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MDACC Proton Therapy Center -2

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

An Overview

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Conflict of Interest

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

Gaps in knowledge → Controversies → Hypotheses → Research → Solutions

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Biologically-Weighted Robust Planning of Proton Therapy

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

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Relative Biological Effectiveness (RBE)

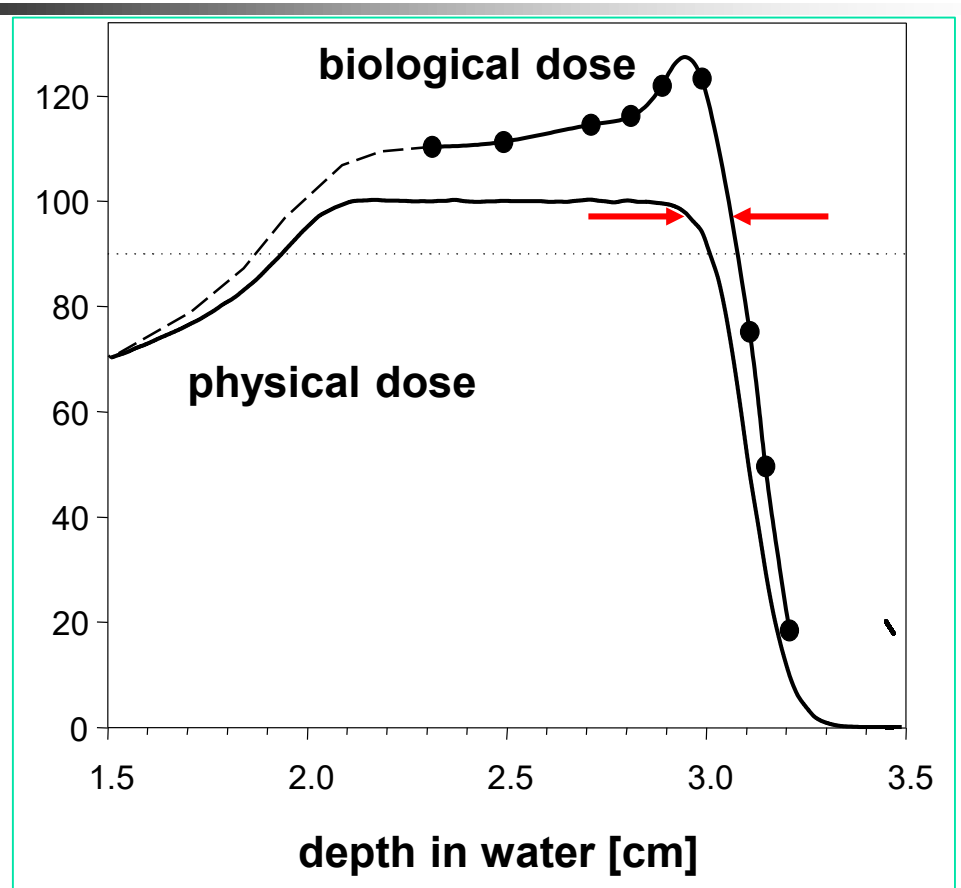
- Current practice: RBE = 1.1
- But, just in case RBE > 1.1 at distal edges …
  - Beams pointing at critical normal structures distal to the target volume are avoided
  - Choice of number and orientations of beams and hinge angles
  - …

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

True but
so do the alternatives

- No clinical evidence suggesting need for change



Paganetti, Goitein,
Med. Phys. 2000: 27, 1119-1126

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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

- Peeler C, Mirkovic D, Titt U, et al. Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma. Radio. Oncol. 2016.
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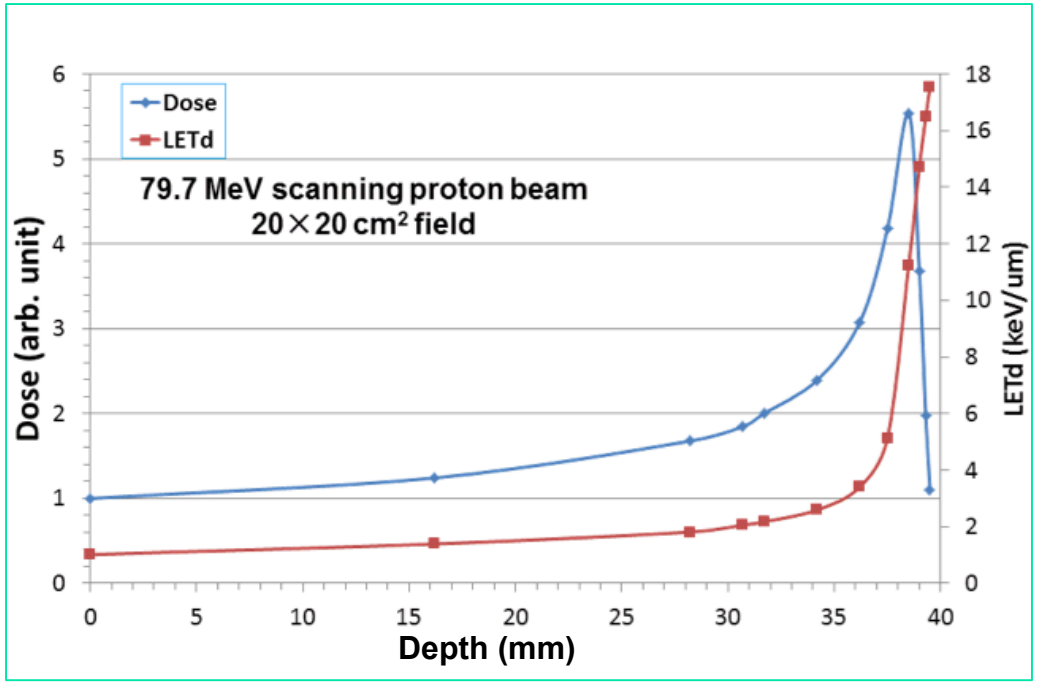
- …

