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Intensity-Modulated Proton Therapy Planning Based on Variable Relative Biological Effectiveness

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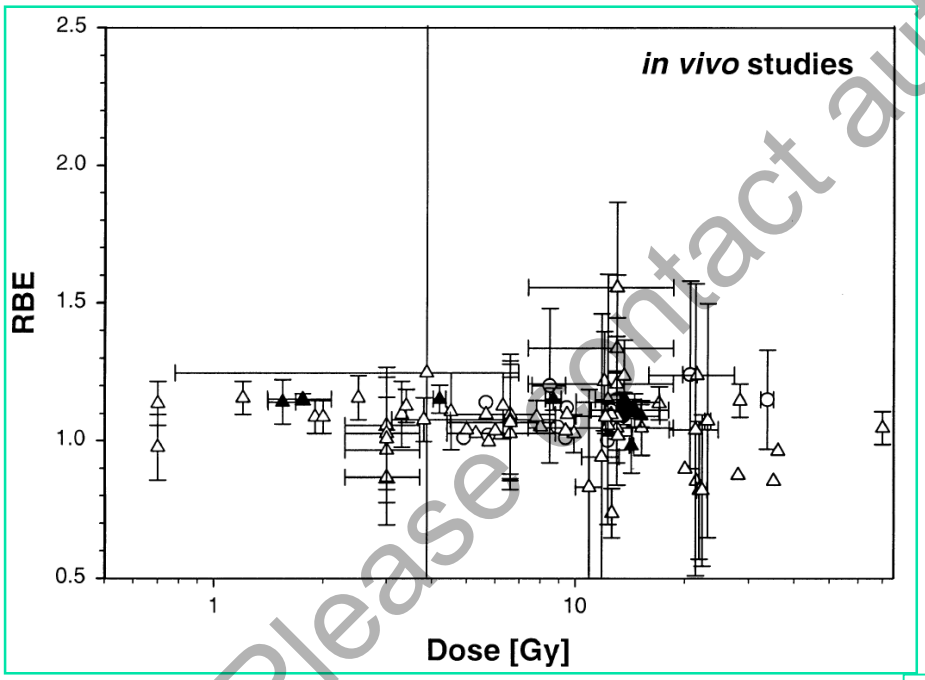
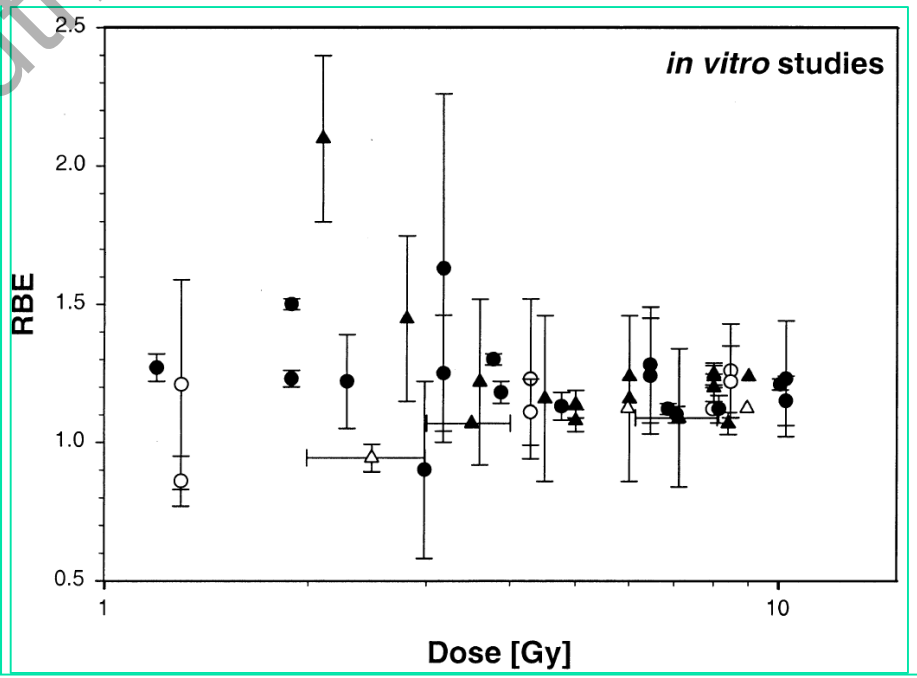
Objectives …

- To debunk the myth(s) surrounding the proton RBE = 1.1 everywhere
- To persuade you that the use of variable proton RBE could
  - Help better understand clinical outcomes
  - Make IMPT safer and more effective
- To argue that we need more and better quality experimental data (some derived from clinical outcomes) to improve models of predicting RBE of protons

The Myth of RBE =1.1

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

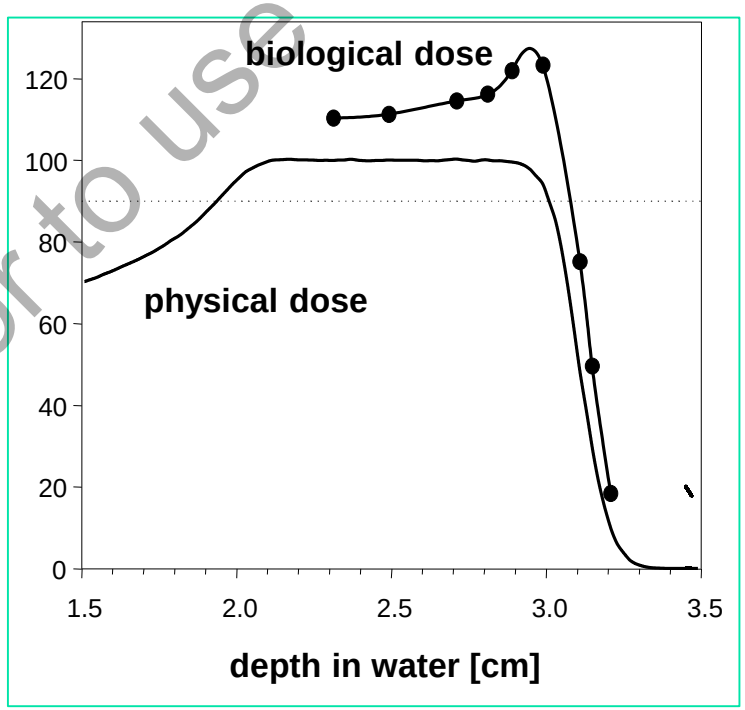




Paganetti, et al, RBE for PBT, IJROBP 2002

RBE = 1.1 – Justification & Claims

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



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

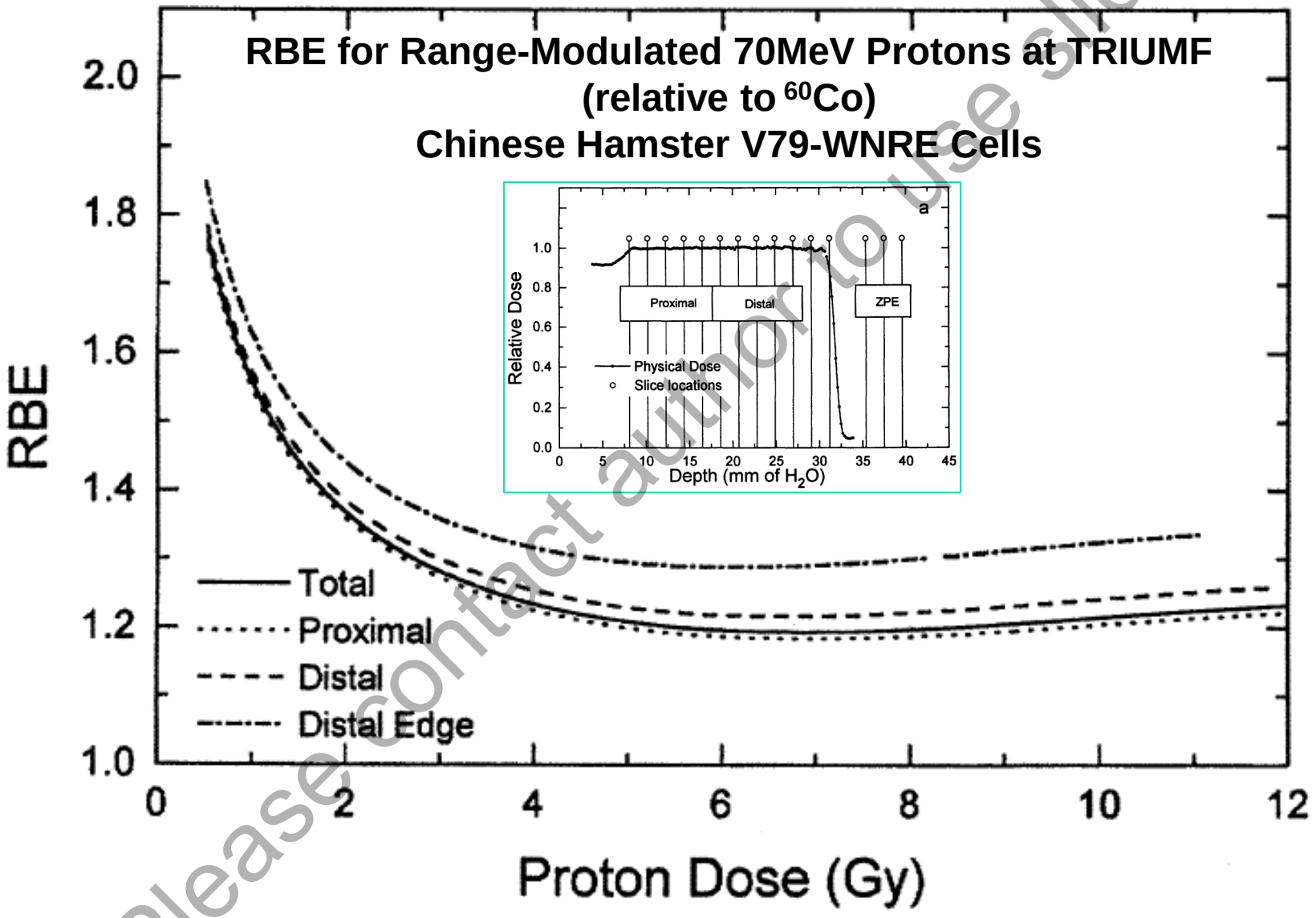
But, jut in case RBE ≠ 1.1 …

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

In Reality
RBE is a Function of Multiple Variables

- Energy (LET) of protons
  - Location along the Bragg peak
- Dose per fraction
- Tissue/cell type, alpha/beta ratio
- End point
- …

