Biologically-Weighted Robust Planning of Proton Therapy Knowledge Gaps, Controversies and Solutions

An Overview

Radhe Mohan, PhD, Professor, MD Anderson Cancer Center
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Conflict of Interest
Biologically-Weighted Robust Planning of Proton Therapy
Knowledge Gaps, Controversies and Solutions

Gaps in knowledge ➔ Controversies ➔ Hypotheses ➔ Research ➔ Solutions
Biologically-Weighted Robust Planning of Proton Therapy

1. Issues related Relative Biological Effectiveness (RBE)
2. Issues related Robustness Evaluation and Optimization
Relative Biological Effectiveness (RBE)

- Current practice: RBE = 1.1
- But, just in case RBE > 1.1 at distal edges ...
  - Beams pointing at critical normal structures distal to the target volume are avoided
  - Choice of number and orientations of beams and hinge angles
  - ...

Justification for Continued Use of RBE = 1.1

- Affects only a tiny region: “An increasing RBE with depth extends the biologically effective range (1-2 mm)”
- Large uncertainties in RBE and the models are inaccurate
- No clinical evidence suggesting need for change

Absence of evidence is not evidence of absence …

- Evidence may be obscured (or diluted) by
  - Numerous confounding factors (e.g., uncertainties)
  - Small sample sizes
  - Limitations of the methods of analyses
  - ...
Evidence of Toxicities, Failures and Below Expectation Outcomes is Beginning to Emerge


...
The Reality: RBE is a Complex, Non-Linear Function of Multiple Variables

- Proton energy spectrum $\rightarrow$ Ionization density $\rightarrow$ Linear Energy Transfer (LET)
  - Varies non-linearly and rapidly around the Bragg peak
- Dose per fraction
- Radiosensitivity of tissue/cell (alpha/beta ratio)
- Endpoint

![Graph showing dose and LET vs. depth for a 79.7 MeV scanning proton beam with a $20 \times 20 \text{ cm}^2$ field.]
Guan, et al 2015 (MDACC)

RBE vs. Fanconi Anemia/BRCA pathway defects

Liu IJROBP 2015, (MGH)

RBE for lung cancer cell lines for the same dose and LET at mid SOBP
Is continued use of RBE = 1.1 appropriate, especially for the heterogeneous dose & LET distributions per beam of (MFO) IMPT?
But what should we do about it?

- Use of variable RBE in planning would be safer and more effective than using RBE = 1.1
  - Even though we do not enough have confidence in current models
- Use LET – Maximize LET in tumors and minimize it in tumors while maintaining RBE = 1.1

Both employ dose averaged LET (LETd)
LET-Based Optimization – Typical ways of doing it

1. Add a LET\(_d\)-based term to IMPT optimization criteria, or
2. Optimize based on simple function of dose and LET e.g., Dose \(\times (1 + \lambda \times \text{LET}_d)\), or
3. Optimize Dose \(\times \text{LET}_d\)
4. Evaluate plans using variable RBE-weighted dose distributions (computed using one of the models)
LET based optimization: Ependymoma Trial (LET Distributions)

RBE = 1.1 Optimized

RBE = 1.1 + LET Optimized

Brainstem

GTV

Brainstem
LET-Based Optimization

- A step in the right direction
- Is it too simplistic?
  - Ultimately, dose and LET distributions have to be converted into biological or clinical effect
- Is it OK to use dose-averaged (or track-averaged) LET?
The use of dose-averaged LET may not be appropriate for computing RBE.
Improvement in proton therapy outcomes requires continued research to improve our understanding RBE and its incorporation in proton treatment planning.

Clinical studies are needed to develop clinically-relevant RBE models for various tumors and normal tissues and endpoints as functions of dosimetric and microdosimetric parameters.
Robustness Evaluation: Evaluating of the Sensitivity of Biologically Effective Proton Dose Distributions to Various (physical and Biological) Uncertainties

Robustness Optimization: Rendering Optimized Dose Distributions Resilient in the Face of Uncertainties
Proton dose distributions are more sensitive than photon dose distributions to …

Set up variations, tumor shrinkage, respiratory motion, weight loss, …

Biological uncertainties

…
IMPT is Especially Vulnerable to Anatomic and Other Uncertainties

Illustration from A. Lomax
Robustness Evaluation

- Bands of DVHs for a sufficient number of uncertainty scenarios
  - Example: $\pm \Delta x, \pm \Delta y, \pm \Delta z, \pm \Delta \text{range}$

- Must ensure that the target remains covered and normal tissues are spared with high probability under all scenarios

- A quantitative metric:
  - “Worst case” DVH and/or
  - Widths of DVH bands at critical points

IMPT Optimized Based on PTV

NSCLC Example – Liu, Zhang and Mohan
Robustness Optimization

- Optimizing IMPT dose distributions incorporating factors that introduce uncertainties: Range, positioning, motion, ...
  - Example: $\pm \Delta x$, $\pm \Delta y$, $\pm \Delta z$, $\pm \Delta \text{range}$, end inhale and exhale respiratory phases, ...

- Iteratively adjusting intensities of beamlet of a sequence of energies while ensuring that the CLINICAL target volume remains covered, and normal tissue constraints are met with high probability under all uncertainty scenarios

- Multiple approaches: Worst-case; mini-max, ...
Robustness Optimization of IMPT – NSCLC Example

IMPT (PTV-Based) vs. Robust IMPT

- CTV: Volume (normalized) vs. Dose (Gy)
- Lung: Volume (normalized) vs. Dose (Gy)
Proton dose distributions are sensitive not only to the respiratory motion of the tumor, but also to motion of the normal anatomy in the path of protons.

Decisions regarding motion management for proton therapy should be based on changes in dose distribution between end-inhale and end-exhale phases, not on the extent of the tumor motion.
Effect of Motion of IMRT vs. PSPT – Motion ~> 10mm
4D Minus Static Dose Distributions

- For photons – Difference < Less 5 Gy (RBE)
- For protons – Difference up to 30 Gy (RBE)
Effect of Motion of IMRT vs. PSPT – Motion < 5 mm
4D Minus Static Dose Distributions

- For photons – Difference < Less 5 Gy (RBE)
- For protons – Difference ~ 10 Gy contralateral lung; Difference ~ 15 Gy near spine & ribs
Additional Thoughts … (2)

- Making a dose distribution robust is like smearing it with some sort of a smoothing function
  - It effectively reduces dose gradients, makes them less shallow
  - It makes dose distribution less sensitive in the face of uncertainties within the target volumes as well as normal tissues
- Gives us more confidence in coverage and sparing
  - WYS = WYG
- But it does not reduce uncertainties
What does robustness actually do?
Some More Thoughts … (3)

- Current robustness optimization approaches do not take **inter-fractional anatomic changes** into account
  - However, reduction in dose gradients may partially account for such changes
- RO may also mitigate the consequences of high LET or RBE in normal tissues
Care must be taking when comparing dose distributions

- Robustly optimized IMPT
- PTV-based optimized IMPT
- IMRT
- PSPT
- LET-based optimized
- RBE-weighted dose optimized
- RBE=1.1 optimized
- ...

Must be compared using robustness metrics

Comparisons must be in the same frame of reference

Must be compared using RBE=1 or variable RBE
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