Radiotherapy and Oncology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

# Optimization of combined proton–photon treatments

Jan Unkelbach [a,*], Mark Bangert [b], Karen De Amorim Bernstein [c], Nicolaus Andratschke [a], Matthias Guckenberger [a]

[a] Department of Radiation Oncology, University Hospital Zürich, Switzerland; [b] Department of Medical Physics in Radiation Oncology, German Cancer Research Center, Heidelberg, Germany; and [c] Department of Radiation Oncology, Massachusetts General Hospital, Boston, USA

ARTICLE INFO

*Article history:*
Received 11 July 2017
Received in revised form 5 December 2017
Accepted 6 December 2017
Available online xxxx

*Keywords:*
Multi-modality radiotherapy
IMRT
IMPT
Treatment plan optimization
Fractionation

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-

* Corresponding author at: Department of Radiation Oncology, University Hospital Zürich, Rämistrasse 100, 8091 Zürich, Switzerland.
*E-mail address:* jan.unkelbach@usz.ch (J. Unkelbach).

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

https://doi.org/10.1016/j.radonc.2017.12.031
0167-8140/

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 $n^\gamma$ 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 $d^\gamma$ 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 $\alpha/\beta$-ratio of 10 for the tumor and an $\alpha/\beta$-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 $n^\gamma$ 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

Please cite this article in press as: Unkelbach J et al. Optimization of combined proton–photon treatments. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2017.12.031

