Credentialing for Clinical Trials - IGRT

Evidence Based Radiation Oncology

Clinical Trials From Collaborative Groups
- e.g. Radiation Therapy Oncology Group (RTOG)
  - Improve the survival outcome and quality of life of adults with cancer through the conduct of high-quality clinical trials.
  - Evaluate new forms of radiotherapy delivery, including SBRT, brachytherapy, 3D-CRT, IMRT, and heavy particle therapy in clinical research.
  - Test new systemic therapies in conjunction with radiotherapy, including chemotherapeutic drugs, hormonal strategies, biologic agents, and new classes of cytostatic, cytotoxic, and targeted therapies.
  - Employ translational research strategies to identify patient subgroups at risk for failure with existing treatments and identify new approaches for these patients.

Levels of Clinical Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Adequately powered, high quality randomized trial, meta-analysis of randomized trials showing statistically consistent results</td>
</tr>
<tr>
<td>II</td>
<td>Randomized trials non-adequately powered, possibly biased, or showing statistically inconsistent results</td>
</tr>
<tr>
<td>III</td>
<td>Non-randomized studies with concurrent controls</td>
</tr>
<tr>
<td>IV</td>
<td>Non-randomized studies with historical controls (i.e. typical single arm phase II trials)</td>
</tr>
<tr>
<td>V</td>
<td>Expert committee review, case reports, retrospective studies</td>
</tr>
</tbody>
</table>

Evaluation of Innovative Treatments in Radiation Therapy Oncology Group Trials: Main Outcomes

Why Credentialing?

(phase 3 trials conducted by the RTOG since its creation in 1968 until 2002
Data on 12,734 patients from 57 trials were evaluated


Acknowledgements

Invitation from Organizers
RTOG Headquarter QA Team
ATC Collaborators
Sources of Uncertainties

- Image Acquisition
- Image Fusion/Structure Delineation
- Prescription variations in clinical trial protocols
- Dose Calculation/Plan Optimization
- Delivery Uncertainty
- TCP/NTCP model uncertainty

Prescription range for head and neck cancer clinical trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Prescription (Gy)</th>
<th>PTV covered to Prescribed dose</th>
<th>Minor variation</th>
<th>Max dose to target volume (95% volume coverage)</th>
<th>Deviation</th>
<th>Max dose to target volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>60/60</td>
<td>58 – 60</td>
<td>95%</td>
<td>8%</td>
<td>&gt; 90%</td>
<td>&lt; 98%</td>
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</tr>
<tr>
<td>60/65</td>
<td>60 – 69</td>
<td>95%</td>
<td>6%</td>
<td>&lt; 98%</td>
<td>&gt; 92%</td>
<td>&gt; 110%</td>
</tr>
<tr>
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</table>

RPC Phantom & Results

- 5% beams > RPC’s ±5% dose or 5 mm electron @ 1st
- 750 institutions (83% of all), ≥20% w. >1 beam > ±5%
- EORTC mailed TLD programme 1993–1996

Impact of Clinical Uncertainty

Example 1

Change in TCP and NTCP
Change in TCP and NTCP

Cumulative distribution of the proportion of human cells surviving fractions corresponding to various estimated changes in (a) tumour control probability (TCP) and (b) normal tissue complication probability (NTCP) for beams of 6 MV or less.

Bentzen et al. European J. of Cancer 36 2000 615

Example 2
Sample Size

Sample Size Calculation: Sigma

\[ \sigma = \frac{1}{\sqrt{\pi}} \]

\[ \sigma_{\text{clin.}} = \sqrt{\sigma_{\text{dose}}^2 + \sigma_{\text{biol.}}^2} \]

\[ \gamma_{\text{clin.}} = \left( \frac{1}{\sqrt{\pi}} \right)^2 \frac{1}{\sqrt{\pi}} \left( \frac{\sigma_{\text{dose}}^2}{\gamma_{\text{biol.}}} + \frac{\sigma_{\text{biol.}}^2}{\gamma_{\text{biol.}}} \right) \]

\[ \sigma_{\text{clin.}} = \sqrt{\sigma_{\text{dose}}^2 + \left( \frac{1}{\gamma_{\text{biol.}}} \right)^2 \sqrt{\pi}} \]

Sample Size Calculation

\[ Z_x + Z_\beta \geq \frac{\Delta R}{\sigma / \sqrt{N}} \]

\[ N_{\text{tot}} = 2 \left( \frac{1}{\sqrt{2\pi}} \right)^{\frac{1}{2}} \left( \frac{Z_x + Z_\beta}{\Delta R} \right)^2 \]

\[ Z_x = 1.645 \quad \text{and} \quad Z_\beta = 0.8416 \]

Population Size Variation

The number of patients required in each arm of the RCT, i.e. sample size, calculated for various response differences, slopes of the biological dose-response curve, clinical vs. biological dose-response curves, and increasing variation in absorbed radiation dose.

