women (mean age: 36.2±12.1 years; range 20-87) having HPV+ with either LSIL (n=377), ASC (n=160) or Pap test negative result (n=260) were evaluated in the colposcopy unit of the Hospital Clinic of Barcelona. All women underwent digital colposcopy and liquid-based cytology specimen (ThinPrep®, Hologic). Colposcopically directed biopsy and/or endocervical curettage were performed when clinically indicated. All cases were stained with p16/Ki67 in cytological samples (CINtec plus, Roche diagnostics). Results were correlated with the presence of histologically confirmed HSIL+ after the complete study of the patients.

Results: After the completion of the study 85 patients (10.7%) had a histologically confirmed HSIL+, 391 (49.0%) had a LSIL and 321 (40.3%) were classified as having no lesion. HSIL+ was diagnosed in 11.4% women with LSIL, 20.6% women with ASC, and 3.5% women with negative Pap test ($p<0.001$). p16/Ki67 dual staining was positive in 66/85 (77.6%) patients with a final diagnosis of HSIL, 226/377 (59.9%) women with LSIL, and 58/321 (18.1%) women with no lesion ($p<0.001$). The sensitivity, specificity, positive and negative predictive values of p16/Ki67 for histologically confirmed HSIL+ were 77.6% (95% confidence interval [CI]: 47.6-100), 60.1 (95%CI: 54.0-91.4), 18.9% (95%CI: 0-1) and 95.7% (95%CI: 82.8-1), respectively.

Conclusions: p16/Ki67 is a valid technique in the triage of HPV+ women with LSIL, ASC or negative Pap test result.

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1225 Undifferentiated Endometrial Carcinomas: Where Do They Fit in?

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Background: Undifferentiated endometrial cancers are rare but believed to be aggressive histologic subtypes of endometrial carcinomas. Few studies exist that demonstrate the natural history of this disease. We aimed to compare these carcinomas to a more commonly diagnosed histology also associated with poor outcomes, uterine carcinosarcomas.

Design: We identified all patients with a diagnosis of uterine undifferentiated carcinoma and carcinosarcoma treated at our institution from 1998 to 2014. All cases were reviewed by expert institutional gynecologic pathologists. Various clinicopathologic data were abstracted and analyzed. Appropriate statistical tests were used.

Results: 15 patients with undifferentiated carcinoma and 88 patients with uterine carcinosarcoma were identified. No statistically significant difference was noted in age (median 66, range 34-87, p=0.147), race (81% white, p=0.231), or BMI (median 28.4, range 18.2-48.3, p=0.915) between cohorts. Similarly, no difference was noted with respect to > 50% myometrial invasion (53% vs 39%, p=0.395), presence of LVSI (73% vs 53%, p=0.172), or overall size (median 6 cm in both cohorts, p=.554). 7/15 (47%) of patients with undifferentiated cancer and 36/88 (41%) with carcinosarcoma represented stage III/IV disease (p=0.306). Adjuvant therapy between cohorts was comparable, with 9/13 (69%) undifferentiated carcinoma and 64/88 (73%) carcinosarcoma patients having received chemotherapy with or without radiation (p=0.393). Median follow-up was 38.4 months for patients with undifferentiated carcinomas and 61.7 months for those with carcinosarcoma. Progression-free survival demonstrated no statistically significant difference between these groups (median 8.9 vs 23.2 months, p=0.711, 95% CI 0.41-1.83).

Conclusions: Although little long-term data currently exists for undifferentiated endometrial carcinomas, our data suggests survival similar to uterine carcinosarcomas, a known aggressive histology. Increased detection of these uncommon endometrial cancers is necessary to gain further insight into their natural history.

1226 Alveolar Soft Part Sarcoma of the Female Genital Tract: An Immunohistochemical and Molecular Cytogenetic Study

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Background: Alveolar soft part sarcoma (ASPS) is rare as a primary gynecologic neoplasm with an estimated 23 cases reported in the past 22 years. The majority of these studies predate conventional IHC analysis or FISH testing for the signature *ASPSCR1-TFE3* fusion; thus, historically, the diagnosis was made by morphologic assessment and supported by use of PAS-D to identify cytoplasmic crystalline inclusions. Given the morphologic overlap of ASPS with both conventional and *TFE3* rearranged forms of PEComa, we analyzed cases of ASPS to correlate its immunohistochemical profile with molecular genetic findings.

Design: Cases of ASPS involving the female genital tract were retrieved from four institutions. An IHC panel of TFE3, HMB45, melanA, TFE3, Desmin, hCaldesmon, SMA was applied. Assessment of *TFE3* by break apart probe, and if rearranged, reflex *ASPSCR1-TFE3* dual color, single fusion FISH, was performed for each case.

Results: Eight cases originally diagnosed as ASPS were identified. All had a similar appearance with a nested or alveolar growth comprised of epithelioid cells with eosinophilic cytoplasm, round-ovoid nucleus and prominent nucleolus. IHC and FISH are summarized in the Table. Six cases had *ASPSCR1-TFE3* fusion, one case failed hybridization but showed an immunophenotype in keeping with ASPS while one case proved to be misclassified owing to its lack of *TFE3* rearrangement and had an immunohistochemical expression pattern of myomelanocytic markers seen in conventional-type PEComa.

	TFE3	HMB45	MelanA	SMA	Desmin	hCaldesmon	ASPSCR1-TFE3
1	+	-	-	-	-	-	+
2	+	-	-	-	-	-	+
3	+	-	-	-	-	-	+
4	+	-	-	-	-	-	+
5	+	-	-	-	-	-	+
6	+	-	-	-	-	-	+
7	+	-	-	NP	-	NP	+
8	-	+ (patchy)	+ (patchy)	NP	+ (diffuse)	NP	-

NP=not performed

Conclusions: ASPS has a distinct immunophenotype of negative HMB45, melanA and muscle marker expression which distinguishes it from PEComa. Immunohistochemistry, and if necessary, FISH, may aid in distinction of these morphologically similar tumors. Proper identification is important as malignant PEComa may be treated with targeted mTOR inhibitor therapy and ASPS, which is typically histologically uniformly bland, should not be misclassified as benign PEComa.

1227 TFE3 Translocation Associated Perivascular Epithelioid Cell Neoplasm (PEComa) of the Gynecologic Tract: Morphology, Immunophenotype, Differential Diagnosis

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Background: *TFE3* translocation associated PEComa is a distinct form of perivascular epithelioid cell neoplasm. Despite its rarity, recent investigation has found a lack of *TSC* mutation in these tumors compared to their nonrearranged counterparts which underscores the importance of recognizing the translocated variant due to hypothetical ineffectiveness of targeted mTOR inhibitor therapy. We compiled the largest series of these tumors arising in the female genital tract to better define their clinicopathologic features and compare recently proposed of GYN-specific criteria for malignant potential.

Design: Cases were identified with the diagnosis "PEComa" and a description of clear cell morphology involving gynecologic organs. IHC consisted of TFE3, HMB45, MelanA, SOX10, MiTF, cathepsinK, SMA, desmin, h-caldesmon. Each tumor was assessed for pattern of invasion, growth pattern, degree of cytologic atypia, LVI, necrosis, multinucleated tumor cells, melanin-containing cells, mitotic figures per 10 and 50 hpf.

Results: Six cases had *TFE3* rearrangement confirmed by break apart probe FISH. Patient age ranged 46 to 66 years and none with a history of TSC. Five cases had purely clear cell epithelioid morphology that showed a spectrum of atypia while one case had a mixture of clear cell epithelioid and spindle cells. A mostly consistent

immunophenotype was observed in the purely clear cell epithelioid cases: diffuse TFE3, HMB45, CathepsinK, either focal or no melanA and variably weak reactivity to smooth muscle markers. The mixed clear cell epithelioid and spindle cell case had a similar IHC pattern in its epithelioid component, but strong muscle marker positivity in its spindle cells. Follow up ranged 1 to 57 months. Three cases demonstrated aggressive behavior and three cases had no evidence of recurrence. The GYN-specific criteria for malignancy showed greater specificity and improved categorization than previously proposed criteria.

Conclusions: *TFE3* translocation associated PEComa often has a distinct of appearance of diffuse clear cell epithelioid morphology with an alveolar or nested architecture morphology and a mostly uniform immunophenotype. Recently proposed GYN-specific prognostic criteria are strongly recommended for use in evaluating rearranged PEComa of the female genital tract. Identification of translocation associated PEComa may offer important clinical insight into behavioral potential and use of targeted therapeutic modalities.

1228 A Survey of DICER1 Hotspot Mutations in a Range of Ovarian Sex Cord Stromal Tumor Subtypes

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Background: Dicer is an RNA III-type endonuclease which plays a key role in the production of mature miRNAs and is involved in the embryonic development of the gonad. "Hotspot" mutations in the *DICER1* gene around metal-binding residues in the RNase IIIb domain have been previously reported in approximately half of ovarian Sertoli Leydig cell tumors (SLCTs) and more rarely in other tumors including embryonal rhabdomyosarcoma (RMS) and juvenile granulosa cell tumor (JGCT). SLCTs frequently display areas of heterologous morphology (HM), including glandular elements and RMS; the relationship between HM and *DICER1* mutation status is unknown. Likewise, the *DICER1* mutation status of pure Sertoli cell tumors (SCT) and gynandroblastomas (GAB) has not been previously studied. We sought to determine whether the *DICER1* mutation status of SLCTs is related to the presence or absence of HM, and whether *DICER1* mutations occur in other sex cord stromal tumors (SCST), including GABs and SCTs.

Design: Twenty-seven SLCTs (including 4 with RMS and 5 with glandular HM), 3 GABs and 8 SCTs were retrieved from the authors' institutions. All cases were reviewed by four pathologists with an interest in gynecologic pathology. DNA was extracted from representative formalin-fixed paraffin-embedded microdissected sections of each case, and subjected to Sanger sequencing using primers flanking the two mutation hotspot metal-binding sites in the RNAse IIIb domain. Sequencing chromatograms were analyzed using the DNAStarLaserGene software.

Results: Hotspot *DICER1* missense mutations were identified in 18 of 27 SLCTs (67%), including 3 of 4 tumors with RMS and 3 of 5 tumors with glandular HM. Furthermore, 2 of 3 GABs and 5 of 8 SCTs tested demonstrated hotspot *DICER1* mutations. The E1705K *DICER1* mutation was identified in all 5 *DICER1* –mutated SCTs and in 16 of 18 *DICER1* –mutated SLCTs. Within each tumor subtype, no morphologic differences were apparent between *DICER1*-mutant and non-mutant tumors.

Conclusions: *DICER1* hotspot mutations occur in a range of ovarian SCSTs, including both GABs and SCTs. In SLCTs, the mutation was identified in tumors with and without HM. These results suggest that *DICER1* hotspot mutations affecting the RNase IIIb domain are common in SCSTs and likely constitute a driver of non-epithelial ovarian tumors.

1229 Whole-Exome Sequencing of Synchronous Endometrioid Carcinomas of the Uterus and Ovary

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Background: Ovarian and uterine endometrioid carcinomas share histologic and genetic features. In a subset of patients (5-10%), synchronous endometrial and ovarian cancers are found. Independent synchronous primary tumors have been shown to be associated with a favorable outcome compared to that of metastatic disease; hence, an accurate diagnosis is required for optimal patient management. In this study we sought to characterize the repertoire of somatic genetic alterations and to define the clonal relationship of synchronous endometrioid endometrial and ovarian cancers.

Design: Five patients with synchronous endometrioid tumors of the uterus and the ovary were included. DNA was extracted from frozen tumor samples and matched normal tissue and subjected to massively parallel whole-exome sequencing (100x coverage). Somatic single nucleotide variants (SNVs) were detected by MuTect, insertions and deletions (indels) by MuTect, Strelka and VarScan2, and copy number alterations by VarScan2 and GISTIC.

Results: All but one tumor pair harbored at least one genetic alteration previously described as a driver genetic event in endometrioid tumors of the uterine corpus and the ovary (e.g. *PTEN, ARID1A, CTNNB1, KRAS* and *PIK3R1*). In four cases, 22-106 identical somatic SNVs and indels were found in both tumors, indicating that these shared a common origin and that one was a metastatic dissemination from the other. Large numbers of private mutations restricted to either the endometrial or the ovarian endometrioid tumor were found. Clonal lineage analysis suggested that in these four cases the likeliest primary tumor was the endometrioid endometrial cancer. In one case, however, no somatic genetic alterations were found in common between the two lesion lesions, indicating that these were independent primary tumors.

Conclusions: Synchronous endometrioid tumors of the uterus and ovary are preferentially clonally related and constitute primary tumors and their respective metastases. In one case we have documented the existence of synchronous independent tumors. Clonal lineage analysis provided information about the likeliest order of events. Massively parallel sequencing analysis is a valuable tool to help distinguish synchronous independent primary tumors from metastatic disease, and potentially guide treatment decisions.

1230 Prognostic Impact of Perineural Invasion in Early Stage Cervical Cancer

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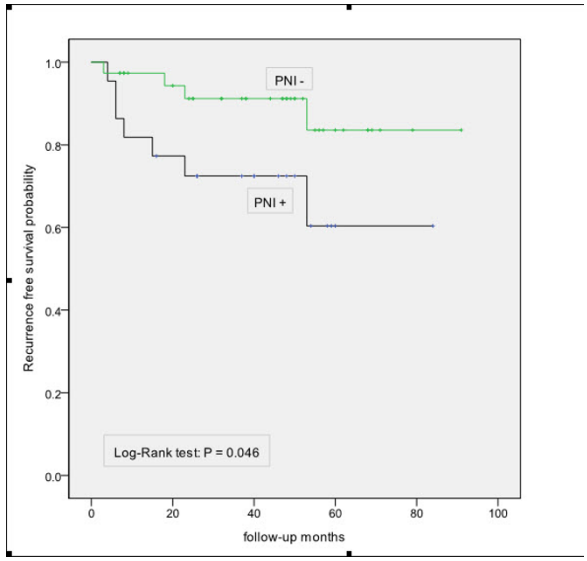
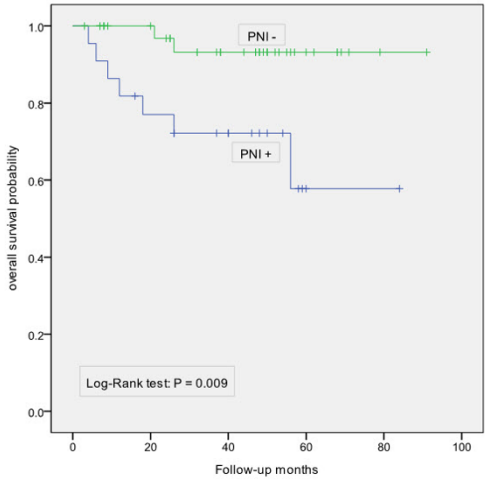
Background: The prognostic significance of perineural invasion in patients with early stage cervical cancer has not been clarified yet.

Design: The histologic slides of 83 patients with early stage cervical cancer (IA-IIB) who underwent radical hysterectomy and pelvic lymphadenectomy were reviewed regarding the occurrence of perineural invasion (PNI). Association between various clinicopathological predictors of outcome and PNI was determined with Perason X^2 analysis. The relevance of PNI among well known risk factors was determined by the Binary logistic regression multivariate analysis.

Results: The study group comprised 51 patients with squamous cell carcinoma, 21 patients with adenocarcinoma, 8 patients with adenosquamous carcinoma and 3 patients with small cell carcinoma of the cervix. Median follow up time was 44 months. PNI was detected in 33.7% of all patients (28/83). PNI was correlated with advanced stage (P = 0.021), depth of stromal invasion ³10mm (P = 0.048), lymphovascular invasion (P = 0.001). There was no association between PNI and lymph node metastasis, size of tumor, histologic type and parametrial invasion. Kaplan-Meier curves did show a significant difference in disease free survival (P = 0.046) and overall survival (P = 0.009) on the basis of the presence of the PNI [Figure 1,2]. Binary Logistic regression analysis was carried out to determine a predictive association of the clinicopathological variables with mortality and PNI was found to be an independent prognostic factor (P = 0.013).