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

- Proton energy spectrum→ Ionization density → Linear Energy Transfer (LET)
  - Varies nonlinearly and rapidly around the Bragg peak
- Dose per fraction
- Radiosensitivity of tissue/cell (alpha/beta ratio)
- Endpoint
- Hi



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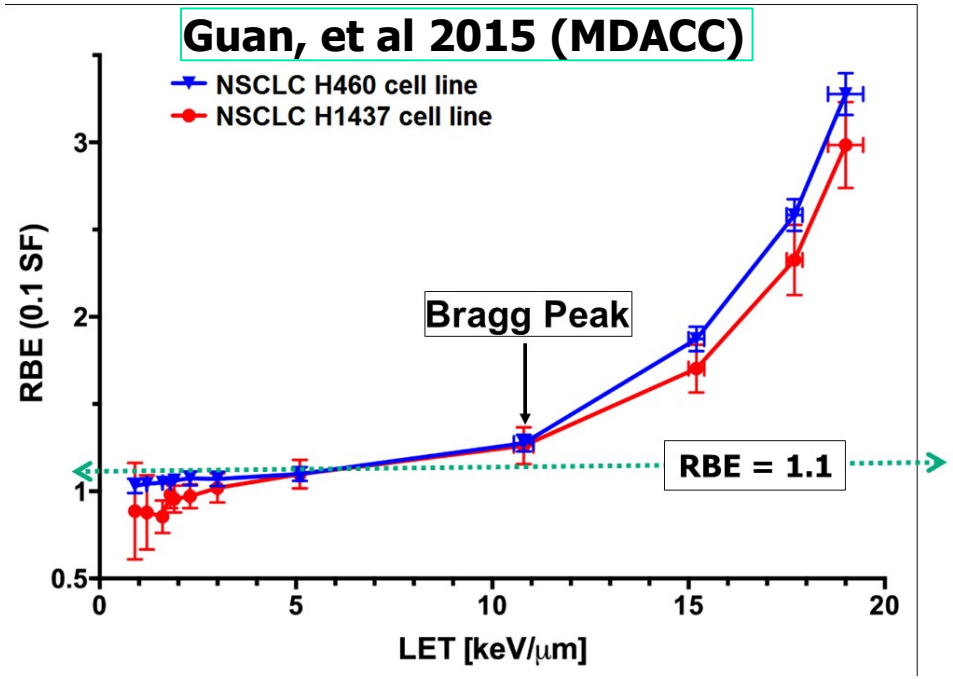
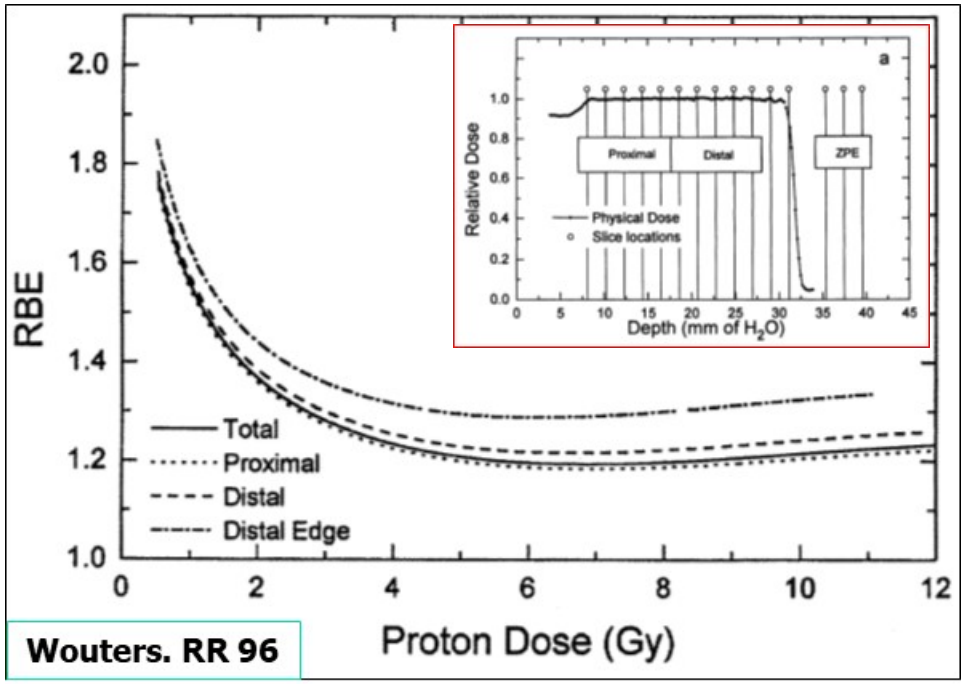
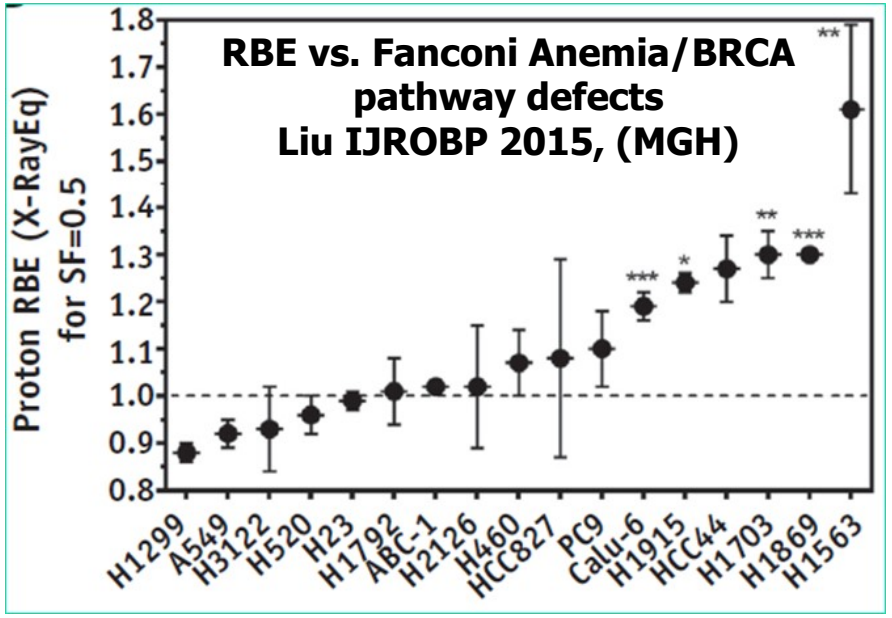




RBE for lung cancer cell lines for the same dose and LET at mid SOBP



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Is continued use of RBE = 1.1 appropriate, Especially for the Heterogeneous Dose & LET Distributions Per Beam of (MFO) IMPT?

