



Dosimetric Impact of Proton Variable Relative Biological Effectiveness (vRBE) in the Treatment of Ocular Cancers

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Abstract

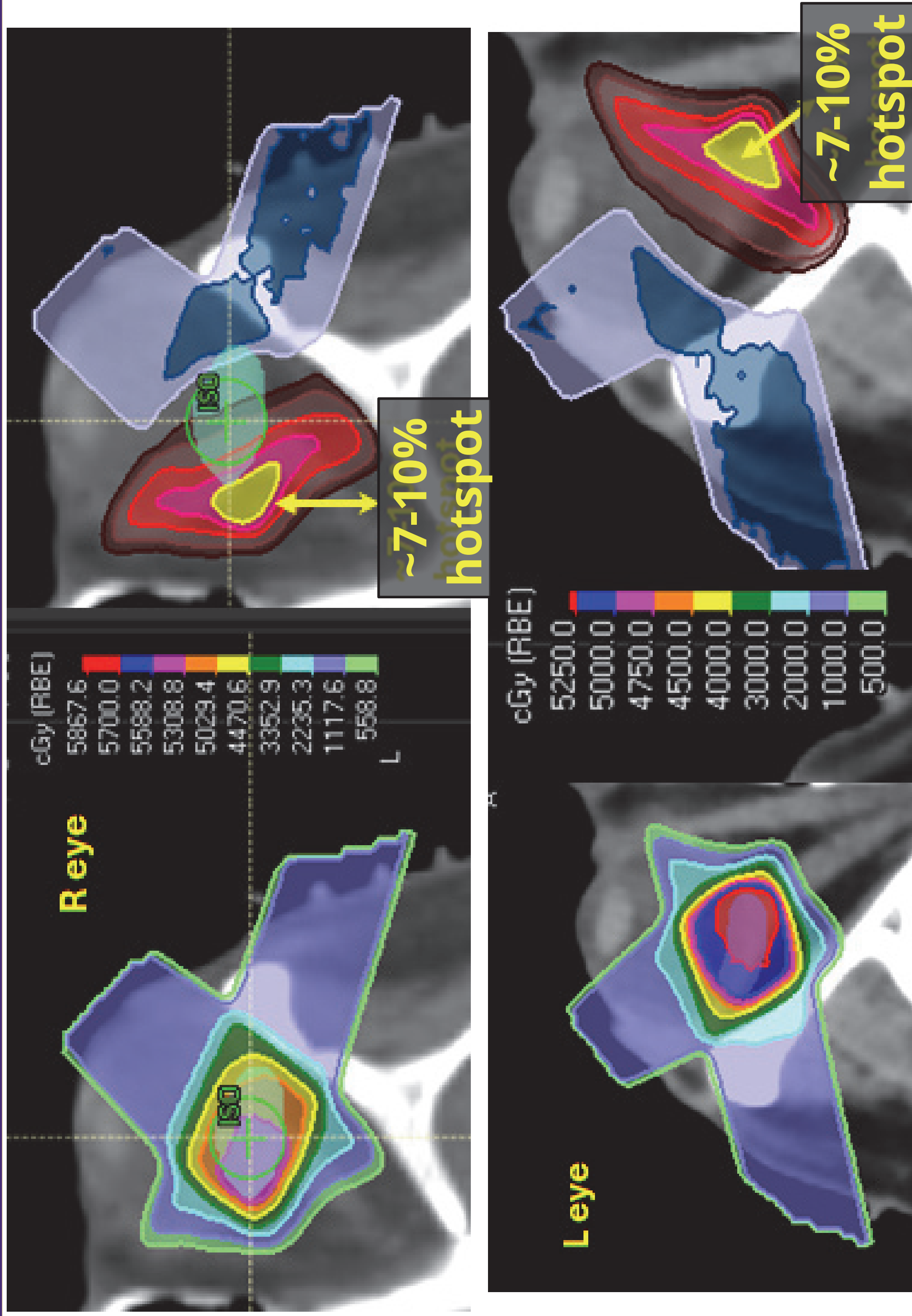
Purpose: Proton radiation therapy (PRT) is an effective modality for ocular cancers. Substantial evidence indicates that proton relative biological effectiveness (RBE) increases with linear energy transfer (LET). *In vitro* DNA double-strand break (DSB) and cell survival studies report an RBE >1.1 for low-energy protons (<10–25 MeV; range <1–6 mm), whereas higher-energy protons have an RBE in the range from about 1.0 to 1.1. This study evaluates the potential dosimetric impact of variable RBE (vRBE) in the treatment of representative ocular tumors.

