fondazione CNAO

National Center of Oncological Hadrontherapy for the treatment of tumours

HIT

Heidelberg Ionenstrahl-Therapie Centrum

UniversitätsKlinikum Heidelberg

Monte Carlo-based RBE investigations in hadrontherapy

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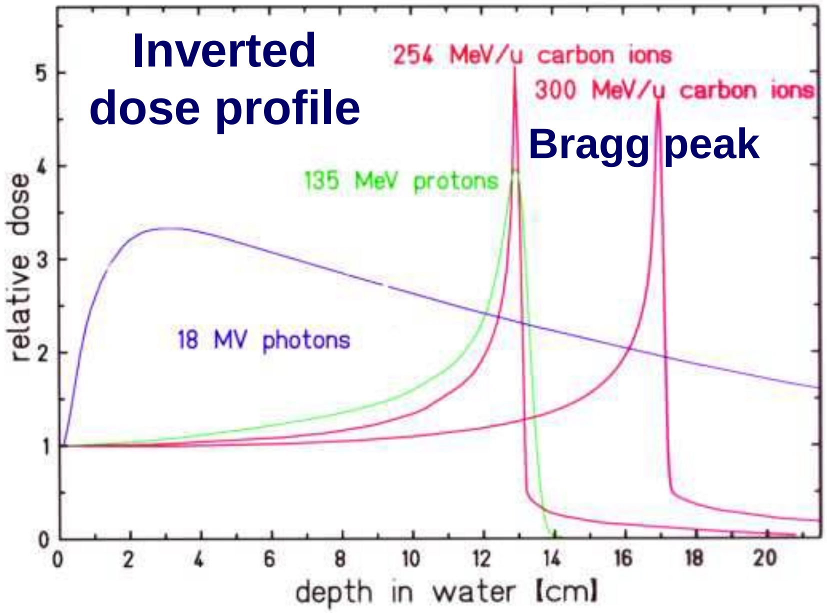
Centro Nazionale Adroterapia Oncologica CNAO

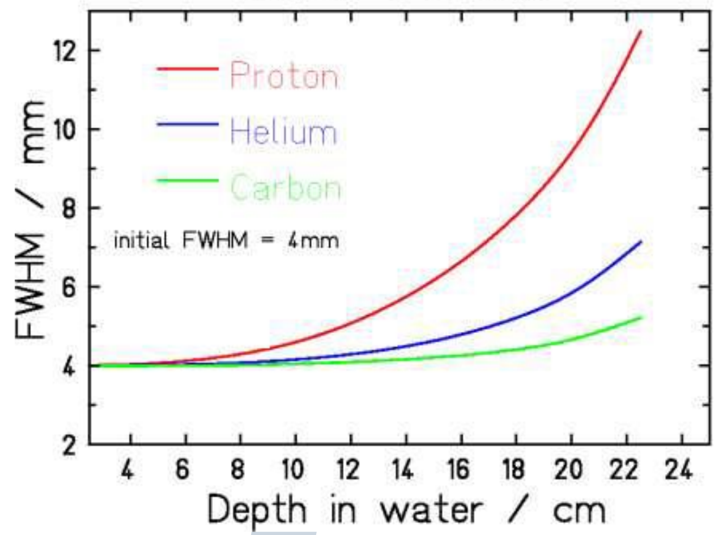
MCMA 2017, Napoli

Rationale for proton and ion beam therapy

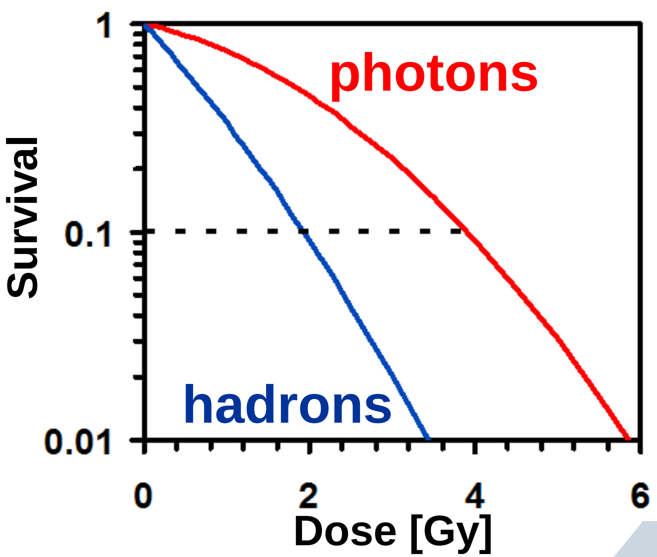
Physics



Lateral scattering



Biology



RBE (relative biological effectiveness):

$$RBE = D_{photon} / D_{hadron}$$

for the same biological effect

The RBE depends on:

- **particle type (p, ^{12}C, …), LET / local energy spectrum, dose**
- **tissue type, biological endpoint**

In clinic: p RBE = 1.1

^{12}C RBE models

How to interface a RBE model to a MC code

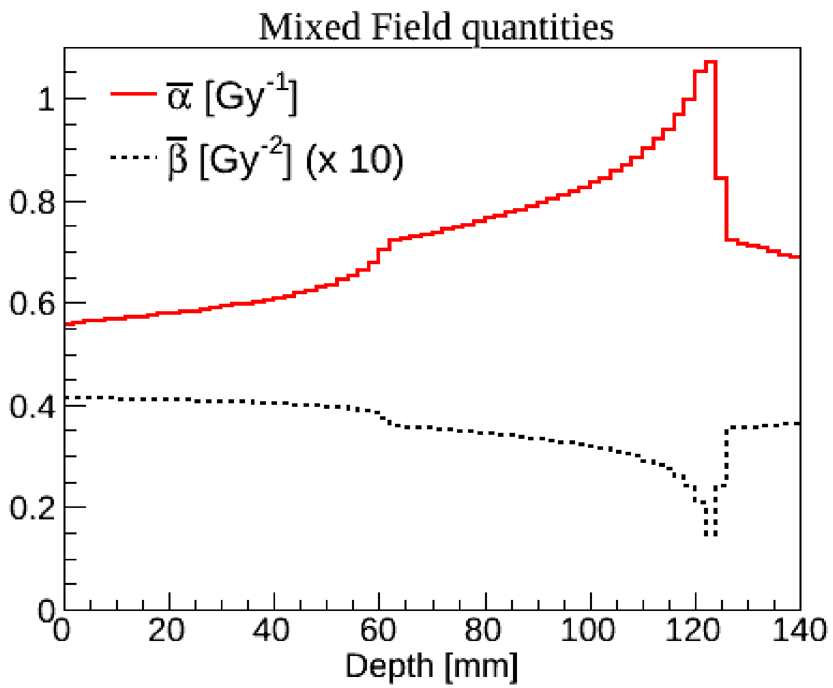
The coupling of the FLUKA code with the LEM (Mairani *et al* 2010) has been performed following the theory of dual radiation action (Kellerer *et al* 1978) calculating the α_D^{mixed} and β_D^{mixed}, i.e. the linear and quadratic term of the mixed radiation field:

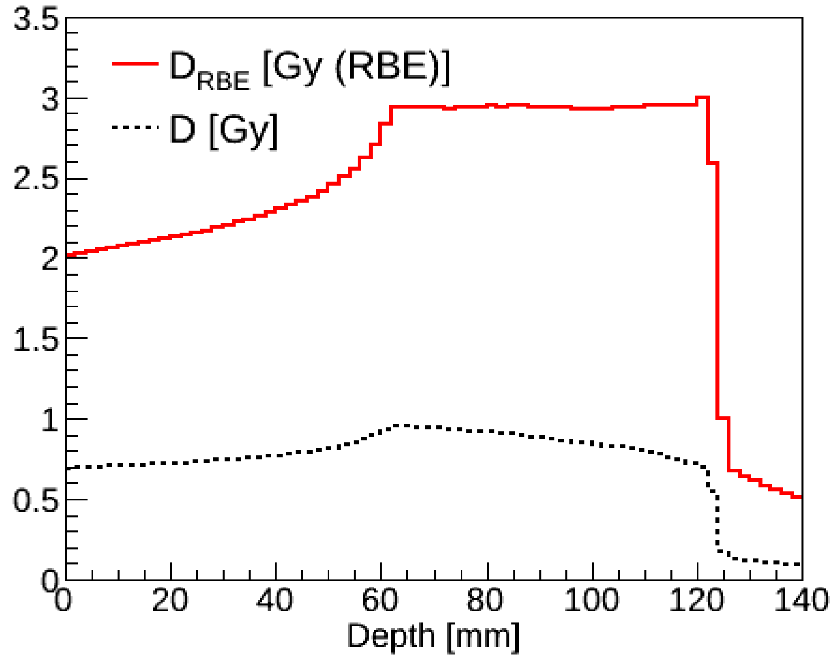
$$\alpha_D^{\text{mixed}} = \frac{\sum_{i=1}^{\text{Ndep}} \alpha_{D,i}^{\text{ion}} D_i}{\sum_{i=1}^{\text{Ndep}} D_i} \qquad (4A)$$

$$\beta_D^{\text{mixed}} = \left(\frac{\sum_{i=1}^{\text{Ndep}} \sqrt{\beta_{D,i}^{\text{ion}}}\, D_i}{\sum_{i=1}^{\text{Ndep}} D_i} \right)^2 \qquad (5A)$$

where N_{dep} is the total number of energy deposition events composing the mixed radiation field. In the simulation, similarly to (Ballarini *et al* 2003), whenever energy is deposited by a certain radiation type, the following two quantities, in addition to the absorbed dose D (to medium or to water, cf appendix A), are stored using 'USRBIN' cards: $\alpha_D^{\text{ion}} D$ and $\sqrt{\beta_{D,i}^{\text{ion}}} \cdot D$. By characterizing each energy deposition event, i.e. determining charge, mass and E_k/n of each particle, we are able to interpolate the correct values of α_D^{ion} and β_D^{ion}.

D_{RBE} = RBE x DOSE [Gy (RBE)]

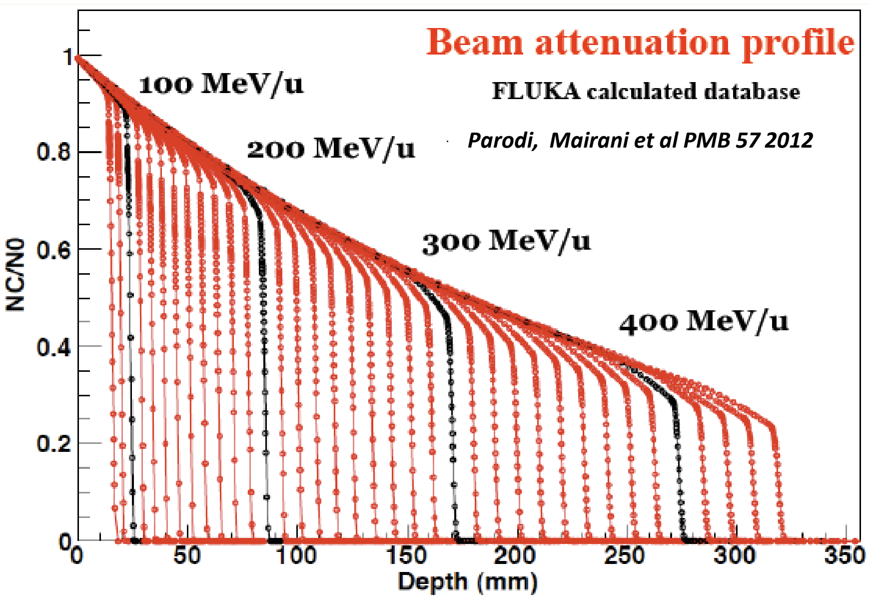


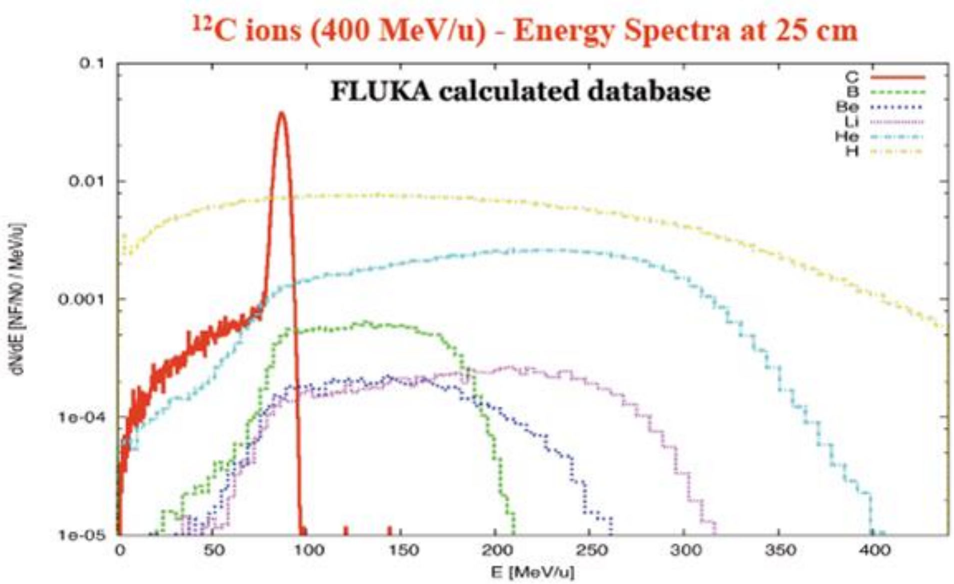


Mixed field in carbon ion beam therapy:

RBE determination based on MC-calculated spectra

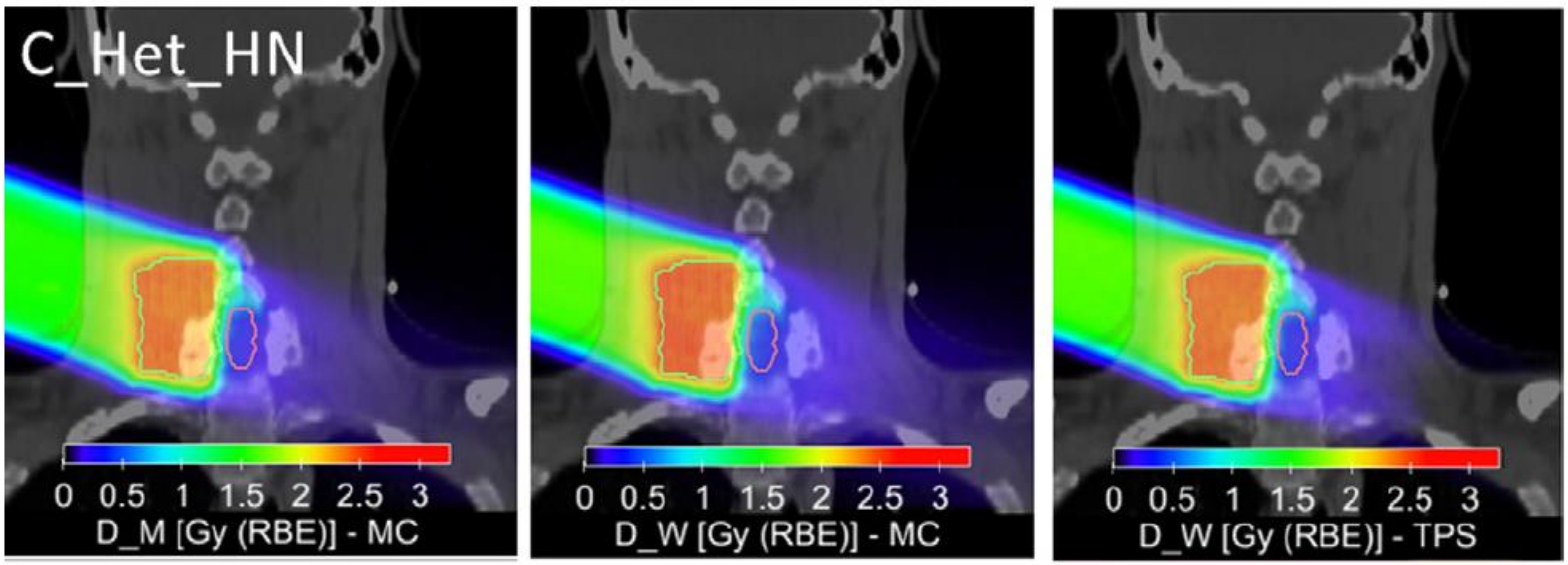
Monte Carlo calculation of fragment spectra in water for ^{12}C (80-440 MeV/u)





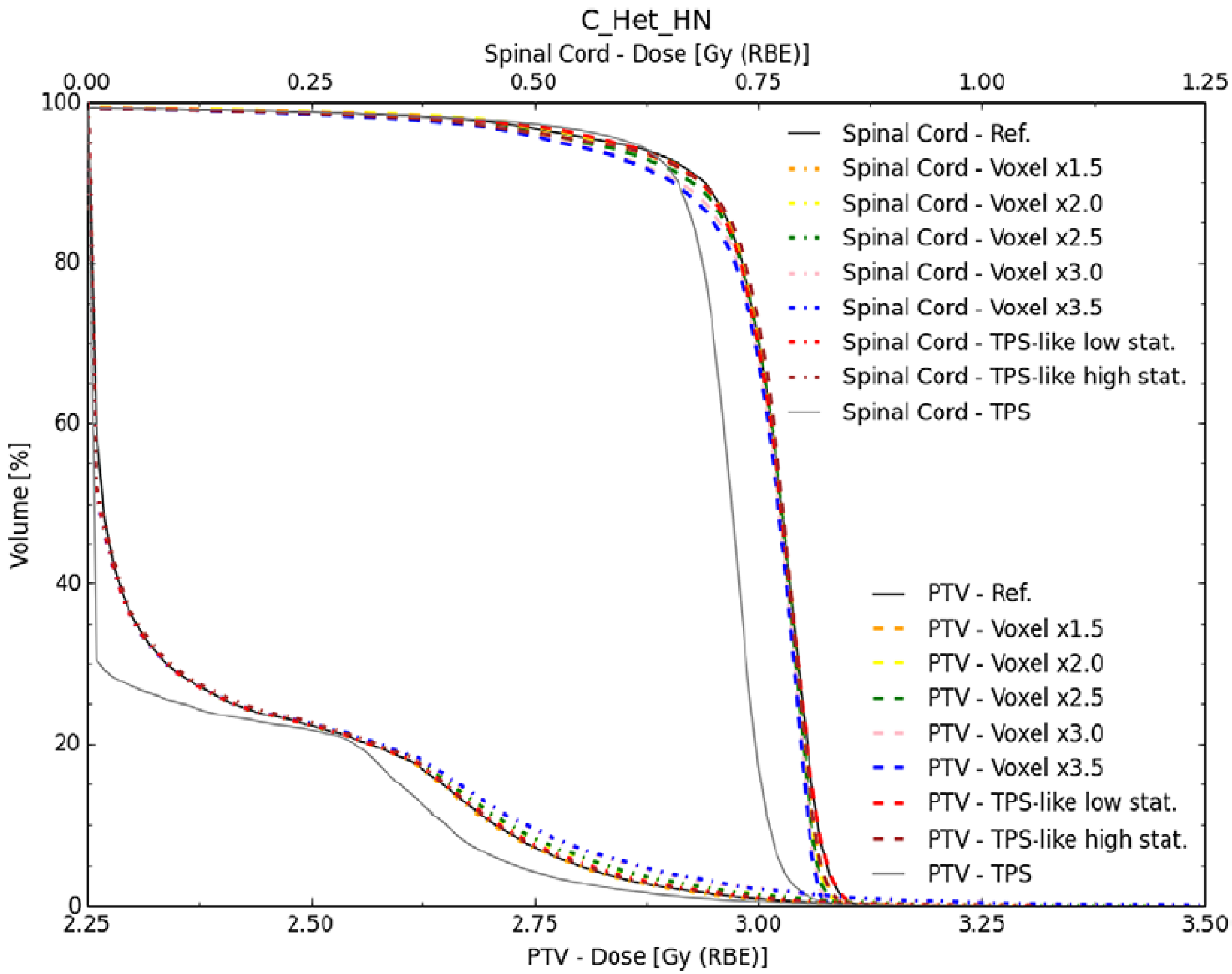
Re-calculations of patient dose distributions

Head and Neck case with carbon ion beams



J. Bauer, F. Sommerer, A. Mairani, et al Physics in Medicine Biology, 2014, 59, 4635

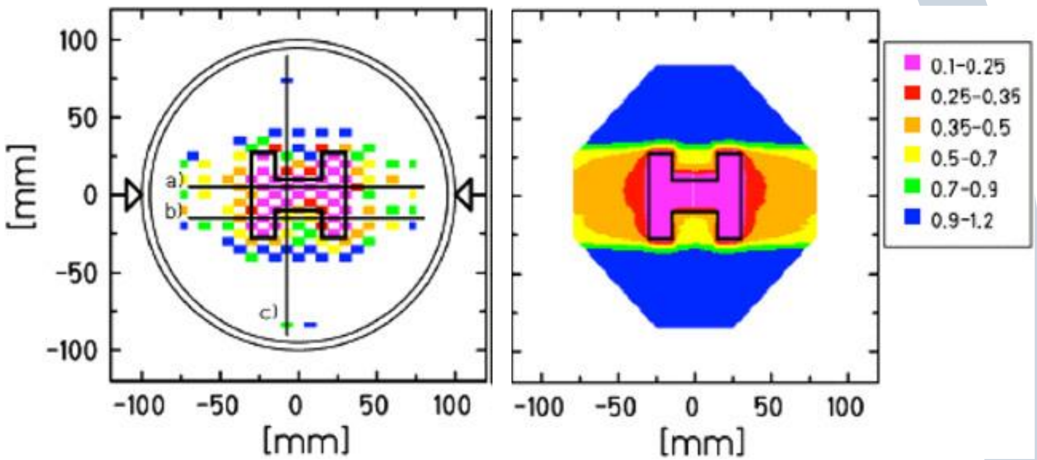
Re-calculations of patient dose distributions



J. Bauer, F. Sommerer, A. Mairani, et al Physics in Medicine Biology, 2014, 59, 4635

Biological calculations in carbon ion therapy

***in vitro* data** **predictions**



A. Mairani, et al Physics in Medicine and Biology 2010, 55, 4273–4289

MC + LEM model

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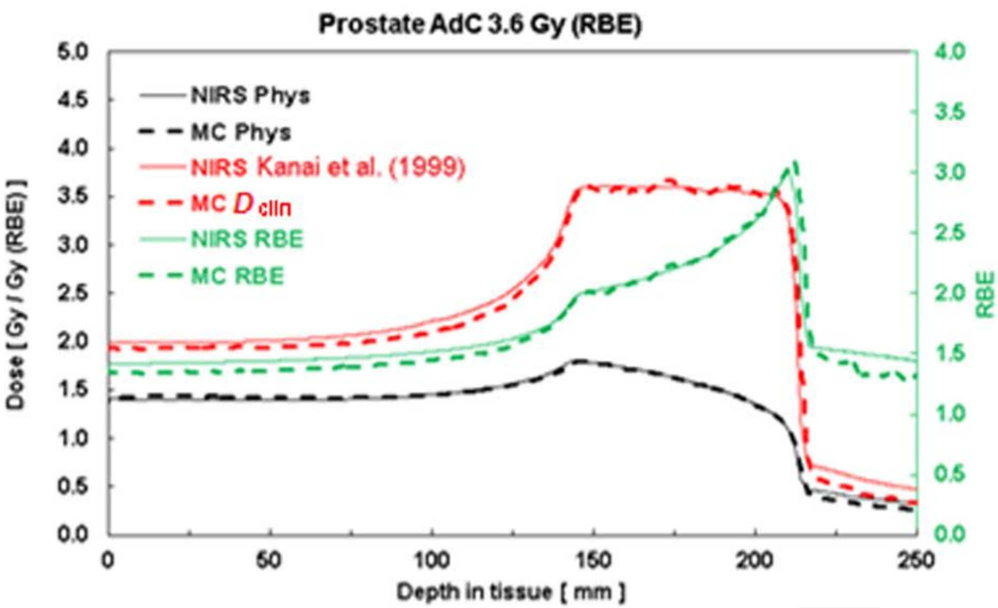
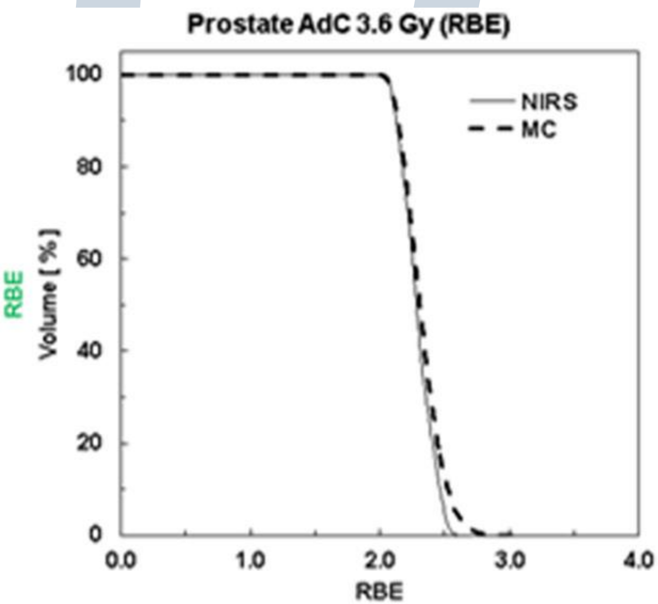
MC + NIRS approach





G. Magro,…,A.Mairani Physics in Medicine and Biology 2017, 56, 3814–3827

Comparing biological models in carbon ion therapy

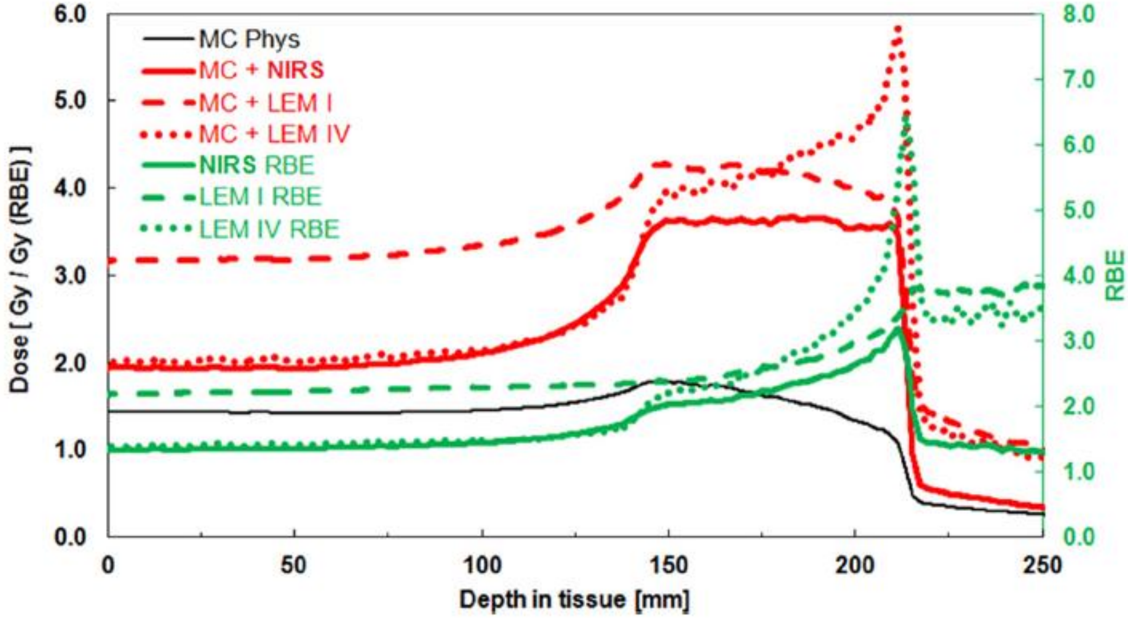
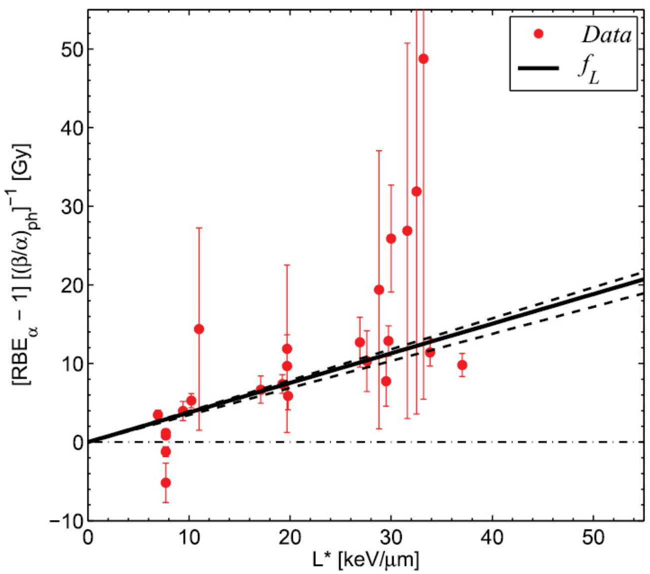
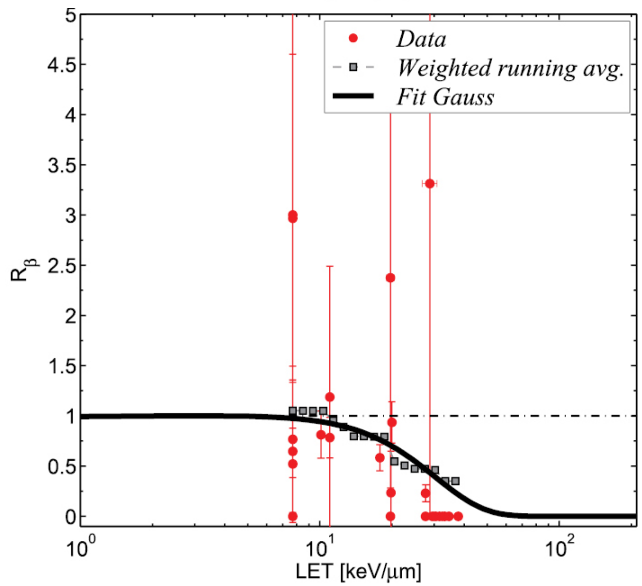


