A User's Guide to QUANTEC*.

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*QUantitative Analysis of Normal Tissue Effects in the Clinic

Purpose of QUANTEC

- Both AAPM and ASTRO recognized ($$):
- Need for a systematic overhaul of our understanding of normal tissue tolerances
- For use in clinical treatment planning and optimization

History of QUANTEC

- 2006 AAPM Science Council
  - Ellen Yorke and Rock Mackie
  - Steering Committee: Deasy, Bentzen, Yorke, Ten-Haken, Jackson, Marks, Eisbruch, Constine
- 2007 1st QUANTEC meeting in Madison Wisconsin
  - Initial review of tolerances involving physicists, bio-statisticians and physicians.
- 2007-2009: Preparation of Papers
  - Reviews and meta analysis of literature on normal tissue complications in 16 organs (~58 authors)
  - 5 Vision articles on future directions
- March 2010: Publication
  - Special Issue of Red Journal (IJROBP 76 S3)

Structure of Organ Specific QUANTEC Articles

- 1) Significance of injury
- 2) Clinically relevant endpoints
  - Time course
  - Ambiguities
- 3) Volume definitions
  - Variations in contouring practice
- 4) Review of literature on dose-volume dependence of endpoints
  - Level of evidence

Structure of Organ Specific QUANTEC Articles

- 5) Patient and other related risk factors
  - E.g. diabetes, smoking, chemotherapy
- 6) Mathematical/Biological Models of the data
  - Lyman, relative seriality, multivariate models
- 7) Special Situations
  - E.g. pediatirc patients, hypo-fractionation
- 8) Recommended Dose-Volume Limits
- 9) Future Studies –
  - Additional knowledge required to improve toxicity prediction
  - Endpoint scoring and data capture in future studies

2) Clinically Relevant Endpoints

- Clinical symptoms
- Time course of the complication

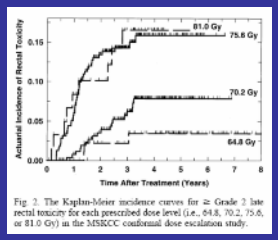


Fig. 2. The Kaplan-Meier incidence curves for ≥ Grade 2 late rectal toxicity for each prescribed dose level (i.e., 64.8, 70.2, 75.6, or 81.0 Gy) in the MSKCC conformal dose escalation study.

* Skwarchuk et al. IJROBP 47 103-113 2000

2) Clinically Relevant Endpoints

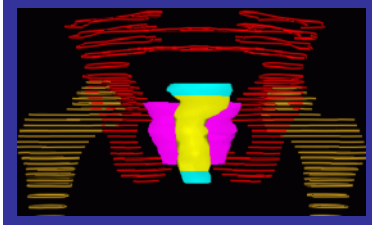
- Studies use different endpoints
  - Grading schemes
    - Pneumonitis Requiring Steroids
      Grade 2 in SWOG, but Grade 3 in RTOG
  - Time for endpoint
    - Different times
    - Actuarial vs non-actuarial
  - Different grades
    - Grade 1: no clinical symptoms
    - Grade 2 : outpatient treatment
    - Grade 3 : requiring hospitalization

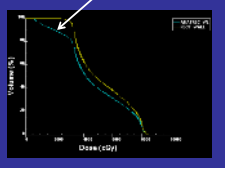
2) Clinically Relevant Endpoints

- Clinical endpoints less severe that in Emami
  - Data more plentiful for lower grades of injury
  - Clinical consequences
    - Larry will explore this point further
  - Ambiguity in diagnosis
- Objective and Functional Endpoints are available for some organs
  - Parotid: salivary flow vs xerostomia

3) Volume Definitions

- Clinical vs anatomic definitions
  - Yellow: MSKCC's clinical definition of rectal wall
    - 0.5 cm sup. and inf. of PTV
  - Cyan: anatomic definition of rectal wall
    - Anal verge to sigmoid colon





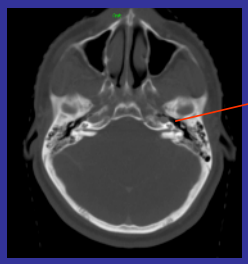
Inclusion of tissue outside the fields introduces extra volume with low dose