Methods: The vRBE **Repair–Misrepair–Fixation (RMF)** model was implemented in a commercial treatment planning system via Python scripting. Retrospective RBE-weighted dose (RWD) was recalculated for four ocular cancer patients treated with hypofractionated PRT (5×10 Gy). All plans used two fields incident on the PTV at ~45°. Sensitivity to biological uncertainty was assessed using: (1) $\alpha/\beta = 2.5$ Gy, target diameter=4 μm (upper bound) and (2) $\alpha/\beta = 100$ Gy (lower bound). The lower bound on the RBE for cell survival approaches the RBE for DSB induction (RBE_{DSB}). Proton RBE increases with decreasing α/β .

Results: Relative to constant RBE planning (cRBE=1.1), vRBE predicted a largely patient-independent distal RWD hot spot (~7–10%) at the field intersection posterior-medial (outside) the PTV. Proximal to the PTV, RWD based on vRBE was 2–3% lower than cRBE. Across the entire of volume irradiated tissue, vRBE ranged from 1.07 to 1.20. For all plans, prescription coverage (PTV V50Gy=95%) increased (2-5%), lacrimal V20 decreased (3-10%), and optic nerve Dmax increased (4-6%).

Conclusions: In hypofractionated ocular PRT, vRBE assessment introduces localized RWD deviations of +3 to 5% within the PTV and predicts distal hot spots absent from cRBE plans. Gentle reshaping of LET distributions may improve the alignment between planned RWD and prescription intent with vRBE rather than cRBE = 1.1, motivating low-risk prospective evaluation of clinical vRBE-guided planning for ocular cancers.

Key Results – Isodose and Dose Difference



Figures 3-5 show representative results for left- and right-eye treatments using pencil beam scanning (PBS). The ocular snout is commissioned for a maximum range of 15 cm (75 mm in patient with a fixed range shifter). Clinically, most of our plans correspond to a proton range in water of no more than 50–60 mm in water. Patients are treated using two fields separated by at least 45 degrees, as illustrated in Figure 3. **Left panel:** RWD distribution (D x vRBE) in right and left eyes. **Right panel:** difference in RWD for constant and vRBE.

Innovation and Impact

A **mechanism-guided RBE model** that explicitly links DNA double strand break (DSB) induction to reproductive cell death has been implemented into a clinical build of RayStation 2024A for proton therapy planning. The script copies a planned treatment optimized using a constant RBE = 1.1 (cRBE = 1.1) and then generates an evaluation plan for the endpoints of reproductive cell death (depends on α/β) or the endpoint of DSB induction (independent of α/β). Published studies of DSB induction and *in vitro* cell survival for protons with kinetic energies less than 10-25 MeV (proton range < 1-6 mm) have an RBE > 1.1 whereas higher-energy protons usually have an RBE in the range from 1.0 to 1.1.

In the **RMF model** (Stewart *et al.* 2018), proton RBE increases as a linear-cubic function of LET; RBE terms proportional to the cube of LET are inversely related to (α/β) . In the RMF, the RBE for cell survival approaches the RBE for DSB induction (RBE_{DSB}) for dose large compared to α/β . We implemented the RMF model into a commercial treatment planning system through a python script. The sensitivity of planned dose to biological uncertainties were evaluated using: (1) $(\alpha/\beta) = 2.5$ Gy, target diameter = 4 μm (upper bound) and (2) $(\alpha/\beta) = 100$ Gy and target diameter = 10 μm (lower bound). The lower bound corresponds to the asymptotic limit of a RBE for cell survival, which depends on α/β , as it approaches RBE_{DSB} independent of α/β . From Stewart *et al.* (2018), proton RBE in the limit of doses small compared to (α/β) is

