

# Robust proton plan optimization considering geometrical and biological uncertainties

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## INTRODUCTION & AIM

Prediction of relative biological effectiveness (RBE) for proton therapy is subject to large uncertainties. This is true for variable RBE models as well as for the constant RBE model of 1.1, which is the standard RBE model in clinical practice.

While geometrical uncertainties, such as patient setup and proton range, often are handled directly in the optimization through some robust optimization framework, biological uncertainties typically are neglected in the optimization phase. To mitigate these uncertainties, we propose a robust optimization method that considers geometrical and biological uncertainties simultaneously.

The proposed method allows for selection of objectives with one or multiple RBE models while ensuring robustness against geometrical uncertainties. In this work, we used two RBE models to prove the concept – the constant RBE of 1.1 and the variable RBE model by Wedenberg et al. [1]. The method could, however, easily be extended with multiple RBE models with various weights and parameter settings.

## MATERIAL & METHODS

IMPT plans of a prostate and an intracranial case were robustly optimized against setup and range uncertainties for the CTV (3% range uncertainty, 3 mm setup uncertainty, giving error 21 scenarios) using minimax optimization in a research version of RayStation v9A.

- Prostate case
  - 2.4 Gy (RBE) per fraction in 30 fractions
  - Assumed  $\alpha/\beta$  of 1.5 Gy for CTV, 3 Gy for organs at risk (OARs)
- Intracranial case
  - 2.0 Gy (RBE) per fraction in 30 fractions
  - Assumed  $\alpha/\beta$  of 10 Gy for CTV and 2 Gy for OARs

Identical RBE-weighted dose ( $D_{RBE}$ ) objectives were used for three different RBE model considerations:

- Plan 1: RBE=1.1
- Plan 2: The Wedenberg (WED) model with  $\alpha/\beta$  as above
- Plan 3: Both RBE=1.1 and the WED model with  $\alpha/\beta$  as above
  - For the robust uniform  $D_{RBE}$  CTV objective, RBE=1.1 had doubled the weight compared to the WED model
  - For all OARs objectives, the WED model had doubled the weight compared to RBE=1.1

The CTV coverage was robust against setup and range errors for both prostate and intracranial cases when applying the corresponding RBE model used in optimization.

The CTV coverage for the intracranial case was comparable for all three plans with similar near-minimum and near-maximum  $D_{RBE}$  ( $D_{RBE, 98\%} \geq 95\%$ ,  $D_{RBE, 2\%} \leq 105\%$  for all plans and both RBE models), as indicated by the dose distributions in Fig. 1. When combining RBE=1.1 and the WED model in the optimization (plan 3), the brainstem  $D_{RBE, 2\%}$  was lowered with approximately 3 Gy (RBE) for both RBE models compared to using only RBE=1.1 (plan 1).

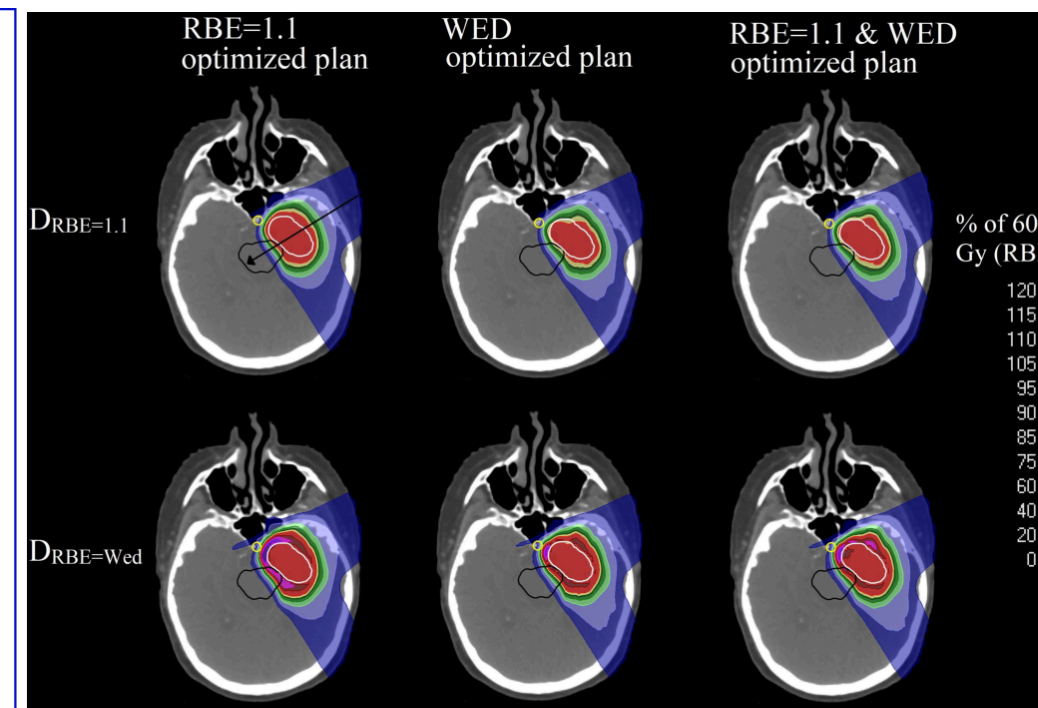
The CTV coverage in percentage for the prostate case was ( $D_{RBE, 98\%} / D_{RBE, 2\%}$ ):