RBE as a Function of Dose and LET



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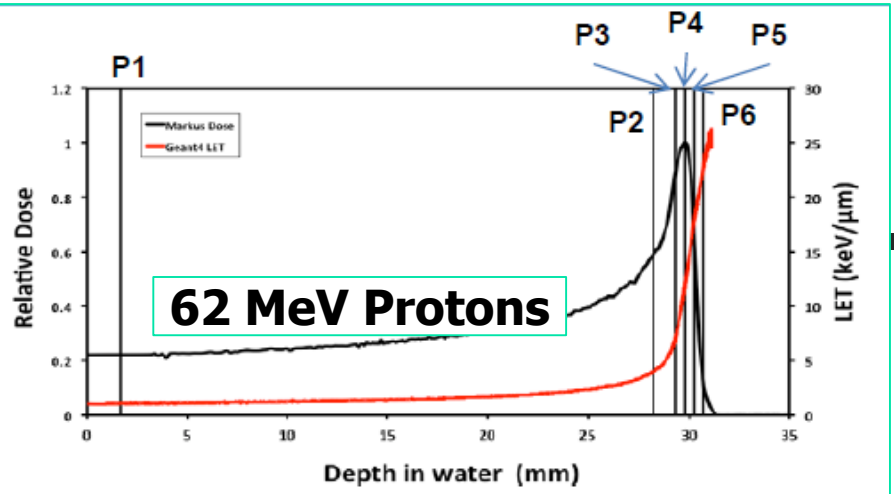
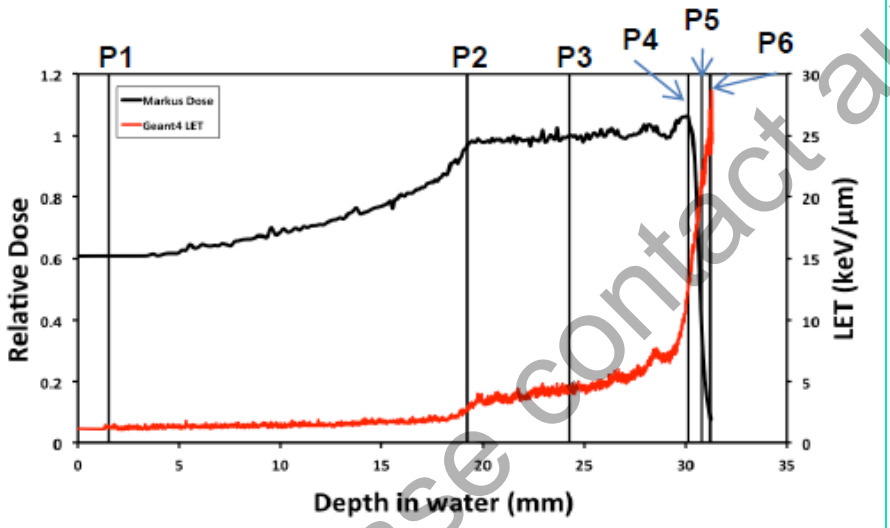
Wouters. Rad Res 96

Prise et al



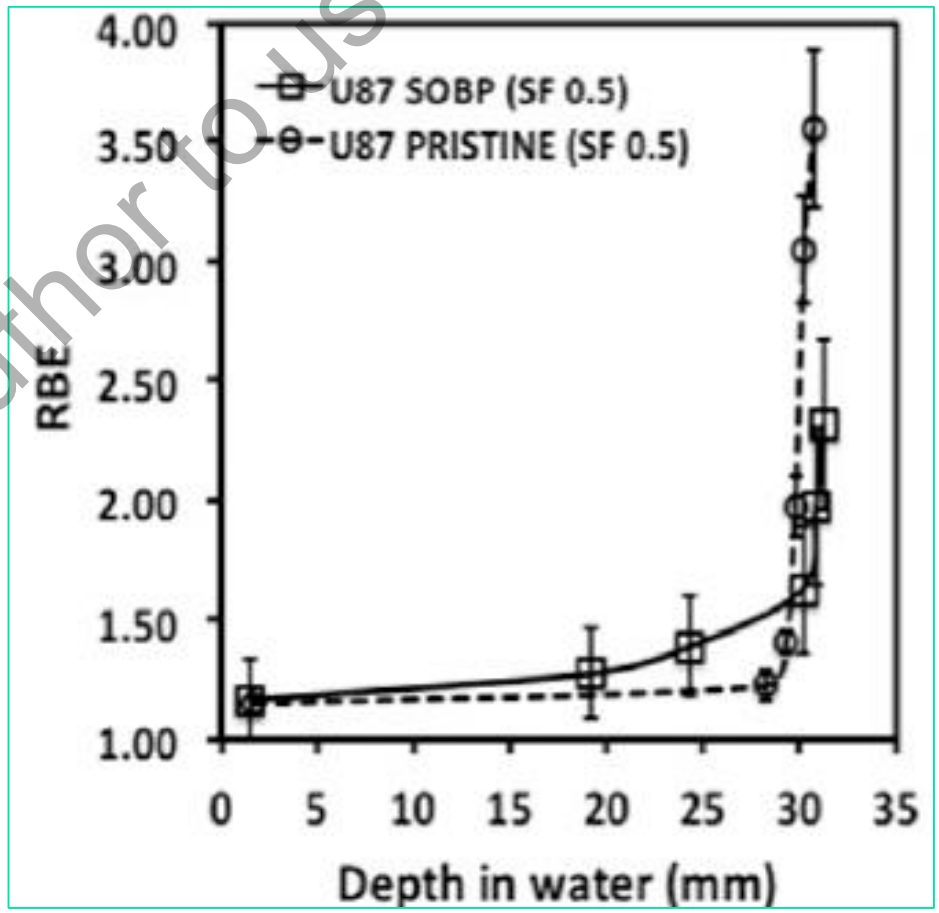
62 MeV Protons

	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

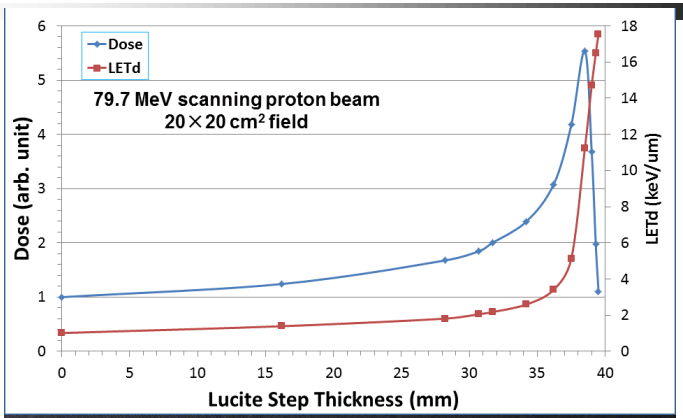


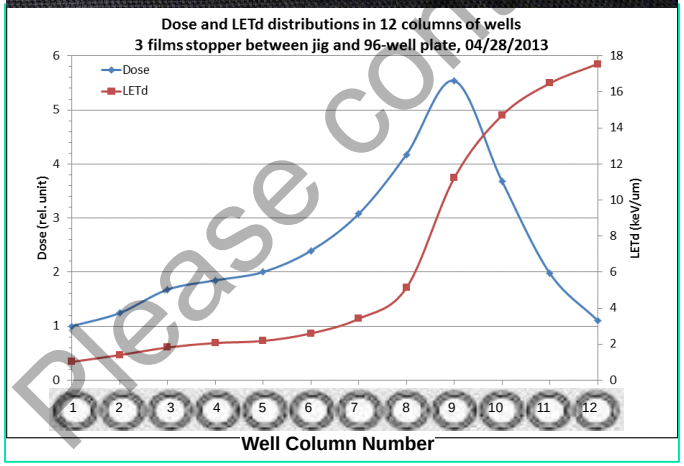
	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	27.42	29.21	29.8	30.7	31.29
LET [keV/µm]	1.11	4.0	7.0	11.9	18.0	22.6

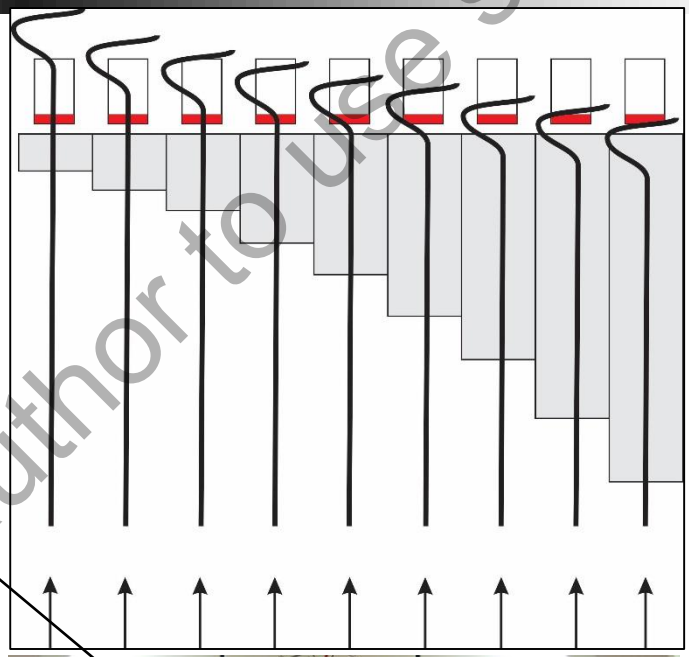
Prise, Schettino et al., submitted

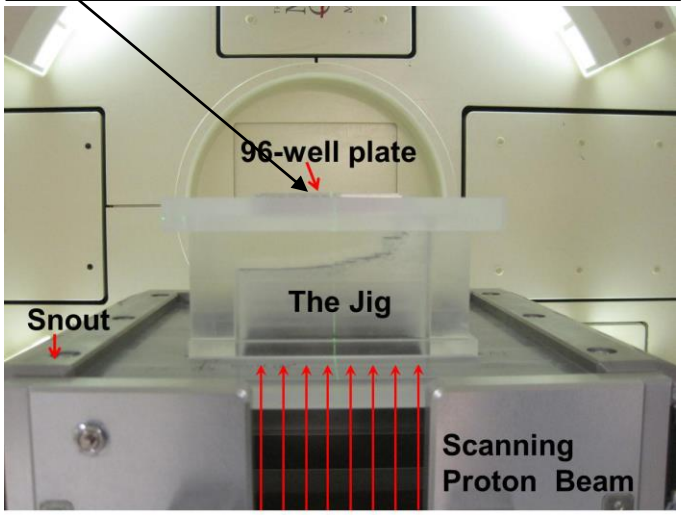


High Precision, High Throughput Experiments (Guan, et al)

