Reporting Standards for Normal Tissue Complication Modeling for Hypofractionated/SBRT Treatments

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  - WG on Hypofractionation/SBRT

Clinical Utility vs Scientific Elegance

- Most papers on outcome of radiotherapy are written to establish a specific scientific point
- Little attention is paid to the clinical utility of the information provided
- With a little effort, clinical utility of an elegant paper can be vastly improved
- What do we need in order to apply results clinically, and use them in meta-analysis?

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

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

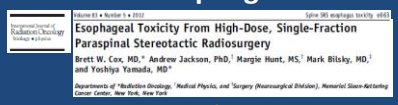
Problems in synthesizing data

- 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 uncertainties) not be stated

In other words:

- Report the numbers of patients with complications and the number treated
  - Elementary statistics increase clinical utility
  - Values with uncertainties can be combined
- Be comprehensive
  - Report as much about the data as possible
- How far can we take this?

Example: DVH Atlas of Severe Esophagitis


Esophageal Toxicity From High-Dose, Single-Fraction Paraspinal Stereotactic Radiosurgery

Brett W. Cox, MD,* Andrew Jackson, PhD,† Margie Hunt, MS,† Mark Bilsky, MD,‡ and Yoshiya Yamada, MD*

- Report the number of paraspinal patients whose esophagus DVH passes above a given dose-volume combination (d_i,v_j)
  - Both with and without severe esophagitis
- Be comprehensive:
  - Do this for each (d_i,v_j) combination

Dose-Volume Atlas for Incidence of Severe Esophagitis from single fraction paraspinal treatments (partial snapshot of Excel file in supplement*)

Vol (cc) ↓

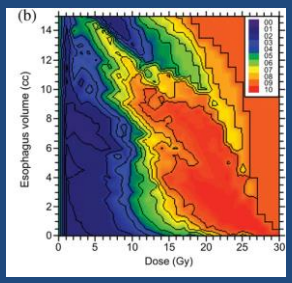
Dose (Gy) →

	0		1		2		3		.....
0	14	204	14	198	14	198	14	198	
0.5	14	204	14	198	14	198	14	196	
1	14	204	14	198	14	197	14	192	
1.5	14	204	14	198	14	192	14	192	
2	14	204	14	196	14	192	14	188	
2.5	14	202	14	191	14	188	14	187	
3	14	201	14	189	14	187	14	184	
3.5	14	201	14	187	13	183	13	182	
4	14	198	13	184	13	181	13	177	
4.5	12	195	12	179	12	175	12	172	
5	12	192	12	174	12	169	12	167	
5.5	12	186	12	168	11	159	11	151	
6	12	180	12	160	11	148	11	148	
6.5	12	171	11	147	9	139	7	132	
7	10	163	9	137	7	130	7	125	
7.5	10	158	8	131	7	124	7	115	
8	9	153	7	126	6	114	6	106	
8.5	9	144	7	117	6	100	6	92	
9	8	127	6	104	6	88	5	80	
9.5	8	123	6	91	6	83	5	71	
10	8	119	6	87	5	75	5	65	
10.5	7	117	6	80	4	68	4	59	
11	7	113	6	76	4	62	4	58	
11.5	6	105	6	73	4	57	4	55	
12	6	99	5	65	4	55	4	52	
12.5	6	92	4	61	4	50	3	47	
13	5	88	4	56	3	47	3	42	
13.5	5	83	4	51	3	42	3	39	
14	5	78	4	45	3	38	3	36	

↑ N comps ↑ N Total

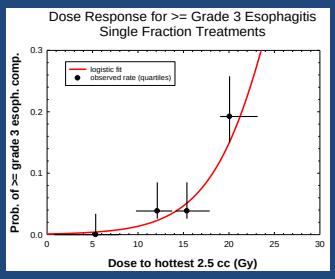
*Cox et al. IJROBP

Probability that true rate of severe esophageal complication > 10%



Cox et al. IJROBP

Severe esophagitis from single fraction paraspinal treatments



Cox et al. IJROBP

Problems in synthesizing data from hypofractionated treatments

- How do we deal with treatments with different fraction number?
  - Many NSCLC studies combine data from 3, 4, 5 fraction treatments
  - Uncertainty in applicability of LQ model for large fraction sizes

How do we deal with treatments with different fraction numbers?

- Solution:
  - Report basic numbers stratified by fraction number
    - Equal doses delivered in the same number of fractions have same effect*
    - E.g. separate atlases for each fraction number
    - Allows for re-analysis using different models of fractionation effects

*Provided treatment time is not an issue

Can we hope to use clinical data to shed light on appropriate fractionation model?

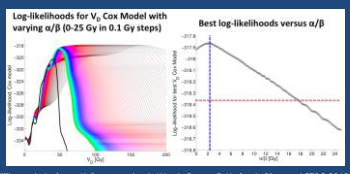
- NSCLC SBRT Fractionation schemes have a very big range of BEDs
  - 5 X 9 Gy; 4 X 12 Gy; 3 X 18 Gy →(α/β = 3 Gy)→ BED = 180 Gy; 240 Gy; 378 Gy
- Can we tell which fractionation model works best to describe the complication data?

Can we hope to use clinical data to shed light on appropriate fractionation model?

- NSCLC SBRT Fractionation schemes have a very big range of BEDs
  - However! Monotonic increase in physical dose is mirrored by monotonic increase in BED
  - Little cross talk between the fractionation schemes
    - Ranking of patients tend not to mix or change with α/β
      - V(d) order unchanged within one fraction # cohort
      - Fraction # cohorts too far apart for much mixing mix
      - Chest wall pain: physical dose may do just as well as BED

Can we hope to use clinical data to shed light on appropriate fractionation model?

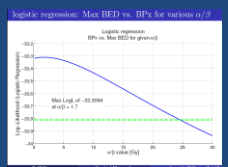
- With large numbers, we may overcome these limitations
  - 61 cases grade ≥2 chest wall pain in 316 tx (physical dose excluded at 95% conf)*



- *S. Din, E. Williams, A. Jackson, K. Rosenzweig , A. Wu, A. Foster, E. Yorke, A. Rimner, ASTRO 2013

Can we hope to use clinical data to shed light on appropriate fractionation model?

- With alternative fractionation schemes, we may overcome these limitations:
  - Data from NSCLC and paraspinal treatments on brachial-plexopathy
  - 1 X 24 Gy breaks the monotonic relation between physical dose and BED*



- *Din S, Yamada Y, Yorke E, Foster A, Poppens E, Thompson M, Rosenzweig KE, Jackson A, Wu AJ, Rimner A . ASTRO 2013

Electronic Supplements:

- Exploit these to the max!
  - No practical limit on the amount of data that can be reported
  - Full patient specific DVH data can be reported and associated with outcome and clinical factors (age/sex etc..)
  - Journals become the peer reviewed data pool
    - With associated quality assurance