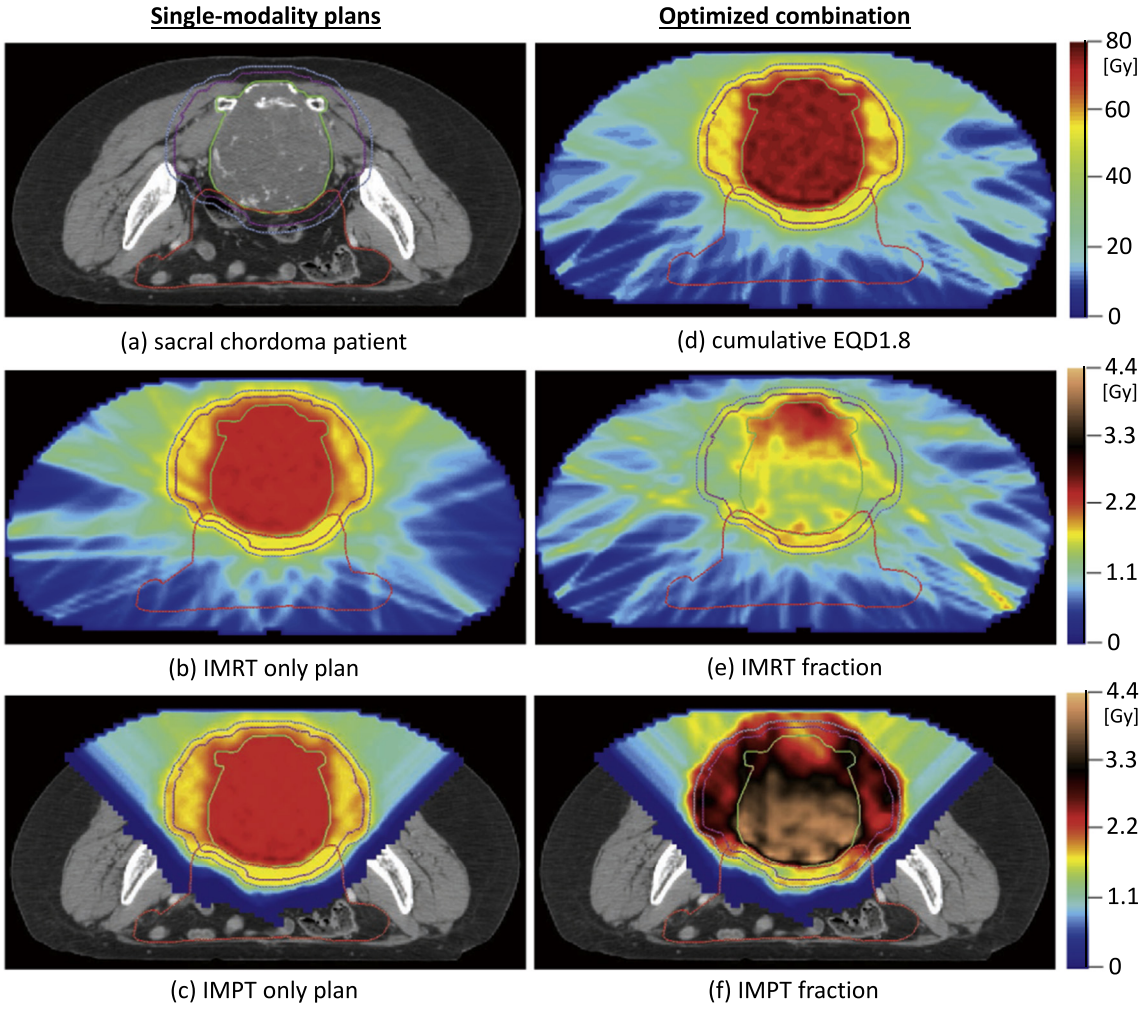


**Fig. 1.** (a) Patient with a sacral chordoma treated in prone position. The contours show the GTV (green), CTV (purple), PTV (blue) and the bowel (red); (b and c) Dose distributions of the single-modality IMRT and IMPT plans; (d–f) Optimized combined proton–photon combination 1 with 10 IMPT and 20 IMRT fractions with (e) IMRT dose distribution, (f) IMPT dose distribution, and (d) cumulative equieffective dose EQD1.8 of the combined treatment. In figures (b, c, e, f) the dose per fraction is shown. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 1**
Isoeffective/isotoxic total physical doses for $n = 10, 20, 30$ fractions and their corresponding BED and equieffective dose EQD1.8.

| | $n = 10$ | $n = 20$ | $n = 30$ | $\alpha/\beta$ | BED | EQD1.8 |
|---|---|---|---|---|---|---|
| GTV dose (Gy) | 55.5 | 65.1 | 70 | 10 | 86.3 | 73.2 |
| PTV dose (Gy) | 44.2 | 50.8 | 54 | 10 | 63.7 | 54 |
| Bowel/rectum (Gy) | 39.4 | 48.6 | 54 | 4 | 78.3 | 54 |

plan, i.e. target coverage and conformity does not deteriorate. For the *optimized combination 1*, we use the same weighted sum of objectives as for generating the single-modality plans. The *optimized combination 2* emphasizes integral dose reduction and is obtained by increasing the weight for objectives 4 and 5 tenfold.

## Results

Fig. 1b and c show the single modality IMRT and IMPT plans, respectively. For the beam characteristics assumed in this work, the IMPT plan is generally superior in terms of physical dose compared to the IMRT plan. In particular, the IMPT plan avoids the dose bath in the gastrointestinal tract.

The right panel in Fig. 1 shows the optimized proton–photon combination 1 using 10 IMPT and 20 IMRT fractions. Fig. 1d shows the cumulative equieffective dose EQDX and illustrates that protons and photons combined yield a conformal treatment plan that delivers the prescribed BED to target volume. The reference dose level was set to X = 1.8 Gy corresponding to the dose per fraction prescribed to the PTV. Fig. 1e and f show the dose distributions per fraction delivered in IMRT and IMPT fractions, respectively. Fig. 2a compares the IMRT and IMPT dose distributions in terms of their DVH. It is observed that IMRT fraction and IMPT fractions deliver similar doses (approximately 1.8 Gy per fraction) to the portion of the bowel and the rectum that overlay the PTV. Hence, near-uniform fractionation is achieved. The maximum dose to the bowel and rectum is constrained to 78.3 Gy $BED_4$, corresponding to 30 times 1.8 Gy. This corresponds to a target $BED_{10}$ of 63.7 Gy. If instead, the same OAR $BED_4$ was delivered in the 10 proton fractions, corresponding to 3.94 Gy per fraction, the target $BED_{10}$ would drop to 54.9 Gy (i.e. CTV and PTV would be underdosed if the dose was not uniformly fractionated over 30 fractions).