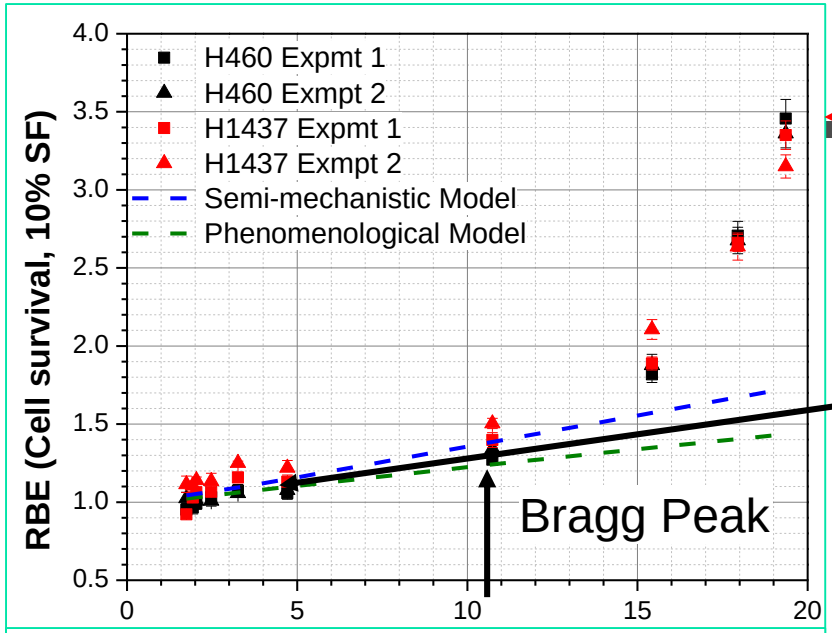


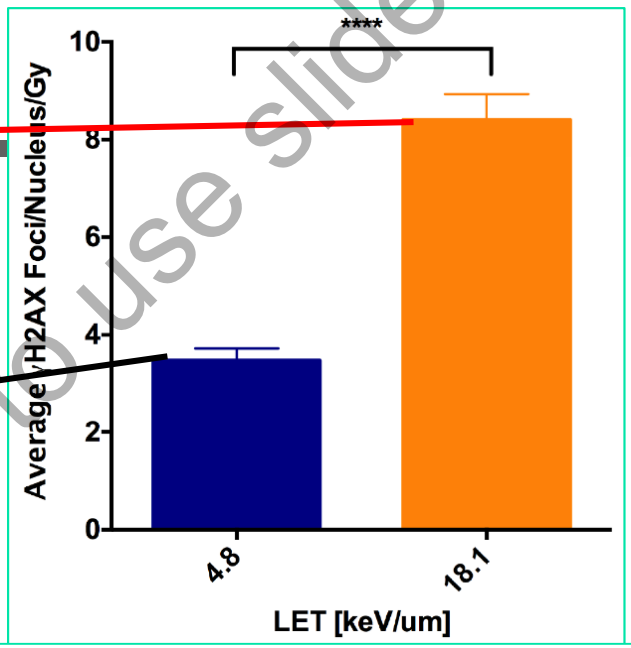


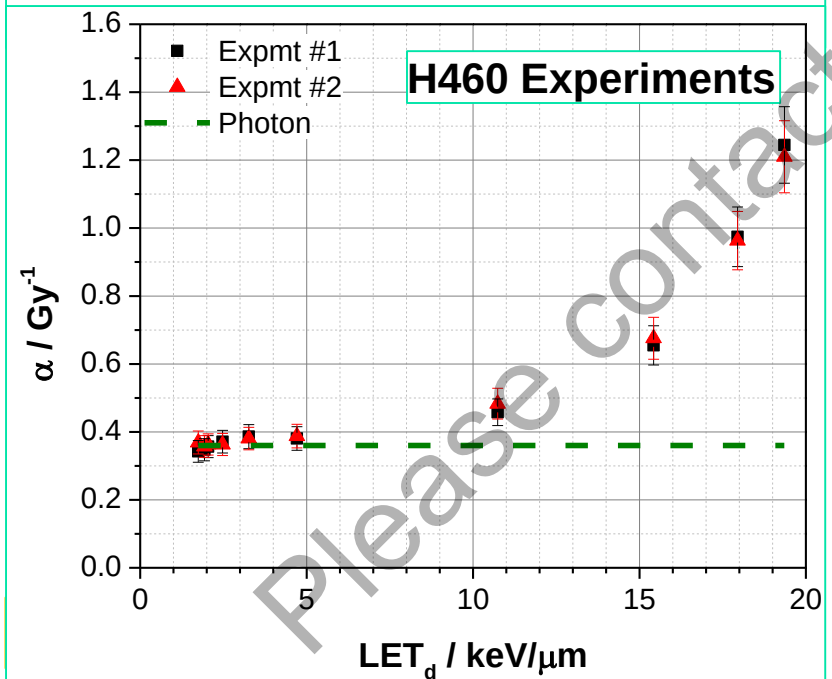


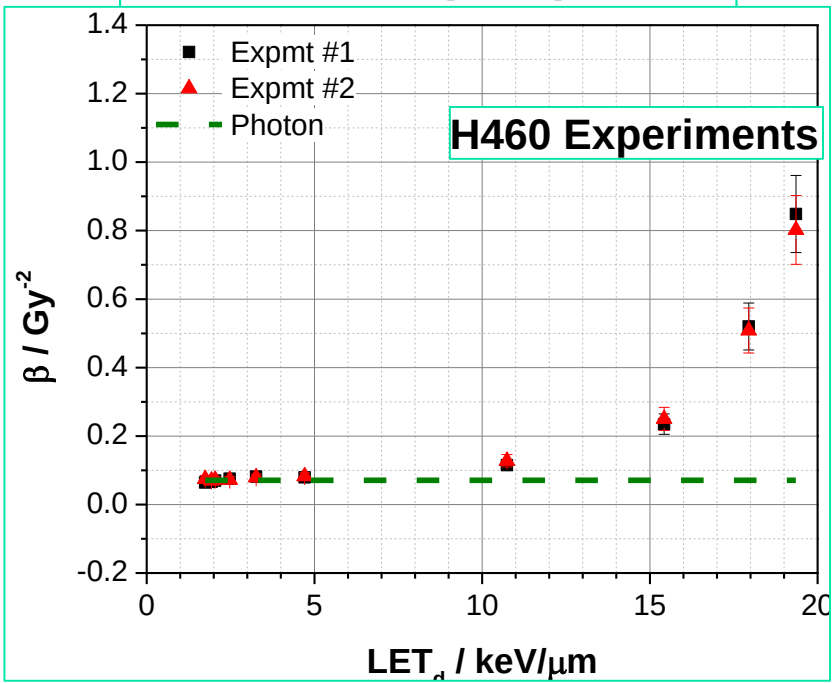


RBE, γH2AX, α_p and β_p Values from for H460 & H1437 Experiments



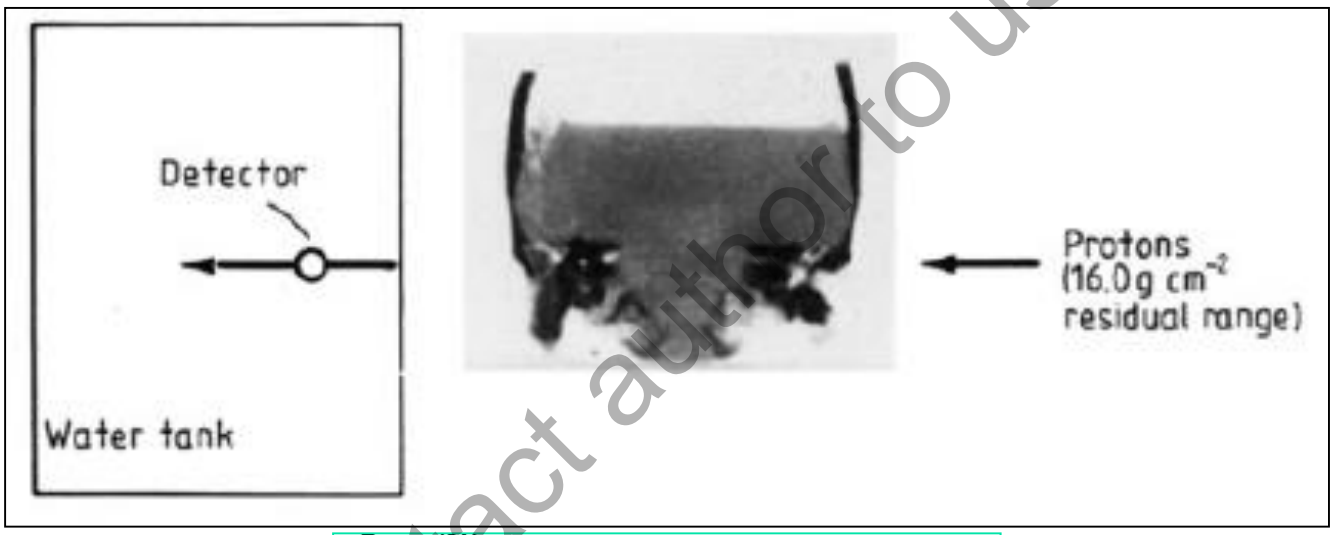


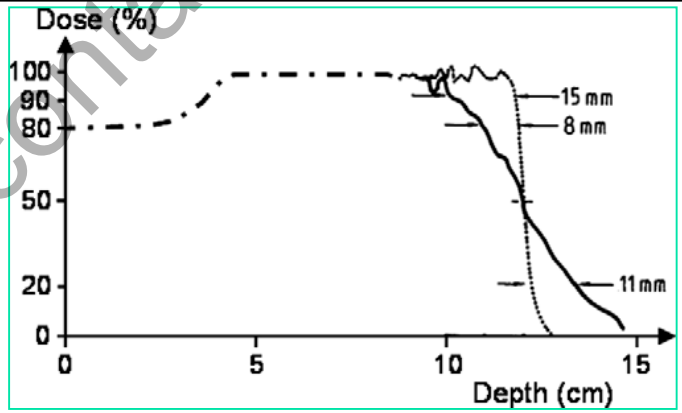




"High RBE Affects a Negligible Region at Distal Edge" -

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

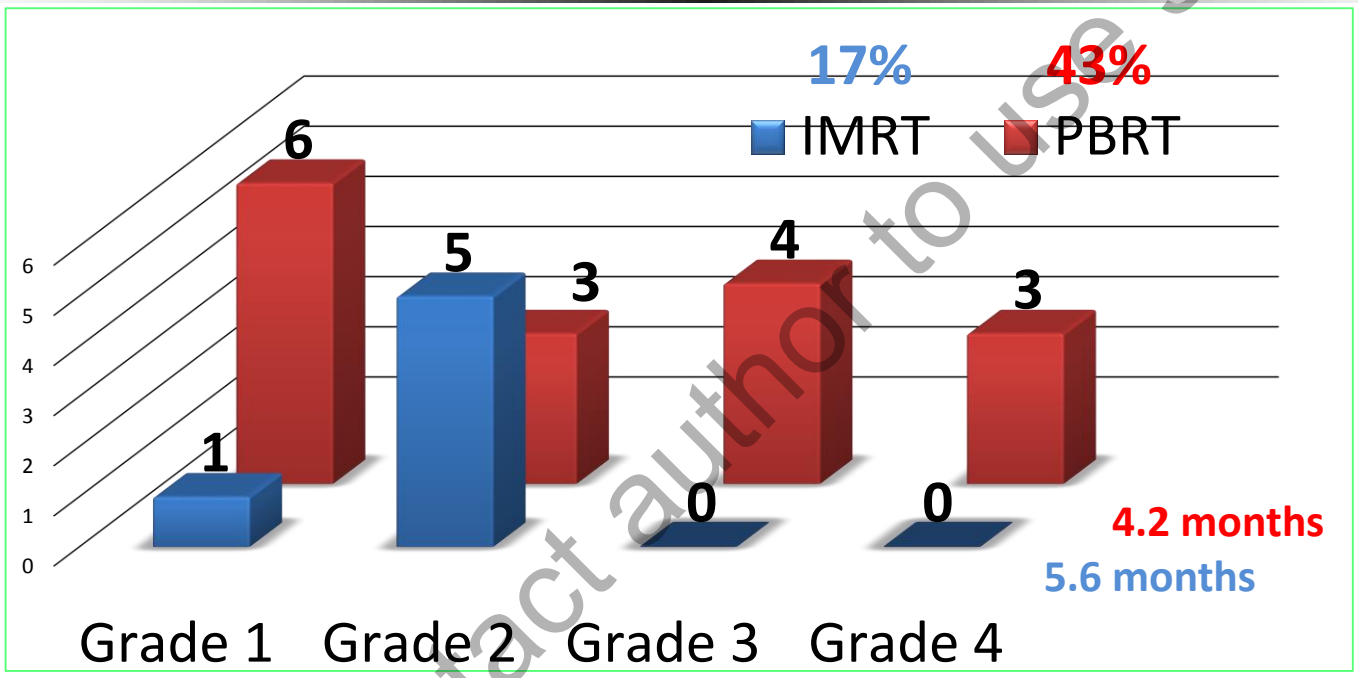
Evidence so far is not unequivocal

Unanticipated Treatment Responses

Some Examples

MR Imaging Changes in 72 Intracranial Ependymoma Patients: Proton Therapy vs. IMRT

