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Original article

Optimization of combined proton–photon treatments

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ABSTRACT

Purpose: Proton treatment slots are a limited resource. Therefore, we consider combined proton–photon treatments in which most fractions are delivered with photons and only a few with protons. We demonstrate how both modalities can be combined to optimally capitalize on the proton's ability to reduce normal tissue dose.

Methods: An optimal combined treatment must account for fractionation effects. We therefore perform simultaneous optimization of intensity-modulated proton (IMPT) and photon (IMRT) plans based on their cumulative biologically effective dose (BED). We demonstrate the method for a sacral chordoma patient, in whom the gross tumor volume (GTV) abuts bowel and rectum.

Results: In an optimal combination, proton and photon fractions deliver similar doses to bowel and rectum to protect these dose-limiting normal tissues through fractionation. However, proton fractions deliver, on average, higher doses to the GTV. Thereby, the photon dose bath is reduced. An optimized 30-fraction treatment with 10 IMPT fractions achieved more than 50% of the integral dose reduction in the gastrointestinal tract that is possible with 30 IMPT fractions (compared to 33% for a simple proton–photon combination in which both modalities deliver the same target dose).

Conclusions: A limited number of proton fractions can best be used if protons hypofractionate parts of the GTV while maintaining near-uniform fractionation in dose-limiting normal tissues.

Proton therapy reduces integral dose to normal tissues compared to conventional radiotherapy treatments with high energy X-rays [1,2]. In recent years, the number of proton radiotherapy centers increased.[1] Nevertheless, proton therapy remains a limited resource that is available to relatively few cancer patients. Hence the question is how to optimally make use of proton therapy.

Currently, it is often a binary decision whether a patient receives proton therapy, i.e. the whole treatment is delivered either with protons only or photons only. Prior research addressed the problem of identifying the patients that are likely to benefit from proton therapy [3–5]. However, institutions with a proton facility that is integrated into a conventional radiotherapy clinic perform or investigate combined treatments, i.e. a subset of fractions is delivered with protons and the remaining fractions are delivered with photons [6–8]. The number of such institutions is likely to increase as hospitals install single-room proton therapy machines [9,10]. Hence, the question arises how a limited total number of proton treatment slots should be distributed over the patient population. In other words: How many proton fractions should be allocated to each patient in order to maximize the clinical benefit of proton therapy on the population level? How many proton fractions are needed for a given patient before a point of diminishing return is reached?

A necessary step to solve these problems is to investigate a more basic question that has not been addressed sufficiently: How can a given number of proton therapy slots be used optimally in a combined proton–photon treatment for a patient at hand? Previous planning studies and treatment protocols manually specified the target volumes and prescription doses for the proton and photon plans, and both plans are created separately [6–8]. In this work, we improve on this by simultaneously optimizing IMRT and IMPT plans while accounting for fractionation effects.

The rationale is as follows. We consider situations where normal tissues are located within or near the target volume, which can only be protected through fractionation. Hence, it is not possible to simply deliver a hypofractionated treatment that uses only the proton fractions at higher dose per fraction. The IMRT fractions must be used to treat the portion of the target volume that overlaps with organs at risk. On the other hand, as protons reduce inte-

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[1] http://www.ptcog.ch

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gral dose to normal tissue, it is desirable to use the proton fractions as much as possible, i.e. to deliver an overproportioned dose with protons. This is possible if parts of the target volume can be hypofractionated. Then, protons can deliver most of the dose to these areas. Consequently, the total amount of dose delivered with X-rays is reduced, leading to a reduction in integral dose to healthy tissues. This yields non-trivial combinations of IMPT and IMRT plans: each plan delivers an inhomogeneous dose to the target volume, but both plans combined yield the prescribed biologically effective dose (BED).

In this report, we demonstrate this concept in detail for a sacral chordoma patient, as these tumors are treated with combined proton–photon treatments at some institutions [7,11]. In order to locally control chordomas with radiotherapy, a high dose of radiation is required [7,11–13]. Proton therapy reduces integral dose delivered to the gastrointestinal tract, and thereby reduces side effects compared to photon therapy. However, the concept is not specific to sacral chordomas. An application to spinal tumors is outlined in the discussion section.

The main contributions of this paper are: (1) We present a treatment planning method to simultaneously optimize IMRT and IMPT treatment plans while accounting for fractionation effects; and (2) we demonstrate that jointly optimized proton–photon combinations may improve on simple combinations in which each modality delivers the same dose per fraction to the target volume.

