TG113: Improving Treatment Consistency and Data Quality for Clinical Trials

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Educational Objectives

1. To describe the goals of TG#113:
   Physics Practice Standards for Clinical Trials
2. To highlight some factors that directly impact clinical trials that involve IMRT and IGRT

Task Group 113

Members
- Robert Dryzmala
- Jon Kruse
- Jean Moran (Chair)
- Art Olch
- Mark Oldham
- Robert Jeraj

Liaisons
- James Galvin – RTOG
- Andrea Molineu – RPC
- Jatinder Palta – RCET, TG100
- James Purdy – ITC
- Marcia Urie – QARC

Outline

- Motivation
- Challenges for multi-institutional trials
- Factors impacting clinical trials
  - Examples for imaging, localization
- Role of benchmarks
- Summary
Motivation

- Physics QA for clinical trials
  - Assure consistency in each part of the treatment planning and delivery process
- Advanced Technology Consortium
  - ITC, QARC, RCET, RTOG, and RPC
  - Organizations provide QA services and some trial and benchmark design
- However, there are no standard guidelines for the physics aspects of clinical trials

Expected Users of TG113

- Physicists & Others
  - Implement trials at department level
  - Involved in all parts of the treatment planning and delivery process
  - Can significantly improve data consistency if guidelines are available
- QA Organizations
  - Credentialing
  - Benchmarks - Dry run, phantom
- Cooperative Groups
  - Trial Design
  - Make trials more specific with respect to physics aspects
- Vendors
  - Data export: Dosimetric, imaging, localization
  - Dose calculation quality – heterogeneity corrections
  - Plan assessment tools
  - Delivery software and devices
  - Equipment

Factors Impacting Data for Clinical Trials

- Patient immobilization
- Imaging for Volume definition
- Patient localization: Setup accuracy
- Treatment planning
- Treatment guidance
- Treatment delivery

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- What is the clinical trial designed to study?
- What are the clinical endpoints?
- What data are collected?
- What level of accuracy is required for the treatment planning and delivery chain?
- Will we want to know more later? e.g. NTCP modeling of lung
Challenges

- Challenges to clinical trials
  - Accrual
  - Time
  - Expense
- Physics issues are not always explicitly included in the design of clinical trials
- These exclusions may dilute the quality of data from a clinical trial
  - Imaging
  - Homogeneous vs. heterogeneous dose calculations
  - Patient setup details

TG113

- Can changes be made to improve the consistency of clinical trials (better data) without overwhelming:
  - Physicians and physicists designing clinical trials?
  - The treatment team participating in trials?
  - The QA centers supporting clinical trials?
- Our work focuses on external beam radiation therapy

Contouring Targets: Effect of Window on Target Volume

Table 3: Mean tumor volume values obtained using mediastinal window and lung window settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>Tumor No. (cm²)</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mean MW</td>
<td>23.8</td>
<td>95.8</td>
</tr>
<tr>
<td>Mean LW</td>
<td>12.9</td>
<td>153.2</td>
</tr>
<tr>
<td>Ratio</td>
<td>2.01</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Abbreviations: MW = mediastinal window; LW = lung window.


To improve consistency in trials

- Protocols can provide guidance for window/gray levels in the trial design
SBRT Dry Run Study: 11 institutions

Breath hold CT
2 mm slices - lung


Effect of Delivery Technique

Minimum PTV: 35-46 Gy
Homogeneity index: 1.05-1.4

Dry Run: SBRT (continued)

- Inter-institutional variations in planning for SBRT for lung cancer, Matsuo et al. IJROBP, 2007, 416-425
- 16.6% variation in target volumes
- Significant differences
  - Treatment delivery technique
  - Dose calculation algorithms
    - Chose to use 1-D methods rather than mix; recalc with CVSP when available
  - ATC supporting digital data submission

Bowden et al. compared mean tumor volume values for volumes drawn with a lung window compared to a mediastinal window for 6 physicians on 6 datasets. The average ratio of the lung window to mediastinal window (LW/MW) was:

- 1: 100% (no difference)
- 25% 2: 120%
- 25% 3: 150%
- 25% 4: 180%
To improve consistency in clinical trials:

- Contouring instructions must be explicit
  - A range of acceptable values can be given
- Treatment planning guidelines must be explicit
  - Some trials specify dose-volume constraints and minor and major variations

Patient Immobilization and Localization

1. Intra-fraction reproducibility
2. Inter-fraction variations over the course of treatment
3. Inter-institutional variations

- Frequency of assessment
- Surrogates for tumor position
- One size fits all may not be appropriate target and OAR margins

What margin should be used in the clinical trial?