Please cite this article in press as: Unkelbach J et al. Optimization of combined proton–photon treatments. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2017.12.031

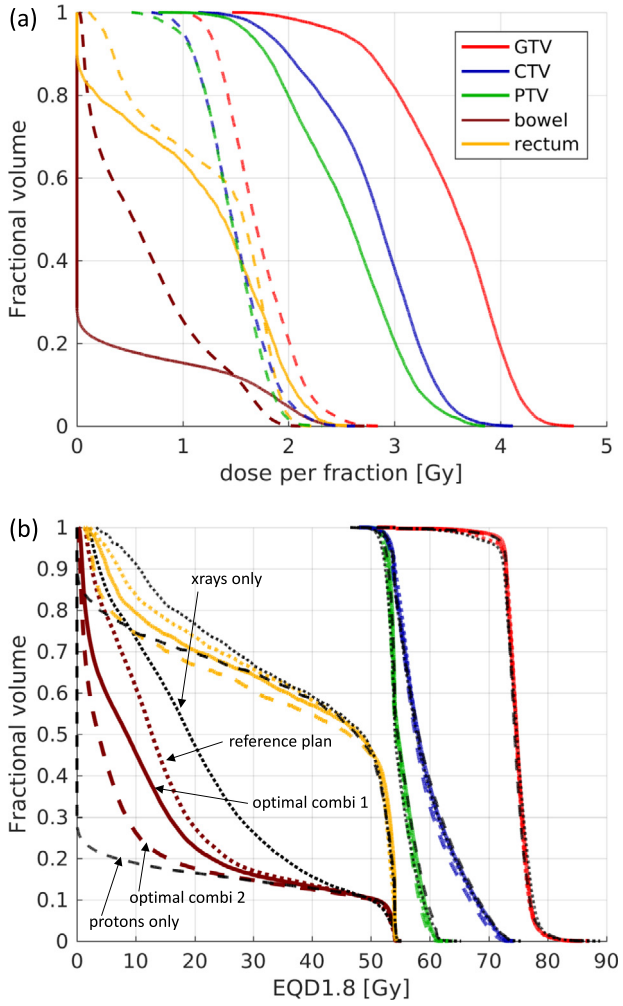


**Fig. 2.** (a) DVH comparison of the IMPT (solid lines) and IMRT (dashed lines) dose distributions for the optimized combination 1. Both plans deliver a similar dose per fraction to the bowel and the rectum in the high dose region, but on average a proton fraction delivers almost twice dose to the GTV. (b) DVH comparison of the EQD1.8 distributions of all 5 plans, confirming that the optimal combinations 1 (solid lines) and 2 (dashed lines) using only 10 proton fractions improve on the reference plan (dotted lines) and realize a large portion of the benefit that 30 proton fractions yield.

In the GTV, however, a photon fraction delivers a mean dose of 1.7 Gy while a proton fraction delivers a mean dose of 3.6 Gy. Recall, in the reference plan each fraction delivers a dose of 2.3 Gy. Hence, on average, a proton fraction delivers about twice the dose of a photon fraction, which can be seen in the DVH comparison in Fig. 2a. Comparing the dose distributions in the reference plan (Fig. 1b and c) and the optimized combination (Fig. 1e and f) further illustrates that the IMRT dose in the optimized combination is reduced compared to the reference plan. In contrast, an IMPT fraction in the optimized combination delivers approximately 4 Gy to the distal portion of the GTV, a substantial increase compared to 2.3 Gy in the reference plan.

Since less dose is delivered with X-rays, the optimized proton–photon combination lowers the integral dose to the gastrointestinal tract compared to the reference plan. In this example, the mean $BED_4$ to the contoured part of the bowel was 13.12 Gy for a 30-fraction IMRT plan and 4.85 Gy for the single-modality IMPT plan. The reference plan with 10 proton fractions, i.e. the simple proportional combination of the single-modality plans, yields a $BED_4$ of 10.41 Gy, i.e. a reduction of 2.7 Gy. This corresponds (as expected) to approximately 33% of what is possible with 30 proton fractions. The optimal combination 1 realizes a mean $BED_4$ of 8.63, i.e. a reduction of 4.5 Gy. This corresponds to 54% of the BED reduction that is possible with 30 proton fractions. In that sense, the optimal proton–photon combination improves substantially on the reference plan. In a simple proportional combination, 16 instead of 10 proton fractions were needed to achieve 54% of the possible mean BED reduction (see also Fig. 3 for visualization).