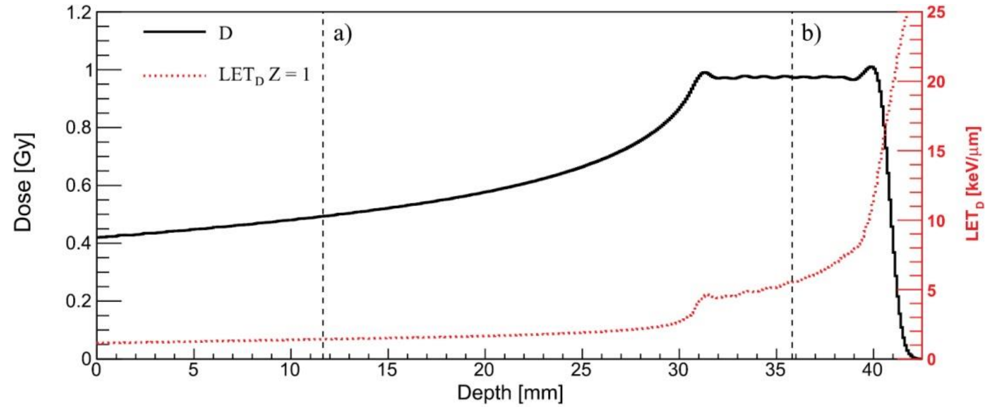
Figure 5. Comparison of effective dose profiles (left *y*-axis, red lines) acquired at the isocenter in the target volume for a prostate AdC (3.6 Gy (RBE)), as computed by the NIRS approach (solid line), the LEM I (dashed line) and LEM IV (dotted line) model coupled with the FLUKA MC code. The corresponding depth physical dose ('Phys') (left *y*-axis, black line) profile is also shown, together with RBE depth profiles (right *y*-axis, green lines).

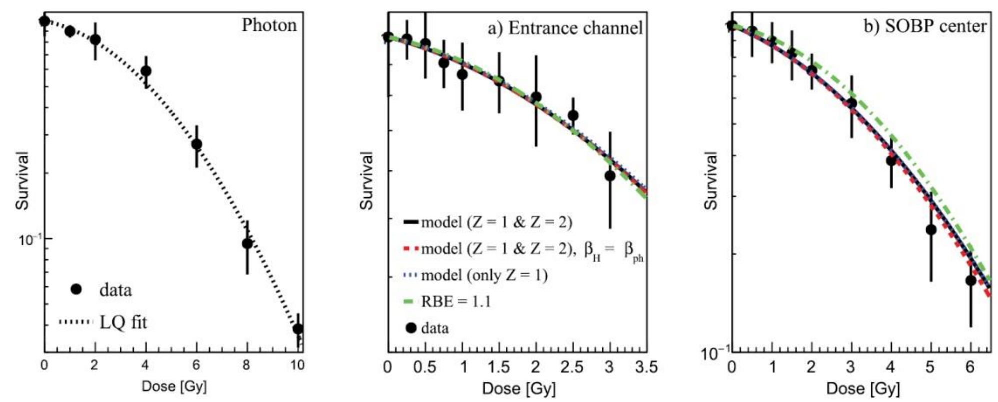
G. Magro,…,A.Mairani Physics in Medicine and Biology 2017, 56, 3814–3827

Beyond the TPS: variable RBE in proton therapy





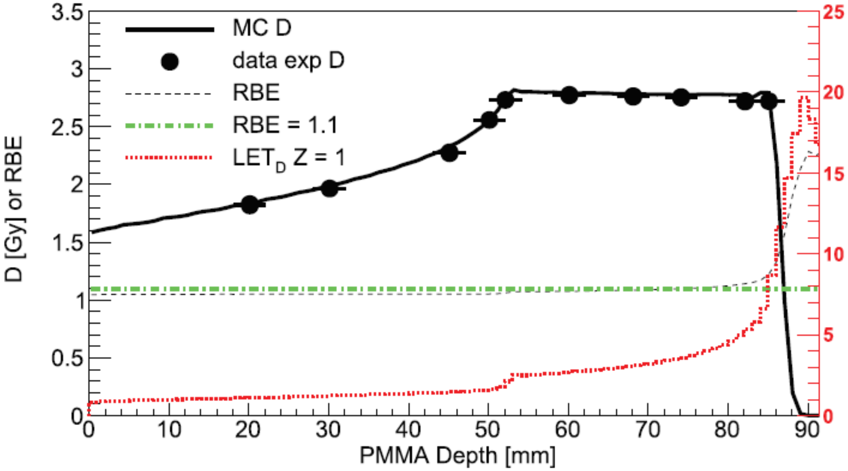


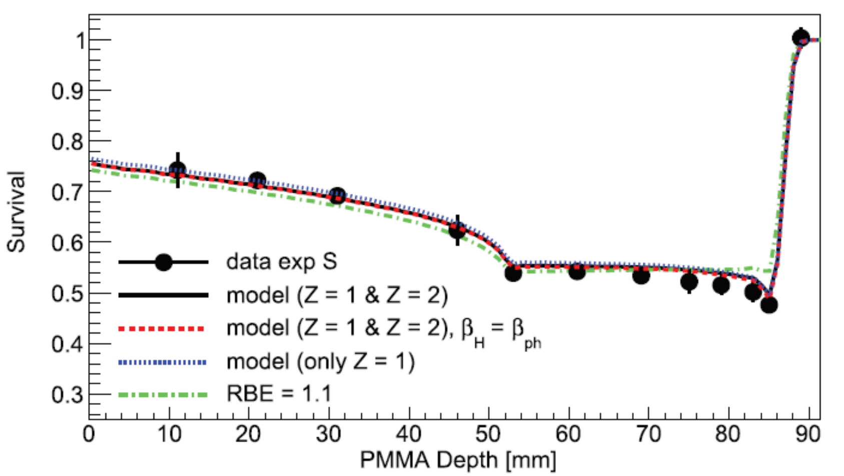


A. Mairani, et al Physics in Medicine and Biology 2017 61: 1378–1395

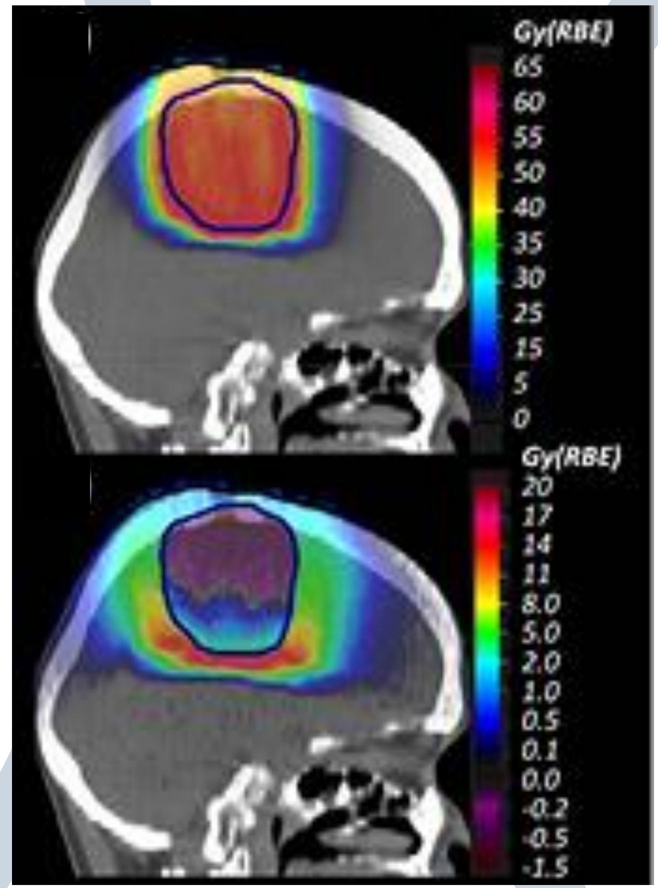
Beyond the TPS: variable RBE in proton therapy

Dosimetric and *in vitro* cell stack experiment: model vs data





Calculation of patient plans with variable RBE (varRBE) models

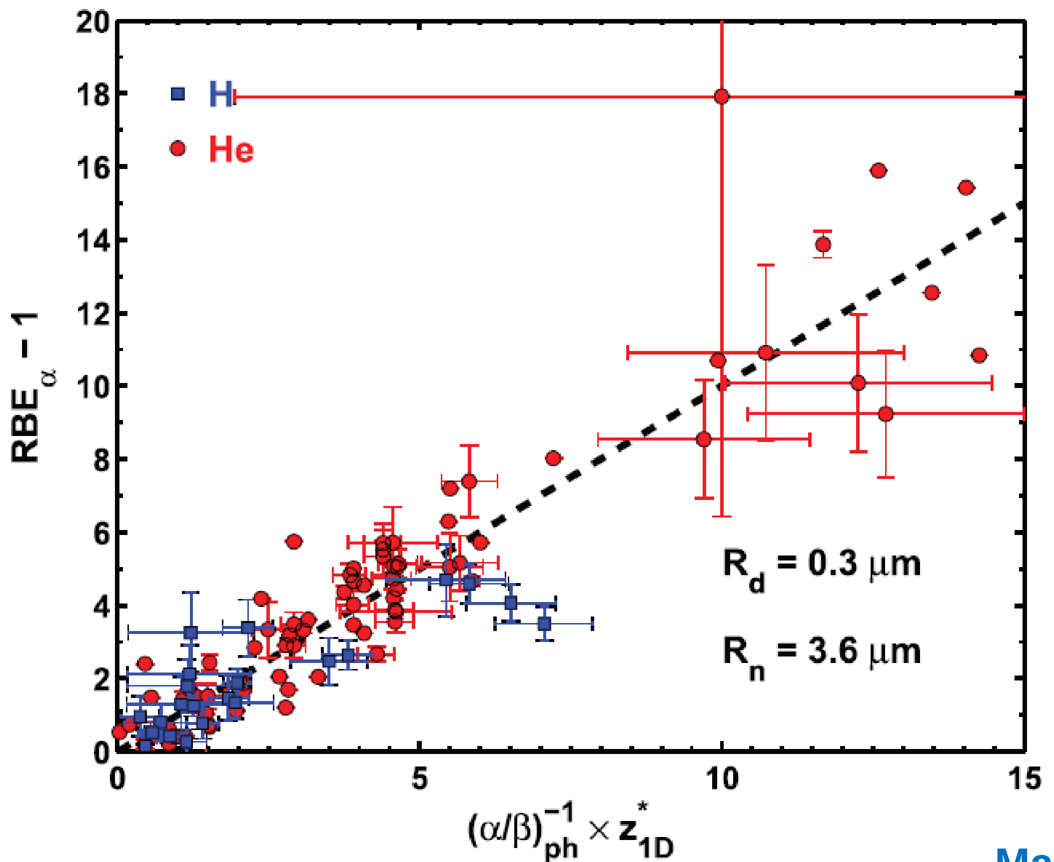


D_{varRBE} assuming varRBE

Dose difference: $D_{varRBE} - D_{RBE=1.1}$

A. Mairani, et al Physics in Medicine and Biology 2017 61: 1378–1395

Beyond the TPS: variable RBE in proton (and He) therapy tuning MKM input parameters