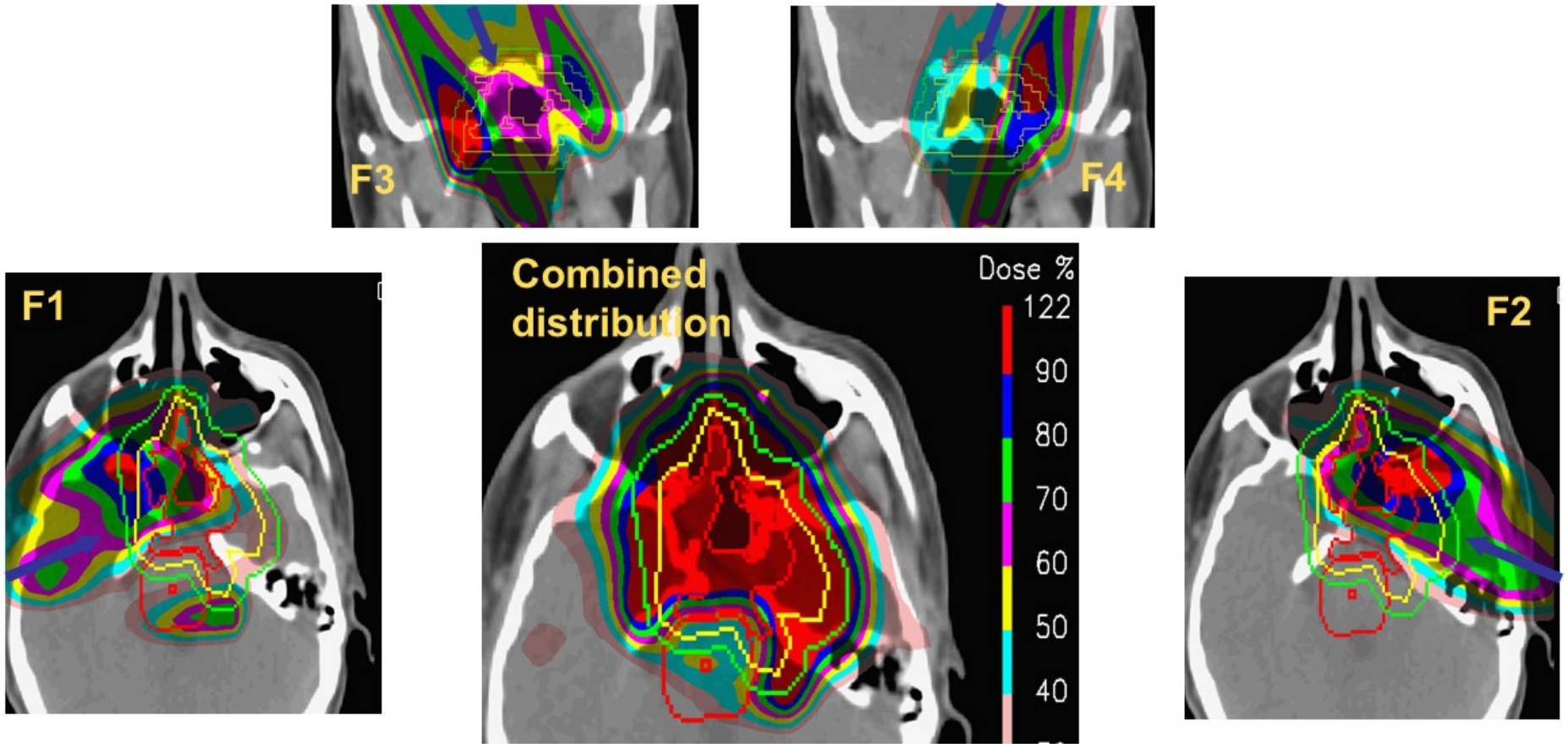


Illustration from A. Lomax

But what should we do about it?

