Evaluarea individualizată a efectivității biologice a protonilor – implicațiile clinice în radioterapia cu protoni

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Individual evaluation of RBE effects in clinical proton therapy

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- It is the national Swedish proton therapy facility treating patients since August 2015.
- It follows in a long tradition of clinical proton treatments in Uppsala.

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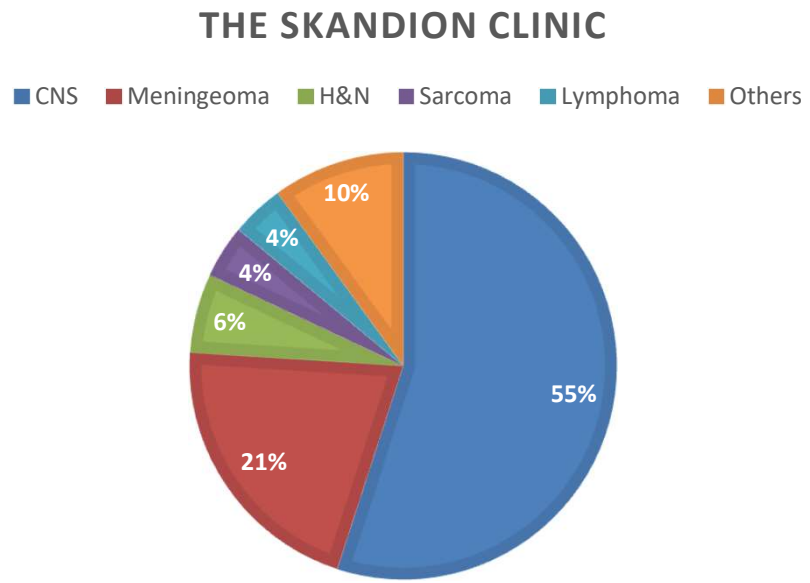
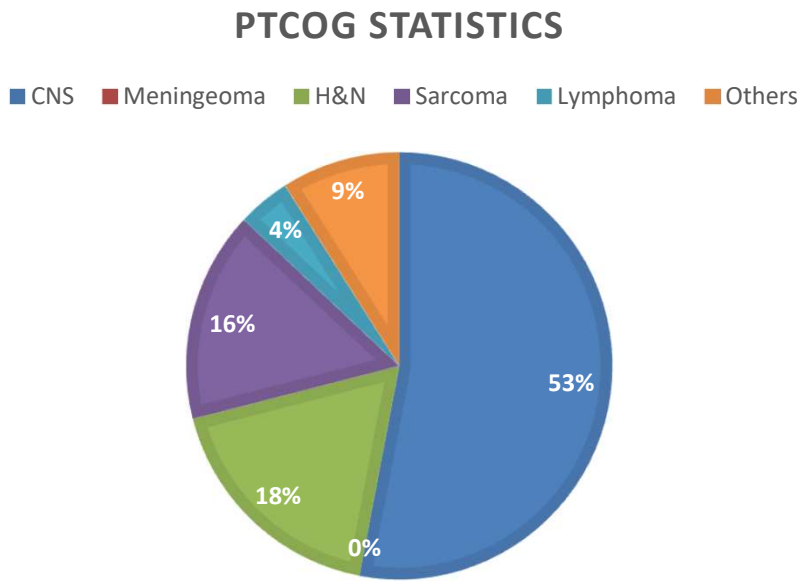
Patients

- Almost 2000 patients started their treatment.
- Approximately 18% are paediatric patients.
- Brain treatments dominate for adult patients.





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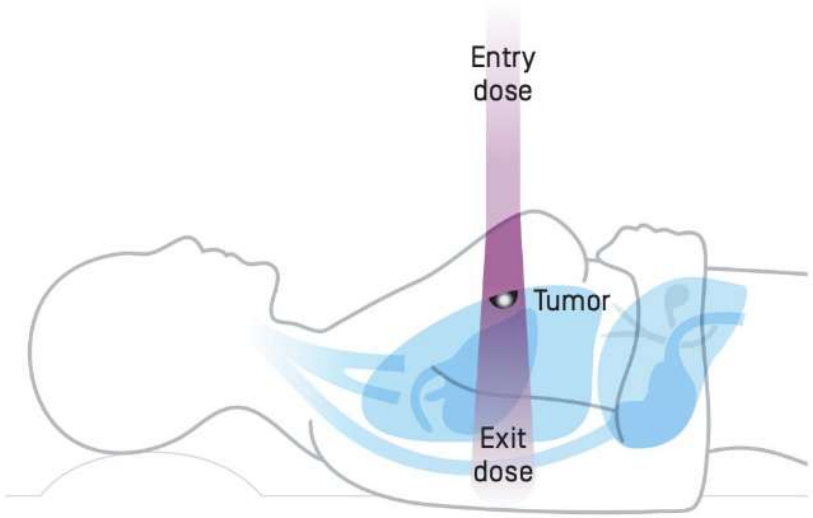
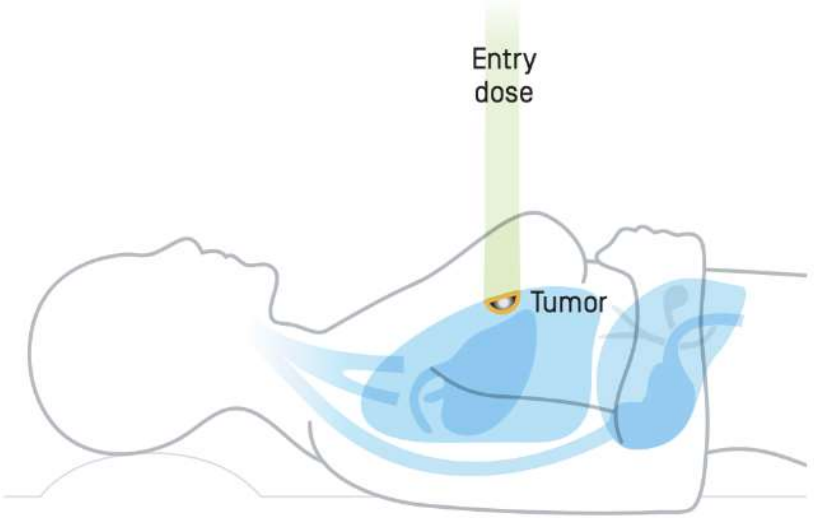
Why protons?