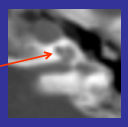
3) Volume Definitions

- Tubular Structures:
  - Inclusion of lumen, or wall only?
- Paired organs:
  - Kidney, lung, parotid glands
  - Ipsilateral vs total volume
- Incomplete Structures (e.g. cord):
  - Use absolute volume DVH if length is not standard
- Inclusion of extra tissue (incapable of exhibiting complication):
  - Introduces noise
  - Weakens correlations with complications

3) Volume Definitions

- Organ size
  - Cochlea: A very small structure only visible on CT with the correct bone window





Small size of the cochlea (~5mm thick) makes it difficult to define properly On relatively thick CT slices

4) Review of dose Volume data*

- Includes only peer reviewed studies
- Excludes data not yet published
- Emphasis placed on prospective data where available

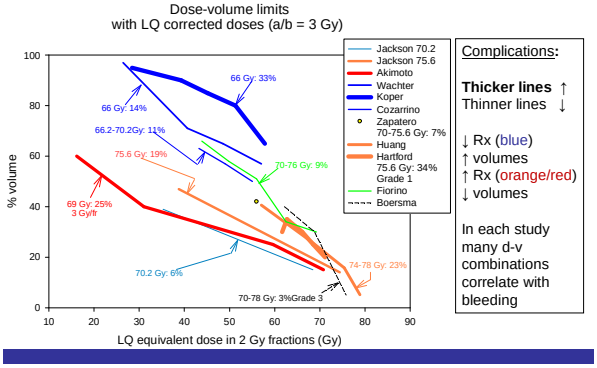
*Separation not clean between this section and 6) Math/Biological Models

4) Review of Dose Volume Data

- Includes only peer reviewed studies
  - Excludes all data not published at the time of writing
  - Emphasis placed on prospective data where available
- Attempted synthesis of variety of dose-volume limits
  - Difficult to combine
  - Different DVH points are incompatible
  - Correlations: cannot find unique thresholds

4) Review of Dose Volume Data

Rectal bleeding: Michalski et al. IJROBP 73 S123-129 2010



Complications:

Thicker lines ↑
Thinner lines ↓

↓ Rx (blue)
↑ volumes
↑ Rx (orange/red)
↓ volumes

In each study many d-v combinations correlate with bleeding

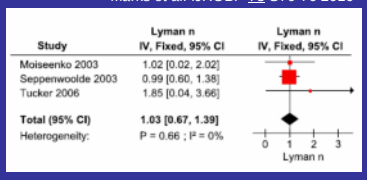
5) Patient related and other risk factors

- In some cases, patient related factors may drastically change the risk of complication
  - Liver: Childs A vs Childs B & C
    - For Childs A Patients (good liver function) TD50 for RILD is ~ 40-46 Gy (mean dose)
    - For pts with Liver Cirrhosis, Hepatitis B Virus TD50 for RILD may be ~ 23 Gy (mean dose)
  - Compare with Liver: Mets vs Primary tumor
    - TD50 for RILD ↑ by ~ 5Gy (mean dose) for Mets

6) Mathematical/Biological Models

- Meta Analysis:
  - Compatible studies
    - endpoints, volumes, dose, models
- Few organs passed all these criteria
  - Biological models: Lung, Rectum

Marks et al. IJROBP 73 S70-76 2010

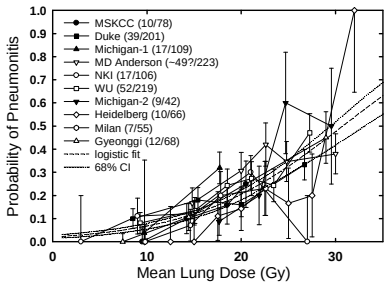


Meta –Analysis of Lyman Model n values for pneumonitis
Result:
Lyman model compatible with mean dose model

6) Mathematical/Biological Models

Clinically significant Pneumonitis: Marks et al. IJROBP 73 S70-76 2010

Symptomatic Pneumonitis vs. Mean Lung Dose



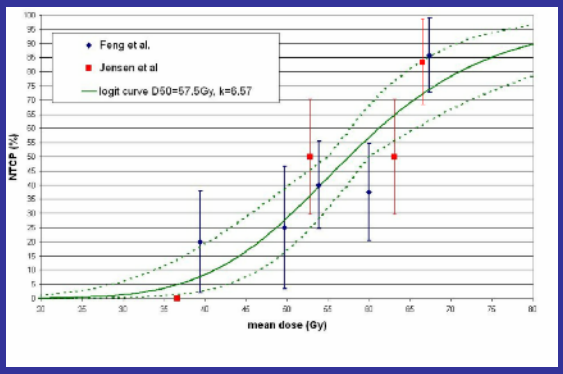
Data Synthesis:

Includes:
1167 pts; 222 cases

Adjustments to data:
Dose calculations
Confidence limits
EUD(n =0.87)→mean dose
Data from authors if implied in paper

Only studies with:
Rate and S.D. of pneumonitis as function of
mean dose whole lung
(EUD n =0.87→mean dose)
NSCLC
≥ Grade 2 (SWOG)
(≥ Grade 1 if few cases)

Probability of aspiration as function of mean dose to Supra-Glottic Larynx



(T. Rancati et al. IJROBP 73 S64-69 2010)

7) Special Situations

- Most of the data comes from:
  - 3DCRT
  - Conventional fractionation
  - Adults
- Most of the data does **not** come from:
  - Hypofractionation
  - Pediatric patients
  - Combinations of Brachytherapy and EBRT
  - Retreatment
  - IMRT?!

8) Recommended Dose Volume Limits

- Intended for clinical use in planning EBRT treatments,
  - but associated with warnings concerning extrapolation of results to new clinical situations
- Quality and limitations of the existing data prompted many caveats
  - In one case (Bladder), authors did not quote limits from published studies
    - Volumes unreliable, follow up Inadequate
    - Relied instead on recommendations from an RTOG protocol

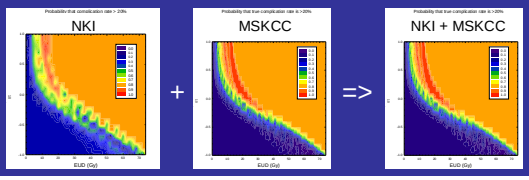
Summary Table of QUANTEC Dose-Volume Constraints

- In the introductory article on use of NTCP models in the clinic
  - Marks et al. IJROBP 73 S10-19 2010
- Based on the recommended dose-volume limits given in each article (section 8)
  - Intended for clinical guidance, but:
    - "Clinicians are strongly advised to refer to the individual articles to check the applicability of these limits to the clinical situation at hand"

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[1]	Endpoint	Dose (Gy), or dose/volume parameters[2]	Rate (%)	Notes on dose/volume parameters
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 < 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	

9) Areas for Future Study

- Individual studies have relatively low numbers of clinical complications
  - Data pooling and meta analysis
  - Meta analysis requires comprehensive reporting
  - Atlases – tools for meta-analysis



9) Areas for Future Study

- Clinical co-factors need to be explored
  - Effects of Chemotherapy
  - Multivariate models
  - Genetic factors
- Regional sensitivity (beyond the DVH)
  - Lung: is the upper lung less sensitive to radiation than the lower lung?
- Relationship between functional tests and clinical complications
  - Do functional tests predict complications?

10) Toxicity Scoring

- Hard to define good endpoints for normal tissue studies
  - Clinically significant (higher grades)
  - Sufficient statistics (lower grades)
  - Unambiguous
- Patient reported outcomes*
  - Observer reported outcomes underestimate patient reported outcomes
  - More data!
  - More specific
    - Separate individual complications
    - Better models

*see e.g. Peeters et al. IJROBP64: 1151-1161, 2006

Conclusions

- QUANTEC is:
  - Updating our clinical understanding of normal tissue tolerances
  - Providing clinical guidelines where possible
    - With appropriate caveats
  - Defining areas of our ignorance
    - recommend studies to remedy this
  - Investigating future directions:
    - Reporting standards
    - Clinically relevant but specific endpoint definitions
    - Inter-institutional data synthesis (atlases or pooling)

Supplementary slides

Mean dose response of pneumonitis

(A. Jackson with L. Marks/S. Kong/J.Deasy/J.Bradley/M. Martel/S. Bentzen in Marks et al. IJROBP 73: S70-76, 2010)

- Patients treated for NSCLC
  - Data from 9 institutions, 10 separate studies
- 1,167 patients with 222 cases of pneumonitis
- ≥ Grade 3 RTOG ~ ≥ Grade 2 SWOG
  - (requiring steroids)
  - accepted ≥ grade 1 definition if few grade 1 cases