- Plan 1 (RBE=1.1 optimized): 99%/102% (RBE=1.1) and 105%/110% (WED model)
- Plan 2 (WED optimized): 88%/97% (RBE=1.1) and 95%/109% (WED model)
- Plan 3 (RBE=1.1 & WED optimized): 95%/99% (RBE=1.1) and 101%/106% (WED model)

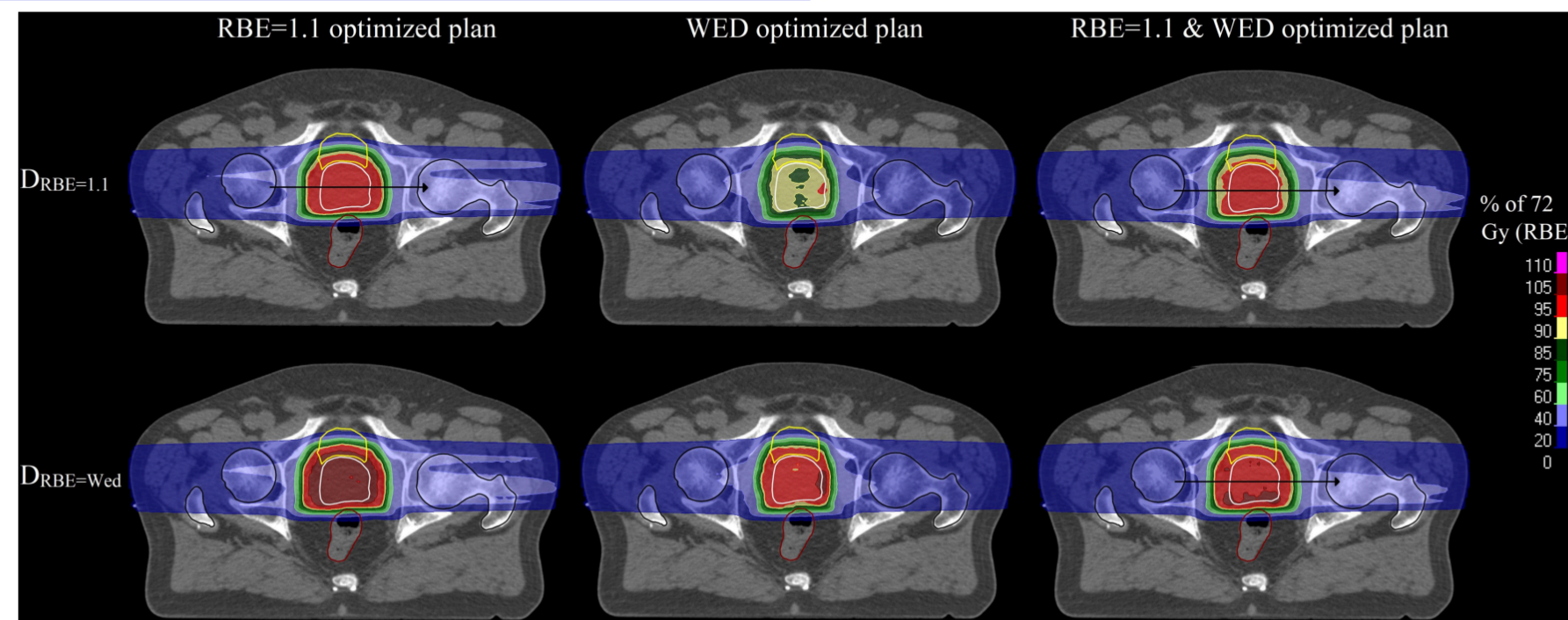
Thus, when combining RBE=1.1 and the WED model in the optimization (plan 3) the CTV coverage was satisfying for both RBE models as indicated by the dose distributions in Fig. 2 and the dose profiles in Fig. 3. This was achieved with similar or lower OAR doses compared to plan 1 and 2.

