HyTEC- The Project and the Product

Ellen Yorke
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History: Quest for Optimal Uncomplicated Tumor Control

- Early 1900’s: Hypofractionation-convenience, technical simplicity
- 1920’s-30’s and on: observed complications lead to ‘conventional fractionation’ for curative treatments
- 1950’s Leksell- Gamma Knife
- Yet most new technology develops with conventional fractionation
HyTEC: ‘Hy’ Dose per Fraction, Hypofractionated Treatment Effects in the Clinic

Steering Committee: Jimm Grimm, Ph.D.  Ellen Yorke, Ph.D.  Lawrence B. Marks, M.D.  Andrew Jackson, Ph.D.  Brian D. Kavanagh, M.D.  Jinyu Xue, Ph.D.

AAPM Working Group on SBRT (WGSBRT), Biological Effects Subcommittee (BESC)
• Preparing for computerized, 3D treatment planning and delivery

• Most severe radiation-induced complication in 28 normal organs
  • The ‘Emami paper’
• Conventional fractionation only. Adults only.
• Due to scarce literature-clinicians’ consensus recommendations.
• TD5/5 and TD50/5 (dose for 5 and 50% complication by 5 years)
Complication depends on dose and irradiated volume

- Simple dose distribution-uniform dose to whole, 2/3 and 1/3 organ, zero to rest
  - ‘partial organ irradiation’ like parallel opposed

- Modeled dose-volume complication incidence as sigmoidal curve

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**Table 1. Normal tissue tolerance to therapeutic irradiation**

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 55 Volume</th>
<th>TD 50/5 Volume</th>
<th>Selected endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney I</td>
<td>5000</td>
<td>3000*</td>
<td>2300</td>
</tr>
<tr>
<td>Kidney II</td>
<td>4000*</td>
<td>2800</td>
<td>Clinical nephritis</td>
</tr>
</tbody>
</table>

**Fitting of Normal Tissue Tolerance Data to an Analytic Function**

C. Burman, Ph.D., 1 G. J. Kutcher, Ph.D., 1 B. Emami, M.D., 2 and M. Goitein, Ph.D. 3

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[Graphs and images showing dose-response curves for lung and spinal cord complications.]
Due to major technological changes a new consensus review of normal tissue complications was published in 2010 in *IJROBP*

**Quantitative Analyses of Normal Tissue Effects in the Clinic**

*Volume 76, Issue 3, Supplement, Pages S1-S160 (1 March 2010)*

**QUANTEC**

- All guidelines from peer-reviewed published data
- 16 organs, range of complications
- Mostly conventional fractionation
- Table of practical dosimetric guidelines per organ

<table>
<thead>
<tr>
<th>Lung</th>
<th>Whole organ</th>
<th>3D-CRT</th>
<th>Symptomatic pneumonitis</th>
<th>V20 ≤ 30%</th>
<th>&lt;20</th>
<th>For combined lung. Gradual dose response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole organ</td>
<td>3D-CRT</td>
<td></td>
<td>Symptomatic pneumonitis</td>
<td>Mean dose = 7</td>
<td>5</td>
<td>Excludes purposeful whole lung irradiation</td>
</tr>
<tr>
<td>Whole organ</td>
<td>3D-CRT</td>
<td></td>
<td>Symptomatic pneumonitis</td>
<td>Mean dose = 13</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Whole organ</td>
<td>3D-CRT</td>
<td></td>
<td>Symptomatic pneumonitis</td>
<td>Mean dose = 20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Whole organ</td>
<td>3D-CRT</td>
<td></td>
<td>Symptomatic pneumonitis</td>
<td>Mean dose = 24</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Whole organ</td>
<td>3D-CRT</td>
<td></td>
<td>Symptomatic pneumonitis</td>
<td>Mean dose = 27</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Significance:** Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.

**Footnote:** Includes a discussion of uncertainties in organ definition (e.g., changes in organ volume/shape during therapy), and the associated impact on DVHs and dose-volume/organ analyses.

**Rationale of Dose/Volume Data:** A series of organs, possibly with associated risk parameters, limitations, and uncertainties.

**Factors Affecting Risk:** Other clinical factors affecting the risk of injury are noted (e.g., combined modality therapy, dose fractionation).

6. **Mathematical/Biological Models:** Models that have been used to derive 3D dose-volume data to clinical outcomes are summarized, along with associated model parameters, limitations, and uncertainties.

7. **Special Situations:** Most of the data discussed relates to conventional fractionation. This section describes situations where the presented data/models may not apply (e.g., hyperfractionation).