The optimal combination 1 discussed above is generated using the same objective function as the single-modality plans. As a result, the improvements over the reference plan are distributed over multiple planning objectives. By shifting most of the benefit to the reduction in integral BED, the optimized combination 2 achieved 78% of the BED reduction in the single-modality proton plan, without degrading target coverage and conformity compared to the reference plan (see further discussion in the supplementary materials, Appendix D).

Fig. 2b compares the DVHs evaluated for equieffective dose EQD1.8 for all 5 plans. All plans are similar in terms of target coverage, although the proton plan and the optimal combination 1 improve on the reference plan. Also, all plans are similar in the high dose region of the bowel and rectum, which overlap with the PTV. The main difference is observed in the low dose region of the bowel, where the optimized proton–photon combinations improve on the reference plan.

Next, we varied the number of proton fractions in a 30-fraction treatment between 1 and 20. Fig. 3 summarizes the mean BED reductions in the bowel. The optimized combinations 1 and 2 with 5 IMPT fractions achieved BED reductions of 36% and 66%, which would require 11 and 20 IMPT fractions in a simple proportional combination of the single-modality plans (see further discussion in the supplementary materials, Appendix C.1.2).

## Discussion

The question how to best take advantage of a few proton fractions is important and timely. First, many countries and health insurers are currently developing guidelines for proton therapy reimbursement. Second, many cancer centers are installing single-room proton machines integrated into conventional radiotherapy departments, so that combined treatments are practical and the allocation problem for proton therapy slots is omnipresent.

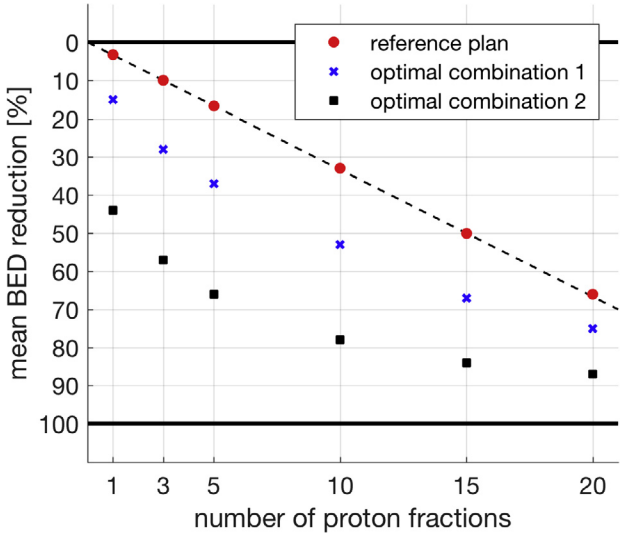


**Fig. 3.** Relative mean BED reductions in the bowel as a function of the number of proton fractions. 0% corresponds to the BED of the single-modality IMRT plan, 100% corresponds to the single-modality IMPT plan.

Please cite this article in press as: Unkelbach J et al. Optimization of combined proton–photon treatments. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2017.12.031

The simple way to combine IMRT and IMPT plans is to optimize both plans separately so that each plan delivers the prescribed dose to the target volume. In this report, we show that one can improve on such simple combinations. The method is applicable if dose-limiting normal tissues overlay the target volume that can only be protected through fractionation, whereas parts of the target volume can be hypofractionated. In such cases, IMPT can deliver most of the dose to the part of the target volume that can be hypofractionated, while IMRT is used primarily to treat the part of the target volume that overlaps with dose-limiting normal tissues. Thereby, the photon dose bath is reduced and the approach better capitalizes on the proton's ability to reduce integral dose.