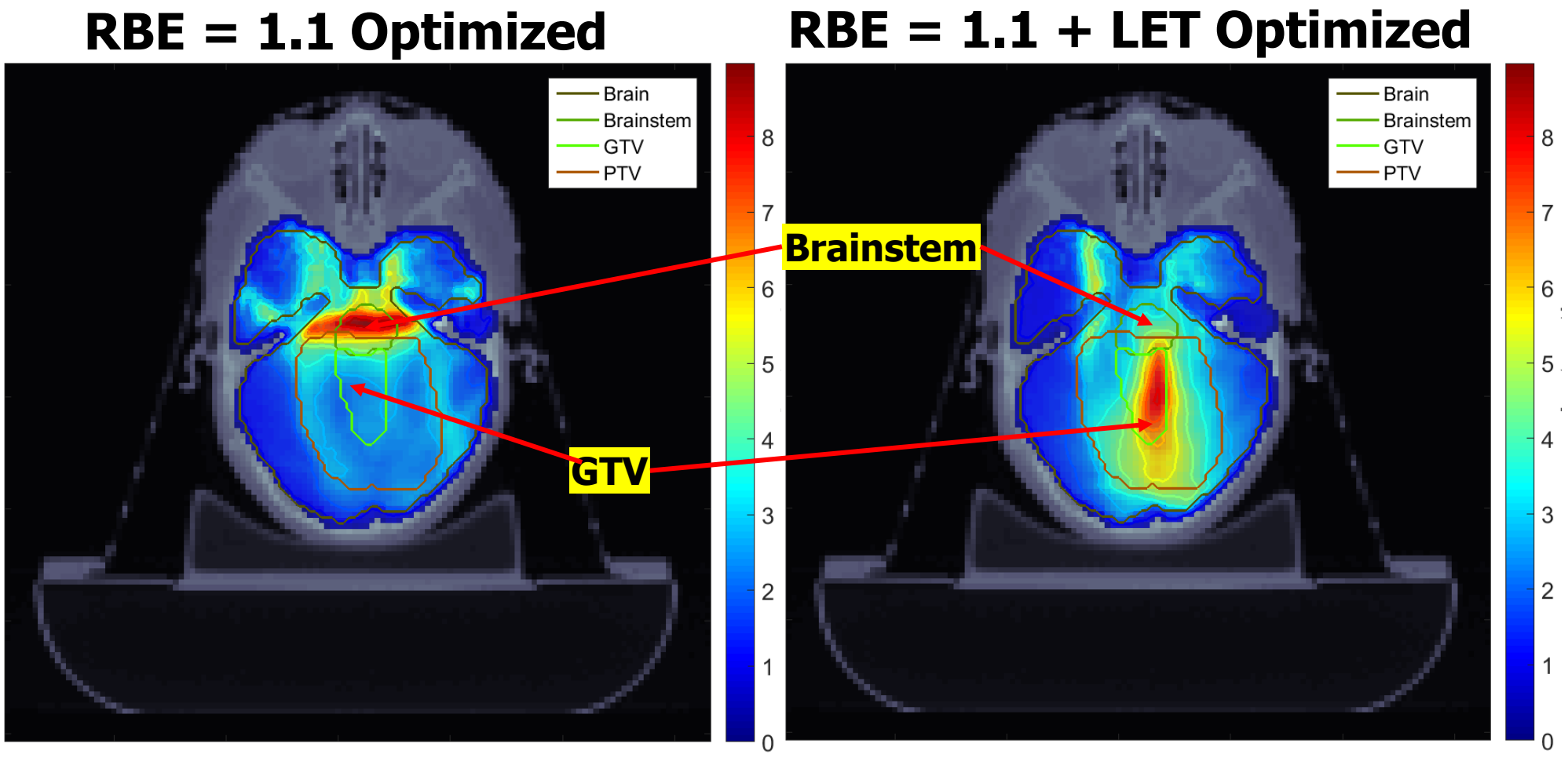
- Use of variable RBE in planning would be safer and more effective than using RBE = 1.1
  - Even though we do not enough have confidence in current models
- Use LET – Maximize LET in tumors and minimize it in tumors while maintaining RBE = 1.1

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 * $(1 + \lambda * LET_d)$, or
3. Optimize Dose * LET_d
4. Evaluate plans using variable RBE-weighted dose distributions (computed using one of the models)

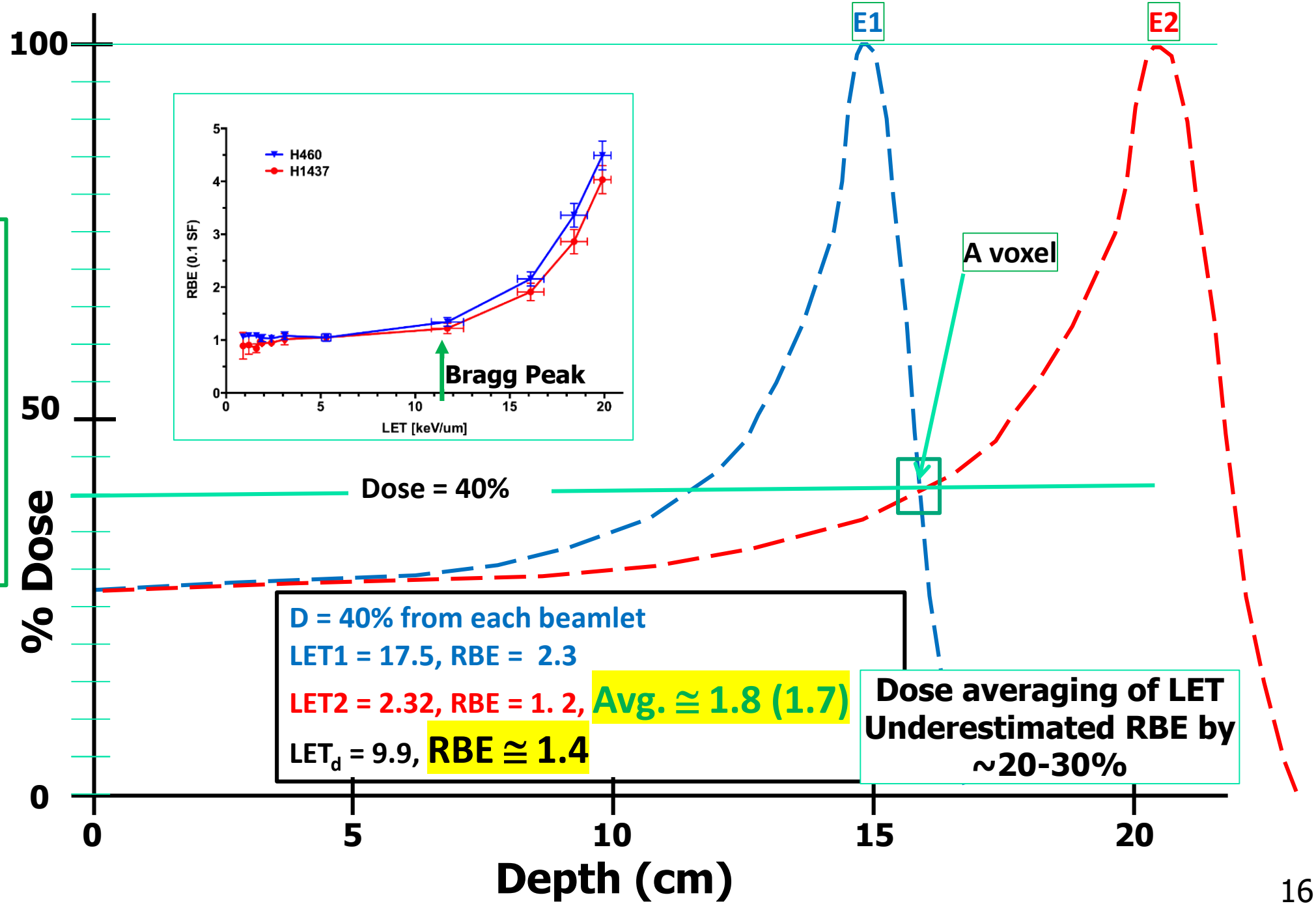
LET based optimization: Ependymoma Trial (LET Distributions)