Diagnostic Imaging and Radiation Oncology
Core Laboratory

Functional Infrastructure

Image Processing

Volumetric Measurements/Segmentation
- MIM Vista FDA Cleared
- Osirix® FDA Cleared
- Velocity FDA Cleared

DICOM Viewer/QC:
- IQ View® FDA Cleared
- Clear Canvas®
- Sante®
- DICOM Works
- MIM Vista for PET QC FDA Cleared
- Velocity
- TRIAD

RECIST Evaluation
- IQ View®
- CEDARA
- Osirix® FDA Cleared

Treatment Planning and Related Systems
- Eclipse
  - Photon Beam Planning-3D, IMRT, RapidArc, Brachy
  - Electron Planning
  - Proton Planning – Passive Scatter, Active Scanning
- Oncentra
  - Photon Beam Planning-3D, IMRT, RapidArc, Brachy
  - Electron Planning
  - Proton Planning – Passive Scatter, Active Scanning
- ITC Remote Review Tools
- MIMvisa – Dose & DVH Analysis
- Velocity – Dose & DVH Analysis
- MOSAIQ
- CERR – Planning, Dose & DVH Analysis

Image Processing

SUV Measurements
- GE
- SIEMENS
- PHILIPS
- MIM Vista
- Velocity
- Matlab/SPM
- Fusion
- MIM Vista
- Velocity
- Matlab/SPM
- Dynamic Contrast MRI
- Apollo Mistran
- MR Spectroscopy
- Acorn NUTS
- Angiography/CTA
- Aquarius iNition-Tera Recon®
1. TRIAD * completed Sept 09
2. Acorn NUTS * completed
3. MIM Vista * completed Sept 09
4. Apollo MIStar
5. IQ View
6. Clear Canvas
7. Sante
8. DICOM Works
9. GE
10. SIEMENS
11. PHILIPS
12. OsiriX
13. Tera Recon
14. MatLab/SPM
15. Velocity * completed

* Developing a “level of confidence” that software meets all requirements and user expectations

Database
- TRIAD
  - Integrated Data Submission
  - Synchronized with CTMS and CTDW
  - DICOM RT Objects Supported
  - All Objects Anonymized and Linked
  - Application Deployment
- MiMvista PACs
- MOSAIQ PACs

Function Infrastructure Research

Data Integrity Quality Assurance / Transfer/Integration
- Radiotherapy CT, Structures, Plan, Dose
- Imaging Datasets
- Other RT Objects

IGRT Credentialing

Protocol IGRT Description and Specifications
- ROI
- 2D-3D, Fiducials, ...
- Correction strategy (offline, daily online corrections, adaptive)
- Fusion Technique

- IGRT Questionnaire
- Image Registration Software Tests

RTOG 0920
A PHASE III STUDY OF POSTOPERATIVE RADIATION THERAPY (IMRT) +/- CETUXIMAB FOR LOCALLY-ADVANCED RESECTED HEAD AND NECK CANCER

Credentialing Requirements
- Facility Questionnaire: Part I and Part II (IGRT)
- IGRT Immobilization/Localization Systems Test
  - Submitting 0920 IGRT Data to the ITC
  - Anonymized Patient Spreadsheet
- RPC Phantom Dosimetry Test (IMRT only)
  - Fill out the RPC Phantom Request Form
  - Phantom irradiation guidelines and forms Head and Neck Phantom
Data Submission
- DICOM format
- “Screen Capture”
- Number of IGRT data sets (5 days, e.g.)

- Planning CT with structures, dose and RT plan in DICOM RT format for a single patient
- IGRT localization images:
  - For 3D: Cone-beam CT (CBCT) in DICOM RT format or
  - For 2D: Screen-captures of the registrations
- Completed IGRT spreadsheet with positioning shifts

2D Submissions
- ExacTrac
- CyberKnife

3D Submissions
- CT-on-Rails
- Robotic Cone Beam
- Elekta Synergy (XVI)
- Varian (2005)
- Tomotherapy Hi*Art
- Siemens MVision
- LINAC Synergy (LX)

IGRT Data Submission Components
- X: 2.61 mm
- Y: -0.02 mm
- Z: 2.59 mm
- Shifts

Review Process
Review Process

- Translation: x (mm) y (mm) z (mm)
- Rotation: x (°) y (°) z (°)

Apply Institution’s Shifts
Evaluate PTV

Preliminary Results

<table>
<thead>
<tr>
<th>Subsets</th>
<th>Number of comparisons</th>
<th>Absolute value of difference of shifts (mm): mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomo vs. Others</td>
<td>6</td>
<td>2.1±1.7 (1.0-5.4) 1.9±1.6 (0.5-4.9) 1.8±1.3 (0.4-3.1)</td>
</tr>
<tr>
<td>Elekta vs. Others</td>
<td>6</td>
<td>2.5±1.8 (0.4-5.0) 1.1±0.5 (0.2-1.5) 2.4±1.0 (1.4-4.0)</td>
</tr>
<tr>
<td>Varian vs. Others</td>
<td>9</td>
<td>3.6±3.2 (1.2-8.6) 3.3±3.0 (1.6-4.4) 2.6±0.6 (1.1-3.2)</td>
</tr>
<tr>
<td>All Inter-</td>
<td>42</td>
<td>3.6±2.2 (0.1-8.6) 1.7±1.4 (0.0-4.9) 1.7±1.1 (0.1-4.0)</td>
</tr>
</tbody>
</table>

Summary

Clinical Trials are Essential for Evidence Based Medicine
Credentialing is an Integral Component of Clinical Trial Process
Credentialing Process Needs to be Comprehensive Medical Physics Expertise is Vital