Photon-based Radiotherapy



Deposits most of its energy outside the tumor

Proton Therapy



Deposits most of its energy inside the tumor

IBA

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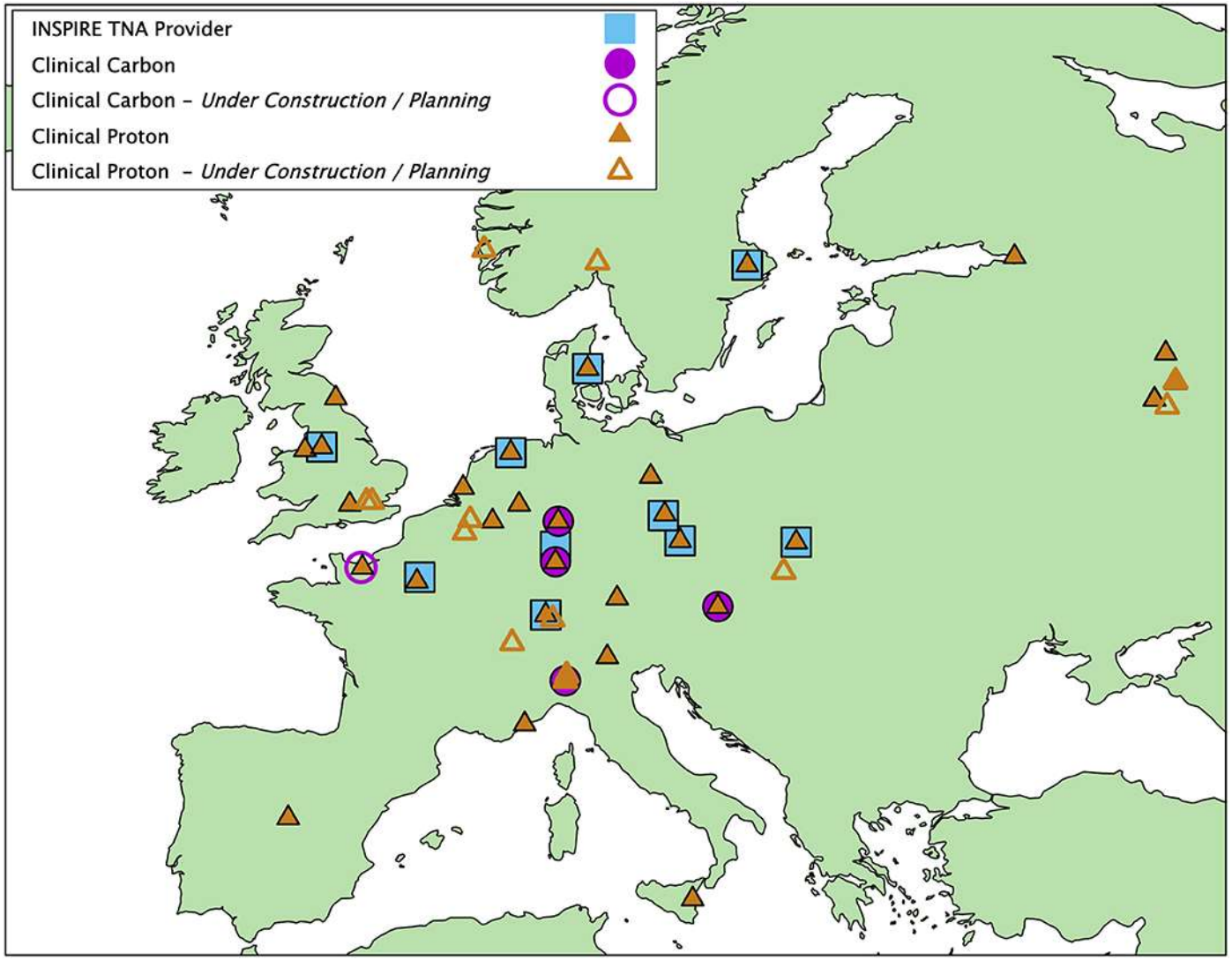
Particle therapy expansion



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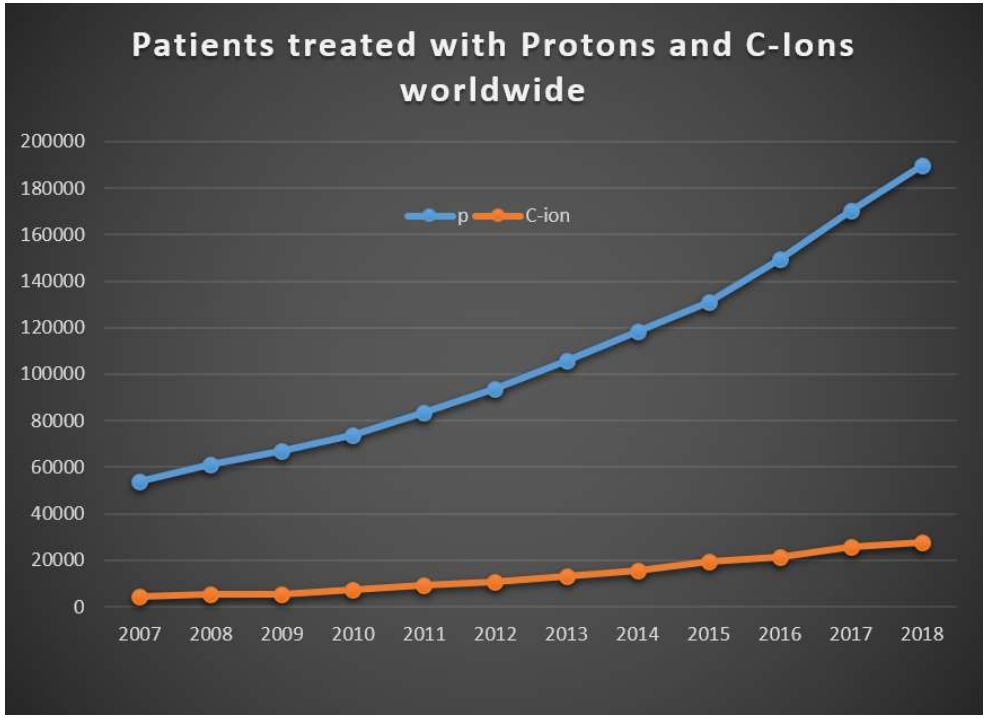
Proton therapy expansion

- Recent years have seen an increased proliferation of proton therapy centres.
- A much larger number of patients might benefit from proton therapy in the near future
- How should they be selected?
- How should they be planned?
- How should the plans be evaluated, especially in comparison to photon plans?



