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MD Anderson Cancer Center
Making Cancer History®

Biological Issues in Proton Therapy and their Clinical Implications

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MD Anderson Cancer Center

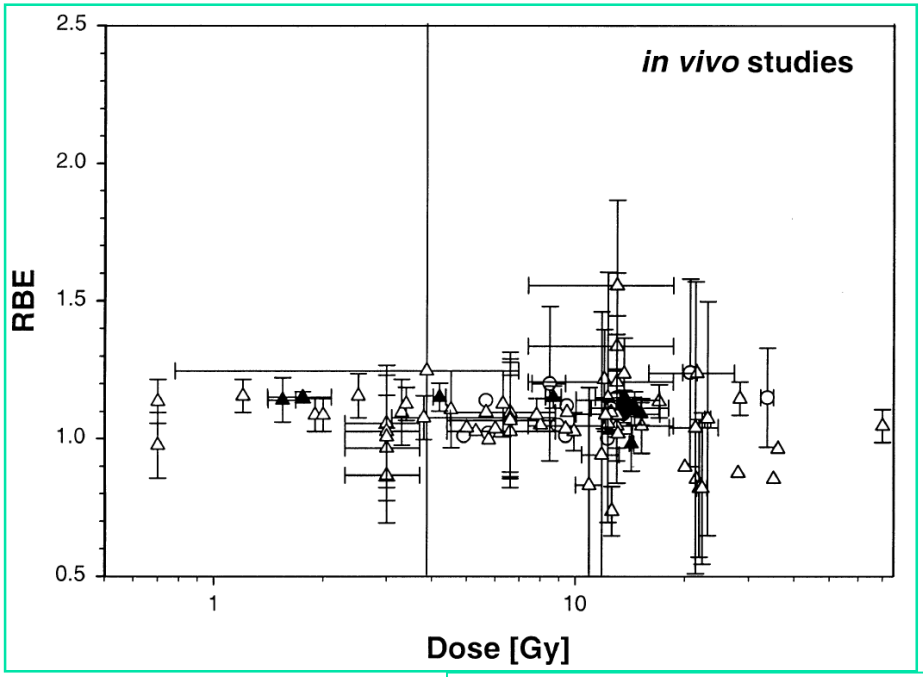
ICTR-PHE 2016
Plenary Session 10:30-12:00
February 17, 2016
Geneva, Switzerland

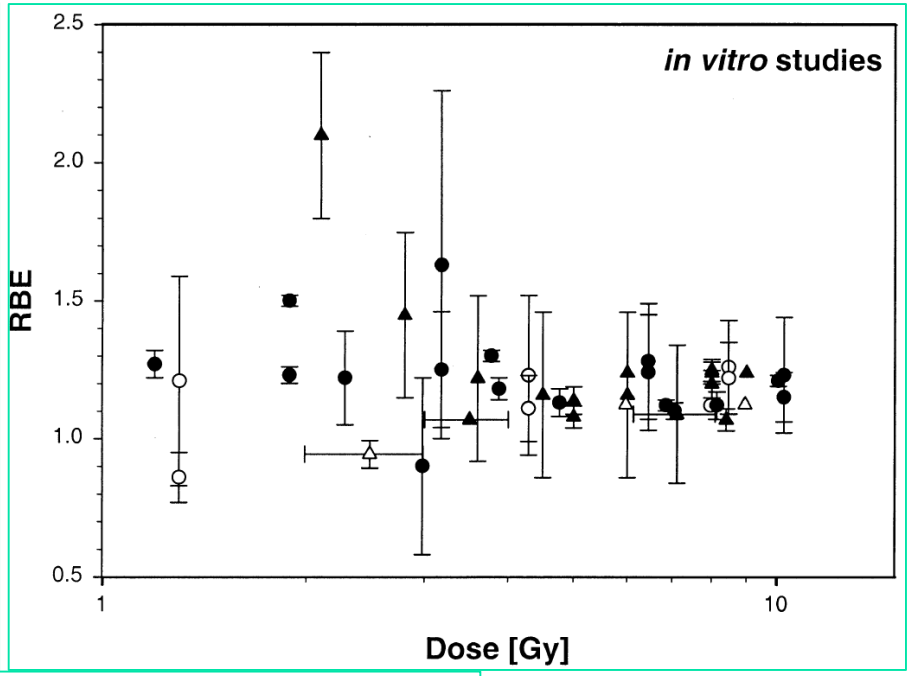
Questions?

- Is it appropriate to continue using RBE of 1.1 in clinical practice?
- Would the use of variable proton RBE
  - Help better understand clinical outcomes?
  - Make IMPT more effective and safer?
- What do we need to do to incorporate variable RBE into proton therapy?

The Myth of RBE =1.1

Based on the average of in-vitro and in-vivo data acquired with limited and inconsistent experiments





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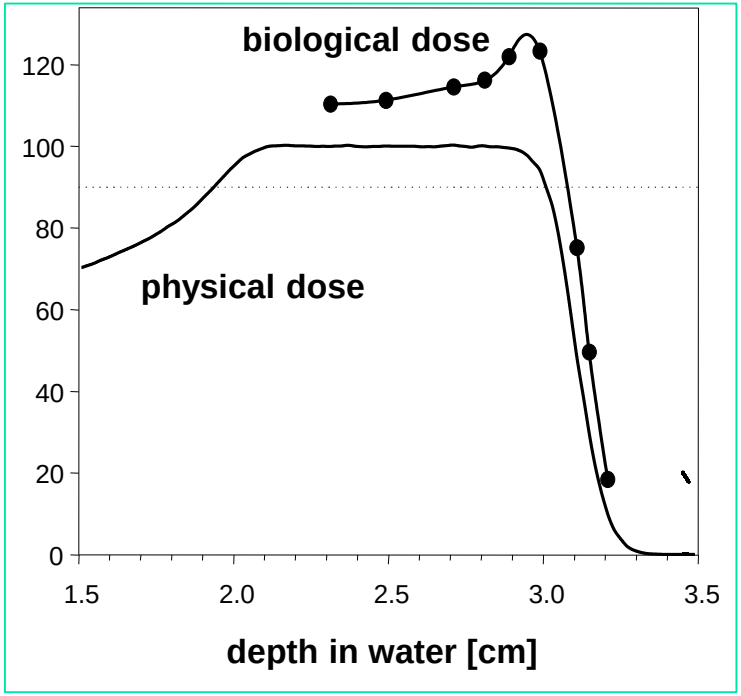
Paganetti, et al, RBE for PBT, IJROBP 2002

RBE = 1.1 – Justification & Claims

- **Affects only a very small region: "An increasing RBE with depth extends biologically effective range (1-2 mm)"**
- **Clinical evidence does not suggest the need for change**



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

"The absence of evidence is not the evidence of absence"

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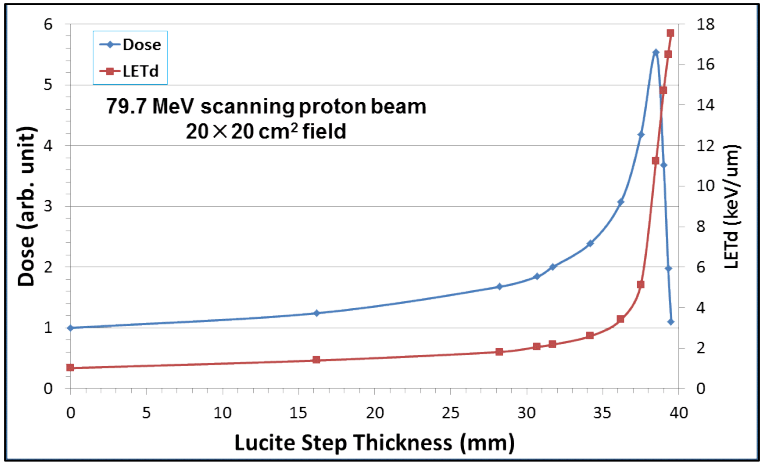
But, jut in case RBE ≠ 1.1 …

Avoid beam directions for which distal edge is in or close to a sensitive critical normal structure

The Reality - RBE is a Function of Multiple Variables

- Energy (LET) of protons
  - Location along the Bragg curve
- Dose per fraction
- Tissue/cell characteristics (α/β)
- End point
- …



RBE is a non-linear function of dose, LET and α/β

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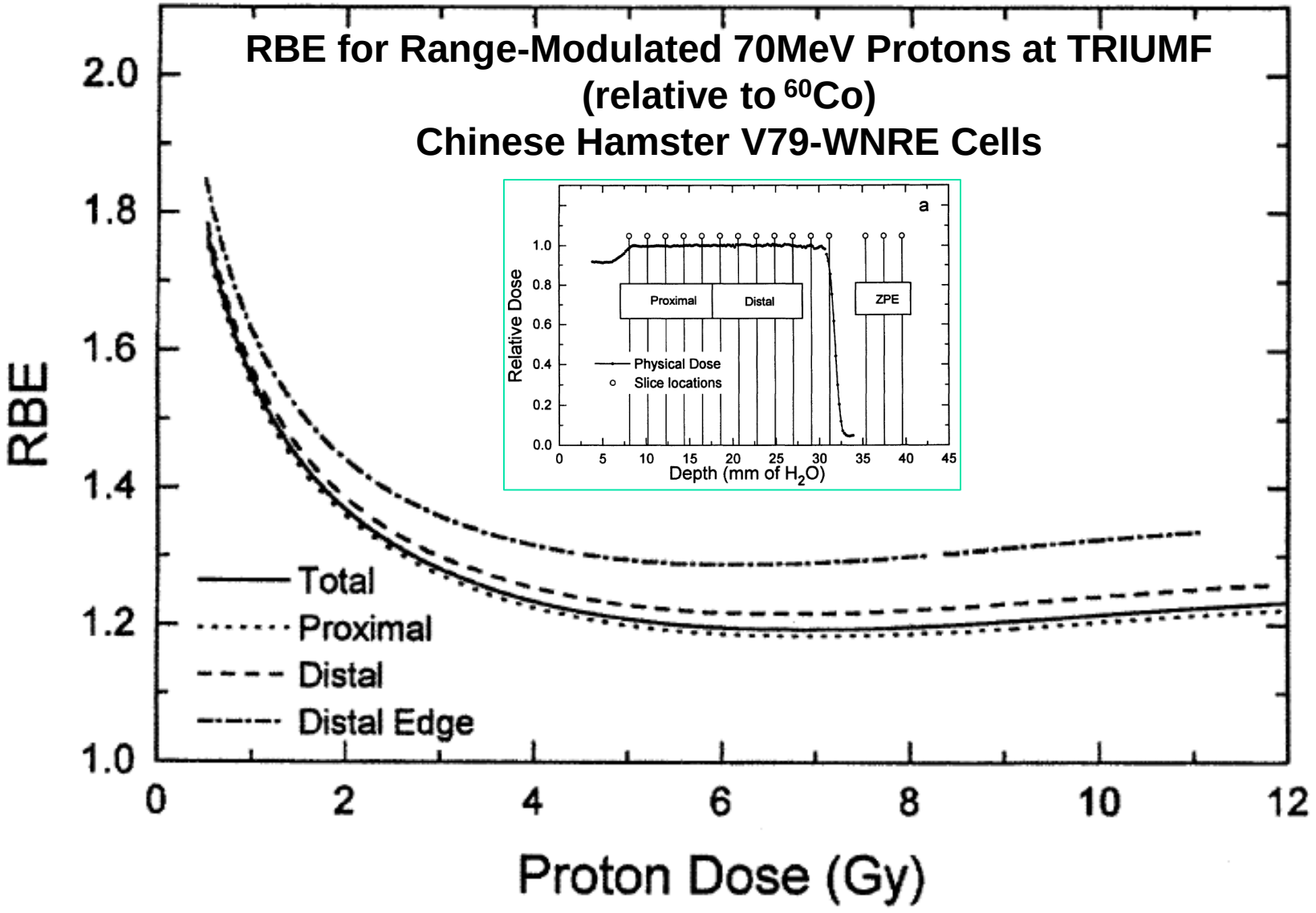
RBE as a Function of Dose and LET