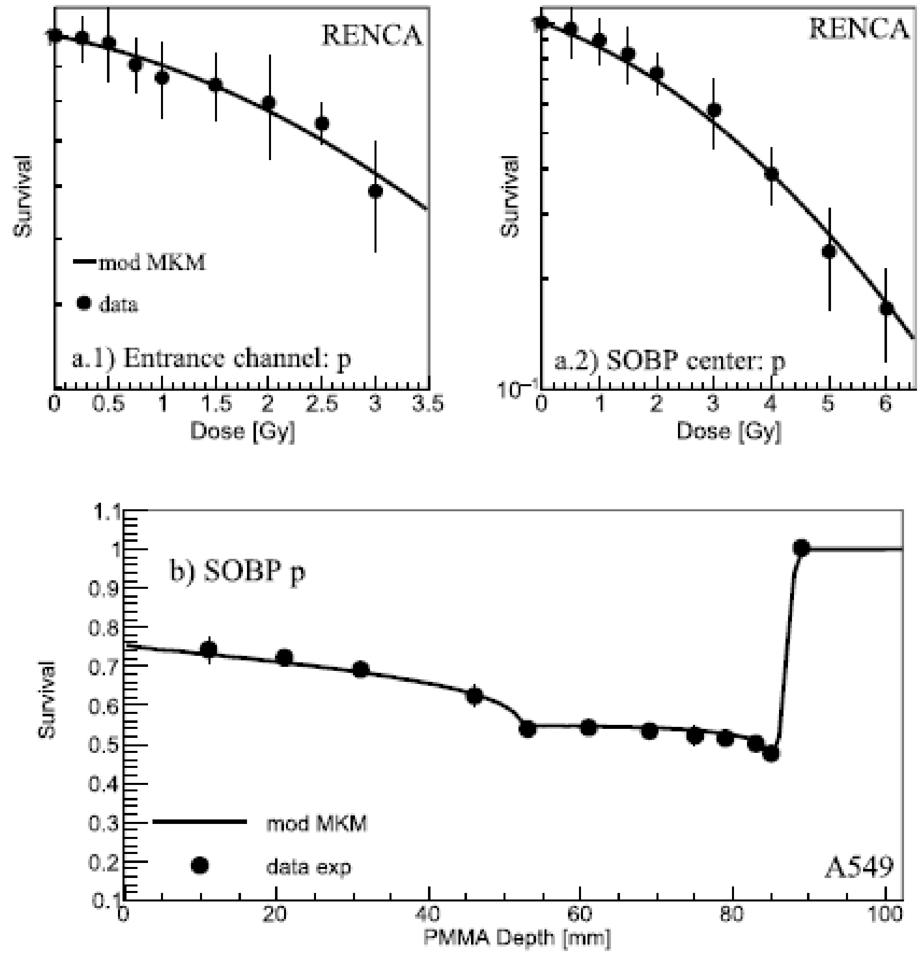
$$\mathrm{RBE}_\alpha \equiv \frac{\alpha_{\mathrm{ion}}}{\alpha_{\mathrm{ph}}} = 1 + \left(\frac{\alpha}{\beta}\right)_{\mathrm{ph}}^{-1} \cdot z^*_{1\mathrm{D}} \,,$$

$$\mathrm{R}_\beta \equiv \frac{\beta_{\mathrm{ion}}}{\beta_{\mathrm{ph}}} = 1.$$

Mairani et al PMB (2017) 62: N244

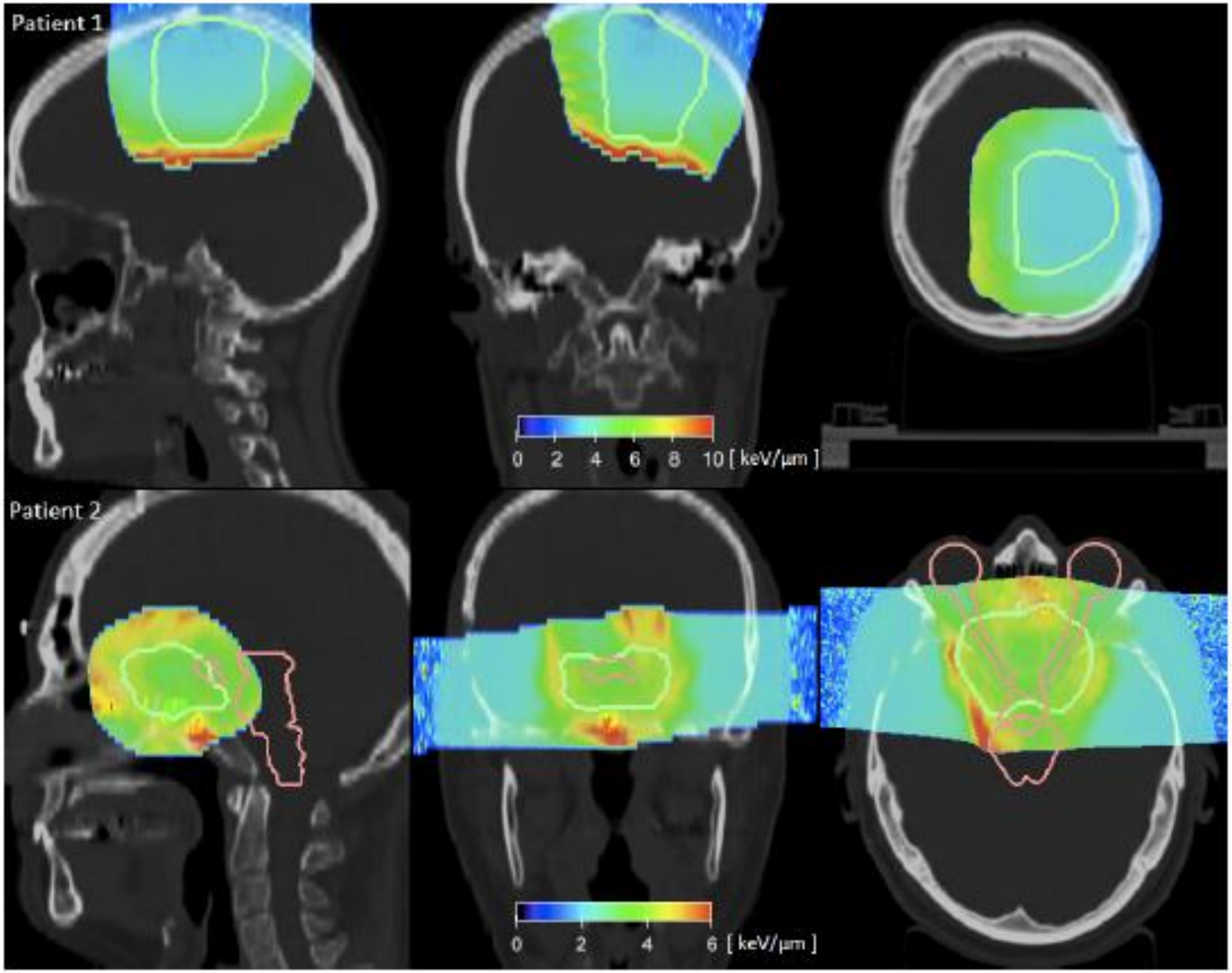
Figure 1. Experimental $\mathrm{RBE}_\alpha - 1$ (points with error bars) as a function of $z^*_{1\mathrm{D}} \cdot (\alpha/\beta)^{-1}_{\mathrm{ph}} \cdot z^*_{1\mathrm{D}}$ values have been calculated using the best fit parameters $R_d = 0.3$ μm and $R_n = 3.6$ μm. The slope of the dashed line graphically displays a 1:1 dependence.

Beyond the TPS: variable RBE in proton (and He) therapy tuning MKM input parameters



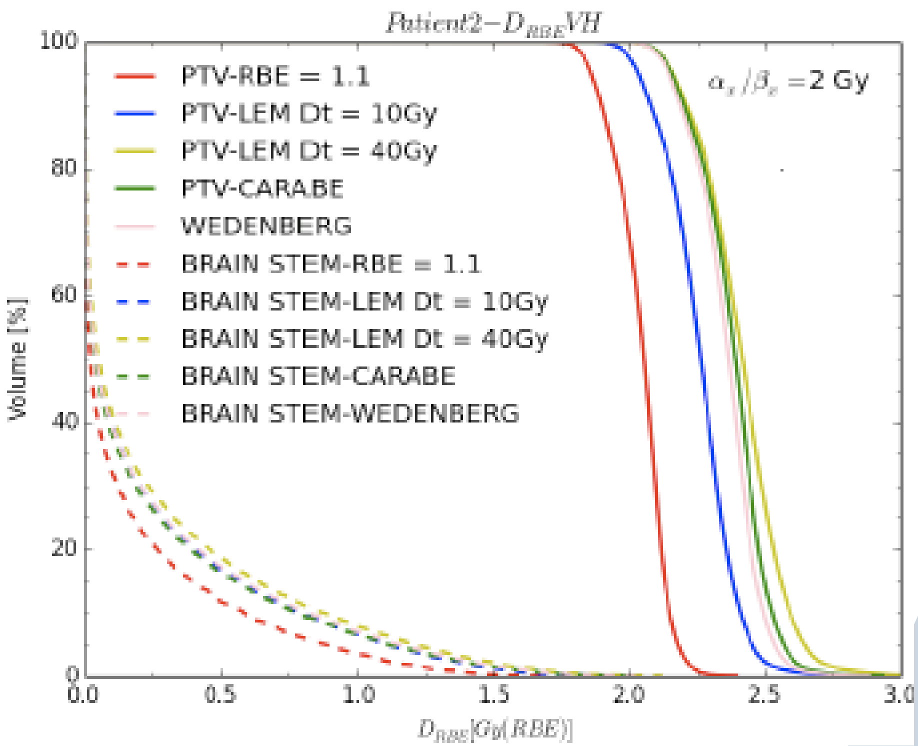
Mairani et al PMB (2017) 62: N244

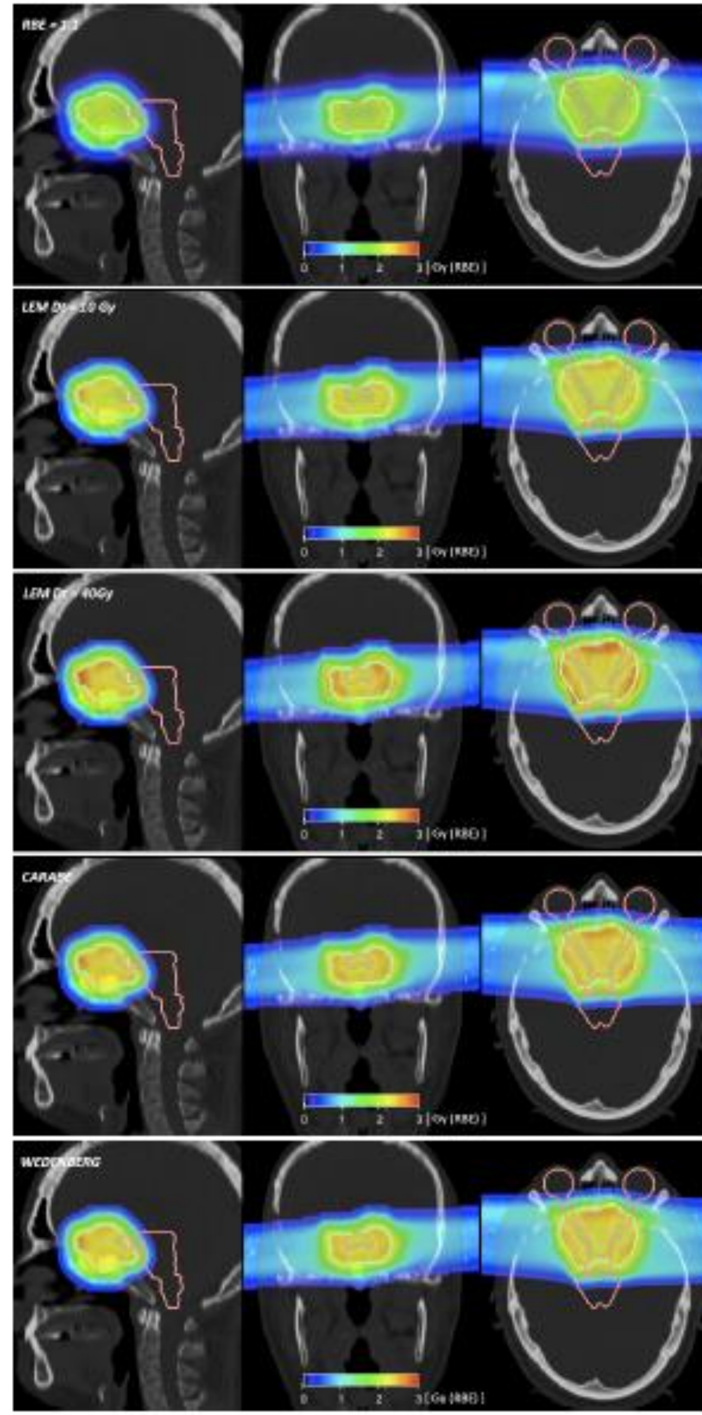
Beyond RBE 1.1 in proton therapy: LET distributions in clinical-like scenario