8. **Recommended Dose/Volume Limits:** The available information is condensed into meaningful dose-volume limits, with associated risk rates, to apply clinically.

9. **Future Toxicity Studies:** Describes areas in need of future study.

10. **Toxicity Scoring:** Recommendations on how to score organ injury.
TIME MARCHES ON

Increasing safe and effective clinical use of stereotactic body radiation therapy -SBRT, aka Stereotactic Ablative Radiotherapy or SABR- for disease sites throughout the body.
HyTEC=Hypofractionated Treatment Effects in the Clinic

Approved in 2011

• AAPM Working Group, under BESC
• Each article has 10 standard sections
• 9 TPC, 7 NTCP, Introduction, 3 ‘Vision’ papers
• Multiple ‘blind’ reviewers per paper
  • chosen by steering committee, TPC, Science Council

Special IJROBP Issue 5/1/21
Member link at AAPM website
High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): An Overview

Jimm Grimm, PhD, Lawrence B. Marks, MD, Andrew Jackson, PhD, Brian D. Kavanagh, MD, Jinju Xue, PhD, and Ellen Yorke, PhD

A summary of the key dose, volume, and outcome data for the organs and tumors considered in HyTEC is provided in Tables 2 and 3. In generating the table entries, preference was given to providing published clinical data when available. Thus, for situations where both clinical and model-based data were available, the clinical data were favored. Further, the NTCP data shown are largely for patients who have received no prior radiation therapy (RT), and the entries reflecting situations with prior RT are so noted. We recognize and emphasize that the data are imperfect. For many tumor sites, local recurrence is difficult to establish with certainty by noninvasive imaging methods, and there are statistical issues (e.g., competing risks, a failure to consistently assess for local failure in patients with systemic disease, and favorable patient selection for both retrospective analyses and prospective studies) that collectively may tend to overestimate the true local control rates across an entire population.

The HyTEC authors took the pragmatic approach of reviewing the available literature and pooling data from publications containing the minimal set of data elements needed for a meaningful analysis (e.g., clearly stated dose schedules, prescription practices, critical structure dose reporting, and clinical outcomes for toxicity or tumor control). From these analyses, the authors synthesized the dose, volume, and outcome data, and when possible, generated associated models, while at the same time acknowledging the uncertainties. We emphasize and acknowledge that the models used in many of these reports are imperfect (e.g., the linear-quadratic model is simplistic), but support their use as a tool to try to pool pool data. Data pooling is fraught with hindrances: retrospective nature of much of the published data; and a lack of clarity and inconsistencies/uncertainties regarding critical items such as (1) dose calculation and specification, (2) image segmentation, (3) outcome definitions (both for toxicity and tumor-control), and (4) accounting for competing risks and variable follow-up durations. The HyTEC effort also involved

- All data from selected peer-reviewed publications
- TCP and NTCP practical guideline tables in Introduction
- Published clinical data favored over model results
- Important for comparing fractionations
Lightening Tour of Radiobiological Effects for HyTEC

- A dose is more potent when delivered in fewer fractions
- HyTEC pools data from various fractionations (1- >5)
  - Isoeffective Dose (few fractions) < Dose (many fractions)
  - Isoeffective doses have the same Biologically Effective Dose or BED
- Many BED models developed over the years

- Widely used: Linear-Quadratic (LQ) model
  - D=total dose, n=# of fractions, α/β = effect-dependent parameter
    - α/β high (≥ 10 Gy) for most TCP, low (≤ 5 Gy) for NTCP
  - **BED=D \((1+D/n)/α/β\)**
    - EQD2 = isoeffective dose (same α/β) in 2 Gy fractions
    - HyTEC also uses Equivalent Dose in specified # fractions

- Most HyTEC articles use LQ
  - Imperfect but simple
  - A few compare LQ to other models
• **Endpoint:** ≥ Grade 3 radiation myelopathy [RM]-highly symptomatic
• PubMed search 1/05-1/18; 40 initial hits triaged to 7 de novo studies, 5 re-irradiation
• No case reports, cauda vs cord or de novo vs reirradiation not separately reported, inadequate followup information
• Due to extreme clinical caution, there are very few RM cases!