Sacral chordomas represent a possible candidate for a first clinical application of this concept since these tumors are currently being treated with simple proton–photon treatments at Massachusetts General Hospital due to limited availability of proton therapy slots. However, there are other possible applications of optimized proton–photon combinations following the same rationale. Fig. 4 illustrates our concept for SBRT for spinal metastasis with epidural involvement [19]. Epidural involvement requires some degree of fractionation to improve the target-to-cauda BED ratio. On the other hand, spinal metastases without epidural involvement can be treated with single-fraction SBRT. Further detail and discussion on Fig. 4 is provided in the supplementary materials, Appendix B. Another potential application is large liver tumors abutting bowel, stomach or duodenum. In this case, protecting these normal tissues requires fractionation, whereas hypofractionation of the GTV with protons would allow for a mean dose reduction in the noninvolved liver. Future work will perform additional treatment planning studies to quantify the benefit of optimized proton–photon treatments for different treatment sites.

The type of combined proton–photon treatment suggested here implies that the dose per fraction varies within the target volume and between proton and photon fractions. For this work, we assume that fractionation effects for this situation can be described by the BED model. Even though it is unclear if the BED model with a constant $\alpha/\beta$-value can adequately describe fractionation effects over the whole range of doses per fraction from extreme hypofractionation to hyperfractionation, we argue that this does not generally question the proposed concept. For the chordoma example using 10 IMPT and 20 IMRT fractions, the dose per fraction in the GTV varies approximately in the range from 1 Gy to 5 Gy, which is close to clinically applied fractionation schemes. Furthermore, the treatment planning methodology can be extended to account

