Clinical considerations of RBE in proton therapy

MASSACHUSETTS GENERAL HOSPITAL
RADIATION ONCOLOGY

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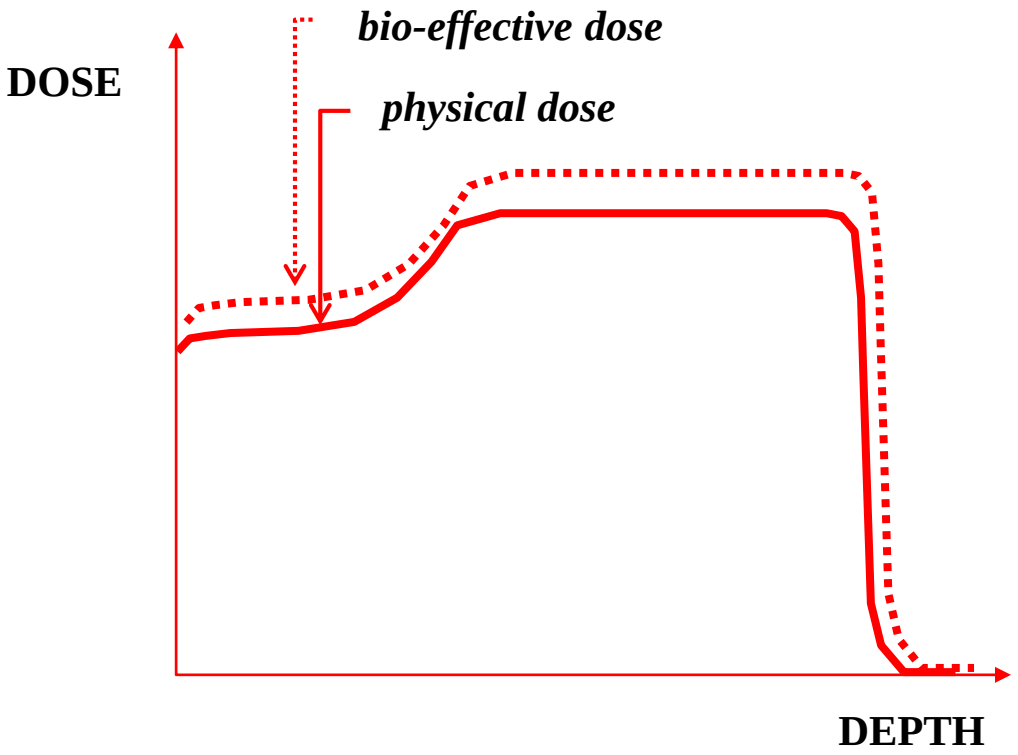
Why do we need the RBE concept in clinical proton therapy ?

- When using different modalities one has to consider the difference in biological effectiveness because prescriptions are based on dose (physics), not outcome (biology; tumor control probability (TCP) or normal tissue complication probability (NTCP)).
- We do not have proton specific dose-response curves (such as Quantec for photons) and as proton doses are more heterogeneous in organs at risk, it might be more realistic to rely on photon doses translated into equivalent uniform doses responses.

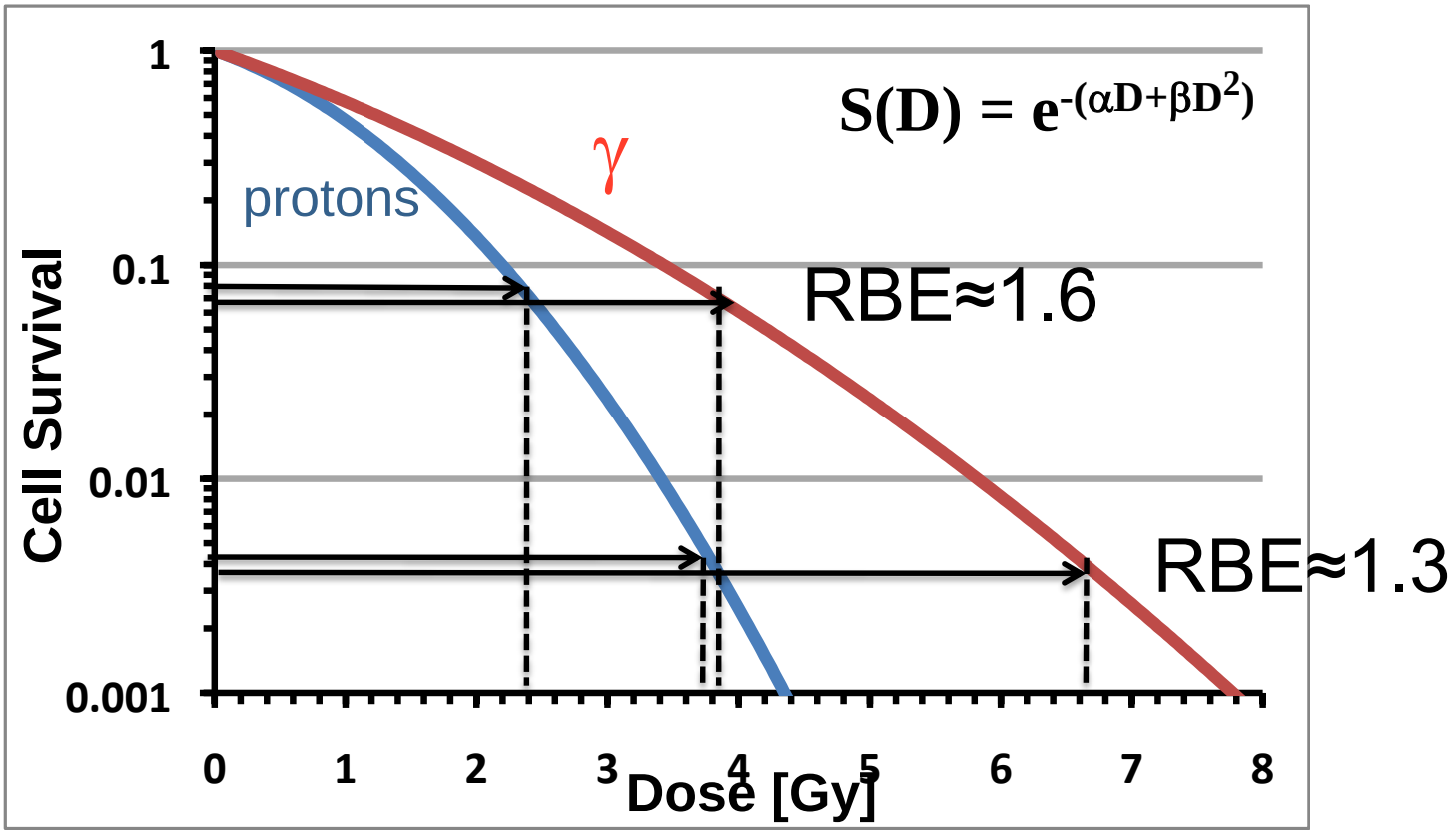
The current clinical practice is the use of an RBE = 1.1



Why do we need the RBE concept in clinical proton therapy ?

What can we expect in terms of RBE variations in patients ?

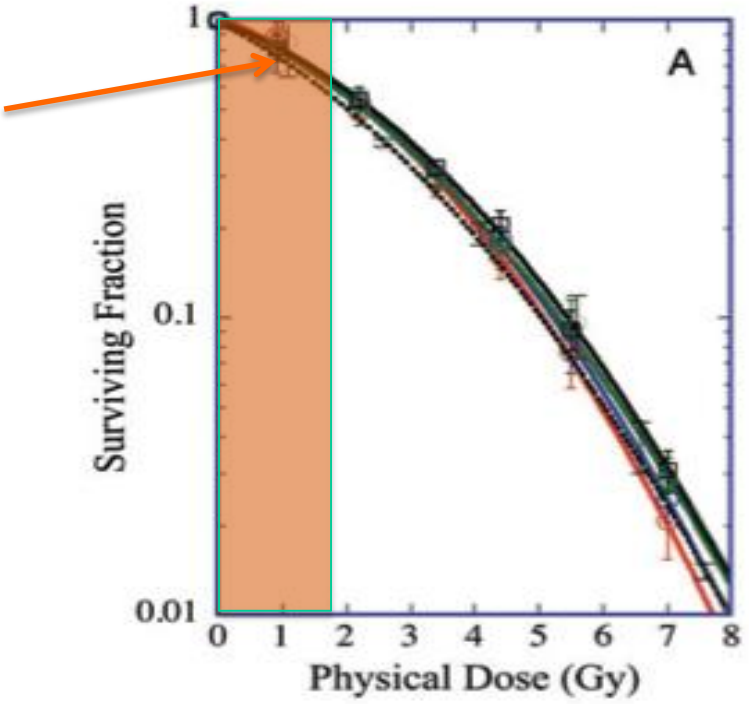
The RBE is expected to decrease with increasing dose



$$RBE\left[L, d_H, (\alpha/\beta)_L\right] = \frac{\sqrt{\left((\alpha/\beta)_L\right)^2 + 4(\alpha/\beta)_L RBE_{\max} d_H + 4RBE_{\min}^2 d_H^2} - (\alpha/\beta)_L}{2d_H}$$

Prescription doses are typically 2Gy/fraction
Precise measurements of cell survival below 2 Gy are sparse.

hypersensitivity,
adaptive response,
… ?



Aoki-Nakano et al. J Rad Res 2014

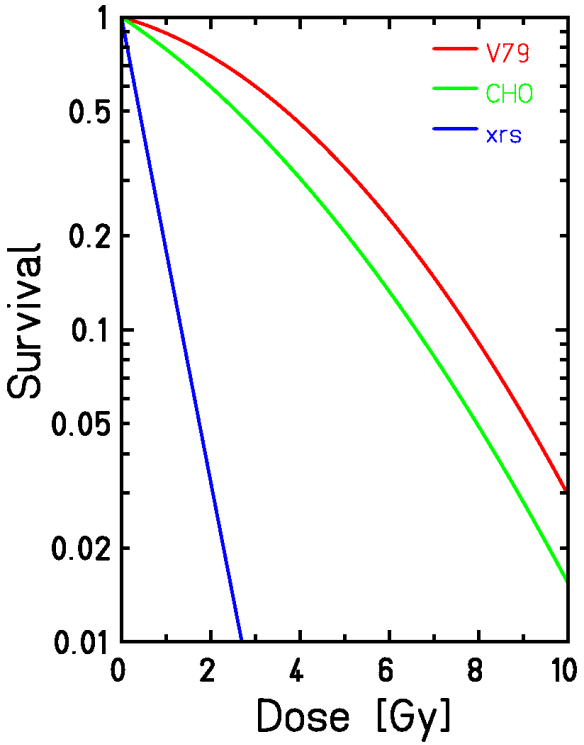
There are only a few data points regarding dose dependency of RBE in vivo below 4 Gy !