Particle Therapy Co-Operative Group

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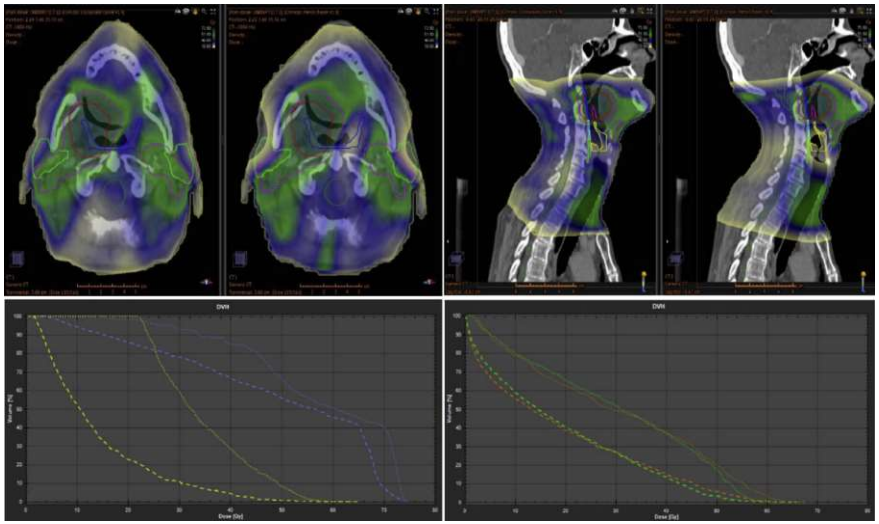
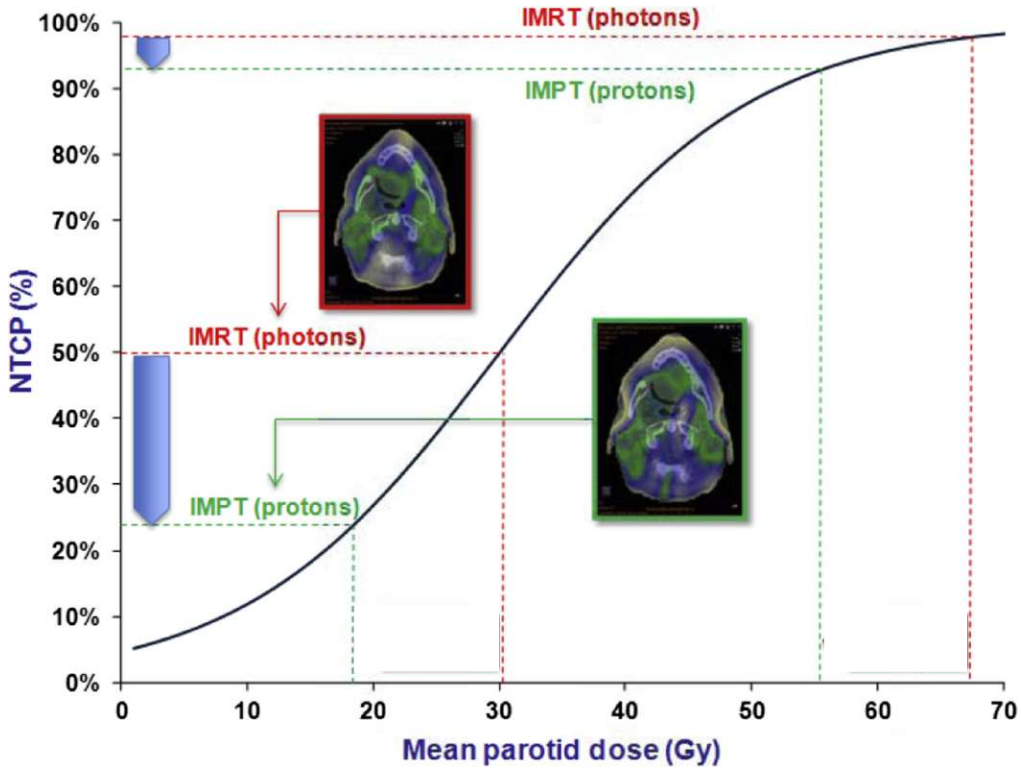
Patient selection at Skandion

- National consensus on referred diagnoses
- Photon and proton plans for each case
- Individual decision for proton therapy depending on dosimetric parameters of interest

The ‘Dutch model’ for patient selection

- Model-based patient selection for proton RT





$\Delta NTCP = NTCP_{photons} - NTCP_{protons}$

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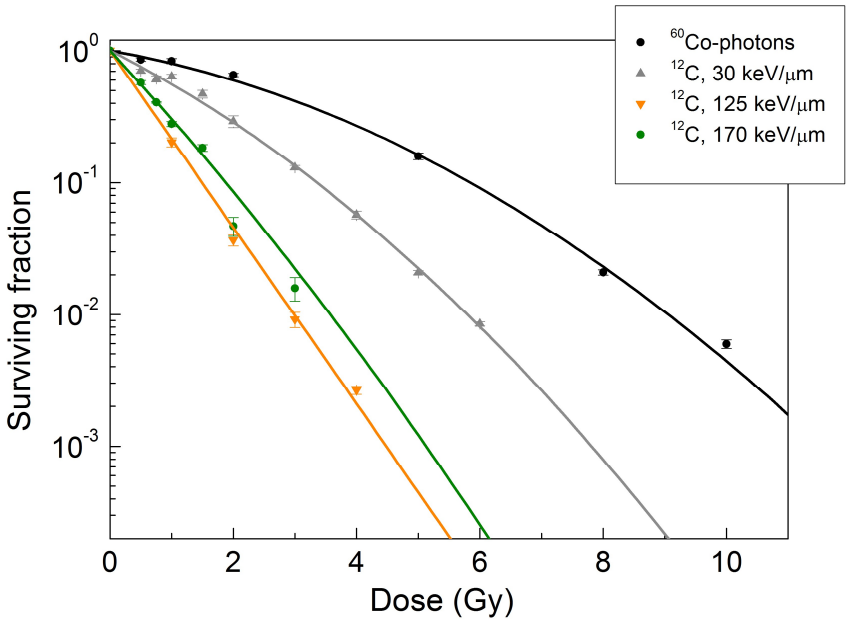
RBE in particle therapy

- RBE (Relative Biological Effectiveness) accounts for differences in radiobiological effect between photons and other particles employed for radiation treatments

$$\mathrm{RBE} = \frac{\text{Dose of reference radiation}}{\text{Dose of test radiation}}$$



- For many particles, including C-ions, the variation of RBE with LET and tissue type is taken into account.
- In contrast, for protons, a single value of 1.1 is used.