Mean dose response of pneumonitis

A.Jackson with L. Marks/S. Kong/J.Deasy/J.Bradley/M. Martel/S. Bentzen in Marks et al. IJROBP 73: S70-76, 2010

- Reporting rate (and S.D.) of pneumonitis as function of mean dose to total lung
  - Numbers of pts w./w.o. pneumonitis
  - Bin locations on quartile plots
- Fit of logistic function [95% conf.]:
  - D50 = 30.75 [29.9 – 31.7] Gy
  - γ50 = 0.907 [0.836 – 0.987]
- Fit of Lyman D50 and m (mean dose: n = 1):
  - D50 = 31.4 [29.0-34.7] Gy
  - m = 0.45 [0.39-0.51]

A.Jackson with L. Marks/S. Kong/J.Deasy/J.Bradley/M. Martel/S. Bentzen
in Marks et al. IJROBP 73: S70-76, 2010

1) MSKCC, Yorke et al. IJROBP 63 2005: 672-682, from Fig 4a) (≥RTOG grade 3, 6 months)
2) Duke, Hernando et al. IJROBP 51 2001: 650-659, from Table 4 (≥CTC grade 1, 6 months)
3) Michigan, Kong et al. IJROBP 65 2006: 1075-1086, from Table 4 and Fig 2a) (≥SWOG grade 2, 6 months) – bin location and time from authors.
4) MD Anderson, Wang et al. IJROBP 66 2006: 1399-1407, from Fig 2 (≥CTC grade 3, 1 year actuarial – includes concurrent chemo patients)
5) NKI, Seppenwoolde et al. IJROBP 60 2004: 748-78, from Fig 3a) (≥SWOG grade 2, 6 months)
6) WU, Hope et al. IJROBP 65 2006: 112-124, from Fig 9c) (≥SWOG grade 2 – no time limit) with bin locations from authors, increased by 11% to ~account for inhomogeneity corrections.
7) Michigan, Martel et al. IJROBP 28 1994: 575-581, from Table 1 (≥SWOG grade 1) with mean doses calculated from relationship between EUD (n=0.87) and mean dose from Kwa et al., Radiotherapy and Oncology 48 1998: 61-69 Fig 2a).
8) Heidelberg, Oetzel et al. IJROBP 33 1995: 455-460, from Fig 2 and text (≥RTOG acute grade 1).
9) Milan, Rancati et al. Radiother. and Oncol. 67 2003: 275-283, from Fig 3 (≥SWOG Grade 2 – no time limit, patients without COPD – includes induction chemo patients).
10) Gyeonggi, Kim et al. Radiology 235 2005: 208-215, from Table 5 (≥RTOG grade 3, 6 months – includes concurrent chemo patients) – median values of mean dose in each bin provided by the authors.
11) Logistic fit: data fit to the form (f/(1+f)), where f=exp(b0+b1*dmean). Best fit values [95% confidence intervals] are b0 = -3.63 [-3.53--3.74], b1 = 0.118 [0.109-0.128], corresponding to D_{50} = 30.75 [29.9 – 31.7] Gy and γ_{50} = 0.907 [0.836 – 0.987].

Rectal dose volume limits

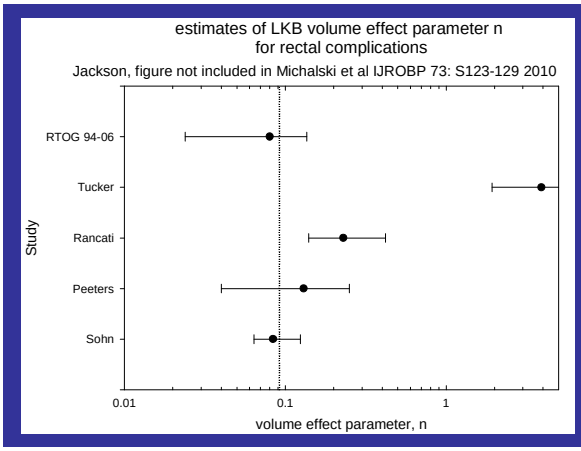
Jackson/Deasy/Gay/Michalski/Tucker
in Michalski et al. IJROBP 73: S123-129, 2010

