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Physics Contribution

Optimal Allocation of Proton Therapy Slots in Combined Proton-Photon Radiation Therapy

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Purpose: Proton therapy is a limited resource that is not available to all patients who may benefit from it. We investigated combined proton-photon treatments, in which some fractions are delivered with protons and the remaining fractions with photons, as an approach to maximize the benefit of limited proton therapy resources at a population level.

Methods and Materials: To quantify differences in normal-tissue complication probability (NTCP) between protons and photons, we considered a cohort of 45 patients with head and neck cancer for whom intensity modulated radiation therapy and intensity modulated proton therapy plans were previously created, in combination with NTCP models for xerostomia and dysphagia considered in the Netherlands for proton patient selection. Assuming limited availability of proton slots, we developed methods to optimally assign proton fractions in combined proton-photon treatments to minimize the average NTCP on a population level. The combined treatments were compared with patient selection strategies in which patients are assigned to single-modality proton or photon treatments.

Results: There is a benefit of combined proton-photon treatments compared with patient selection, owing to the nonlinearity of NTCP functions; that is, the initial proton fractions are the most beneficial, whereas additional proton fractions have a decreasing benefit when a flatter part of the NTCP curve is reached. This effect was small for the patient cohort and NTCP

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models considered, but it may be larger if dose-response relationships are better known. In addition, when proton slots are limited, patient selection methods face a trade-off between leaving slots unused and blocking slots for future patients who may have a larger benefit. Combined proton-photon treatments with flexible proton slot assignment provide a method to make optimal use of all available resources.

Conclusions: Combined proton-photon treatments allow for better use of limited proton therapy resources. The benefit over patient selection schemes depends on the NTCP models and the dose differences between protons and photons.

Introduction

Proton therapy is widely considered a superior treatment modality in terms of the dose distribution compared with conventional photon-based radiation therapy, and its clinical value is being investigated in the context of clinical studies.[1,2] As a rule of thumb, protons allow a reduction of the integral dose to normal tissues by a factor of 2 to 3.[3,4] However, proton therapy is not widely available. Currently, approximately 80 proton therapy centers with a total of approximately 200 treatment rooms are in operation worldwide,[5] compared with more than 12,000 conventional radiation therapy units.[6] Consequently, only a small percentage of patients with an indication for radiation therapy are treated with protons,[7] and not all patients who may benefit from proton therapy have access to it.[8]

Strategies for selecting patients for proton therapy vary among institutions, countries, and health care systems.[9-15] In most countries, several treatments are considered standard indications for proton therapy, including pediatric patients and tumors in the proximity of the base of the skull or the spinal cord (eg, chordoma and chondrosarcoma).[9,15,16] Some treatment sites are not routinely referred for proton therapy, but planning studies comparing intensity modulated proton therapy (IMPT) to photon-based intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) have shown a potential advantage of proton therapy. One example is head and neck squamous cell carcinoma (HNSCC). For HNSCC, several planning studies have found dose reductions through IMPT in critical organs such as the parotid glands, the pharyngeal constrictor muscles, and the oral cavity.[17-19] Dose reduction is expected to lower normal-tissue complication probabilities (NTCPs) for common adverse effects such as xerostomia and dysphagia.[20-22]

However, the incidence of HNSCC is too high to refer all patients to proton therapy. Currently, patient selection schemes based on NTCP models are being developed and promoted, especially in the Netherlands, as a forward-looking concept for selecting patients for proton therapy.[13,23] In this approach, both photon and proton treatment plans are created, and the dose difference between the 2 modalities is translated into an expected NTCP difference using agreed-on NTCP models. Subsequently, patients in whom the NTCP reduction through protons exceeds a threshold are referred to proton therapy, whereas the remaining patients receive photon therapy. This can be understood as an approach to maximize the benefit of limited proton therapy resources for the health care system as a whole.

In this study, we further investigated how a limited number of proton therapy slots can be used optimally to maximize the benefit of proton therapy for a population of patients with HNSCC. As the measure of benefit, we aimed to minimize the expected total number of complications in a patient population. To that end, we investigated whether there is a role for combined proton-photon treatments in which several fractions are delivered with IMPT and the remaining fractions with IMRT/VMAT.

The rationale as to why combined proton-photon treatments with optimal allocation of proton fractions may outperform single-modality treatments with optimal proton patient selection is 2-fold:

1. On the convex part of the NTCP curve, the first proton fractions are the most beneficial ones. Because there is a constant reduction in dose per additional proton fraction and a decreasing steepness of the NTCP curve for smaller dose values (see the illustration in Fig. 1), the benefit of any additional proton fraction decreases with an increasing number of proton fractions. Thus, there may be a point of diminishing return, and it may be more beneficial to give (first) proton fractions to other patients.
2. Assuming there is a given number of proton slots available each day to treat patients with HNSCC, any single-modality patient selection strategy faces a trade-off between leaving a proton slot unused and blocking a proton slot for future patients for whom it may have a greater benefit. Instead, flexible allocation of proton fractions in combined proton-photon treatments may make optimal use of all available proton slots.

In this article, we present a method to optimally distribute a limited number of IMPT slots over a patient population to answer the question of how many proton fractions each patient should receive, rather than which patients should receive IMPT only and which IMRT only. The method's benefit in a population of patients with HNSCC is compared with a patient-wise selection for single-modality treatment based on a threshold of the change in NTCP (ΔNTCP).