G. Giovannini,...A. Mairani, K. Parodi Radiation Oncology (2016) 11:68

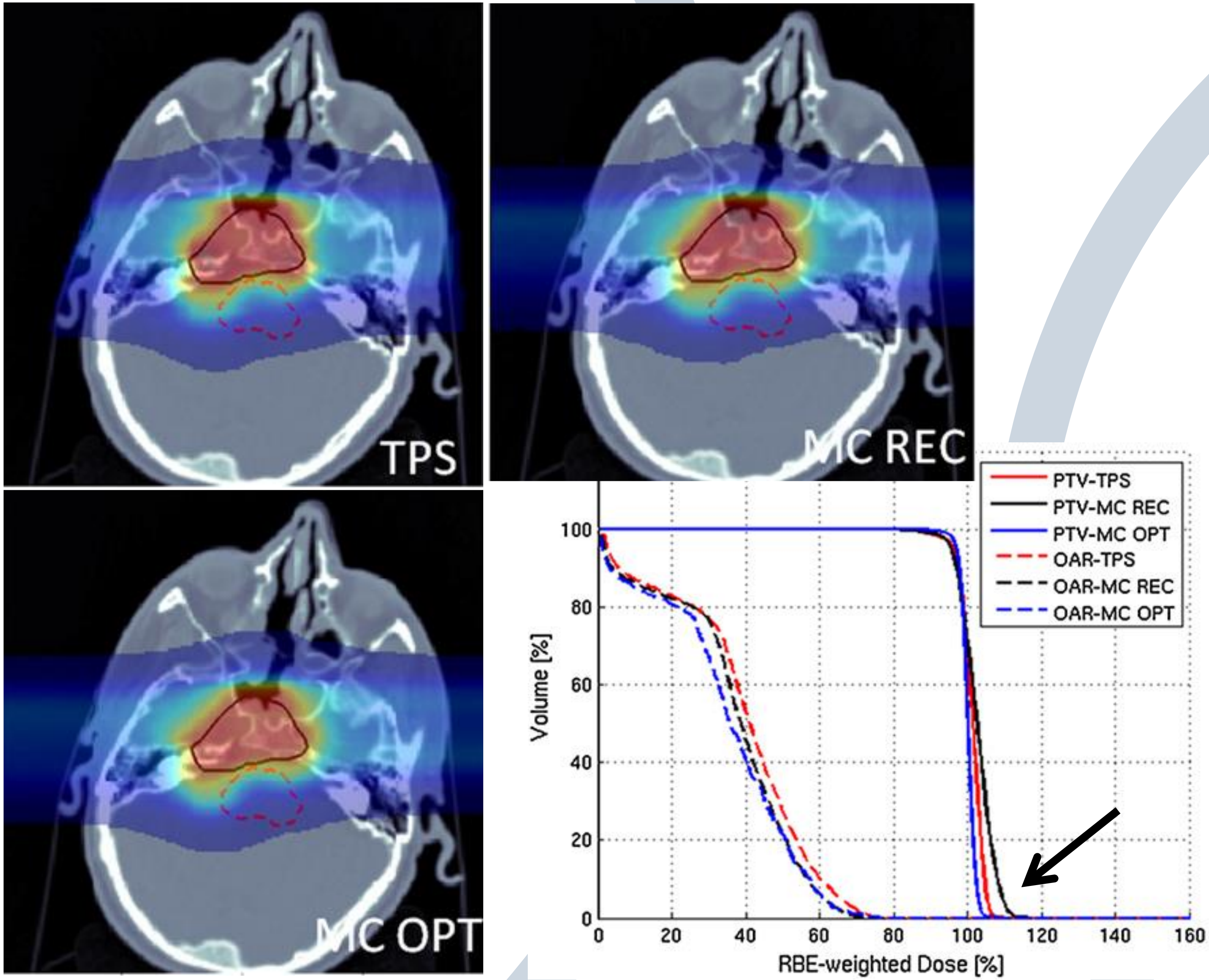
D_{RBE} distributions in clinical-like scenario with $(\alpha/\beta)_{ph}$ = 2 Gy



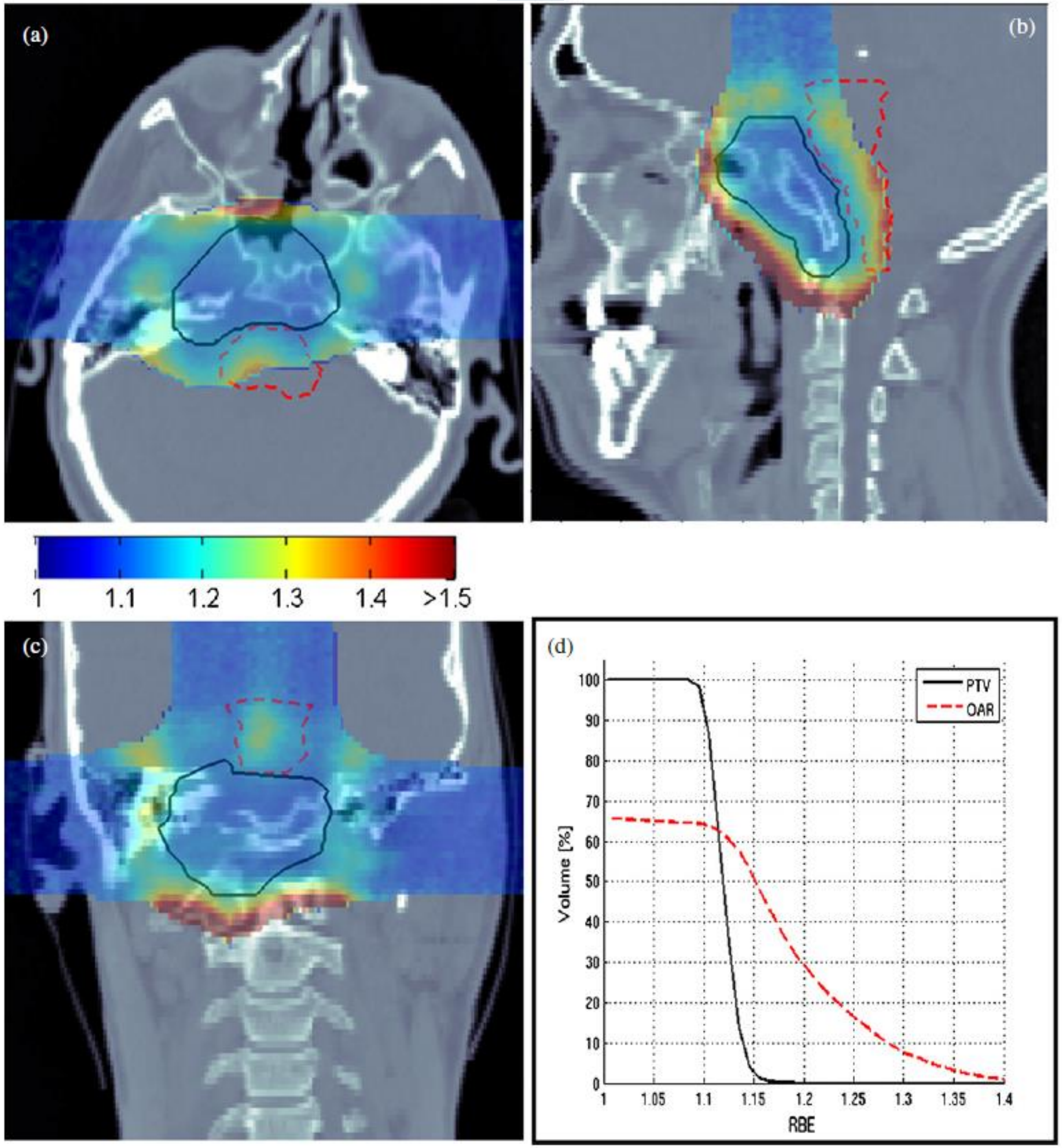


G. Giovannini,...A. Mairani, K. Parodi
Radiation Oncology (2016) 11:68

Monte Carlo-based Treatment Planning Tool



A. Mairani, et al. Physics in Medicine and Biology 58 (2013) 2471–2490



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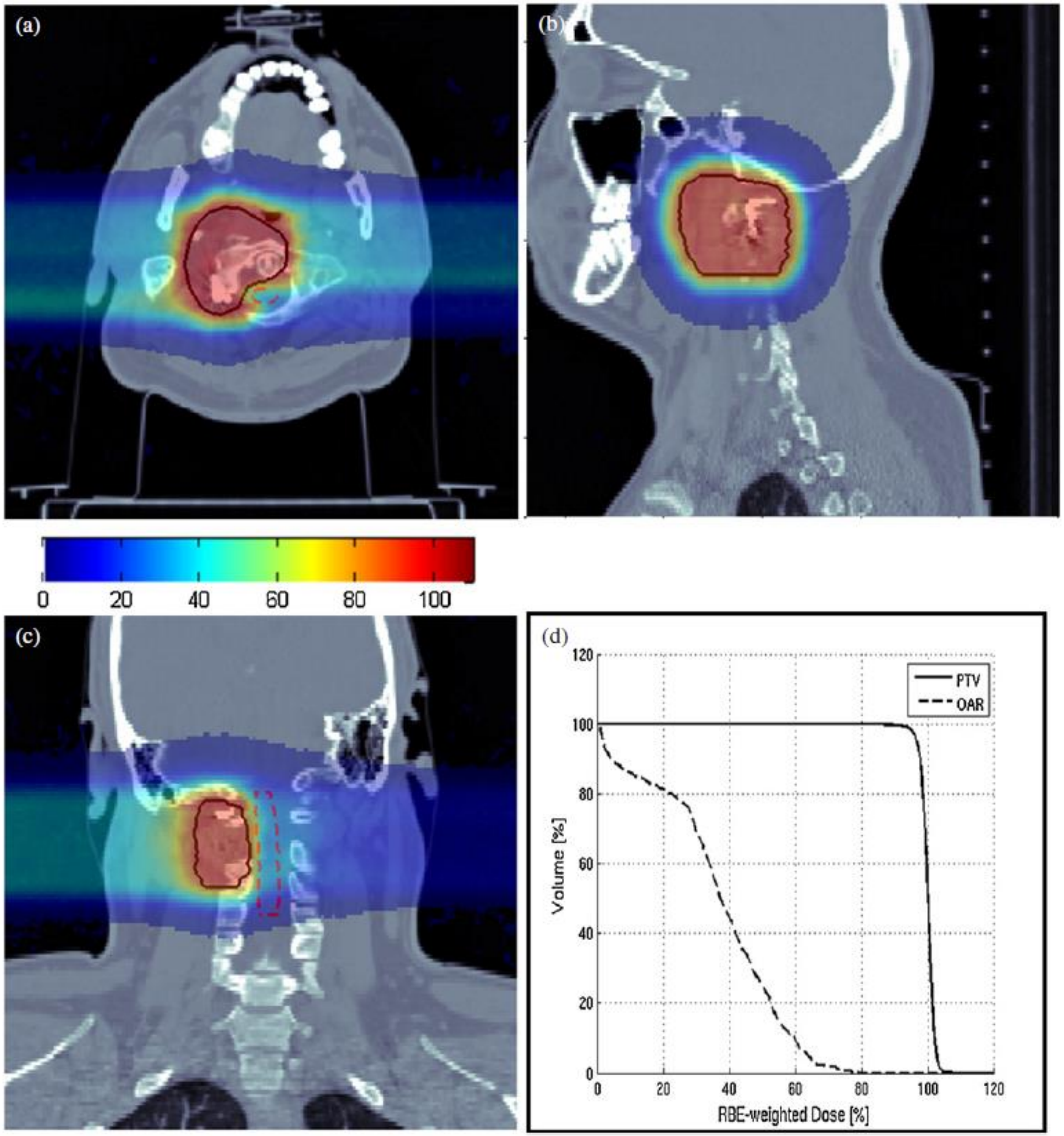
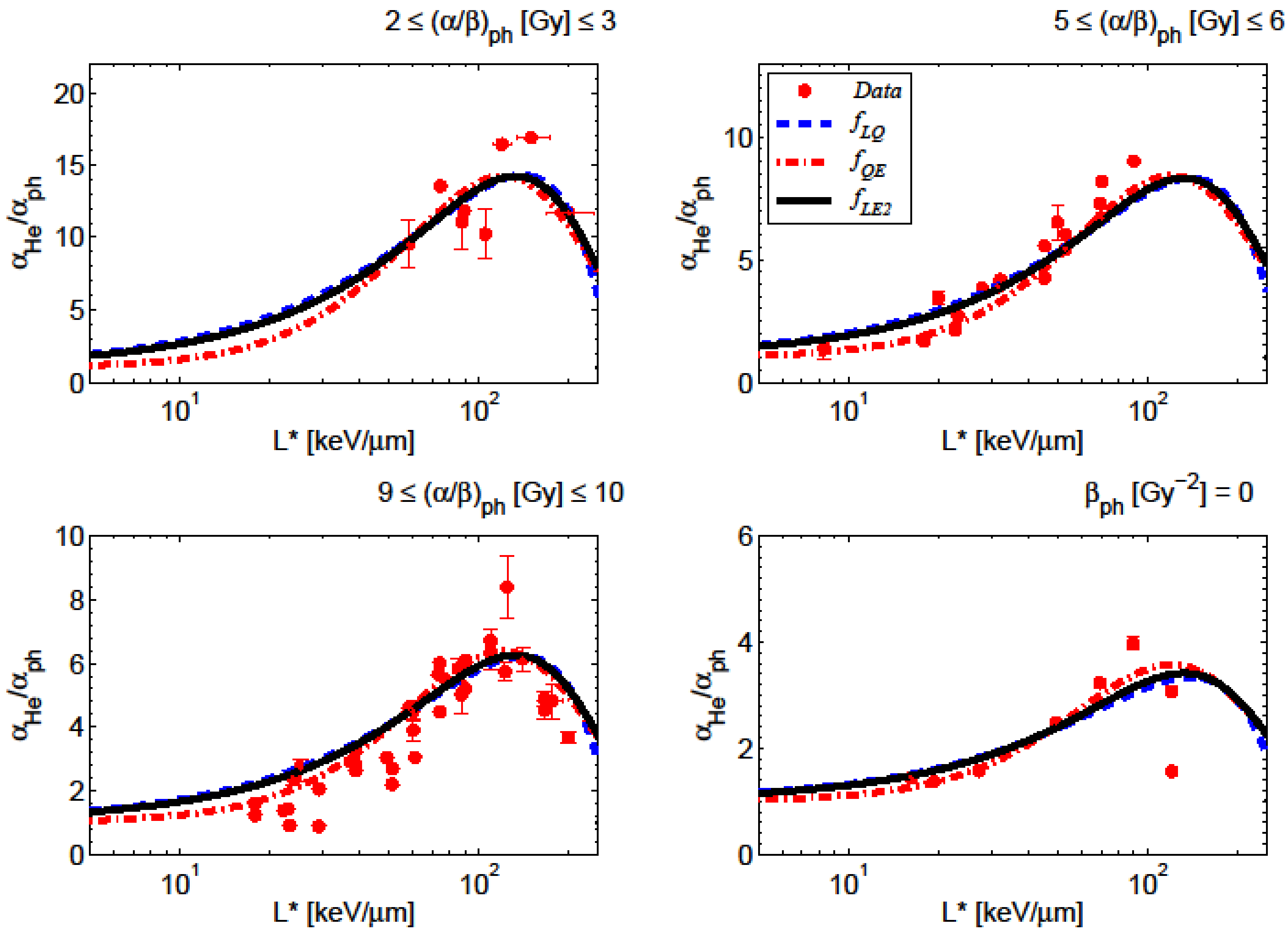
Monte Carlo-based Treatment Planning Tool