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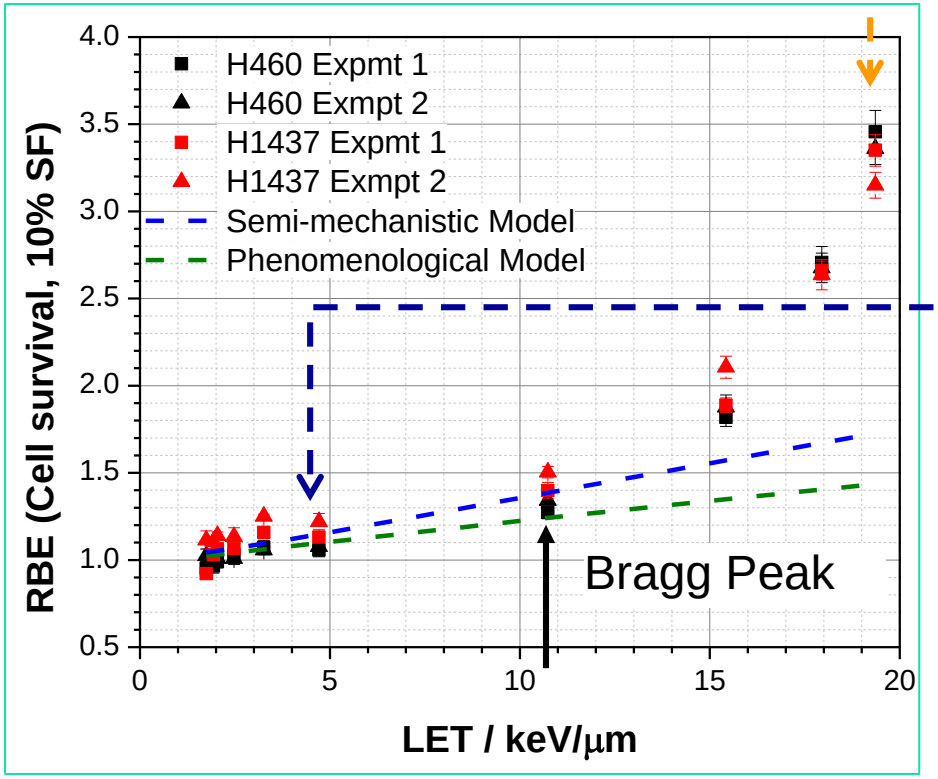
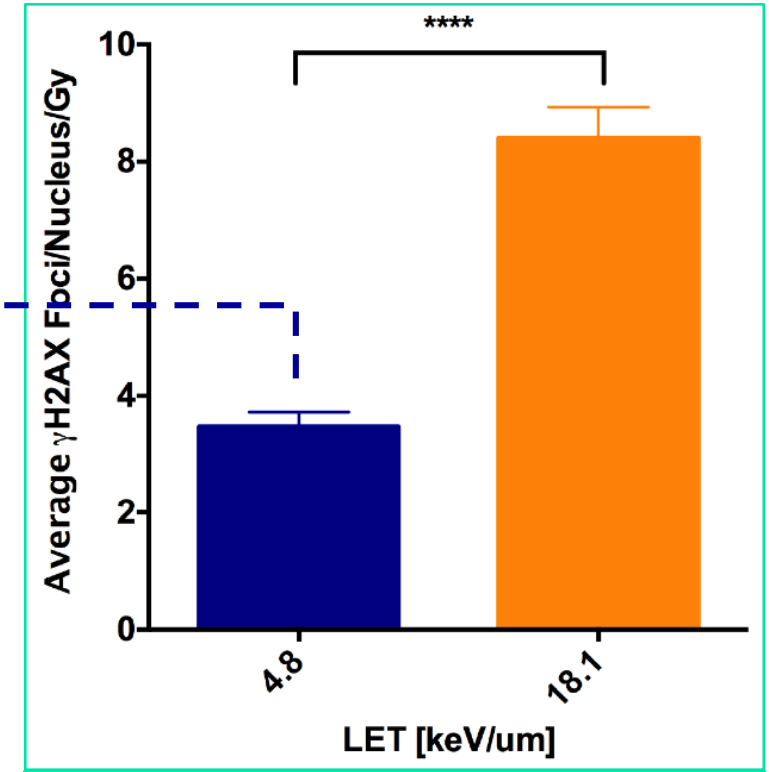
RBE and γH2AX for H460 & H1437 Lung Cancer Cell Lines





Average nuclear foci per Gy at 2 hour after 1.7 Gy irradiation for H460

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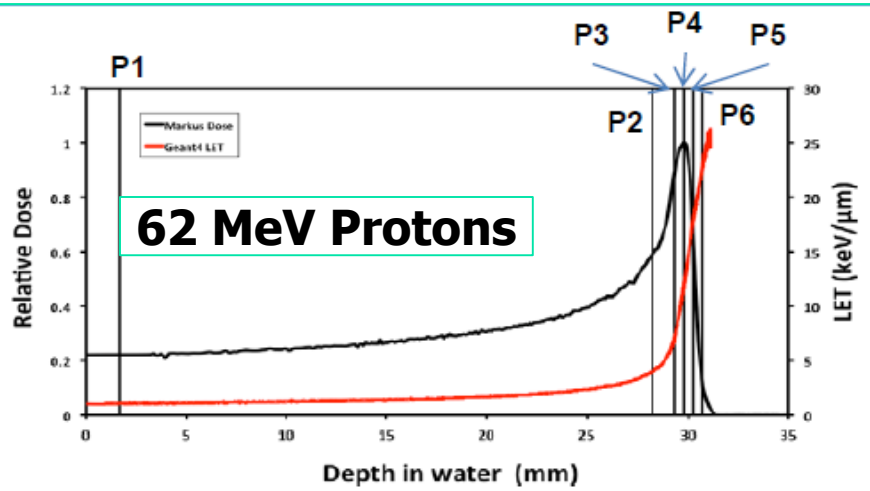
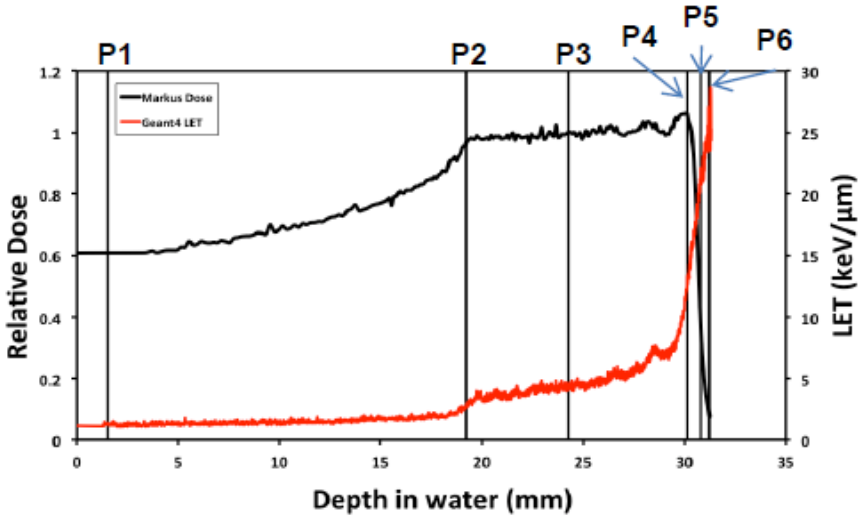
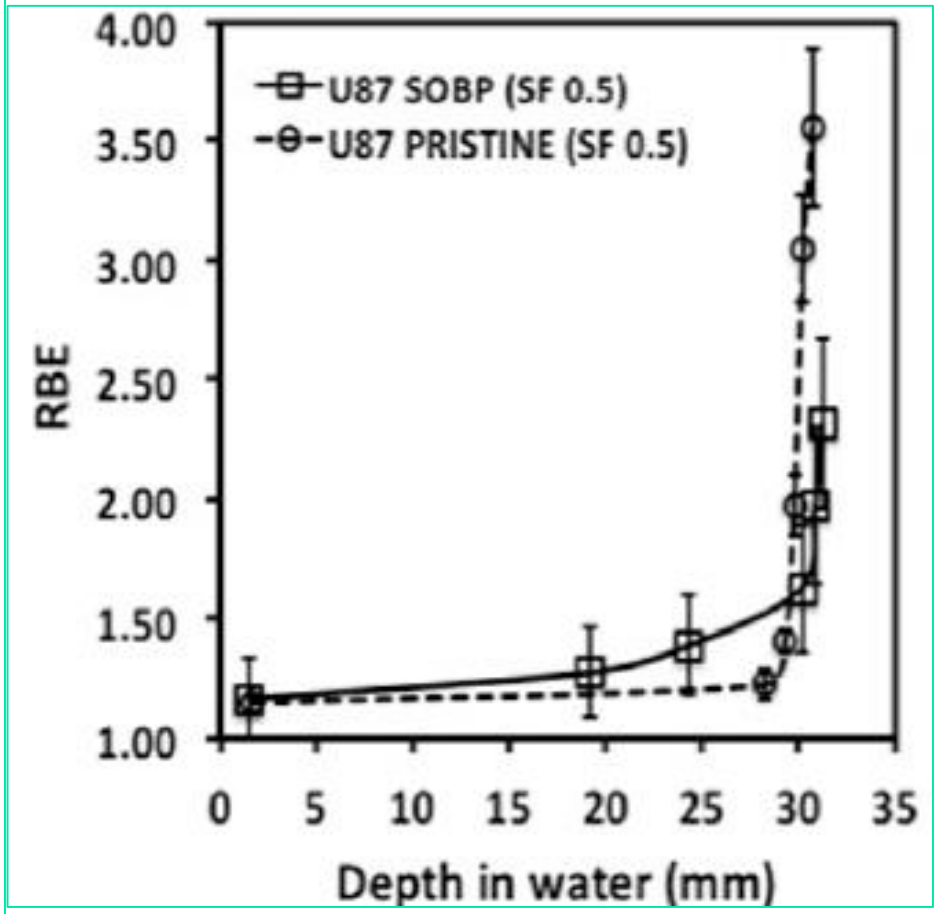
Prise et al



	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	20.23	24.59	27.69	29.48	30.08
LET [keV/µm]	1.2	2.6	4.5	13.4	21.7	25.9



	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	27.42	29.21	29.8	30.7	31.29
LET [keV/µm]	1.11	4.0	7.0	11.9	18.0	22.6



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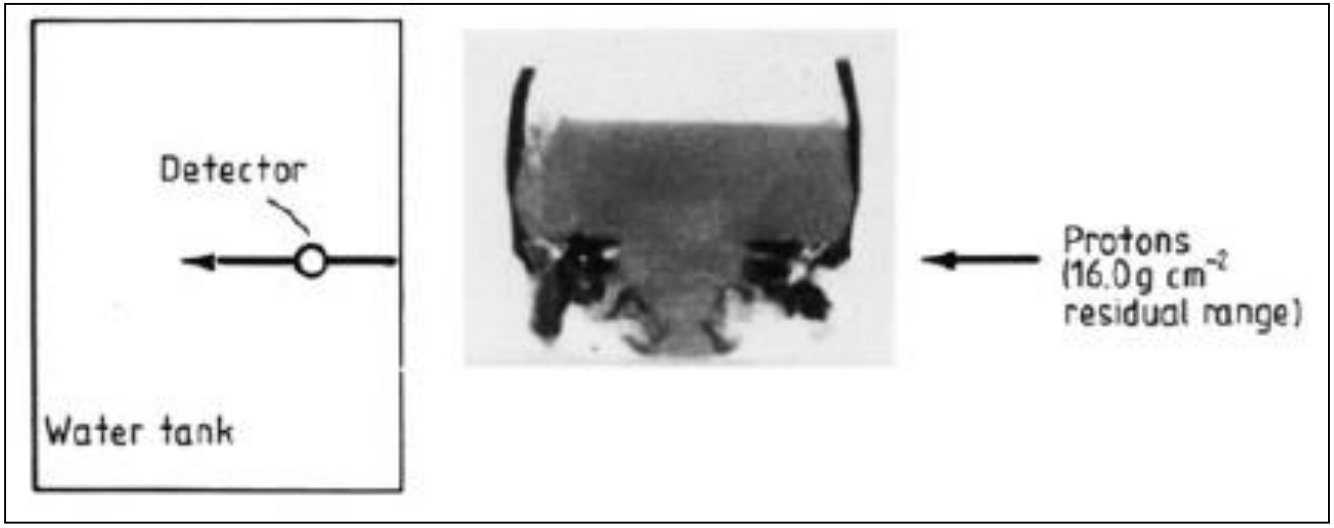
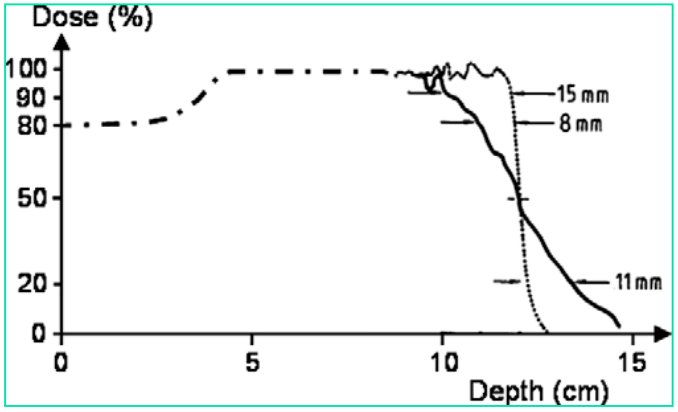
"High RBE Affects a Negligible Region at Distal Edge" -

But the Distal Edge May be Degraded by Passage Through Tissues, particularly Complex Heterogeneities





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Urie, et al, Phys. Med. Biol., 1986, Vol. 31, No. 1, 1-15.

