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Aim:

In proton therapy, a radiobiological effectiveness ratio (RBE) of 1.1 (RBE1.1) is often used to describe the higher cell kill per Gy observed with protons compared to x-rays. In reality, RBE depends on dose, linear energy transfer (LET), biological end point and tissue type. Using a single fixed value of RBE may not therefore be accurate for all situations and may affect dose calculation and outcome. In this work, we investigate the effect of potential variation in RBE on modelled secondary cancer risk following proton therapy (figure 1), comparing a fixed RBE or 1.1 to results calculated using the “MinMax” model [1].

Materials & Methods:

An in-house developed MATLAB code for modelling malignant induction probability (MIP) from voxel-by-voxel maps of organ type and dose [2]. Published models were implemented to calculate structure-specific RBE using both a fixed value of 1.1 and also the “MinMax” RBE model from Carabe-Fernandez, et al[1] which is a function of dose d , α and β and RBE_{min} and RBE_{max}

$$RBE = \frac{-\alpha + \sqrt{\alpha^2 + 4\beta d(RBE_{max}\alpha + RBE_{min}^2\beta d)}}{2\beta d}$$

MIP was then calculated using linear quadratic (LQ), linear (LIN), and linear-no-threshold (LNT) models for proton therapy plans for example adult and teenage medulloblastoma (MB) patients using both RBE models.

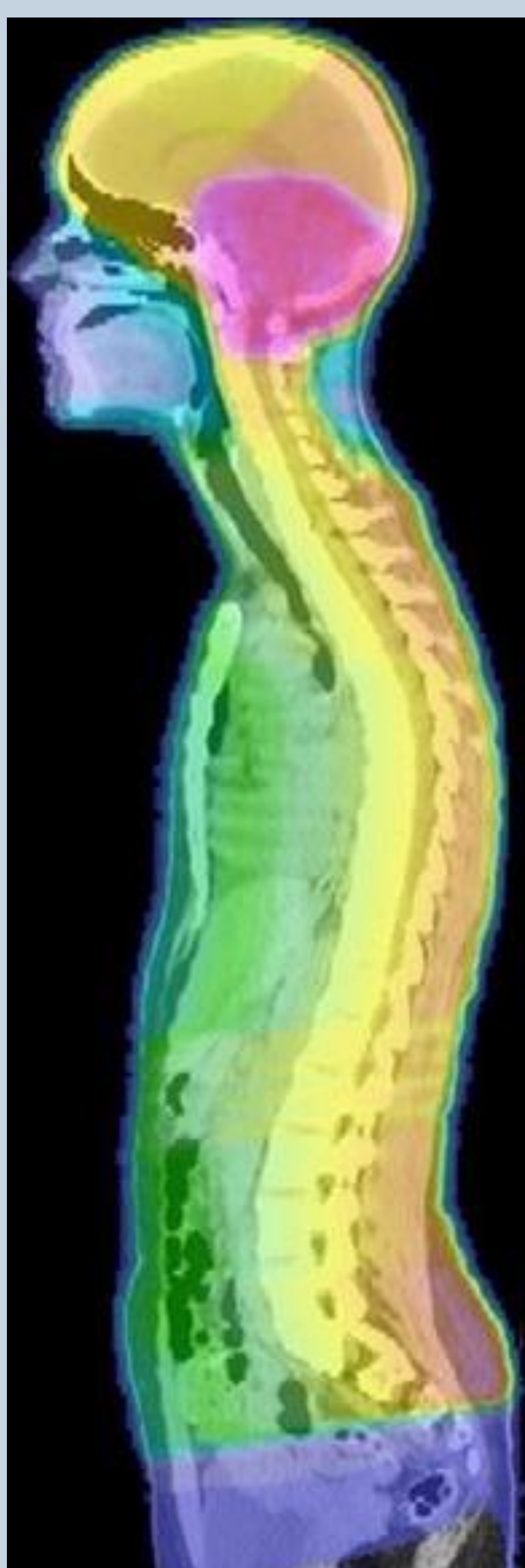
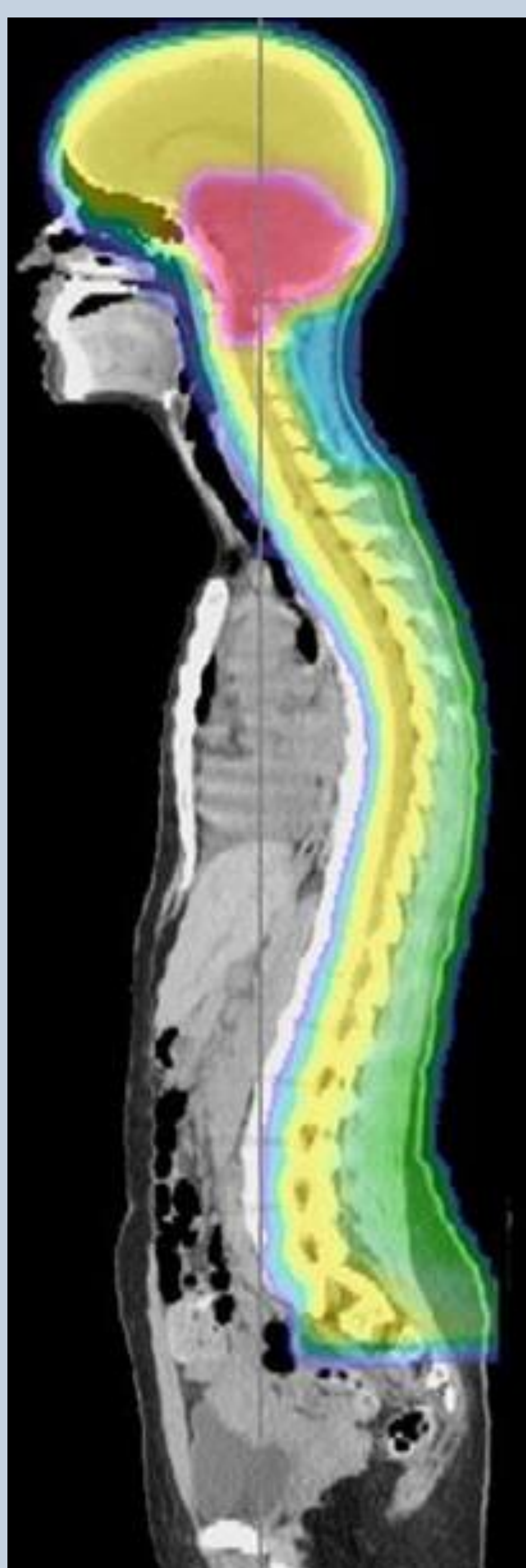