Conclusions: PNI is associated with multiple high risk factors and is a valuable independent prognostic factor for assessing patients with early stage cervical cancer.





1231 Old Versus New FIGO Staging System for Predicting Outcome in Uterine Endometrial Stromal Sarcomas

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Background: Low-Grade Endometrial Stromal Sarcormas (ESS) are rare uterine tumors usually with an indolent behavior. Traditionally ESS have been staged using the 1988 International Federation of Gynecology and Obstetrics (FIGO) for carcinomas of uterine body. Recently, a new FIGO staging system (2009) has been proposed. It takes into account tumor size and local/regional extension excluding cervical, serosal involvement and vaginal metastases as criteria for upstaging the tumor. Furthermore, adnexal involvement is now staged as IIA (before IIIA) while abdominal cavity involvement is considered stage III. The purpose of this study was to compare which FIGO staging system could be more accurate in predicting survival in patients with ESS.

Design: 56 patients diagnosed with ESS between 1980 and 2012 at the participating institutions were restrospectively staged using the 1988 and 2009 FIGO staging systems. Overall survival (OS) was defined as an interval between date of death or last follow up (FU). The OS rates for the staging systems were estimated using the Kaplan-Meier method.

Results: Table 1 lists the distribution of 56 patients according to stage in both 1988 and 2009 FIGO systems. 43 patients had identical stage in both systems and 13 were downstaged with the 2009 system, mostly from stage III to II (12). The median length of FU was 84 (range: 12-288) months. Table 2 shows FU status. With the new staging, only one patient with stage IB died of disease while 4 and 5 with stage IA and IB respectively had recurrences, with stage IA recurring earlier than IB tumors.

	New FIGO				
Old FIGO	I	II	III	IV	n patients
I	34	0	0	0	34
II	1	3	0	0	4
III	0	12	5	0	17
IV	0	0	0	1	1
Total of patients	35	15	5	1	56

Patient status	No. (%)
Alive without disease	45 (80.4%)
Alive with disease	7 (12.5%)
Died of disease	3 (5.3%)
Died of other causes	1 (1.8%)

Conclusions: Our study shows that neither FIGO staging system is adequate in classifying patients with ESS into meaningful groups. Comparison between the old and new FIGO staging systems did not show statiscally significant differences for predicting patient outcome. Division of new stage I based on tumor size (IA and IB) did not help to predict recurrences. Among patients with downstaged tumors there is no evidence that the new system improved prediction of recurrence.

1232 CTNNB1 Mutations in Advanced Stage and/or Recurrent Endometrial Endometrioid Adenocarcinoma

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Background: Mutations of the *CTNNB1* gene in the Wnt/β-catenin pathway have been recently associated with worse survival in grade 1/2, stage I/II endometrial endometrioid adenocarcinoma (EEC) and a higher rate of recurrence in therapy-naive, FIGO grade 1, Stage IA EEC. The relevance of *CTNNB1* mutation in advanced stage/recurrent endometrial carcinomas of all histotypes and grades have not yet been defined. We report a series of cases of advanced FIGO stage and/or recurrent endometrial carcinomas that had *CTNNB1* mutations identified by targeted next generation sequencing (NGS).

Design: Sixty-seven endometrial carcinomas (32 endometrioid, 29 non-endometrioid and 6 mixed) were subjected to NGS using a pan-cancer panel of hotspot mutations in 46 or 50 genes using DNA extracted from formalin fixed paraffin embedded tumor. All cases were either advanced stage or recurrent at the time of clinical testing. The clinicopathologic findings and spectrum of somatic mutations in *CTNNB1* mutated cases were compared with those from *CTNNB1* wild-type cases.

Results: Missense mutations in exon 3 of *CTNNB1* gene were identified in 9/32 endometrioid carcinomas (28%); no mutations were identified in the non-endometrioid or mixed carcinomas. Women with *CTNNB1* mutant tumors had a lower mean age (58 vs 64 years) and a lower median BMI (29 vs. 31) than those with *CTNNB1* wild-type carcinomas.

Lymphovascular invasion was more common in *CTNNB1* mutated cases (100% vs. 65%, *P*=.04), but there was no significant difference in lymph node metastases (67% vs. 42%, *P*=0.32) compared to *CTNNNB1* wild-type cases.

Additional somatic mutations were more frequent in the *CTNNB1* mutated tumors (100% vs. 74%; *P*=.0002) and involved mutations in *PIK3CA*, *PTEN* and *FGFR2* genes. Interestingly, despite more mutations overall, the *CTNNB1* mutant group had fewer *KRAS* mutations compared to the *CTNNB1* wild type group (11% vs. 39%).

Conclusions: We have shown that *CTNNB1* mutations do occur in advanced stage/recurrent endometrial carcinomas. Mutations are restricted to endometrioid histology. In addition to being prognostic for low grade, low stage endometrial carcinoma, *CTNNB1* mutation may also provide a therapeutic target, as there are agents in early phase clinical trials targeting the Wnt/ β-catenin pathway. Fewer *KRAS* mutations in the *CTNNB1* mutant group could positively impact targeting this pathway therapeutically, as the presence of *KRAS* mutation is known to inhibit efficacy of other targeted therapy strategies.

1233 Primary Ovarian Endometrioid Adenocarcinoma With Mucinous Metaplasia (POEM): An Under Recognized Entity With Therapeutic Implications

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Background: Mucinous metaplasia is well-recognized in endometrial endometrioid adenocarcinoma (EEC), but not in ovarian endometrioid carcinoma.Misdiagnosis has therapeautic implications as ovarian mucinous carcinomas are increasingly being treated with chemotherapy regimens used for colonic tumors.In this study, we present our experience with cases of POEM and highlight the pathologic features that can lead to their correct identification.

Design: 37 cases of POEM with available slides and follow up (f/u) from 2000-2014 were reviewed.Pathologic parameters recorded included laterality, tumor size, initial diagnosis, presence of endometriosis, type of borderline component, amount of mucinous metaplasia, other endometrioid adenocarcinoma associated cytologic changes, tumor grade, presence and pattern of invasion, tumor stage and concurrent endometrial pathology.Clinical parameters including patient age, adjuvant chemotherapy and f/u were recorded.

Results: Patients' (pts) age ranged from 26-71yrs (mean, 51).Tumor laterality: 18 left, 10 right, 9 bilateral.Tumor size ranged from 2.5 to 48 cm(mean 12.7).All 32 consult cases, reclassified as POEM, were initially diagnosed as:22 mucinous carcinoma/adenocarcinoma,NOS (59%), 10 mucinous borderline tumor with foci suspicious for carcinoma (27%).According to the tumor grade, cases were distributed as:grades 1 and 2 (32 cases), grade 3 (5 cases).The percentage of mucinous metaplasia in POEM ranged from 5-95% (mean 47%).Squamous metaplasia was seen in 17 cases, while 18 and 6 cases had secretory and clear changes, respectively. 26 cases showed only expansile invasion (EI), 9 EI and infiltrative invasion and 2 only infiltrative invasion.The histology of the borderline component was endocervical (12), endometrioid (3) or mixed (21).18 cases had endometriosis.Tumor stage of POEMs: 23 Stage-I, 3 Stage-II, 3 Stage-III and 2 Stage-IV.16 cases had concurrent grade 1 EEC (5), grade 2 EEC (9) or complex atypical hyperplasia (2). 20 pts. received adjuvant chemotherapy.F/u ranged from 1-96 mos (mean 11).At most recent f/u, 28 pts are alive without evidence of disease while 4 died of disease and 5 died of other causes.

Conclusions: POEMs are under recognized and due to mucinous metaplasia can be misdiagnosed as ovarian mucinous carcinomas, resulting in incorrect therapy.

These tumors are frequently associated with a borderline tumor-either mixed or endocervical type (89%), endometriosis (48%) and EEC (43%).

Presence of squamous metaplasia, secretory change or a nonintestinal type borderline tumor can facilitate the correct diagnosis of POEM.

1234 Targeted Next Generation Sequencing (NGS) for the Identification of Clinically Actionable Mutations in Advanced Stage/Recurrent Endometrial Carcinoma (EC)

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Background: Advanced stage/recurrent EC are typically resistant to standard chemotherapy and are associated with poor survival. A criticism of many of the published reports on molecular changes in EC is that primarily early stage, non-recurrent tumors were studied. We therefore analyzed NGS results in patients with endometrioid (EEC), serous (ESC) and malignant mixed Müllerian tumors (E-MMMT) to identify the spectrum of clinically actionable mutations in advanced stage/recurrent disease.

Design: Clinical NGS was performed in 67 advanced stage/recurrent endometrial carcinomas (32 EEC, 16 ESC, 6 mixed EEC-ESC and 13 E-MMMT). An NGS panel of hotspot regions in 46 or 50 genes was performed using tumor DNA extracted from formalin fixed paraffin embedded tissue. Eighteen genes in this panel are clinically actionable, defined as a somatic mutation for which a matched genotype selected therapeutic clinical trial exists. NGS results from 95 ovarian high grade serous carcinomas (O-HGS) were also reviewed for comparison.

Results: In EEC, mutations were identified in 17/50 (34%) genes on the panel. The most common mutations were *PTEN* (59%), *PIK3CA* (53%), *KRAS* (32%), *CTNNB1* (26%), *FGFR2* (10%) and *TP53* (9%). At least 1 actionable mutation was present in 29/32 (91%) cases of EEC; concurrent *KRAS* mutation was noted in 7/29 cases.

The mutation spectra of ESC and E-MMMT were similar, involving 7/50 (14%) genes on the panel, including *TP53* (80%), *FBXW7* (27%), *PIK3CA* (17%), *KRAS* (10%) and *PTEN* (7%). Compared to EEC, actionable mutations were seen in significantly fewer ESC and E-MMT (7/29, 21%, *P*<.0001). These included 5 cases with *PTEN* mutations, 1 case with *PTEN* and *PIK3CA* mutation, and 1 case with *KDR* mutation.

In comparison, actionable mutations were seen in only 8/95 (8.4%) O-HGS and involved *PIK3CA* (3), *FGFR2* (3), *EGFR* (1) and *ERBB2* (1). Endometrial carcinoma with mixed EEC and ESC histology had a higher frequency of actionable mutations (5/6, 83%) comparable to that of EEC.

Conclusions: Actionable mutations are present in advanced stage/recurrent endometrial carcinoma, especially for endometrioid histology. Despite related histology to the ovarian counterparts, ESC and E-MMT had more actionable mutations than for ovarian non-endometrioid carcinomas. *FBXW7* mutation, which is thought to increase signaling through the PI3K/AKT/mTOR pathway, is especially common in ESC and E-MMT and may provide an alternative mechanism of pathway activation independent of *PTEN* or *PIK3CA* mutation.

1235 Chemotherapy Response Score: Validation of a 3-Tier Histopathological Scoring System for Assessing Response To Neoadjuvant Chemotherapy in High-Grade Serous Tubo-Ovarian Carcinoma

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Background: Advanced stage tubo-ovarian high-grade serous carcinomas (HGSC) are increasingly treated with neoadjuvant chemotherapy followed by interval debulking surgery. There is no validated system for assessing response to chemotherapy based on histopathological examination of interval debulking specimens. We previously developed a 3-tier scoring system, the Chemotherapy Response Score (CRS), and found assessment of response in the omentum to be superior to that in adnexal tissues in terms of reproducibility and prognostic relevance. In this study we sought to validate this scoring system in an independent cohort of patients.

Design: 71 cases of advanced stage high-grade serous carcinoma treated with neoadjuvant chemotherapy followed by interval debulking surgery were identified. The section of omentum showing the greatest response to chemotherapy was selected and scored independently by 3 pathologists blinded to outcome.

The CRS system is as follows:

CRS 1: No or minimal tumour response

CRS 2: Appreciable tumour response with residual tumour, both readily identified

CRS 3: Complete or near-complete response.

Results: Interobserver agreement: There was substantial overall agreement between the 3 pathologists with absolute agreement in 79% cases, Fleiss' kappa score 0.67 ($p<0.01$) and Kendall's coefficient of concordance 0.79.

Correlation with clinical outcome: 19 of 71 (27%) cases showed a marked response to chemotherapy (CRS 3) and these patients had significantly improved progression free survival compared to cases with minimal or moderate response to chemotherapy (CRS 1 or 2) (RR 3.60, 95% CI 1.69-7.66, $p<0.001$). There was also a statistically non-significant excess of mortality risk for cases with CRS 1 or 2 (RR 1.81, 95% CI 0.79-4.14, $p=0.16$).

Conclusions: The CRS system for assessing tissue response to neoadjuvant chemotherapy has been validated in an independent cohort of cases, and is found to be easy to apply, reproducible, and prognostically relevant.

1236 DNA Genotyping To Distinguish the Origin of Teratoma-Associated Ovarian Mucinous Tumors: Related Tumors or Coincidence?

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Background: The association of ovarian mucinous tumors with teratomas is well documented, suggesting that at least some ovarian mucinous tumors arise from teratomas. Teratomas – being of germ cell origin - are often genetically distinct from somatic cells, therefore providing a molecular basis for DNA genotyping to separate teratoma-derived mucinous tumors from metastatic ones. We assessed the potential clinical utility of DNA genotyping in the differential diagnosis of ovarian mucinous tumors.

Design: Eight cases of ovarian mucinous borderline tumors and three mucinous carcinomas associated with teratomas were retrieved from our departmental archives and the diagnosis was confirmed by reviewing all H&E slides. Target tissues of concern (teratoma, mucinous tumor and paired normal tissue) were microscopically dissected, followed by DNA extraction. Genotyping was performed by AmpFlSTR Identifiler PCR Amplification system, followed by capillary electrophoresis.

Results: Of the 8 mucinous tumors, DNA genotyping was informative in five cases including three borderline tumors and two mucinous carcinomas (Table 1). Homozygosity or partial homozygosity was observed in the teratomatous component in 5 cases and in the mucinous tumor component in 4 cases. Genotypic concordance between the teratoma and mucinous tumor component was seen in 4 cases, consistent with a clonal origin of the two tumor components. One mucinous borderline tumor showed no homozygosity (Table 1, case 2) in contrast to the complete homozygosity in the teratoma, suggesting disparate tumor origins.

Case	Diagnosis	Homozygous in Teratoma (T)*	Homozygous in Mucinous (M)*	Agreement between T and M	Arising from Teratoma
1	Borderline	10/10	6/7A	6/7A	Yes
2	Borderline	6/6	0/8	0/6	No
3	Borderline	10/10	10/10	10/10	Yes
4	Carcinoma	2/8B	12/12	2/8B	Yes
5	Carcinoma	7/12	6/12	9/12	Yes

*Results shown as a fraction of informative loci; discrepancies are seen with PCR amplification failure.
[A]Difference is an an allele expressed in mucinous tumor not present in normal tissue.
[B]Discrepancy may be due to contamination with surrounding normal tissue.

Conclusions: When associated with a teratoma, ovarian mucinous borderline tumors and mucinous carcinomas may frequently arise from the teratoma, which was observed in 4 of 5 informative cases in the current study. DNA genotyping may serve as a powerful ancillary marker to confirm the teratoma origin of ovarian mucinous tumors.

1237 Crosstalk Between E-Cadherin Expression and Cell Proliferation in the Progression of Squamous Cell Carcinoma of the Uterine Cervix

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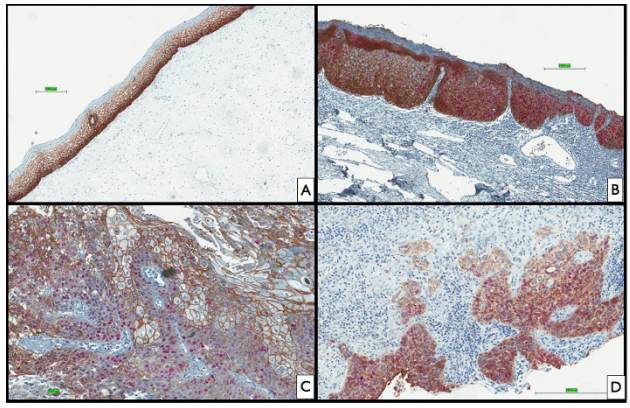
Background: Several cell signals are responsible to enhanced cell proliferation and promoted tumor cell migration and invasion. An appropriate cell-cell adhesion mediated by cadherins is required for the growth, survival and proliferation of epithelial cells. In this study, we investigated the relationship of the loss of expression of E-cadherin (e-CAD) and cell proliferation in neoplastic progression from intraepithelial to invasive carcinoma.