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**Table 1**  De novo spine SBRT literature that met the inclusion criteria for this review

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of patients</th>
<th>Dose reporting structure</th>
<th>prescribed dose in Gy (range) / number of fractions (range)</th>
<th>Median spinal cord dose $D_{max}$, Gy</th>
<th>Median spinal cord EQD2, Gy</th>
<th>Median follow-up, mo</th>
<th>No. of cases of RM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2012&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>131</td>
<td>Thecal sac</td>
<td>Mean EQD2&lt;sub&gt;2&lt;/sub&gt; 50.7/NS</td>
<td>50 (18-30)/1 (1-3)</td>
<td>1 Fox 22.7 (range, 17.8-30.9); 2 Fox 22.0 (range, 21.3-26.6); 5 Fox 21.9 (range, 19-25.4)</td>
<td>Mean 48.68 ± 20.97</td>
<td>Mean 21.7</td>
</tr>
<tr>
<td>Daily 2011&lt;sup&gt;12&lt;/sup&gt;</td>
<td>19</td>
<td>Cord</td>
<td>NS</td>
<td>20 (18-30)/1 (1-3)</td>
<td>1 Fox 140.17; 2 Fox 71.5; 3 Fox 50.92</td>
<td>Mean 33.7</td>
<td>1</td>
</tr>
<tr>
<td>Gerstken 2012&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>26</td>
<td>Cord</td>
<td>Mean 16 (12-24)/1 (1-3)</td>
<td>Mean 8.7 (range, 4-11.5)</td>
<td>Mean 23.27</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Sahlgren 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>12</td>
<td>Thecal sac</td>
<td>Mean 21 (20-40)/1 (1-5)</td>
<td>Mean 20.9 (range, 4.3-23.1)</td>
<td>Mean 46.85</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Sahlgren 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>14</td>
<td>Thecal sac</td>
<td>Mean 24 (7-40)/3 (1-5)</td>
<td>Mean 16.8 (range, 10.7-26)</td>
<td>Mean 28 (range, 15-37)</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Sahlgren 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>46</td>
<td>Thecal sac</td>
<td>NS / 1 (5)</td>
<td>NS</td>
<td>Mean 35.6</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Richter et al. 2017&lt;sup&gt;25&lt;/sup&gt;</td>
<td>228</td>
<td>Cord</td>
<td>Mean 24 (18-34)/1 (1)</td>
<td>13.85 (range, 9.61-13.21)</td>
<td>Mean 54.88 (range, 27.89-65.44)</td>
<td>Mean 15</td>
<td>2</td>
</tr>
</tbody>
</table>

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**Table 2**  Reirradiation spine SBRT literature that met the inclusion criteria for this review

<table>
<thead>
<tr>
<th>Paper</th>
<th>No. of patients</th>
<th>Dose reporting structure</th>
<th>Median prescribed dose (range) / number of fractions (range)</th>
<th>Median prescribed dose of prior RT (range) / number of fractions (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang 2012&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>54</td>
<td>Thecal sac</td>
<td>Mean EQD2&lt;sub&gt;2&lt;/sub&gt; 34.1 / NS</td>
<td>NS</td>
</tr>
<tr>
<td>Goyal 2005&lt;sup&gt;12,24&lt;/sup&gt;</td>
<td>3</td>
<td>Cord</td>
<td>Mean 24 (18-30)/1 (1-5)</td>
<td>Mean 35.6</td>
</tr>
<tr>
<td>Sahlgren 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>25</td>
<td>Thecal sac</td>
<td>Mean 24 (18-30)/1 (1-5)</td>
<td>Mean 35.6</td>
</tr>
<tr>
<td>Sahlgren 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>14</td>
<td>Thecal sac</td>
<td>Mean 24 (18-30)/1 (1-5)</td>
<td>Mean 35.6</td>
</tr>
<tr>
<td>Thibault 2012&lt;sup&gt;26,27&lt;/sup&gt;</td>
<td>16</td>
<td>Cord PRV (+1.5 mm)</td>
<td>30 (20-35)/4 / (4-2.5)</td>
<td>Mean 20.3/20.3</td>
</tr>
<tr>
<td>Thibault 2012&lt;sup&gt;26,27&lt;/sup&gt;</td>
<td>24</td>
<td>Cord PRV (+1.5 mm)</td>
<td>30 (24-35)/4 / (4-2.5)</td>
<td>Mean 22.5/22.5</td>
</tr>
</tbody>
</table>

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**Abbreviations:** $D_{max}$ - maximum dose; EQD2 - equivalent dose in 2 Gy per fraction radiotherapy; SBRT - stereotactic body radiation therapy.

* The results from only the patients who met the inclusion criteria are reported in this current manuscript. The two systems of patients in our institutional study.

* Cumulative EQD2, estimated using summary data presented in paper.

* The data presented are the controls, not the outcomes of radiation myelopathy.