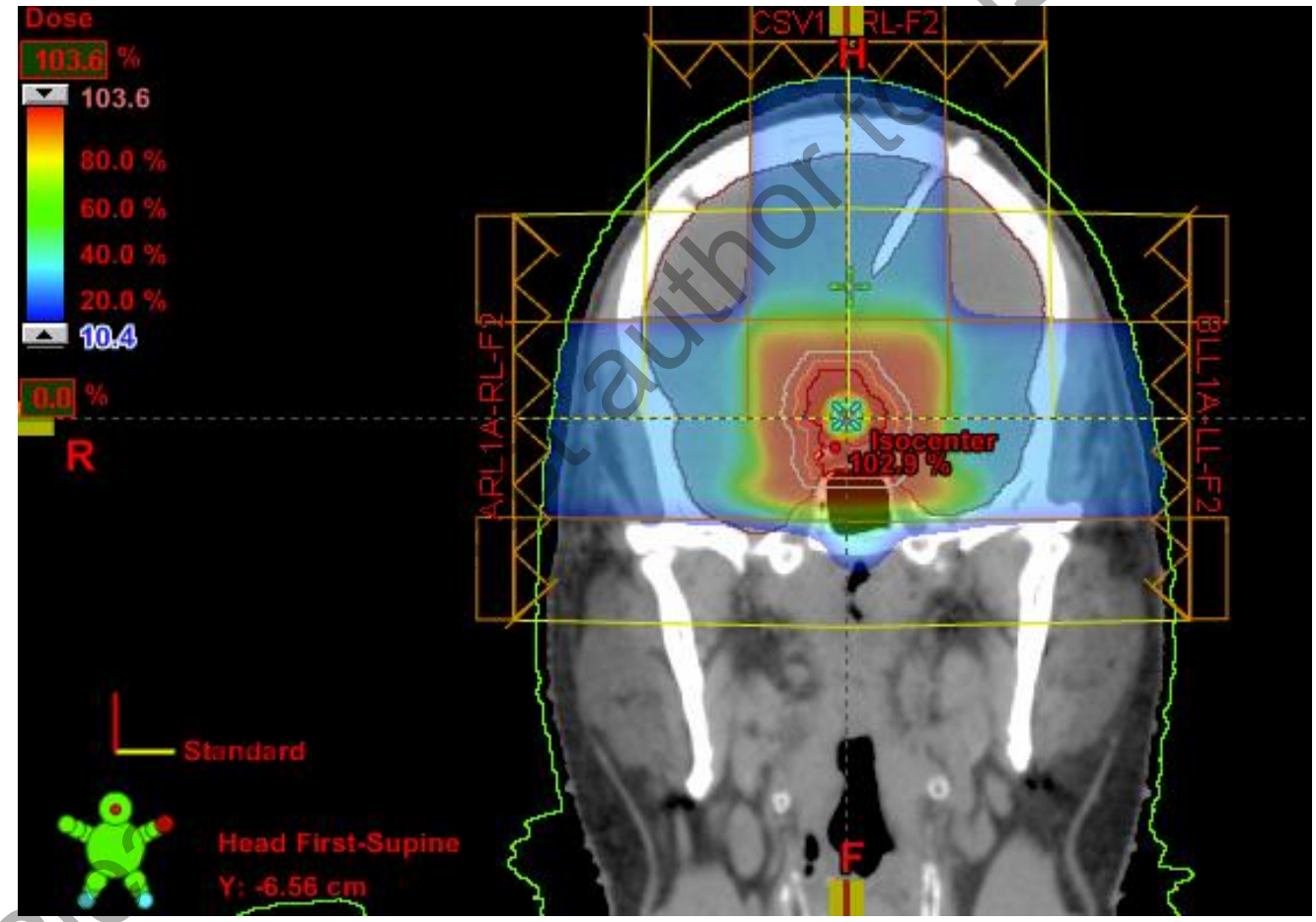
(J. Gunther, et al, ASTRO 2014 and IJROBP 2015)



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

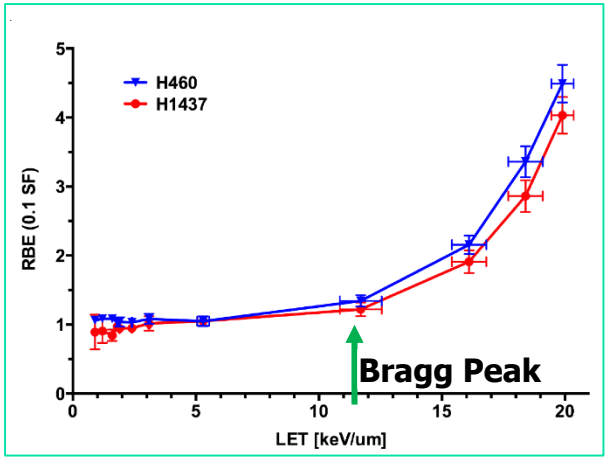
Brain Necrosis in CNS Patients - Possible Consequences of Variable RBE

40 year old male with craniopharyngioma

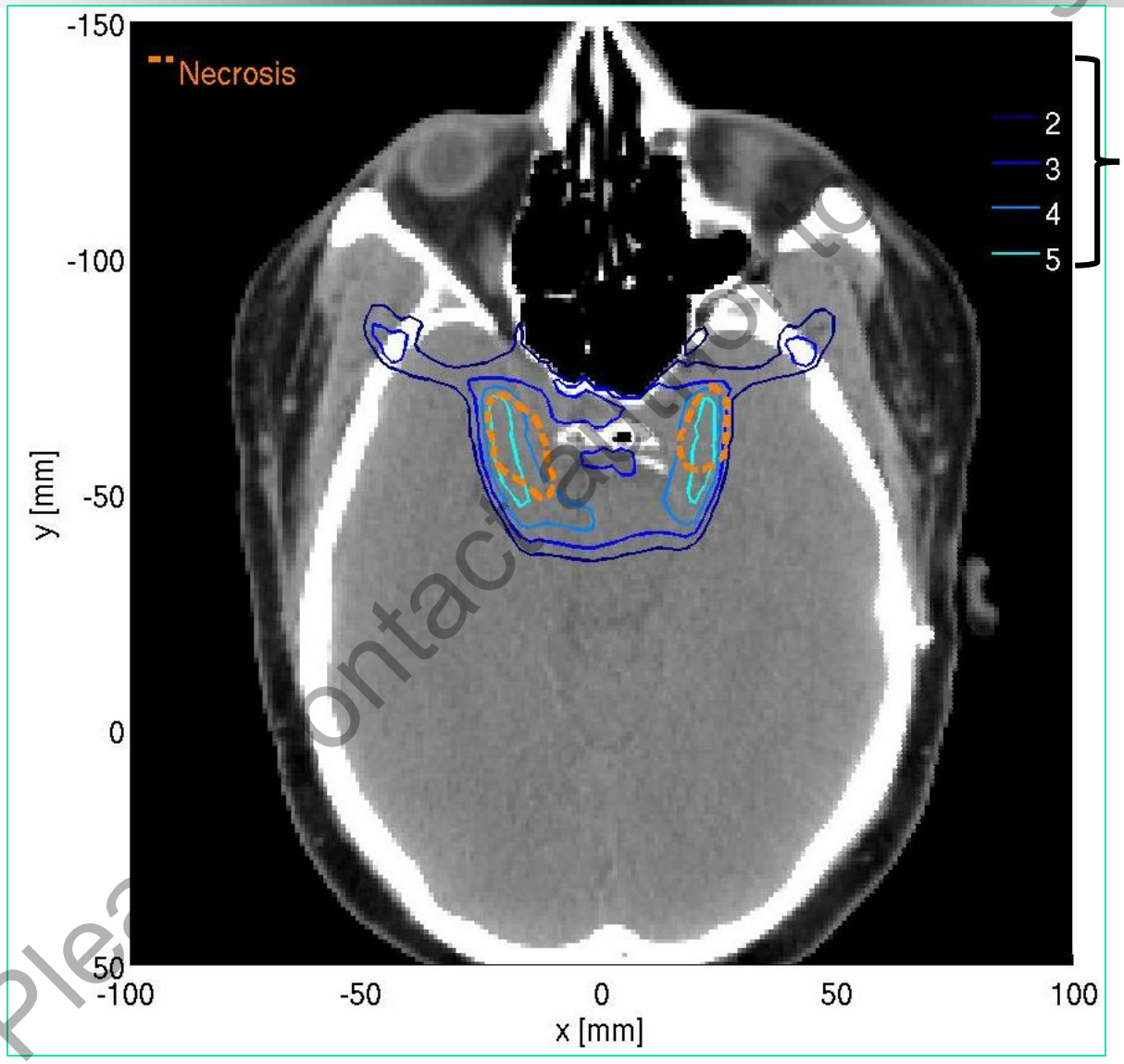


To Determine Whether RBE Could be a Factor …

- Calculate variable RBE-weighted dose distributions for treatment plans designed / optimized based on RBE=1.1
- Various models of computing RBE –
  - Linear scaling model (LS - Wilkens, Oelfke)
  - Repair, misrepair, fixation model (RMF - Stewart)
  - MGH model (Paganetti)
  - LEM (Scholz)
  - …
- Current models
  - Lead to similar results
  - Use dose-averaged LET and assume RBE to be a linear function LET_d
    - Probably underestimate RBE