Design: We selected from our files cases with histologically normal ectocervix (20 cases), high-grade intraepithelial neoplasia (43 cases), and invasive carcinoma (43 cases). Cases were double stained with e-CAD and Ki-67, and evaluated using color-deconvolution algorithm (Aperio, USA).

Results: The maximum expression was observed in high-grade lesions with e-CAD preserved and high proliferative index (figure 1B). In invasive carcinoma, there are different patterns of expression. Large tumor nests show e-CAD preserved in the central cells of the nest with downregulation in the cell nest limits. The expression of Ki-67 in these large nests showed an inverted pattern: low proliferative index in the central areas, but high proliferative index in cells at the border of the nest (figure 1C). When invasive small nests and tumor budding are present, we observed e-CAD downregulation and low proliferative index (figure 1D).



Expression of E-cadherin (Brown, membrane) and Ki-67 (red, nucleus) during cervical carcinoma progression. A. Expression of e-cadherin in normal ectocervix; B. in carcinoma in situ there is a concomitant expression of KI-67/e-CAD in virtually 100% of the cells; C. strong expression of e-CAD with very few cells KI-67+ at the core of the tumor; please note the diference the in edge of the tumor with marked loss of e-CAD and high proliferative index; D. invasive buds showing downregulation of e-CAD and low proliferative index

The two graphs on figure 2 demonstrated the differences observed in Ki-67 and eCAD expression in the cervical carcinoma neoplastic progression.

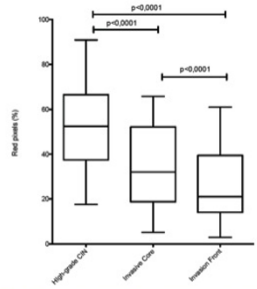


Figure 2: Ki-67 expression in high-grade CIN and invasive carcinoma (central area and invasion front) showing the difference of expression between the groups

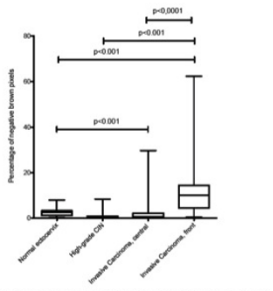


Figure 3: Downregulation of e-CAD in normal ectocervix, high grade CIN, and invasive carcinoma, central core of the tumor nests and invasion front. The results show a downregulation of e-CAD in invasive lesions, more prominent in the invasion front. Only significant differences are indicated

Conclusions: These different patterns demonstrate the importance of adhesion of the tumor cells to proliferate. In conclusion, e-CAD regulation is a very dynamic process during neoplastic progression and cell proliferation is dependent of cell anchorage and preserved adhesion.

1238 Management of Cytology Negative High-Risk Human Papillomavirus Positive Cervical Smears

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Background: Human papillomavirus (HPV) is widely accepted to cause almost all cervical squamous cell carcinoma, with genotypes 16 and 18 causing most cases worldwide and other high-risk types causing a minority. With the development of vaccines to prevent HPV 16 and 18 infection and molecular testing to improve screening, it is hoped that rates of cervical cancer and cervical intraepithelial neoplasia (CIN) will decrease. Studies suggest tailoring management to HPV genotype due to the increased oncogenic properties of HPV 16 and 18 compared to other high-risk types, specifically recommending more aggressive treatment of cytology negative HPV 16 and 18 positive patients. Here, for each HPV type, we compare initial cytologic diagnoses at the time of HPV testing to definitive tissue diagnoses.

Design: From July 2013 to June 2014, 720 women at a single institution tested positive for high-risk HPV using a nucleic acid test that detects 14 high-risk HPV types and speciates them as 16, 18, or other. HPV testing was performed with a concurrent

cervical cytology reported according to the 2001 Bethesda System. 328 of the 720 women had concurrent or subsequent colposcopy and biopsy, which was used as the definitive tissue diagnosis.

Results: While there was no significant relationship between the HPV genotype and the concurrent cervical cytology results, the rate of CIN on biopsy was significantly higher when positive for HPV 16 and 18 compared to other types (p=0.04), which comports with prior studies. The biopsy rate was higher in patients positive for HPV 16 (60%) and HPV 18 (42%) compared to other HPV types (31%), confirming adherence to different treatment arms of algorithms based on HPV results. In patients with negative cytology, however, no significant difference was seen in the rate of CIN on biopsy for HPV 16 and 18 patients (15%) versus other types (22%,p=0.45).

Conclusions: Our results confirm prior studies demonstrating HPV 16 and 18 to be more oncogenic than other HPV types. Thus, management algorithms suggest performing colposcopy if positive for HPV 16 or 18, even if cytology is negative. However, our results show that in patients with negative cytology, the rate of CIN on biopsy is similar if positive for a high-risk HPV type other than 16 or 18. Therefore, we propose performing colposcopy if positive for any high-risk HPV genotype, regardless of cytology results. Moreover, with greater vaccination prevalence, HPV 16 and 18 disease is likely to decrease, but the risk remains from exposure to other high-risk HPV types, emphasizing the importance of molecular testing and cytology screening.

1239 Implementation of an Age-Based HPV Testing Protocol Improves Adherence To National Cervical Cancer Screening Guidelines

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Background: Adherence to national cervical cancer screening guidelines among clients of our outpatient laboratory is limited, particularly with regard to HPV testing. Current guidelines use patient age as a primary determinant of when HPV testing is appropriate. In March 2013, we introduced the option for clients to create a standing order for HPV testing using an age-based protocol (SOABP) based on current guidelines. In this study, we sought to determine if implementation of the SOABP improved adherence to guidelines for HPV testing.

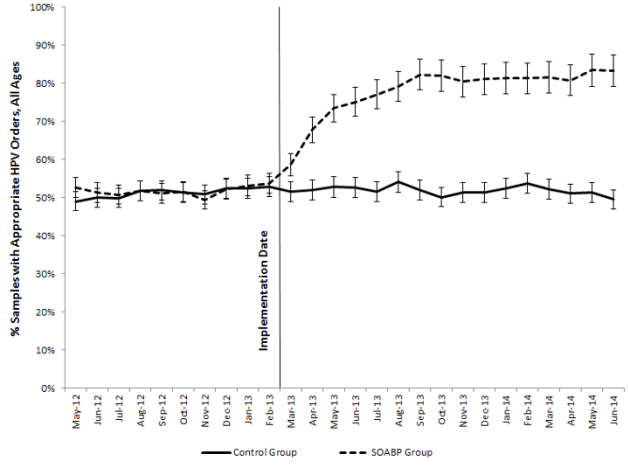
Design: Between May 2012 and June 2014, 295 providers (143 practices) implemented the SOABP. For each liquid-based cytology sample (n=107,893) submitted by these providers during the study interval, we determined the percentage of samples with HPV testing ordered in accordance with the guidelines, based on patient age and cytology result. We compared results before and after implementation of the SOABP. Over the same time interval, we also determined the percentage of samples (n=241,961) with HPV testing ordered in accordance with guidelines in a control group of practices (n=148) who did not implement the SOABP.

Results: After implementation of the SOABP, there was an increase in the percentage of samples with HPV tests ordered in accordance with guidelines (Table 1). A similar increase was not observed in the control group (Figure 1).

Table 1. % Samples with Appropriate HPV Test Orders in Providers Implementing the SOABP

Patient Age Group (years)	% Samples with Appropriately Ordered HPV Tests (95% CI)	
	Before SOABP	After SOABP
All	55.9 (55.5-56.3)	80.7 (80.3-81.0)
	68.8 (66.6-71.0)	77.8 (75.0-80.4)
21-29	73.0 (72.3-73.7)	92.1 (91.6-92.6)
≥30	49.7 (49.2-50.1)	77.4 (77.0-77.8)

Figure 1. % Samples with Appropriate HPV Test Orders over Study Interval, SOABP vs Control Group



Conclusions: An age-based protocol for HPV testing implemented in our laboratory improved adherence to national cervical cancer screening guidelines. Until such time when clinical decision support systems available at the point of care render such strategies obsolete, simple protocols implemented at the level of the laboratory can result in improved adherence to clinical practice guidelines.

1240 Granulosa Theca Cell Tumor of the Ovary: A Report of Twenty-Two Cases of an Entity That Should Be Distinguished From Diffuse Adult Granulosa Cell Tumor

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Background: For many years, the designation "granulosa-theca cell tumor" was used for the most common malignant sex-cord stromal tumor. More recently, the designation "granulosa cell tumor" has been preferentially used because the theca component has been considered secondary. We believe based on our experience the older designation has merit for a subset of tumors, having a somewhat distinctive profile.

Design: A retrospective five year search of our consultation files was performed to identify granulosa cell tumors with a conspicuous thecoma or thecoma-like component. Basic clinical features were recorded, and the gross and microscopic characteristics of the tumors were evaluated.

Results: Twenty-two cases were identified, occurring in patients 12 to 86 years of age (mean 55). Half the patients presented with a pelvic mass; in the others, the tumors were incidental findings. All tumors were unilateral, and with two exceptions, all were 6 cm or smaller. The two larger tumors (13.5 and 18 cm) were mostly cystic with solid components of up to 6 cm. When specimen integrity could be evaluated, nearly all tumors were intact with two being fragmented. The sectioned surface was typically solid and yellow to yellow-white (16/22) with cysts present in six. Low-power microscopic examination showed a predominantly diffuse growth but large typically ill-defined nodules were present in all cases. On higher power, delicate cords were discerned in all cases, often more prominent at the periphery. Classic patterns of granulosa cell tumor (nests, trabeculae, microfollicles) were absent. The tumor cells typically had moderate amounts of pale occasionally vacuolated cytoplasm, but in areas typically judged granulosa in nature cytoplasm was scant. In many areas, distinction between thecoma and granulosa components was difficult and often aided by reticulin stains, demonstrating either prominent intercellular fibrils or a nested pattern. Cytologic atypia was limited (1/22) and mitotic figures infrequent (5/22).

Conclusions: The designation granulosa cell tumor includes neoplasms with a great diversity of gross and microscopic features. A subset, which typically are small (a favorable prognostic feature) and associated with a prominent thecomatous component, represent a somewhat repetitive appearance and on basic principles are likely to have a good outcome and should be designated "granulosa-theca cell tumor" to set them apart from other granulosa cell tumors.

1241 Uterine Smooth Muscle Tumors: How Many Sections Ensure a Correct Diagnosis?

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Background: There is significant variability in how uterine smooth muscle neoplasms are grossed with significant variability noted regarding how many sections should be submitted when evaluating hysterectomy specimens. Standard practice suggests sampling at least one section of the lesion per largest centimeter dimension of the tumor (1/cm) to ensure that areas of atypia are sampled. Two lesions specifically, atypical leiomyomas (AL) and smooth muscle tumors of uncertain malignant potential (STUMP), can be grossly unremarkable and pathologists strive to ensure that these diagnoses are not missed by sampling smooth muscle tumors extensively. Our goal is to determine the minimum number of slides that could be submitted without missing a diagnosis of AL or STUMP.

Design: We retrospectively reviewed 15 cases diagnosed as AL and 10 cases diagnosed as STUMP over the last ten years using set criteria. We then examined how many slides were submitted from the lesion and compared this to how many slides contained worrisome histologic features (WHF). Worrisome features included atypia, mitotic index, necrosis, cellularity, epithelioid growth patterns, and myxoid components.

Results: A geometric distribution was used to demonstrate the probability that WHF of AL or STUMP were identified for a given number of slides. On average, AL and STUMPs contained WHF that would have been identified if a single slide was submitted 98.1% and 95.7%, respectively. A geometric distribution for the lowest yield cases of AL and STUMPs was also performed

Number slides examined	1	2	3	4	5
AL					
Mean probability of finding WHF	0.981	0.999639	0.9999931	0.9999999	1
Lowest probability of finding WHF	0.5	0.75	0.875	0.9375	0.96875
STUMP					
Mean probability of finding WHF	0.957	0.998151	0.9999205	0.9999966	0.9999999
Lowest probability of finding WHF	0.571	0.815959	0.9210464	0.9661289	0.9854693

The probability of finding WHF, regardless of lesion size, increases with increased tissue submission. Correlation with number of slides submitted and probability of finding WHF are also summarized.

Conclusions: The widespread presence of WHF in these lesions suggests that initial sampling could be reduced, with additional tissue submission if one encounters WHF on initial slide review. The outcome suggests that laboratory costs and time could be reduced without significant detriment to patient care.

1242 The Role of Regulatory Macrophages in the Progression of Endometrial Hyperplasia To Endometrial Carcinoma

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Background: It is well known that microenvironment plays essential roles in the progression of precursor or in-situ lesion towards carcinoma. Regulatory macrophage (M2 macrophage) is one of the central regulators. They are recruited and interact with other cells to set up the microenvironment. Although the roles of regulatory macrophage were studied in other organ systems, the understandings of its roles in the progression of endometrial hyperplasia to adenocarcinoma are limited. To address this question, we compare the regulatory macrophages infiltrate pattern between complex atypical endometrial hyperplasia and well differentiated endometrioid adenocarcinoma.

Design: Hysterectomy specimens from our institution archives were searched. Eight complex atypical endometrial hyperplasia (hyperplasia group) and nine well differentiated endometrioid adenocarcinoma (carcinoma group) were randomly selected. Formalin-fixed, paraffin-embedded tissues from these specimens were retrieved and stained with antibodies of CD68, CD163, and CD204 to highlight the regulatory macrophages. Five high power views with highest density of regulatory macrophages of each case were selected for quantification. The regulatory macrophages and stromal cells were counted and the percentages of regulatory macrophages were calculated. The student T test was performed.

Results: The number and pattern of distribution of regulatory macrophages were significantly different between hyperplasia and carcinoma groups. The carcinoma group had significantly higher regulatory macrophages in the stroma (average: 41.7% of stomal cells, n=9) than the hyperplasia group (average: 17.6% of stomal cells, n=8), with $P < 0.001$. The regulatory macrophages in carcinoma group had a denser infiltration surrounding the tumor glands or nests, whereas the distribution in hyperplasia group had a more diffuse pattern in the stroma. In addition, there were more regulatory macrophages within the glandular lumen in carcinoma group, whereas minimal or no regulatory macrophages were in hyperplasia group.

Conclusions: Typically, Endometrioid adenocarcinoma is preceded by endometrial hyperplasia. Characterization of the regulatory mechanisms involving this progression will have significant impacts in patients' management. Our findings demonstrate a significant role of the regulatory macrophages in this critical transition. We will further characterize the involved cytokines and subsets of lymphocytes to elucidate the regulatory networks in the microenvironment of endometrial adenocarcinoma.

1243 Expression Analysis of HPV 16 Encoded microRNAs, HPV16-miR-H1 and HPV16-miR-H2, in Cervical Carcinoma

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Background: According to the WHO 2013 report, cervical cancer is the fourth most common cancer of the women worldwide after breast, colorectal and lung cancer. Human papillomavirus (HPV) infection is the major cause for all most all the cervical cancer cases. HPV16 and HPV18 types accounts for 70% of cervical cancer. HPV16 type also causes anal and oropharyngeal cancer; more than 50% of the cases of oropharyngeal cancer detected in the United States are linked to HPV16. HPV16 encoded miRNAs were recently discovered by Qian et al, 2013. Given the importance of HPV16 infection in cancer, in the present study we have evaluated HPV16 encoded miRNAs and miR-146a and miR-205 in cervical carcinoma cases.

Design: FFPE tissues of Ca cervix (n=20), chronic cervicitis (n=4) and one normal cervix were taken for this study. Expression of p53, ki-67 and p16 was measured by IHC. Detection of HPV16/18 was carried out using a ISH kit from BioGenex. In situ detection of HPV16-miR-H1 (H1), HPV16-miR-H2 (H2), miR-146a and miR-205 was carried out using an ISH probe and detection system (microRNA probes and DF400-50KE, BioGenex).

