The Critical Importance of High Quality in Radiation Therapy

Stephen F. Kry, PhD

ICARO-2
Vienna

June, 2017
Quality in Radiation Therapy

• Radiation therapy is versatile and important for many patients
• Intuitively, quality is very important
  – Get the right dose to the right place
• Achieving optimal quality can be challenging

• Introduction to these sessions:
  – What accuracy is needed in RT?
  – How important is good quality?
What accuracy is necessary?

• What is the right dose?
  – How right is “right”?

• ICRU Report 24 (1976)
  – “…the available evidence… points to the need for an accuracy of +/- 5% in the deliver of an absorbed dose to a target volume if the eradication of the primary tumor is sought.”
  – Biological variability in an endpoint is <5%
Underlying ICRU data
Further evidence:

• Tumor control: Randomized photon vs electron treatment
  – Same nominal dose, but significantly poorer tumor control with electrons
  – Turned out there was a 7%-low calibration error in the electrons

• Normal tissue complication: GYN reactions
  – Excessive GI and skin reactions observed
  – Investigation identified a 7-10%-high output calibration error
  – Other patients did not show errors

• Reported in Dutreix Radiother Oncol 1984
Dose response

- Variations make sense in terms of basic dose response biology
- Sensitivity depends on where we are on the dose response curve
  - if we are on the shoulder, not as sensitive
- Usually we’re somewhere on this slope and therefore sensitive to dose variations
Further consideration

- 5% is the total uncertainty
- There are many components that make up this uncertainty budget
  - Uncertainty in individual components must be much less
- Dose calculation: 2% is often quoted
  - AAPM TG-65 report: Tissue inhomogeneity corrections for megavoltage photon beams.
How important is good quality?

• We need to be within 5%
• Previous slides showed observable effects from very specific conditions of dose variation

• What about the bigger question of how quality affects radiotherapy outcomes in contemporary RT?
A contemporary example: TROG 02.02

- Cisplatin (CIS) vs Cisplatin + tirapazamine (TPZ)
- All patients: 70 Gy in 35 fx using a shrinking field technique
- Hypothesis: 10% improvement in 2 year overall survival
- 861 patients
RT Quality

• Quality assessed in terms of protocol compliance: delivering standard of care.
• Correct RT from outset (n=502)
• RT corrected during tx (n=86)
  – Median <10 treatment days to finalize changes
• RT not correct, but not expected to have major impact (n=105)
• RT not correct, expected to have major impact (n=97)
What is the nature of RT errors?

- 97 RT cases were deficient and expected to cause outcome problems
  - Inadequate planning/coverage (41)
  - Incorrect dose prescription (25)
  - Incorrect target definition (24)
  - Excessively prolonged treatment (7)
- Inadequate dose or missing the target
- Based on plan, but equivalent to
  - Poor beam model that overestimates dose
  - Miscalibrated beam
  - Incorrect alignment
How important is it?

2 year overall survival: 70% vs 50%
Put into perspective

• Justification for this multimillion dollar phase 3 clinical trial was:

• A hypothesized 10% improvement in 2 y overall survival!

• Versus a 20% difference based on the quality of RT!!

• The quality of RT is critical to patient survival
The impact of radiotherapy quality on treatment outcome would likely increase with the introduction and increasing use of more advanced radiotherapy techniques, such as intensity-modulated radiation therapy and stereotactic radiotherapy.”
This pattern persists

- Protocol compliance as surrogate for RT quality
- Poorer protocol compliance leads to poorer outcomes
  - Poorer tumor control
  - Poorer survival
- Outcomes for patients who received the protocol treatment vs. those with >5-10% dose deviations

Radiotherapy Protocol Deviations and Clinical Outcomes: A Meta-analysis of Cooperative Group Clinical Trials

Nitin Ohri, Xinglei Shen, Adam P. Dicker, Laura A. Doyle, Amy S. Harrison, Timothy N. Showalter

Manuscript received August 13, 2012; revised November 27, 2012; accepted November 27, 2012.
Protocol compliance summary:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Hazard ratio for Overall Survival</th>
<th>Hazard ratio for Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 73-01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SWOG 7628</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POG 9031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIOP/UKCCSG PNET-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TROG 02.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 97-04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMBINED</td>
<td>HR = 1.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI = 1.28 to 2.35</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial (outcome)</th>
<th>Hazard ratio associated with radiotherapy deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>POG 8346 (LC)</td>
<td>HR = 1.79</td>
</tr>
<tr>
<td>SFOP 93/94 (Relapse)</td>
<td>95% CI = 1.15 to 2.78</td>
</tr>
<tr>
<td>POG 9031 (EFS)</td>
<td></td>
</tr>
<tr>
<td>SIOP/UKCCSG PNET-3 (EFS)</td>
<td></td>
</tr>
<tr>
<td>TROG 02.02 (LRC)</td>
<td></td>
</tr>
<tr>
<td>RTOG 97-04 (Failure)</td>
<td></td>
</tr>
<tr>
<td>COMBINED</td>
<td></td>
</tr>
</tbody>
</table>

Failure to give an optimal dose leads to poorer outcomes
• For many tumors and side effects, we need to be within ~5%
  – Need to be within 2% for dose calculation
• If we don’t achieve that, we dramatically compromise patient outcomes
  – Overall survival substantially reduced when quality is not adequate
But there’s more

• Radiotherapy practice is based on evidence
• Evidence comes from clinical trials
  – gold standard
• Low quality undermines these trials; no answer
  – risk obscuring discovery of optimal treatments, and progression and innovation

• Consider these points when audit results are presented