Supplementary material

for the paper

Optimization of combined proton-photon treatments

A Treatment plan optimization details

In this section we detail the treatment plan optimization methods. Simultaneous treatment plan optimization for IMRT and IMPT is based on objective and constraint functions evaluated for cumulative BED b. For the chordoma patient discussed in this paper we use the following objective function for treatment planning:

$$
\begin{aligned}
f(\boldsymbol{b}) &= \frac{10}{N_G}\sum_{i\in G}(86.3-b_i)_+^2 \quad \text{(GTV underdose, } \alpha/\beta=10) && (3)\\
&+ \frac{10}{N_C}\sum_{i\in C}(63.7-b_i)_+^2 \quad \text{(CTV underdose, } \alpha/\beta=10) && (4)\\
&+ \frac{10}{N_P}\sum_{i\in P}(63.7-b_i)_+^2 \quad \text{(PTV underdose, } \alpha/\beta=10) && (5)\\
&+ \frac{2}{N_G}\sum_{i\in G}(b_i-90.7)_+^2 \quad \text{(GTV overdose, } \alpha/\beta=10) && (6)\\
&+ \frac{5}{N_C}\sum_{i\in C}(b_i-110.8)_+^2 \quad \text{(CTV overdose, } \alpha/\beta=4) && (7)\\
&+ \frac{5}{N_P}\sum_{i\in P}(b_i-90)_+^2 \quad \text{(PTV overdose, } \alpha/\beta=4) && (8)\\
&+ \frac{1}{N_R}\sum_{i\in R}\left(b_i-b_i^{\max}\right)_+^2 \quad \text{(conformity, } \alpha/\beta=4) && (9)\\
&+ \frac{1}{N_O}\sum_{i\in O}b_i \quad \text{(mean BED in OARs, } \alpha/\beta=4) && (10)\\
&+ \frac{1}{N_H}\sum_{i\in H}b_i \quad \text{(mean BED remaining healthy tissues, } \alpha/\beta=4) && (11)
\end{aligned}
$$

and the following set of constraints:

$$b_i \leq 78.3 \quad \forall i \in O \quad \text{(maximum BED in OARs, } \alpha/\beta = 4) \tag{12}$$

$$b_i = n^\gamma d_i^\gamma + \frac{n^\gamma (d_i^\gamma)^2}{(\alpha/\beta)_i} + n^p d_i^p + \frac{n^p (d_i^p)^2}{(\alpha/\beta)_i} \quad \forall i, \quad \text{(BED in voxel } i) \tag{13}$$

$$d_i^p = \sum_j D_{ij}^p x_j^p \quad \forall i, \quad \text{(proton dose in voxel } i) \tag{14}$$

$$d_i^\gamma = \sum_k D_{ik}^\gamma x_k^\gamma \quad \forall i, \quad \text{(photon dose in voxel } i) \tag{15}$$

$$x_j^p \geq 0 \quad \forall j, \quad \text{(non-negative proton fluence)} \tag{16}$$

$$x_k^\gamma \geq 0 \quad \forall k, \quad \text{(non-negative photon fluence)} \tag{17}$$

Here, x_j^p denotes the fluence of pencil beam j in the IMPT plan and x_k^γ denotes the fluence of beamlet k in the IMRT plan. d_i^p and d_i^γ denote the physical doses per fraction in voxel i for the proton and photon plans, respectively. The dose-deposition matrix elements D_{ij}^p and D_{ik}^γ denotes the dose contributions of pencil beams j and beamlets k to voxel i for unit fluence. G, C, and P denote the set of voxels contained in the GTV, CTV, and PTV, respectively; R is the set of voxels in a 1 cm margin of normal tissue surrounding the PTV; O denotes the union of voxels in the bowel, rectum and bladder; and H is the set of all normal tissue voxels outside of the PTV that are not in O.