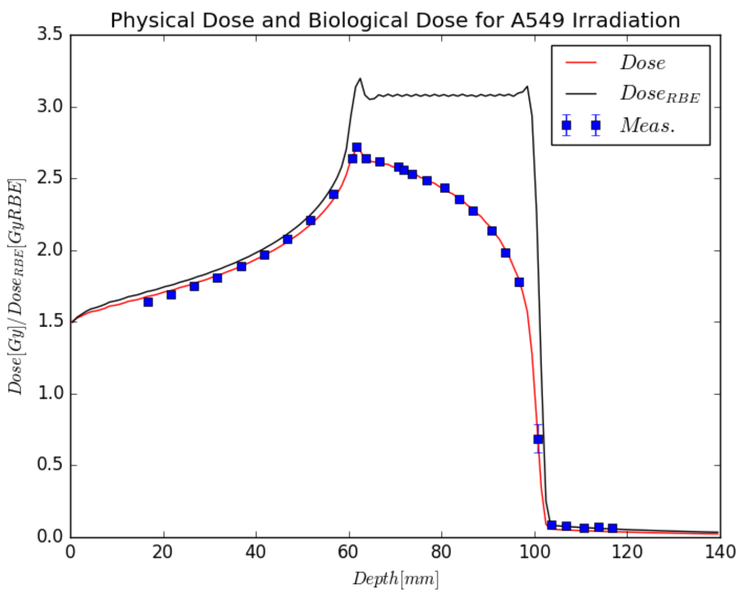
A. Mairani, et al. Physics in Medicine and Biology 58 (2013) 2471–2490

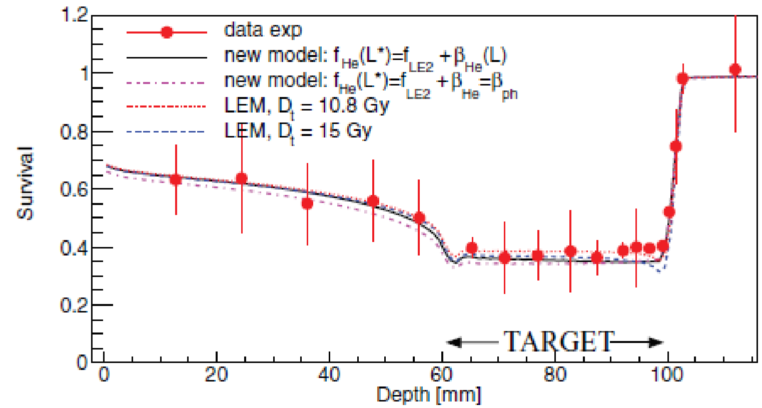
He RBE model development

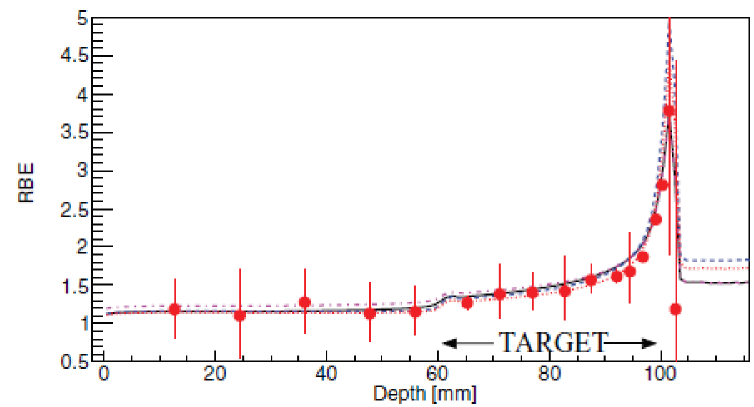


Mairani et al 2016 PMB 61 888, Mairani et al 2016 *PMB 61 4283*

RBE model validation





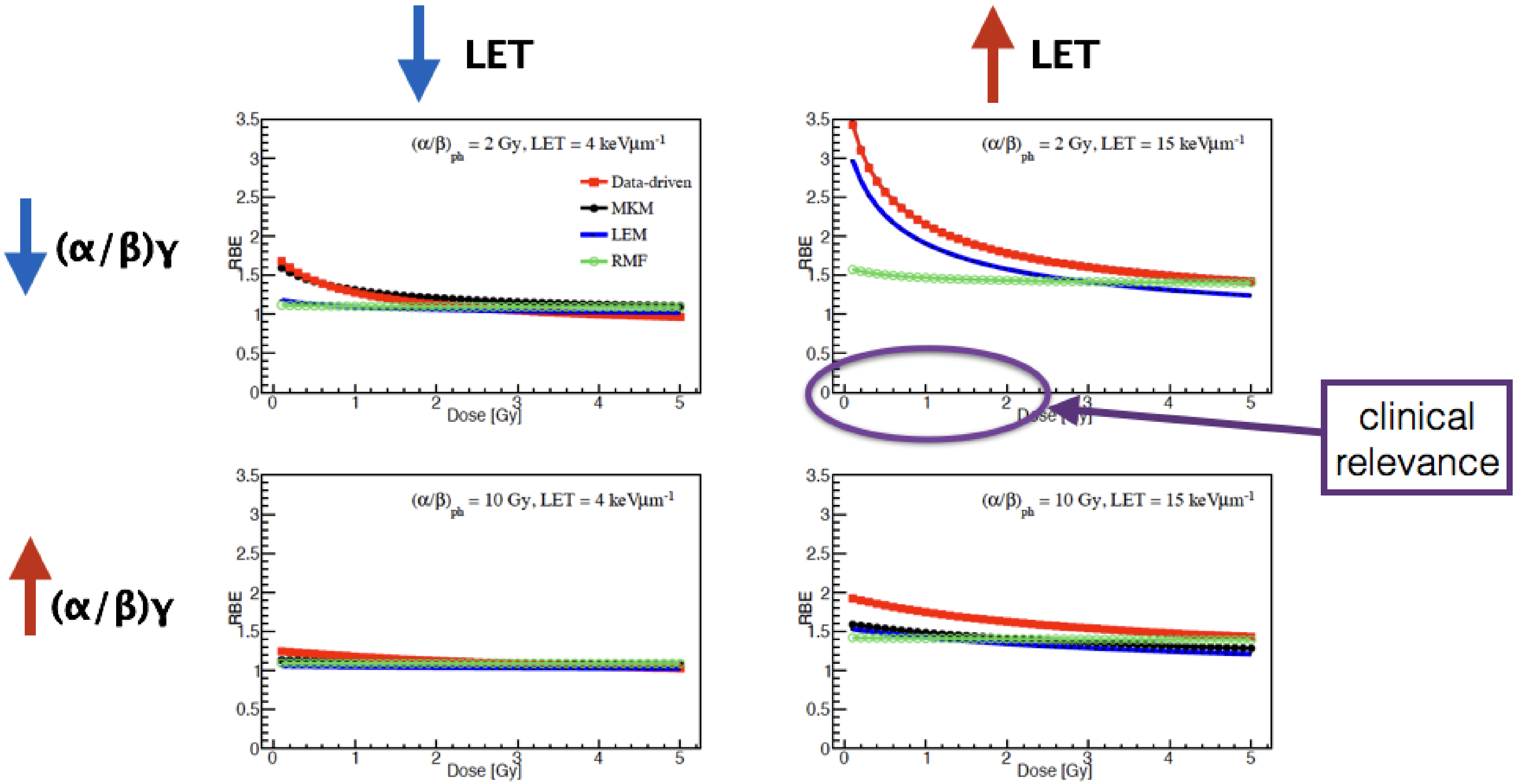


1 – Bio. Optimized SOBP
2 – Measurements verifications
3 – Cell Survival (A549) + RBE

→ **Validated in-house model for He (5%) and H (2%)**

Mairani et al 2016 *PMB 61 4283*

RBE model validation

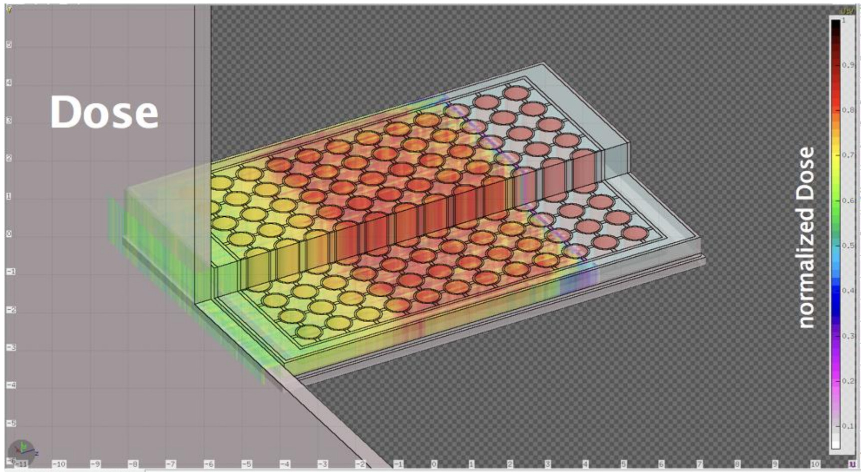


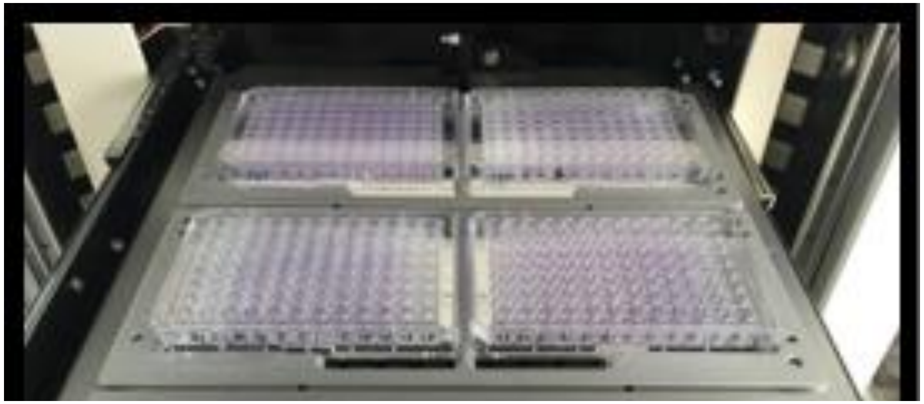
- Variability of prediction: **RBE(Dose, LET, [α/β]γ)**

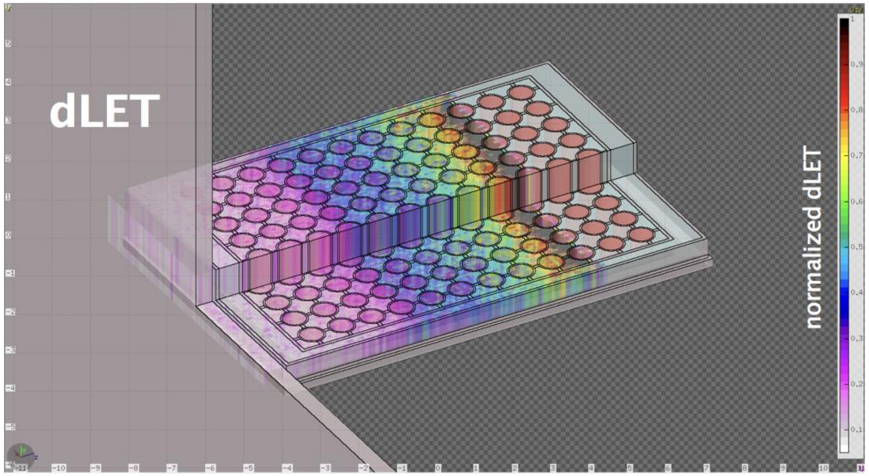
Mein,…,Mairani to be submitted

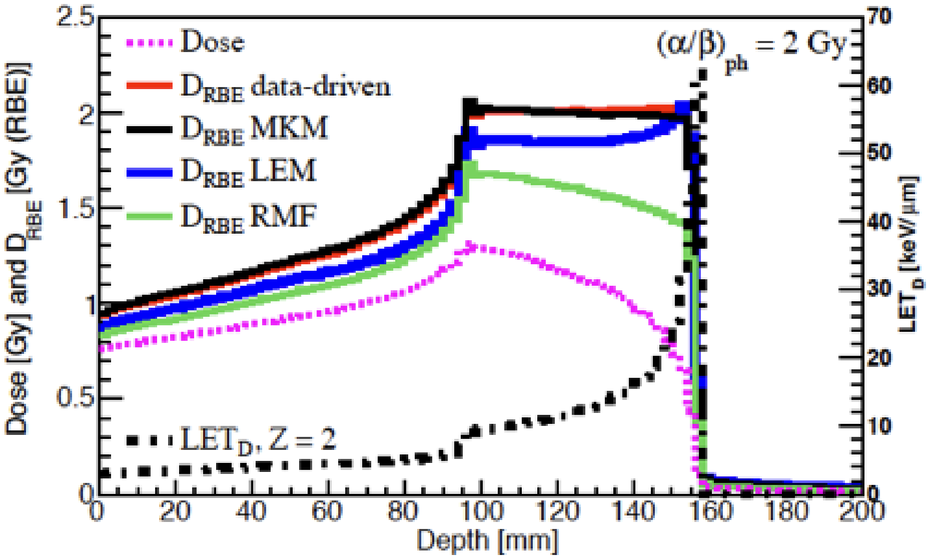
RBE model validation

- Clinical-like fields (SOBP) with 96 well plate approach to clonogenic assay









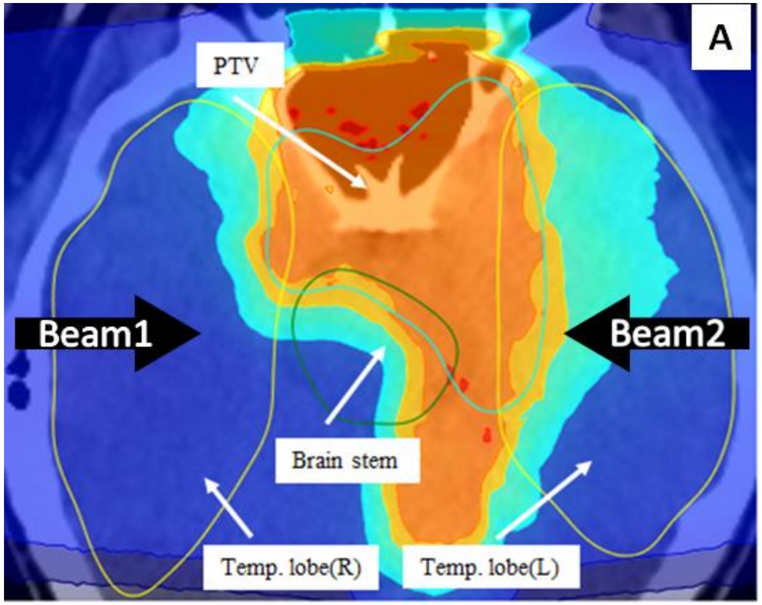
S. Mein Monte Carlo calculation of RBE and in-vitro validation for helium ion-beam therapy