Figure 1: The 3 DCRT plan (left) and the proton plan (right) using RBE of 1.1.



MIP - Adult			
Model	$RBE_{1.1}$	RBE_{MinMax}	$RBE_{1.1} \cdot RBE_{MinMax}$
LQ	0.099	0.097	1.03
LIN	0.078	0.076	1.03
LNT	0.643	0.655	0.98

MIP -Teen			
Model	$RBE_{1.1}$	RBE_{MinMax}	$RBE_{1.1} \cdot RBE_{MinMax}$
LQ	0.068	0.066	1.02
LIN	0.057	0.056	1.02
LNT	0.554	0.567	0.98

Figure 2: Values of whole body MIP using RBE of 1.1 (RBE1.1) and RBE using the described model (RBEMinMax) and the relationship between them for the adult patient (top) and the teenage patient (bottom) .

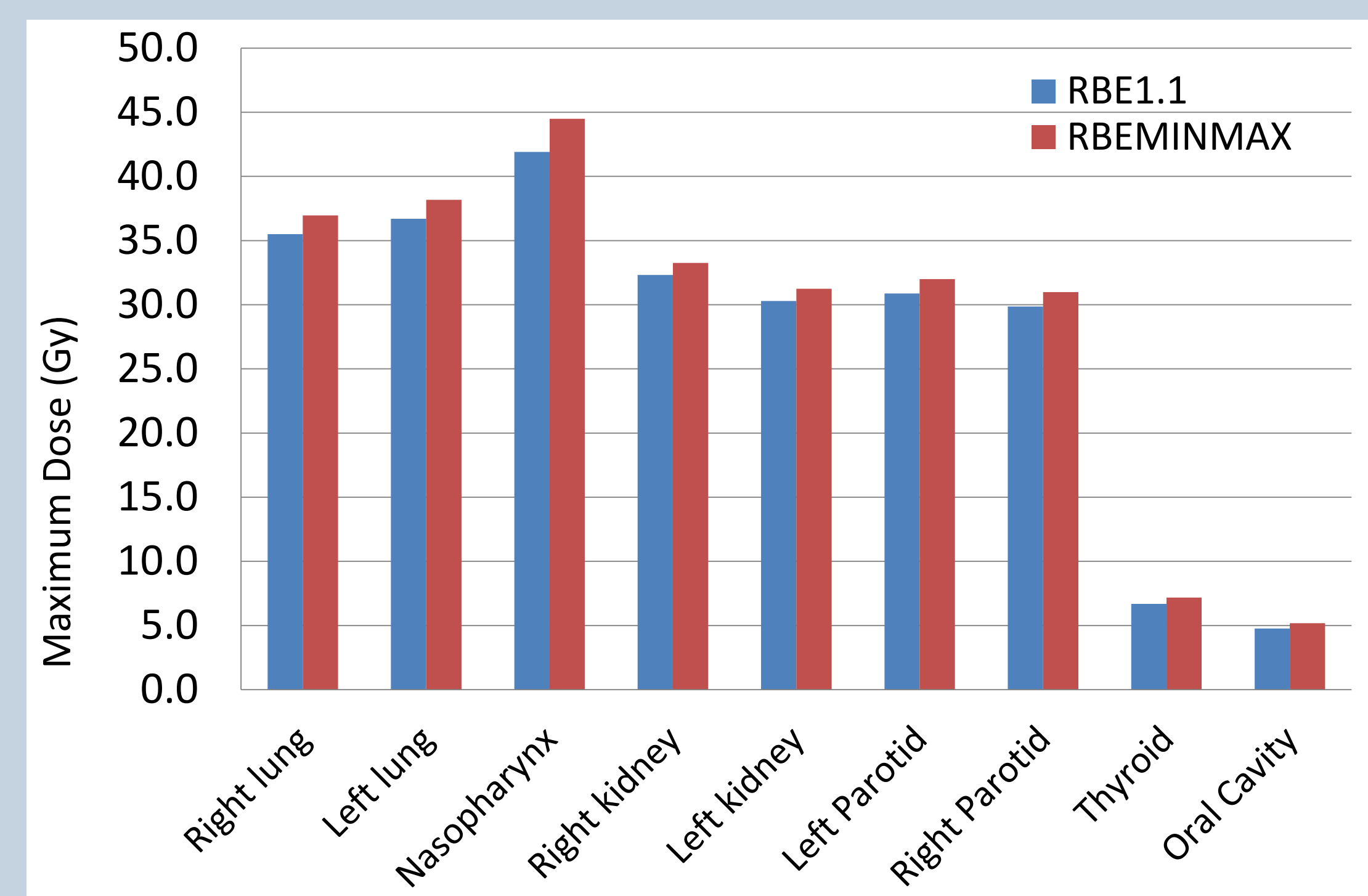
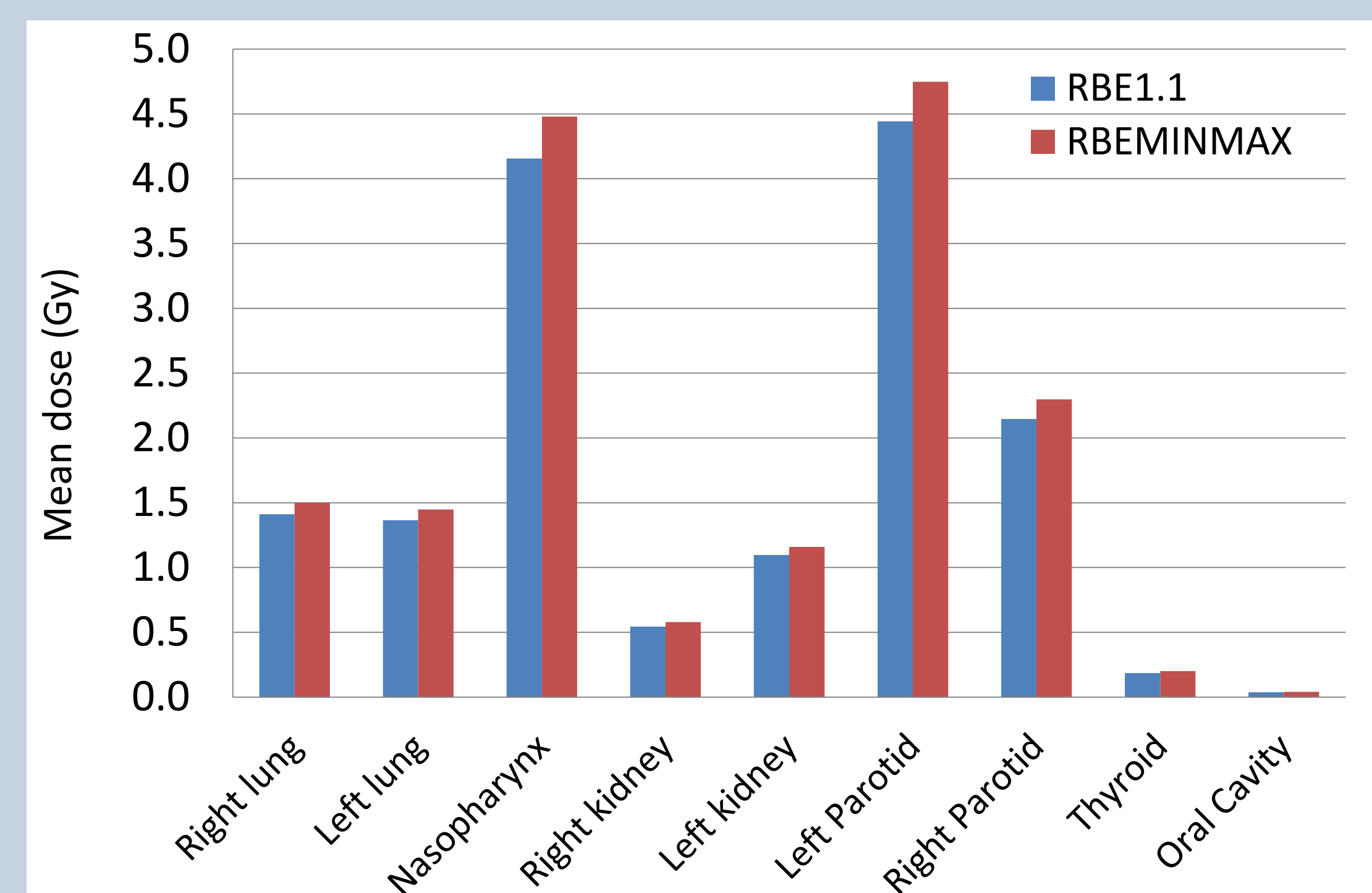