The maximum BED $b_i^{\max}$ in the conformity objective depends linearly on the euclidean distance z_i of a normal tissue voxel i from the PTV contour:

$$b_i^{\max} = 78.3 - z_i\,(78.3 - 33.1) \tag{18}$$

Hence, a falloff of the BED from 78.3 Gy at the edge of the PTV to 33.1 Gy at 1cm distance is aimed for, corresponding to a physical dose fall-off from 54 Gy to 27 Gy for a uniformly fractionated 30-fraction treatment.

For optimization of combined proton-photon treatments, we add constraints to enforce that the optimized combination is no worse than the reference plan in any of the objectives. For example, for GTV underdose we add the constraint

$$\frac{10}{N_G} \sum_{i \in G} (86.3 - b_i)_+^2 \leq f_G^\star \tag{19}$$

where $f_G^\star$ is the corresponding objective value in the reference plan.

To find a local minimum of the optimization problem, we use our own implementation of the L-BFGS quasi-Newton method [3], together with an augmented Lagrangian method for handling constraints [1]. Calculation of the dose-deposition matrices D_{ij}^p and D_{ik}^γ is performed with the open-source radiotherapy planning research platform matRad [2].

B Spinal metastasis example

B.1 Motivation

SBRT has become an established treatment regimen for spinal metastasis. Different fractionation schemes are in use including single fraction SBRT with doses of approximately 20 Gy. For tumors with involvement of the dura, a larger number of fractions is required to improve the ratio of tumor BED to spinal cord BED. For a subset of patients it is desirable to reduce the dose to other normal tissues surrounding the tumor, e.g. in the case of prior radiotherapy. This can be achieved through proton therapy, however, for patients with metastatic disease the number of available proton therapy slots may be limited.

B.2 Treatment planning problem

Figure 4 in the main manuscript shows a spinal metastasis patient in whom the target volume (black contour) abuts and surrounds the cauda (red contour). Surrounding the cauda, we consider planning risk volume (PRV), which consists of a 3 mm expansion of the cauda (blue contour). However, the PRV is also part of the target volume.

We consider a treatment with 5 fractions in which 4 fractions are to be delivered with xrays and only one fraction is delivered with protons. In this example, we assumed $\alpha/\beta = 10$ in the tumor and $\alpha/\beta = 2$ in all normal tissues. We consider the following treatment planning problem:

Constraints:

1. The maximum BED_2 to the cauda is constrained to a BED_2 of 60 Gy, corresponding to a single fraction dose of 10 Gy.

2. In the PRV surrounding the cauda, the BED_2 is constrained to 112 Gy, corresponding to a single fraction dose of 14 Gy.

Objectives:

1. A BED_{10} of 60 Gy is prescribed to the target volume. This corresponds to 20 Gy delivered in a single fraction, or 35 Gy delivered in 5 equal fractions. The PRV is also part of the target volume, and hence the BED_{10} should be as high as possible.

2. The plan is to be conformal. A BED falloff to half the prescription dose at 1 cm distance from the target is aimed for.

3. Mean BED_2 to the union of all normal tissue is minimized.

B.3 Results

Figures 4e and 4f in the main manuscript shows the dose distributions of the IMRT and the IMPT fractions for an optimal combination of the two modalities. Figure 4d shows the cumulative equieffective dose EQD7 for the combined treatment. In the part of the target volume

adjacent to the spinal cord, the target BED_{10} is maximized if the dose is fractionated uniformly, i.e. split evenly into 5 fractions. In the PRV, the maximum allowed BED_2 of 112 Gy corresponds to a uniformly fractionated treatment with 5 fractions that deliver 5.77 Gy each. This corresponds to a target BED_{10} of 45.5 Gy. In contrast, the maximum single fraction dose of 14 Gy corresponds to a target BED_{10} of 33.6 Gy. Hence, the underdose of the target volume in the PRV is minimized if all fractions deliver the same dose.