LET-Based Optimization

- A step in the right direction
- Is it too simplistic?
  - Ultimately, dose and LET distributions have to be converted into biological of 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



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Improvement in proton therapy outcomes requires continued research to improve our understanding RBE and its incorporation in proton treatment planning

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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

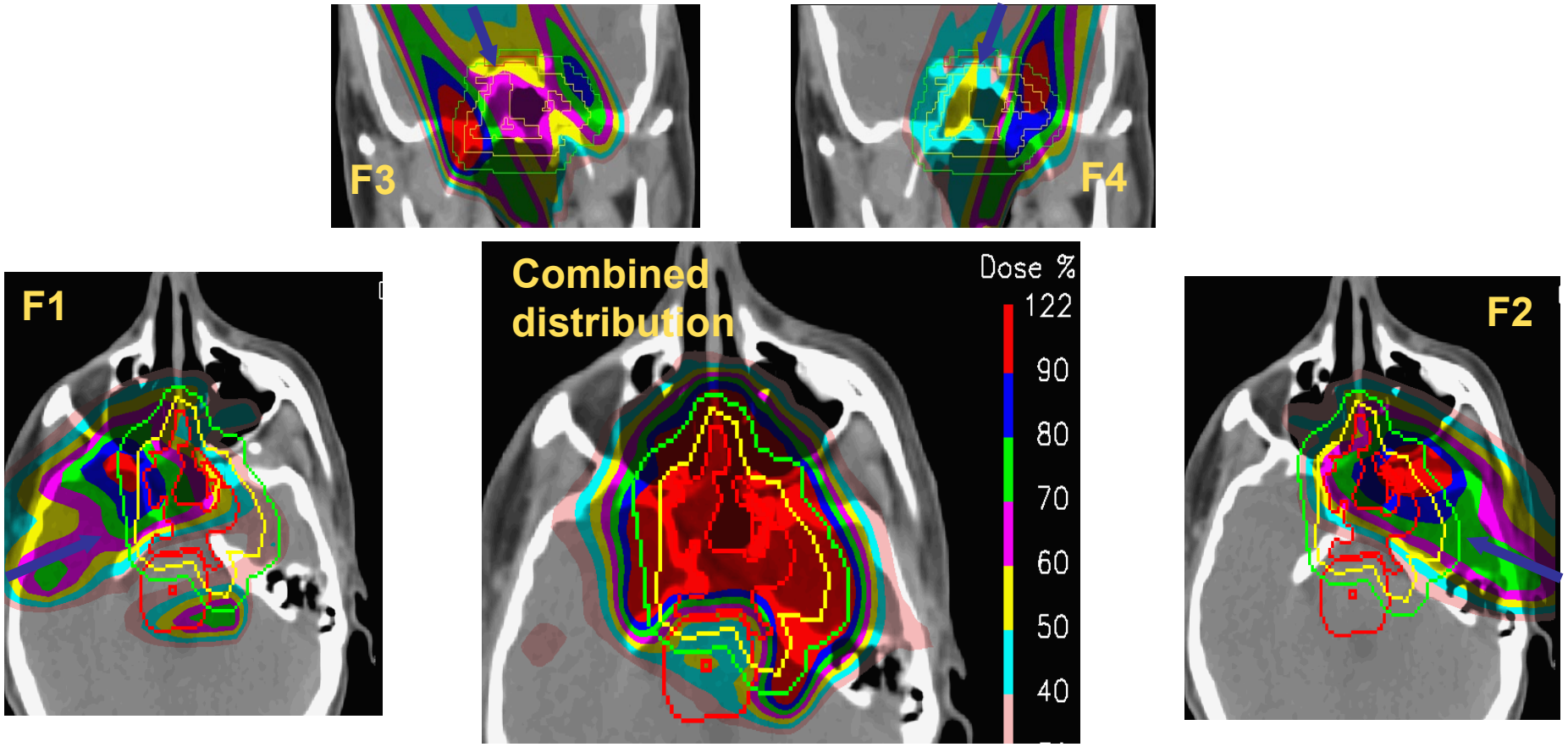
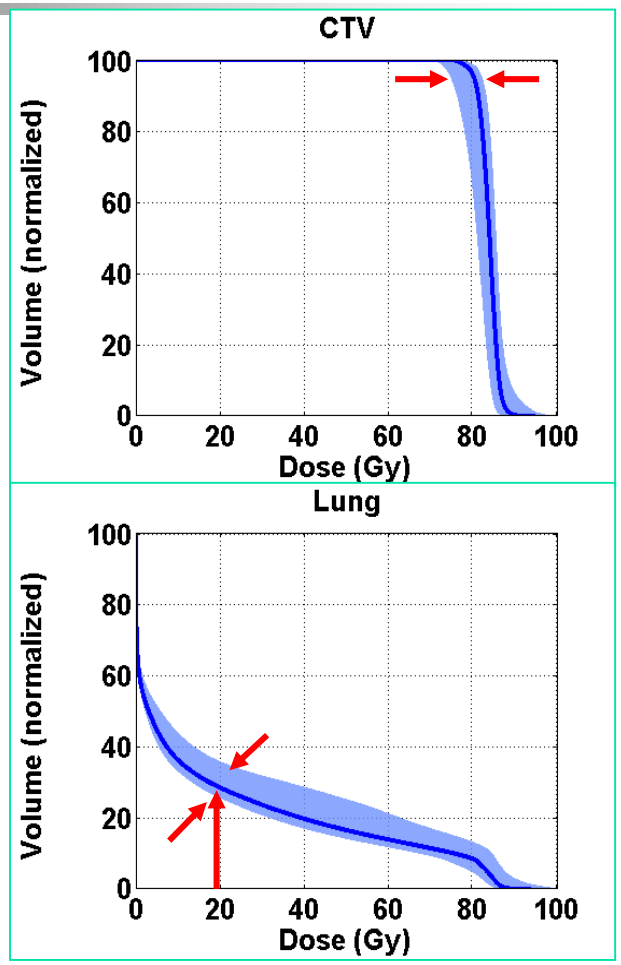