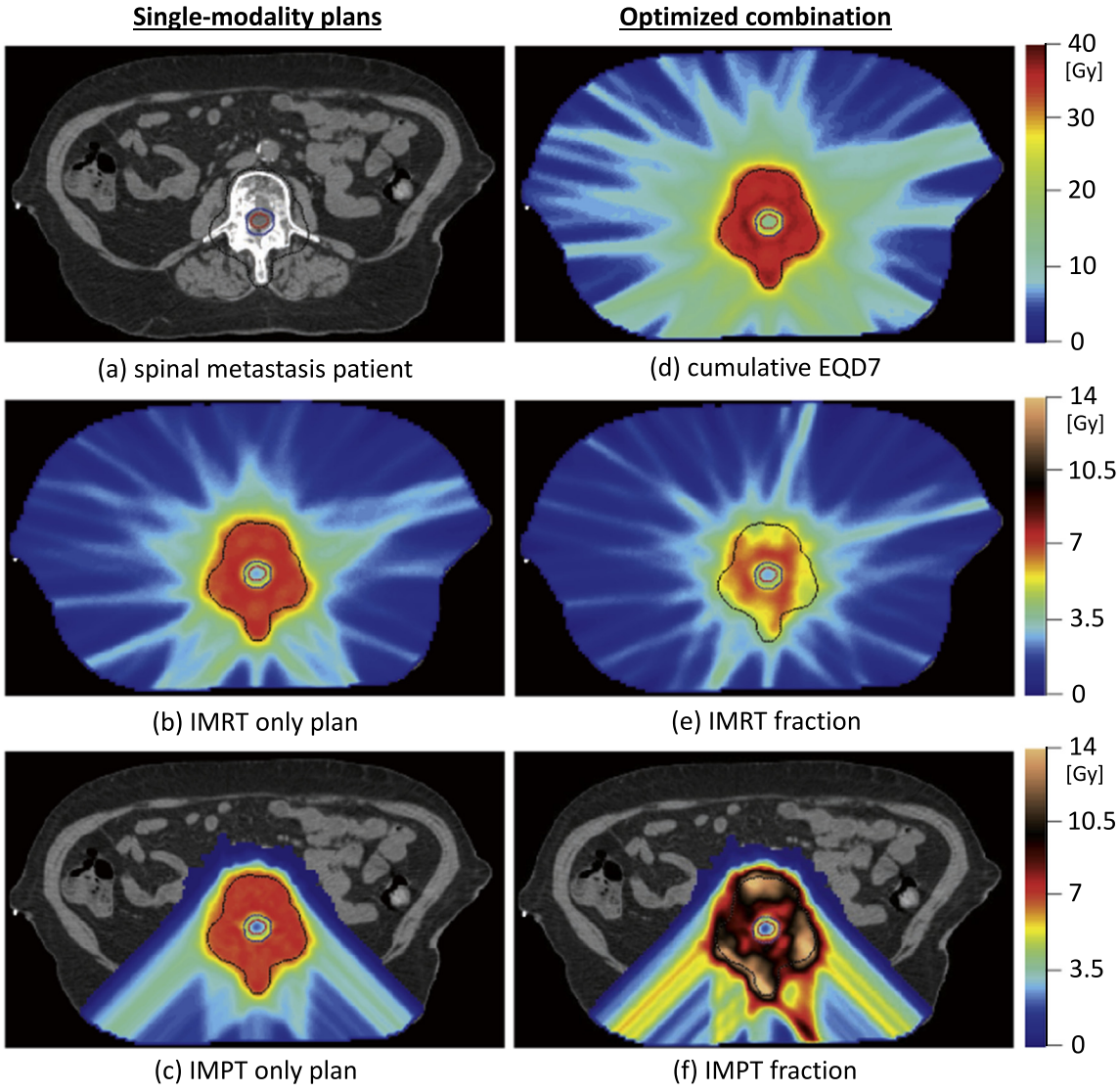


**Fig. 4.** Dose per fraction for a combined 5-fraction treatment for a spinal metastasis consisting of 1 IMPT and 4 IMRT fractions. Protection of the spinal cord requires fractionation while most of the remaining target volume can be hypofractionated with protons. In this case, a single IMPT fraction achieves 50% of the integral BED reduction that is possible with 5 IMPT fractions.

Please cite this article in press as: Unkelbach J et al. Optimization of combined proton–photon treatments. Radiother Oncol (2018), https://doi.org/10.1016/j.radonc.2017.12.031

for limitations in the validity of the BED model. A trivial extension would be to add constraints on the dose per fraction in the target volume. For example, constraints can be added to enforce that an IMRT fraction delivers at least a specified minimum dose and an IMPT fraction delivers at most a specified maximum dose. Thereby, the range of doses per fraction can be adjusted to a range where the BED model is trusted. More detailed discussion on how $\alpha/\beta$-values could be specified in practice is provided in the supplementary materials, Appendix C.1.1.

In addition, we point out the following aspects:

- Other institutions have previously applied the concept of adding a proton or carbon ion boost to an IMRT plan [6]. These prior works manually specify the desired dose distributions of both plans. Our method improves on that by using mathematical algorithms to truly optimize the combination of both modalities (see supplementary materials, Appendix C.2 for further discussion of prior works).
- The work presented here is related to a concept called spatiotemporal fractionation [20–23], which aims to optimally exploit fractionation effects by delivering distinct dose distributions in different fractions (see supplementary materials, Appendix C.3).
- Treatment planning for combined IMRT and IMPT plans is performed simultaneously in a single optimization procedure. Hence, planning such treatments would not increase the planning effort substantially.
- Future work is needed to address the problem of range and setup uncertainty. To that end, robust optimization techniques [24–29] that directly incorporate uncertainty in treatment plan optimization can be applied.
- A widespread application of BED based simultaneous optimization of IMRT and IMPT plans requires that the method is implemented in commercial treatment planning systems. However, as the next step to demonstrate initial clinical feasibility of the type of combined proton–photon treatment suggested here, such treatment plans could be generated in research software and subsequently be reproduced in commercial planning systems (see supplementary materials, Appendix C.4 for further details).

## Conclusion

This report considers combined proton–photon treatments in the context of fractionation. We investigate how a limited number of IMPT fractions can be combined with IMRT fractions to optimally exploit the protons' ability to reduce integral dose to normal tissues. It is shown that the best multi-modality treatment is a non-trivial combination of protons and photons, in which both IMRT and IMPT fractions deliver inhomogeneous target dose distributions. These plans are designed such that IMRT and IMPT fractions deliver similar doses per fraction to dose-limiting normal tissues within or near the target volume, and thereby optimally exploit the fractionation effect. Meanwhile, protons deliver most of the dose to target regions that can be hypofractionated and thereby reduce the dose delivered with X-rays – leading to a net reduction in the dose bath in normal tissues.

## Conflict of interest statement

None.

## Acknowledgements

None.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2017.12.031.