Plan Comparisons

Methods

- Meningiomas treated with proton (4 patients)
- **Re-optimization** with **FLUKA–MCTP** for **helium** ions **AND protons**
- **Dose** in PTV 1.8 GyRBE

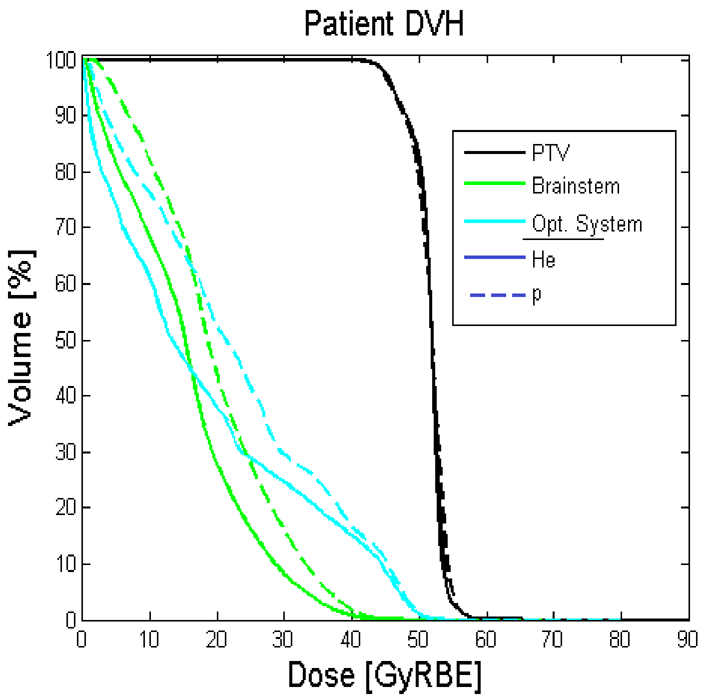
- Tissue types CNS α/β = 2 Gy , PTV α/β = 3.7 Gy
- **Protons** without RiFi, **variable RBE** (calculated "online")
- **Helium** ions with RiFi, **variable RBE** (calculated "online")
- Comparisons : DVH for **PTV** and **OAR**

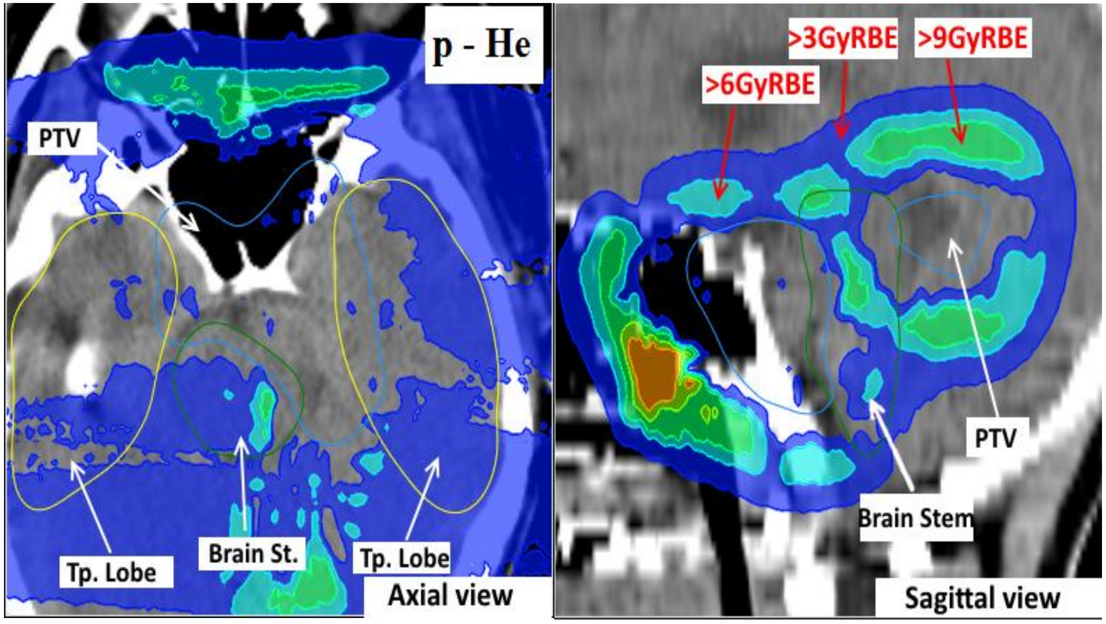


Tessonnier PhD Thesis and Tessonnier, Mairani et al under review

Plan Comparisons

Results





Comparable **PTV coverage**

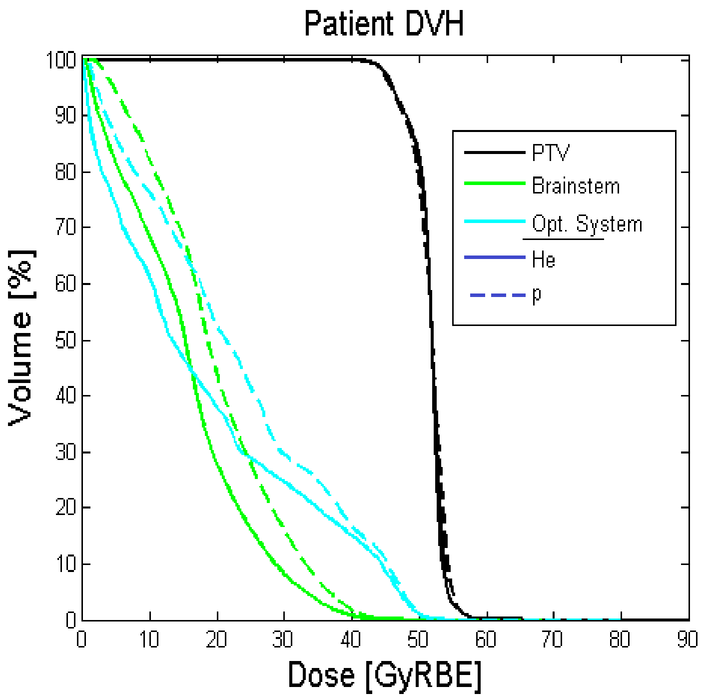
Better sparing of OAR with He

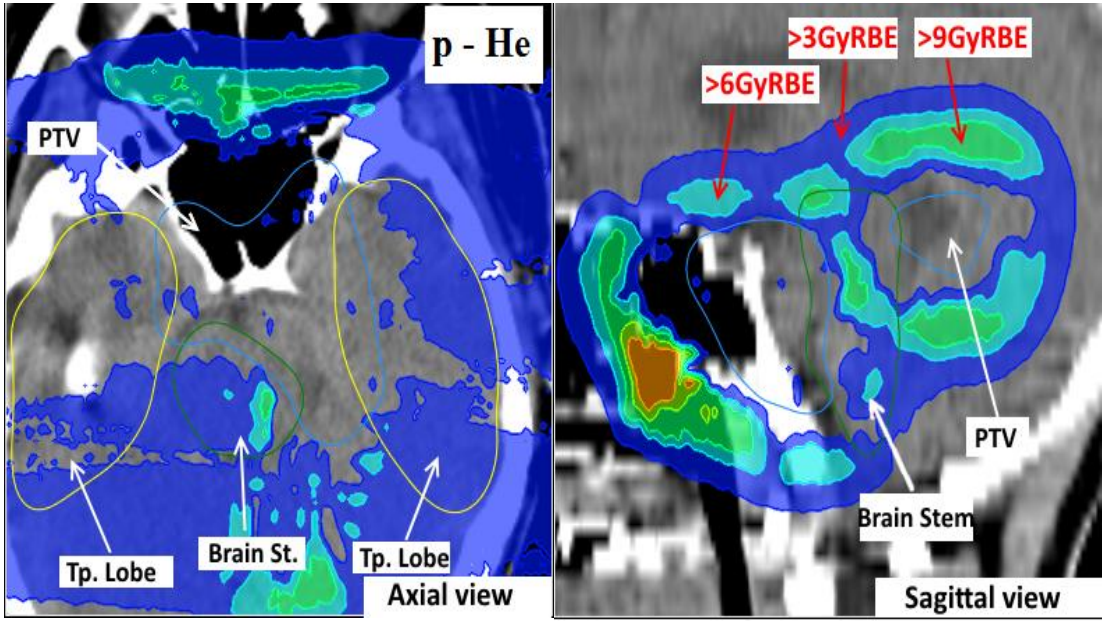
Less dose to normal tissues

Tessonnier, Mairani et al under review

Plan Comparisons

Results





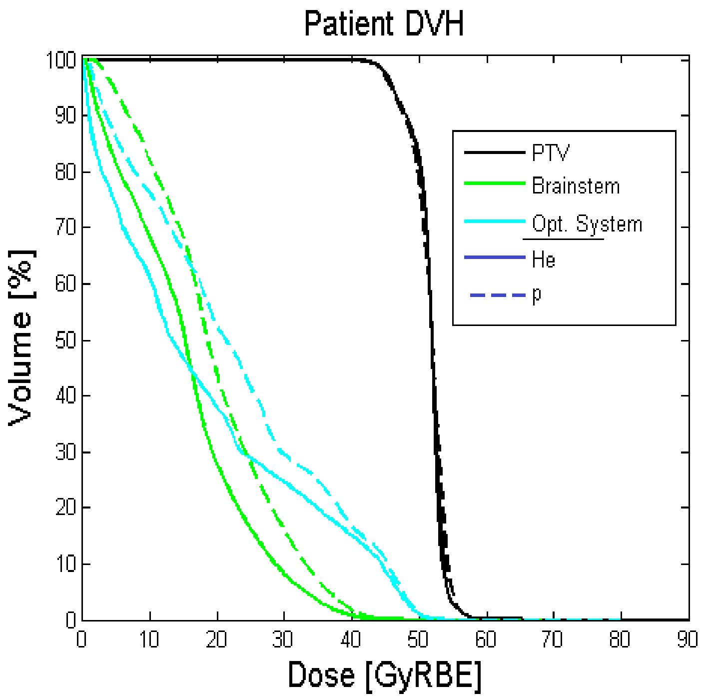
Higher benefits for large depth (lateral/distal fall-off)

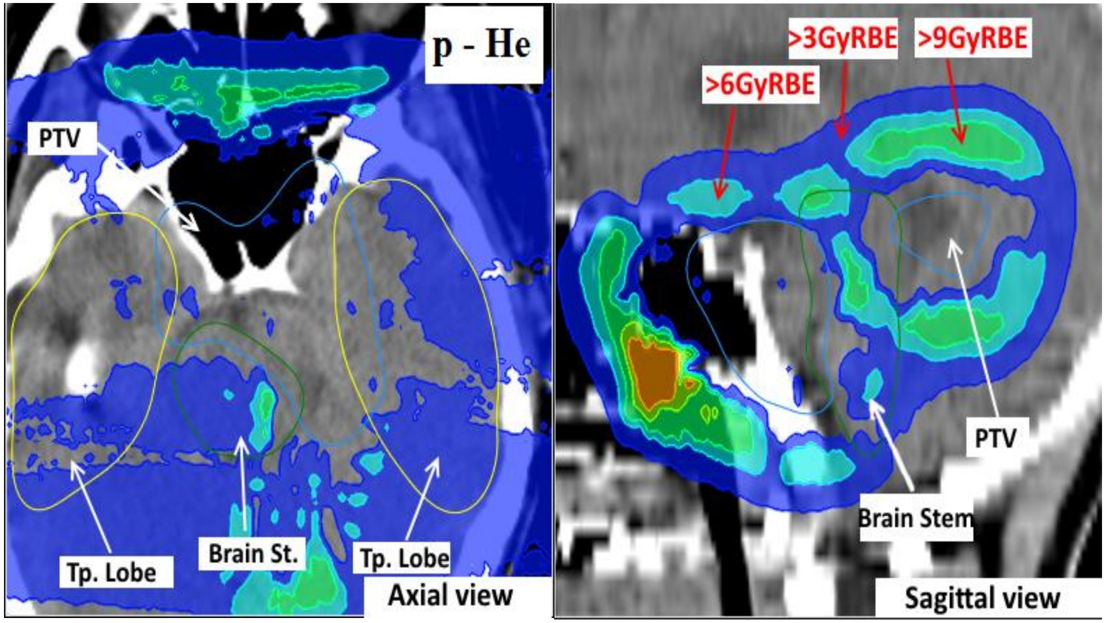
→ **Promising results** from **plan comparison between He and protons**