However, posterior proton beams can avoid the dose bath in the gastrointestinal tract. In the optimal combination, the proton fraction delivers on average higher doses to the peripheral parts of the target volume that are not adjacent to the spinal cord. In this example, one proton fraction could achieve 50% of the integral dose reduction that 5 proton fractions yield (as opposed to 20% which a simple proportional combination of the single-modality plans yields).

C Further discussion

C.1 Modelling of fractionation effects using the BED model

C.1.1 Selection of the α/β-ratio

In this work, we use the BED model to describe fractionation effects. In this subsection, we outline how the α/β-ratio could be selected in practice to ensure validity of the BED model in the most relevant range of doses per fraction. The main input for adequately describing fractionation effects is the specification of fractionation schemes that are assumed to be isoeffective/isotoxic. In the sacral chordoma example with 10 IMPT and 20 IMRT fractions, prescription doses and normal tissue constraints are specified for a standard fractionated 30-fraction regimen and a hypofractionated 10-fraction regimen. Subsequently, the α/β-ratios for the tumor and normal tissue endpoints are calculated such that the two specified fractionation schemes are isoeffective/isotoxic within the BED model. This procedure ensures that BED based treatment plan optimization will reproduce the desired prescription doses and dose constraints for the extreme cases, i.e. uniform fractionation where protons and photons deliver the same dose per fraction, and extreme hypofractionation where all dose is delivered with protons. In other words, the BED model would be constructed such that fractionation effects are modeled as desired for large doses per fraction.

C.1.2 Combined treatments with a small number of proton fractions

For the sacral chordoma case, combined treatments with 10 IMPT and 20 IMRT fractions deliver doses per fraction in the range of approximately 1 Gy to 5 Gy, which is comparable to currently used fractionation schemes. Figure 3 shows that even a single proton fraction achieves a substantial integral dose reduction of 15% and 44%. However, in these plans, the proton fraction delivers an average GTV dose of approximately 10 Gy, and doses exceeding 15 Gy in parts of the GTV. Hence, such a treatment would differ substantially from currently used fractionation schemes, which may represent a concern. In order to reduce uncertainties in biological effectiveness, it may be desired to limit the dose per fraction to values where

clinical experience exists. This can be achieved by selecting a sufficiently large number of proton fractions, or by enforcing constraints on the dose per fraction during treatment plan optimization.

C.2 Relation to proton or carbon ion boost treatments

Other institutions have previously applied the concept of adding a proton or carbon ion boost to an IMRT plan [6]. In a typical scenario, a particle therapy boost is delivered to the GTV while an IMRT plan treats a larger CTV. A hypofractionated proton boost delivered to the GTV may represent the type of treatment that comes closest to what we propose in this report. However, in previous planning studies and treatment protocols, the target volumes and prescription doses are manually specified. In that sense, the method proposed here represents an optimized boost concept where mathematical optimization techniques are used to simultaneously optimize proton boost and photon base plans while incorporating fractionation effects. As a result, the proton boost plan treats not only the GTV but also delivers some dose to the PTV to maximize the fractionation effect in overlapping critical structures. In addition, the dose that the photon base plan delivers to the target is lowered to further reduce the dose bath in the normal tissue.

C.3 Relation to the concept of spatiotemporal fractionation

The work presented here is related to a concept called spatiotemporal fractionation [20-23], which deliver distinct dose distributions in different fractions. These dose distributions are designed such that each fraction hypofractionates alternating parts of the target volume while delivering similar doses to normal tissues. Spatiotemporal fractionation has previously been studied for IMPT [21,22] and IMRT [20, 23], but only for single-modality treatments. The optimization of combined proton-photon treatments described in this report can be considered as an extension of spatiotemporal fractionation, in which different sets of fractions are delivered with different radiation modalities. However, the rationale is different. For single-modality spatiotemporal fractionation schemes, partial hypofractionation of the target volume allows for a physical dose reduction in the target, which in turn translate into a biological dose reduction in the normal tissue where near-uniform fractionation is achieved. For combined proton-photon treatments, physical dose reduction in the target is only a secondary effect while the main advantage arises from an overproportioned use of protons, which lowers integral dose to normal tissues per se and does not rely on near-uniform fractionation in these tissues.