- Should a single margin be specified for all trials?
- What about immobilization?
- What about imaging protocol? Is it off-line or adaptive? Is it daily or weekly?
- Should clinics use the same margin because the patient is on a multi-institutional trial even if their methods are different?
  - What is the true delivered dose? Do we know?
  - How can we interpret the data?
Treatment Guidance

- Image guidance methods
  - Cameras
  - RF beacons
  - kV fluoroscopic imaging
  - MV cine loops

- Type of intervention depends on the frequency of the event
  - Real-time evaluation is needed to address intra-fraction motion
  - Fiducials

Example: Image Guidance – HN MVCT: Bony anatomy registration

- Error As a Function of % Image Guidance
  - Error > 3 mm
  - Error > 5 mm
  - Error > 10 mm

Example: Treatment Guidance

- 3 transponders
- Implanted transrectally under ultrasound guidance
- 10 minute procedure
- Consistent with gold marker implant effects
- Good positional stability over 8 weeks ($\sigma_{ave} = 0.8$ mm)
To improve consistency in trials:

- Margins should be based on each institution's image guidance protocols

Or

- The trial should specify the acceptable methods and frequency of interventions

- Patient enrollment information should include immobilization method and localization information
  - Frequency
  - Action level

Treatment Delivery

- Does it matter if the treatment is:
  - Delivered with a conventional Linac or something else (Tomotherapy, Cyberknife)?
  - Static, IMRT, or arc delivery?
  - Is motion management needed?

- Some part of the credentialing process may be dependent on delivery technique
  - Process appropriate margins can be used incorporating other factors

Credentialing for Clinical Trials

- Facility questionnaire
  - Information about department, equipment and software used for patient care

- Dry run
  - Hard copy or electronic submission of a treatment plan that intends to meet the guidelines of the protocol

- Additional testing depends on the trial and QA organization

- Benchmarks, e.g. phantom irradiation
RPC: IMRT H&N Phantom

• Primary PTV
  4 cm diameter
  4 TLD
• Secondary PTV
  2 cm diameter
  2 TLD
• Organ at risk
  1 cm diameter
  2 TLD
• Axial and sagittal
  radiographic films

Designed in collaboration with RTOG; Molineu et al., IJROBP, October 2005

Importance of Credentialing
RPC: IMRT H&N Phantom Results

• 163 irradiations were analyzed
• 115 irradiations passed the criteria
  • 28 institutions irradiated multiple times
• 48 irradiations did not pass the criteria
• 128 institutions are represented

~30% of institutions fail the criteria on the first irradiation.

RPC: Explanations for Failures

<table>
<thead>
<tr>
<th>Explanation</th>
<th>Min # of occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect output factors in TPS</td>
<td>1</td>
</tr>
<tr>
<td>Incorrect PDD in TPS</td>
<td>1</td>
</tr>
<tr>
<td>Inadequacies in beam modeling at leaf ends (Cadman, et al; PMB 2002)</td>
<td>14</td>
</tr>
<tr>
<td>Not adjusting MU to account for dose differences measured with ion chamber</td>
<td>3</td>
</tr>
<tr>
<td>Errors in couch indexing with Peacock system</td>
<td>2</td>
</tr>
<tr>
<td>2 mm tolerance on MLC leaf position</td>
<td>1</td>
</tr>
<tr>
<td>Setup errors</td>
<td>7</td>
</tr>
<tr>
<td>Target malfunction</td>
<td>1</td>
</tr>
</tbody>
</table>

Effect of Leaf Position Offset on IMRT

Effect of Leaf Position Offset on IMRT

Uncorrected leaf offset -3.12% errors
Leaf offset corrected +/- 5% errors


The number of institutions who pass the benchmark irradiation of the RPC head and neck phantom is:

- 10%
- 5%
- 10%
- 30%
- 45%

Inaccuracy in the modeling of curved multileaf collimator leaves was shown to result in dosimetric errors up to:

- 2%
- 12%
- 25%
- 30%

To improve consistency in clinical trials:

- There is a clear role for dosimetric verification when complex technologies are being introduced
- RPC phantom found dosimetric errors that would have adversely affected trial results
- Request immobilization and setup information as part of patient enrollment on a clinical trial
How should new technologies be incorporated into clinical trials?

- We do not want to limit participation in clinical trials, but we do want delivery to be as accurate as possible.
- Results should also represent how patients will be treated in a variety of hospital settings.
- Focus is on physics issues that affect the consistency of data acquired during clinical trials.
  - Expect improved confidence in the data submitted as part of a clinical trial.
  - Should improve interpretation of studies looking at tissue response.

TG 113 Summary

- Emphasis on process improvements to decrease the variability in clinical trials (and improve our knowledge of differences).
- Design of trials: Allow for variable margins based on immobilization and localization methods.
- Continue to require credentialing as new technologies are implemented at different centers and as benchmarks continue to show significant failures.
- Looking forward: Trials on treatment assessment.
- We are in the process of completing our written report for submission to Therapy Physics Committee and then submission for publication.