Results: HPV 16 and HPV 18 were found to be positive in the 80% (16/20) of the cases, both HPV types 16 and 18 hand concordance in infection. Chronic cervicitis did not show any HPV16 or HPV18 infection, but p53 and ki-67 expression was seen. HPV 16 encoded miRNAs, HPV16-miR-H1 and H2 were positive in all the Ca Cervix cases where HPV16 was also positive, however expression levels of H2 were higher than H1. One case of Ca Cervix typically showed higher expression of H1 but not H2, p16 expression was also higher but miR-146a and miR-205 were down-regulated in this case. P16, p53 and ki-67 showed moderate to high expression in cervical cancer cases without any significant correlation with miRNA expression.

Conclusions: microRNA encoded by virus, may regulate both cellular and viral miRNA and also possibly regulate the switch from latent to lytic infection. HPV16 encoded miRNAs were detected in all the cervical cancer cases infected with HPV16. H2 miRNA expression was higher in comparison to H1. Whether the expression of HPV16 encoded miRNA has role in pathogenesis or switching from latent to lytic infection need to be validated in the larger sample size.

1244 Clinical Significance of Lymphovascular Invasion in High Grade Endometrial Carcinomas Including FIGO 3 Endometrioid, Serous and Clear Cell Carcinoma

Sumi Thomas, Sudeshna Bandyopadhyay, Haleema Saeed, Baraa Alosh, Eman Abdulfatah, Zaid Al-Wahab, Morgan Taylor, David Mutch, Sean Dowdy, Robert Soslow, Yaser Hussein, Esther Oliva, Marisa Nucci, Robert Morris, Mohamed Elshaikh, Adnan Munkarah, Rouba Ali-Fehmi. Wayne State University, Detroit, MI; Mayo Clinic, Rochester, MN; Washington University, St. Louis, MO; Memorial Sloan Kettering Cancer Center, New York, NY; Harvard University, Boston, MA.

Background: Lymphovascular space invasion(LVI) is an established independent poor prognostic factor in endometrial carcinomas(EC).It is clinically used to stratify the risk in EC patients.FIGO3 endometrioid(E3C), serous(SC) and clear cell(CC) carcinomas are aggressive tumors with high mortality.We aimed to analyze the clinical significance of LVI in high-grade EC and its relationship to other prognostic factors.

Design: 406 high-grade ECs:109 E3C,132 SC and 165 CC were identified from 5 institutions.Representative slides were reviewed by 2GYN pathologists using WHO criteria. LVI is defined as presence of neoplastic cells within endothelial-lined channels best assessed in the periphery of the tumor. Cases with recorded LVI status were included.

Results: 388 of 406 cases had LVI status;211(54%) with LVI and 177(46%) without LVI. LVI was higher in E3C and SC than CC($P<.001$) and associated with tumor size ^{3}2cm($P=.03$),deep myometrial invasion(MI)($P<.001$),adnexal involvement(AI)($P<.001$) and advanced FIGO stage($P=.004$) and higher proportion of positive lymph nodes(LN). Cases with LVI had significantly worse survival(median 70vs.114 months;$P=.005$) and remained a poor prognostic factor after adjusting for stage.(HR=1.4 95%CI 1-1.9,$P=.026$)

Table 1: Relationship of LVI and clinicopathological features

	LVI absent, n=177	LVI present, n=211	
Histology*			
E3C	29(29)	72(71)	
SC	41(33)	84(67)	
CC	107(66)	55(34)	
Tumor size*			
	28(57)	21(43)	0.03
≥2cm	103(40)	158(60)	
MI*			
No	48(65)	26(35)	
	85(53)	74(46)	
≥50%	41(27)	109(73)	
AI			
No	154(51)	148(49)	
Yes	23(27)	63(73)	
With LN sampling**			
Negative	119(55)	98(45)	
Positive	25(30)	57(70)	
FIGO stage			
I, II	120(52)	112(48)	0.004
III, IV	57(36)	99(64)	
Recurrence*			
No	132(45)	161(55)	0.72
Yes	44(47)	49(53)	

*Missing data: entries do not add up to N
**Subset of N; 299

Conclusions: LVI was common in high grade EC and more frequent in E3C and SC than CC. LVI was associated with larger tumor size,deep MI,AI,LN metastasis and advanced stage. It is a poor prognostic factor thereby meriting careful pathological assessment.

1245 Endometrial FIGO Grade 3 Endometrioid, Serous and Clear Cell Carcinoma: A Multi-Institutional Comparative Study of 406 Cases

Sumi Thomas, Sudeshna Bandyopadhyay, Haleema Saeed, Baraa Alosh, Eman Abdulfatah, Zaid Al-Wahab, Morgan Taylor, David Mutch, Sean Dowdy, Robert Soslow, Yaser Hussein, Esther Oliva, Marisa Nucci, Robert Morris, Mohamed Elshaikh, Adnan Munkarah, Rouba Ali-Fehmi. Wayne State University, Detroit, MI; Mayo Clinic, Rochester, MN; Memorial Sloan Kettering Cancer Center, New York, NY; Washington University, St. Louis, MO; Harvard University, Boston, MA.

Background: Endometrial FIGO3 endometrioid(E3C), serous(SC) and clear cell(CC) carcinomas are aggressive but variable in their prognosis. The study aimed to compare clinicopathological and outcome variables.

Design: 406 high-grade EC including 109E3C,132SC and 165CC patients(pts) were identified from 5 institutions.Representative slides were reviewed by 2GYN

pathologists using WHO criteria. Age,race,FIGO stage,tumor size,myometrial invasion(MI),lymphovascular invasion(LVI),adnexal involvement(AI),recurrence and survival were analyzed.

Results: SC was more in Blacks and CC more in Whites(P<.001). SC and CC pts were older(P=.002) and presented more at stageIII/IV than E3C(P=.011). Deep MI was more in E3C than SC and CC(P=.003). E3C and SC had more LVI than CC(P<.001). AI was higher in SC(P<.001). CC had highest recurrence(p<.001) and shorter disease free interval than E3C and SC(mean 133vs.174 and 156mon;P<.001). SC had worse 5yr-survival than E3C and CC(46%vs64 and 58%;P=.006) but stage matched survival was not different.[table 1] By Cox regression analysis,advanced stage,age and LVI were independent prognostic factors.

Table1:Characteristics of E3C, SC and CC

N=406	E3C,n=109(%)	SC,n=132(%)	CC,n=165(%)	
Median age(yrs)	61(27-90)	65(37-91)	67(36-90)	.002
Race*				
Blacks	56(52)	41(31)	101(70)	
Whites	52(48)	91(69)	44(30)	
FIGO Stage				
I,II	79(73)	72(55)	95(58)	.011
III,IV	30(27)	60(45)	70(42)	
Tumor Size*cm				
	9(9)	21(18)	22(20)	.08
≥2	87(91)	99(82)	86(80)	
MI*				
No	9(8)	31(24)	38(24)	.003
	44(40)	53(40)	70(44)	
≥50%	56(52)	48(36)	52(32)	
LVI*				
No	29(29)	41(33)	107(66)	
Yes	72(71)	84(67)	55(34)	
AI				
No	93(85)	86(65)	139(84)	
Yes	16(15)	46(35)	26(16)	
Recurrence*				
No	93(85)	112(85)	101(62)	
Yes	16(15)	20(15)	61(38)	

*Missing data: entries do not add up to N

Conclusions: Significant differences in clinicopathological parameters exist among E3C,SC and CC. CC had a higher recurrence and SC had the worst survival. Although this is a large clinical study cohort,comprehensive molecular analysis is needed to further understand the biology of these diseases.

1246 BRG1 Immunohistochemistry in the Diagnosis of Small Cell Carcinoma of the Ovary, Hypercalcemic Type

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Background: Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is an uncommon undifferentiated ovarian malignancy which presents both diagnostic and therapeutic difficulties. Insights into the tumor have been limited due to its rarity and lack of specific biomarkers to assist in classification and until recently the histogenesis has been completely unknown. Recently it has been shown that germline and somatic *SMARCA4* mutations characterize SCCOHT. SMARCA4 encodes the protein BRG1. We showed in a prior publication that 38/40 SCCOHT lacked functional SMARCA4/BRG1 using genomic analysis and exhibited absence of immunohistochemical staining. In the current study, we aimed to investigate whether loss of BRG1 protein expression is specific for SCCOHT.

Design: The study cohort consisted of morphologic mimics of SCCOHT, including sex cord stromal tumors (adult, juvenile granulosa cell tumor, unclassified sex cord stromal tumor, Sertoli-Leydig tumor and others), undifferentiated carcinoma (UC), neuroendocrine carcinomas (NEC), germ cell tumors (GCT), small round blue cell tumors (SRBCT), including primitive neuroectodermal tumor, Wilms tumor, neuroblastoma and desmoplastic small round cell tumor, and miscellaneous tumors (MIS) such as malignant lymphoma and malignant melanoma. In some cases, whole tissue sections were stained with BRG1. In addition, a tissue micorarray was constructed and stained. The nuclear staining was scored as retained, lost or equivocal, the latter most commonly due to absence of a positive internal control.

Results: Table 1

	AGCT	JGCT	SLCT	GCT	SRBCT	UC and NEC	MIS
Retained	14	3	18	35	42	2	2
Lost	0	0	0	0	0	1	1
Equivocal	3	0	0	7	2	2	1

Conclusions: In this study of BRG1 immunohistochemistry in morphologic mimics of SCCOHT, the majority of cases showed retained nuclear expression suggesting that this is a relatively specific marker, although there was loss of staining in a small number of mimics. A significant number of cases were equivocal due to absence of an internal positive control and this may be attributable to the age of the cases. Staining of whole tissue sections is being performed to resolve the equivocal cases.

1247 Endometrial Surface Epithelial Change (ESEC) in Endometrial Samplings: A Banal-Appearing Histologic Marker of Underlying Endometrioid Adenocarcinoma in Postmenopausal Women

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Background: The surface of the endometrium may display a number of benign but confusing epithelial entities, most of which represent so-called Mullerian 'metaplasias'. These should be separated from the entity we have designated as endometrial surface epithelial changes (ESEC) that 1) almost exclusively occur in postmenopausal (PMP) women, 2) are frequently present on the surface of endometrial endometrioid adenocarcinoma (EMCA), and less frequently, atypical hyperplasia (AH), and 3) exhibit recognizable histologic changes that differ from EMCA. Superficial sampling of EMCAs may remove only the ESEC and result in underdiagnosis of the underlying cancer.

Design: Examination of endometrial biopsies and curettings between 2007-2014 revealed 289 cases showing at least one of the following histologic patterns of ESEC: 1) microglandular-type, mimicking endocervical microglandular hyperplasia, 2) architecturally complex mucinous proliferations, or 3) papillary clusters without fibrovascular cores. All exhibited minimal nuclear atypia. Typical metaplastic changes were excluded. In follow-up hysterectomy specimens that contained an EMCA, FIGO grade, pTNM stage, tumor size, and patient age were recorded.

Results: Of 289 endometrial initial specimens, 43% contained only ESEC while the remaining 57% showed ESEC associated with EMCA or less commonly AH. Almost half (46%) of ESEC-only group on initial sampling had EMCA in subsequent specimens. In the ESEC-only group with benign follow-up, the background endometrium showed anovulatory endometrium, polyp, breakdown, or metaplasia.

	Initial ESEC-only	Initial ESEC+EMCA/AH
No. of cases	124	165
F/U available	89	151
No AH/EMCA on f/u (%)	40 (44.9)	7 (4.6)
AH on f/u (%)	8 (8.9)	9 (6.0)
EMCA on f/u (%)	41 (46.1)	135 (89.4)
Mean tumor size (cm)	1.1	2.7
Tumor ≤ 2 cm	80.0%	32.3%
Mean Age (Range) (yrs)	59.8 (41-84)	62.2 (37-93)

Conclusions: ESEC is a recognizable histologic entity that differs from ordinary, invariably benign, endometrial metaplasias with which it may easily be confused. Its recognition is important since nearly half of the initial endometrial samplings containing only ESEC showed EMCA in a subsequent hysterectomy or curettage. A correct diagnosis of ESEC in the initial endometrial sampling of PMP women is clinically important since it may draw attention to the likely presence of a concurrent EMCA or precursor and prevent a delay in treatment.

1248 Expression of Cell Cycle and Steroid Hormone Receptors in 6 Different Types Uterine Smooth Muscle Tumors: Immunohistochemical Analysis and Potential Application

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Background: Uterine smooth muscle tumors (USMT) consist of leiomyoma (ULM), mitotically-active leiomyoma (MALM), cellular leiomyoma (CLM), atypical leiomyoma (ALM), uncertain malignant potential (STUMP) and leiomyosarcoma (LMS) and differential diagnosis remains a challenge in problematic cases. Recent progress into the molecular biology of USMT led us to further investigate these problematic USMT.

Design: We retrospectively collected 167 cases of uterine smooth muscle tumors, including 40 ULM, 7 MALM, 22 CLM, 42 ALM, 18 STUMP and 38 LMS. All cases were reviewed to confirm the diagnosis based on WHO and Stanford scheme. Tissue microarrays were prepared and immunohistochemical (IHC) stains for 7 biomarkers of cell cycle and steroid hormone receptors were performed. Semi-quantitative scores (pathologist review) and digital quantitation scores (NDP analyzer) from each marker and tumor types were then statistically analyzed.

Results: We first used a ROCcurve to verify the sensitivity and specificity and to establish a cut-off for all nuclear markers (Table 1). Overall, ER, PR, and Ki-67 were the most significant markers differentiating LMS from other subtypes (p<0.001). In

contrast, LMS, STUMP and ALM shared similar immunoreactivity for p53, p16, p21 and RB genes. While they appeared to cluster differently than the other subtypes, no significance was found (p>0.05). We also noted that ALM can be distinguished from CLM and ULM by cell cycle markers (Table 1). Based on our established cut-off values, when combining ER, PR and Ki-67 to differentiate LMS from ALM/STUMP, sensitivity was 81.6% and the specificity was 90% (p<0.0001).

IHC	ER%	PR%	Ki-67%	P53%	P16%	P21%	RB%
Cut-off	40	25	25	30	60	80	5
LMS	24	22	81	53	76	42	34
ALM	67	95	7	33	57	59	57
STUMP	71	88	18	56	39	50	50
CLM	91	100	0	23	18	6	27
MALM	83	100	0	0	14	0	67
ULM	80	80	2	0	6	14	13
Myometrium	87	87	0	0	2	0	0

Conclusions: We tested and evaluated a potential immunopanel using semi-quantitative and quantitative methods which could be used in the differential diagnosis of different subtypes of uterine smooth muscle tumors. In particular, we found that ER, PR, and Ki-67 were the most valuable markers in differentiating LMS from other tumor types.

1249 Two Types of Atypical Leiomyoma: Histologic, Immunohistochemical, and Clinical Correlation

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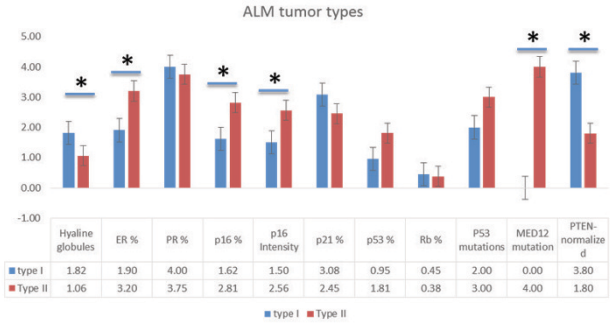
Background: In the literature, atypical leiomyoma (ALM) has many different names and this is largely due to its heterogeneity and presence of different histologic features, including 'true atypia' and 'degenerative atypia.' Debates about the biologic, histologic and clinical nature of ALM often impact our daily practice. We initiated this study to evaluate the histologic heterogeneity of ALM in correlation with biomarkers and clinical findings.

Design: We retrospectively collected 42 ALM cases from our institution and reviewed all cases to confirm the diagnosis based on the Stanford scheme. Data for each case, including patient age, tumor size, and clinical follow up, was recorded. Detailed histologic features, including growth pattern, cytologic features (nuclear size, shape, chromatin, nucleoli, cytoplasm), and differentiation were scored and analyzed. Finally, selected immunomarkers were examined.