Methods and Materials

Patient cohort and treatment plans

To quantify the dosimetric differences of proton and photon treatments, we considered a cohort of 45 patients with

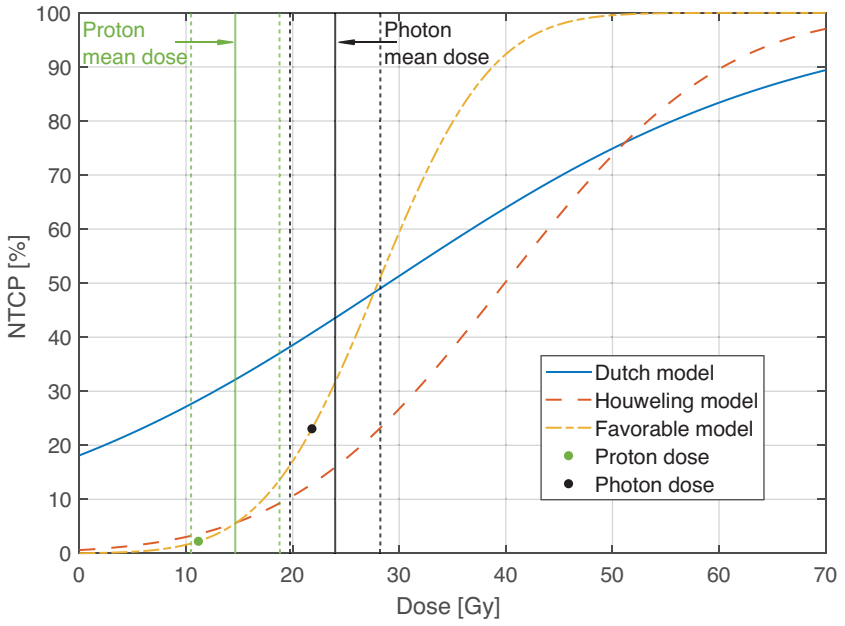

Fig. 1. Dutch (blue), Houweling (red), and favorable (yellow) normal tissue complication probability (NTCP) models for xerostomia. The vertical lines show the mean of the contralateral parotid mean doses ±1 standard deviation for photons (black) and protons (green) over the 45 patients with head and neck cancer squamous cell carcinoma. The green and black points show the NTCP values of patient 10 for protons and photons on the favorable model, illustrating one of the rationales for combined treatments. Adding a single proton fraction to a pure intensity modulated radiation therapy treatment yields a larger NTCP reduction compared with adding a last proton fraction to complete a pure intensity modulated proton therapy treatment because the patient is located at a steeper section of the NTCP curve.

locally advanced HNSCC in different locations. This patient cohort was previously studied in the context of patient selection for proton therapy[2] and the dose escalation potential of proton therapy.[24] For all patients, IMPT and IMRT plans for a simultaneous integrated boost (SIB) treatment were available; this treatment delivers 70 Gy (relative biological effectiveness [RBE]) to a boost gross tumor volume (GTV_{SIB}) and 54 Gy(RBE) to the remaining planning target volumes (PTV_{all}) in 30 fractions (see further details in Appendix EA).

NTCP models

To calculate NTCP values for IMRT, IMPT, and combined treatments, we focused on the NTCP models that have been agreed on in the Netherlands for selecting patients for proton therapy ("Landelijk Indicatie Protocol Protonen Therapie - Hoofd-Halstumoren", private communication, 2017). We considered NTCP models for (1) patient-rated moderate to severe xerostomia 6 months after completion of radiation therapy, based on the European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire Head and Neck Module (EORTC QLQ-H&N35), and (2) physician-rated grade 2-4 dysphagia 6 months after treatment, as described by Christiansen et al[25] and Beetz et al[26] but with updated parameters according to "Landelijk Indicatie Protocol Protonen Therapie." The general form of the NTCP model is the following:

$$NTCP = \left(1 + e^{(a - b*d)}\right)^{-1} \quad (1)$$

For xerostomia, the model parameters are a = 1.507 and b = 0.052; d is the mean dose to the contralateral parotid gland. For dysphagia, the model parameters are a = 3.303 and b = 0.024; d is the sum of the mean doses in the oral cavity and in the superior pharyngeal constrictor muscle (PCM).

To investigate how the findings of this study depended on the NTCP model, we considered 2 additional models, which are illustrated in Figure 1:

1. The model published by Houweling et al[27] (Houweling model) for grade 4 xerostomia 1 year after radiation therapy, accessed by salivary flow measurement, which is described by $NTCP = \Phi([d^{mean} - D_{50}] / [m \cdot D_{50}])$, with parameters D_{50} = 39.9 Gy and m = 0.4, where Φ is the cumulative distribution function of the standard normal distribution.
2. A hypothetical model representing a steeper NTCP curve, which uses the same functional representation as the Houweling model but with parameters D_{50} = 28 Gy and m = 0.3. We refer to this as the Favorable model, as it is designed to show a larger potential benefit of combined treatments.

NTCP calculation for combined treatments

Let d_j^{γ} and d_j^{p} denote the photon and proton mean doses per fraction for patient j for a given organ, where d_j^{p} represents an RBE-weighted dose. The IMPT plans used as input to this work were generated under the assumption of a constant RBE of 1.1, representing current clinical practice. However, the methodology developed in this paper would apply without modifications if IMPT plans were generated for an alternative RBE model. We consider a combined photon-proton treatment with n_j^{p} proton fractions and n_j^{γ} photon fractions, where $n_j^{p} \in \{0, 1, 2..., 30\}$ and $n_j^{\gamma} = 30 - n_j^{p}$ throughout this work. Two methods for calculating NTCP values for combined proton-photon treatments are investigated:

1. NTCP models are evaluated for the cumulative mean dose d_j in the organ, which is given by the sum of photon and proton doses:

$$d_j = n_j^{\gamma} d_j^{\gamma} + n_j^{p} d_j^{p} \tag{2}$$

2. When IMRT and IMPT fractions deliver different doses to organs at risk, treatments are not uniformly fractionated. Hence, a combined proton-photon treatment may have a higher biological effect than a uniformly fractionated treatment with the same cumulative dose. To account for this, we evaluated NTCP models for a fractionation-corrected dose

$$d_j^{eff} = (n_j^{p} + n_j^{\gamma}) \left[-\frac{\alpha/\beta}{2} + \sqrt{\left(\frac{\alpha/\beta}{2}\right)^2 + \frac{\alpha/\beta}{(n_j^{p} + n_j^{\gamma})} BED_j} \right] \tag{3}$$

$$BED_j = n_j^{\gamma} d_j^{\gamma} \left(1 + \frac{d_j^{\gamma}}{\alpha/\beta}\right) + n_j^{p} d_j^{p} \left(1 + \frac{d_j^{p}}{\alpha/\beta}\right)$$

which is defined as the cumulative dose delivered in a 30-fraction treatment with equal doses per fraction, which yields the same biologically effective dose (BED) as a given combined proton-photon treatment.[28,29]

The differences in the results of the 2 methods were small. In this article, we report the results for the first method (Equation 2). Results obtained using the BED-corrected dose with $\alpha/\beta = 3$ are reported in Appendix EI.