Illustration from A. Lomax

Robustness Evaluation

IMPT Optimized Based on PTV

- **Bands of DVHs for a sufficient number uncertainty scenarios**
  - **Example: ± Δx, ± Δy, ± Δz, ± Δrange**
- **Must ensure that the target remains covered and normal tissues are spared with high probability under all scenarios**
- **A quantitative metrics:**
  - **"Worst case" DVH and/or**
  - **Widths of DVH bands at critical points**

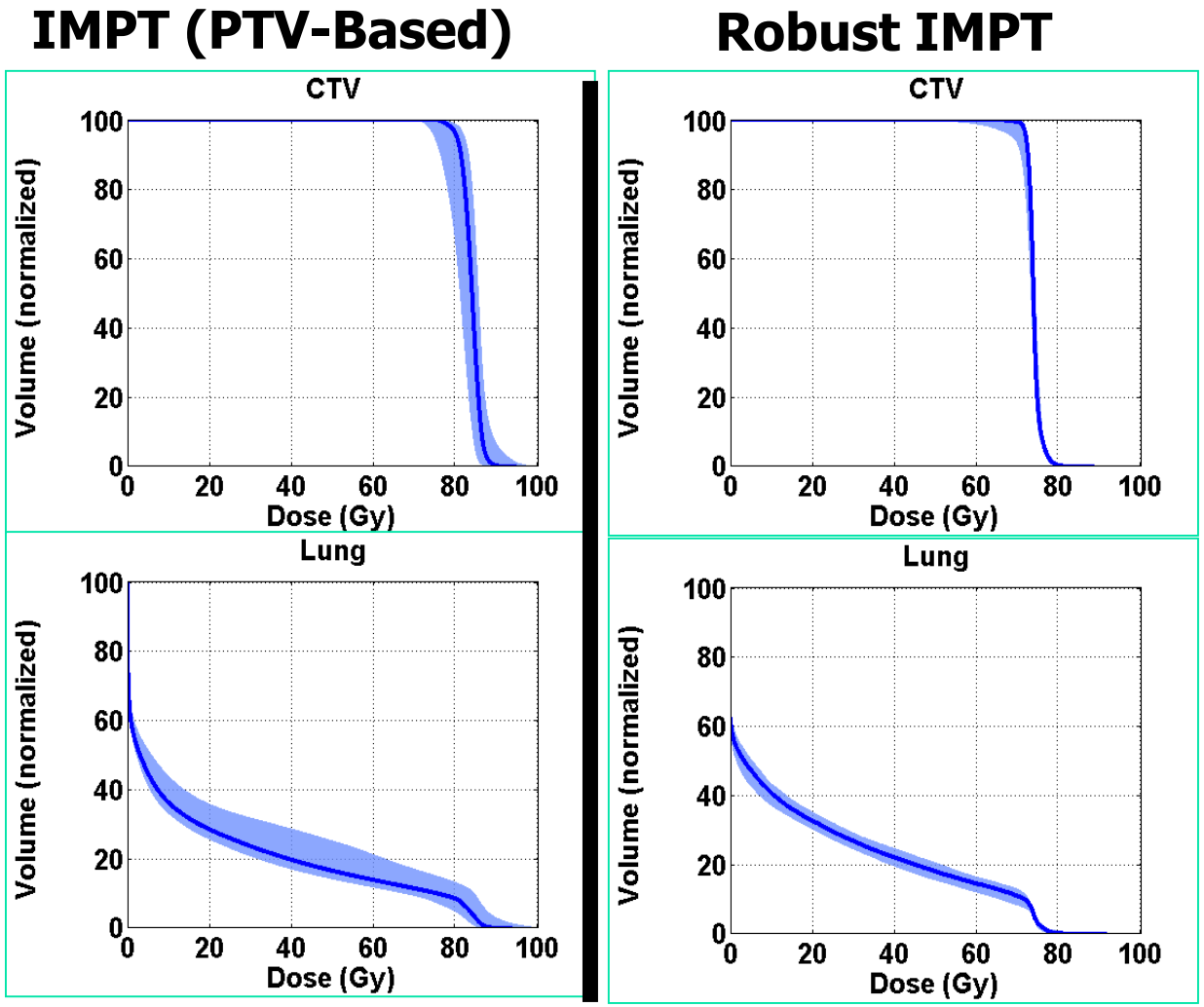


NSCLC Example – Liu, Zhang and Mohan

Robustness Optimization

- **Optimizing IMPT dose distributions incorporating factors that introduce uncertainties: Range, positioning, motion, …**
  - **Example: ± Δx, ± Δy, ± Δz, ± Δrange, 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