Results: Patient age ranged from 28 to 62 with a mean age of 44 years. ALM had a different gross appearance than ULM and the tumor size ranged from 1.6 to 22 cm with a mean of 8 cm. Histologically, the tumors varied case by case. Based on the defined histologic and cytologic parameters, we found that there were generally two distinct types of ALM. Type I ALM had diffuse cytologic atypia. Nuclei were round or oval with single/multiple pleomorphic nuclei, coarse chromatin and frequent nucleoli. Type II ALM showed mostly focal or multifocal nuclear atypia. Nuclei were large, irregular, and spindled with degenerative changes shown by smudged nuclei. Nucleoli were rarely seen. We further compared the clinical, immunohistochemical and molecular changes in these two types of ALM and they are summarized in Table 1. In brief, Type I and Type II showed significant differences between hyaline globule distribution, ER and p16 staining, MED12 mutations, and PTEN mutations.



Conclusions: Our results suggest that ALM are histologically heterogeneous and they can be further classified into two different subtypes based on histology, immunoprofile, and molecular findings. We have previously found that some ALM share molecular changes with LMS and we hope to further determine if either type of ALM is more closely related to LMS.

1250 Minute Lymphangioleiomyomatosis in Pelvic and Paraaortic Lymph Nodes: A Study of 8 Cases

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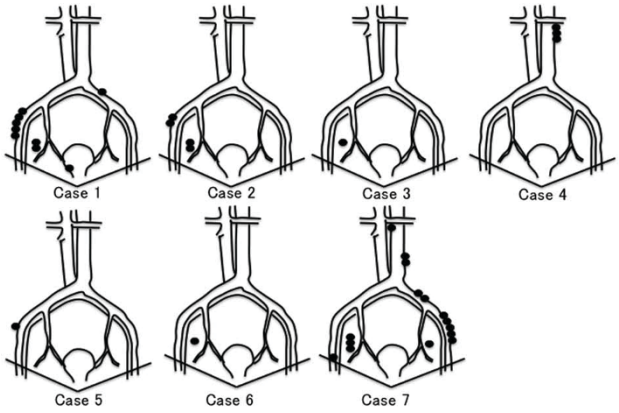
Background: Lymphangioleiomyomatosis (LAM) is a rare neoplasm of unknown origin, most commonly seen in the lungs. A recent observation that patients with pulmonary LAM frequently have the same tumor in gynecological organs suggests the tumor originating in the pelvic region. Rare case reports also described incidental minute LAMs in pelvic lymph nodes (LNs), which may be another argument for the hypothesis. However, significance of the subclinical nodal tumor remains uncertain. This study was conducted to elucidate clinicopathological features of minute LAMs incidentally found in pelvic and/or paraaortic LNs (LN-LAMs).

Design: Eight cases of LN-LAM were collected from our institutions' pathology archives and consultation files.

Results: The median age of the patients was 62 years (range 40-72). Five were postmenopausal. LN-LAMs were incidentally found in radical resection specimens for gynecological cancers: endometrial endometrioid carcinomas (n=5), endometrial carcinosarcoma (n=1), and ovarian high-grade serous carcinomas (n=2). No symptoms associated with LAMs were recorded preoperatively. LN-LAMs consisted of epithelioid and myoid cells loosely arranged in nests along the subcapsular sinus. The cells were immunohistochemically positive for a-SMA, desmin, HMB-45, and ER in all cases. Affected lymph nodes were one to 15 in number, >5 in two cases. LN-LAMs, one to 13 mm in size, were radiologically undetectable. In 7 cases, in which affected LNs could be mapped, positive nodes were supposedly present in either pelvis (n=5) or paraaorta (n=1), and both (n=1).



Case 1 had another incidental 10-mm LAM in the myometrium. She was also found to have lung cysts consistent with LAM on retrospective review of her lung CT. In the remaining 7, LAMs were only found in LNs with no relevant lesions in the uterus and adnexa. Clinically detectable LAMs have not appeared during follow-ups (mean 18, range 2-72 months).

Conclusions: LN-LAMs can be incidentally found in the pelvis and/or paraaorta of both reproductive and postmenopausal women. Although LN-LAMs may help us to identify clinically unsuspected pulmonary LAMs, most LN-LAMs lack extranodal involvement and seem to have little clinical significance for now.

1251 Mismatch Repair Protein Expression Loss in Epithelial Ovarian Cancer: A Guide for Targeted Screening

Kavita Varma, Eman Abdulfatah, Sumi Thomas, Haleema Saeed, Sharon Alford, Sudeshna Bandyopadhyay, Dhananjay Chitale, Adnan Munkarah, Rouba Ali-Fehmi. Wayne State University, Karmanos Cancer Institute, Detroit, MI; Henry Ford Hospital, Detroit, MI.

Background: Limited data is reported in the literature regarding defective DNA mismatch repair protein (dMMR) in ovarian carcinoma(OC). Its significance and implications remain to be fully investigated. The aim of this study was to evaluate frequency of dMMR in OC and their clinicopathologic features.

Design: 560 OC pts from 2 institutions were included:367 serous carcinoma (SC),41 endometrioid carcinoma (EC),24 clear cell (CC),70 mucinous,54 mixed,4 undifferentiated carcinoma (UC). Tissue microarrays (TMA) were immunohistochemically stained for MLH1, MSH2, PMS2 and MSH6 proteins. Absence of expression of any of the aforementioned proteins in the tumor with positive lymphocytes (control) was considered to be dMMR.

Results: dMMR was noted in 20/560(3.6%) pts., with the highest frequency in UC(3/4,75%) followed by CC(7/24,29.1%), mixed(5/54,9.3%), SC(4/367,1.9%), , EC(1/41,2.4%) and 0 mucinous. Of the pts with dMMR age ≤50yrs was more frequent (13/20, 65%), 16 of 20 pts were CA (65%), Caucasians (CA)(16/20,80%) FIGO stages included Stage I+II (10/20, 50%) and Stage III+IV (10/20,50%). Family history of cancer, available on 13 pts including breast, colon, brain, pancreas, prostate, hematopoietic and ovary was noted in 7/13(53.8%).One pt with UC had synchronous endometrial carcinoma and another with SC had synchronous breast carcinoma (2/20, 10%). The most common defective MMR protein was PMS2 (12/20, 44.4%) of which 9 had defective PMS2 alone, 1 had MLH1/PMS2 loss, 1 had MSH2/PMS2 and 1 had MSH6/PMS2 loss.

dMMR protein expression profile of positive cases

	MLH1	MSH2	PMS2	MSH6
CC	-	+	-	+
CC	-	+	+	-
CC	+	+	-	+
CC	-	+	+	+
CC	+	+	+	-
CC	+	-	+	-
CC	-	+	+	+
UC	+	+	-	+
UC	+	+	-	+
UC	-	+	+	+
EC	+	+	-	+
MIXED	+	+	-	+
MIXED	+	+	-	+
MIXED	-	+	+	+
MIXED	+	+	-	+
MIXED	-	-	+	-
SC	+	-	-	+
SC	+	+	-	+
SC	+	+	-	+
SC	+	+	-	-
TOTAL	7 (25.9%)	3 (11.1%)	12 (44.4%)	5 (18.5%)

Conclusions: dMMR was found in 3.6% of OC, most frequent in the UC type followed by CC. Predominant defective protein was PMS2. dMMR was frequent in CA and pts ≤50yrs. More studies are necessary to understand and validate the significance of dMMR in Ovarian carcinoma.

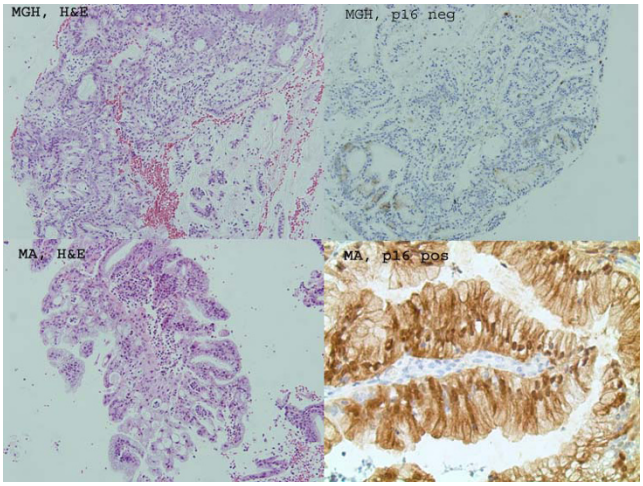
1252 Utility of Immunohistochemical Panel in Identifying Neoplastic Mucinous Lesions in Endometrial (EM) Sampling

Kavita Varma, Denyo Zakhia, Daniel Schultz, Arthur Gaba, Ziying Zhang. Henry Ford Hospital, Detroit, MI.

Background: Complex endometrial hyperplasia with mucinous metaplasia (CEHMM) or well differentiated mucinous adenocarcinoma (MA) can have a deceptively bland cytology. Interpretation of mucinous epithelial cells in EM samplings can be difficult in routine practice since neoplastic EM mucinous epithelium can have histologic similarities to benign endocervical epithelium. Evaluation of architectural complexity is often limited. Our aim is to establish an immunostain panel to distinguish neoplastic endometrial mucinous epithelium from benign endocervical contamination.

Design: We selected all cases of EM biopsy or curetting from 1/2000-9/2013 with presence of mucinous epithelium; and follow up hysterectomy proven to be either CEHMM or MA. 10 cases of endocervical microglandular hyperplasia (MGH) from ECC were randomly selected as control group. Immunostains performed include p16, MIB-1, ER, vimentin, mCEA. P16 stain was graded as neg, focal+ [<50% cells cytoplasmic and nuclear (C&N) stain], and diffuse+ [>50% cells with C&N stain]. Intense cytoplasmic stain in >10% cells was scored as + for vimentin and mCEA. Nuclear stain in >10% cells was scored as + for MIB-1 and ER.

Results: Our search generated 24 cases (6 CEHMM and 18 MA), age from 45-55y. All 24 cases and 10 endocervical MGH control cases stain+ for ER and neg for mCEA. The immunostain results for p16, vimentin, and MIB-1 are summarized in Table 1



	p16 diffuse+	p16 focal+	p16-	Vimentin+	Vimentin-	MIB-1+	MIB-1-
CEHMM (6)	1	5	0	5	1	0	6
MA (18)	15	3	0	17	1	18	0
MGH (10)	0	0	10	0	10	0	10

Conclusions: Interpretation of cytologically bland mucin-containing columnar epithelial cells in EM sampling should be evaluated with caution. When in morphological doubt, p16, vimentin and MIB-1 can be used to ascertain origin. Negative staining for p16, MIB-1, and vimentin indicates benign endocervical contamination. In contrast, positive staining for p16 and vimentin remains the most consistent with endometrial origin. MIB-1 stain in >10% of the cells plus diffuse p16 positivity are associated with endometrial mucinous adenocarcinoma. In present study, ER and mCEA have shown no value for ascertaining the origin.

1253 Screening Endometrial Adenocarcinoma Precursor Lesions for Lynch Syndrome

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Background: Universal screening of patients with endometrial and colorectal adenocarcinoma for Lynch Syndrome with immunohistochemical (IHC) analysis for loss of expression (LOE) of DNA mismatch-repair (MMR) proteins is developing as the standard of care. Screening the premalignant lesion of colorectal carcinoma, adenomatous polyps, has not been shown to be an effective strategy for identifying novel cases of Lynch Syndrome. The benefit of evaluating the precursor of endometrial carcinoma, endometrial hyperplasia (intraepithelial neoplasia), in such a manner has yet to be defined. In the present study, we sought to determine the: (1) incidence and type of MMR protein LOE in the precursor lesion of endometrial adenocarcinoma, and (2) agreement of IHC results in endometrial biopsy (EMB) specimens with subsequent uterine resections.

Design: A retrospective review identified 113 endometrial biopsies meeting criteria for endometrial intraepithelial neoplasia (EIN) between 2009 and 2014. Slides made from tissue microarray blocks were evaluated using antibodies against MLH1, PMS2, MSH2, and MSH6. Fifty-five subsequent hysterectomy specimens were retrieved and assessed for MMR protein LOE. Cases with MLH1 LOE were evaluated for gene promoter hypermethylation by PCR analysis.

Results: Of 113 endometrial biopsies with EIN, 4.4% (5/113) exhibited loss of MMR protein expression. The majority (4/5) demonstrated defective expression of MLH1, of which, all exhibited inactivation via promoter hypermethylation. A single case displayed an absence of MSH6. Age was not significantly associated with MMR deficiency or a specific MMR protein phenotype. The sensitivity of IHC in an EMB for predicting LOE in a subsequent uterine resection was 75%, with a specificity of 100%.

Conclusions: The utility of evaluating EIN with MMR protein IHC as a screen for Lynch Syndrome is limited. Sporadic hypermethylation of MLH1 appears to be the primary mechanism underlying defective MMR protein expression in EIN. Amongst our cohort, only 1 patient (<1%) had a mutation suggestive of a hereditary inheritance. Although highly specific, the sensitivity of IHC in an EMB for detecting LOE in a subsequent hysterectomy was suboptimal. Hence, screening women with EIN for Lynch Syndrome was ineffective, regardless of age.

1254 Ovarian Seromucinous Tumors: A Clinicopathologic Review of 23 Cases

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Background: Ovarian seromucinous (endocervical-type) tumors are a group of neoplasms with the architecture of serous tumors but with epithelium comprised of multiple cell types, including endocervical-type mucinous, serous, indifferent, and endometrioid cells. These tumors often arise in a background of endometriosis and have been shown to be genetically related to endometrioid and clear cell carcinomas. Since their thorough characterization in 2002, few additional studies have investigated the clinical behavior of these tumors over the long-term. We present the clinicopathological characteristics of 23 seromucinous tumors.

Design: We searched our institutional and consultative archives for ovarian seromucinous tumors. Cases were subdivided into 5 groups using previously published criteria: seromucinous adenofibroma (AF), atypical proliferative seromucinous tumor (APSMT), APSMT with microinvasion (APSMT-MI), APSMT with intraepithelial carcinoma (APSMT-IC), and seromucinous carcinoma (SMCA). Relevant clinicopathological data was recorded when available.

Results: Clinicopathological summary data is shown in table 1. One tumor was AF. Follow-up was available in 16 (average 73 months; range <1 to 136). In most cases, the dominant cell type was serous. In SMCA, epithelial confluence (>5mm) was seen in 3 (100%) and stromal invasion in 1 (33%). Invasive implants could manifest as psammocarcinoma or feature abundant mucinous epithelium.

Tumor Type	n	Mean Age	Implants	FIGO Stage	Follow-up
APSMT	14	48	None=11 Non-invasive=2 Invasive=1 UNK=1	IA=8 IB=1 IC=3 IIC=1 UNK=1	NED=11 UNK=3
APSMT-MI	3	61	None=2 Invasive=1	IA=2 IIC=1	NED=2 UNK=1
APSMT-IC	2	65	None=1 Invasive=1	IIC=1 IIIB=1	NED=1 UNK=1
SMCA	3	61	None=1 Invasive=1 UNK=1	IA=1 UNK=2	NED=1 UNK=2

APSMT = atypical proliferative seromucinous tumor; MI = microinvasion; IC = intraepithelial carcinoma; SMCA = seromucinous carcinoma; NED = no evidence disease; UNK = unknown

Conclusions: APSMTs, even those with microinvasion or intraepithelial carcinoma, often present at a low-stage and behave indolently. The pattern of extra-ovarian disease is similar to low-grade serous tumors. The morphology of invasive implants can have architectural and cytologic variability (i.e. psammocarcinoma or cystic masses of mixed cell type). In our study group, seromucinous tumors in patients > 60 years were more often microinvasive, contained intraepithelial carcinoma, or qualify as carcinoma.

