Outcomes Modeling:
NTCP - Normal Tissue Complication Probability

What's Really Changed over the last 20+ years?

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“Essentially, all models are wrong, but some are useful.”

George E.P. Box, 1987

Introduction

- “Traditional” radiation oncology dose escalation trials assign groups of patients to increasing “tumor” dose levels until an unacceptable level of complications appear.

- This generally evolves on a sequential basis, regardless of tumor size or the distribution of radiation dose to surrounding normal tissues.
Introduction

- This can be a poor strategy for treatments limited primarily by complications to so-called volume-effect normal tissues which encompass the tumors, such as may be the case for tumors located in the liver or lung.
Introduction

- A better scheme for Phase I/II dose escalation trials limited by these volume effect organs would attempt to treat sequential groups of patients with dose “distributions” that might be expected to lead to similar anticipated levels of complications
  + (but of course with different tumor doses);

- with sequential escalation of each potential iso-complication level until an MTD profile is realized
  + (which would inherently include the volume effect).
Introduction

- The use of normal tissue complication probability (NTCP) models prospectively, in the treatment planning process, facilitates this type of normal tissue iso-complication based dose escalation.

- This talk will summarize experiences in iso-NTCP dose escalation and planning at the University of Michigan for tumors in the liver and lungs.
ca. 1990 *Tolerance Doses simple*

- No Models
- Mostly whole organ irradiation
  - or uniform partial organ irradiation
- Some published complications rates
Whole Liver Irradiation
Whole liver tolerance doses ca. 1990

- NTCP (%)
- Volume (%)
- Dose (Gy)

Graphs showing dose-response relationships for NTCP and volume with respect to dose.
Radiation treatment of liver cancer

- Higher tumor doses appear to be beneficial
- Low tolerance of whole liver to radiation (35 Gy)
- Hope to deliver higher tumor doses through partial liver irradiation
- Need to understand dose/volume relationships of toxicity
ca. 1990 *Modeling was simple*

- No Models
- Some published complications rates
- Get consensus of a group of experts
  - TD5 and TD50
  - For 1/3, 2/3 and 3/3
- A set of ground breaking, useful guidelines for “uniform partial organ irradiation”
TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

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What do you think the TD5 is for uniform irradiation of 1/3 of ..... 

Er, ah,  
4500 “rads” 
...maybe 5000? 
Would anyone believe 4837.5?
Was this sufficient?

Solid lines: some data
Dashed lines: estimates

Important region for 3DCRT…but no data

0 20 40 60 80 100
Dose (Gy)

0 100
Volume (%)
Late 1980s - Early 1990s

- Hint of a model better than no model at all
- Start to probe for signatures of volume effect
Liver Normal Tissue Studies

- In 1987 we began a series of outcomes studies using 3D conformal therapy based on two concepts:
  1. we had the ability to significantly reduce the dose to the normal liver
  2. conformal treatment planning permitted us to quantify the fraction of normal liver irradiated
Partial volume liver irradiation

AN APPLICATION OF DOSE VOLUME HISTOGRAMS TO THE TREATMENT OF INTRAHEPATIC MALIGNANCIES WITH RADIATION THERAPY

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UM Liver Cancer Early Study

Dose based on the volume of normal liver receiving >50% of the prescription dose.
Liver NTCP Lyman model parameter adjustment

THE USE OF 3-D DOSE VOLUME ANALYSIS TO PREDICT RADIATION HEPATITIS

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Iso-NTCP curves

Original

Revised
Our results suggested that an NTCP model based on patient data (rather than literature estimates) could be used prospectively to safely deliver far higher doses of radiation with a more consistent risk of complication than would have been previously been considered possible for patients with intrahepatic cancer.
Mid 1990s-200x - Using updated models to establish better parameters

- Having established some faith in the existence of the volume effect
- Explore a wider set of the dose-volume space using the model as a guide
- Update parameters when unacceptable complication rates are reached/near
UM Prospective dose escalation studies based on normal tissue tolerance

- We developed a methodology for normal tissue based dose escalation that allowed direct accountability for the effective volume of normal tissue irradiated using:
  - The Lyman NTCP description, and
  - A distinctive property of the effective volume DVH reduction scheme.
Iso-NTCP dose escalation

USE OF $V_{\text{eff}}$ AND ISO-NTCP IN THE IMPLEMENTATION OF DOSE ESCALATION PROTOCOLS

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\( V_{\text{eff}} \) for Iso-NTCP dose prescription

\[
V_{\text{eff}} = \sum \{ v_i \cdot \left( \frac{D_i}{D_{\text{ref}}} \right)^{1/n} \}
\]
UM liver & lung cancer protocol methods

- The goal for the treatment planner was to minimizing the effective volume $V_{\text{eff}}$ for the normal liver or lung which in turn allowed for the maximum safe tumor dose to be given at the current iso-NTCP level.