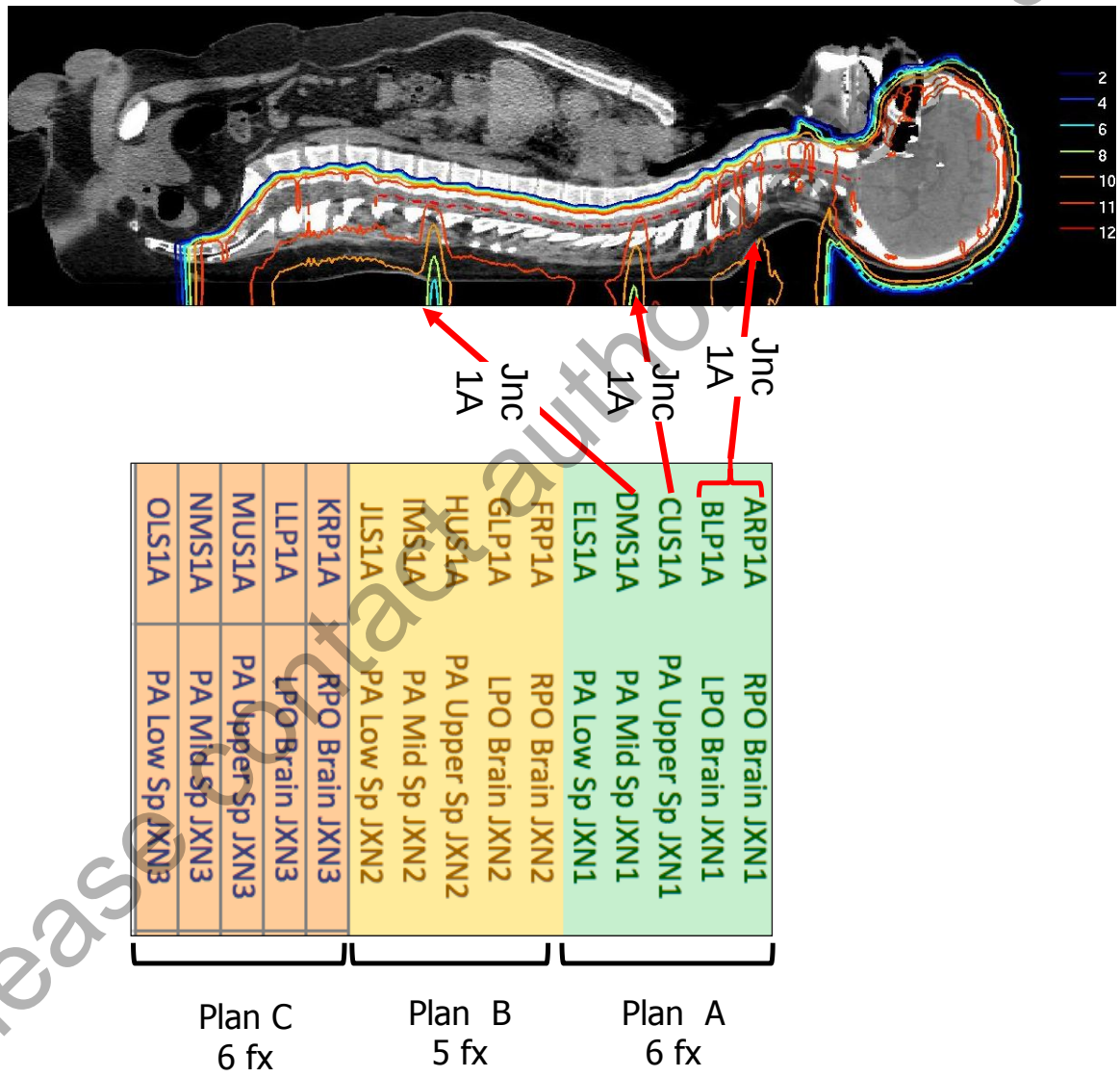


Possible Consequences of Variable RBE - Brain Necrosis in CNS Patients

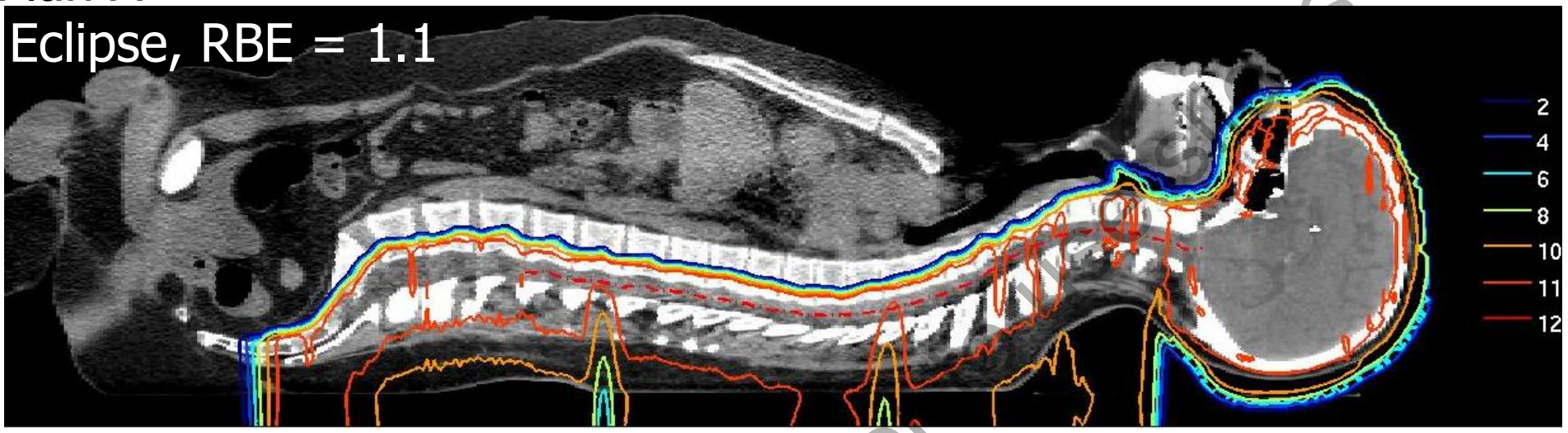


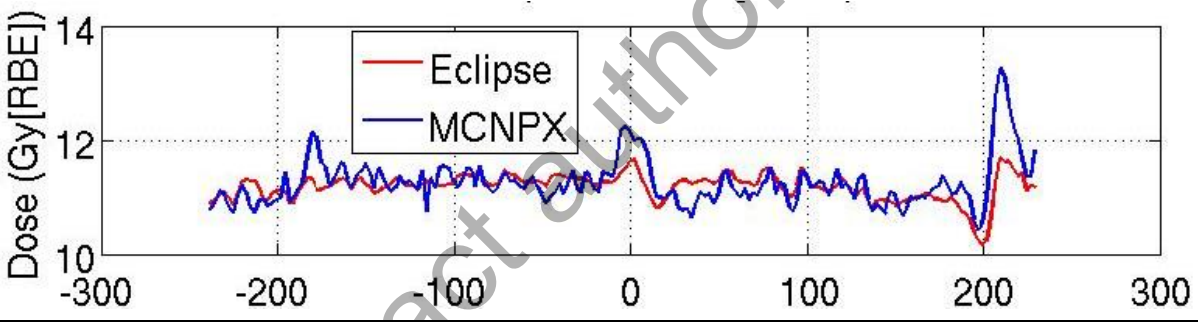
Excess dose with variable RBE - Prescription 52 Gy(RBE)

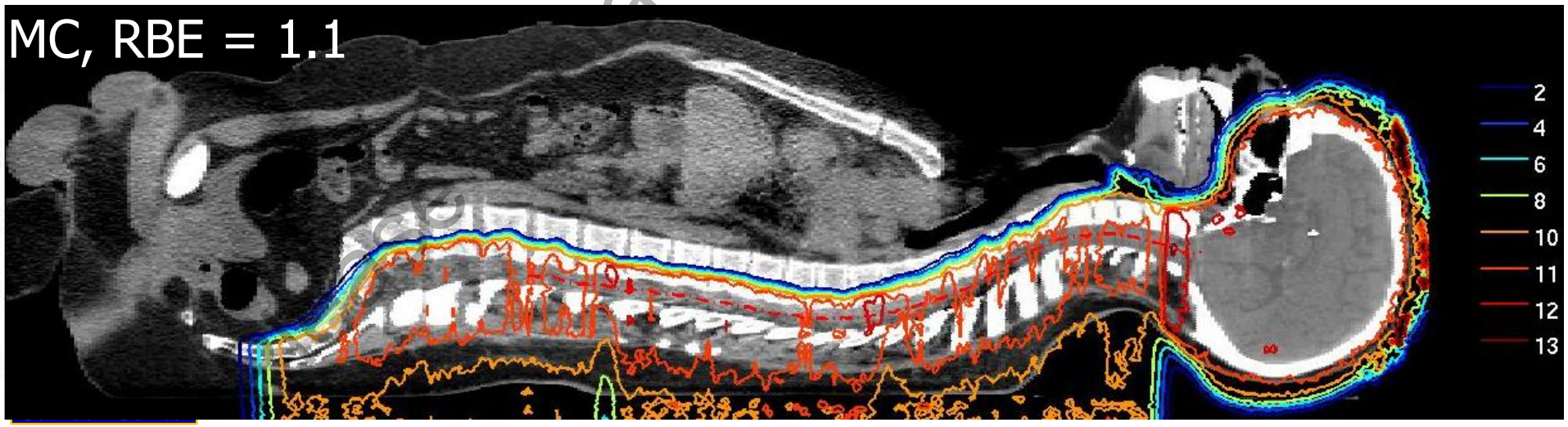
CSI – Spine Injury Treatment fields



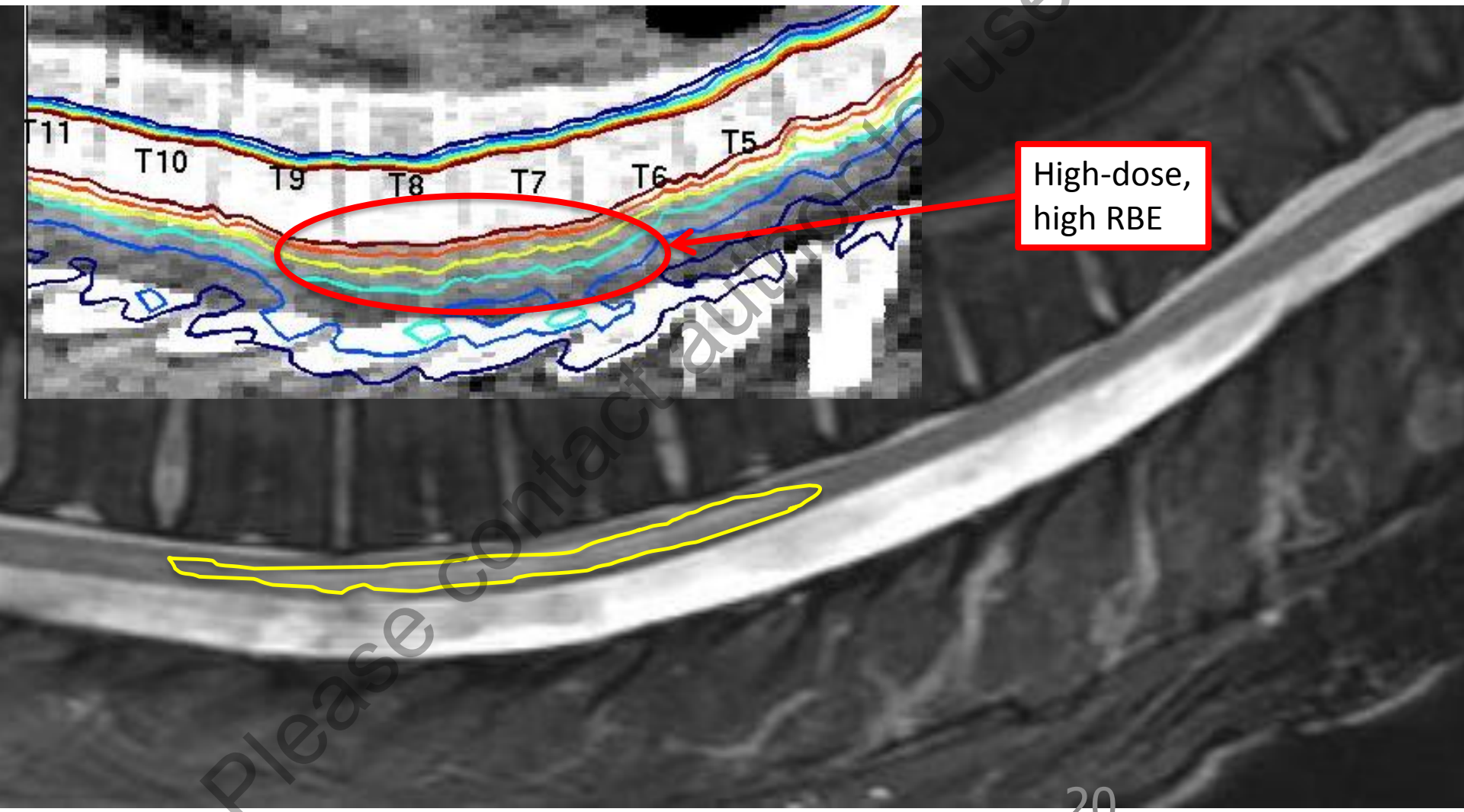
Plan A


Eclipse, RBE = 1.1
2
4
6
8
10
11
12


Dose (Gy[RBE])
14
12
10
-300
-200
-100
0
100
200
300
Eclipse
MCNPX


MC, RBE = 1.1
2
4
6
8
10
11
12
13

Post treatment MRs



Possible Factors

- Hot spots obscured by insufficient accuracy of computed dose: ~8%
- Fractionation strategy (shifting of junctions every 5 or six fractions instead of every day): 5 - 10%
  - Higher complexity of double strand breaks and greater repair half time of spinal cord for protons
- Variable RBE: 5 – 10%
- Intensive chemotherapy
- …