Using the cumulative mean doses d_j (or alternatively, d_j^{eff}) for the applicable organ at risk, any of the NTCP models defined can be evaluated. Let $NTCP_j(n_j^{p})$ denote the NTCP value for patient j as a function of the number of proton fractions n_j^{p}. Furthermore, let $NTCP_{jk} = NTCP_j(n_j^{p} = k)$ denote the NTCP value for patient j if the patient receives exactly k proton fractions and $30 - k$ photon fractions. To quantify the benefit of proton therapy at a population level, we consider the average NTCP over a patient cohort:

$$\langle \mathrm{NTCP} \rangle = \frac{1}{M} \sum_{j=1}^{M} \mathrm{NTCP}_j(n_j^{p}) \tag{4}$$

where M is the number of patients in the cohort. The mean doses in the contralateral parotid gland, the superior PCM, and the oral cavity for IMRT and IMPT plans for each of the 45 patients are provided in Appendix EJ.

In addition to individual NTCP models, we considered the case in which both xerostomia and dysphagia are considered simultaneously for proton slot allocation. In this case, we considered an equally weighted sum of both complication risks, $NTCP^{Sum}$, which is simply the sum of the NTCP values for xerostomia and dysphagia according to the Dutch models of Equation 1. Note that the sum of 2 NTCP values does not formally represent a probability. However, all of the formalism presented in this article applies without changes.

Optimal proton slot allocation for a given patient cohort

First, we consider an idealized scenario in which all 45 patients with HNSCC are known at the time of distributing the proton slots. Although this is a hypothetical situation, it allows us to investigate whether there is a benefit of combined proton-photon treatments that originates from a decreasing benefit of additional proton fractions on the convex part of the NTCP curve. We assume that because of limited resources, only a percentage of the total number of fractions can be delivered with protons (ie, the total number of proton slots available is less than the total number of fractions needed to treat all 45 patients with protons).

The goal is to maximize the benefit of protons by optimally distributing the available proton fractions over the patient cohort, allowing for combined proton-photon treatments as well as single-modality proton and photon treatments as a special case thereof. To that end, we determine the number of proton fractions per patient, n_j^{p}, such that the average number of complications is minimized. Formally, this can be stated as the following optimization problem:

$$\underset{n_j^{p}}{\text{minimize}} \quad \frac{1}{M} \sum_{j=1}^{M} NTCP_j(n_j^{p}) \tag{5}$$

$$\text{subject to} \quad \sum_{j=1}^{M} n_j^{p} \leq N_{avail} \tag{6}$$

$$n_j^{p} \in \{0,\ 1,\ 2, \ldots,\ 30\} \ \forall j \tag{7}$$

This optimization problem can be solved to optimality by reformulating the problem as a linear binary integer programming problem[30] as described in Appendix EB. Note that if $NTCP_j$ denotes an equally weighted sum of different toxicities, the objective function (Equation 5) minimizes the total number of all complications in the patient cohort.

Combined proton-photon treatments with the optimal allocation of proton fractions are compared with an optimal patient-selection strategy for single-modality treatments (either pure IMPT or pure IMRT) based on the difference in NTCP values. To that end, we calculate the NTCP

difference for each patient:

$$\Delta NTCP_j = NTCP_j(n_j^p = 0) - NTCP_j(n_j^p = 30)$$

Patients with the highest ΔNTCP are assigned to pure IMPT until the number of proton slots is depleted. The rest of the patients receive pure IMRT.

Proton slot allocation during the continuous operation of a department

In reality, patients with newly diagnosed HNSCC start radiation therapy continuously throughout the year. Instead of allocating a total number of proton fractions over a given patient cohort, one must decide for each incoming patient whether the patient will receive protons or photons. We now consider a radiation therapy department in which both protons and photons are available, but the number of proton slots available for the treatment of patients with HNSCC is smaller than the average number of patients with HNSCC receiving treatment at a given time.

For this situation, we compare combined proton-photon treatments with a threshold-based strategy for proton patient selection. More specifically, we compare the following 2 strategies:

1. Combined proton-photon treatments with daily proton slot reassignment. In this strategy, the available proton slots are assigned on a daily basis among the patients currently receiving treatment. In this case, a patient may receive proton fractions on some days and photon fractions on other days, depending on the other patients who are receiving treatment. To assign proton slots on a given day, we determine the patients receiving treatment who would benefit the most from receiving one additional proton fraction. Assuming that a patient j has so far received k proton fractions, we consider the incremental NTCP difference:

$$\Delta NTCP_{kj} = NTCP_{kj} - NTCP_{(k+1)j} \quad (8)$$

   This quantifies the benefit of receiving an additional proton fraction on the given day, while assuming that the remaining fractions will be delivered with photons. On each day, the available proton slots are assigned to the patients with the highest $\Delta NTCP_{kj}$. The remaining patients receive a photon fraction on that day.
2. Single-modality treatments with threshold-based patient selection. The daily proton slot reassignment strategy is compared with threshold-based patient selection. In this case, an incoming patient is assigned to IMPT for the whole treatment if both of the following conditions hold:
   - The NTCP improvement of pure IMPT compared with pure IMRT ($\Delta NTCP_j$) of the incoming patient j exceeds a threshold (eg, 5%, 10%, or 15%); and
   - a proton slot is available on the day the patient arrives.