"Clinical data do not suggest that RBE is different from 1.1" – But …

Unexplained toxicities and recurrences are encountered

May be attributable to multiple factors including the assumption of RBE of 1.1

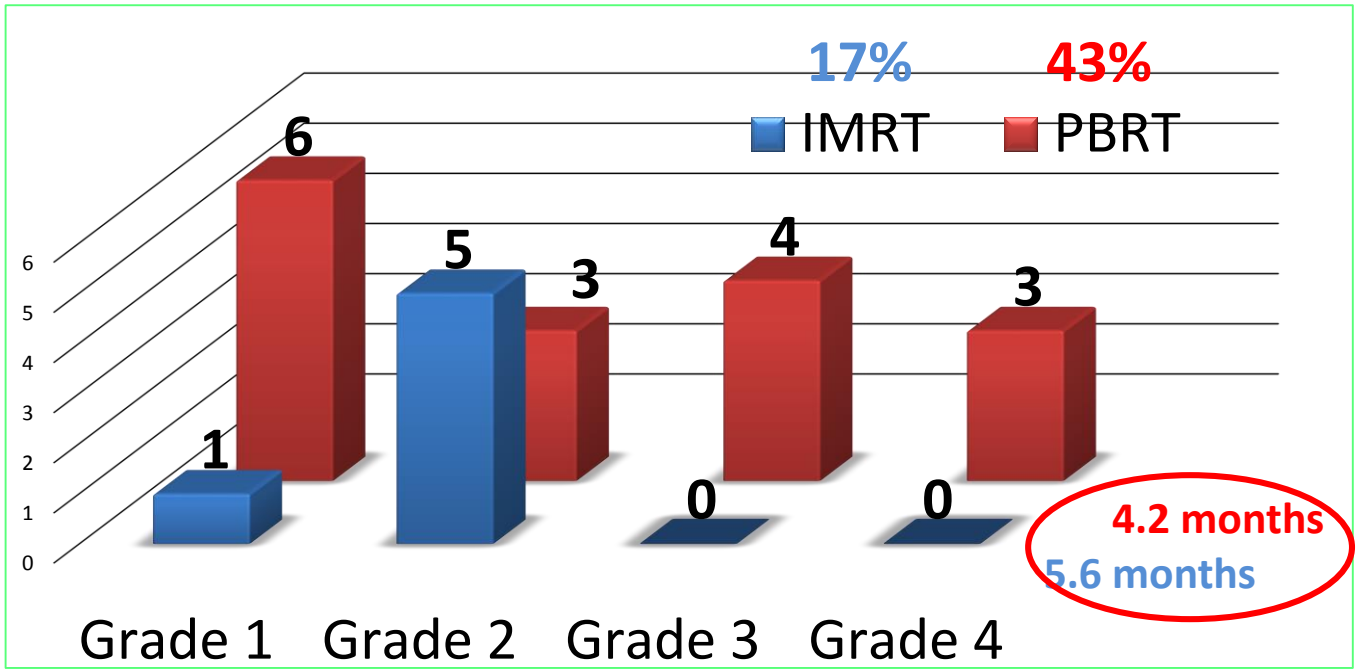
Evidence so far is not unequivocal

Unanticipated Treatment Responses

Some Examples

MR Imaging Changes in 72 Intracranial Ependymoma Patients: Proton Therapy vs. IMRT (36 matched pairs)

(J. Gunther, et al, ASTRO 2014 and IJROBP 2015)



Grade	1	2	3	4
T2 Hyperintensity	+	+	+	+
T1 Enhancement	-	+	+	+
Hemorrhage	-	-	+	+/-
Focal Necrosis	-	-	-	+

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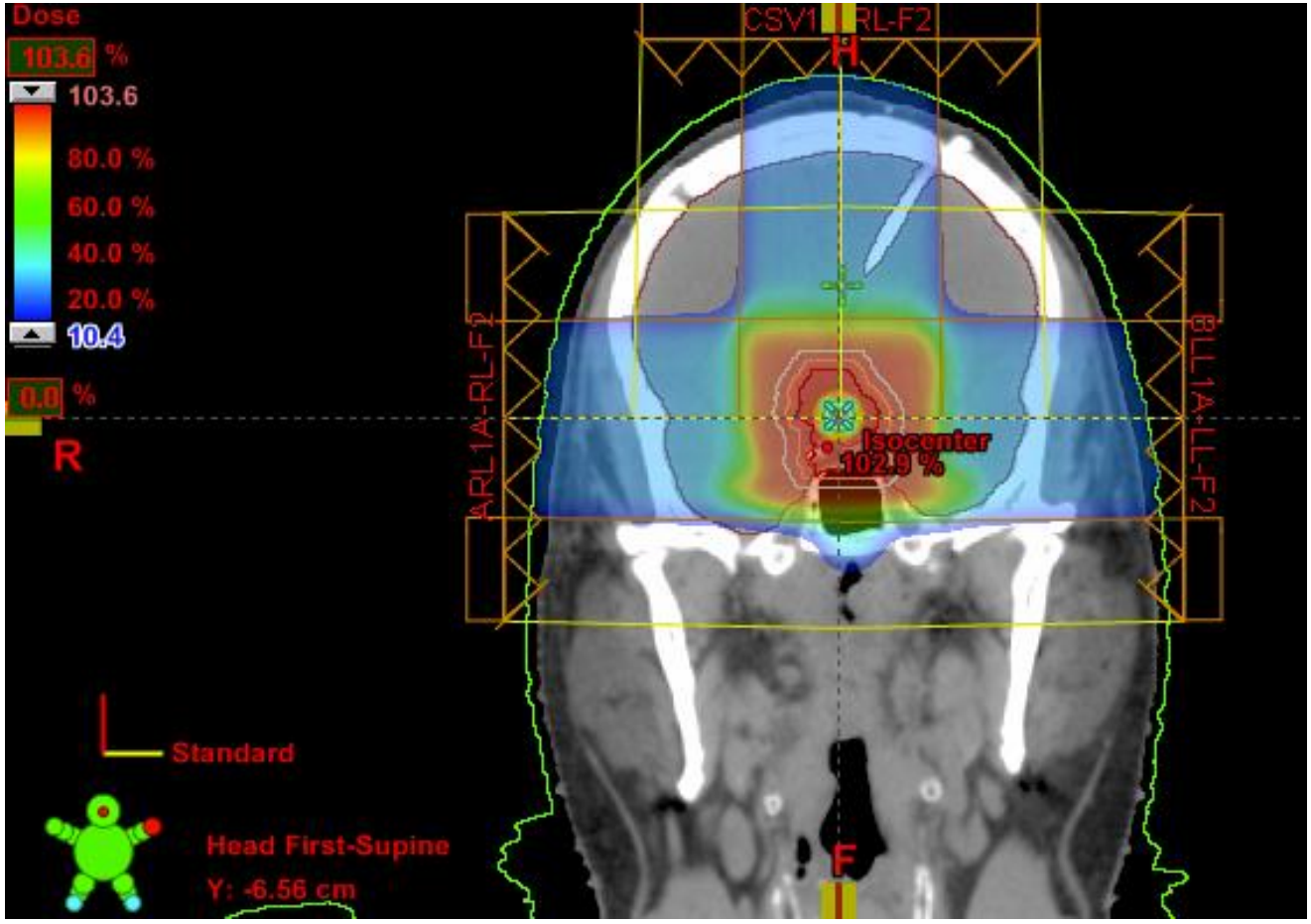
Brain Necrosis in a CNS Patient

40 year old male with craniopharyngioma



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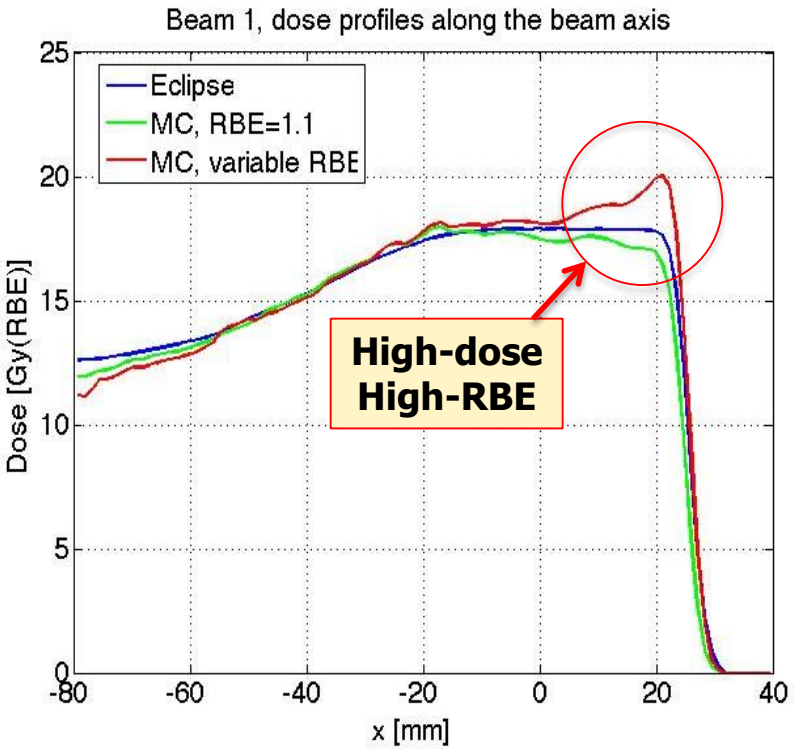
Variable RBE-Weighted Dose

- **Used a Linear Scaling Model (Wilkens) with parameters for brain necrosis (Frese 2011) to compute variable RBE dose**
- **Variable RBE dose increases at the end of range of the proton beam**



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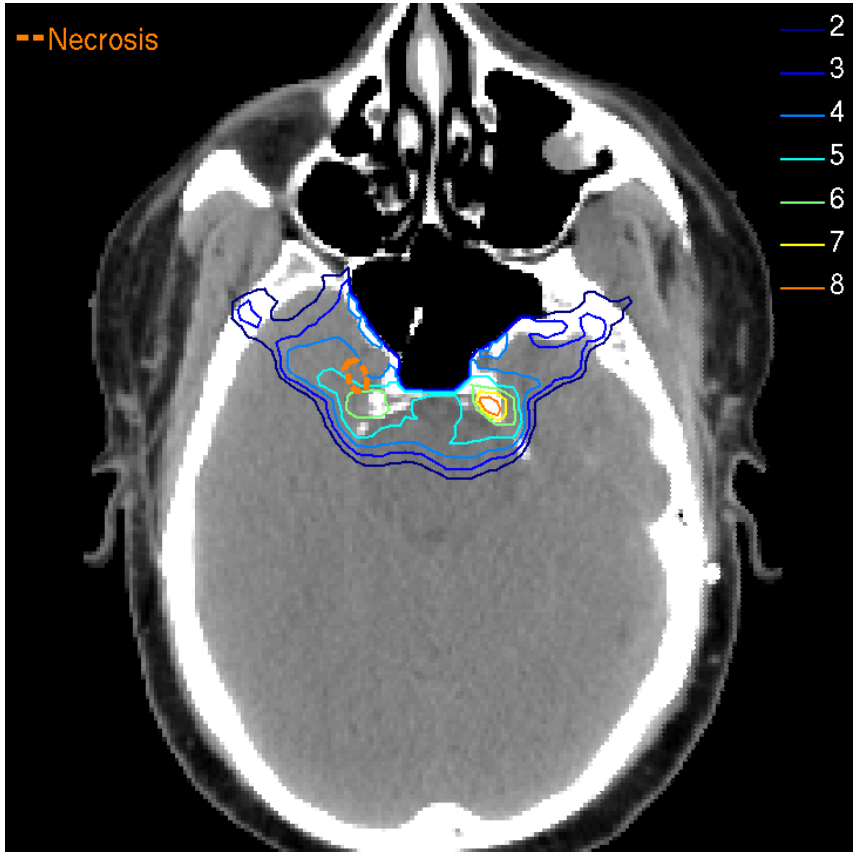
Investigation of correlation between high-dose-high-RBE volume and necrosis volume