Figure 3: Mean dose (top) and maximum dose (bottom) for selected structures from the adult patient's plan using RBE1.1 and RBEMinMax and the relation between them.

Results:

Results are shown in Figures 2. The difference in MIP calculated using either a fixed RBE of 1.1 or the RBE MinMax model is ~2-3%. For the LIN and LQ models, which include a radiation cell kill, the MinMax model produces lower risk estimates than the fixed RBE of 1.1. The reverse is seen for the LNT model, which tends to overestimate MIP at high dose. The effect on mean dose varies between organs and is between 6% and 8% (figure 3) . The clinical implications of the difference in RBE will depend on beam characteristics, dose, structures concerned, and the volume irradiated.

Conclusions:

Using a fixed RBE of 1.1 makes proton therapy dose and dose-dependent predictions less accurate. Our results using the “MinMax” RBE calculation model show that decreased accuracy may have clinical implications, with dosimetric errors on 6% to 8%, which agrees with published literature [3,4]. The effect on secondary cancer risk was significant, at 2 – 3 %, but is relatively small compared to the overall uncertainties in second cancer prediction.

Malignant induction models: Linear-no-threshold: $MIP_{LNT} = \lambda D$ λ is the linear coefficient, D is the total dose, linear quadratic model: $MIP_{LQ} = n(\gamma d + \delta d^2) e^{-n(\alpha d + \beta d^2)}$, linear model: $MIP_{LIN} = \lambda D e^{-n(\alpha d + \beta d^2)}$ n is the number of fractions, d is the dose per fraction, γ and δ are the malignant induction coefficients, α and β are radiosensitivity parameters.

[1] Carabe-Fernandez A, Dale R G, Bleddyn J (2007) The incorporation of the concept of minimum RBE (RBemin) into the linear-quadratic model and the potential for improved radiobiological analysis of high-LET treatments. Int.J.Radiat. Biol. 83(1),27–39.

[2] Timlin C, et al (2015) 3D calculation of radiation-induced second cancer risk including dose and tissue response heterogeneities. Med. Phys. 42, 866.

[3] Jones B, et al (2012) Dilemmas concerning dose distribution and the influence of relative biological effect in proton beam therapy of medulloblastoma. Br J Radiol. 2012 Oct;85(1018):e912-8.

[4] Jones B (2014) Patterns of Failure After Proton Therapy in Medulloblastoma. Int J Radiation Oncol Biol Phys, Vol. 90, No. 1, pp. 25-26.

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