C.4 Steps towards an initial clinical application

A widespread application of BED based simultaneous optimization of IMRT and IMPT plans requires that the method is implemented in commercial treatment planning systems (TPS). However, to facilitate a first clinical implementation of this approach, proton-photon combinations optimized using research software could be reproduced in a certified commercial TPS. The approach we consider is as follows. We first optimize the proton-photon combinations using research treatment planning software. In the second step, both the IMPT and IMRT

plan are recalculated in the commissioned clinical TPS. If no significant deviations between optimized and recalculated plans is observed, the plans could be delivered as is. Otherwise a third step follows where the IMRT plan is reoptimized in the clinical TPS. To that end, the IMPT plan is fixed to the recalculated plan. Its dose distribution is treated as an already delivered dose. Based on that, the missing dose that has to be delivered with IMRT is calculated. This serves as an input for a new optimization of the IMRT plan within the clinical TPS.

D Emphasizing integral dose reduction

The optimal combination 1 in figure 1 was optimized for the same objective function as the single-modality plans, i.e. for the same relative weighting of planning goals. As a consequence, the improvement of the optimized proton-photon combination over the reference plan is distributed over multiple objectives. The optimized combination improves on integral normal tissue BED, but also on GTV underdose and conformity. Alternatively, the benefit of optimized proton-photon combinations can be directed towards minimizing integral normal tissue BED. To that end, we constrain all objectives to its values in the reference plan, and we increase the weight of objectives (10-11) by a factor of 10 (optimal combination 2). The resulting treatment plan is shown in figures 6 and 5. An IMPT fraction delivers an average dose of 4.2 Gy to the GTV while an IMRT fraction delivers only 1.3 Gy. Hence, compared to the plan in figures 1 and 2, the proton fraction is used even more.

Figure 5 reveals that the focus on improving integral BED comes with an increased deviation from uniform fractionation in the part of the bowel that overlaps the PTV. This generally leads to underdosing of the PTV in this region, however, the underdosing is small. Underdosing of the target volumes is, on average, not higher than in the reference plan as enforced by the constraints on objectives (3-5). This is further analysed in figure 7. The figure shows the BED_{10} in the target volume as a function of the dose delivered in a proton fraction, for the situation that the maximum allowed BED_4 of 78.3 Gy is delivered to the normal tissue. The bottom part of the figure shows the associated dose delivered in a xray fraction. The tumor BED is maximized for uniform fractionation when both modalities deliver 1.8 Gy per fraction. Deviations from uniform fractionation lowers the tumor BED, however, moderate deviations lead to only minor underdose. For example, if protons deliver 2.5 Gy per fraction and xrays deliver 1.4 Gy, the tumor BED decreases to 63.07 Gy. This corresponds to only a 1% BED reduction considering that a BED of 63.72 Gy is achieved for uniform fractionation at 1.8 Gy.