- 100% of the necrosis volume inside of high-dose-high-RBE ROI.
- Dose difference statistics for the necrosis volume for prescribed dose of 52 Gy(RBE)
  - Max = 6.8 Gy (RBE)
  - Avg = 3.6 Gy (RBE)
  - Min = 1.4 Gy (RBE)



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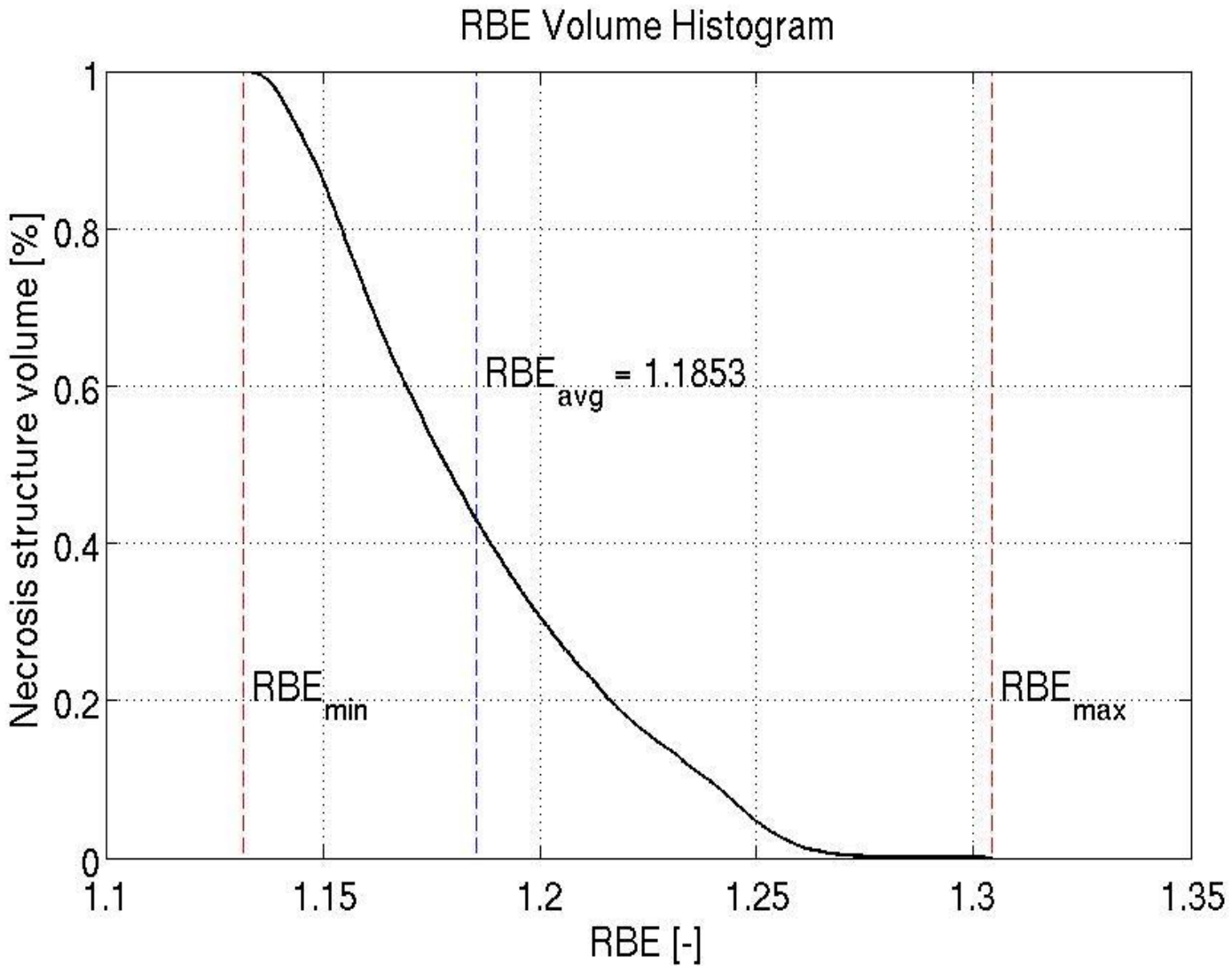
RBE-Necrosis Volume Histogram



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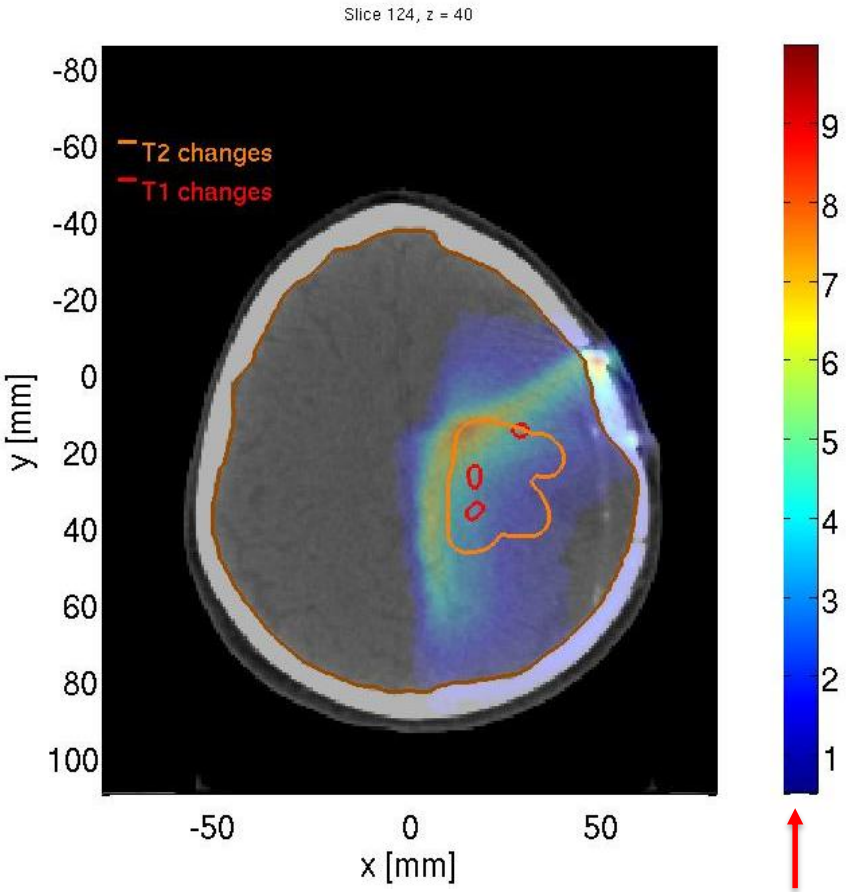
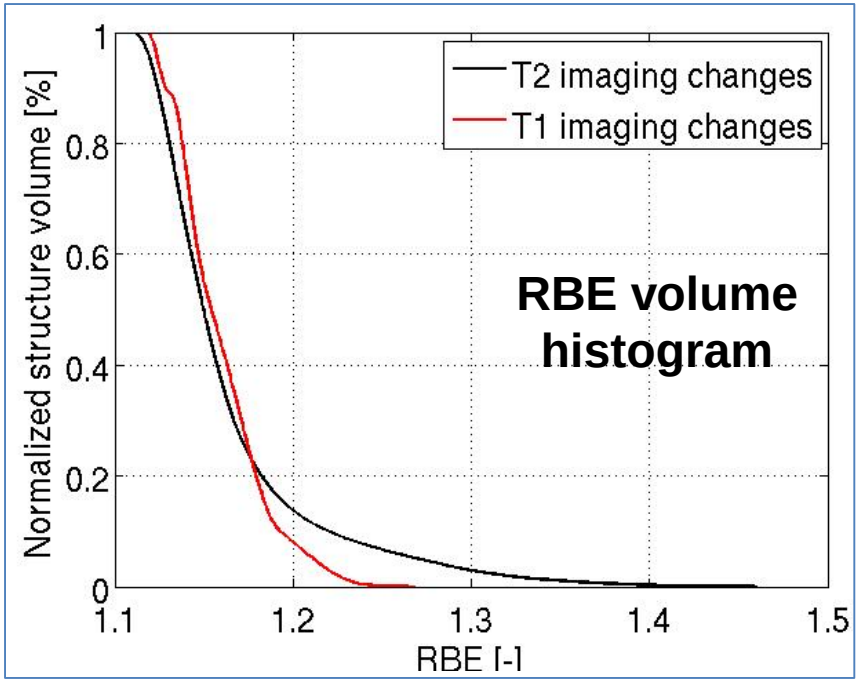
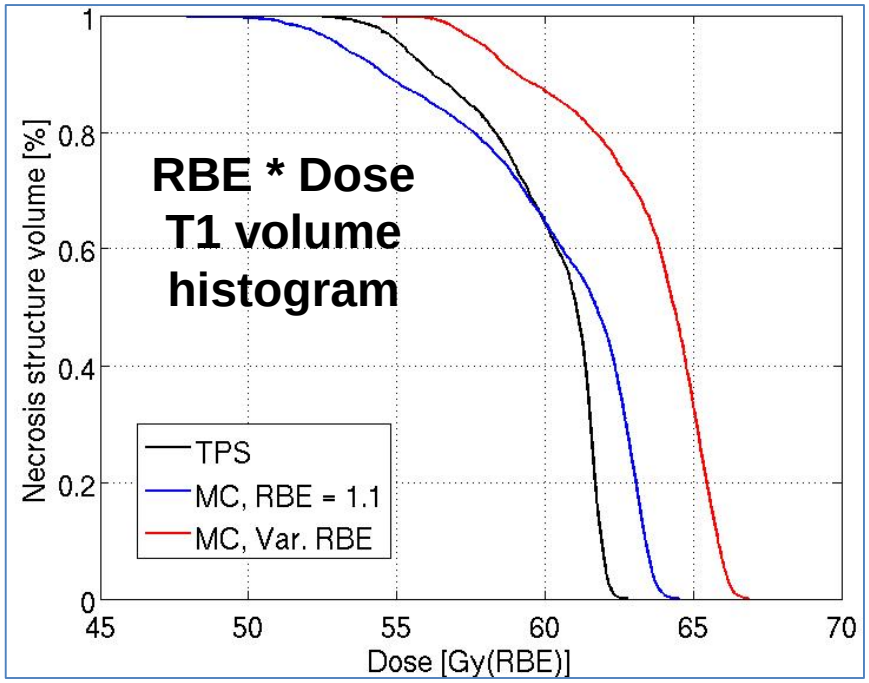
2-Year Old Female with Supratentorial Anaplastic Ependymoma

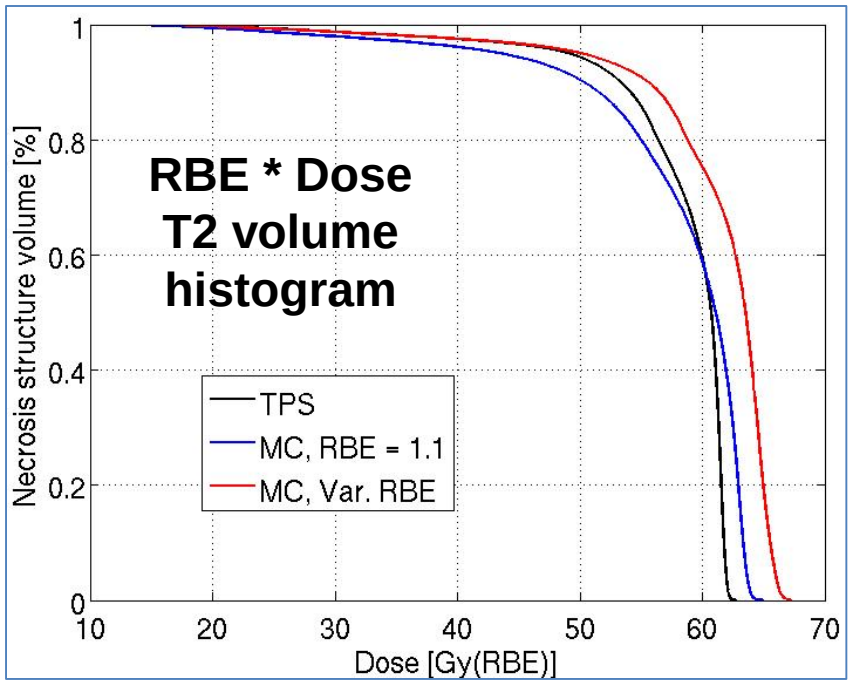
- **Investigated correlation between high-dose-high-RBE volume and the necrosis (increased T1/T2 signal) volume**