- This contrasted with standard dose trials which delivered target dose without regard to the volume of normal tissue.
Focal Liver 3DCRT - Larger Target

![Diagram showing dose-volume relationship for focal liver 3DCRT with a larger target, indicating a dose of 60 Gy.]
Focal Liver 3DCRT - Smaller Target

![Graph showing dose vs. volume percentage.](image)

- Dose (Gy): 0, 20, 40, 60, 80, 100
- Volume (%): 80
Iso-NTCP dose escalation

- The result was a framework for gathering partial organ tolerance data in a systematic, prospective fashion.
- Moreover, it allowed the introduction of new technologies without alteration of the protocols objectives
  - More conformal $\rightarrow$ lower $V_{eff}$ $\rightarrow$ higher $D_{ref}$
  - Same iso-NTCP level
Iso-NTCP dose escalation

- Incorporation of the concepts removed some of the arbitrariness often associated with dose escalation studies that didn't consider the volume of tissue irradiated.
- The data resulting from studies which used the methodology were of value for further NTCP model parameterizations.
Liver Lyman model NTCP parameters

ANALYSIS OF RADIATION-INDUCED LIVER DISEASE USING THE LYMAN NTCP MODEL

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LKB Model Parameters (early 2000s)

Original Emami-Burman Parameters

ISO-NTCP \( \text{(TD}_{50}=45; n=0.32; m=0.15) \)

Derived Parameters

ISO-NTCP \( \text{(TD}_{50}=42.4; n=0.94; m=0.16) \)
QUANTEC: ORGAN-SPECIFIC PAPER

Abdomen: Liver

RADIATION-ASSOCIATED LIVER INJURY

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# QUANTEC Liver Summary Table

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume segmented</th>
<th>Irradiation type (Partial organ or as stated)*</th>
<th>Endpoint</th>
<th>Dose (Gy), or dose/volume parameters*</th>
<th>Rate (%)</th>
<th>Notes on dose/volume parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Whole liver – GTV</td>
<td>3D-CRT or Whole organ</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 30-32</td>
<td>Excluding patients with preexisting liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients</td>
</tr>
<tr>
<td></td>
<td>Whole liver – GTV</td>
<td>3D-CRT</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole liver – GTV</td>
<td>3D-CRT or Whole organ</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 28</td>
<td>In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding Hepatitis B reactivation as an endpoint</td>
</tr>
<tr>
<td></td>
<td>Whole liver – GTV</td>
<td>3D-CRT</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whole liver – GTV</td>
<td>SBRT (hypofraction)</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 13</td>
<td>3 fractions, primary liver cancer</td>
</tr>
<tr>
<td></td>
<td>Whole liver – GTV</td>
<td>SBRT (hypofraction)</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 15</td>
<td>3 fractions, for liver metastases</td>
</tr>
<tr>
<td></td>
<td>&gt; 700 cc of normal liver</td>
<td>SBRT (hypofraction)</td>
<td>Classical RILD</td>
<td>Mean dose</td>
<td>&lt; 15</td>
<td>Critical volume based, in 3-5 fractions</td>
</tr>
</tbody>
</table>

L. Marks, et al., IJROBP, 76:S10-S19, 2010
20+ years of outcomes modeling

- There are many more data in different dose/volume regions than in 1990.
- This situation will continue to improve.
- Outcomes models continue to play a role in iso-toxicity RT protocols,
  especially for tumors in so-called volume effect organs.
20+ years of outcomes modeling

- (overly?) simple mathematical models where nearly everything seems to be related to mean dose
- Assumes all patients are representative of a uniform cohort
- Assumes homogeneously responding tumors and normal tissues
- Assumes previous experience still applies to modern therapeutic approaches
Does iso-NTCP individualize therapy?

- Population based NTCP parameters
  - Permit design of protocols that can maximize target dose for each patient at an equal level of risk (e.g., 10% NTCP)

- Therefore, as the patients, their tumors and geometries are all different:
  - each will get their own individualized maximum tolerated dose treatment,
  - *but, as a member of the population!*
    - i.e., each patient will have a 10 in 100 chance of getting the dose limiting complication
10 of 100 patients will have a complication
However, we can’t tell which 10 of 100 they will be!

You (only) have a 10 in 100 chance of developing a complication.
10 of 100 patients will have a complication (which 10?)
What if we could identify which 10 of 100?
What if we could identify the sensitive subgroup?

- We could decrease the risk of complication if we could determine during therapy the 10% of patients who are at greatest risk for toxicity.

- Moreover, we could potentially increase dose for the 90% of those who would experience no severe toxicity using the current population-based approach.
How can we identify subgroups?

- Requires additional patient specific information
- Validated, efficient means of obtaining equivalent (or inferred) data
- With recognition that the patient model changes over the course of treatment
How can we identify subgroups?

- Subgroup characteristics
  - Anatomic
  - Biological
  - Functional

- Tools to identify
  - Physiological imaging
  - Cytokines and other biomarkers
  - Other predictive assays or characteristics
Standard Radiation Therapy

- Treatment based on a population estimate of what might control a tumor
- Estimated risk of normal tissue damage based on the most sensitive 5-10% of the population
- Treatment delivered to the initially prescribed dose
  - Stop only for unacceptable acute toxicity
Response-based adaptive therapy

- Assess pretreatment the patient’s tumor and normal tissues
  - Genetically
  - With functional and molecular imaging
  - With plasma cytokines

- Determine during treatment:
  - If, and what parts of, the tumor are responding
  - If, and what parts of, the normal tissues are being injured
Response-based adaptive therapy

- Adapt therapy to the individual patient’s response
  - redistribute dose to the resistant part of the tumor
  - while sparing the functioning normal tissues
Examples - Preliminary Data

- Poster 20: Optimization of Response-Based, Adaptive Therapy
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