Note that plan 1 instead predicts overdoses to the CTV when applying the WED model, whereas plan 2 predicts underdosages when applying the constant RBE=1.1 (see Figs. 2 and 3). Whether these predicted under- or overdoses are acceptable or not is subject for a clinical decision.

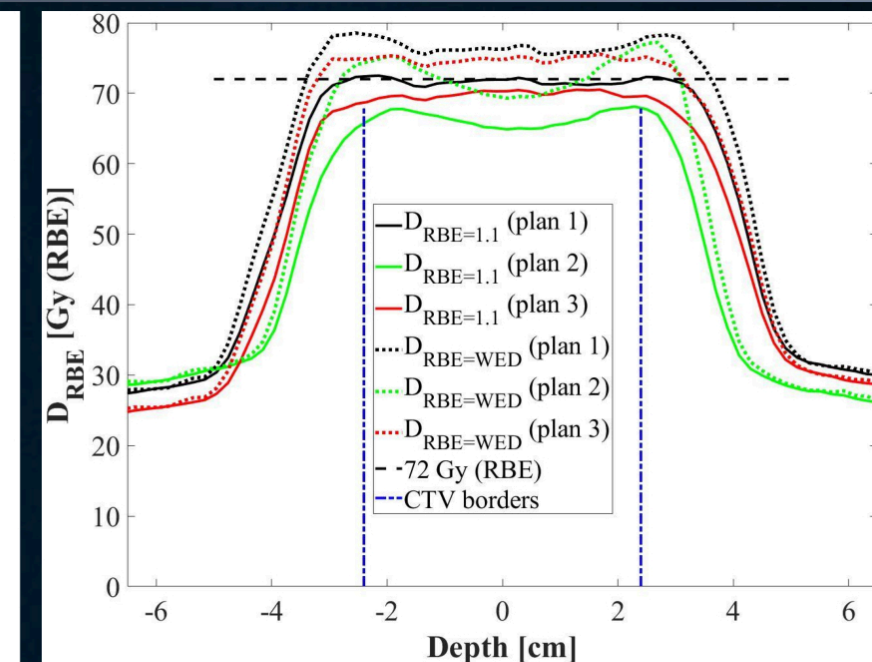
## RESULTS



**Fig. 1.**  $D_{RBE}$  in % of the prescribed  $D_{RBE}$  of 60 Gy (RBE) for the three RBE optimizations for the intracranial case. The upper row shows the  $D_{RBE}$  assuming RBE=1.1 and the bottom row assuming the Wedenberg RBE model ( $\alpha/\beta=10$  Gy for CTV and 2 Gy outside). All plans are robust against range and setup (3%/3 mm). The CTV is delineated in white, the brainstem in black and the pituitary gland in yellow.



**Fig. 2.**  $D_{RBE}$  in % of the prescribed  $D_{RBE}$  of 72 Gy (RBE) for the three RBE optimizations for the prostate case. The upper row shows the  $D_{RBE}$  assuming RBE=1.1 and the bottom row assuming the Wedenberg RBE model ( $\alpha/\beta=1.5$  Gy for CTV and 3 Gy outside). All plans are robust against range and setup (3%/3 mm). The CTV is delineated in white, the rectum in brown, the bladder in yellow and the femoral heads in black. The arrows indicate the position of the dose profiles shown in Fig. 3.



**Fig. 3.**  $D_{RBE}$  profiles (patient's right-to-left, position seen in Fig. 2) evaluated using RBE=1.1 (full lines) and the Wedenberg RBE model (dotted lines). The prescribed  $D_{RBE}$  of 72 Gy (RBE) in 30 fractions is shown (dashed black line) together with the CTV borders (blue dash-dotted line).

## CONCLUSIONS

The proposed method simultaneously mitigates the RBE model dependence while ensuring robustness against geometrical uncertainties. The method is flexible, where the user defines model weightings, and the method also works for multiple RBE models with multiple model parameter settings.

As proton therapy planning is moving towards an inclusion of the variability of the proton RBE, robust optimization strategies like this are likely to impact the future clinical practice.

## REFERENCES

- Wedenberg M, Lind B and Hårdemark B. A model for the relative biological effectiveness of protons: The tissue specific parameter  $\alpha / \beta$  of photons is a predictor for the sensitivity to LET changes *Acta Oncol.* 2013; 52: 580-588