RBE computed using Wilkens LSM





Assertion

- **Even though our current knowledge of proton RBE is limited, it is preferable to use variable RBE than constant RBE of 1.1**
  - **For the evaluation of proton dose distributions to understand and explain unforeseen toxicities and recurrences**
  - **In IMPT optimization to deposit dose in target volumes preferentially with higher RBE protons and away from critical structures**

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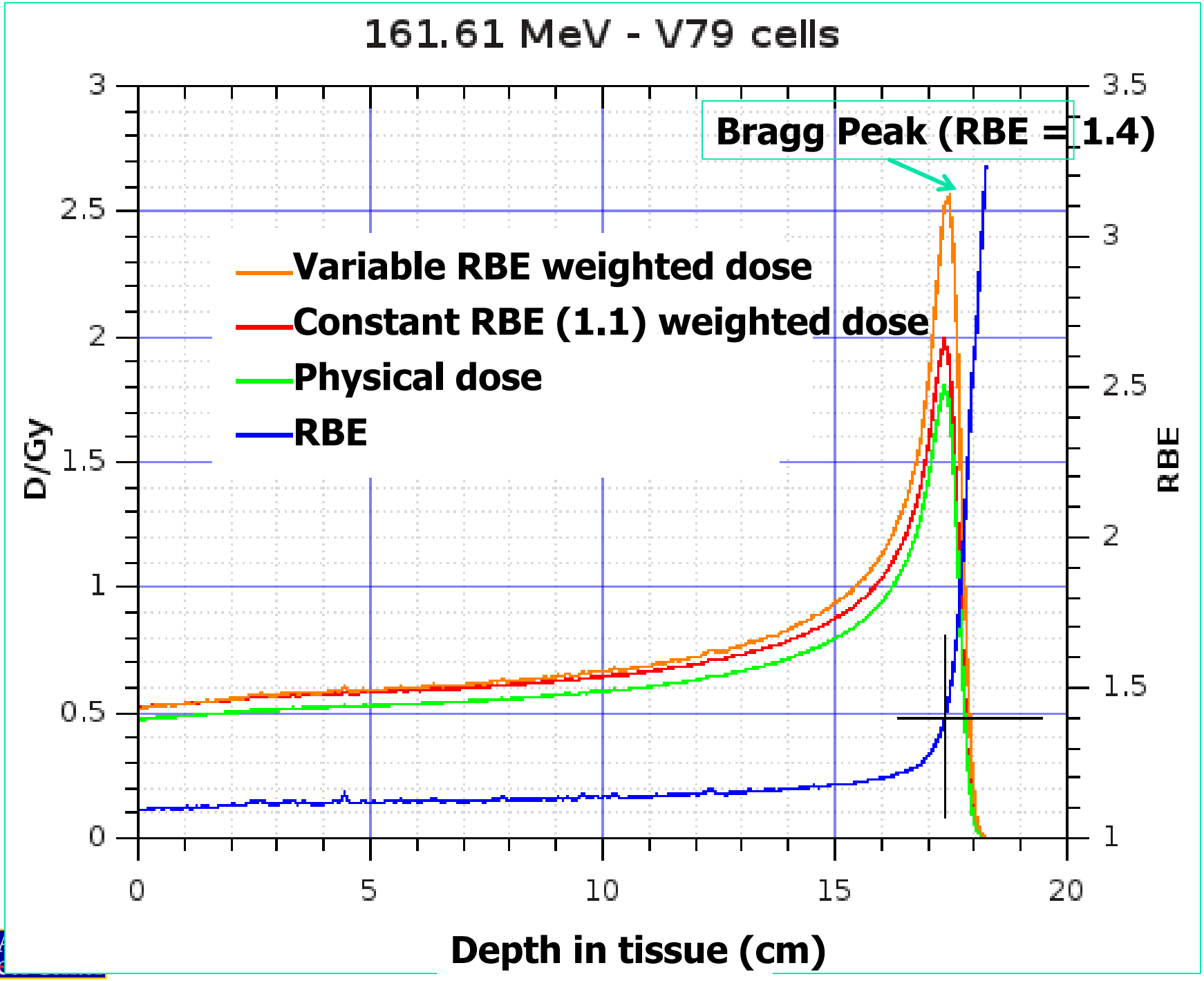
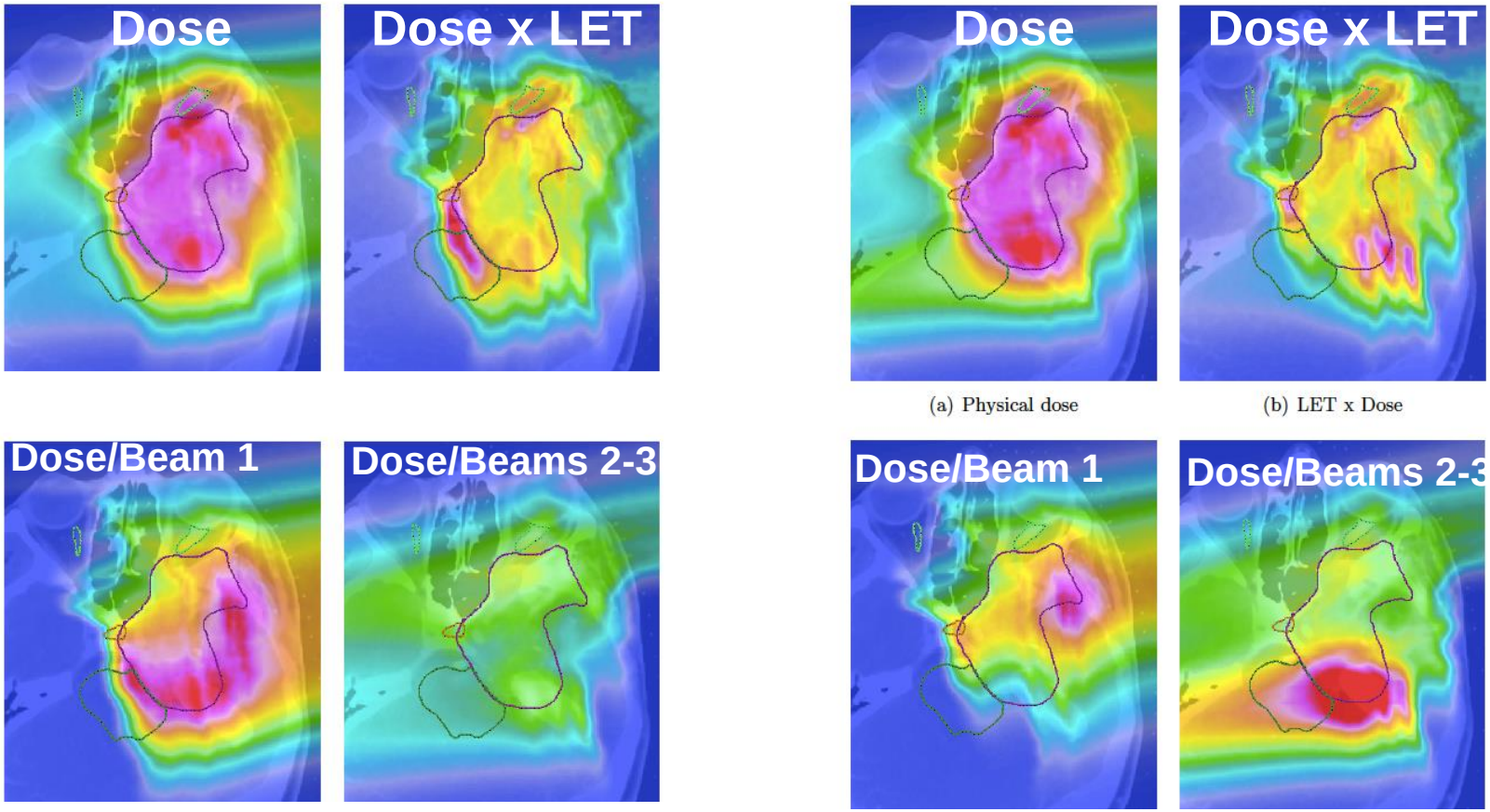

161.61 MeV - V79 cells
Bragg Peak (RBE = 1.4)
Variable RBE weighted dose
Constant RBE (1.1) weighted dose
Physical dose
RBE
D/Gy
RBE
Depth in tissue (cm)
0
0.5
1
1.5
2
2.5
3
1
1.5
2
2.5
3
3.5
0
5
10
15
20

How can we incorporate RBE variability in IMPT optimization?

Different approaches

1. **Optimize IMPT using criteria based on dose*LET (Unkelbach, MGH)**
2. **Assume RBE to be lower than 1.1 in the target and higher in critical normal structures (Jones, Oxford)**
3. **RBE-weighted dose IMPT optimization**
   - **Using current RBE models and models to be developed**

LET-based inverse optimization

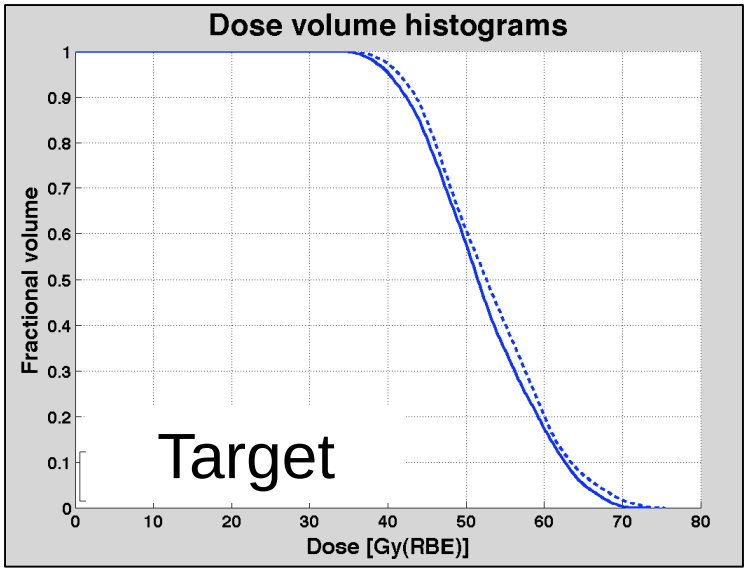


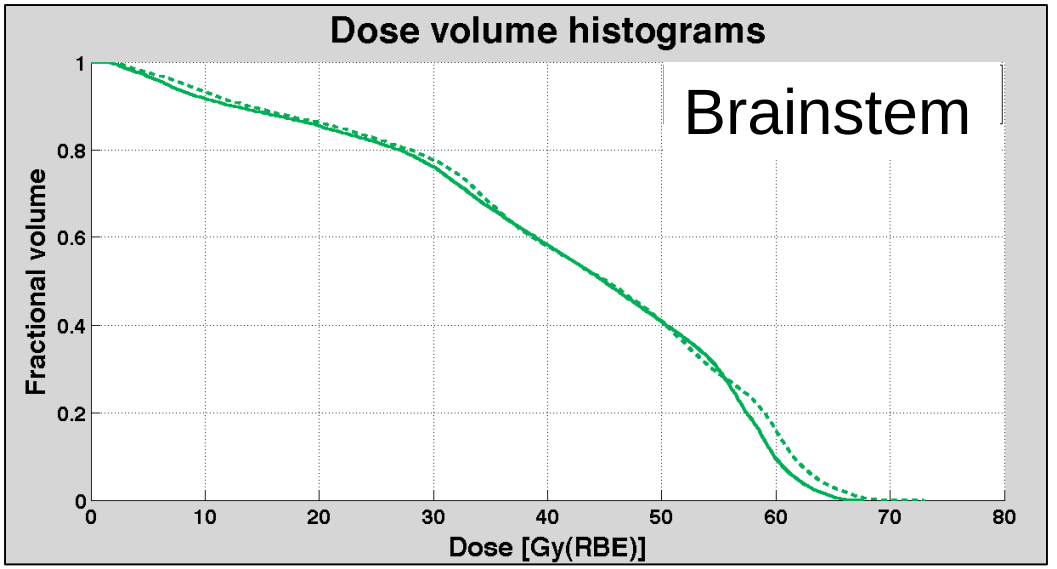
Plan 1: optimized based on physical dose objectives alone