   Once patients are assigned to IMPT, the proton slots are blocked for the next 30 days. If one of the two conditions is not fulfilled, patients are assigned to IMRT.

To evaluate and compare both strategies, we calculate the average NTCP value by simulating the operation of a radiation therapy department over a long period of time. As an example, we assume that the department treats on average 100 patients with head and neck cancer per year, meaning that on average, 2 newly diagnosed patients per week start treatment. For a 30-fraction treatment scheme, patients receive treatment for 6 weeks, meaning that on average, 12 patients receive treatment on any given day. We assume here that a constant number of proton slots is available each day and that this number is smaller than what would be needed to treat all patients with protons.

Each iteration of the simulation corresponds to 1 working day, and the following steps are carried out:

1. We randomly decide if a new patient starts treatment on the given day. In this work, we assume a 40% probability that a new patient with HNSCC will start treatment on a given day (corresponding to an average of 2 patients per week).
2. If a new patient starts treatment, the proton and photon mean doses in the contralateral parotid gland, the oral cavity, and the superior PCM are sampled from a 6D Gaussian distribution. Samples in which the mean dose in 1 organ exceeds the GTV_{SIB} prescription dose of 70 Gy (RBE) and/or in which the proton dose exceeds the photon dose in 1 of the organs are discarded. The mean and covariance matrix of the Gaussian distribution are calculated from the doses of the 45 patients with HNSCC. The new patient is considered to be receiving treatment from then on.
3. For the daily slot reallocation strategy, the available proton slots are distributed among the patients receiving treatment, as described. For the threshold-based single-modality patient selection, it is decided whether a new patient (if present) is assigned a proton slot for the next 30 days (if available on the given day).
4. All patients receiving treatment receive 1 fraction.

Simulations are carried out for a period of 12,000 days, corresponding to approximately 4800 patients. The patients treated in the first and last 400 days are discarded to avoid results being affected by the initialization of the simulation. Based on the remaining patients, the average NTCP value, ⟨ NTCP ⟩, was calculated.

Results

Optimal proton slot allocation for the given patient cohort

Proton slot allocation for the Dutch NTCP models

We consider the Dutch NTCP models according to Equation 1. For the patient cohort considered, IMPT reduces the NTCP values compared with IMRT for both xerostomia

and dysphagia for all 45 patients with HNSCC (Fig. 2a); that is, for every single patient, a single-modality IMPT treatment would have been optimal. The average NTCP values for xerostomia/dysphagia were reduced from 43.6%/26.2% for IMRT to 32.3%/22.0% for IMPT. If all patients are treated with IMPT instead of IMRT, an average reduction of 15.5% of the sum of both toxicities ($\Delta NTCP^{Sum}$) would be expected (Table 1). The individual $\Delta NTCP^{Sum}$ values varied between 4.8% and 23.8% (Fig. 2B).

Figure 2C shows the optimal distribution of proton fractions over the patient cohort that minimizes the sum of the NTCP values for xerostomia and dysphagia, assuming that only 20% of all fractions (270 out of 1350) can be delivered with protons. In this example, 4 patients receive only protons and 29 patients receive only photons. 12 patients receive a combined proton-photon treatment. Patients with higher $\Delta NTCP^{Sum}$ values usually receive a larger number of proton fractions. However, there are small deviations from this general rule because the optimal number of proton fractions depends not only on the $\Delta NTCP^{Sum}$ but also on the local slope of the NTCP curve. For example, patient 17 had a slightly larger benefit than patient 16 from receiving 5 proton fractions, even though, in a patient selection scheme, patient 16 would have a slightly larger benefit from receiving 30 proton fractions.

When 20% of all fractions are delivered with protons, combined proton-photon treatments with optimal proton fraction allocation can reduce the average summed NTCP by 4.01% compared with treating all patients with photons (65.78% vs 69.79%), as summarized in Table 1. For the optimal patient-selection strategy (in which the 9 patients with the highest $\Delta NTCP$ are treated with protons only and the remaining patients with photons only), the average summed NTCP was 65.84%, only slightly higher than for combined treatments. To further put these numbers in perspective, the average NTCP reduction can be expressed as percentage of the NTCP gain for treating all patients with protons only. If 20% of patients are randomly selected for proton therapy (without any NTCP modeling), 20% of the 15.49% benefit of protons over photons would, in expectation, be realized. Patient selection based on $\Delta NTCP$ increased this benefit to 25.5% ([69.79 − 65.84]/[69.79 − 54.30]). Combined proton-photon treatments with optimal proton fraction allocation increased the realized benefit to 25.9%. If 60% of all fractions were delivered with protons, combined proton-photon therapy could realize 67.8% of the possible benefit, compared with 67.7% for patient selection (Table 1).

For comparison, we also investigated combined proton-photon treatments with a uniform distribution of proton slots where each of the 45 patients receives 6 proton fractions (20% of all fractions). The average summed NTCP was 66.53%, corresponding to 21.1% of the benefit of delivering all fractions with protons. Thus, uniformly distributing the proton slots was slightly better than randomly selecting patients, because it exploits the convex shape of the NTCP curve. However, it does not exploit the difference in NTCP between patients and consequently performed worse than patient selection.

The optimal proton slot allocation for minimizing the average NTCP for xerostomia and dysphagia individually rather than the sum is described in Appendix EC. When considering the 2 toxicities separately, proton slots may be given to different patients, because patients in whom IMPT lowers the contralateral parotid gland dose may be different from patients in whom the dose to the oral cavity and the superior PCM may be lowered. However, in all cases, only a small improvement in average NTCP was observed for combined proton-photon therapy over patient selection for single-modality treatment.