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Proton RBE

- RBE=1.1 was adopted by most clinical centres following the ICRU recommendations.

In summary, the available data on *in vitro* and *in vivo* systems (including acute- and late-reacting tissues) are consistent with a tissue-independent mean RBE value of 1.10. Further, there is no suggestion from studies on *in vivo* systems of an increase in RBE as absorbed dose is reduced to $< 3–4$ Gy. This finding for protons of no dose dependence of RBE is in contrast with those for fast neutrons, where RBE increases steeply as absorbed dose is decreased below 4 Gy (Field, 1977). The fact that the proton RBE data do not conform to the expectations from the neutron data may, in part, reflect the difficulty in demonstrating the modest changes in relatively small RBE values.

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Proton RBE

- Experimental data indicate a complex variation of the RBE for protons.

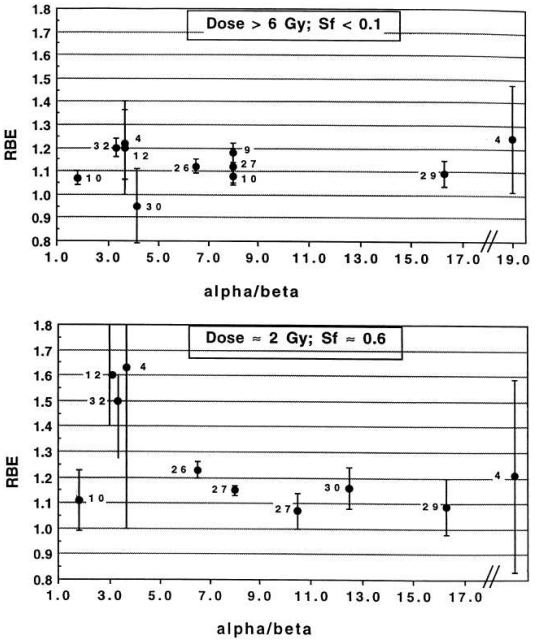

Fig. 1. RBE values are plotted as a function of the estimated α/β values for the target cells or tissues (see text for further details). Confidence intervals are as stated in the source manuscript or interpolated from the information provided and represent one standard deviation [4,10,26,29,30] or the 95% confidence interval [9,10,27,32]. For Ref. [10] the mean and standard deviation of the RBEs measured at three positions in SOBPs and for Ref. [32] the mean RBE for all positions in the SOBP are shown. All other data pertain to the mid-SOBP protons. Source reference numbers are adjacent to data points.

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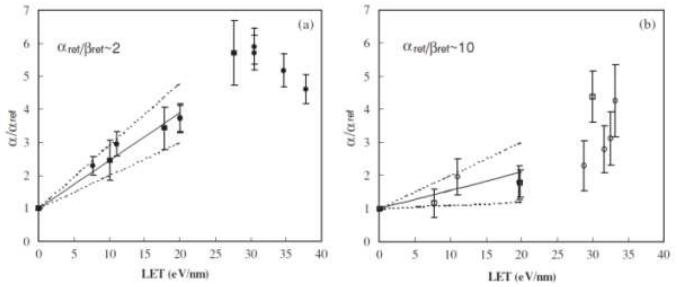

Figure 2. α/α_{ref} values as a function of LET for protons and the corresponding fit of these data with the estimated minimum and maximum limits for $\alpha_{ref}/\beta_{ref} = 2$ Gy (a) and $\alpha_{ref}/\beta_{ref} = 10$ Gy (b). ■: V79-379A cells with $\alpha_{ref}/\beta_{ref} = 2.7$ Gy (Folkard *et al* 1996), ●: V79-753B cells with $\alpha_{ref}/\beta_{ref} = 2.8$ Gy (Belli *et al* 1993, 1998) (a). □: SQ20B cells with $\alpha_{ref}/\beta_{ref} = 7.6$ Gy (Belli *et al* 2000). ○: C3H10T1/2 cells with $\alpha_{ref}/\beta_{ref} = 15$ Gy (Bettega *et al* 1998).

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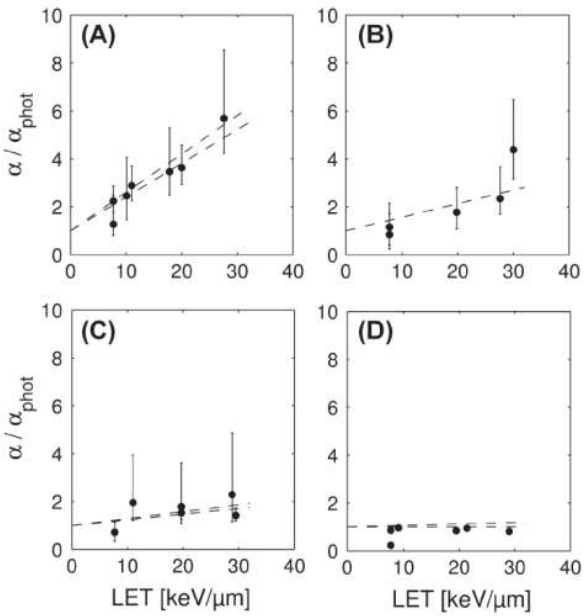

Figure 1. Experimentally obtained α/α_{phot} values as a function of LET. Panel A with $(\alpha/\beta)_{phot}$ 2.7–3.1: V79-379A cells [12], V79-753B cells [10], and DLD1 cells [17]. Panel B with $(\alpha/\beta)_{phot}$ 7.7–7.7: SQ20B [13], and C1-1 cells [16]. Panel C with $(\alpha/\beta)_{phot}$ 15–18: C3H10T1/2 [11], and SCC25 [13]. Panel D with $(\alpha/\beta)_{phot} \geq 70$: HCT116 [17], M/10 cells and HF19 cells [13]. The error bars show the 95% CI. The dashed lines are obtained with Equation 2 where the highest and lowest $(\alpha/\beta)_{phot}$ in each panel is used.