Plan 2: minimizing the mean of LETxDose in the brainstem

© J. Unkelbach, B. Gorrison

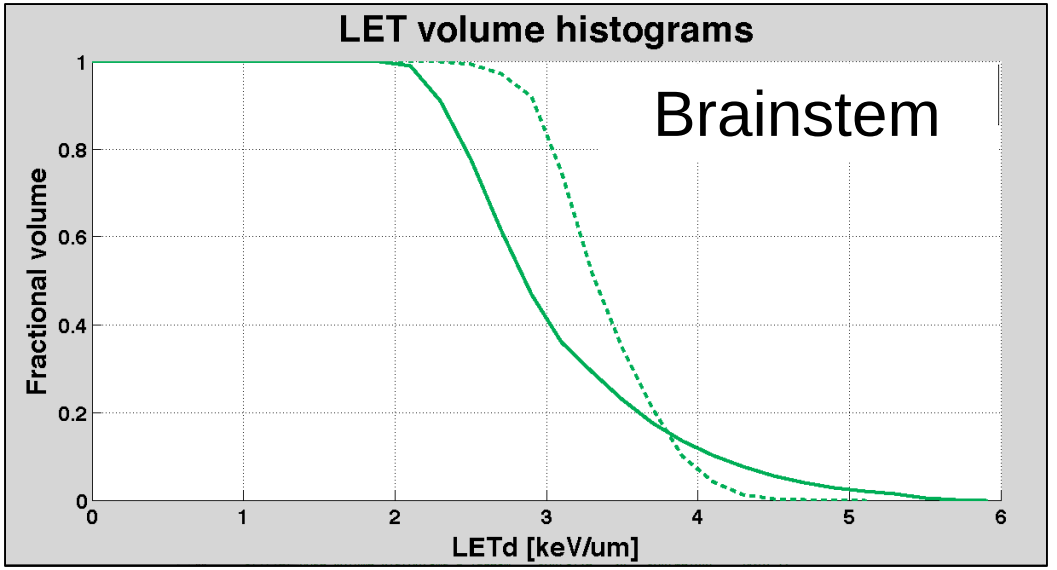
Biological treatment planning





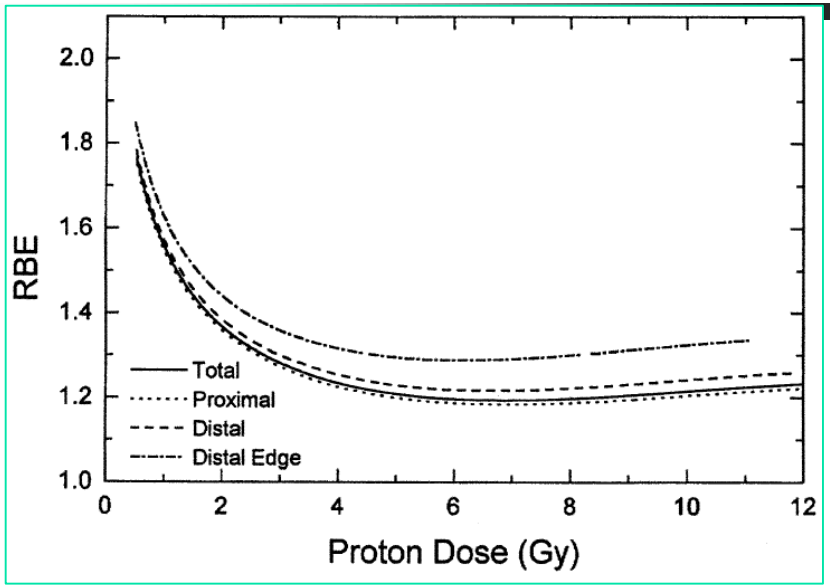
Plan 1: Dashed; optimized based on physical dose objectives alone

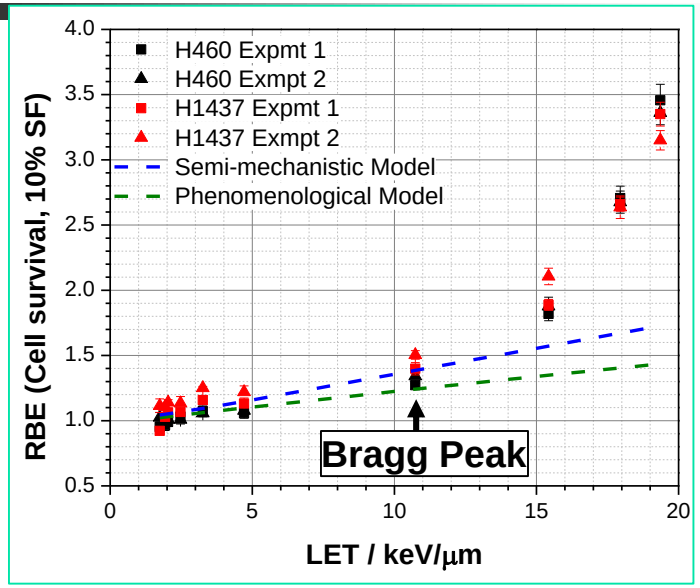
Plan 2: Solid; minimizing the mean of LETxDose in the brainstem

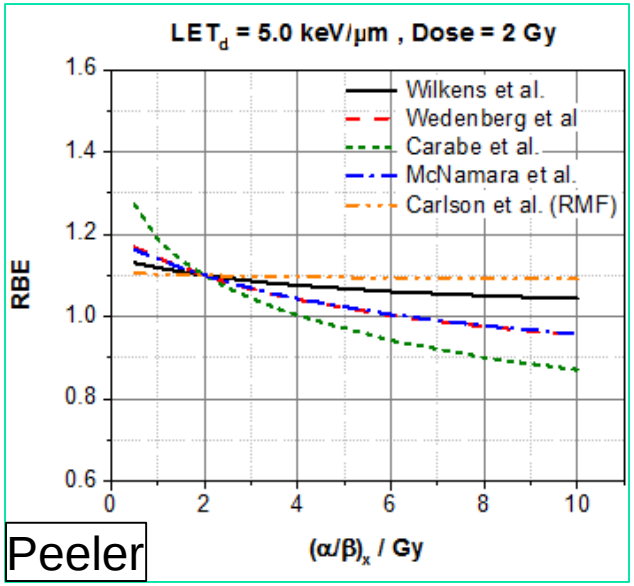


Dose * LET

Is it an appropriate surrogate for biological effect?







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Variable RBE-Weighted Optimization (WIP @ MDACC)

- Define criteria in terms of
  - RBE-weighted dose or
  - Biological effect (e.g., using LQ model)
- Considers non-linear dependence RBE on dose and alpha/beta
- Future models may consider non-linear dependence on LET

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Work-in-Progress
Initial Approach

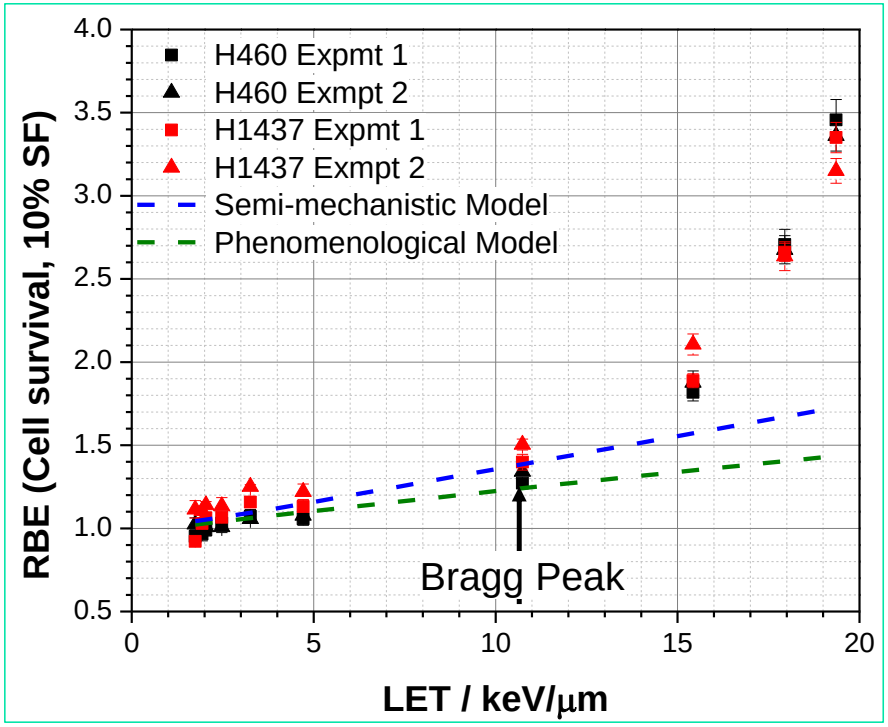
- **Wilkens Linear Scaling model + Frese parameters**
- **Criteria defined in terms of biological effect**

$$\mathrm{RBE}(D_p, \alpha_x, \beta_x, \alpha_p, \beta_p) = \frac{\sqrt{\alpha_x^2 + 4\beta_x D_p(\alpha_p + \beta_p D_p)} - \alpha_x}{2\beta_x D_p}.$$

$$\alpha_p(L) = \alpha_0 + \lambda L$$

L = Dose-averaged LET

$\alpha_0 = \alpha_x$ and $\beta_p = \beta_x$



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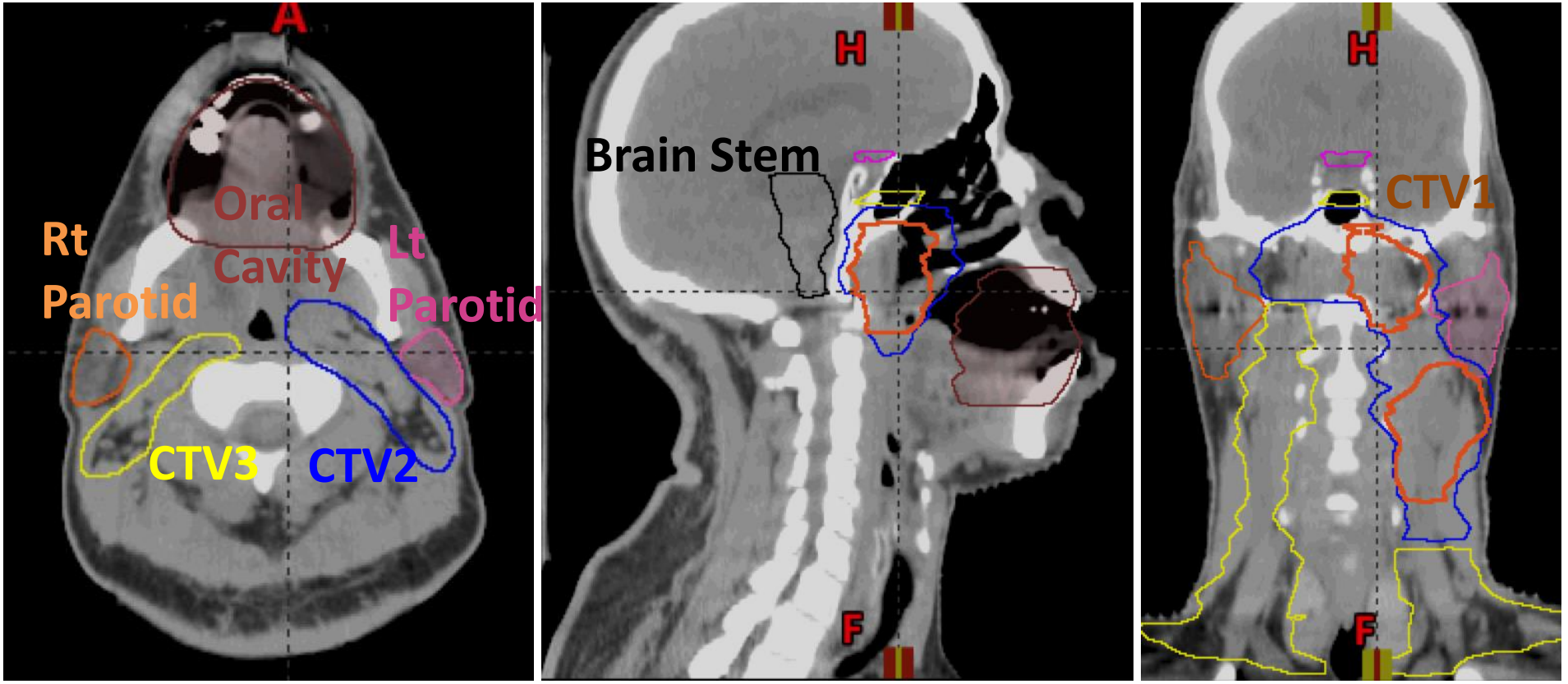
IMPT Optimized Using Variable RBE
Head and Neck Example