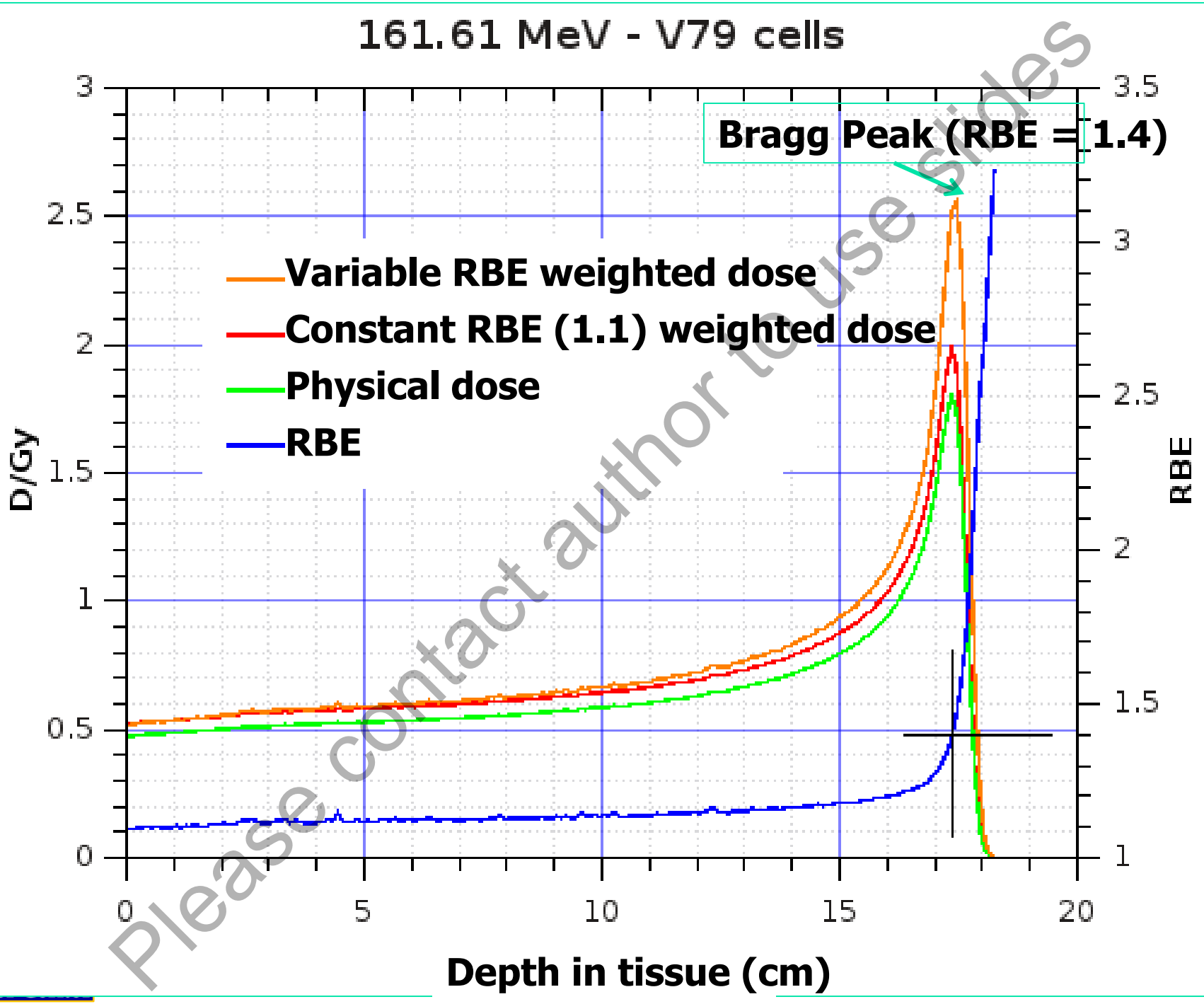
Insistence on the use of RBE of 1.1 seems to be crumbling - finally

Consideration of Variable RBE in Evaluation of Proton Dose Distributions

To explain unforeseen toxicities and recurrences

Consideration of Variable RBE in Optimization of IMPT Dose Distributions

For safer and clinically advantageous dose distributions

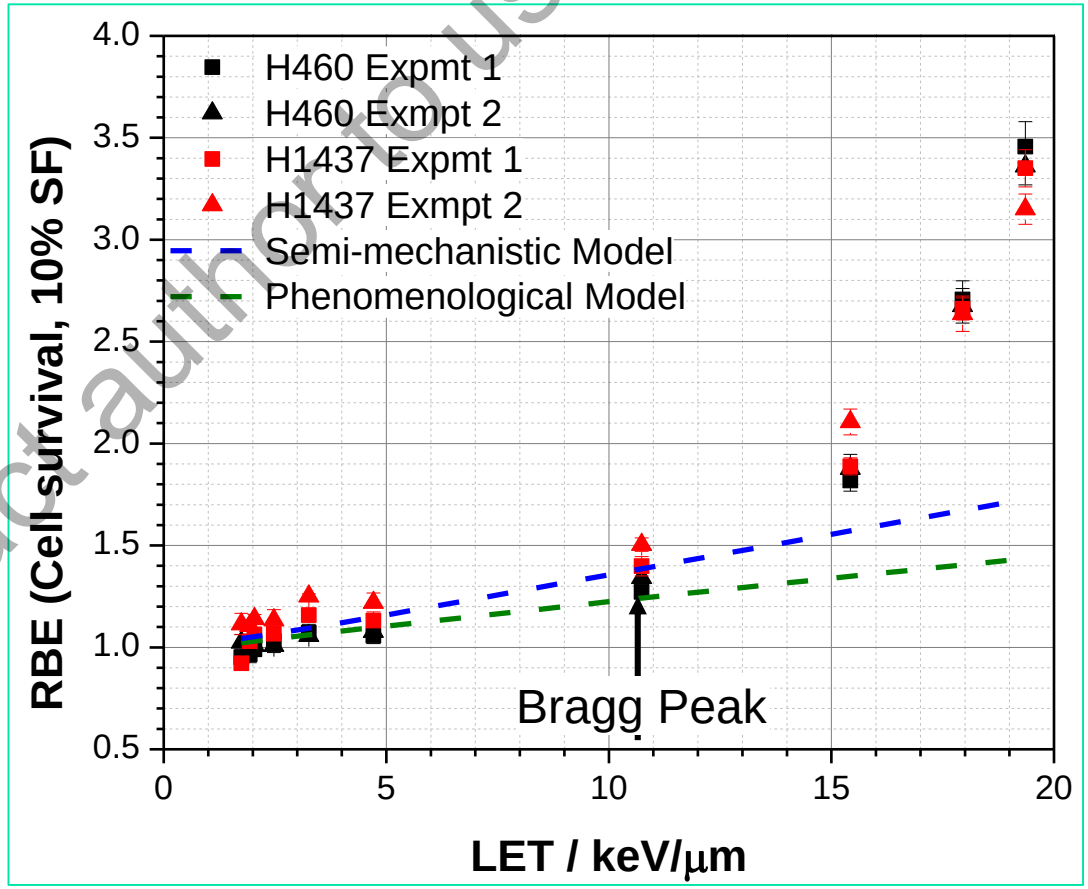


IMPT Based on Variable RBE

- **Different approaches to defining optimization criteria (plan score function) in terms -**
  - **Variable RBE-weighted dose**
  - **Biological effect (e.g., using LQ model)**
- **RBE or biological effect computed using available models**

Current Approach at MDACC

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



The Phenomenological RBE model

The biological effect described by linear-quadratic (LQ) model

$$SF = \exp(-\alpha D - \beta D^2).$$

Biological effect $\mathcal{E} = -\ln(N/N_0) = \alpha D + \beta D^2$

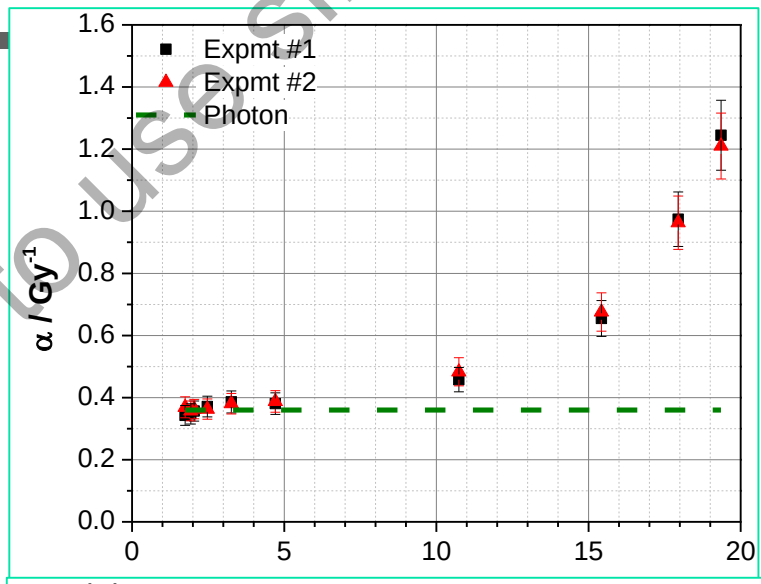
A Reference radiation (photons) α_x and β_x, and a proton beam α_p and β_p, RBE = D_x / Dp

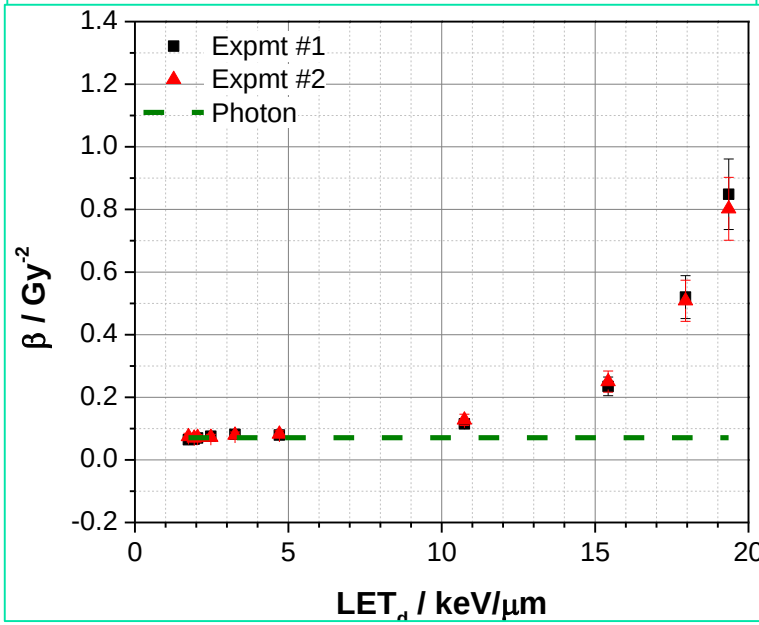
$$\mathrm{RBE}(D_p, \alpha_x, \beta_x, \alpha_p, \beta_p) = \frac{\sqrt{\alpha_x^2 + 4\beta_x D_p(\alpha_p + \beta_p D_p)} - \alpha_x}{2\beta_x D_p}.$$