1255 Is p16 Staining of CIN II on Cervical Biopsy Predictive of HSIL on Subsequent Cone Biopsy?

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Background: Although a significant number of CIN II cases progress to CIN III, regression of CIN II is also common. ACOG has recommended conservative management of young patients with CIN II due to frequent regression. p16 expression has been shown to help improve the diagnostic accuracy of CIN II and CIN III and its use has been recommended to guide management of CIN II. In the current study we examined the correlation of p16 findings in cervical biopsies with CIN II with findings in subsequent cervical cone biopsies.

Design: The computerized records of NYU Hospital Systems were searched for cases with a histological diagnosis of CIN II in cervical biopsies from 2004 to 2010. Cases were selected if there were subsequent excisional specimens (LEEP or Cone biopsy). Immunostains for p16 were performed on adjacent sections of biopsies. No staining and patchy staining was graded as negative; diffuse and strong block staining was graded as positive.

Results: There were a total of 22 patients who qualified for the study, with a mean age of 34 years, and a range of 20 to 51 years. 21 of the 22 patients showed diffuse strong positive staining for p16. The staining extended for a height of 100% of epithelium in 14/21 patients, and 50% or greater height of epithelium in all 21 cases with strong diffuse staining. Of the 21 patients with strong diffuse staining on cervical biopsy, 10 had CIN III, 6 had CIN II or CIN I-II, 2 had CIN I, and 3 had no CIN on subsequent cone biopsy. The only patient with patchy p16 staining on cervical biopsy had CIN III on cone biopsy.

Conclusions: p16 showed diffuse positive staining in almost all biopsies with CIN II and therefore was unable to select for patients with greater likelihood of CIN III in subsequent cervical cone biopsy. Only one biopsy lacked diffuse p16 expression-subsequent cone biopsy in this case showed CIN III.

Our data suggests that each laboratory needs to examine the frequency of p16 staining in their CIN II cases to evaluate potential utility of this marker in their cases for further guiding the decision to perform or not to perform a cone biopsy. If p16 is positive in all or nearly all CIN II cases in a laboratory, it is not going to be a useful maker in that laboratory.

There is some evidence of concordance of p16 expression and probability of progression to higher grade dysplasia. However, many CIN II cases negative for p16 progress and vice versa. Additional biomarkers are needed for minimizing the cases that progress with a negative p16 staining and cases that regress with a positive p16 staining.

1256 Preoperative Detection of Uterine Leiomyosarcoma By Endometrial Biopsy: An Examination of Clinical and Histologic Features

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Background: In the era of minimally invasive surgery, a need to identify women with uterine leiomyosarcoma (ULMS) pre-operatively has emerged. While the sensitivity of endometrial sampling (ES) in epithelial-based tumors is well established, the available data for its utility in diagnosing uterine sarcoma is limited. In this study, we attempt to determine the preoperative sensitivity of ES for ULMS and the effect of histologic and clinical variables on the sensitivity.

Design: Our retrospective IRB-approved study included all ULMS cases treated at participating institutions between January 2005 and August 2012 (n=329). Cases in which pathologists from the participating institutions had reviewed both the patient's ES and uterine resection specimen were identified. Histologic features of ULMS including grade, presence of necrosis, tumor size, mitotic rate, and lymphovascular invasion were recorded. Data abstracted from the longitudinal medical record included age, presenting symptom, and method of preoperative biopsy.

Results: Of 329 cases identified, 24 cases had both ES and uterine pathology reviewed by a pathologist at one of the participating institutions. 15 patients (62.5%) underwent preoperative pipelle endometrial biopsy (EMB), and 9 (37.5%) had dilation and curettage (D&C). 13 (54.2%) of the pre-operative biopsies showed either ULMS or an atypical spindle cell proliferation. Women sampled by D&C were significantly more likely to have a preoperative diagnosis of ULMS than women sampled by EMB (77.8% v 40%, p=0.036). No tumor histologic features were significantly associated with ES sensitivity. Tumors of a higher grade (grade 3/high), however, tended to have positive biopsies compared to tumors of a lower grade (2/intermediate) (61% v 33.3%, p=0. 128). Age and presenting symptom were not significantly associated with ES sensitivity, though women presenting with post-menopausal bleeding tended to have positive biopsies compared to others (66.7% v 41.6%, p =0.110).

Conclusions: Preoperative ES will identify ULMS or an atypical spindle cell proliferation in 54.2% of patients with ULMS. D&C is significantly more likely than EMB to detect ULMS preoperatively. Further studies are warranted to explore the utility of D&C as a diagnostic tool in patients with uterine masses clinically presumed to be fibroids.

1257 Universal Lynch Screening in Endometrial Cancers: An Examination of Immunohistochemical Subgroups and Associated Clinical and Histologic Features

Jaclyn Watkins, Lynette Sholl, Brooke Howitt. Brigham & Women's Hospital, Boston, MA.

Background: Endometrial carcinoma (EMC) is the first malignancy diagnosed in 50% of women with Lynch syndrome (LS). Although screening for LS in colorectal cancer (CRC) is widely accepted, universal screening in EMC is still debated.

Design: Our prospective IRB-approved study included all EMC resected from 10/2013-9/2014 (n=125). All tumor slides were assessed for morphologic features including histologic subtype (endometrioid E, serous S, undifferentiated U), grade (G), and tumor infiltrating lymphocytes. Patient age, BMI, and personal or family history (FH) of malignancy were recorded. Immunohistochemistry for MMR proteins MSH2, MSH6, MLH1, and PMS2 was performed.

Results: The average age in our cohort was 62.7y (range 27-87y). Histotypes included E (100; 80%: 78 G1, 17 G2, 12 G3, and 2 biphasic G1/3), S (10; 8%), carcinosarcoma (2; 1.6%), U (2; 1.6%), mixed E and S (7; 5.6%), and other mixed subtypes (3; 2.4%). MMR abnormalities included loss of MSH2/MSH6 (3; 2.4%; all E), loss of MSH6 (1; 0.8%; mixed E and U), or loss of MLH1/PMS2 (20; 16%; 19 pure E and 1 mixed E and U). In cases with MLH1 loss, 1 case (5%) was unmethylated. Patients with presumed LS were overall younger than those with MMR-intact tumors (48.5 vs. 62.8y, p=0.006); however, of the 5 cases with presumed LS (loss of MSH2/MSH6, MSH6 only, or MLH1 without promoter methylation), only 3 were < 50 y, (accounting for 27.3% of EMC in women < 50y). None of the patients had a prior history of cancer. The patient with an unmethylated MLH1 deficient tumor had a paternal history of MLH1 germline mutation, and multiple relatives with CRC and EMC. Of the 4 remaining MMR-deficient cases, 1 had a FH of maternal breast cancer, and another had a FH of maternal breast cancer and multiple maternal relatives with EMC. The remaining 2 had unremarkable FH. Tumors with MLH1 methylation were more likely to be G3 (p=0.006).

Conclusions: Screening guidelines for LS in EMC based on age, FH, and tumor morphology would miss 40% of presumed LS patients at our institution accounting for 4% of EMC. LS-related tumors displayed no prototypical histomorphology. Tumors with MLH1 methylation were the only MMR deficient tumors to display a significantly different morphology, having a statistically significant association with G3 EMC. Our findings support the use of universal screening for LS using MMR IHC in women with EMC.

1258 Unusual Mismatch Repair Immunohistochemical Patterns in Endometrial Carcinoma

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Background: Immunohistochemistry (IHC) for mismatch repair (MMR) proteins can be used to screen for Lynch Syndrome (LS). Universal screening in colon cancer has brought to light various non-LS related patterns of staining, described as "heterogenous" or "subclonal" staining. These unusual patterns of MMR expression have yet to be explored in endometrial carcinomas (EMC).

Design: As part of a prospective study of universal Lynch screening of resected EMC by MMR IHC (n=125), cases with EMC, both with and without concurrent EIN, that demonstrated distinct, subclonal loss of MMR proteins (MSH2, MSH6, MLH1, and/or PMS2) were identified. Tumors showing diffusely patchy or heterogeneous staining were not included in this study. EMC with complete loss of MLH1/PMS2 with coexisting EIN were also evaluated as a second cohort. H&E slides were evaluated for histologic subtype (endometrioid E, serous S) and grade (G). *MLH1* promoter methylation and MMR gene mutational status were reviewed when available.

Results: Overall, 14 cases were included, consisting of two groups.

Group 1 consisted of 7 EMC demonstrating unusual subclonal MMR staining patterns within the EMC. 5/7 (4% of overall cohort) displayed subclonal loss of MLH1/PMS2 (4 E-G1 and 1 mixed E-G3 and S). Three of these cases were tested for *MLH1* promoter methylation, with confirmatory results. In the mixed E-G3/S tumor, the subclonal loss occurred in the endometrioid component. One case (E, G2) displayed subclonal MSH6 loss with intact, but weak, MSH2 staining. This tumor had a *MSH6* p.E1254 deletion present in 27% of sequence reads. Another case (E, G1) had subclonal loss of MLH1 in the setting of complete loss of PMS2 (consistent with LS).

Group 2 consisted of 7 EMC with coexisting EIN, all with complete MLH1/PMS2 loss in the EMC. 5/7 (all E; 3 G1, 1 G2, 1 G3) showed concurrent loss of MLH1/PMS2 in the adjacent EIN. 2/7 (both E, 1 G1, 1 G2-3) displayed MLH1/PMS2 intact staining in the coexisting EIN.

Conclusions: Focal loss of MLH1/PMS2 in EMC results from subclonal *MLH1* promoter methylation. These patterns suggest that *MLH1* methylation is a later event in the development of some EMC. Subclonal loss of MMR proteins not known to undergo epigenetic silencing appears to be due to somatic mutation.

1259 A Retrospective Comparison of the 1994 and 2014 WHO Classifications of Endometrial Hyperplasia

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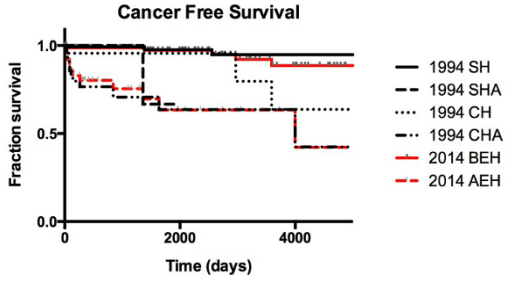
Background: Endometrial carcinoma is the most common malignancy of the female reproductive tract and approximately 47,000 new cases and 8,000 deaths occur in the United States each year. Endometrial carcinoma frequently arises in a background of endometrial hyperplasia, which is separated into 4 categories based on the 1994 WHO classification: simple hyperplasia (SH), simple hyperplasia with atypia (SHA), complex hyperplasia (CH), and complex hyperplasia with atypia (CHA). The 2014 WHO classification has revised this system into 2 categories based on cytologic atypia: benign hyperplasia (BEH), and atypical hyperplasia (AEH). This project compares the 1994 and 2014 classifications in predicting cancer free survival.

Design: Patients diagnosed with endometrial hyperplasia from 1999-2001 at our institution were classified using the 1994 and 2014 WHO criteria. Median follow-up time was 592 days. Time to development of endometrial carcinoma was compared by Kaplan Meier analysis.

Results: 274 patients were categorized by 1994 (191 SH, 7 SHA, 24 CH, 52 CHA) and 2014 (BEH 215, AEH 59) criteria. Kaplan Meier analysis showed that patients with CHA developed carcinoma more rapidly than patients with SH ($p<0.0001$) but was not statistically different from CH ($p=0.11$) or SHA ($p=0.41$). Patients with CH ($p=0.017$) and SHA ($p=0.012$) did not develop carcinoma more rapidly than patients with SH after correction for multiple comparisons. Patients with AEH developed carcinoma more rapidly than patients with BEH ($p<0.0001$) but was not statistically different from SHA ($p=0.46$) or CHA ($p=0.73$). Similarly, BEH was not different from SH ($p=0.44$) or CH ($p=0.08$).

Conclusions: These data support the adoption of the 2014 WHO classification of endometrial hyperplasia.



Development of Carcinoma	YES	NO	No Follow-up	Total	%
1994 Simple Hyperplasia	4	145	42	191	2.09
1994 Simple Hyperplasia with Atypia	1	6	0	7	14.29
1994 Complex Hyperplasia	3	20	1	24	12.5
1994 Complex Hyperplasia with Atypia	12	37	3	52	23.08
2014 Benign Endometrial Hyperplasia	7	165	43	215	3.26
2014 Atypical Endometrial Hyperplasia	13	43	3	59	22.03

1260 Mucosal Proliferations in Completely Dissected Fallopian Tubes in a Blinded Study of Ovarian Serous Cystadenoma, Borderline Tumor and Low Grade Serous Carcinoma: Does a Precursor Tubal Lesion Exist?

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Background: Papillary proliferation and shedding of the fallopian tube mucosa onto the ovary has been proposed as an origin of ovarian serous borderline tumor (SBOT) and low grade serous carcinoma (LGSC) (Kurman et al. AJSP. 2011; 35: 1605). In this model, such tubal lesions would be expected to be present in tubes from the earliest stage (FIGO IA/B) SBOT and LGSC. However, this proposal has not been tested in completely dissected fallopian tubes from a spectrum of serous cystadenomas, SBOTs, and LGSCs of early or advanced stages.

Design: Fallopian tubes were thinly sliced and completely examined microscopically from ovarian serous cystadenoma (n=25); FIGO IA/B SBOT (n=15); FIGO IC or higher SBOT (n=29); and LGSC (n=2). For this study, the fallopian tube slides were reviewed without knowing the ovary diagnosis. Mucosal changes were classified as Type 1: non-papillary mucosal crowding, stratification, and/or tufting. Type 2: simple small papillae with a fibrous core, either attached to or detached from the mucosa, without cell crowding or stratification. Type 3: detached intraluminal papillae, buds, or nests (with or without psammoma bodies) resembling the epithelial component of extra-ovarian implants of SBOT.

Results: No significant differences in the incidence of Type 1 or Type 2 mucosal changes were observed between cystadenoma, FIGO IA/B SBOT, FIGO IC or higher SBOT, and LGSC. Of these, the most common change was multifocal micro-foci of mild mucosal crowding (36%,33%,52%,50%, $p>0.05$). Type 3 detached epithelium was only detected in FIGO 1C or higher SBOT (26%) but not in cystadenoma or FIGO IA/B SBOT. None of the cases contained serous tubal intraepithelial carcinoma.

Conclusions: Serous borderline tumor-like epithelium floating in the fallopian tube lumen (Type 3) likely originates from the ovary rather than from the tube since it was never seen in tubes of early stage SBOT or cystadenoma. Mild tubal mucosal hyperplasia and papillary structures (Type 1 and 2) are within the spectrum of normal tubal anatomy. Evidence for progression of tubal mucosal proliferation to ovarian borderline tumor remains to be demonstrated.

1261 Histopathologic Characteristics of Immature Neuroepithelial Tubules in Ovarian Immature Teratoma

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Background: Immature teratoma is defined as a tumor containing immature embryonal-type tissues, mostly in the form of immature neuroepithelial tubules (INT) or rosettes. Clear recognition of INT is important not only for the decision of postoperative treatment and prognosis of the patients, but for differential diagnosis from yolk sac tumor, mixed germ cell tumor and mature teratoma containing immature endodermal tubule (IET) or mature ependymal tubules (MET). Histologically, INT usually consists of multilayered hyperchromatic nuclei with or without pigmentation, but INT is often indistinguishable from IET or MET, in that both structures are lined by stratified nuclei. We aimed to further characterize the histopathologic features of INT with its differential histopathologic features from IET and MET and to find useful immunohistochemical markers for INT that can be used in the difficult cases.

Design: 35 ovarian immature teratomas were retrieved from database of Asan Medical Center, Seoul, Korea. Of 72 slides from 35 cases, 129 foci containing INTs, 21 foci for IET, and 16 for MET were separately encircled. Various histopathologic features including presence or absence of basement membrane (BM) around the tubules, background of the tubules, numbers of cellular layers and mitoses, and nuclear shape were evaluated. Immunostaining for Nestin, which is a marker for neural stem cells, was performed to test a diagnostic utility. Immunostains for Ki67 and AFP were also performed in selected cases.