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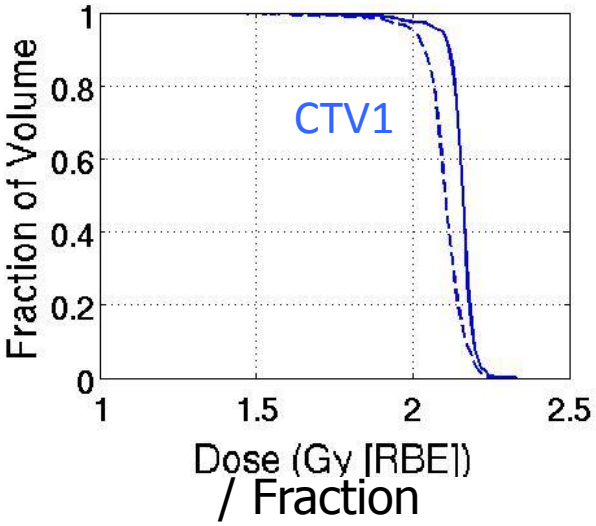
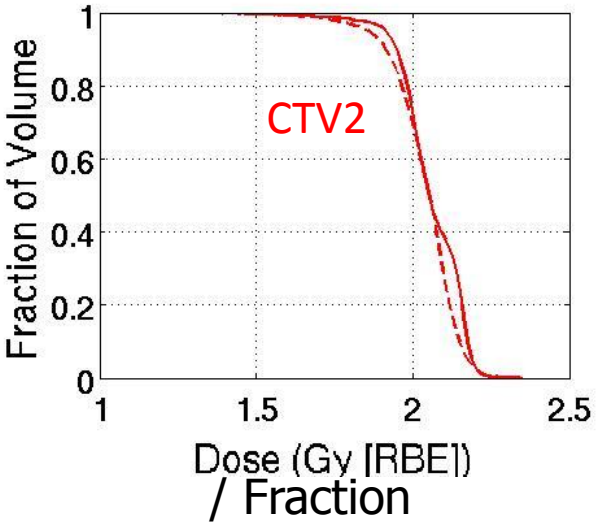
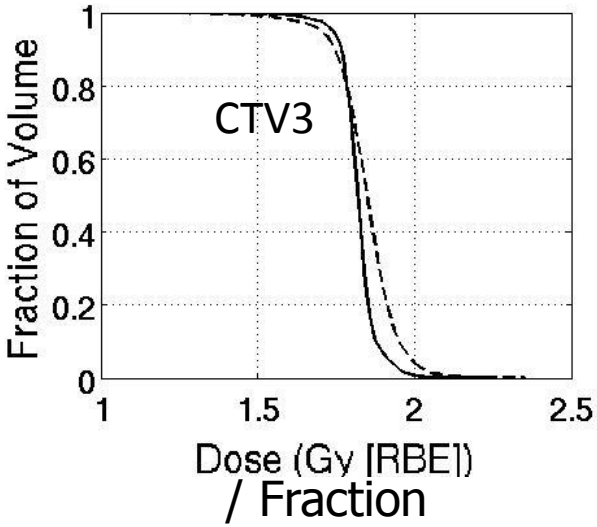
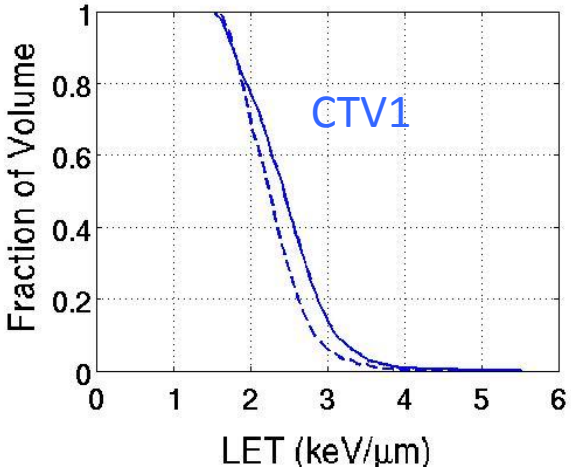
IMPT Plans Recalculated Using Variable RBE

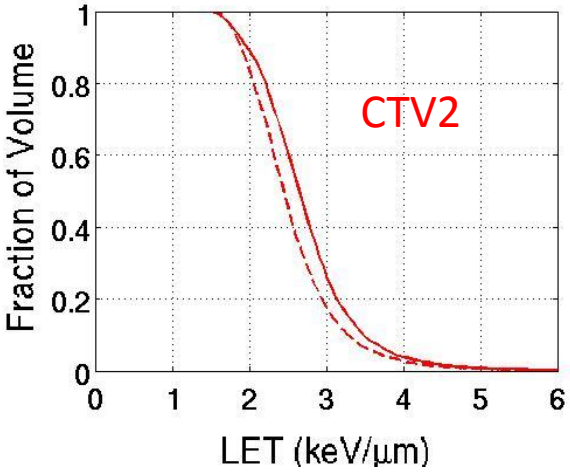
——— Variable RBE optimization – – – - Fixed RBE optimization