Methods and materials

Patient

We demonstrate combined proton–photon treatments for the patient shown in Fig. 1a. The GTV has a volume of 630 cc and abuts rectum, bowel and bladder. The CTV is approximately a 0–15 mm expansion of the GTV, respecting anatomical boundaries of microscopic tumor invasion. The PTV is a 5 mm expansion of the CTV. For this patient, most of the GTV can be hypofractionated with protons, however, protecting rectum, bowel and bladder relies on fractionation.

Modeling of fractionation effects

In this work, we use the BED model [14] to describe fractionation effects. For a combined proton–photon treatment with n^γ X-ray fractions and n^p proton fractions, we assume that the cumulative BED of both treatments combined is given by

$$b = n^\gamma \left(d^\gamma + \frac{(d^\gamma)^2}{\alpha/\beta} \right) + n^p \left(d^p + \frac{(d^p)^2}{\alpha/\beta} \right) \quad (1)$$

where d^γ and d^p doses per fraction for photons and protons, respectively. Thus, in this work we assume that the BED formalism can be extended to non-stationary fractionation schemes where proton and photon fractions may deliver a different dose per fraction. The proton dose d^p includes a constant relative biologically effectiveness (RBE) factor of 1.1 corresponding to current clinical practice, which we do not make explicit in our notation. The BED of a proton plan is calculated by applying the BED formula to the RBE-weighted dose. Hence, a potential dependence of RBE on the dose per fraction is not modeled.

For the chordoma case we consider a standard fractionated treatment with 30 fractions as the reference. We assume an α/β-ratio of 10 for the tumor and an α/β-ratio of 4 for all healthy tissues. This corresponds to the assumption that the fractionation schemes in Table 1 are isoeffective.

For visualization and quantitative interpretation, the BED can be scaled by a factor $1/[1 + X/(\alpha/\beta)]$, where X is a reference dose level. This yields the equieffective dose [15]

$$EQDX = \frac{b}{\left[1 + \frac{X}{(\alpha/\beta)}\right]} \quad (2)$$

EQDX can be interpreted as the total physical dose that needs to be delivered in a uniformly fractionated treatment with a dose per fraction of X Gy to achieve the BED b.

Treatment plan optimization

We developed a novel treatment plan optimization method to simultaneously optimize IMRT and IMPT plans. This is performed based on the cumulative BED according to Eq. (1). Traditional treatment plan optimization for IMRT and IMPT is based on objective and constraint functions evaluated for physical dose. Here, we apply the same functions with the difference that these are evaluated for cumulative BED rather than physical dose. For the chordoma case, we consider the following treatment planning problem:

Constraints:

1. The maximum BED_4 to the bowel, rectum and bladder is constrained to 78.3 Gy, corresponding to 54 Gy physical dose delivered in 30 fractions.

Objectives:

1. A BED_{10} of 86.3 Gy is prescribed to the GTV, and a BED_{10} of 63.7 Gy is prescribed to the CTV and the PTV (implemented via quadratic penalty functions). This corresponds to 70 Gy and 54 Gy in 30 fractions, respectively.
2. A BED_4 exceeding 110.8 Gy in the CTV and 90 Gy in the PTV is penalized quadratically, corresponding to 70 Gy and 60 Gy in 30 fractions, respectively.
3. The plan is to be conformal. A dose falloff to half the PTV prescription dose at 1 cm distance from the PTV is aimed for.
4. The mean BED_4 to the union of the OARs (rectum, bladder and bowel) is minimized.
5. The mean BED_4 to the remaining healthy tissue is minimized.

We consider an IMRT plan consisting of 19 equispaced coplanar beams, which approximates the best possible rotation therapy plan that can be delivered with tomotherapy or volumetric modulated arc therapy (VMAT) [16]. We assume a beamlet resolution of 5 × 5 mm. The IMPT plan consists of 3 posterior beams at 0° and ±45°. Dose calculations for proton and photon beams have been performed using the open-source radiotherapy research platform matRad.[2] [17,18]. The initial sigma of the Gaussian proton pencil beams at the patient surface ranges from 5.0 mm for a proton energy of 31.7 MeV to 2.3 mm for an energy of 236.1 MeV. Details of treatment plan optimization are described in the supplementary materials, Appendix A.

To quantify the benefit of optimized proton–photon treatments we use the following procedure: Initially, we optimize a single-modality 30-fraction IMRT plan and a single-modality 30-fraction IMPT plan based on the same objective function. From these single-modality plans we generate a *reference plan*, which represents the simple proportional combination of the single-modality plans (i.e. a treatment that delivers the IMPT plan n^p times and the IMRT plan n^γ times with $n^p + n^\gamma = 30$). Finally, we optimize two combined proton–photon plans. To that end, all objectives are constrained to be no worse than their values in the reference

[2] http://www.matrad.org

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