Dependence on the NTCP model

To investigate how the benefit of combined treatments depends on the NTCP model, we consider the 3 models illustrated in Figure 1. In Figure 3 and Table 1, we consider the allocation of limited proton fractions over the given cohort of 45 patients with HNSCC based on the 3 models. For the Dutch xerostomia model, there was only a very small benefit of combined proton-photon treatments for any number of available proton slots, because the NTCP curve is approximately linear between a pure IMRT and a pure IMPT treatment. For a given patient, each additional proton fraction yields approximately the same incremental NTCP improvement (ie, the benefit of additional proton fractions does not diminish). In fact, for a strictly linear dose-response relation, the solution to the optimal allocation of proton fractions in combined proton-photon treatments yields a patient selection scheme.

The parameters of the favorable model were chosen such that photon treatments are located in the steep part of the NTCP curve, whereas proton treatments are located at lower values, where the NTCP curve flattens. Therefore, the first proton fraction given to a patient has a larger benefit, whereas a diminishing return is observed for later ones. In this case, a benefit of combined proton-photon treatments compared with patient selection arises from the nonlinearity of the NTCP curve. The benefit for the Houweling model is between that of the Dutch model and the favorable model.

The average NTCP reductions for treating all 45 patients with protons only instead of photons only were 11.3%, 10.5%, and 25.7% for the Dutch, Houweling, and favorable model, respectively (Table 1). If 20% of all fractions are delivered with protons, 28.4%, 33.8%, and 35.1%, respectively, of that maximum improvement is realized through single-modality patient selection, compared with 28.6%, 35.8%, and 37.9%, respectively, for combined proton-photon treatments.

Proton slot allocation during the continuous operation of a clinic

Figure 4 illustrates the simulation of daily allocation of proton fractions based on the summed NTCP values for Dutch

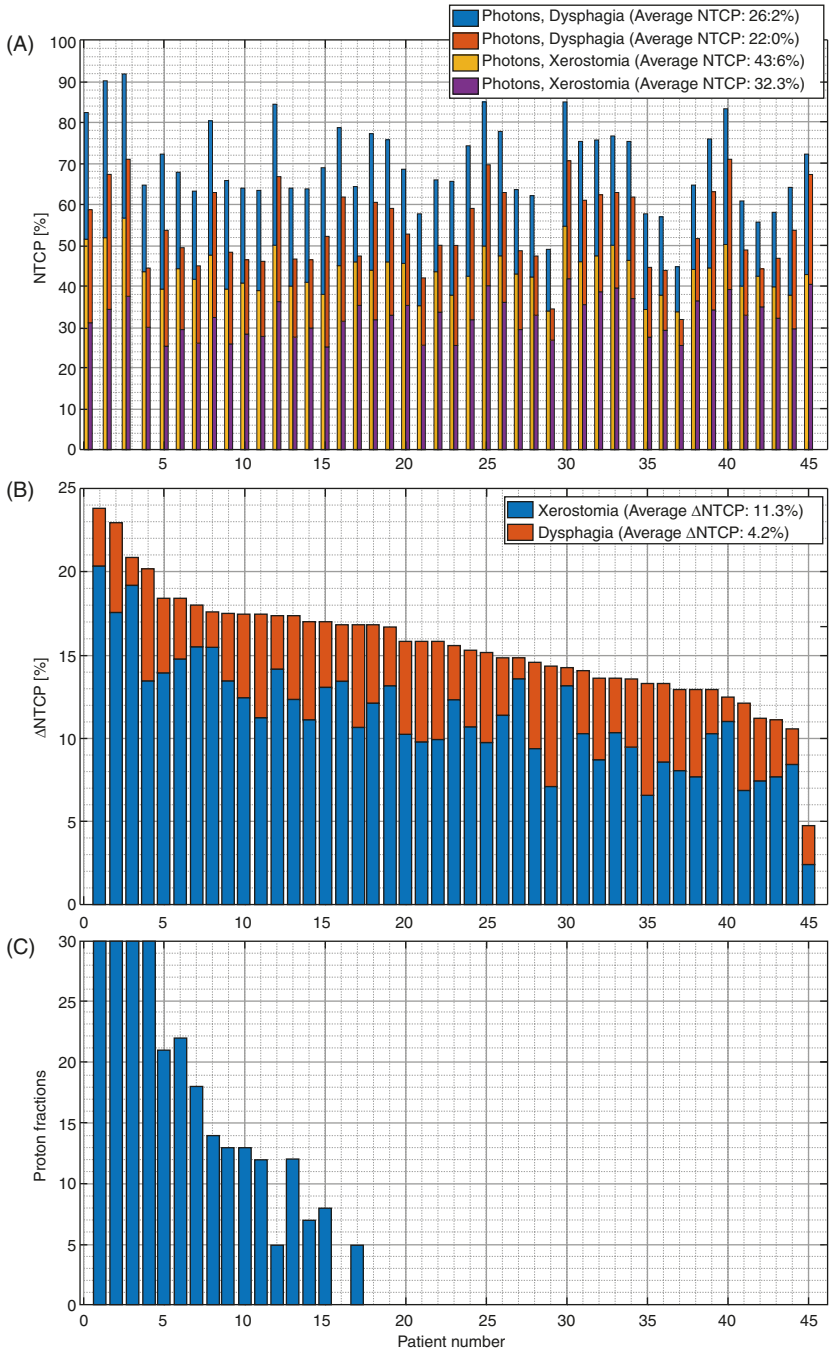

Fig. 2. (A) Cumulative normal tissue complication probability (NTCP) and (B) $\Delta NTCP$ values for the Dutch models for the 45 patients with head and neck cancer squamous cell carcinoma for the intensity modulated radiation therapy and intensity modulated proton therapy plans, with indicated portions related to xerostomia and dysphagia. (C) Allocation of 270 proton fractions that minimizes the sum of the NTCP values for xerostomia and dysphagia in the whole population. The patients are ordered according to their $\Delta NTCP^{sum}$.

xerostomia and dysphagia models. We assume 3 available proton slots per day and a 40% probability that a new patient starts treatment on any given day. In this example, 6 patients receive IMPT only, 39 patients receive a combined proton and photon treatment, and 55 patients receive IMRT only. In total, 777 out of 3000 fractions are delivered with protons, reflecting that 3 proton slots per day are available, whereas 12 patients, on average, are receiving treatment.