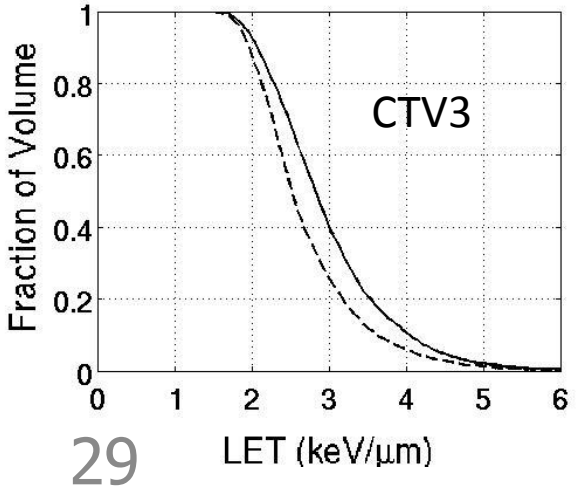




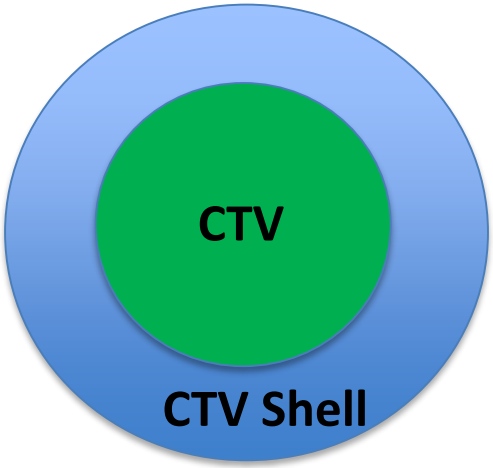


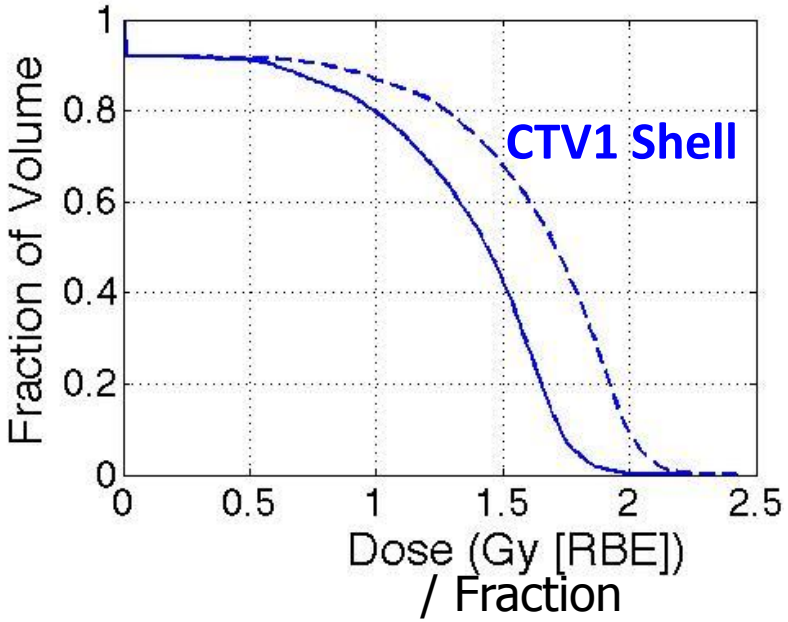


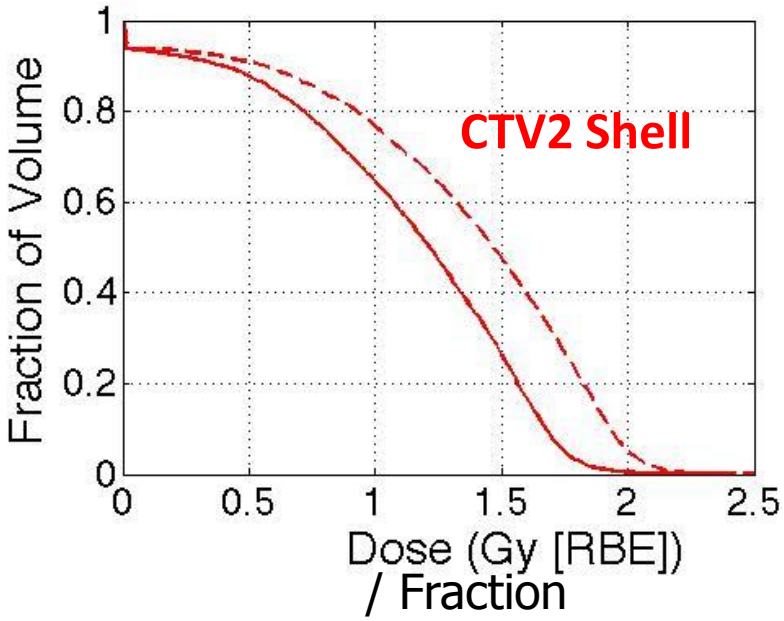


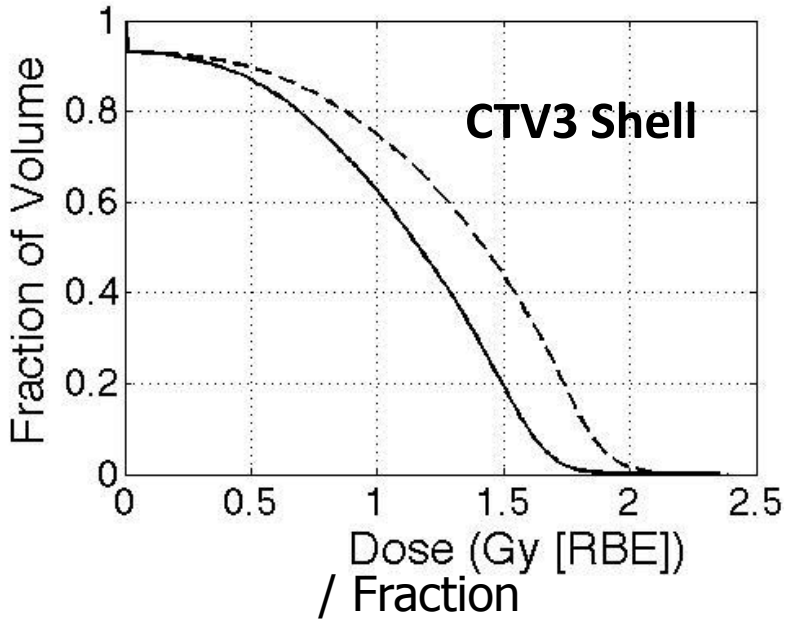


——— Variable RBE optimization – – – – Fixed RBE optimization







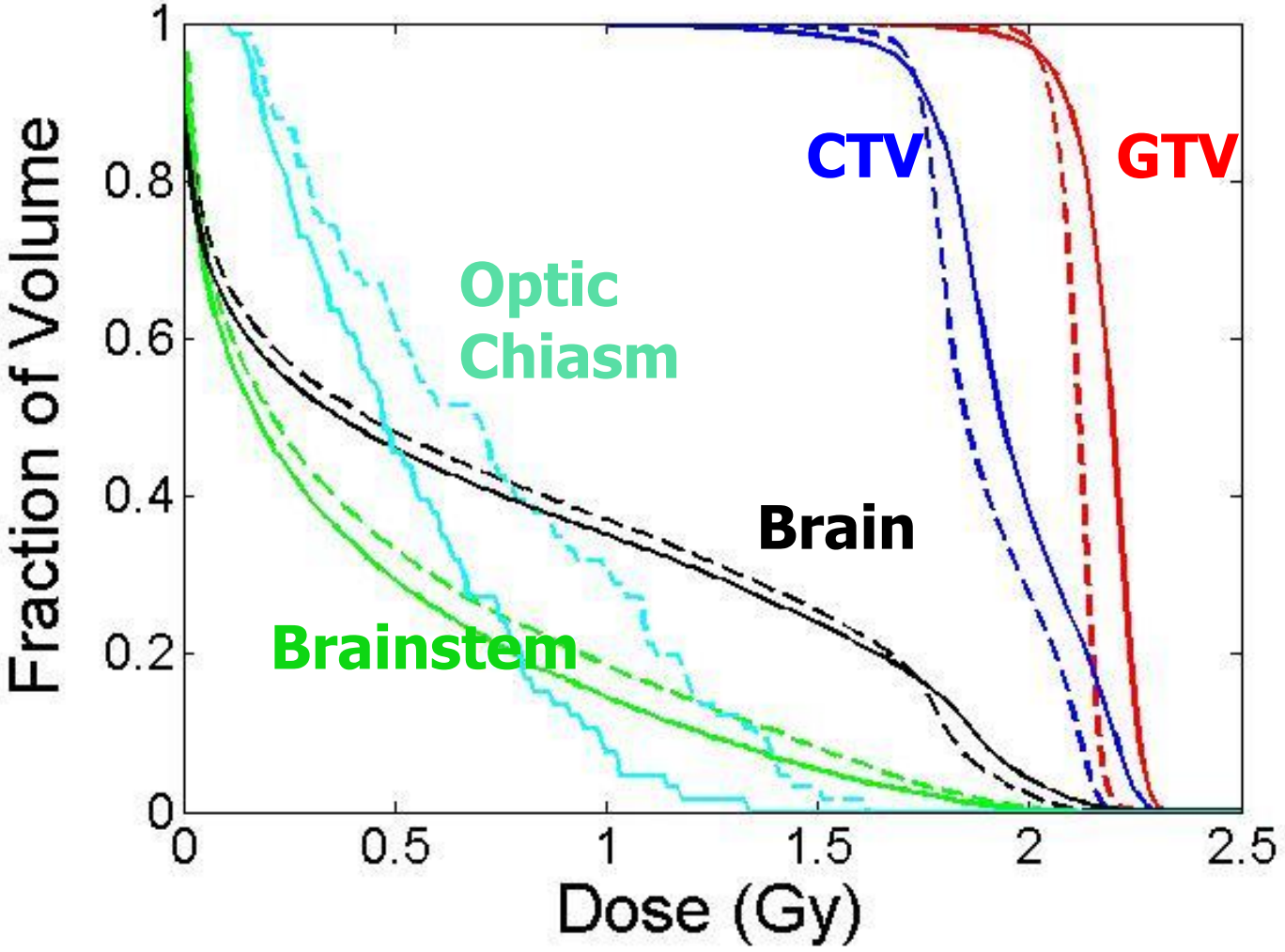


A GBM Example: Variable vs. Fixed RBE Optimization

Fixed RBE (1.1) Dose Representation

Normalized to 95% GTV to Receive 2 Gy

——— Variable RBE optimization – – – – Fixed RBE optimization



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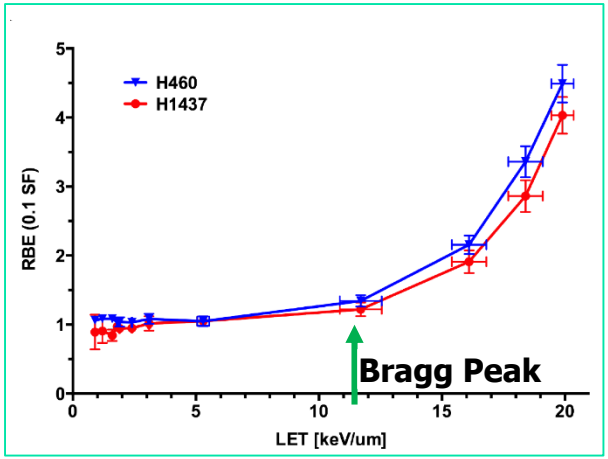
Limitations of Current Proton RBE Models

- **Based on insufficient and inconsistent data**
- **Assumption of RBE**
  - **as a linear function of LET**
  - **Dependence on dose (of fluence)-averaged LET**



Current Models Likely Underestimate RBE Especially at Points Around the Bragg Peak

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Message

- RBE = 1.1 still the standard of practice
- May contribute to unanticipated toxicities and recurrences
- Use of variable RBE, even with its currently limited knowledge and insufficiently developed models may lead to safer and more effective IMPT

Going Forward …

- Acquire more high quality in-vitro and in-vivo data
- Deduce RBE as a function of dose and LET from clinical data
  - Image-biomarkers
  - Treatment response
- Improve RBE models

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Thank You

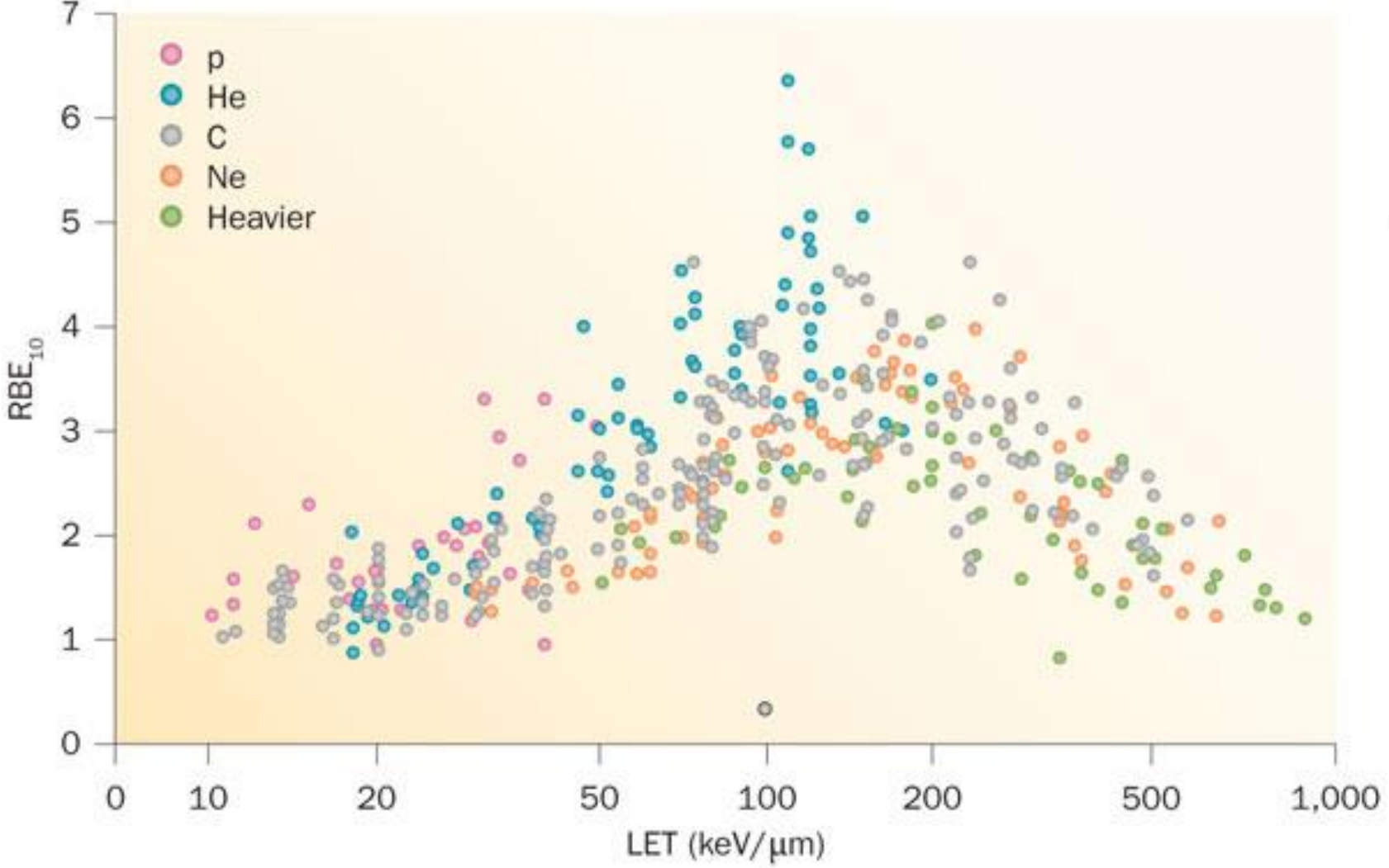

FIGURE 7 | RBE versus LET from published experiments on *in vitro* cell lines.

From the following article:

Charged particle therapy—optimization, challenges and future directions

Jay S. Loeffler & Marco Durante

Nature Reviews Clinical Oncology **10**, 411-424 (July 2013)
doi:10.1038/nrclinonc.2013.79

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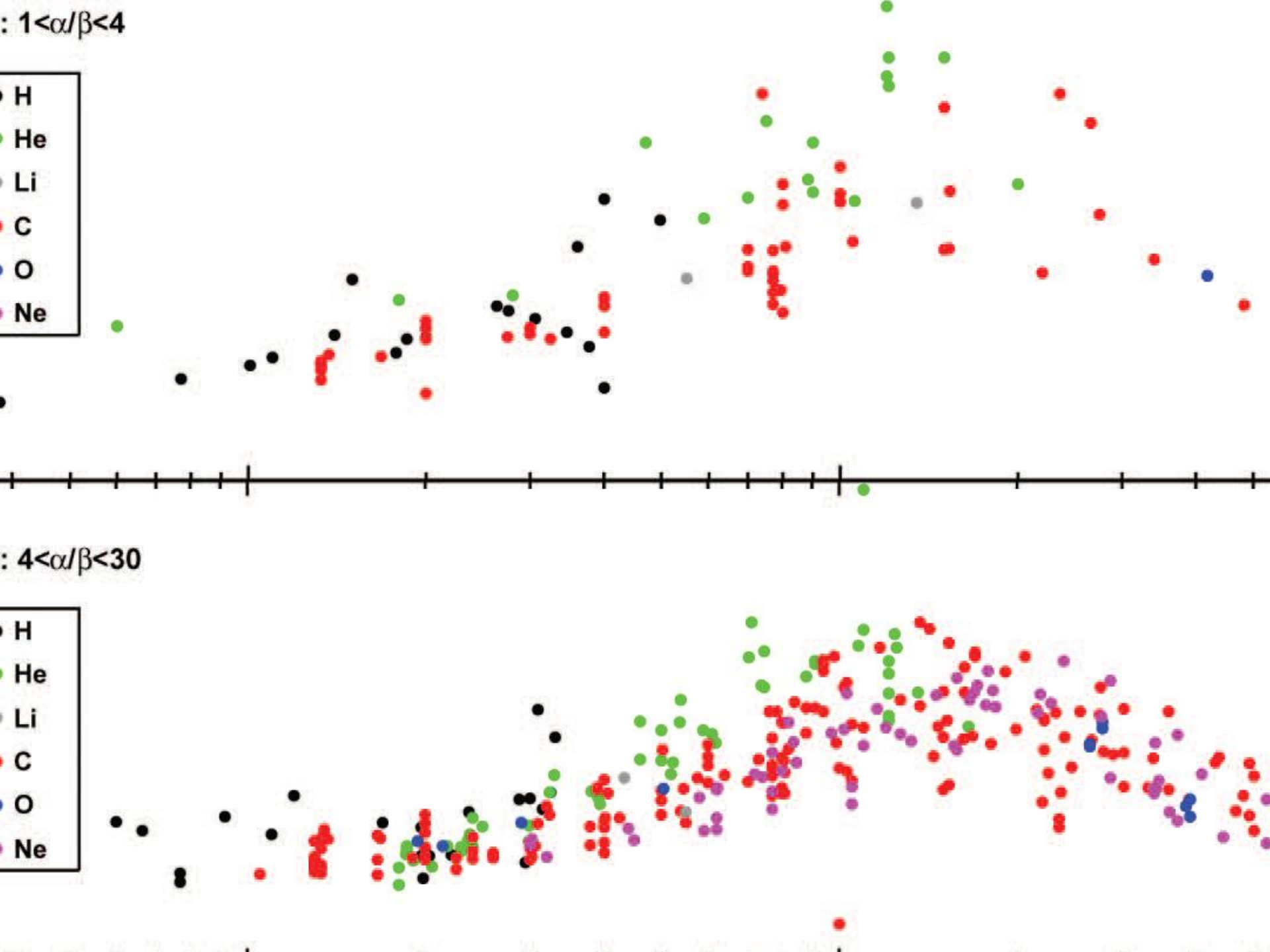
: 1<α/β<4
H
He
Li
C
O
Ne
: 4<α/β<30
H
He
Li
C
O
Ne

"If at first, the idea is not absurd, then there is no hope for it."

Albert Einstein