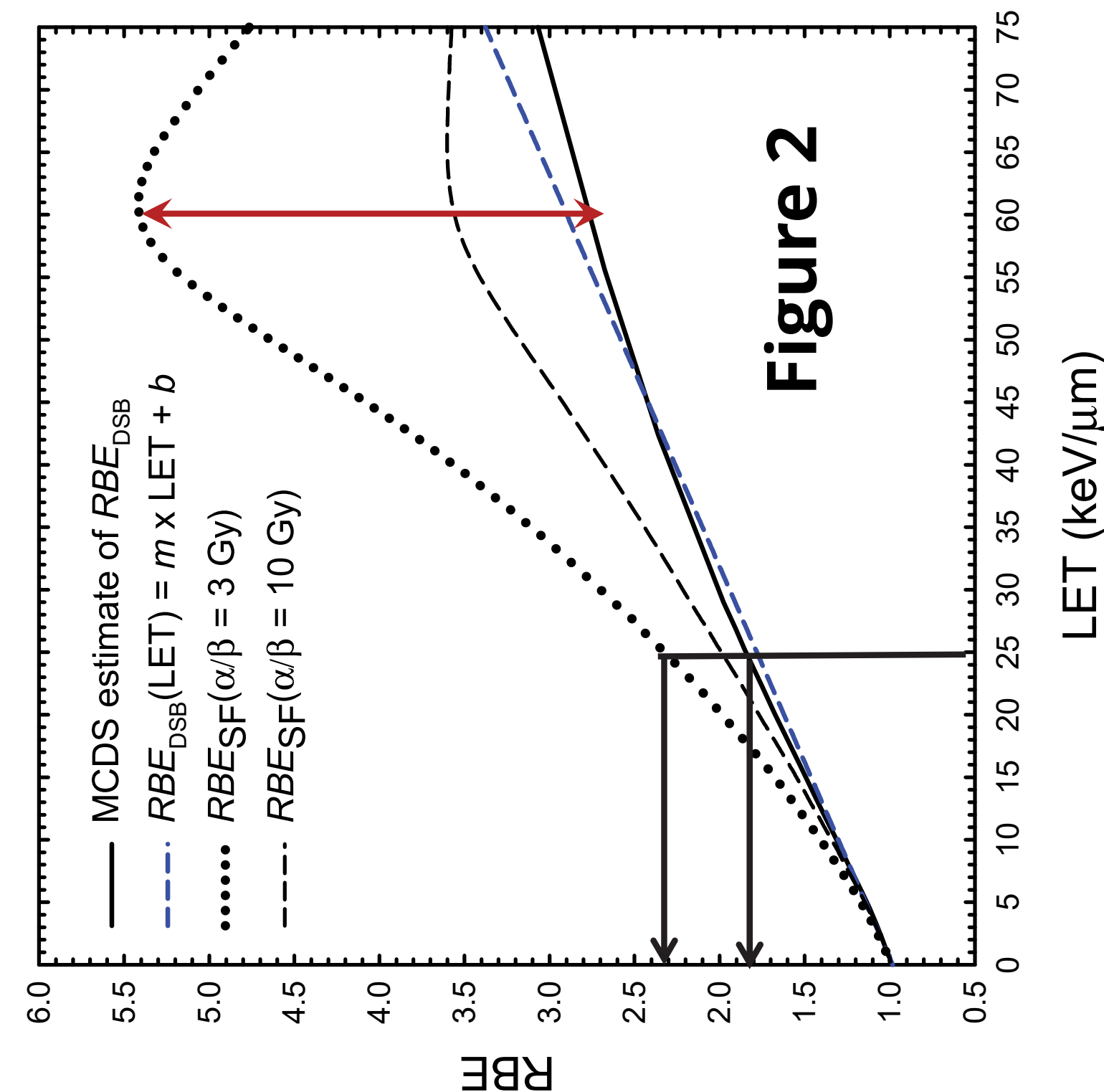
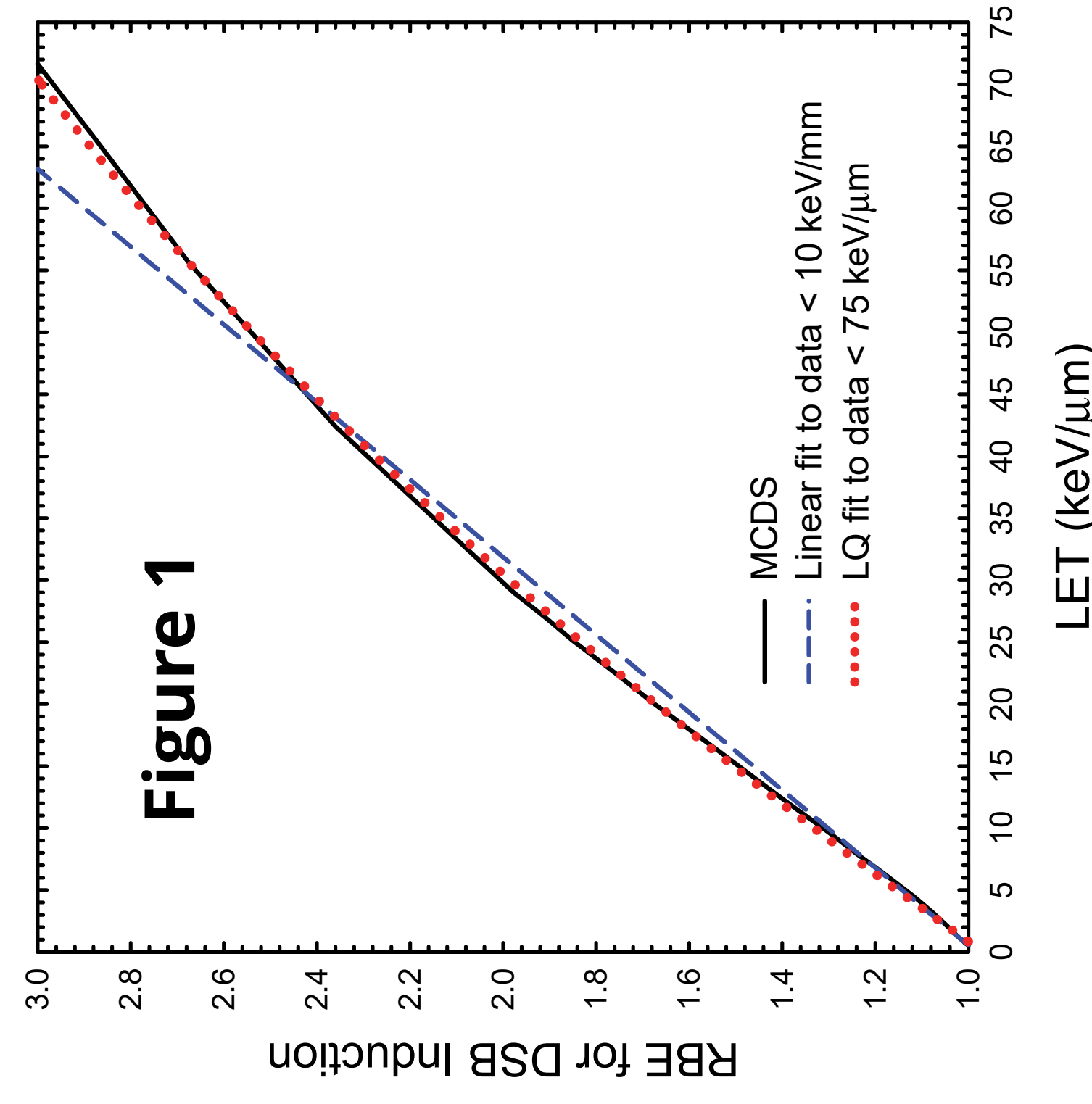
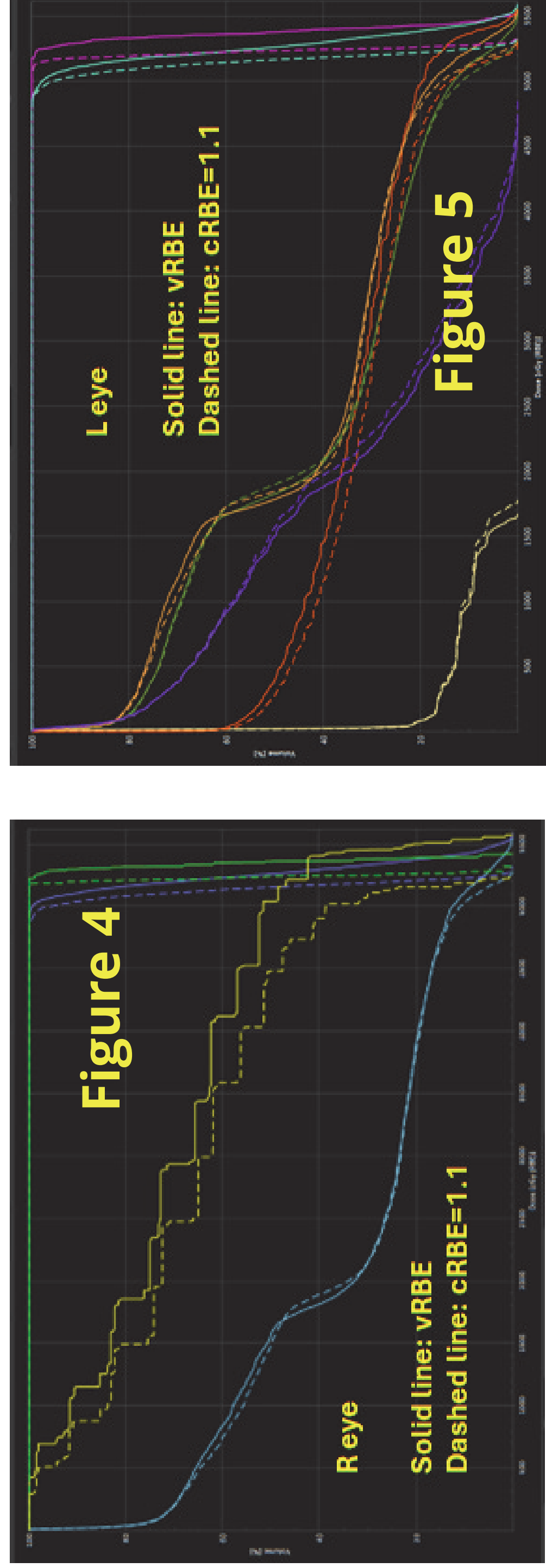
$$RBE_{LD} = RBE_{DSB} (1 + 2\bar{z}_F RBE_{DSB} / \alpha / \beta), \text{ “low dose” RBE}$$
$$\text{where } \bar{z}_F \equiv LET / \rho d^2.$$