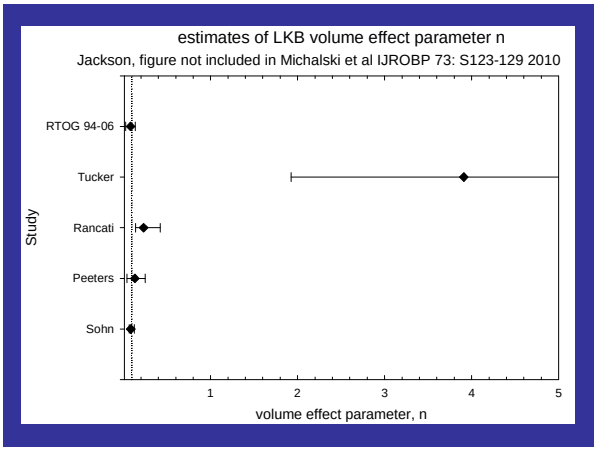
- Published limits having sig. correlation with ≥ grade 2 rectal bleeding
- Color coded to indicate prescription dose
  - Blue = 66-70 Gy
  - Red = 83 Gy (LQ equivalent dose in 2 Gy fr)
- Thickness of line indicates overall complication rate in study

Rectal lyman model fits

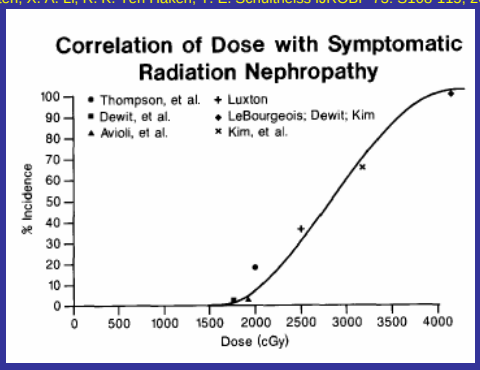
- 5 published studies fitting LKB model to rectal complication data
  - includes Tucker, RTOG 94-06 IJROBP
    - E pub July 2010 (also ASTRO 2007, IJROBP)
- Forrest plot of “n” values (n=1/a)
  - 1 S.D. indicated
- Meta analysis:
  - value of “n” = 0.09 (95% conf: 0.04-0.17)

Jackson, end result (but not figures) included in
Michalski et al IJROBP 73: S123-129 2010





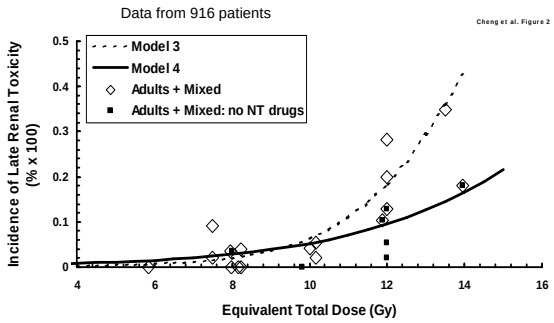
Kidney
(L. Dawson, A. Paulino, B. Kavanagh, C. Pan, S. K. Das, M. Miften, X. A. Li, R. K. Ten Haken, T. E. Schultheiss IJROBP 73: S108-115, 2010)



From: Cassady JR. Clinical radiation nephropathy. *IJROBP* 1995;31:1249-1256.

Dawson et al. IJROBP 73: S108-115, 2010

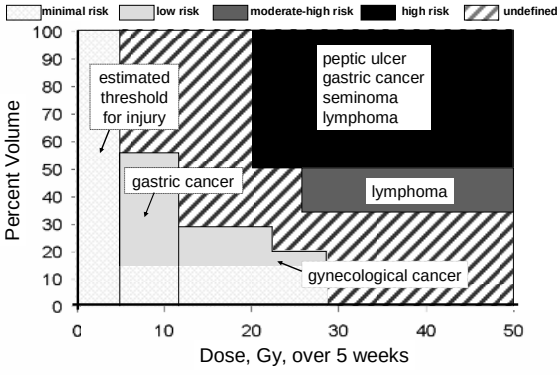
Bilateral Whole Kidney RT - TBI



Cheng J, Schultheiss T, Wong J. Impact of Drug Therapy, Radiation Dose and Dose Rate on Renal Toxicity following Bone Marrow Transplantation. *IJROBP 71: 1436-1443,* 2008.