Results: Histologically, BM was either absent (59.7%) or poorly developed (40.3%) around INT, but it was clearly identified around IET. INT and MET were surrounded by neuroglial background, whereas IET was surrounded by spindle cells. Mean number of layers (11 vs. 7.3 vs. 2.7) and mitoses (5.7 vs. 2.5 vs. 0.3) were significantly higher in INT and IET compared to MET ($p<0.001$), but retinal like areas showed low mitoses and low Ki67 labeling index. Ki67 labeling index was significantly higher in INT and IET compared to MET. Nestin was expressed only in the INT, but not in IET and MET.

Conclusions: INT can be further defined as a multilayered tubule in the neuroglial background with either absent or poorly formed BM. It can be differentiated from MET when it have 6 or more nuclear layers or 3 or more mitoses per high power field with an exception in retina-like differentiated areas. Nestin is a useful differential marker for identifying INT from IET and MET in the difficult cases.

1262 Assessment of HER2/neu in Uterine, Ovarian, and Peritoneal Carcinomas: A Retrospective Study of 134 Cases

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Background: HER2/*neu* overexpression/gene amplification is well studied in breast and gastric carcinomas. However, unlike in breast and gastric carcinomas, the determination of HER2 status in gynecologic cancers has not been well studied as either a prognostic indicator or predictive biomarker for response to anti-HER2 treatment such as trastuzumab. In this study, we evaluated the HER2 status of malignant uterine, ovarian, and peritoneal carcinomas and correlated HER2 positive cases with clinical follow-up.

Design: In this retrospective study, uterine, ovarian, and peritoneal carcinomas from 2005-2014 with HER2 studies were evaluated. HER2 immunohistochemistry (IHC) was performed and graded utilizing the 2013 ASCO/CAP scoring criteria for breast carcinoma. Cases with corresponding fluorescence *in situ* hybridization (FISH) studies were evaluated similarly. A 3+ staining pattern by IHC and/or HER2 amplification was considered positive for HER2. An equivocal staining pattern (2+) without a corresponding FISH study was excluded.

Results: 134 cases were evaluated. 43 cases had corresponding FISH studies. Histologic subtypes were categorized as pure serous (37.3%), pure clear cell (7.5%), "mixed" (23.1%), endometrioid (23.9%), and "other" (8.2%). HER2 positivity was seen in 10/134 cases (7.5%) by IHC and/or FISH, including 5 pure serous (4 uterine, 1 ovarian), 3 pure clear cell (3 ovarian), 1 mixed ovarian serous and clear cell ("mixed"), and 1 poorly differentiated uterine carcinoma ("other"). Two out of ten (2/10) HER2 positive cases were positive by IHC only (no corresponding FISH study). The remaining eight cases (8/10) had corresponding FISH studies that were all positive for HER2 amplification. The IHC and FISH concordance rate was 75%. The IHC and FISH discordance rate was 25%. Follow-up was available for 3 patients (2 with concordant IHC/FISH and 1 IHC only); all received trastuzumab and showed excellent response. Intratumoral heterogeneity was seen in 1.5% (2/134) of all cases.

Conclusions: In our study, HER2 positivity was only seen in serous and clear cell subtypes and poorly differentiated carcinoma. While follow-up data is limited, patients with concordant IHC/FISH studies or positive IHC alone showed excellent response to trastuzumab therapy. Since up to 25% of cases may have discordant IHC/FISH results, we propose performing HER2 testing, by both IHC and FISH, in all serous, clear cell, and poorly differentiated carcinomas.

1263 Lower Female Genital Tract Tumors With Adenoid Cystic Differentiation: P16 Expression and High-Risk HPV Detection

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Background: Lower female genital tract tumors with adenoid cystic differentiation are rare and data on their relationship with high-risk human papillomavirus (HPV) are limited. Clinicopathologic features of a case series are reported.

Design: Tumors with adenoid cystic differentiation, either pure or as part of a carcinoma with mixed differentiation, arising in the lower female genital tract were evaluated by immunohistochemistry for p16 expression, by in situ hybridization (ISH) using one or more probes for high-risk HPV (a high-risk probe, a wide spectrum probe, and separate type-specific probes for HPV 16 and HPV 18), and when possible by polymerase chain reaction (PCR) for high-risk HPV.

Results: Eight cases of cervical (7) and vulvar (1) carcinomas with adenoid cystic differentiation were identified in patients ranging in age from 48-86 years (mean: 68, median: 70). Six cervical carcinomas with various combinations of at least two patterns of mixed differentiation, including adenoid cystic, adenoid basal, squamous (basaloid or keratinizing), and small cell components, displayed diffuse p16 expression. HPV 16 was identified by ISH in 3 tumors and HPV 45 was identified by PCR in 1 tumor for which ISH failed to detect HPV; 2 tumors with diffuse p16 expression had no detectable HPV by ISH but material was not available to perform PCR. In contrast, 2 pure adenoid cystic carcinomas (1 cervical, 1 vulvar) exhibited non-diffuse p16 expression and had no detectable HPV by ISH.

Conclusions: Lower female genital tract carcinomas with adenoid cystic differentiation appear to comprise two distinct groups, namely, carcinomas with mixed differentiation (adenoid cystic, adenoid basal, and squamous) which are high-risk HPV-related and can be identified by diffuse p16 expression and pure adenoid cystic carcinomas which appear to be unrelated to high-risk HPV and can be identified by non-diffuse p16 expression.

1264 The Utility of Phosphohistone-H3 (PHH3), Ki-67, and p16 in Characterizing Uterine Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP)

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Background: Uterine smooth muscle tumors (USMT) are extremely common. The majority are leiomyomas (LM) which pose little diagnostic difficulty. Leiomyosarcomas (LMS) exhibit frankly malignant features including moderate to severe nuclear atypia, high mitotic index and tumor necrosis, making diagnosis similarly uncomplicated. A subset of USMT cannot be diagnosed unequivocally as LM or LMS, thus are classified as STUMP. The latter represents a heterogeneous group of rare tumors that have been the subject of only a few published studies, with no well-established diagnostic criteria. In this study, we sought to characterize STUMP by utilizing immunostaining for the mitosis-specific marker PHH3, Ki-67 proliferation index (PI) and p16, a cyclin dependent kinase inhibitor.

Design: Twenty consecutive STUMP cases from the authors' institution between 1995 and 2013 were achieved. Thirty consecutive LMS and thirty-four LM cases were included as controls. Ki-67 was scored as the average fraction of total cells, and PHH3 was scored as the total number of labeled tumor cells, both from 10 high power fields where immunolabeling was prevalent. P16 expression was evaluated by an H-score based on both percentage of positively stained cells and immunointensity.

Results: STUMP could be distinguished from LMS by Ki-67 (mean score 7.1 vs. 38.1; $p<0.001$) or PHH3 (8.1 vs. 47.4; $p<0.001$), whereas neither marker reliably separated STUMP from LM. Interestingly, 22 of 30 LMS (73.3%) showed diffuse and strong p16 staining with H-score >200. Of 8 LMS with p16 score ≤ 30, 5 exhibited either significantly increased Ki-67 PI (≥ 25%) or PHH3 labeling (≥ 25/10 HPF). The p16 expression in STUMP and LM was significantly lower when compared to that in LMS (mean score 27.6 and 7.5 vs. 204.9, $p<0.001$). Two tumors classified as STUMP and 1 tumor classified as LM demonstrated strong p16 expression with H-score of 130, 190 and 110, respectively. Overall survival of USMT patients were determined and mapped on to a Kaplan-Meier curve. Univariate analysis revealed that patients with LM and STUMP showed a similar overall survival rate, which was significantly different from those with LMS ($p<0.001$).

Conclusions: While H&E remains the most important tool in diagnosing USMT, PHH3, Ki-67 and p16 can serve as adjuncts for classification of equivocal lesions. LM and STUMP patients with high p16 expression may warrant close follow-up. Our data also suggest that STUMP and LM have similar biologic behavior, thus these patients should receive similar surveillance.

1265 Solitary Fibrous Tumor of the Female Genital Tract: A Clinicopathologic Analysis of 6 Cases

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Background: Solitary fibrous tumor (SFT) is an uncommon spindle cell neoplasm of fibroblastic origin, first described as a tumor of the pleura. Numerous extra-pleural SFT have since been reported; however SFT of the female genital tract is rare, with fewer than 20 reported cases. Thus, the aim of this study was to 1) augment the current understanding and 2) raise awareness of this rare entity by analyzing the clinical features and morphologic spectrum of 6 SFT involving the female genital tract (FGT).

Design: Cases of SFT diagnosed in the Women's and Perinatal Division from 2005-2014 were included in this study. Follow-up data were abstracted from the electronic medical records.

Results:

Table 1: Clinicopathologic features of SFT of the female genital tract

Case no.	Age	Primary Site	Diagnosis	Size (cm)	Mit/ 10HPF	Stat6	CD34	Follow-up
1	34	Vulva	Atypical SFT	4.5	1	ND	ND	N/A
2	63	Vulva	Atypical SFT	5.7	1	+	+	N/A
3	74	Uterus (corpus)	Malignant SFT	9.5	10	-	-	Disease free; 44 mo
4	81	Uterus (corpus)	SFT	10	1	+	ND	Lung metastases; 2 mo
5	72	Uterus (cervix)	Malignant SFT	14.5	5	+	-	Pelvic recurrence; 2 mo
6	81	Ovary	Malignant SFT	25	56	+	+	Pelvic recurrence, lung metastaes; 6 mo

N/A, not available; ND, not done.

The findings are summarized in Table 1. The mean age was 67 (range 34-81) years. The tumors were primary in the vulva (2), uterus (3), or ovary (1) (mean size, 11.5 cm). All tumors demonstrated classic histologic features of SFT: "patternless" growth pattern with marked variation in cellularity, prominent branching "hemangiopericytoma-like" vessels, and dense collagen bundles. 3/6 SFT were classified as malignant based on mitotic counts > 4/10 HPF (range 1-56). Two tumors were designated "atypical" on the basis of significant nuclear atypia. Strong nuclear STAT6 expression was seen in 80% (4/5) and CD34 was positive in 50% (2/4). Clinical follow-up was available for 4 cases (mean 13.5, range 2- 44 months). Overall 3/4 had recurrence or metastasis (2 malignant SFT and 1 SFT without overt histologic features of malignancy).

Conclusions: The morphologic and immunohistochemical features of SFT of the FGT are similar to those at other anatomic sites. Although numbers are small, gynecologic SFT are more frequently malignant (67%) compared to SFT at other sites (~ 10-15%). Given that a "benign" SFT by histologic criteria metastasized to the lung, SFT in the FGT is best considered as having uncertain biologic potential similar to those occurring outside FGT. SFT should be considered in the differential diagnosis of cellular spindle cell lesions in the FGT.

1266 Down-Regulation of HAUSP Protein in High Grade Ovarian Serous Carcinoma Is p53-Independent

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Background: Herpesvirus-associated ubiquitin-specific protease (HAUSP) plays an important role in regulation of proteins involved in the cell cycle by de-ubiquitilation. HAUSP is also a key regulator of p53-mdm2 pathway by stabilizing wild type p53 protein. However, the relationship between HAUSP expression and p53 mutation has not been characterized and the expression of HAUSP in ovarian cancer is largely unknown. We examined the expression of HAUSP in high grade ovarian serous carcinoma and compared it with benign fallopian tubal epithelium.

Design: Tissue microarrays, containing 47 cases of stage III high grade ovarian serous carcinoma (HG-OSC) and 40 cases of benign fallopian tubes, were included in the study. Immunohistochemistry (IHC) was performed with anti-HAUSP antibody (Bethyl Laboratories, Montgomery, TX) and p53 antibody. Nuclear staining intensity of HAUSP was qualitatively scored on a 0-3+ scale.

Results: Strong to moderate HAUSP immunostaining was seen in all 40 cases of benign fallopian tubes. Among HG-OSC cases, total loss of HAUSP expression was observed in 25/47 (53.2%) cases and focal weak staining pattern (1+) of HAUSP was seen in 14/47 (29.8%) cases. Seven (14.9%) cases maintained moderate 2+ (4 cases) or strong 3+ (3 cases) HAUSP staining patterns. p53 immunostaining showed 40/47 (85.1%) of cases had either strong p53 positivity (probably missense mutations) or total negativity (indicating missense mutations). When compared HAUSP expression with p53 staining, there was no significant correlation between HAUSP and p53 expression patterns ($P=0.7$).

Conclusions: HAUSP is highly expressed in benign fallopian tubal epithelium. Loss or significant down-regulation of HAUSP protein expression was seen in 85% of HG-OSC cases. There is no significant correlation between HAUSP and p53 expression. Our study indicates that down-regulation of HAUSP expression is likely involved in the ovarian carcinogenesis.

1267 Mutational Status of KRAS, BRAF, NRAS and PIK3CA in Primary Clear Cell Ovarian Carcinoma

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Background: Ovarian clear cell carcinoma (OCCC) represents a subtype of epithelial ovarian cancer with specific biological features and aggressive clinical behaviour.

Design: We conducted a genomic profiling of a consecutive series of 22 patients admitted at our Institution between December 2006 and June 2012, with a proven diagnosis of OCCC. In all cases, final diagnosis was established according to FIGO and WHO criteria. All women received complete surgical staging. The PyroMark Q24 system (Qiagen GmbH, Hilden, Germany) was used for pyrosequencing analysis of KRAS, NRAS, BRAF and PIK3CA hot spot regions on 2.5-mm sections of formalin fixed paraffin-embedded tissues from primary OCCCs.

Results: Pyrosequencing analysis revealed the presence of mutations at codon 12 in exon 2 of KRAS in 3 of 22 (14 %) cases The following mutations were found: p.G12V(gly12®val12), p.G12A (gly12®ala12), and p.G12S (gly12®cys12). Concerning PIK3CA we found mutations at exon 9 (c.1633G>A; p.E545K) and exon 20 (c.1633G>A; p.E545K) in 6 of 22 cases (27,3%). We found no mutations in the hot-spot regions of NRAS (exons 2, 3, 4) or BRAF (exon 15).

The frequency of KRAS mutation observed in our study (14%) appears significantly lower than in other ovarian carcinoma subtypes, and almost double compared to the frequency reported for ovarian endometrioid carcinomas (7 %). Interestingly, we found KRAS mutations only in codon 12, exon 2, but not in codon 13, exon 2 nor in NRAS or BRAF. Furthermore, we confirmed the absence of BRAF hot spot mutations in OCCCs, and PIK3CA mutations in 27% (6/22) equally distributed in exon 9 (p.545K) and 20 (p.H1047R). The type of mutations found are in line with the results of the Japanese and Taiwan series suggesting pathogenesis and progression of OCCC are common to different ethnic groups.

Conclusions: Considering the poor response to platinum-based chemotherapy protocols, our study suggest that therapeutic approaches with new biological agents targeting PIK3CA should be tested in OCCCs. Furthermore, it may be useful to evaluate through clinical trials the correlation between drugs efficacy and genomic profile.

1268 Prognostic Significance of the Morphologic Features of Ovarian Carcinomas Before and After Chemotherapy

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Background: The significance of the features of post-chemotherapy ovarian carcinomas for predicting clinical outcomes is not well studied. We correlated the morphologic features of ovarian carcinomas before and after chemotherapy with patient survival.

Design: We collected 20 cases of ovarian carcinoma, operated between years 2000 and 2007, in which both pre- and post-chemotherapy histiopathological specimens were available. We assessed cellular and stromal features of the tumors and the change in these parameters between pre- and post-chemotherapy tumors, which we correlated with survival.