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

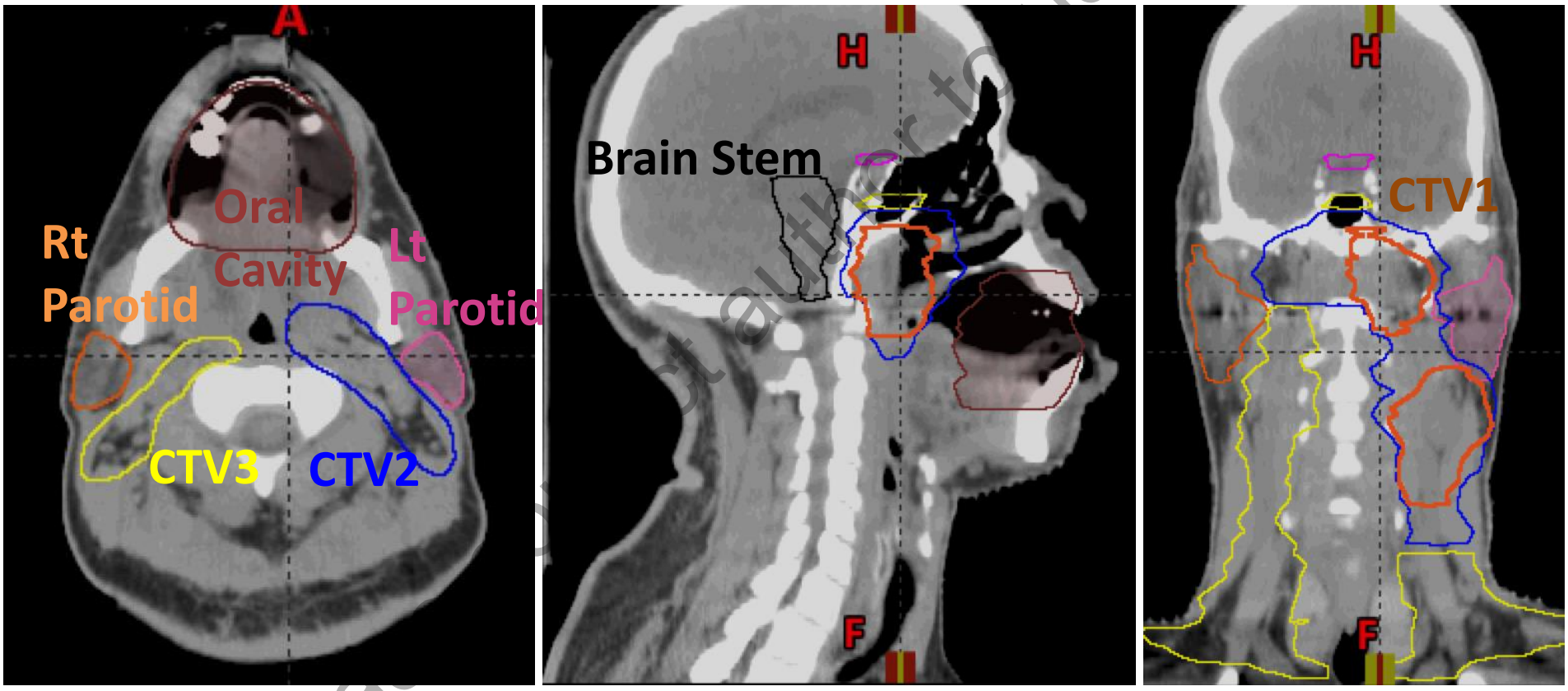
L = Dose-averaged LET

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





IMPT Optimized Using Variable RBE
Head and Neck Example



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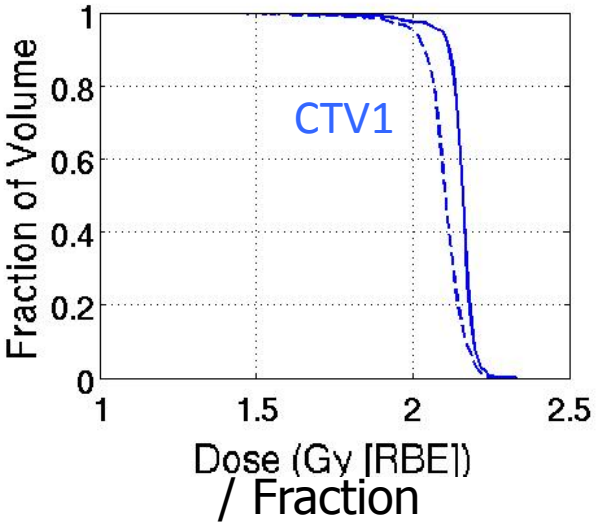
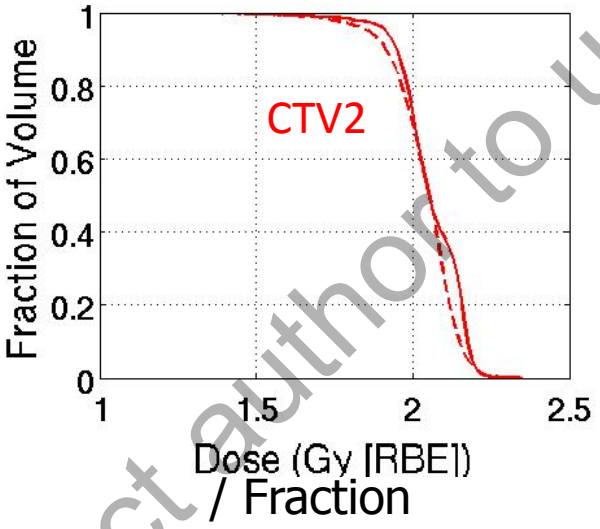
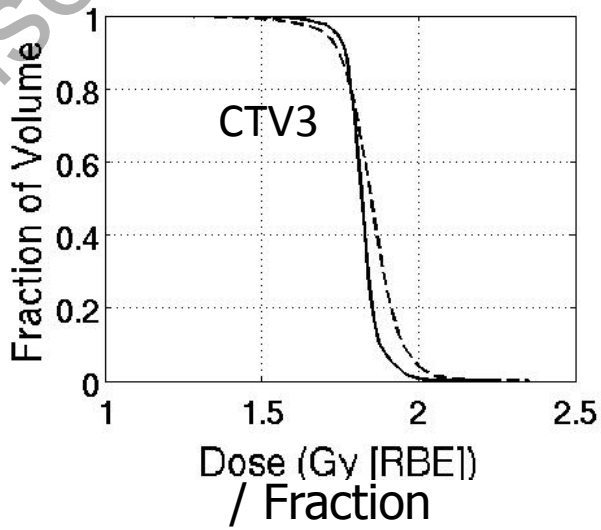
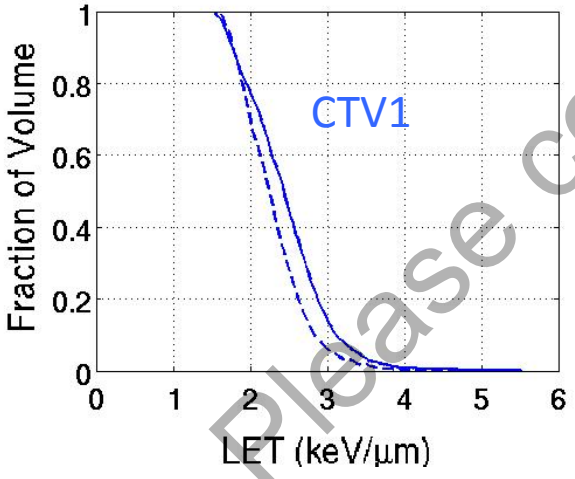
IMPT Plans Recalculated Using Variable RBE

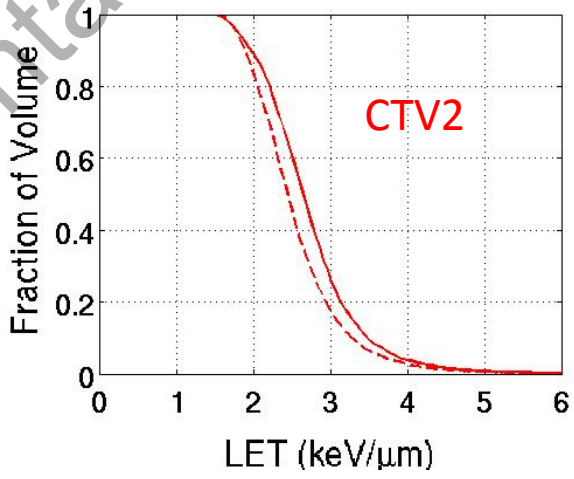
Variable RBE optimization — — — Fixed RBE optimization