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Much more data needed for reirradiation
Challenges defining anatomic Volumes

Spinal canal?
Thecal sac?
Spinal cord seen in myelogram or MRI?
Spinal cord with PRV margin?

‘Whichever approach is used clinically for segmenting the spinal cord, the clinician should be mindful of how past studies have reported spinal cord doses and to what structure the doses were being reported.’

Larger structures may be safer but they penalize paraspinal target coverage
From Figure 1

**Sahgal Model**
- Thecal Sac
- \(\alpha/\beta = 2\) Gy, 1-5 fraction cases
- 9 Grade 4 RMs from collaborating group + 66 no-RM controls
- Conservative
- Single fraction Thecal Sac \(D_{\text{max}} \leq 12.4\) Gy for predicted RM<1-5%

**Katsoulakis-Gibbs (K-G) Model**
- Spinal cord
- \(\alpha/\beta = 3\) Gy  K: 259 single-fraction    G: 19 cases, BED(\(\alpha/\beta = 3\) Gy)
- K: 2 RMs    G: 1 RM
- Single fraction cord \(D_{\text{max}} \leq 14\) Gy for predicted RM<1-5%

**Comparison with other published data**
“…..steep increases in risk above single fraction \(D_{\text{max}} of 15\) Gy”
HyTEC Introduction NTCP Table

"It is up to individual physicians to determine their own practice and what limits they wish to apply; all of these tolerance limits are suggestions and are not absolute. There are significant limitations to the data that cannot be overcome unless large, prospective, multi-institutional cooperative registries of dose tolerance thresholds are created and modelled."

Consistent with other expert Dmax

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume segmented</th>
<th>Number of fractions</th>
<th>Endpoint</th>
<th>D_{max} (Gy) or dose-volume parameters</th>
<th>Rate (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Spinal cord,</td>
<td>1</td>
<td>Myelopathy</td>
<td>D_{max} &lt; 12.4-14 Gy</td>
<td>1-5%</td>
<td>These data are for patients without prior RT (from Table 5 in paper).</td>
</tr>
<tr>
<td></td>
<td>canal, or</td>
<td>2</td>
<td></td>
<td>D_{max} &lt; 17-19.3 Gy</td>
<td>1-5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>thecal sac[]</td>
<td>3</td>
<td></td>
<td>D_{max} &lt; 20.3-23.1 Gy</td>
<td>1-5%</td>
<td>Information for the setting of re-irradiation are in Table 4 of the</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td></td>
<td>D_{max} &lt; 23-26.2 Gy</td>
<td>1-5%</td>
<td>paper. Consistent with QUANTEC.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td></td>
<td>D_{max} &lt; 25.3-28.8 Gy</td>
<td>1-5%</td>
<td></td>
</tr>
</tbody>
</table>

\[\] A range of doses and complication rates are reported, reflecting the heterogeneity and uncertainty in the data. The spinal cord, canal, and the thecal sac have each been used in different models of radiation myelopathy.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Spinal cord and thecal sac D_{max} values recommended in previous publications compared with model-derived limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Existing expert-based recommendations for D_{max}</td>
</tr>
<tr>
<td></td>
<td>AAPM TG101[1]</td>
</tr>
<tr>
<td>No. fractions</td>
<td>Gy</td>
</tr>
<tr>
<td>2</td>
<td>18.3</td>
</tr>
<tr>
<td>3</td>
<td>22.5</td>
</tr>
<tr>
<td>4</td>
<td>25.6</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviations: AAPM TG101 = American Association of Physicists in Medicine Task Group 101; CT = computerized tomography; D_{max} = maximum dose; LQ = linear quadratic; MRI = magnetic resonance imaging; RM = radiation myelopathy.

\[1\] The spinal cord itself (from CT myelogram or MRI) was used as the dose reporting structure by Kastoulatakis et al\[3\] and Gibbs et al\[3\] and the thecal sac was used as a surrogate structure for the spinal cord by Sahgal et al\[3\]. Numbers in italics denote LQ-based extrapolations from the single-fraction limit. Note that because of the uncertainties involved, the decimal place may not be meaningful, and an approximately equivalent set of median rounded limits from the recommendations/models would be 14, 18, 22, 26, and 28 Gy for 1 to 5 fractions, respectively.
Now onward:

- **Dr. Anand Mahadevan**: An in-depth look at the HyTEC process with pancreas TCP as the example.

- **Dr. Andrew Jackson**: A physicist’s and modeler’s perspective on how HyTEC used data from outcomes publications and suggestions as to how future studies can be made more informative.

- **Dr. Larry Marks**: A radiation oncologist’s perspective on HyTEC and the future.