## References

[1] Smith AR. Vision 20/20: proton therapy. Med Phys 2009;36:556–68.
[2] Mohan R, Grosshans D. Proton therapy – present and future. Adv Drug Deliv Rev 2017;109:26–44.
[3] Langendijk JA et al. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013;107:267–73.
[4] Delaney AR et al. Using a knowledge-based planning solution to select patients for proton therapy. Radiother Oncol 2017.
[5] Hall DC et al. Predicting patient-specific dosimetric benefits of proton therapy for skull-base tumors using a geometric knowledge-based method. Int J Radiat Oncol Biol Phys 2017;97:1087–94.
[6] Combs SE, Debus J. Treatment with heavy charged particles: systematic review of clinical data and current clinical (comparative) trials. Acta Oncol 2013;52:1272–86.
[7] DeLaney TF et al. Long-term results of Phase II study of high dose photon/proton radiotherapy in the management of spine chordomas, chondrosarcomas, and other sarcomas. J Surg Oncol 2014;110:115–22.
[8] Jakobi A et al. NTCP reduction for advanced head and neck cancer patients using proton therapy for complete or sequential boost treatment versus photon therapy. Acta Oncol 2015;54:1658–64.
[9] Flanz J, Bortfeld T. Evolution of technology to optimize the delivery of proton therapy: the third generation. Semin Radiat Oncol 2013;23:142–8.
[10] Zhao T et al. Commissioning and initial experience with the first clinical gantry-mounted proton therapy system. J Appl Clin Med Phys 2016;17:5868.
[11] Park L et al. Sacral chordomas: impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. Int J Radiat Oncol Biol Phys 2006;65:1514–21.
[12] Catton C et al. Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol 1996;41:67–72.
[13] De Amorim Bernstein K, DeLaney T. Chordomas and chondrosarcomas – the role of radiation therapy. J Surg Oncol 2016;114:564–9.
[14] Fowler JF. 21 years of biologically effective dose. Br J Radiol 2010;83:554–68.
[15] Bentzen SM et al. Bioeffect modeling and equieffective dose concepts in radiation oncology–terminology, quantities and units. Radiother Oncol 2012;105:266–8.
[16] Unkelbach J et al. Optimization approaches to volumetric modulated arc therapy planning. Med Phys 2015;42:1367–77.
[17] Cisternas, E., et al. matRad – a multi-modality open source 3D treatment planning toolkit. In: World congress on medical physics and biomedical engineering, June 7–12, Toronto, Canada, Springer; 2015.
[18] Wieser Hans-Peter, Cisternas E, Wahl Niklas, Ulrich Silke, Stadler Alexander, Mescher Henning, et al. Development of the open-source dose calculation and optimization toolkit matRad. Med Phys 2017.
[19] Husain ZA et al. Stereotactic body radiotherapy for de novo spinal metastases: systematic review. J Neurosurg Spine 2017:1–8.
[20] Unkelbach J et al. Spatiotemporal fractionation schemes for irradiating large cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys 2016;95:1067–74.
[21] Unkelbach J, Papp D. The emergence of nonuniform spatiotemporal fractionation schemes within the standard BED model. Med Phys 2015;42:2234–41.
[22] Unkelbach J, Zeng C, Engelsman M. Simultaneous optimization of dose distributions and fractionation schemes in particle radiotherapy. Med Phys 2013;40:091702.
[23] Unkelbach J. Non-uniform spatiotemporal fractionation schemes in photon radiotherapy. In: World congress on medical physics and biomedical engineering, June 7–12, Toronto, Canada, Springer; 2015.
[24] Unkelbach J et al. Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. Med Phys 2009;36:149–63.
[25] Unkelbach J, Chan TC, Bortfeld T. Accounting for range uncertainties in the optimization of intensity modulated proton therapy. Phys Med Biol 2007;52:2755–73.
[26] Fredriksson A, Forsgren A, Hardemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. Med Phys 2011;38:1672–84.
[27] Liu W et al. Robust optimization of intensity modulated proton therapy. Med Phys 2012;39:1079–91.
[28] Pflugfelder D, Wilkens JJ, Oelfke U. Worst case optimization: a method to account for uncertainties in the optimization of intensity modulated proton therapy. Phys Med Biol 2008;53:1689–700.
[29] Bangert M, Hennig P, Oelfke U. Analytical probabilistic modeling for radiation therapy treatment planning. Phys Med Biol 2013;58:5401–19.