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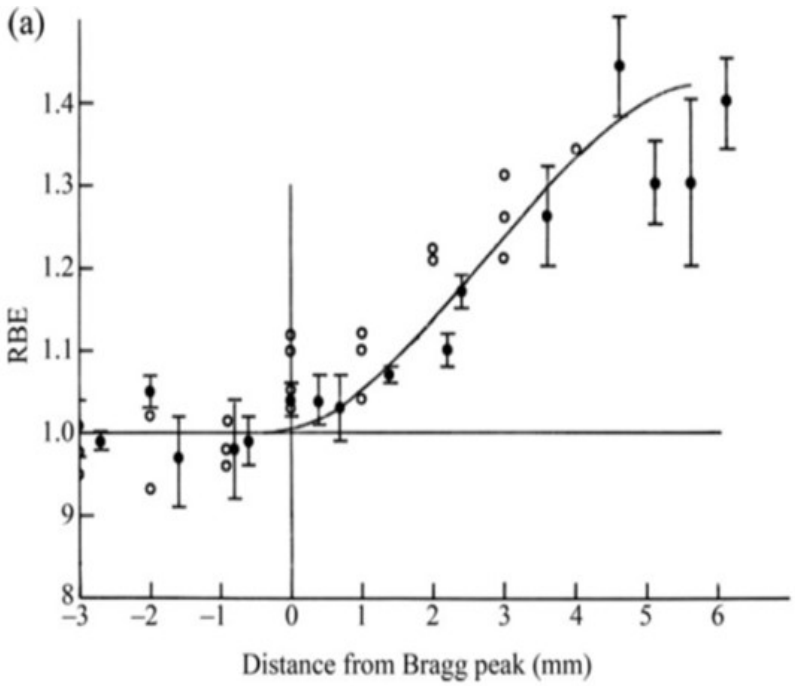
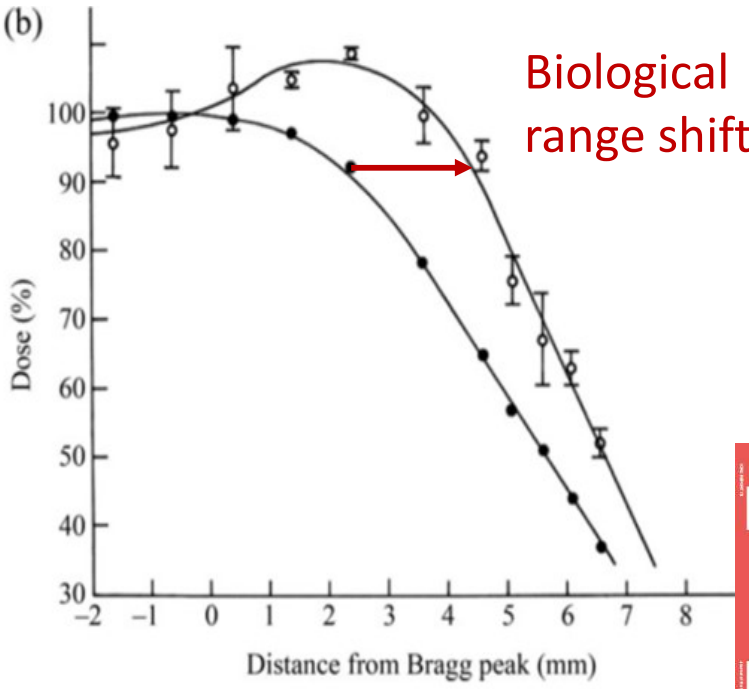
Proton RBE

- The increased RBE in the distal part of the proton range could lead to a ‘biological range shift’.





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Clinical implications of proton RBE

- Clinical implications of proton RBE variations are increasingly discussed.

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RBE for proton radiation therapy – a Nordic view in the international perspective

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Review Article

Does the uncertainty in relative biological effectiveness affect patient treatment in proton therapy?

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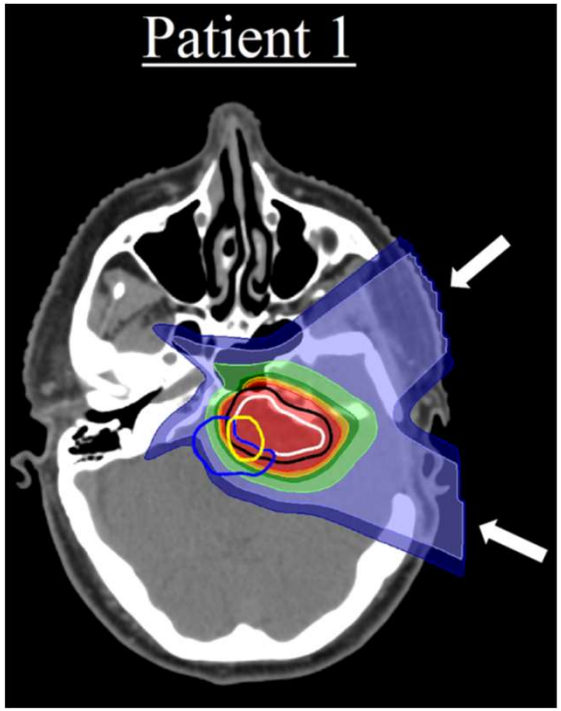
Clinical evidence of proton RBE

- The emergence of clinical evidence for proton RBE effects is strongly influenced by the available patient numbers.
- A systematic analysis is warranted and implies international cooperation.
- It also implies a close analysis of individual dose and RBE distributions and also other individual factors.

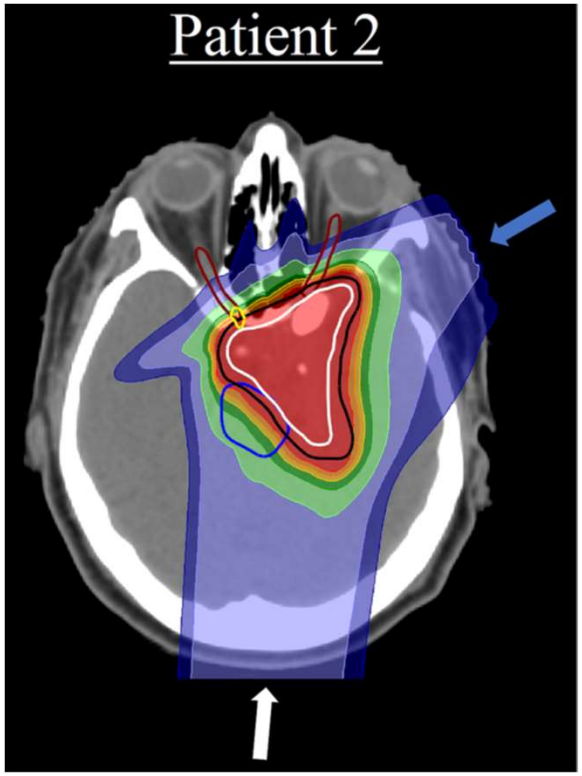
Cases of suspected treatment-related toxicities

- Patient case 1 had a Schwannoma grade I tumor compressing the brainstem and was treated with 54 Gy (RBE) in 30 fractions. The patient developed brainstem complications 5 months after treatment with left-sided hemi-paresis, double vision and vertigo. Initially this was interpreted as tumor progression due to significant tumor compression of the brainstem. The delineated toxicity volume was located in the brainstem and in the part of the CTV most adjacent to it.