The RBE is expected to decrease with increasing α/β

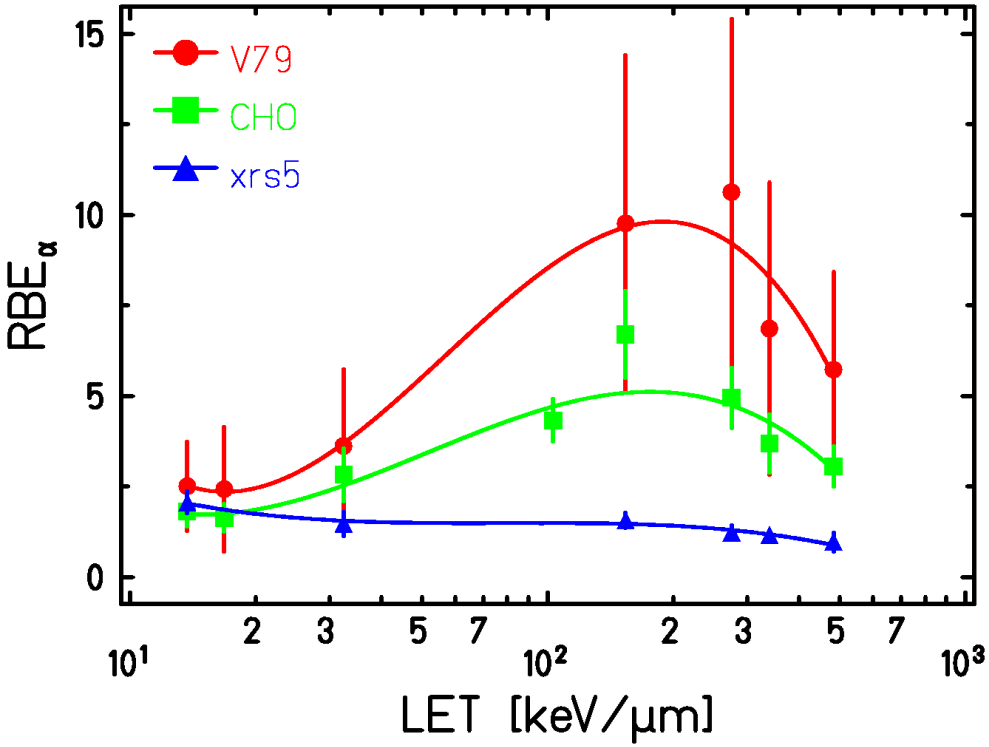
$$S(D) = e^{-(\alpha D + \beta D^2)}$$

Cells with higher repair capacity (low α/β) show a higher RBE

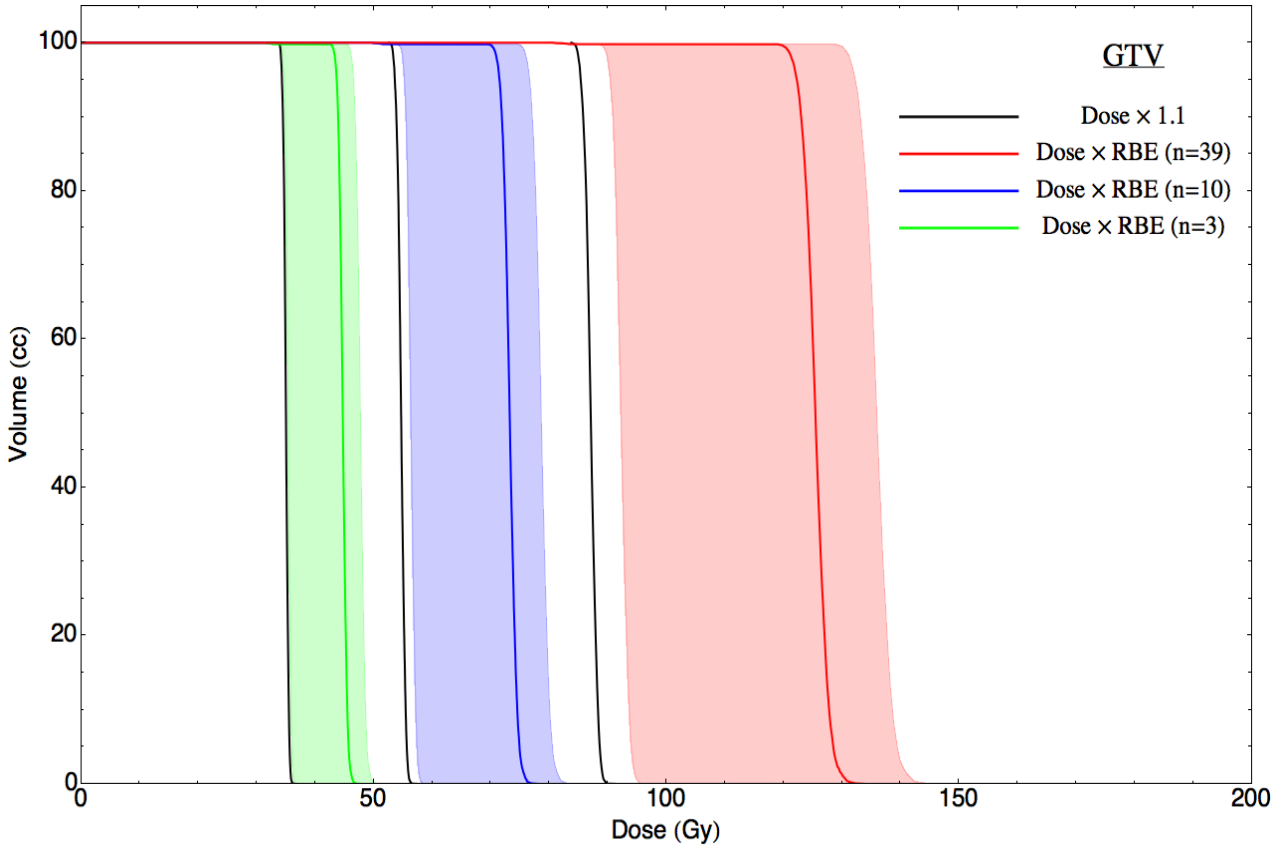
Photons



Carbon ions



Uncertainties due to α/β uncertainties (e.g. prostate)



A Carabe, S España, C Grassberger, H Paganetti: Phys Med Biol 2013 58: 2103-2117

What are the relevant experimental data to define an RBE for a clinical endpoint?

- Tumor control probability: Cell survival
- Normal tissue complication probability: ???

RBE for normal tissue complication probability (NTCP)

Effect of interest (organ level):

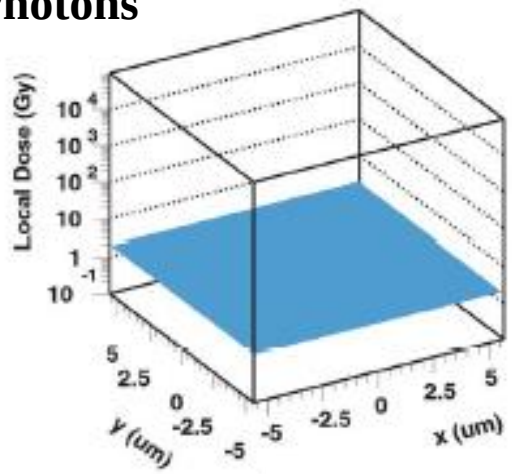
- early effects such as erythema
- late effects such as lung fibrosis, lung function, spinal cord injury, or necrosis

Typically measured (cellular level):

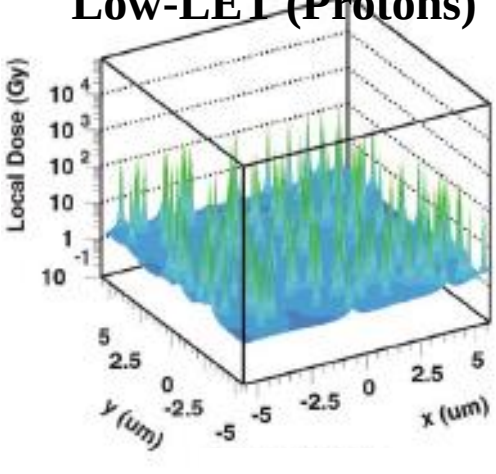
- Double-strand break induction
- Foci formation
- Chromosome aberrations
- Micronuclei formation
- Cell cycle disruption …

The RBE is expected to increase with increasing LET

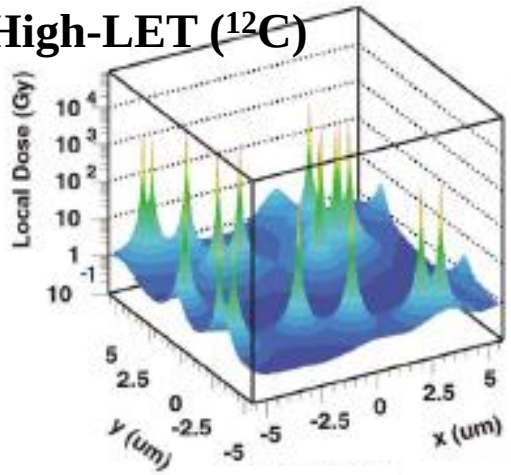
Photons



Low-LET (Protons)