Tessonnier, Mairani et al under review

Plan Comparisons

Results





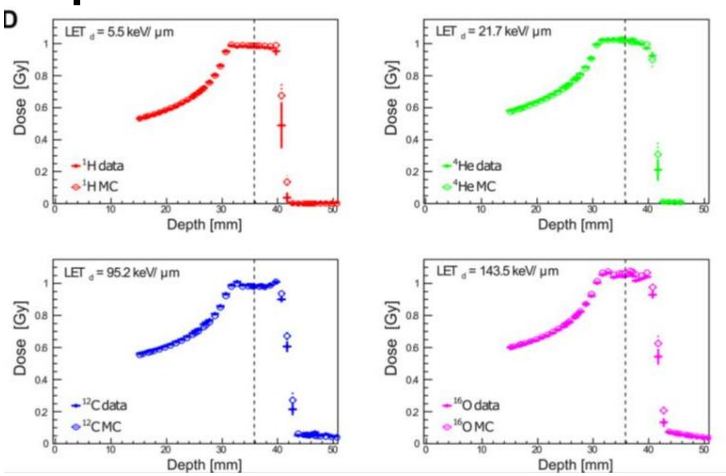
Other cases investigated…

RBE p fixed **≠ α/β** **≠ Dose** **+/- RiFi**

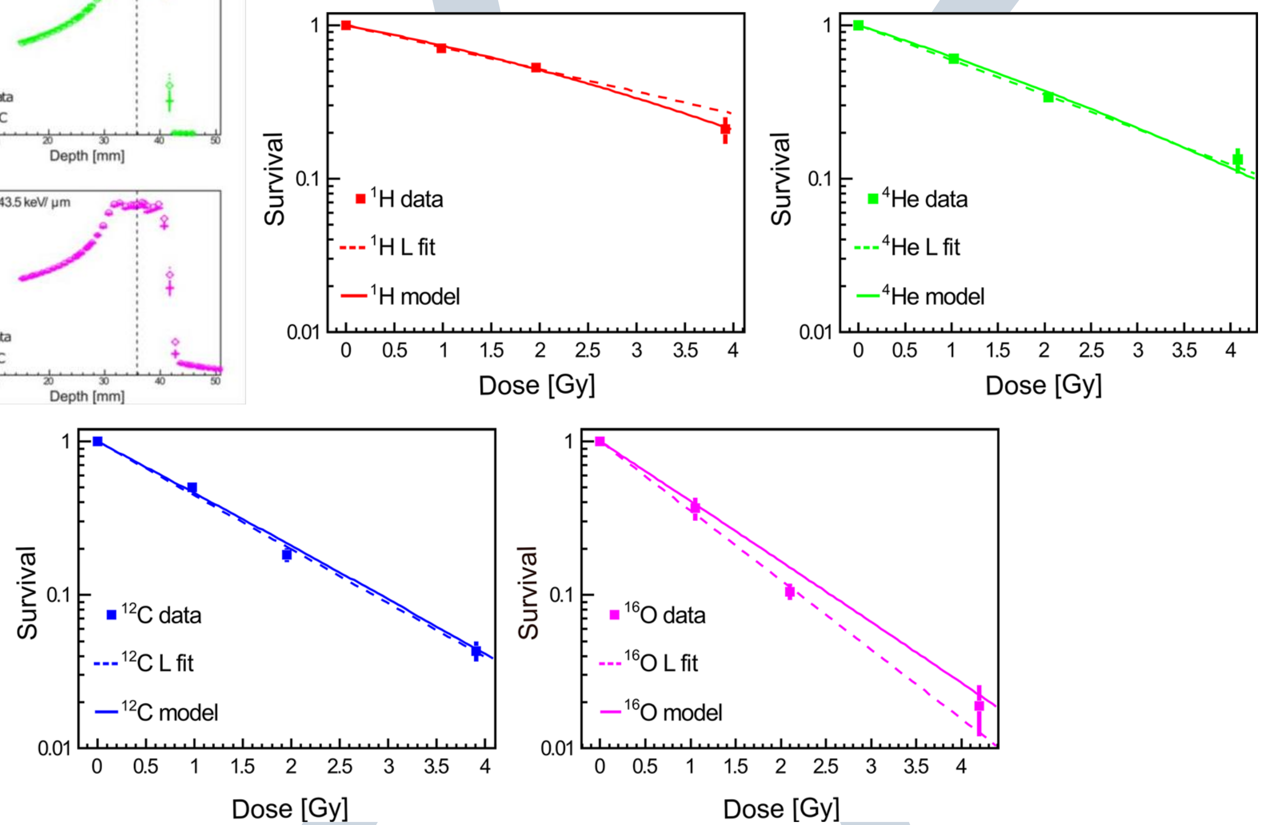
Tessonnier, Mairani et al under review

Novel Ions at HIT: physics and biology I

MC predictions vs dosimetric data



MC predictions vs in vitro clonogenic data



I. Dokic and A. Mairani et al Oncotarget. 2016; 7:56676-56689

Novel Ions at HIT: physics and biology II

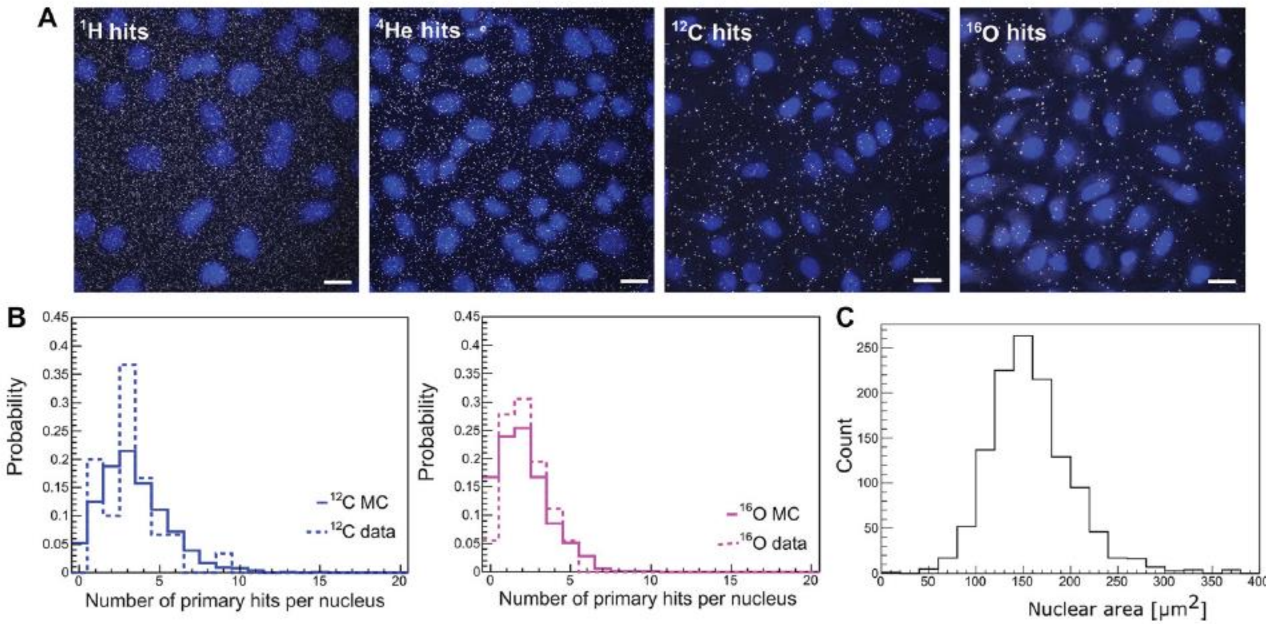
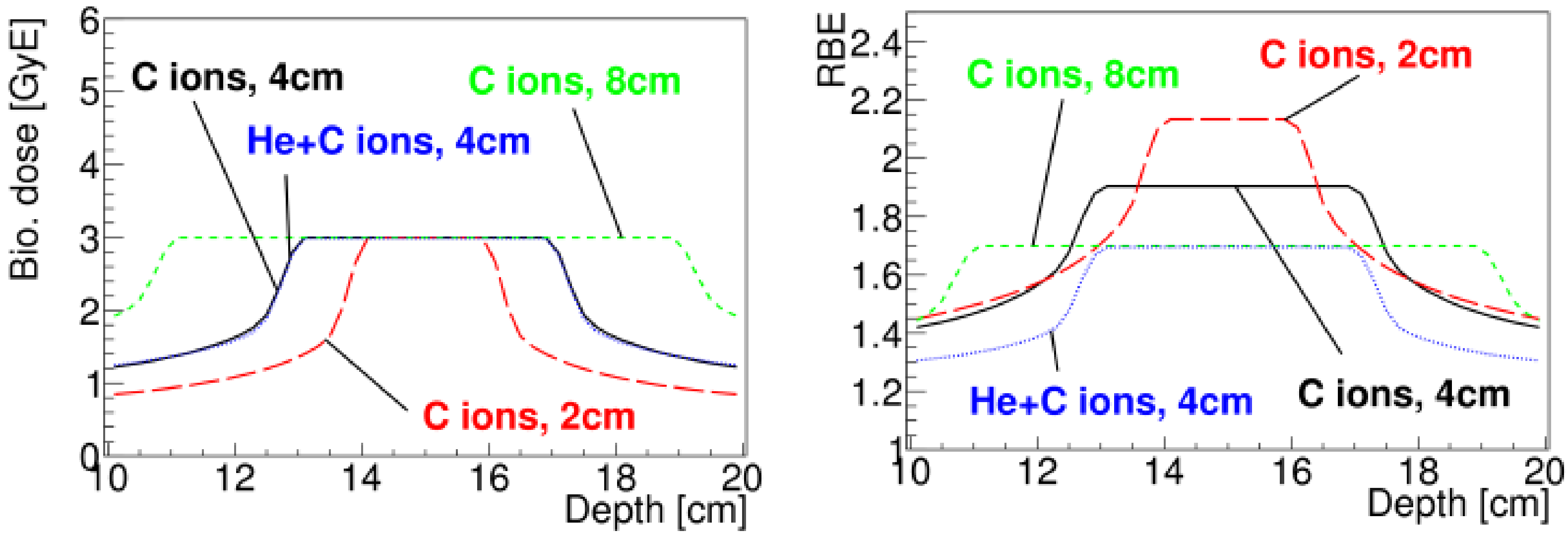


Figure 4: Particle hit per cell nucleus. Cell-Fit-HD was employed to detect the number of primary ion hits per cell nucleus. (**A**) White dots represent particle traversals and blue areas the cell nuclei (DAPI stained). Scale bar: 20 μm. (**B**) A high correlation between experimental (3.2 ± 0.3 for ^{12}C-beams and 2.2 ± 0.2 for ^{16}O-beams) vs. simulation (3.4 for ^{12}C-beams and 2.1 for ^{16}O-beams) based nuclear hit distribution was found. Y-axis represents the probability of particle hits per nucleus. (**C**) Nuclear area size distribution. Images of DAPI-stained nuclei were obtained. To measure nuclear area the Z-stack images of DAPI staining were background subtracted using ImageJ's Rolling ball radius. The images were further maximum Z-projected and segmented using Median filter to more precisely define the nuclear border. The images were thresholded and nuclear area was finally measured using the Analyze Particles tools. All the image processing was performed automatically using the ImageJ macro with constant settings (n = 1239).

I. Dokic and A. Mairani et al Oncotarget. 2016; 7:56676-56689

Dual ion fields

Example: He+C fields with const. RBE in PTV to have a constant radiation quality as a function of field size



+ Reduces risk for possible relative misestimations as a function of field size (and also field depth)

– Dilutes (the probably advantageous) high-LET component of C ions.

+ However for treatments with higher-LET ions, such as oxygen, the mixture with lower-Z ions could additionally help to reduce the fragmentation tail.

Böhlen,…,Mairani PMB 57 2012

Dual ion fields

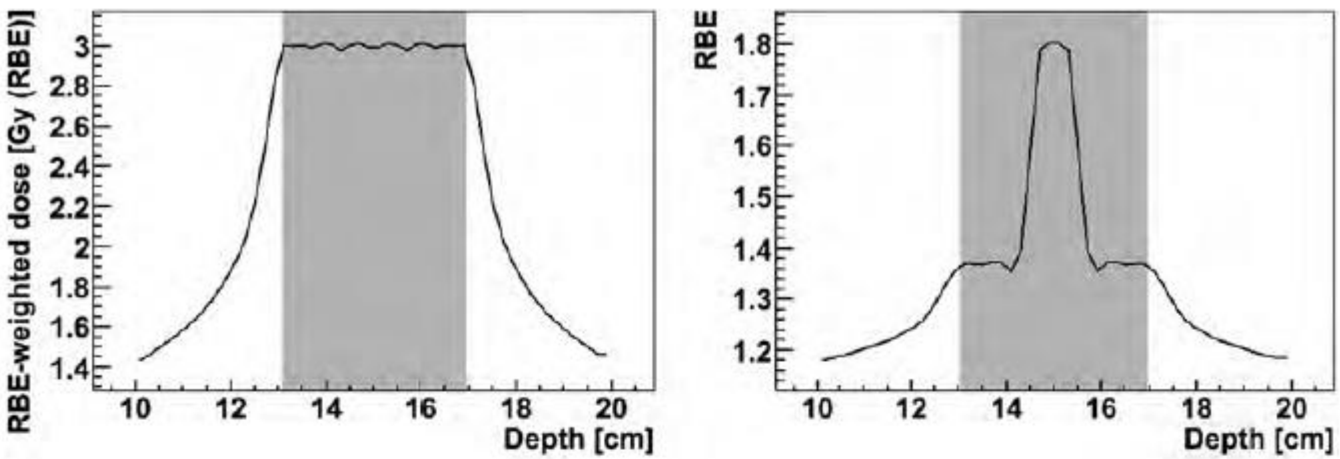


Fig. 5. A 4-cm SOBP obtained using a combination of opposed fields of proton and carbon ion pencil beams. A constant RBE-weighted dose in the target volume is achieved while delivering a 'high-LET boost' to a central hypoxic area with carbon ions, associated with a higher RBE, and delivering the dose around the boost region preferably by low-LET protons. The left and right panels show the RBE-weighted dose and RBE along the central axis of the field. The plan was optimized using the LEM-IV model for the proton and carbon ion beams with parameters for human salivary gland cells. The area with the fine stripes marks the target volume including the boost volume.

Böhlen,…,Mairani Rad Res 54 2013

- Allows to optimize for **wanted radiation quality** (based on RBE, LET, lineal energy, …?)
  - Independently of field size and depth
- Also usable for orthogonal and patched field geometries
- **Similarity to "LET painting"**-approach → region with uniform rad. quality

Bassler et al Acta Oncol 54 2013

Thank you
for
Your Attention!