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

• 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)**

<table>
<thead>
<tr>
<th>Vol (cc)</th>
<th>Dose (Gy)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
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<td>5</td>
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<td>9</td>
<td>10</td>
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</tbody>
</table>

Probability that true rate of severe esophageal complication > 10%

![Graph showing Dose Response for >= Grade 3 Esophagitis Single Fraction Treatments](image)

Severe esophagitis from single fraction paraspinal treatments

![Graph showing Probability of >= grade 3 esophageal complications](image)
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 \(\Rightarrow (\frac{\alpha}{\beta} = 3 \text{ Gy}) \Rightarrow\)
  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 $\alpha/\beta$
      - V(d) order unchanged within one fraction # cohort
      - Fraction # cohorts too far apart for much mixing
      - 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)*

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*

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

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

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