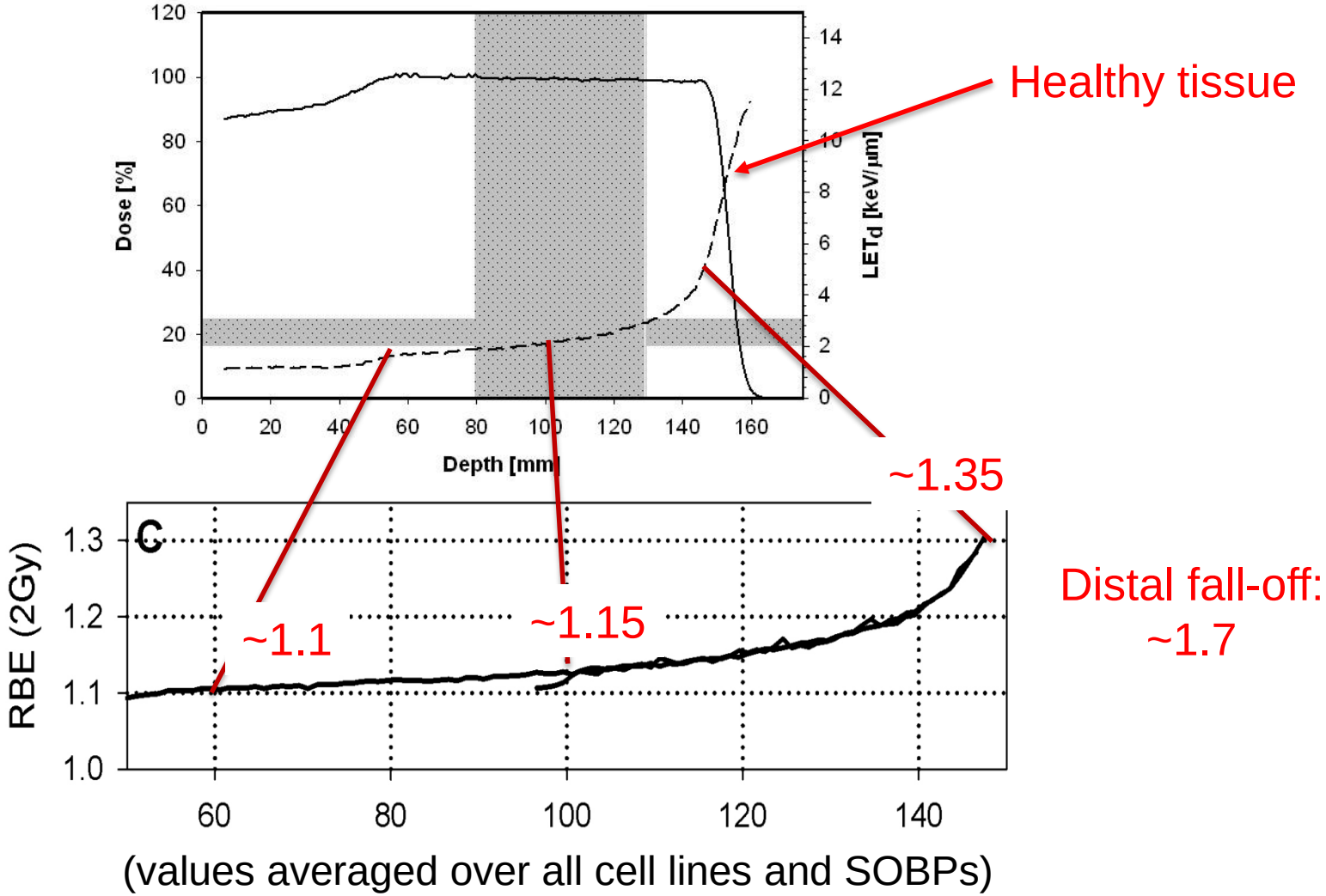


High-LET (^{12}C)



M. Krämer et al.:
Techn. Cancer Res. Treatm. 2, 427-436, 2003

Radiation is more effective when energy depositions are more concentrated in space



1.1 is a conservative estimate!

Paganetti H: Phys Med Biol 2014 59: R419-R472

IOP Publishing | Institute of Physics and Engineering in Medicine
Physics in Medicine & Biology
Phys. Med. Biol. 60 (2015) 8399–8416
doi:10.1088/0031-9155/60/21/8399

The RBE as a function of dose, LET and α/β

A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published *in vitro* cell survival data

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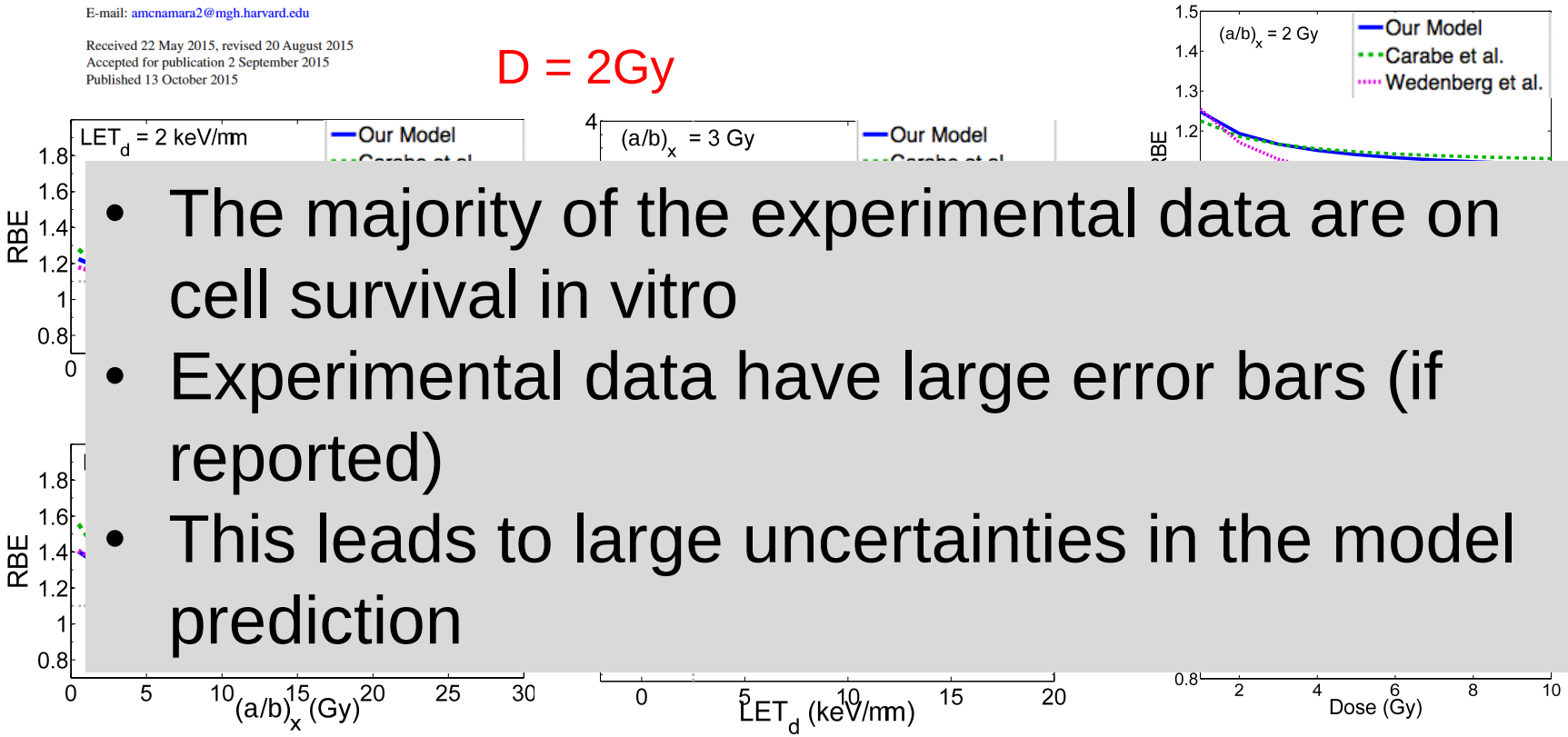
D = 2Gy



- The majority of the experimental data are on cell survival in vitro
- Experimental data have large error bars (if reported)
- This leads to large uncertainties in the model prediction

LET_d = 2.5 keV/µm

Why do we need the RBE concept in clinical proton therapy ?

What can we expect in terms of RBE variations in patients ?

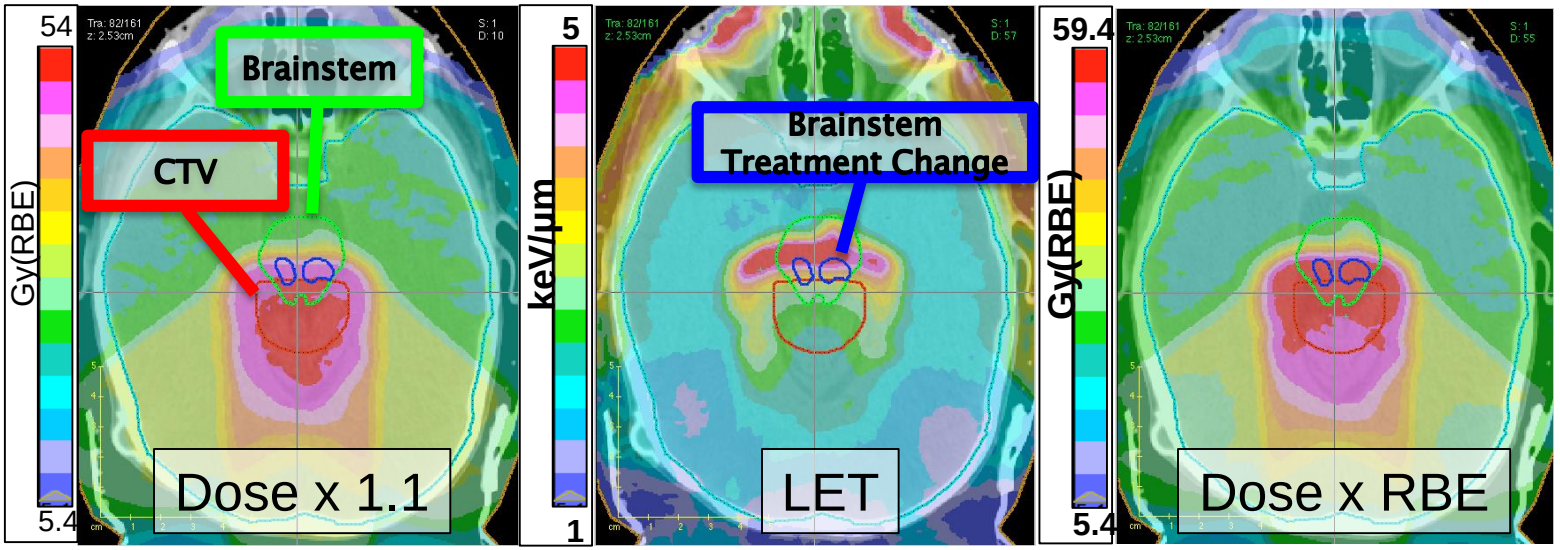
Is there clinical evidence that it matters ?