Figure 4A illustrates several scenarios that may occur in the daily slot allocation strategy. Patients may receive proton therapy at the beginning of their treatment and switch to photons when other patients with a larger benefit from protons start treatment (eg, patients 13, 15, 48, 55, and 77). Similarly, patients may start with photons but switch to protons when patients receiving greater benefit from protons finish treatment (eg, patients 88, 94, and 95). When 2

Table 1 Comparison of the average NTCP values between patient selection and combined proton-photon treatments

Proton slot allocation over the given cohort of 45 patients						
			Patient selection (single modality)		Combined proton-photon RT	
NTCP Model	Only photons	Only protons	20% protons	60% protons	20% protons	60% protons
Dutch ($NTCP^{Sum}$)	69.79%	54.30%	65.84% (25.5%)	59.31% (67.7%)	65.78% (25.9%)	59.29% (67.8%)
Dutch (xerostomia)	43.62%	32.33%	40.41% (28.4%)	35.63% (70.8%)	40.39% (28.6%)	35.62% (70.9%)
Houweling (xerostomia)	16.75%	6.26%	13.20% (33.8%)	8.86% (75.2%)	12.99% (35.8%)	8.62% (77.5%)
Favorable	33.40%	7.67%	24.36% (35.1%)	13.39% (77.8%)	23.64% (37.9%)	12.32% (81.9%)

Simulation of the continuous operation of a department for 4499 patients						
			Patient selection with optimal threshold		Daily proton slot reallocation	
NTCP Model	Only photons	Only protons	3 slots	6 slots	3 slots	6 slots
Dutch ($NTCP^{Sum}$)	68.06%	52.35%	64.22% (24.4%)	60.67% (47.0%)	63.16% (31.2%)	59.05% (57.4%)
Dutch (xerostomia)	43.04%	32.05%	40.19% (25.7%)	37.92% (48.4%)	39.35% (33.6%)	36.40% (60.4%)
Houweling (xerostomia)	15.98%	6.05%	13.18% (28.2%)	11.06% (49.6%)	11.93% (40.8%)	9.32% (67.1%)
Favorable	31.55%	7.19%	24.42% (29.3%)	19.52% (49.4%)	20.88% (43.8%)	14.15% (71.4%)

Abbreviations: NTCP = normal tissue complication probability; RT = radiation therapy.

The first row in each section of the table corresponds to the summed NTCP values for xerostomia and dysphagia for the Dutch models, and the next 3 rows correspond to the models in Figure 1. Numbers in parentheses indicate the percentage of the benefit relative to what is achievable when treating all patients with protons.

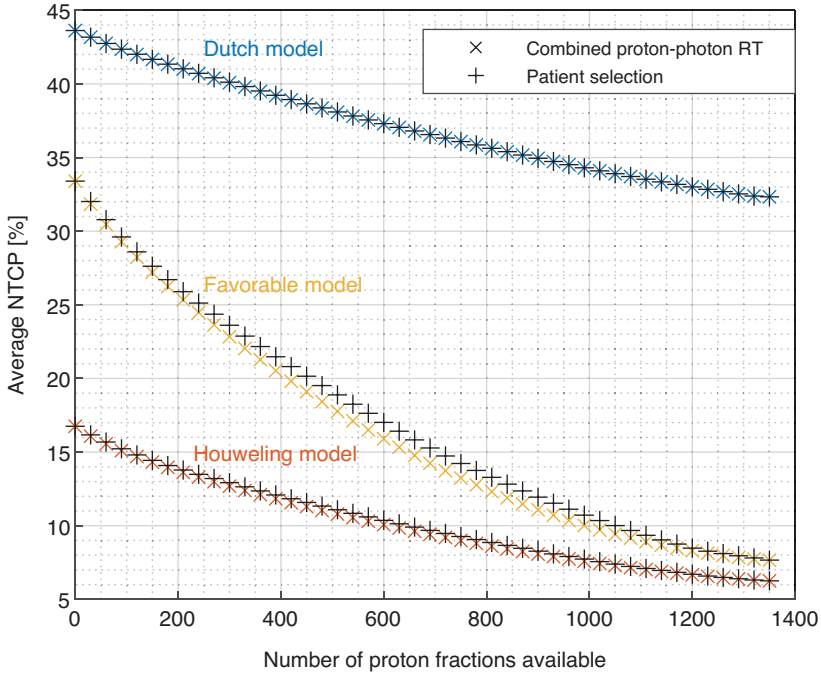

Fig. 3. Average normal tissue complication probability values as a function of the number of available proton fractions (N_{avail}) for combined proton-photon treatments (x) and patient selection (+).