Results: The mean patient age was 61 years (range, 24-86 years). The tumors included 1 clear cell carcinoma, 1 endometrioid carcinoma, 2 malignant mesodermal mixed tumors, 3 low-grade micropapillary serous carcinomas and 13 high-grade serous carcinomas. The mean length of post-surgery follow-up was 39 months (range, 5-128 months), and 3 of the 20 patients survived. The pre-chemotherapy features that showed significant negative correlation with survival included extensive microcalcification ($p<0.0001$), necrosis of more than 25% of the tumor ($p=0.005$), pyknosis of more than 10% of the tumor ($p=0.007$), and absence of hemosiderin ($p=0.019$). The post-chemotherapy features that showed significant negative correlation with survival were either absent or marked hemosiderin deposition ($p=0.027$), while tumor mitotic count greater than 25 per 10 high power fields showed a negative trend ($p=0.055$). The changes between pre- and post-chemotherapy features that showed significant negative correlation with survival included decreased microcalcification ($p=0.024$) and decreased tumor nuclear inclusions ($p=0.036$). Then we divided our patients into high responders to chemotherapy (moderate to marked decrease in tumor cellularity) and low responders. The high responders post-chemotherapy had smaller tumors ($p=0.049$) and more tumor necrosis ($p=0.013$). They also had a trend toward lower pre-chemotherapy calcification ($p=0.056$), lower post-chemotherapy adenofibromatous features ($p=0.06$), and lower pre- and post-chemotherapy desmoplasia (p values 0.08 and 0.09, respectively).

Conclusions: Pre-chemotherapy features of ovarian carcinomas are more predictive of survival. Degenerative tumor changes before treatment and a lack of such changes after treatment appear ominous. Microcalcification and the stromal features, rarely mentioned in pathology reports, were found to be important.

1269 Predictive Value of Serous Carcinoma Component for Metastasis and Recurrence in Stage I Malignant Mixed Mullerian Tumor, Possible Role of HB-EGF

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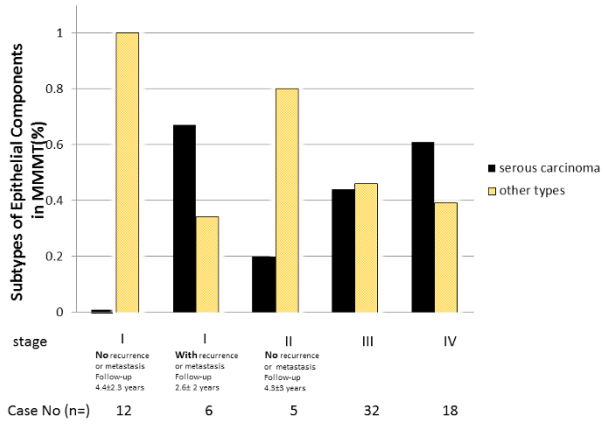
Background: Malignant Mixed Mullerian Tumor (MMMT) is an aggressive epithelial tumor with mesenchymal components. Recurrence and metastasis develop even in early stage tumors. Heparin binding-epidermal growth factor like growth factor (HB-EGF) is a secretary ligand functioning in epithelial-mesenchymal transition, tumor growth and metastasis. Previous studies have shown expression of HB-EGF in MMMT. We aim to study whether the differential epithelial components and expression of HB-EGF are related to recurrence/metastasis (RM) of stage I MMMT.

Design: Consecutive 72 MMMT cases collected from 3 hospitals in Hawaii from 2000 to 2011 were included in this study. Paraffin embedded tissue microarrays (TMA) with 2-14 representative foci for each case were prepared and subjected to immunohistochemical staining using HB-EGF, EGFR and integrin-α5 antibodies.

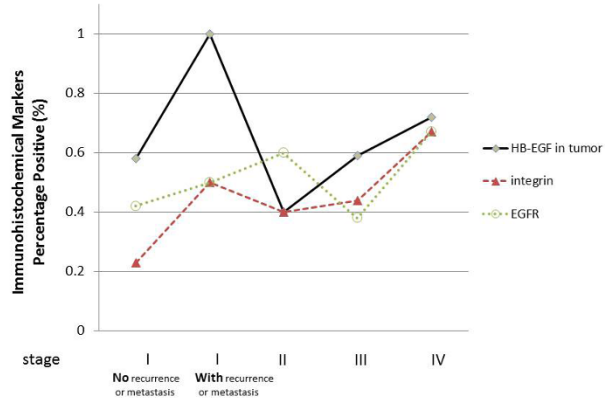
Results: The TNM stage distributions in this series are stage I(17), II(5), III(32) and IV(18). Six out of 12 (6/12, 50%) cases of stage I disease had RM. The percentage of serous carcinoma increases from stage II (1/5, 20%), to III (14/32, 44%) and IV (11/18, 61%). The percentage of serous carcinoma in stage I disease with and without RM is 0% (0/12) and 67% (4/6) respectively.

Figure 1 Distribution of serous carcinoma component in all stages of MMMT



Correspondingly, the HB-EGF expression shows the same trend of stepwise increase from stage II (40%), to III (59%) and IV (72%). HB-EGF expression in stage I disease with and without RM is 100% (6/6), and 58% (7/12) respectively.

HB-EGF expression in different stages of MMMT



Serous carcinoma component has a sensitivity of 78% and specificity of 100% in predicting RM in stage I MMMT.

Conclusions: We have identified serous carcinoma component as a potential morphologic marker predicting RM in stage I MMMMT and suggest possible role of HB-EGF in this progression.

1270 Prior High Risk HPV Testing and Pap Test Results of 377 Invasive Cervical Cancers in China's Largest CAP Certified Laboratory

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Background: FDA approved Roche HPV test can be used as primary test for cervical cancer screening. But the data about the HPV testing results prior cervical cancers is very limited.

Design: Cases with a histological diagnosis of invasive cervical carcinoma were retrieved from pathology archive at Guangzhou Kingmed Diagnostics, China between 2011-1 and 2014-6. Prior HC2 HPV testing and Pap results within one year before cancer diagnosis were recorded.

Results: 377 patients including 332 squamous cell carcinomas (SCC) and 45 adenocarcinomas (ADC) with HC2 HPV testing within 1 year before histological diagnosis were included in the study. The average ages were 45.8 years for SCC and 43.8 years for ADC. HPV was detected in 316 of 332 patients (95.2%) with SCC, and in 34 of 45 patients (75.6%) with ADC. HPV positive rate is significantly lower in patients with ADC than that in patients with SCC. 114 patients had HPV testing and also Pap test results within 1 year before the histological diagnosis. Only 3 (2.6%) out of 114 patients showed negative Pap results. 7 of 8 (87.5%) cases with negative HPV testing results had abnormal Pap tests, including 2 cases of ASC-H, 2 of HSIL, 2 of carcinoma, 1 of AGC.

Conclusions: This is the largest study investigating prior hrHPV testing and its correlation to cytology results in patients with invasive cervical carcinoma. Our data demonstrate 7.2% of patients with invasive cervical carcinoma had negative HPV testing within one year before histological diagnosis. HPV negative rate is much higher in patients with ADC (24.4%). Interestingly, negative Pap test rate is lower than HPV negative rate within one year before histological diagnosis. These data expose limitations for the potential use of HPV testing as a primary screening method and suggest co-testing with both cytology and HPV testing to be a preferred method.

Table1.HrHPV results one year prior histological diagnoses of cervical cancers.

Types	Cases	HPV positive(%)	HPV negative(%)
SCC	332	316(95.2)	16(4.8)
ADC	45	34(75.6)	11(24.4)
Total	377	350(92.8)	27(7.2)

1271 Probable Causes of Recurrent Low-Grade Endometrioid Cancers

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Background: Endometrial carcinoma is the most common gynecologic malignancy and has two major histological types, endometrial endometrioid carcinoma (EEC) and endometrial serous carcinoma (ESC). EECs typically have a much better prognosis than those ESCs. However, there are approximately 10% of patients with low-grade EECs who recur within a few years after total hysterectomy and staging. Such patients have a poor clinical course. It is currently unclear what causes the tumor recurrence.

Design: We have collected a total of 40 EEC patients who had tumor recurrence in less than 4 years after surgery. These included 30 FIGO grade 1 and 10 FIGO grade 2 EECs. Clinicopathologic data were recorded. All cases were histologically reviewed and the representative tumor sections were subsequently examined by immunohistochemistry [(p53, IMP3, and MMR protein (MLH1, PMS2. MSH2, MSH6)] and by PCR analysis for K-ras (codons 12 and 13) gene.

Results: BMI of the patients ranged from 21 to 27 with an average of 23.5. Patients' age ranged from 35 to 76 with average of 55.6 years. Among the 40 recurrent EEC cases, 6 (15%) were ESC (confirmed with p53 and IMP3 staining), 8 (20%) were Lynch syndrome associated endometrial cancer (confirmed with MMR protein staining and subsequent DNA sequence analysis), 5 (12.5%) were positive for IMP3, and 7 (17.5%) had K-ras mutation in either codon 12 or 13. Interestingly, among the 7 EEC cases with K-ras mutation, 6 of them showed significant (>30% of total tumor volume) mucinous differentiation. It is unclear what the genetic alterations are for the remaining 14 (35%) cases.

Conclusions: The majority recurrent cases may be caused by genetic alterations of TP53, IMP3, K-ras or Lynch syndrome associated DNA repair genes. It is necessary to evaluate apparently "low-grade" endometrioid carcinoma carefully to rule out serous or mucinous endometrial cancer. This is particularly true for those patients without clinical evidence of estrogen overstimulation or without endometrial hyperplasia in the background. Correct identifying such cancer patients before or after definitive surgery will have a significant clinical impact for patient care.

1272 p16 INK4a/ProExC/Mib-1 Have Similar Expression Patterns in Both HPV 16/18 and Non-16/18 High Risk HPV Positive Cervical Dysplasia and Help With the Diagnosis of Deceiving Dysplasia

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Background: HPV infection is a well-known causative agent for the vast majority of cervical dysplasias and cancers in women. The HPV genotype-specific histologic features and expression patterns of $p16^{INK4a}$, ProExC and Mib-1 in cervical squamous dysplasia are not fully studied.

Design: From 1/2010 to 4/2011, 808 SurePath cervical specimens from the dysplasia clinic were collected and tested for 40 HPV genotypes by DNA microarray. Immunohistochemical stains for $p16^{INK4a}$/ProExC/Mib-1 were performed on 115 biopsies sampled within 6 months of the Pap tests. The expression patterns (p16: block positive, patchy positive and negative; ProExC and Mib-1: basal positive (1+), lower 1/3 positive (2+) and more than lower 1/3 positive (3+)) and intensity scores (percentage of positive cells in epithelium) were recorded. The histologic patterns were classified into conventional dysplasia and deceiving dysplasia that was characterized by atypical squamous cells with enlarged nuclei and increased N/C ratios, vesicular chromatin, lack of hyperchromasia, and few mitotic figures. Correlation of histology, immunohistochemistry and HPV genotypes was performed.

Results: All 115 cases had dysplastic changes with 52 cases of CIN2+. Dysplasia cases with HPV 16/18 had 62.5% with p16 block positivity, 65.0% with ProExC 3+ positivity (intensity score 30-100%) and 62.5% with Mib-1 3+ positivity (intensity score 20-95%), respectively. Dysplasia cases with non-16/18 high risk HPV (HR-HPV) infection had 55.1% with p16 block positivity, 40.8% with ProExC 3+ positivity (intensity score 30-95%) and 61.2% with Mib-1 3+ positivity (intensity score 5-95%), respectively. Strikingly, only 3 of 21 cases with deceiving dysplasia (14.3%) had conventional CIN2+ lesions, while p16/ProExC/Mib-1showed block and/or 3+ positivity in 18 cases (85.7%) (14 cases with p16 block positive, 4 cases with Mib-1 3+ positive and 2 cases with both ProExC and Mib-1 3+ positive). Interestingly, the majority of the deceiving dysplasia cases were infected by non-16/18 HR-HPV (n=14, 66.7%) with only a few by HPV 16/18 (n=2, 9.5%).

Conclusions: The expression patterns of p16/ProExC/Mib-1 do not differentiate cervical dysplasia caused by HPV 16/18 from those caused by non-16/18 HR-HPV genotypes (p=0.73/0.2/1.0). However, p16/ProExC/Mib-1 can significantly aid in the detection of deceiving dysplasia compared to H&E stain alone ($p<0.001$), and deceiving dysplasia was more commonly positive for non-16/18 HR-HPV in this cohort.

Head and Neck Pathology

1273 SMARCB1(INI1)-Deficient Sinonasal Carcinomas: Expanding the Morphological Spectrum of a Recently Described Entity

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Background: Recently, a variant of sinonasal tract carcinoma characterized by complete loss of nuclear SMARCB1 (INI1) has been described. A majority of reported cases (total: 13) showed a predominantly undifferentiated basaloid "blue" appearance.

Design: To define its clinicopathological spectrum, we identified 8 additional cases of this rare entity from our files and from four other collaborative institutions, in addition to our previously reported three original cases (total: 11 patients). We performed immunohistochemistry, HPV genetic testing and fluorescence in situ hybridization (FISH) studies.

Results: Patients were 9 women and 2 men (aged 28-76; mean, 46). All presented with advanced local disease (pT4). No family history of rhabdoid tumors or history of prior exposure to radiation was known. Surgery (radical or partial resection) and adjuvant or palliative chemo-/radiation was the treatment in all cases. All but one of 7 patients with detailed follow-up developed metastases and 2 died of disease at 22 and 102 months, respectively. Histological examination showed a predominance of basaloid (7), eosinophilic/rhabdoid (2), oncocytoid (1) and squamoid (1) cell features. Diffuse or partial p16 expression was observed in most of cases but none contained high risk HPV DNA. Immunohistochemistry showed strong expression of pancytokeratin with variable expression of CK5, p63, vimentin and focal reactivity for neuroendocrine markers. All cases showed complete loss of nuclear SMARCB1 expression by immunohistochemistry. SMARCB1 FISH analysis was successful in 5 cases: 1 showed biallelic deletion, and two cases each showed monoallelic deletion and intact SMARCB1.

Conclusions: SMARCB1-deficient carcinomas of sinonasal tract represent a distinctive emerging entity among poorly differentiated/ undifferentiated sinonasal carcinomas with predilection for middle-aged women, variable heterogeneous (mainly basaloid) morphology and variably aggressive clinical course. Their molecular pathogenesis seems to be heterogeneous as well. While some cases show biallelic SMARCB1 deletions, others feature monoallelic alterations or even lack SMARCB1 alterations by FISH suggesting other yet unidentified molecular mechanisms responsible for the SMARCB1 loss.

1274 Telomere Shortening in Oral Epithelium in Relation To ADH-1B and ALDH-2 Genotypes and Clinicopathologic Findings

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Background: Telomeres are repetitive G-rich DNA sequences and associated binding proteins found at the ends of eukaryotic chromosomes, and appear to play a key role in preventing genomic instability. Progressive telomere shortening with age or chronic inflammation may lead to genomic instability that characterizes the early stage of carcinogenesis. Certain risk factors, such as drinking alcoholic beverages, smoking, or papilloma viral infection, predispose the oral mucosa to squamous cell carcinoma. It is known that the ALDH-2 and ADH-1B genotypes influence the risk of cancer due to alcohol drinking. In the esophagus, iodine-unstained areas and their multiplicity revealed by chromoendoscopy are known to be related to telomere shortening. In the present study, we analyzed telomere lengths in the oral mucosa in relation to cancer risk factors.

Design: All tissues were examined histopathologically. Using our Q-FISH technique, we estimated telomere lengths of epithelial basal cells in the background mucosa from 23 cases of mucosal carcinoma, 12 cases of dysplasia, and 22 non-neoplastic cases. ALDH2 and ADH1B genotypes were determined using DNA extracted from paraffin sections. We analyzed telomere lengths in relation to drinking, smoking, p16 immunoreactivity, and cancer multiplicity.

Results: Telomeres in the backgrounds of dysplasia and mucosal carcinoma were significantly shorter than in controls. In the ADH1B less active type (*ADH1B*1/*1*) they were shorter than in the adult control group ($p = 0.038$), but not significantly shorter in the ALDH2 inactive type (*ALDH*1/*2 or *2/*2*) ($p = 0.841$). Drinkers and patients with multiple oral cancers tended to have shorter telomeres, but not to a significant degree. There was no significant correlation of telomere length with smoking index or p16 positivity.

Conclusions: Telomeres in the oral epithelium are shorter in cases of oral dysplasia or mucosal carcinoma than in non-neoplastic controls. In addition, telomeres are shorter in the ADH1B less active group than in the active group, despite the lack of any evident difference in the esophageal epithelium of alcoholics. Telomeres in the oral epithelium may be directly affected by alcohol drinking.