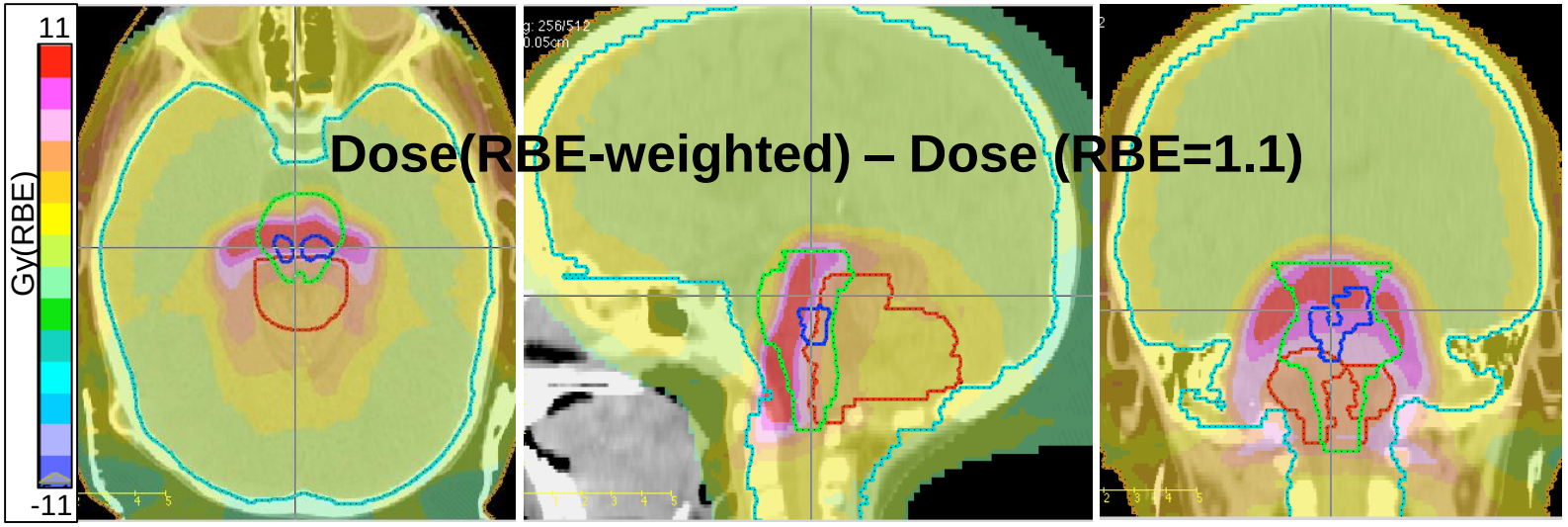
Evidence 1 (?):

Lung density changes following chest RT

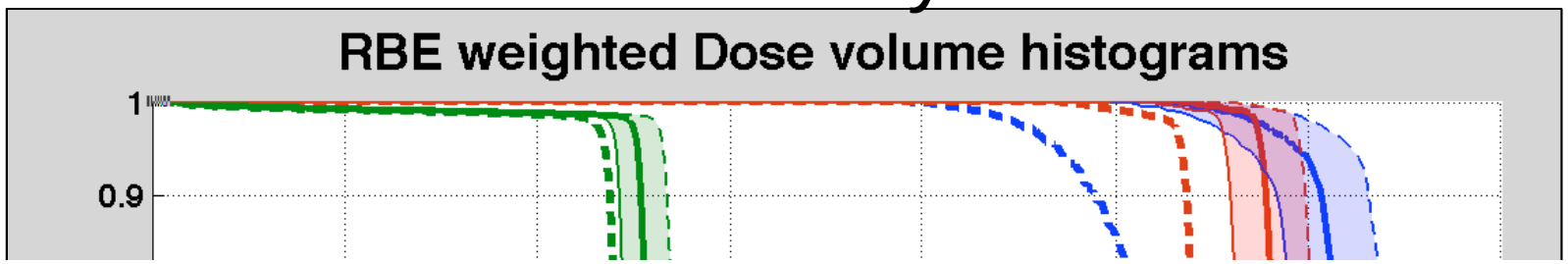
Tracy Underwood

Evidence 2 (?): Radiographic (MRI) tissue changes (e.g. necrosis)





Correlation of toxicity and LET

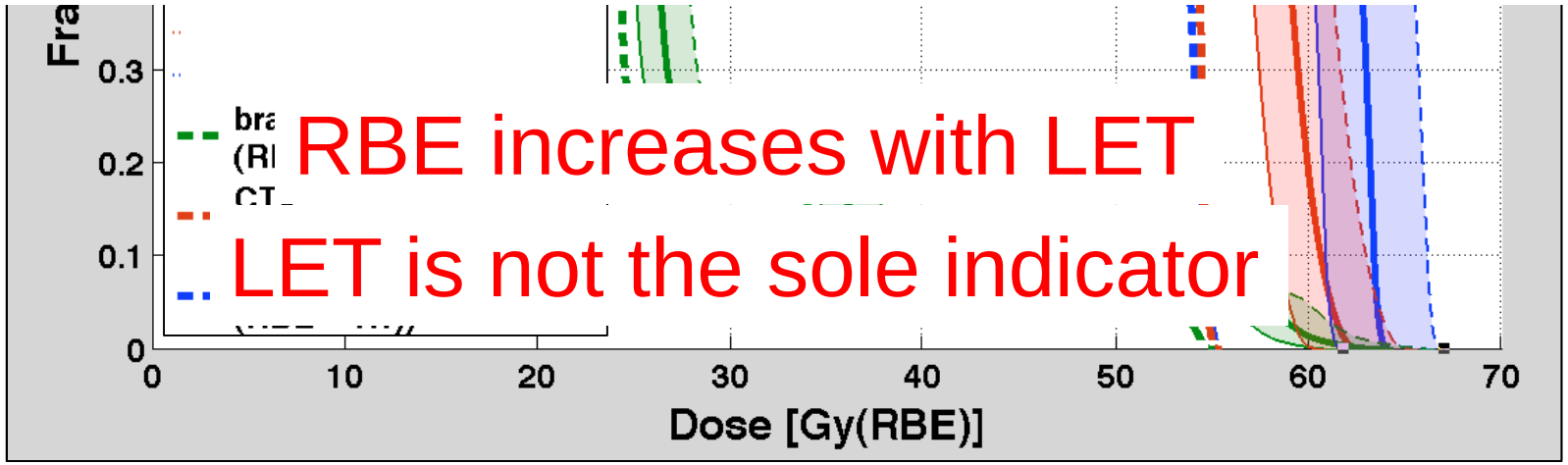


Note:

All 119 cases had similar LET distributions

Only 4 with symptomatic treatment change

Only 1 symptomatic change correlated with LET



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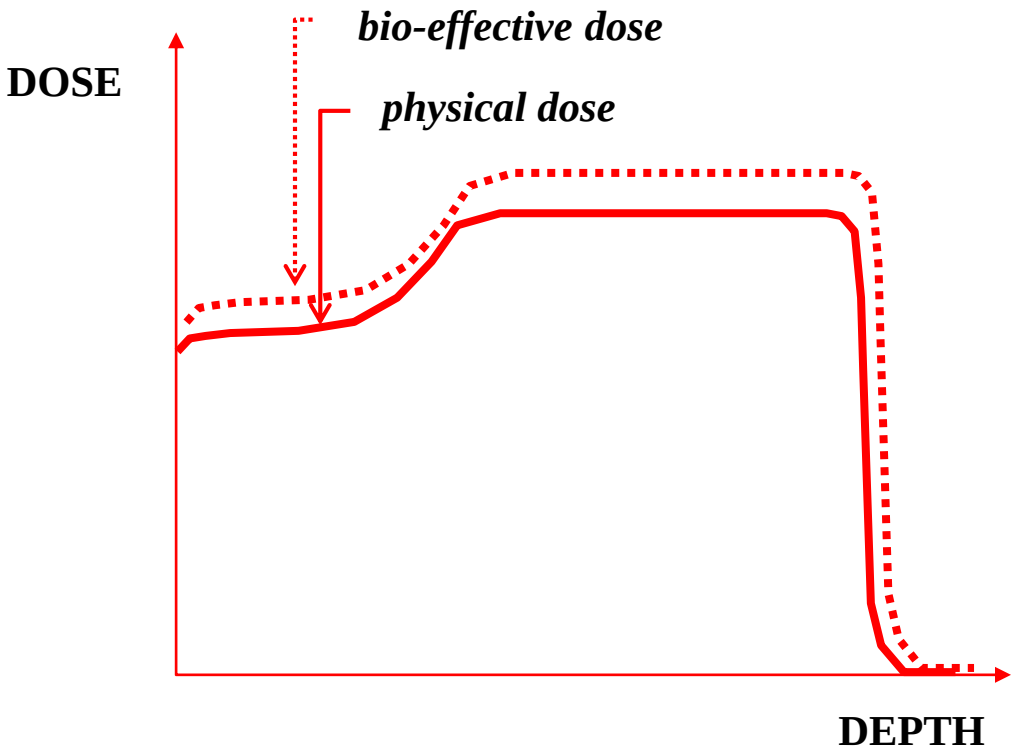
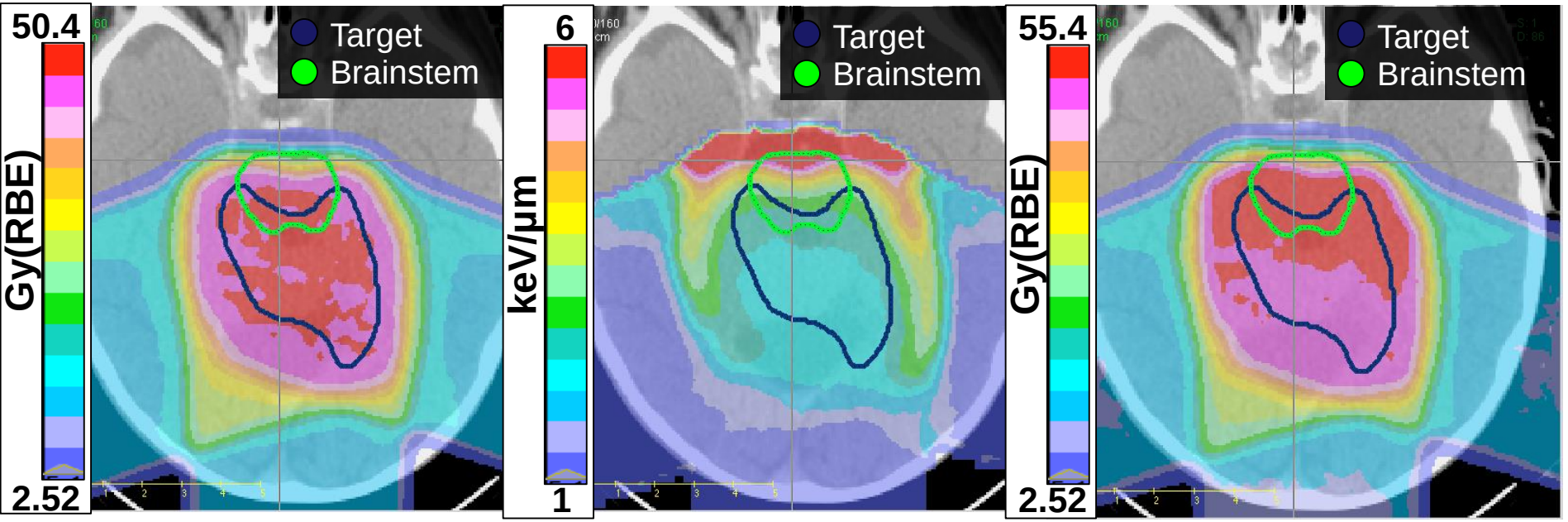