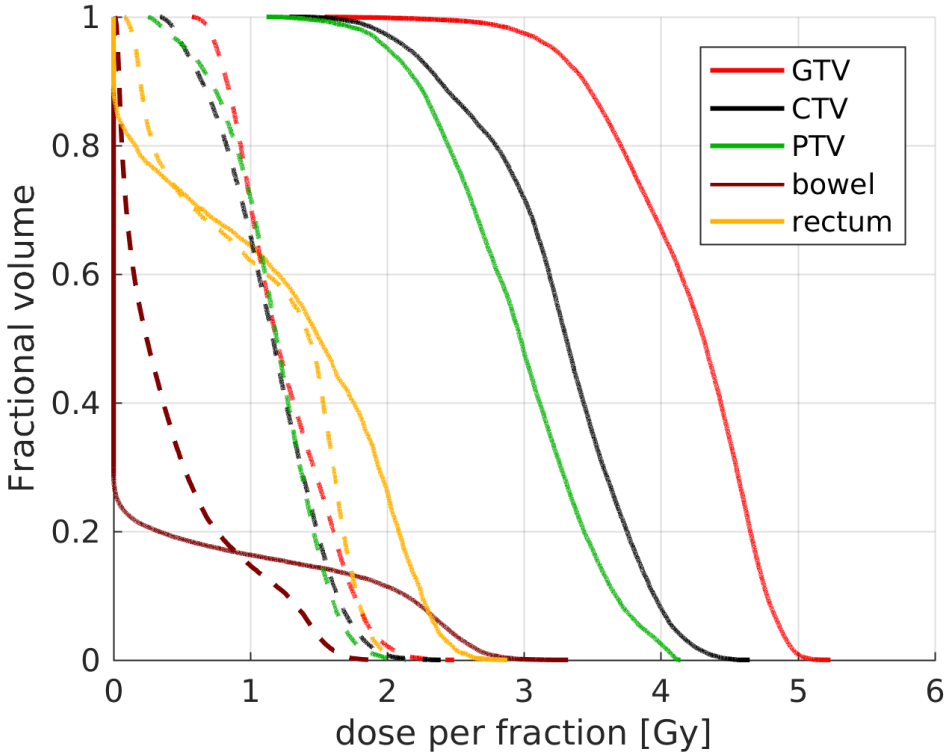

Figure 5: DVH comparison for the dose per fraction of the IMRT plan (dashed lines) and the IMPT plan (solid lines) for optimal combination 2 using 10 IMPT and 20 IMRT fractions. This plan is obtained by increasing the weights of the mean BED objectives (10-11) ten-fold.