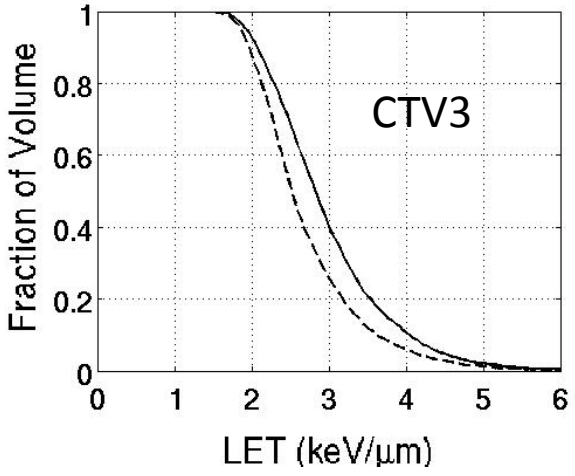




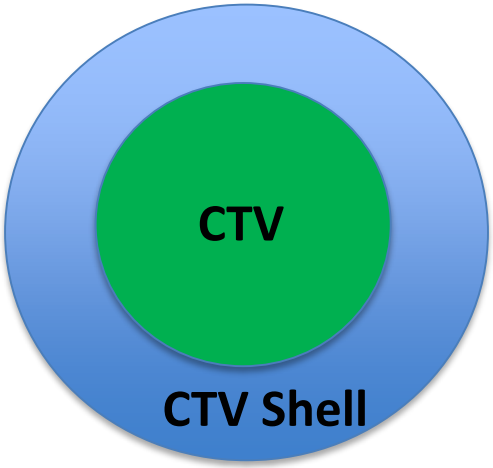


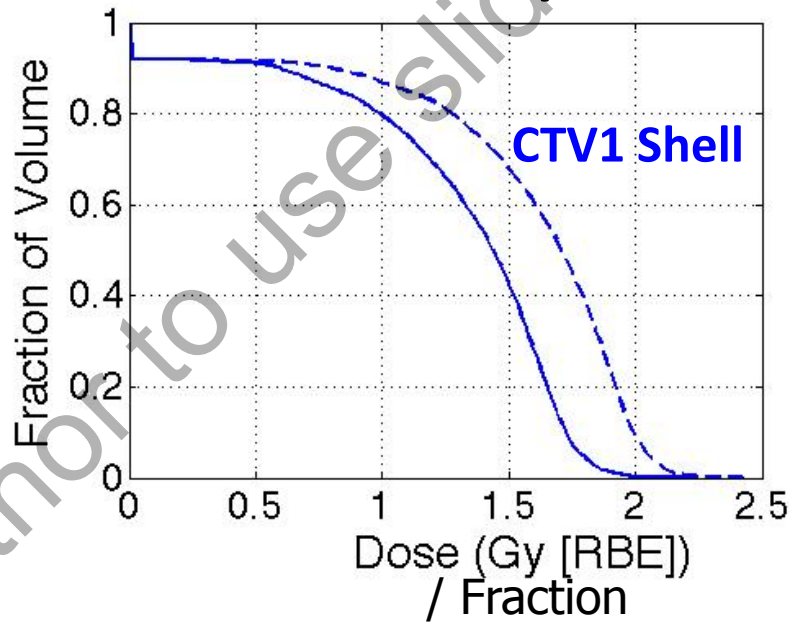


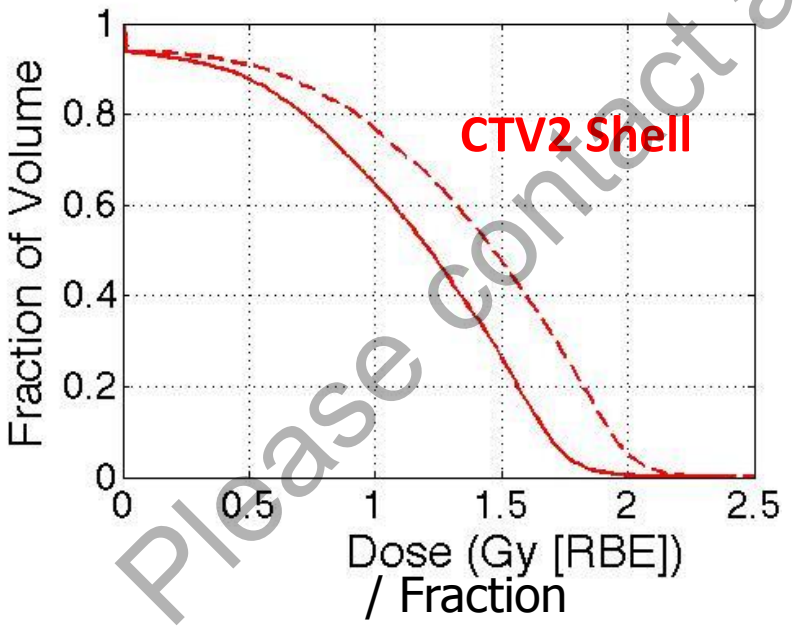


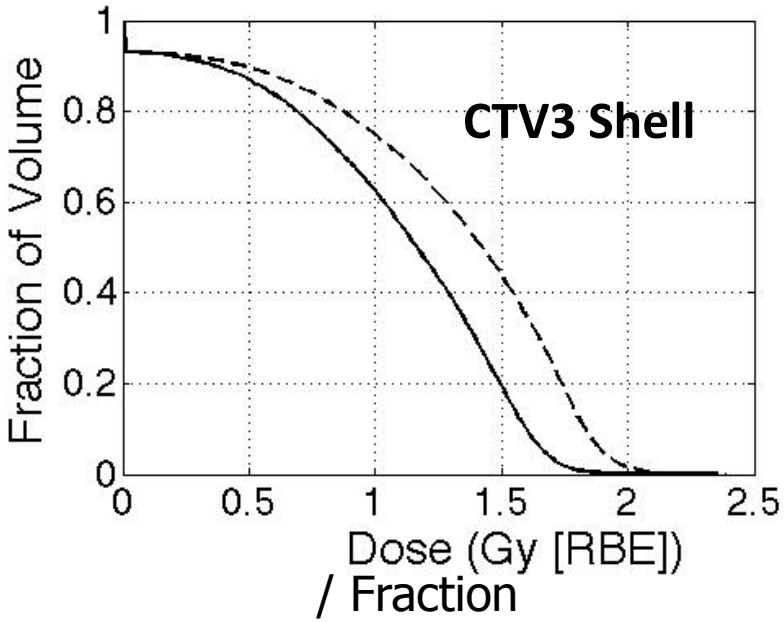


——— Variable RBE optimization – – – – Fixed RBE optimization



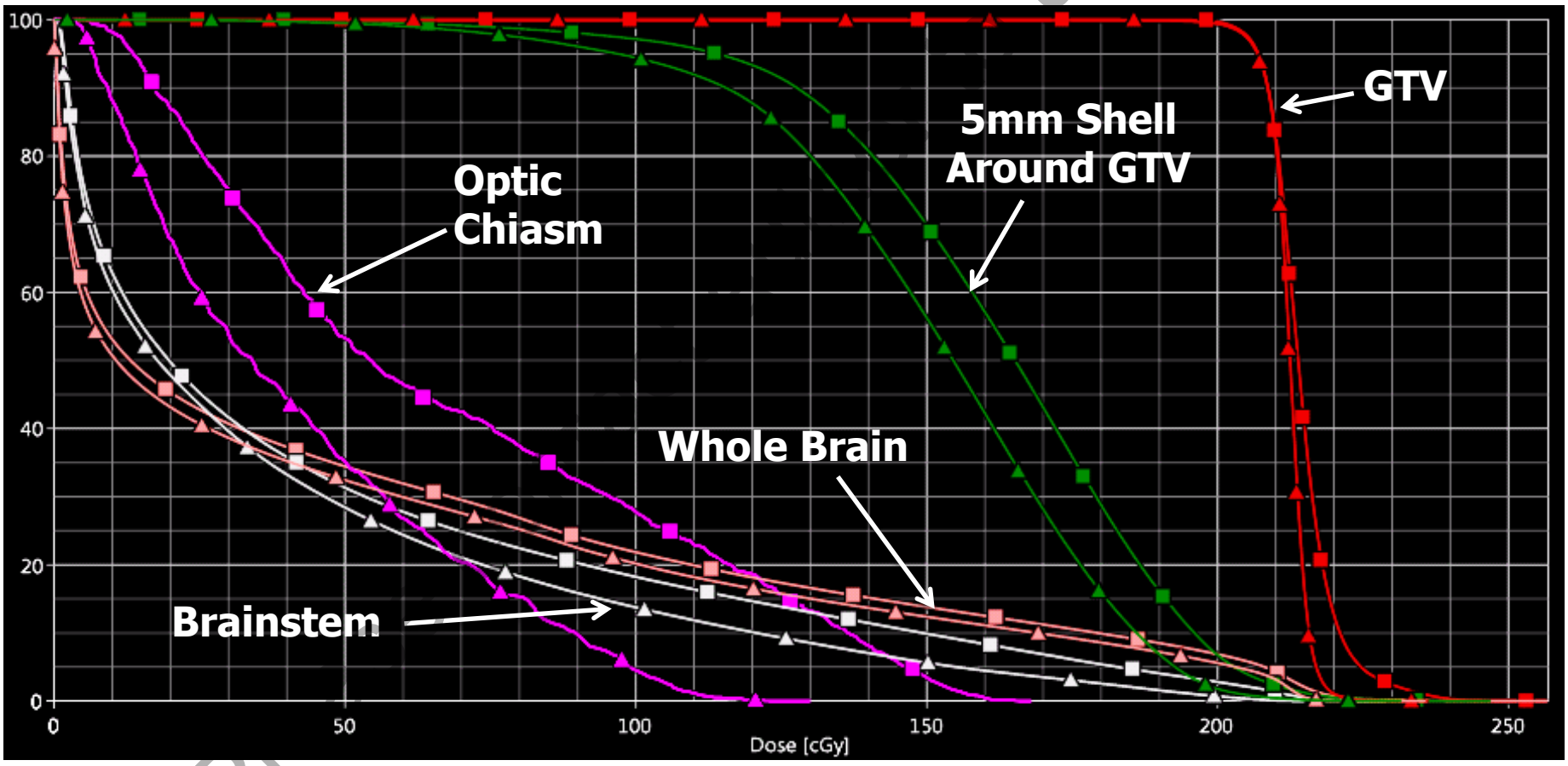






Brain Tumor Example (variable RBE weighted dose)

Squares: Constant RBE Opt. **Triangles: Variable RBE Opt.**



Limitations of Current Proton RBE Models

- **Assumption of RBE as linear (or near linear) function of LET**
- **LET dependence on averaged dose of fluence**
- **Insufficient experimental data**

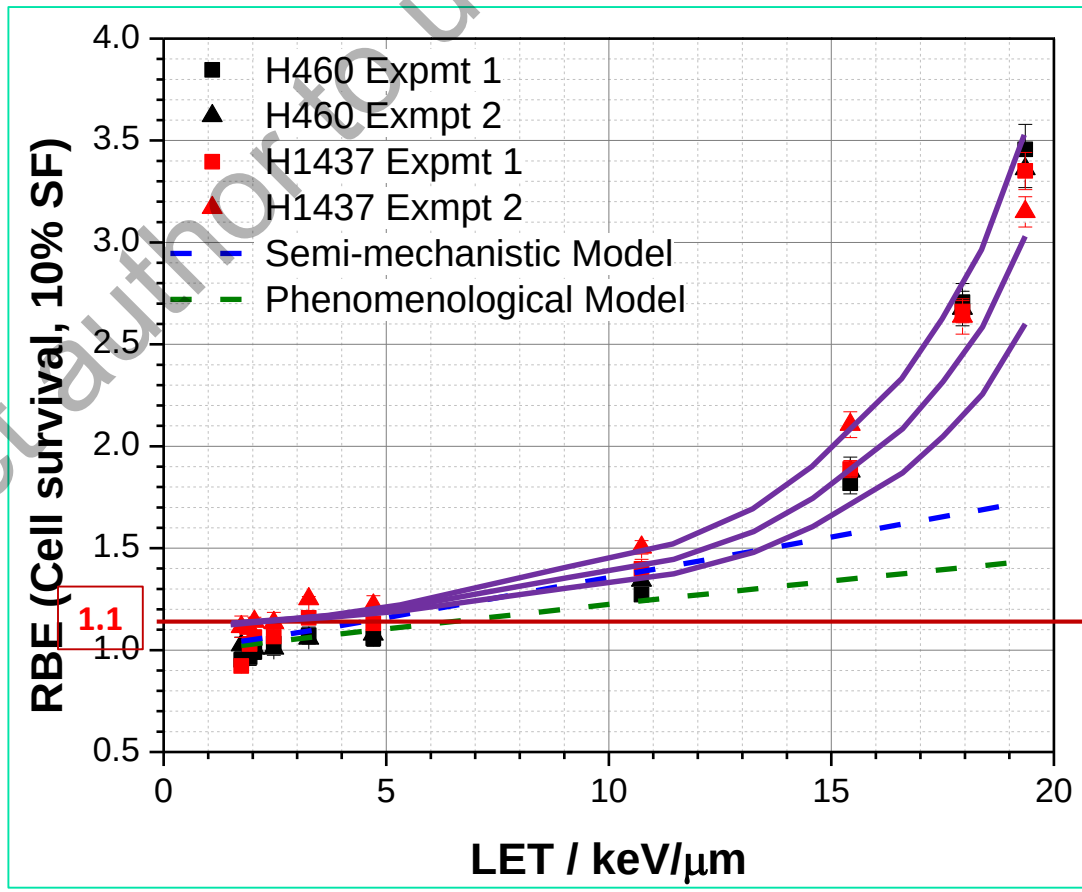
Current Models Likely Underestimate RBE

Summary

- 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

Summary

- **If concerned -**
  - **Renormalize to achieve no less dose to target and no more dose to normal tissues than achieved with RBE = 1.1**
  - **Increase to max RBE in small steps**



Future Research

- Improvements in models
  - Incorporate non-linearity of alpha and beta as functions of LET
- Experimental acquisition of more in-vitro and in-vivo data
- Derivation RBE as a function of dose and LET from clinical data
  - Image-biomarkers
  - Treatment response
- Application in a GBM trial

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- Uwe Titt, PhD
- Pablo Yepes, PhD

- NCI P01 and U19 CA021239

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

Albert Einstein

Thank You