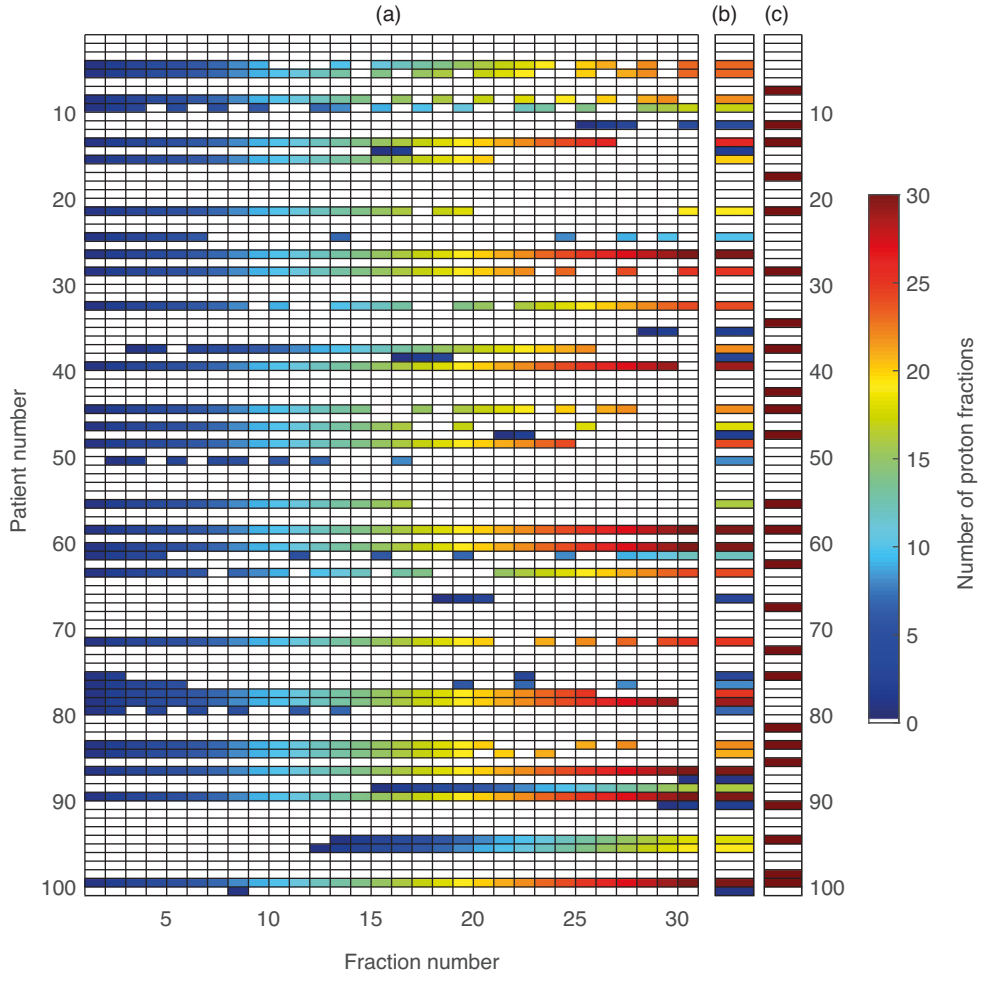

Fig. 4. Proton slot allocation in the simulation of the operation of a radiation therapy department over the period of approximately 1 year (281 working days), assuming only 3 proton slots available per day. (A) allocation of the 3 daily available proton slots to 100 consecutive patients with head and neck cancer squamous cell carcinoma (randomly extracted from the simulation) in combined proton-photon treatments. Each row corresponds to a patient, and each column corresponds to the fraction number. If a patient receives a proton fraction, the corresponding element is filled with a color that encodes the total number of proton fractions received until that day by the patient. If the patient receives a photon fraction, the corresponding element is white. (B) Total number of proton fractions received by each patient. (C) Patients selected for proton therapy only based on a $\Delta NTCP$ threshold of 14% for the same sequence of patients as in (A) and (B). *Abbreviation:* ΔNTCP = change in normal tissue complication probability.

patients with very similar benefits from protons are receiving treatment at the same time, a proton slot may alternate between patients (eg, patients 8 and 9). Further details are provided in Appendix ED.

For the threshold-based patient selection scheme (Fig. 4C) with a 14% $\Delta NTCP^{Sum}$ threshold, 24 patients receive IMPT and 76 patients receive IMRT. In this scenario, 115 proton fractions are unused as a result of waiting for a new patient in whom the benefit from protons exceeds the threshold of 14%. Also, 53 patients who exceed the threshold of 14% do not receive IMPT because all proton slots were blocked on the day they started treatment.

The daily slot allocation strategy for combined proton-photon treatments leads to a reduction of the average $NTCP^{Sum}$ values compared with the threshold-based patient selection for any number of available proton slots and for any threshold, as shown in Figure 5A. For the patient selection strategy and 3 available proton slots per day, a 14% threshold yielded the smallest average $NTCP^{Sum}$ value (Fig. 5B). For this optimal threshold, patient selection reduced the average $NTCP^{Sum}$ to 64.22%, compared with 68.06% for pure IMRT treatments for all patients (Table 1). The daily slot allocation strategy lowered the average $NTCP^{Sum}$ to 63.16%. The main reason for this improvement was that the daily slot reallocation strategy makes use of all proton slots on every day, whereas some proton slots are unused in the patient selection scheme or are blocked by patients with less benefit. Treating all patients with protons would yield an average $\Delta NTCP^{Sum}$ of 52.35% (Table 1).