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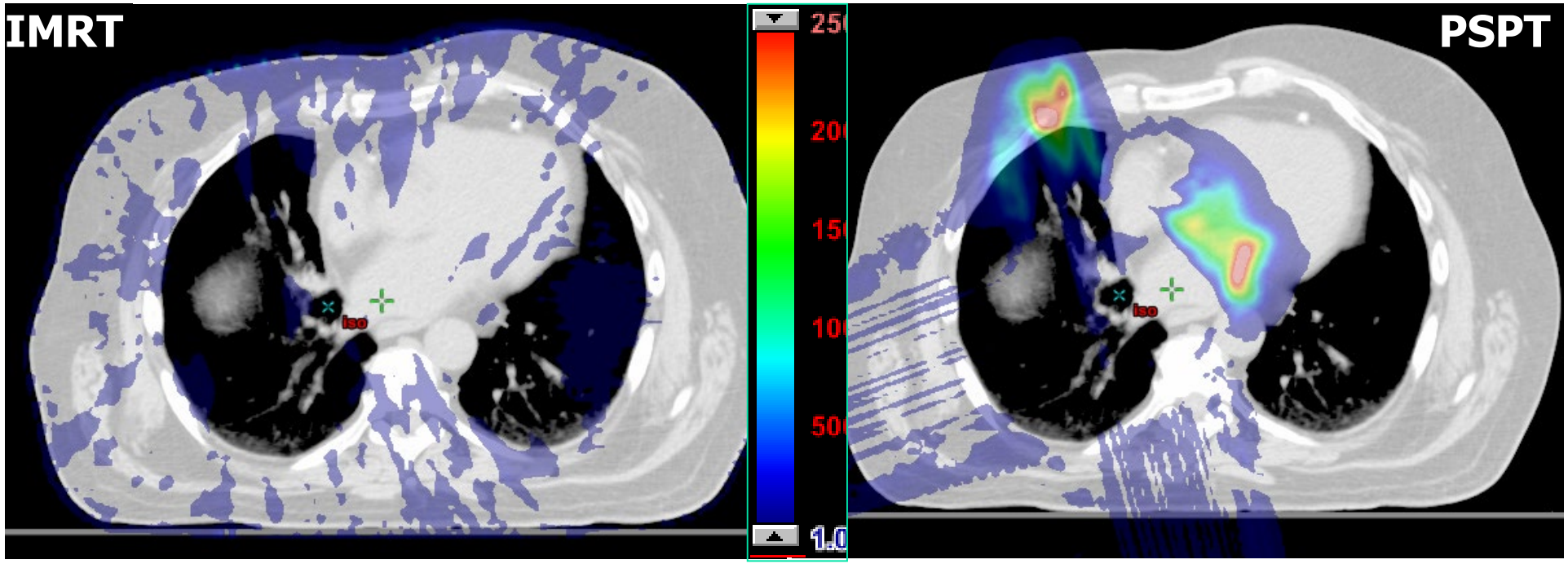
Additional Thoughts About Robustness Evaluation & Optimization to Provoke Debate (1)

- **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)



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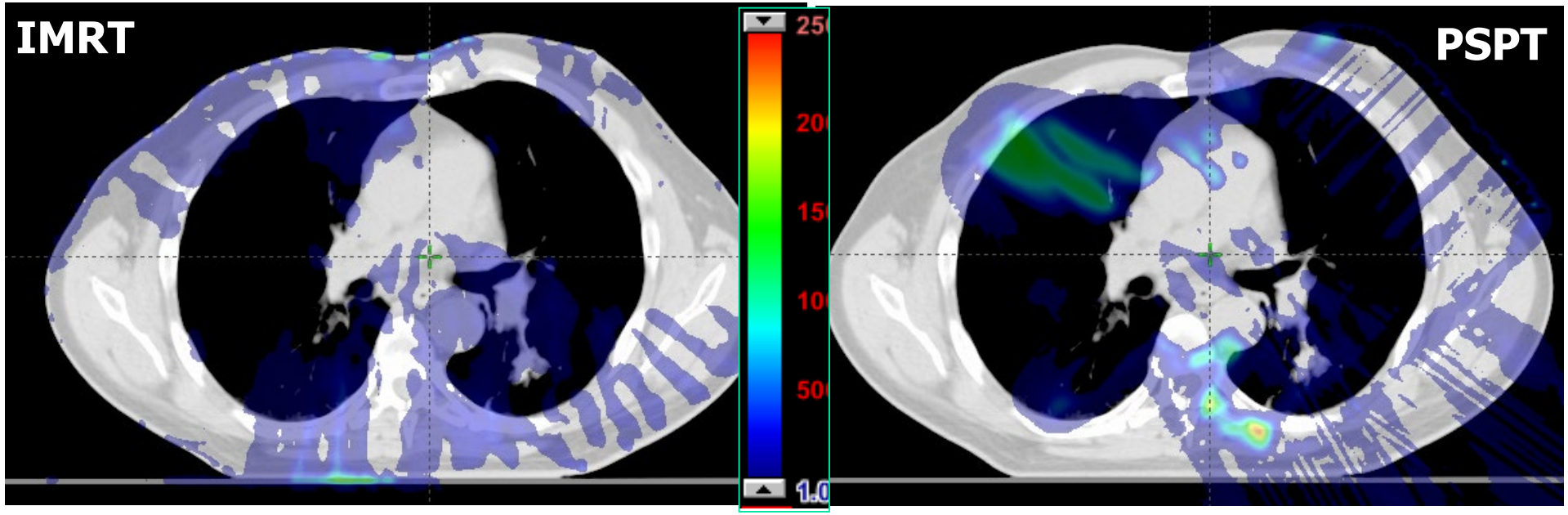
Matney, et al