Variable RBE values are considered in a non-quantified way similar to range uncertainties

Example 1: RBE concerns for the brainstem for ependymoma

Planning technique maximizing target conformality

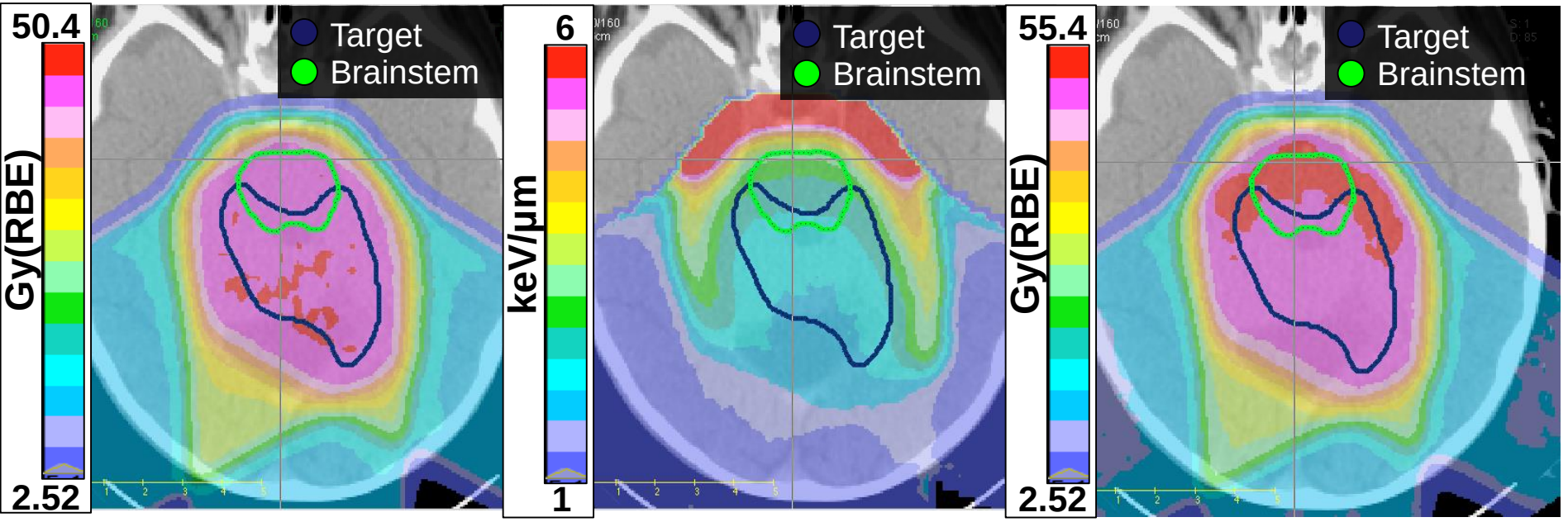


Dose x 1.1 LET Dose x RBE

Giantsoudi, Adams, Shannon, Paganetti: Proton Treatment Techniques for Posterior Fossa Tumors: Consequences for LET and Dose/Volume Parameters for the Brainstem and Organs at Risk. Int J Radiat Oncol Biol Phys 2016 in press

Example 1: RBE concerns for the brainstem for ependymoma

Planning technique minimizing maximum LET in the brainstem



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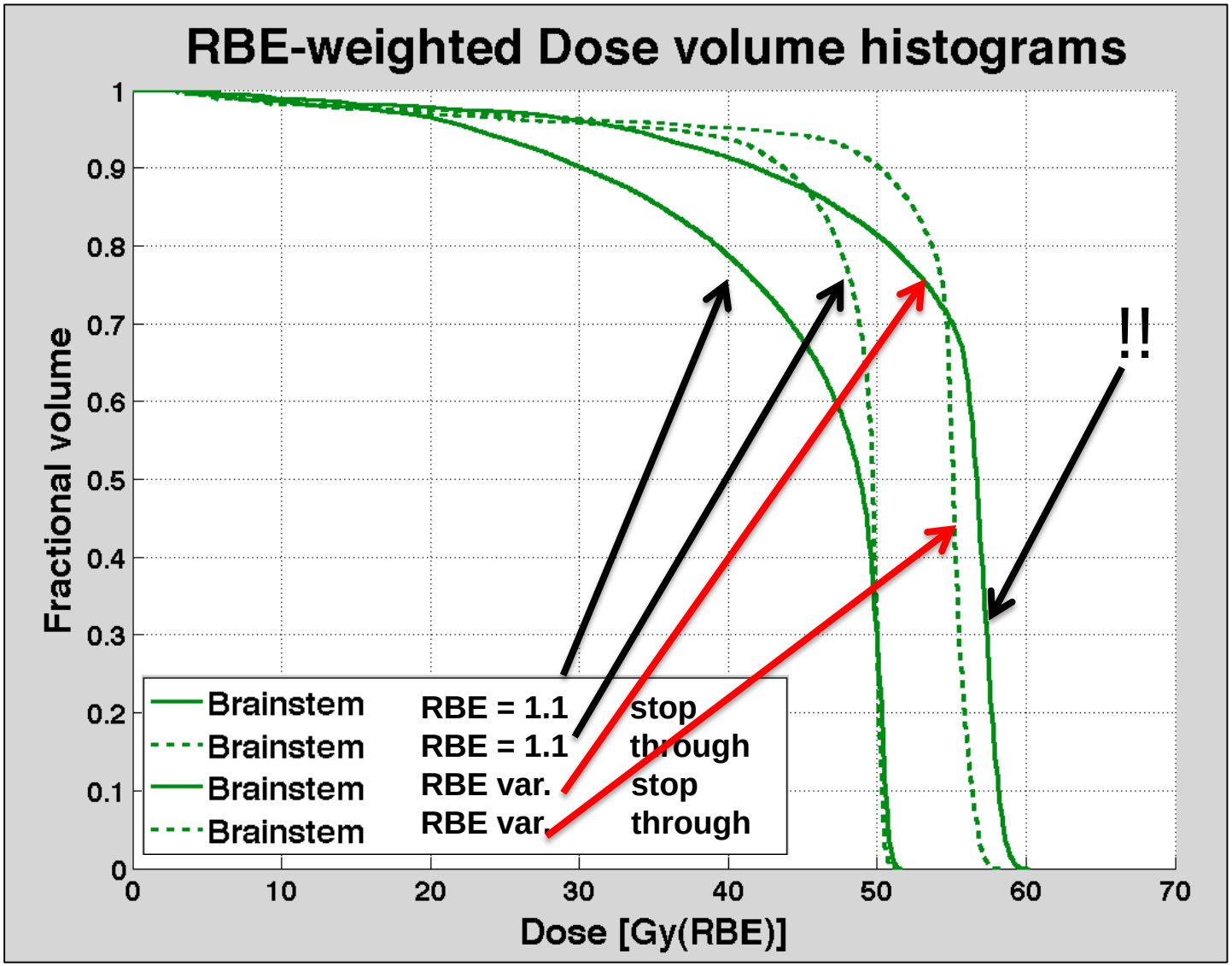

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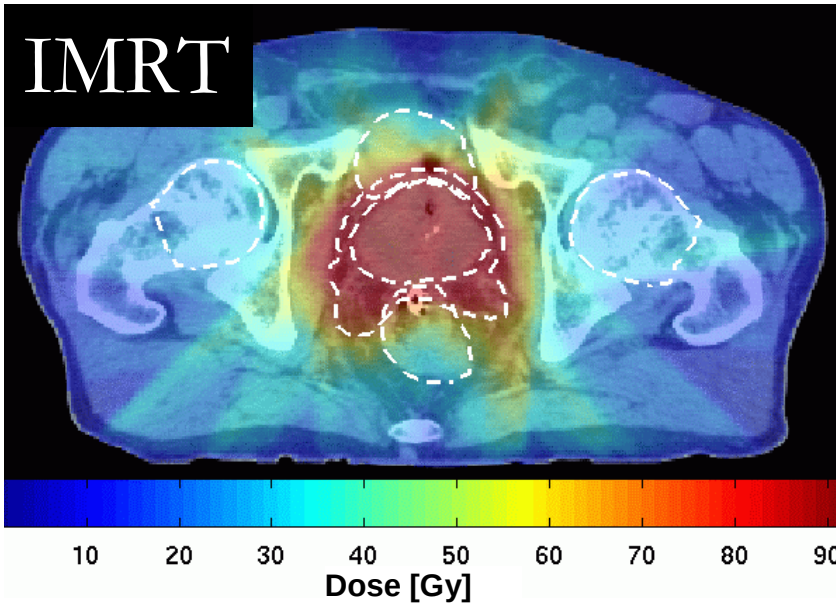
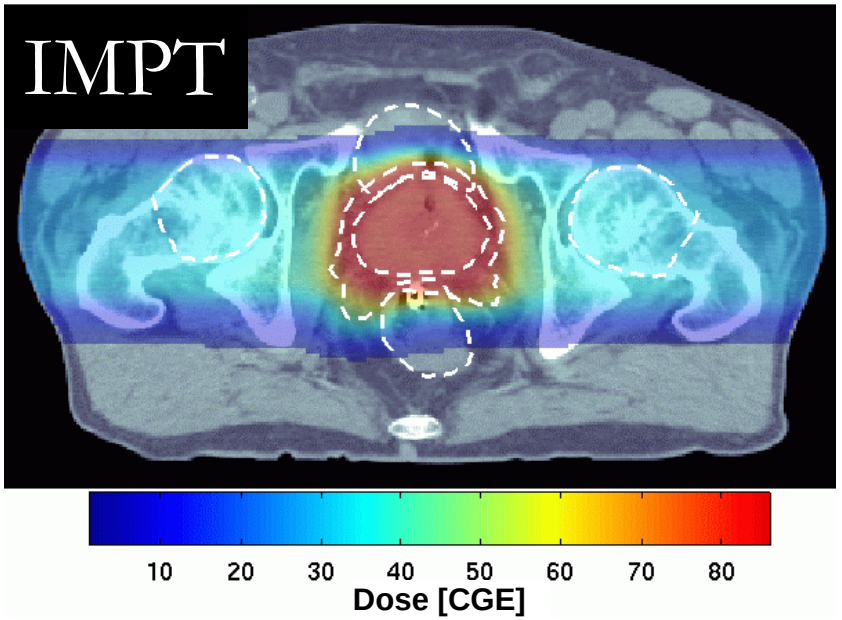
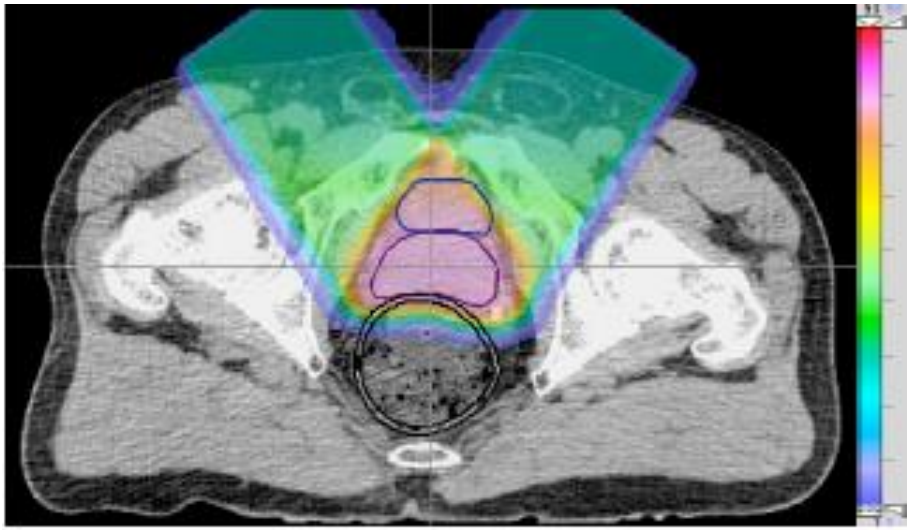
Example 2: RBE concerns for the rectum in prostate cancer