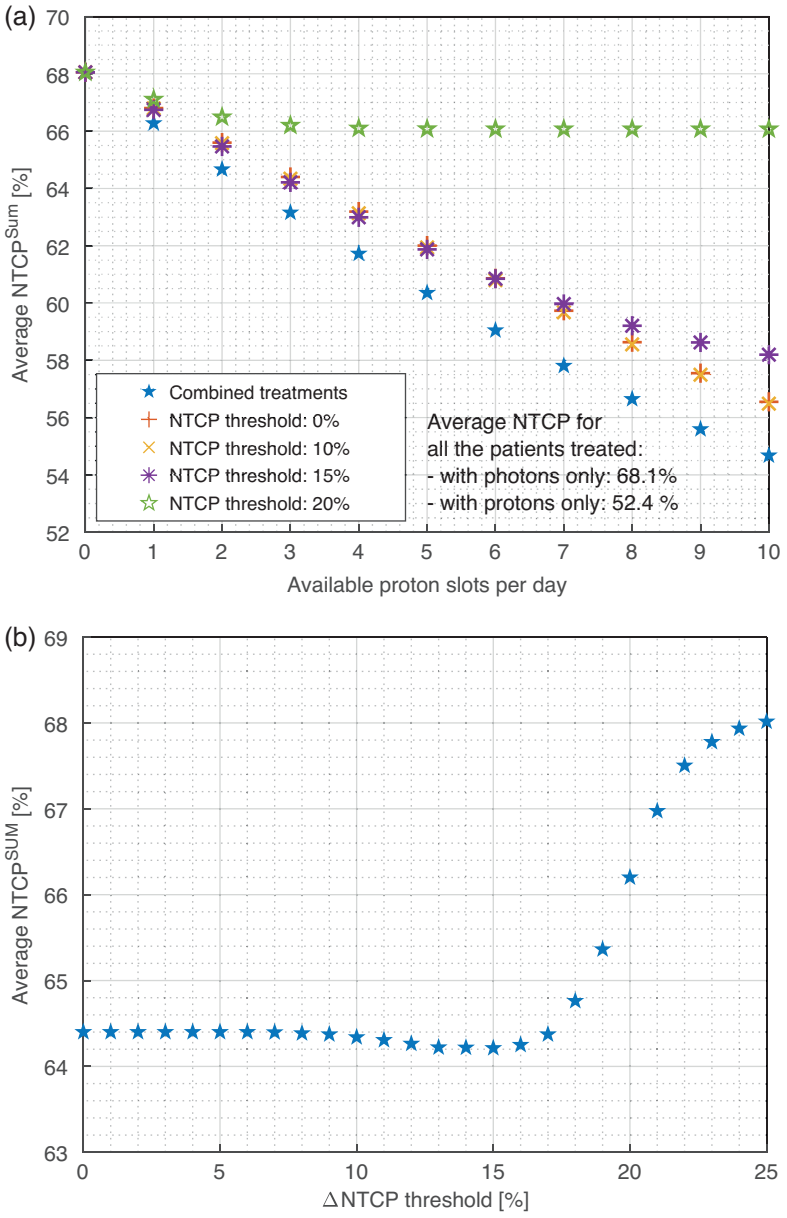

Fig. 5. (A) Average $NTCP^{Sum}$ as a function of the daily available proton slots for the combined treatments with daily slot reallocation (blue stars) and the single-modality treatment (patient selection) assuming different $NTCP^{Sum}$ thresholds. (B) Average $NTCP^{Sum}$ for threshold-based patient selection with 3 proton slots per day as function of the $\Delta NTCP^{Sum}$ threshold. *Abbreviation:* ΔNTCP = change in normal tissue complication probability.

Further discussion of the patient selection threshold (Fig. 5B) is provided in Appendix EE.

Finally, we investigated how the benefit of daily slot reallocation over patient selection depends on the NTCP model (Table 1 and Appendix EF). Similar to what is observed for slot allocation over a given cohort, the benefit of combined treatments increases when the NTCP curve is nonlinear in the range between proton and photon doses. For example, for the favorable model and 3 available slots per day, combined treatments realized 43.8% of the maximum benefit of treating all patients with protons only, whereas patient selection with an optimal threshold realized only 29.3%.

Discussion

Currently, concepts for selecting radiation therapy patients for proton therapy based on NTCP models are being developed, promoted, and implemented in individual countries.[31,32] The goal of such patient selection schemes is to maximize the benefit of limited proton therapy resources for the health care system as a whole. In this work, we investigated whether the benefit of proton therapy for a population of patients could be further increased via combined proton-photon treatments, in which some fractions are delivered with protons and others with photons.

Recently, several groups have investigated the optimization of combined proton-photon treatments.[33-36] The main difference in our work is that we consider the optimal use of limited proton resources for a population of patients. Previous studies have instead focused on the design of a combined proton-photon treatment for an individual patient. A detailed discussion of how this work relates to other work on combined proton-photon treatments is provided in Appendix EG.

First, we investigated whether there is an advantage of combined treatments owing to a diminishing return of additional proton fractions on the convex part of the NTCP curve. It turned out that the optimal use of limited proton fractions, which minimizes the expected number of complications in a patient cohort, indeed contains combined proton-photon treatments. However, the improvement over optimal patient selection was small for the cohort of patients with head and neck cancer under consideration in combination with the NTCP models proposed in the Netherlands. The advantage of combined proton-photon treatments would increase if the dose differences between proton and photon plans spanned a larger, nonlinear section of the NTCP curve. This may become the case if (1) dose-response relations become better known (eg, by discovering additional biomarkers), resulting in steeper NTCP curves, and (2) dosimetric differences between protons and photons become larger through further improvements in IMPT planning and delivery. In this work, we used step-and-shoot IMRT plans with 7 beams and IMPT plans with 3 beams. It is expected that both plans could be improved with VMAT and a larger number of beams.

Second, we considered the real-world problem of proton slot allocation during the continuous operation of a radiation therapy clinic, assuming a limited number of available proton slots for treating patients with head and neck cancer. In that situation, a patient selection method based on the NTCP threshold faces the trade-off between leaving proton slots unused if the NTCP threshold is high or blocking slots with patients with mediocre benefit from proton therapy if the threshold is low. Combining proton-photon treatments with daily slot allocation has the advantage of all proton slots being used effectively. If a new patient starts treatment who has a larger benefit from proton therapy than the other patients currently receiving treatment, a proton treatment slot can be assigned to that patient.

In a clinical setting, some conditions may differ from the assumptions made in this work, and there are challenges in combined proton-photon treatments regarding clinical workflow and patient scheduling. Further discussion on some of these aspects is provided in Appendix EH.

Conclusion

From a global health system perspective, limited proton therapy resources can be more efficiently used with combined proton-photon treatments and daily proton slot allocation rather than single-modality treatments, even with optimal patient selection.

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