Here, d is the approximate diameter of the cell nucleus (~ 3-6 μm for human cells). The RBE for cell survival in the limit of doses large compared to (α/β) is $RBE_{HD} = RBE_{DSB}$. For protons, RBE_{DSB} is a linear quadratic function of LET (**Figure 1**)

$$RBE_{HD} = RBE_{DSB} = a \cdot LET^2 + b \cdot LET + c, \text{ “high dose” RBE}$$

where $a = 6.771 \times 10^{-3}$, $b = 2.553 \times 10^{-2}$, and $c = 9.969 \times 10^{-1}$.

Key Results – Dose-Volume Histograms (DVH)



For the most clinically relevant range of proton kinetic energies (less than 25 keV/ μm), the RBE for cell survival, which depends on α/β , is larger than RBE_{DSB} by no more than 30% (α/β from 3-10 Gy). At 25 keV/ μm (tip of Bragg peak), proton RBE is likely in the range from 1.8 to 2.6 (**Figure 2**). For two-field ocular treatments treated with PRT, the dose-averaged variable RBE ranges from about 1.07 to 1.2. Sample DVH and isodose plots for representative patients are shown in **Figure 3-5**.

Reference and Contact

Stewart RD, Carlson DJ, Butkus MP, Hawkins R, Friedrich T, Scholz M. A comparison of mechanism-inspired models for particle relative biological effectiveness (RBE). *Med Phys.* 2018 Nov; **45**(11): e925-e952. doi: 10.1002/mp.13207. PMID: 30421808.

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RayStation script implementing the RMF vRBE model available upon request to Rob Stewart