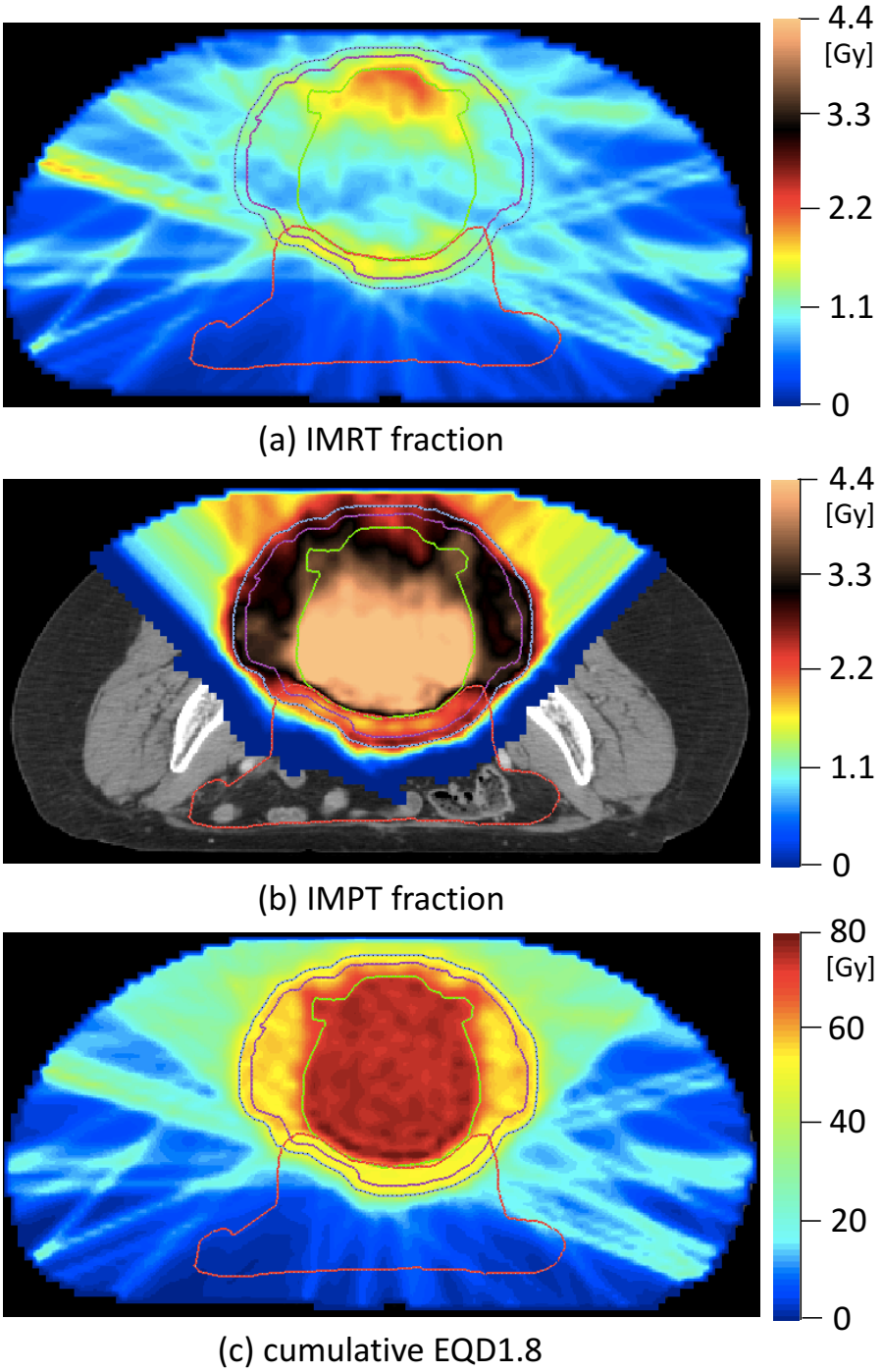

Figure 6: Optimized proton-photon combination 2 that emphasizes the reduction of integral BED using 10 IMPT and 20 IMRT fractions. (a) Dose per fraction of the IMRT plan; (b) Dose per fraction of the IMPT plan; (c) Cumulative equieffective dose EQD1.8 of both modalities combined.

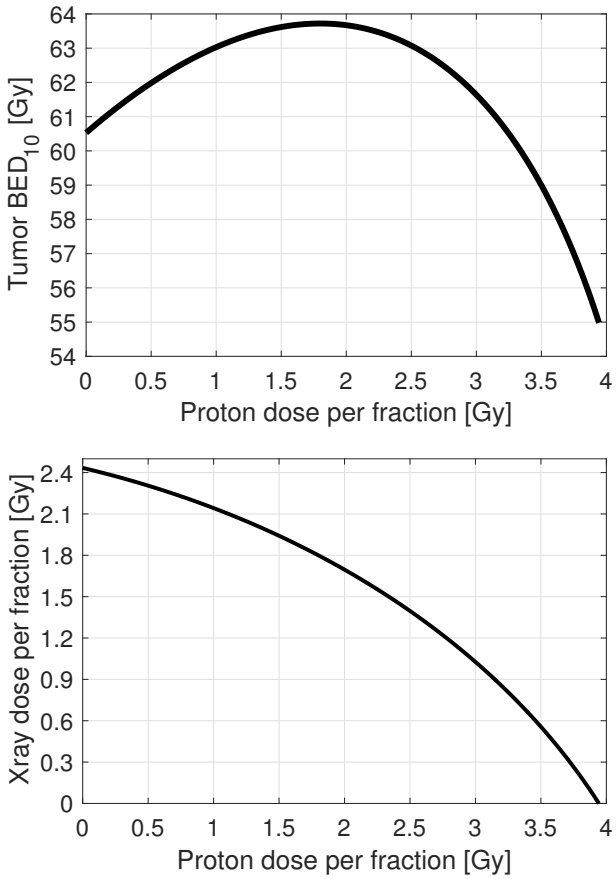

Figure 7: (Top) Tumor BED as a function of the dose delivered in a proton fraction, for the situation that the maximum BED constraint of 78.3 Gy is tight. (Bottom) Corresponding dose per fraction delivered with xrays.

References

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