Cases of suspected treatment-related toxicities

- Patient case 2 had a meningioma grade I tumor and was treated with 50.4 Gy (RBE) in 28 fractions. The patient developed right-sided unilateral blindness 9 months after treatment. The delineated toxicity volume was located in the posterior part of the right optical nerve.



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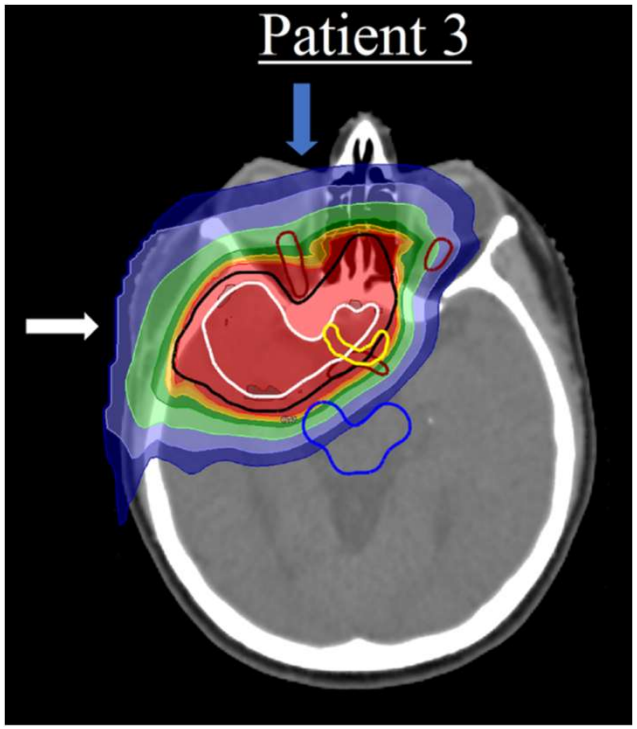
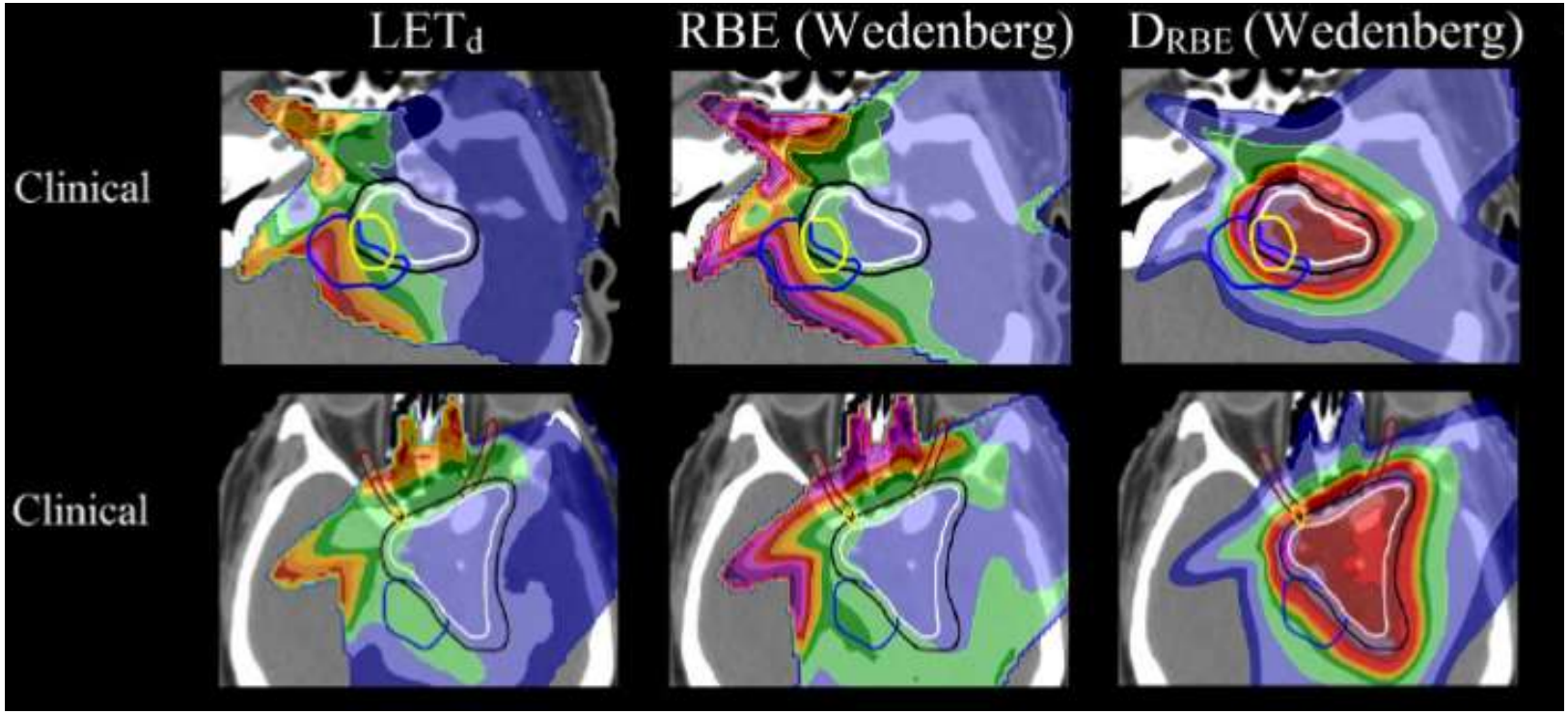
Cases of suspected treatment-related toxicities

- Patient case 3 had a frontal oligoastrocytoma grade II tumor and was treated with 54 Gy (RBE) in 30 fractions. The patient developed left-sided unilateral blindness 8-10 months after treatment. The delineated toxicity volume was located in the chiasma (primarily on the left side), reaching into the posterior part of the left optical nerve.



Clinical RBE distributions

- Individual RBE distributions may impact upon the treatment plans.