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



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Matney, et al

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

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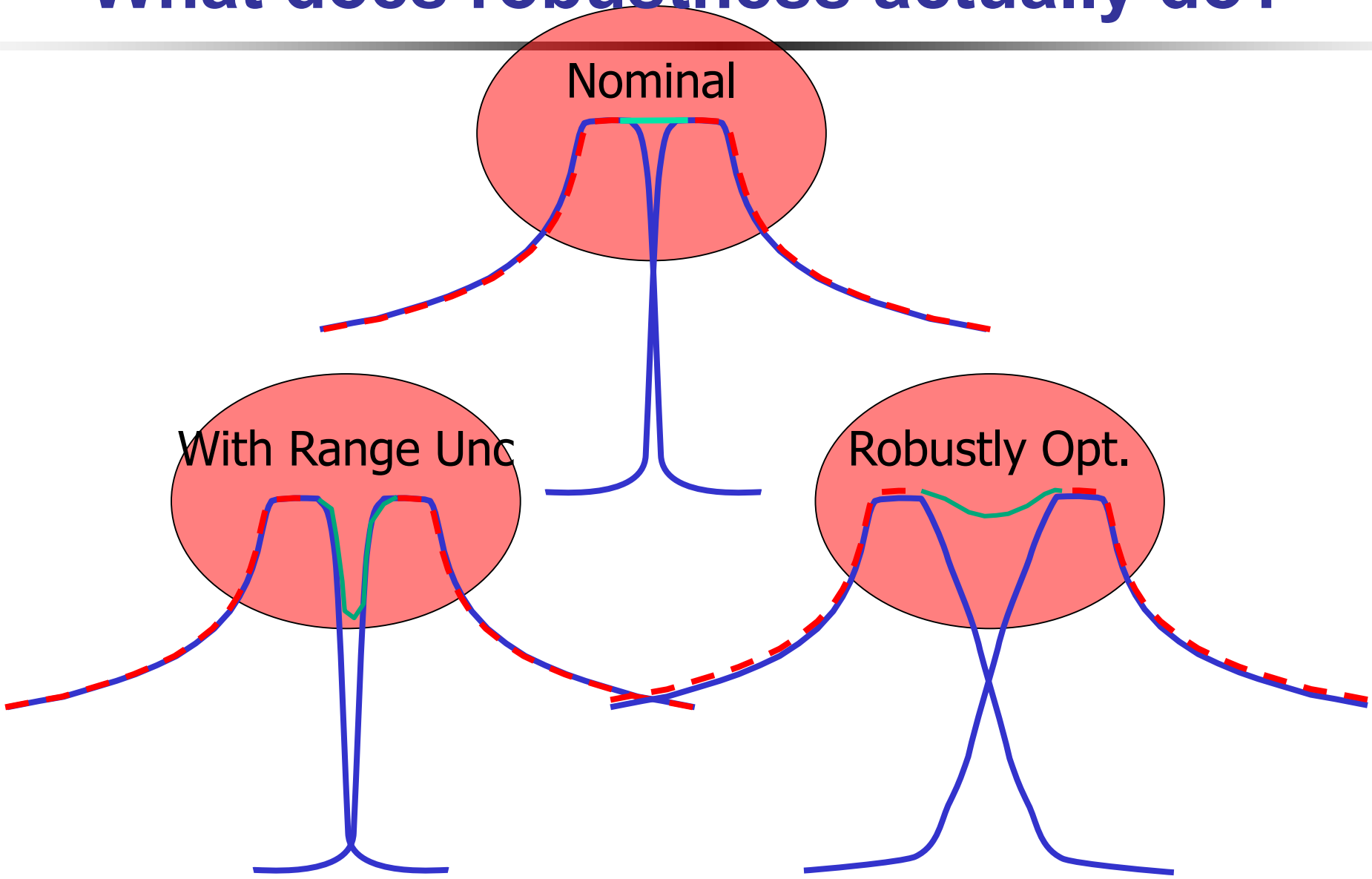
What does robustness actually do?



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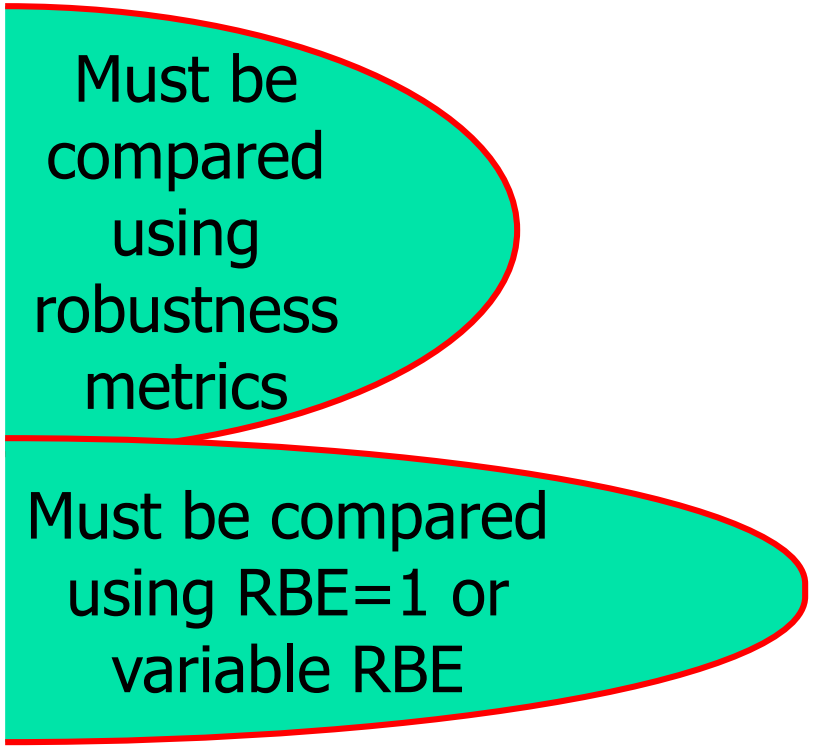
Some More Thoughts … (3)

- 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

Even More Thoughts … (4)

- **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**
  - **…**



- **<u>Comparisons must be in the same frame of reference</u>**

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Thank You for Your Attention

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