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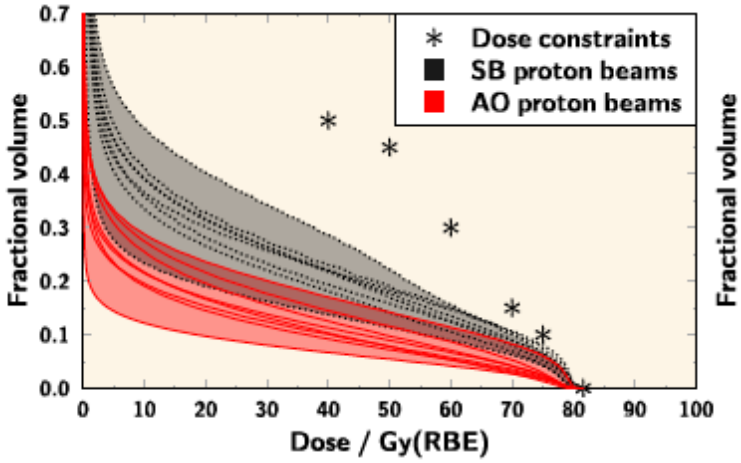
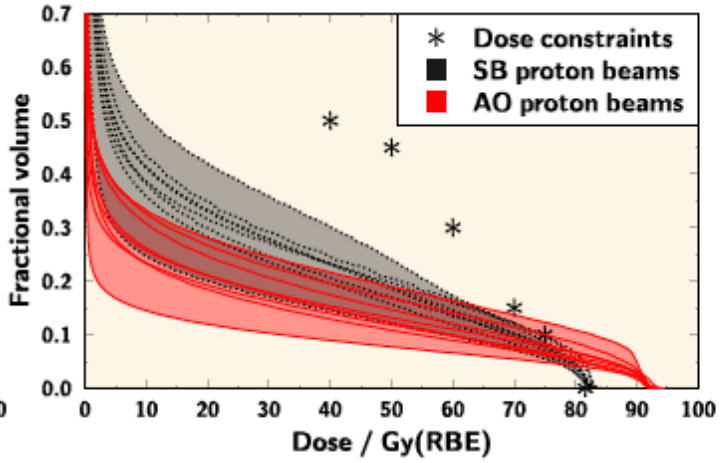
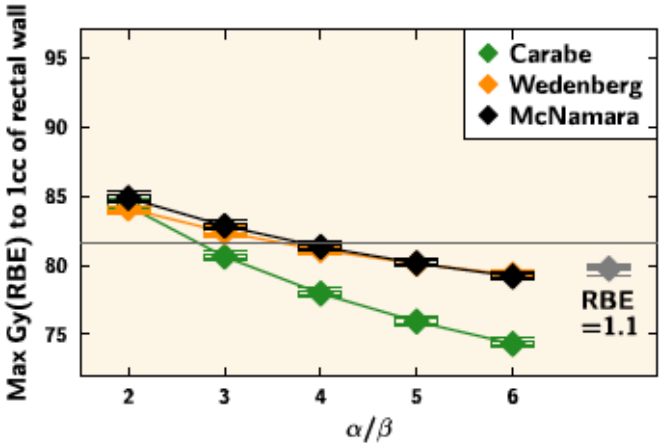
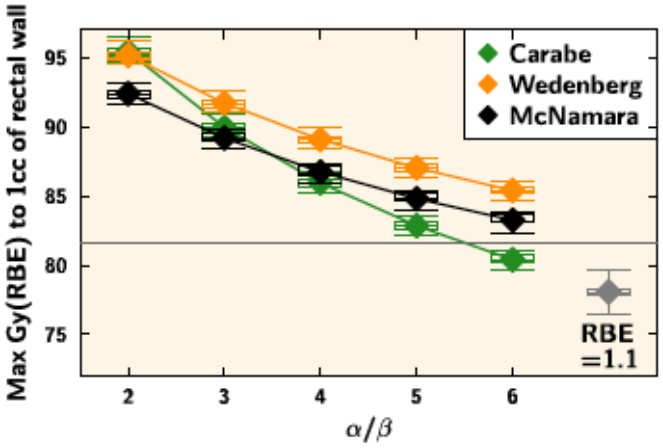




DVH data for eight patients showing rectum dose assuming RBE=1.1 (left) and variable RBE with the Wedenberg model, α/β=3 Gy (right)





Max Gy(RBE) dose to 1cc of the rectal wall. Box and whisker plots for eight patients assuming either RBE=1.1 or variable RBE (three models plus a range of α/β ratios) for SB proton plans (left) and AO proton plans (right)

Why do we need the RBE concept in clinical proton therapy ?

What can we expect in terms of RBE variations in patients ?

Is there clinical evidence that it matters ?

Are we considering potential RBE effects in the clinic ?

Should we do more ?

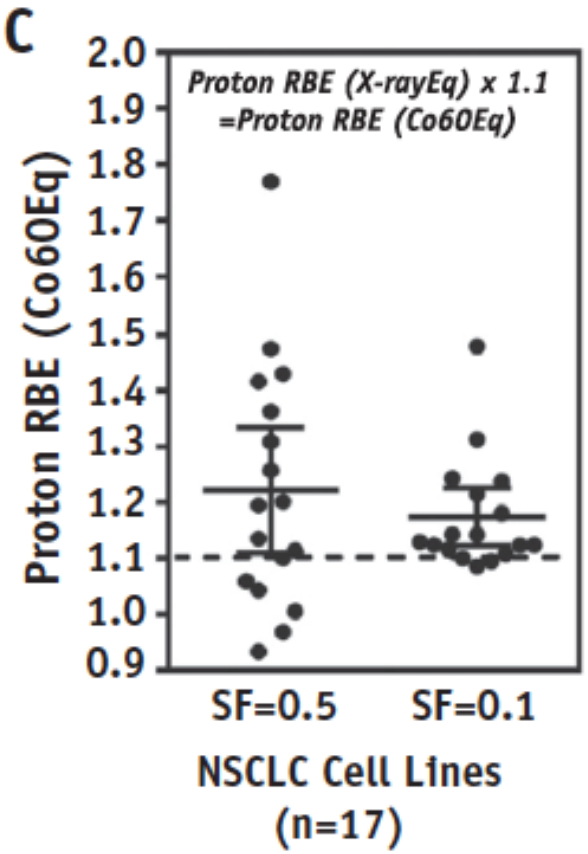
Yes - Example 2: Inter-patient variability

"Links Fanconi Anemia/BRCA pathway defects to elevated proton RBE"

Liu Q et al. Int J Radiat Oncol Biol Phys 2015 91: 1081-1089

"Repair kinetics in HR-deficient cells were significantly delayed after proton irradiation, with elevated amounts of residual gH2AX foci"

Grosse N et al. Int J Radiat Oncol Biol Phys 2014 88: 175-181



Why do we need the RBE concept in clinical proton therapy ?

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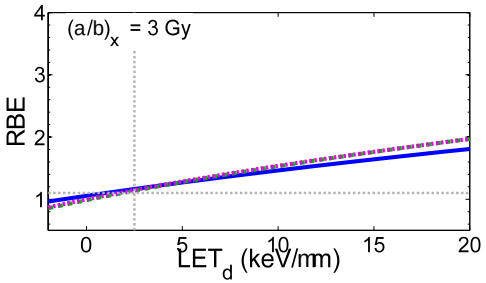
Are we considering potential RBE effects in the clinic ?

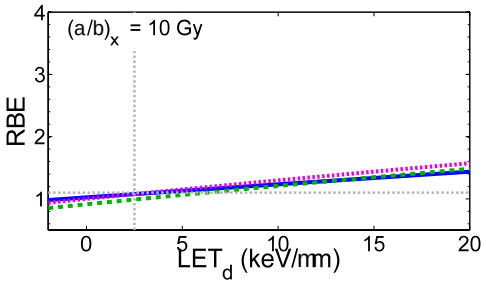
Should we do more ?

Can we do more ?

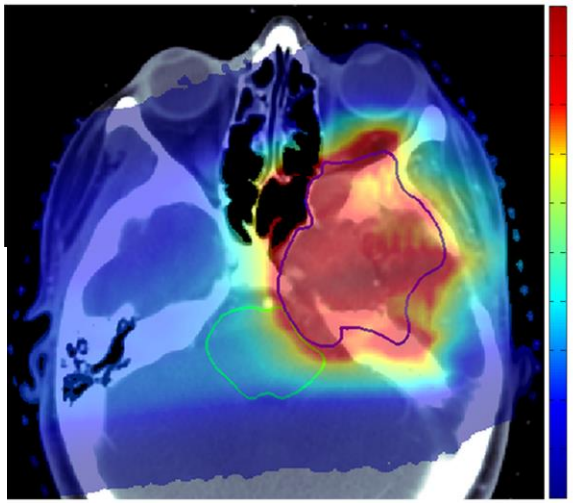
Can we do something without knowing RBE values ?