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RBE evaluations at Skandion

- High LET/RBE values were found in toxicity areas.

	Patient 1 (Brainstem necrosis)	Patient 2 (Right RION)	Patient 3 (Left RION)
$D_{RBE=1.1}$	53.8 Gy RBE	49.7 Gy RBE	52.1 Gy RBE
LET_d	3.7 eV/nm	3.4 eV/nm	4.4 eV/nm
RBE Wedenberg	1.28	1.26	1.33
$D_{RBE\ Wedenberg}$	62.5 Gy RBE	57.0 Gy RBE	63.0 Gy RBE

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RBE-specific treatment evaluation

- Can one account for RBE distributions at plan evaluation?

NTCP evaluations

		RBE=1.1			RBE Wedenberg	
	Plan	$D_{RBE=1.1}$	NTCP	LET_d	$D_{RBE\ Wed}$	NTCP
Patient 1	Clinical	28.0/55.0	0.8	5.7/9.4	37.8/65.9	15.5
Brainstem						
Patient 2	Clinical	11.1/51.2	0.1	4.9/8.6	14.3/58.7	1.8
Optic nerve R						
Patient 3	Clinical	50.0/54.5	3.7	4.7/8.0	61.4/65.2	45.7
Chiasm						

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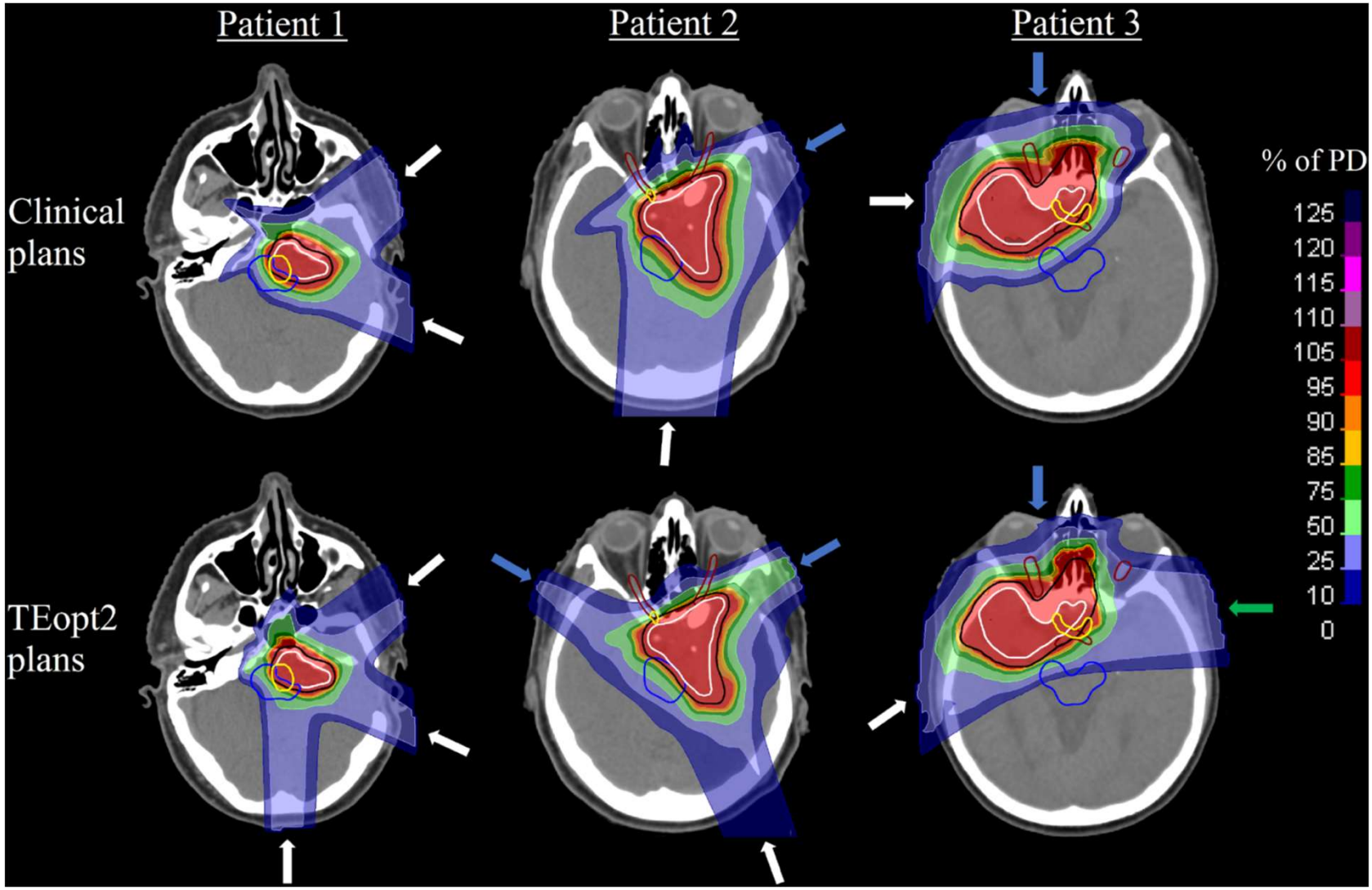
RBE-specific treatment individualisation

- Can one account for individual RBE variations during plan optimisation?