Dawson et al. IJROBP 73: S108-115, 2010

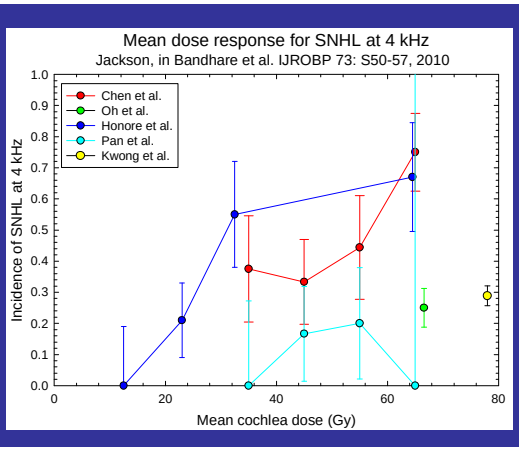
Bilateral Partial Kidney RT



Late Hearing Loss

(A. Jackson, N. Bandare, W. Mendenhall)

- Hearing loss tests from 3 studies as function of mean cochlea dose
  - (post-treatment vs pre-treatment)
- Differences in way endpoint is defined
  - Ispi- relative to contra-lateral hearing loss vs hearing loss
- Dose reconstruction
  - 1 study, doses reconstructed with surrogate CT scans
  - 1 study, ipsi- doses relative to contra-lateral



Necessity of combining data sets

- Number of complications in any given treatment series is usually low
  - False negatives
  - No statistical power to determine model parameters
- Dose-volume exposures correlated in individual series
  - Introduces phony correlations with complications (False positives)
  - Insufficient range of dose-volume combinations to determine model parameters

Problems in synthesizing data

- Endpoint definitions:
  - Need to be clinically relevant
  - Need to be specific
    - Rectal bleeding or incontinence vs grade 2 RTOG toxicity
      - Different comps. have different dose-volume effects
  - Need to be standardized

Problems in synthesizing data

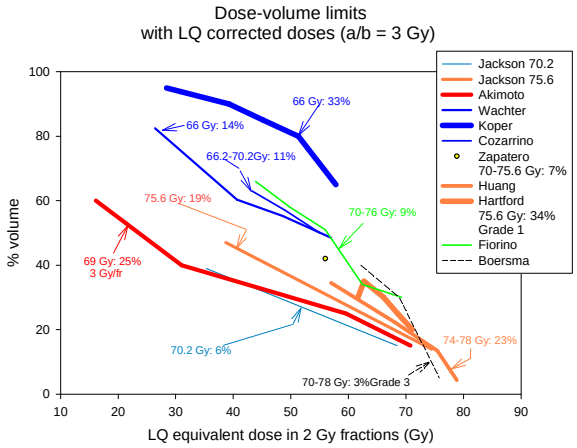
- Variety of dose volume limits proposed
  - These cannot be combined
- Variety of models may be fit
  - Responses cannot be combined
    - gEUD responses with different "a" values cannot be combined

Problems in synthesizing data

- Standard of reporting is **POOR**
  - Lack of basic statistics (numbers not stated!)
    - Schultheiss 1994: "**The information in this report would be of greater clinical use if some indication had been provided of the total number of patients from which the myelopathy cases were drawn**"
  - Locations of bins in e.g. quartile plots not given
  - Model parameters (and errors) not be stated

In other words:

- Report the numbers of patients with complications and the number treated
  - Elementary statistics increase clinical utility
- Be comprehensive
  - Report as much about the data as possible


Dose-volume limits
with LQ corrected doses (a/b = 3 Gy)
% volume
LQ equivalent dose in 2 Gy fractions (Gy)
Jackson 70.2
Jackson 75.6
Akimoto
Wachter
Koper
Cozarrino
Zapatero
70-75.6 Gy: 7%
Huang
Hartford
75.6 Gy: 34%
Grade 1
Fiorino
Boersma
66 Gy: 33%
66 Gy: 14%
66.2-70.2Gy: 11%
75.6 Gy: 19%
70-76 Gy: 9%
69 Gy: 25%
3 Gy/fr
70.2 Gy: 6%
74-78 Gy: 23%
70-78 Gy: 3%Grade 3