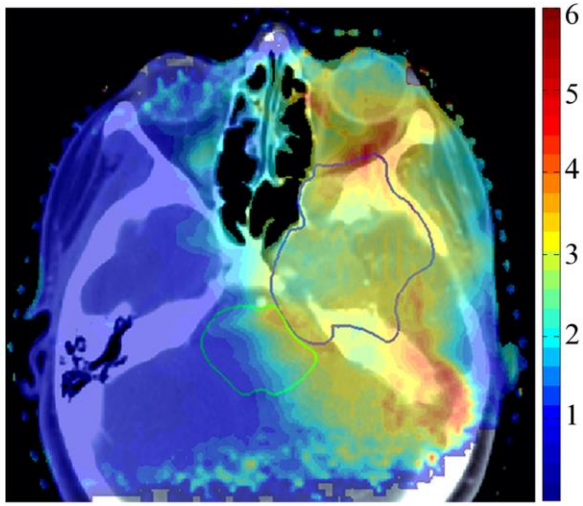
PLAN 1





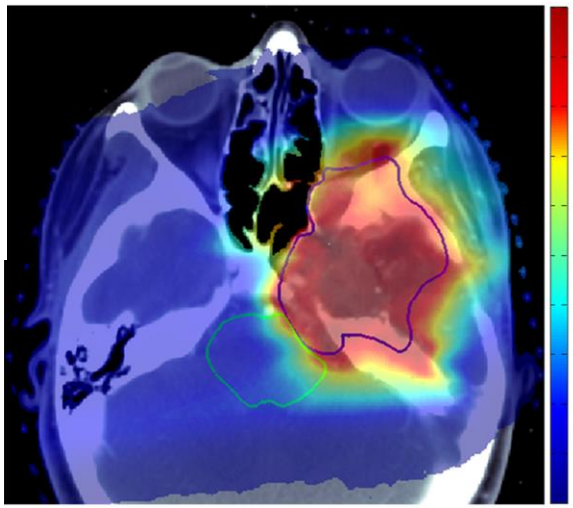
PLAN 2

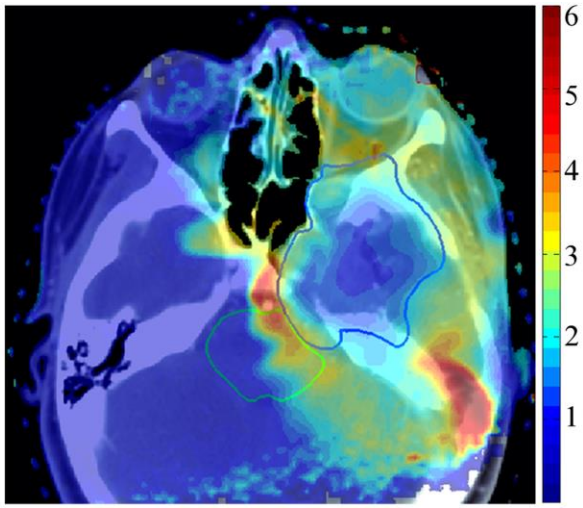




Dose

LET_d





Grassberger C. et al. Int J Radiat Oncol Biol Phys 2011 80: 1559-1566

LET based optimization:

consider simple RBE model

$$S = \exp\left(-\alpha d\right) \quad \alpha = \alpha_0 \left(1 + c LET\right)$$

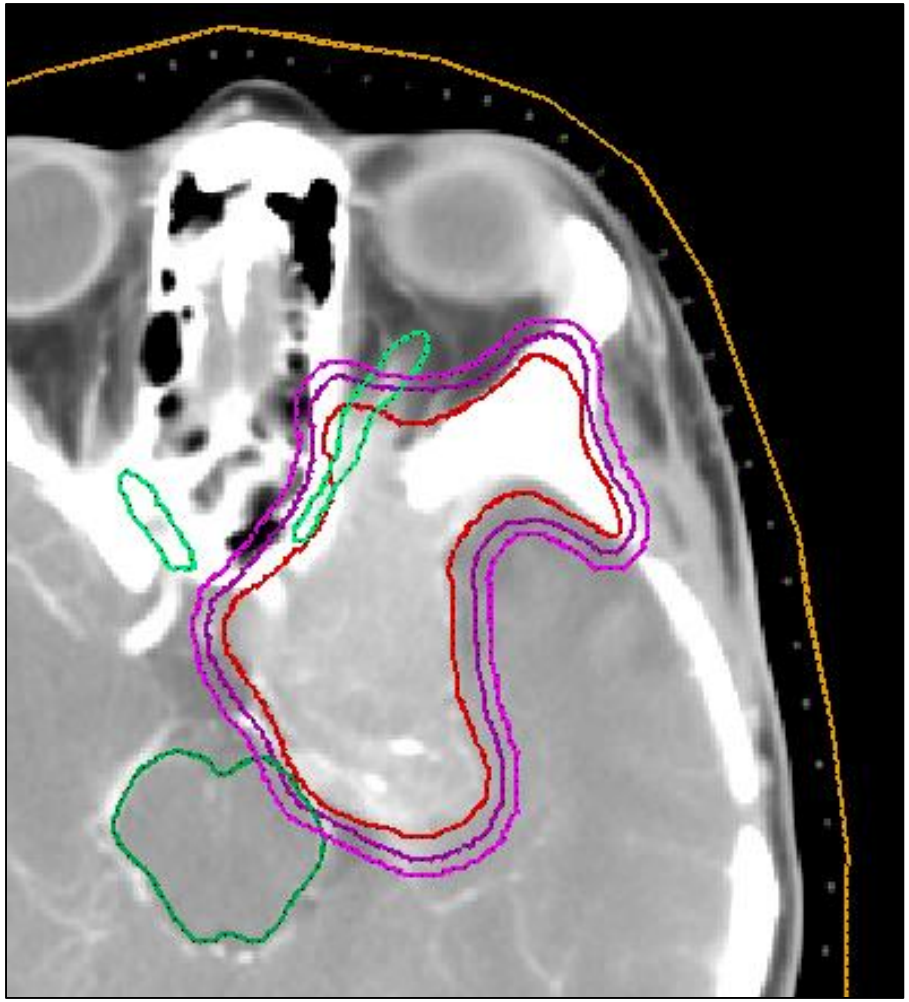
$$RBE \times d = -\frac{\log(S)}{\alpha_0}$$

$$= \underbrace{\left(1 + c LET\right)}_{\text{RBE}} d = d + \underbrace{c LET \times d}_{\text{biological extra dose}}$$

Goal: avoid high LET in serial critical structures near and within the target

Unkelbach, Botas, Giantsoudi, Gorissen, Paganetti: Reoptimization of Intensity Modulated Proton Therapy Plans Based on Linear Energy Transfer. Int J Radiat Oncol Biol Phys 2016

LET optimization - Example 1: atypical meningioma



CTV overlaps with

- **optic nerve**
- **chiasm**
- **brainstem**

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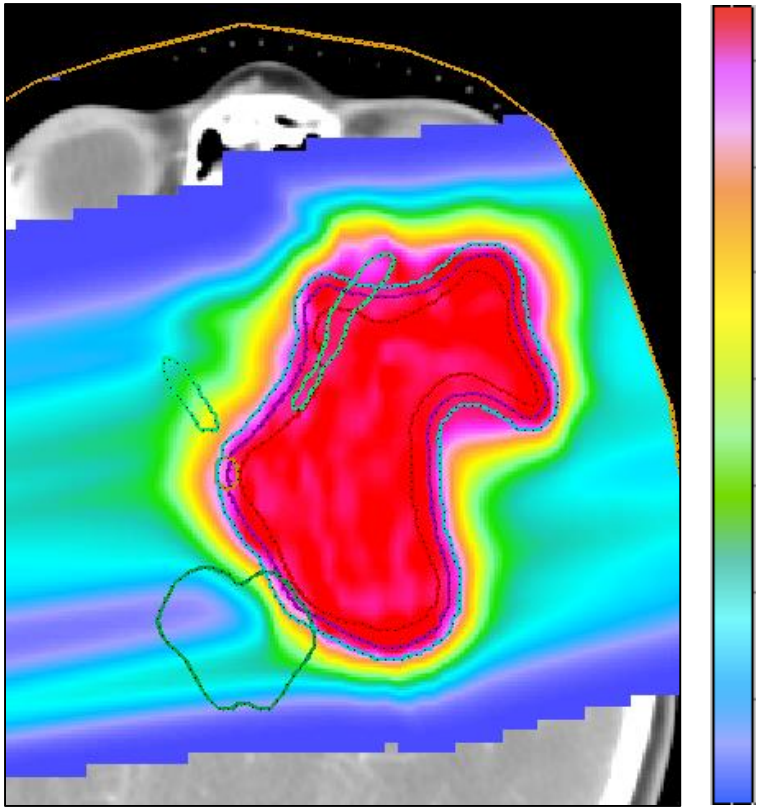
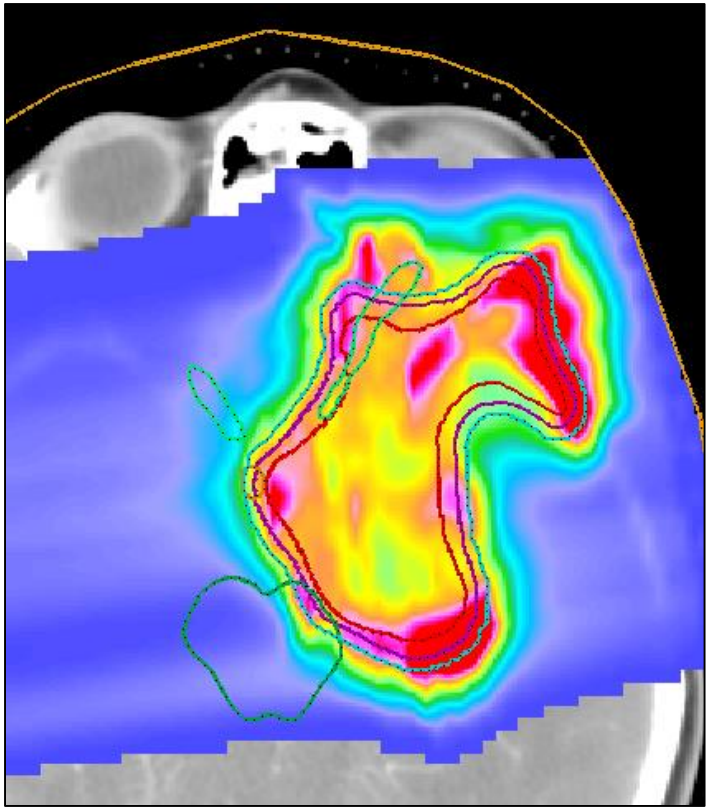


physical dose



LET x dose

Unkelbach, Botas, Giantsoudi, Gorissen, Paganetti: Reoptimization of Intensity Modulated Proton Therapy Plans Based on Linear Energy Transfer. Int J Radiat Oncol Biol Phys 2016