Alternative optimisation approaches



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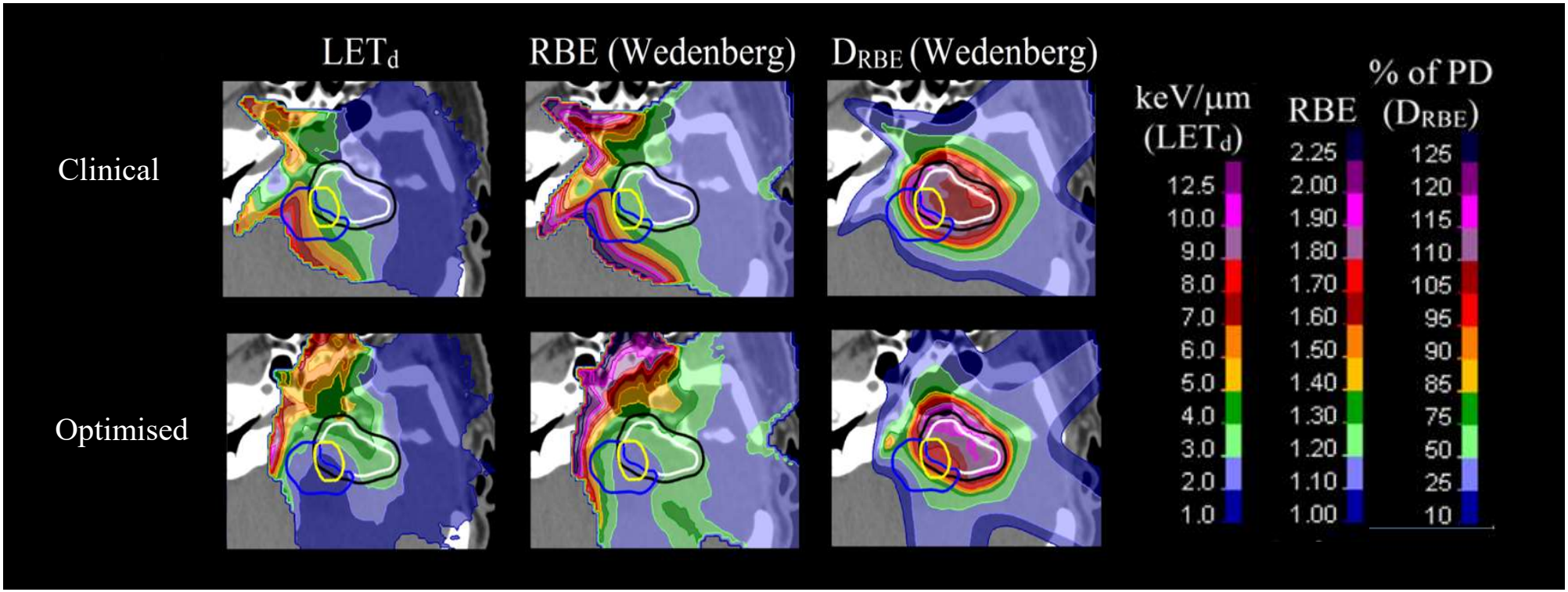
Alternative optimisation approaches



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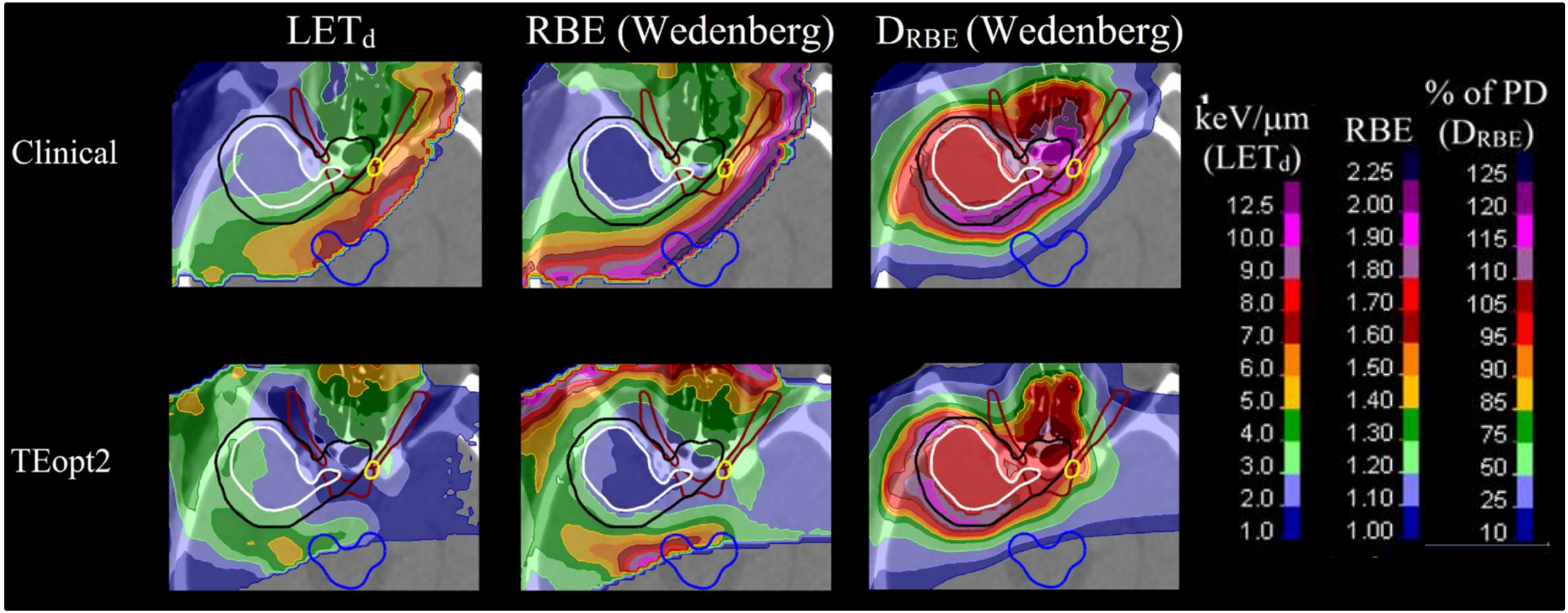
Alternative optimisation approaches



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NTCP evaluations

		RBE=1.1			RBE Wedenberg	
	Plan	$D_{RBE=1.1}$	NTCP	LET_d	$D_{RBE\ Wed}$	NTCP
Patient 1	Clinical	28.0/55.0	0.8	5.7/9.4	37.8/65.9	15.5
Brainstem	TEopt1	25.3/54.6	0.6	3.9/5.7	31.3/63.9	8.0
	TEopt2	24.7/54.9	0.6	2.2/4.1	27.3/58.0	1.9
Patient 2	Clinical	11.1/51.2	0.10	4.9/8.6	14.3/58.7	1.8
Optic nerve R	TEopt1	8.2/48.5	0.05	3.2/5.5	9.9/53.4	0.4
	TEopt2	8.4/47.9	0.05	2.2/3.2	9.7/51.8	0.3
Patient 3	Clinical	50.0/54.5	3.7	4.7/8.0	61.4/65.2	45.7
Chiasm	TEopt1	48.3/54.1	2.4	3.6/5.7	56.4/63.1	23.2
	TEopt2	48.7/53.0	1.7	1.7/2.2	50.6/54.6	3.8

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Conclusions

- The correlation found between high LET/RBE and areas with suspected toxicity does not automatically imply causality.
- Evaluating RBE distributions can avoid underestimations of the RBE-weighted doses to the CTV and OARs.
- Optimising individual plans accounting for RBE variations may lead to plans with clinically acceptable CTV and OAR doses.

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