Method

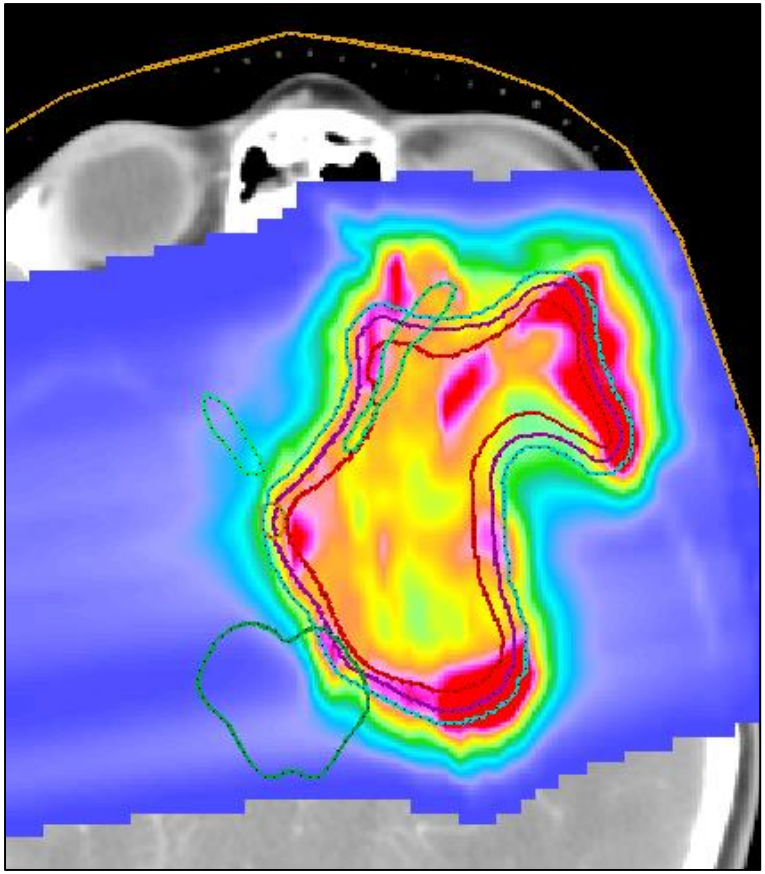
1. Physical dose objectives

- **homogeneous prescription of 50 Gy (physical dose)**
- **optics, brainstem, pituitary below 50 Gy**
- **brainstem gEUD**
- **brain mean dose**

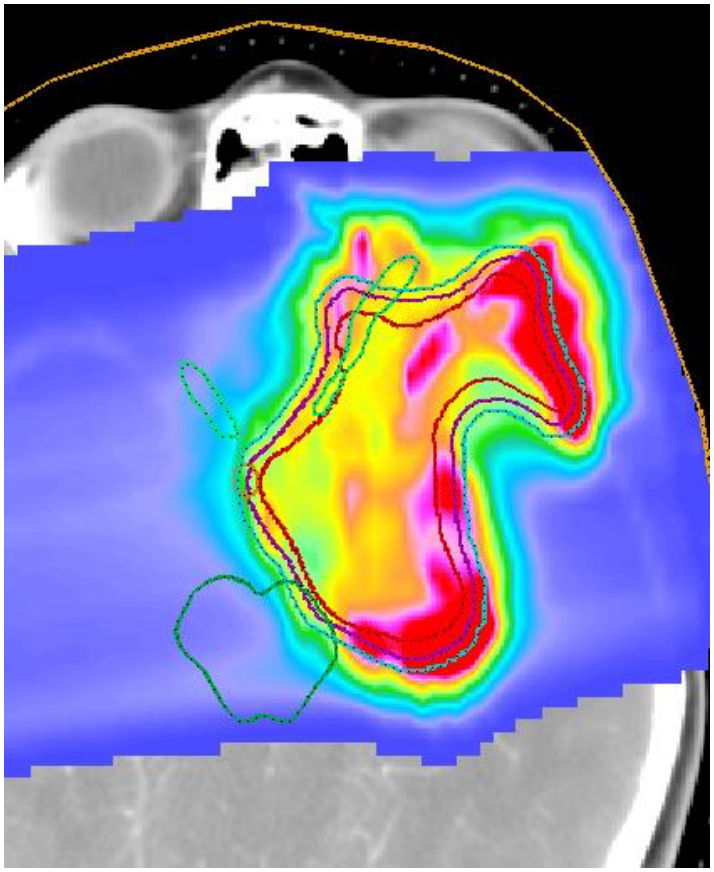
2. Re-optimization (prioritized optimization)

- **allow 3% increase in brainstem gEUD and mean brain dose**
- **other objective remain the same**

LET optimization - Example 1: atypical meningioma



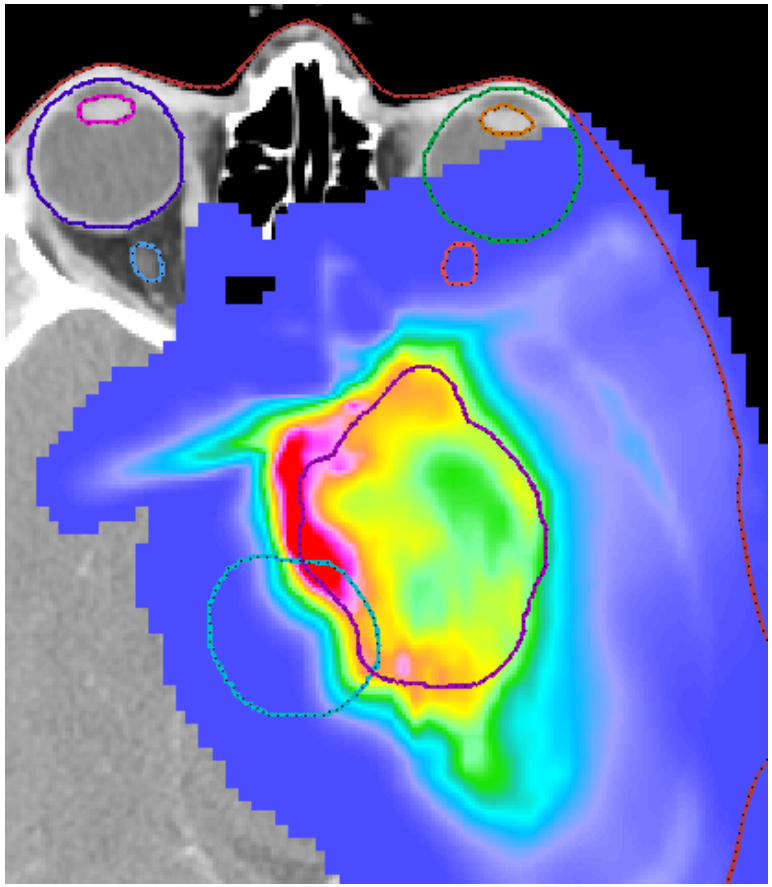
reference plan



re-optimized

Unkelbach, Botas, Giantsoudi, Gorissen, Paganetti: Reoptimization of Intensity Modulated Proton Therapy Plans Based on Linear Energy Transfer. Int J Radiat Oncol Biol Phys 2016

LET optimization - Example 2: base-of-skull chordoma



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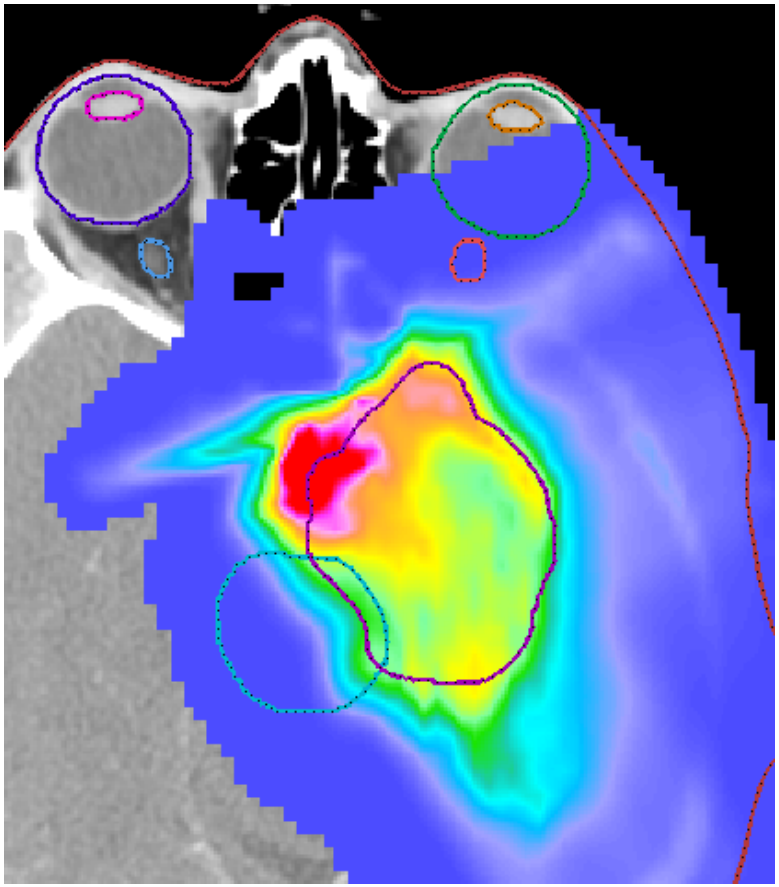

re-optimized

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Take-Home Messages

- Proton therapy uses a generic RBE of 1.1 because of substantial uncertainties in RBE as a function of dose, endpoint and LET
- The RBE is potentially higher towards the distal end of an SOBP and for low α/β.
- The relevance of endpoints other than cell survival for defining clinical RBEs is unclear.
- There is no evidence (yet) for a correlation between LET and toxicity or recurrence
- For a given dose and organ, the RBE dependency on LET is monotone (reasonably linear)
- RBE/LET optimization may improve treatment outcome
- Inter-patient variability (biomarkers?) is not well understood

MGH Radiation Oncology

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Drosoula Giantsoudi
Pablo Botas
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