Optimal allocation of proton therapy slots in combined proton-photon radiotherapy

Loizeau, N.; Fabiano, S.; Papp, D.; Stützer, K.; Jakobi, A.; Bandurska-Luque, A.; Troost, E. G. C.; Richter, C.; Unkelbach, J.;

Originally published:

April 2021

International Journal of Radiation Oncology Biology Physics 111(2021)1, 196-207

DOI: https://doi.org/10.1016/j.ijrobp.2021.03.054

Perma-Link to Publication Repository of HZDR:

https://www.hzdr.de/publications/Publ-31581

Title:

Optimal allocation of proton therapy slots in combined proton-photon radiotherapy

Short title:

Optimal allocation of limited proton resources

First and corresponding author

Nicolas Loizeau, Physics Institute, University of Zürich, Zürich, Switzerland;

Department of Radiation Oncology, University Hospital Zürich, Zürich, Switzerland

Phone: +41 79 390 64 25

Email: nicolas.loizeau@hotmail.com

Mailing address: University Hospital Zürich, Department of Radiation Oncology,

Rämistrasse 100 , 8091 Zürich, Switzerland

Coauthors

Silvia Fabiano, Department of Radiation Oncology, University Hospital Zürich, Zürich, Switzerland

Dávid Papp, Department of Mathematics, North Carolina State University, USA

Kristin Stützer, OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany; Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany

Annika Jakobi, OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany;

Anna Bandurska-Luque, OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany; Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; current address: Greater Poland Cancer Centre, Poznan, Poland;

Esther G.C. Troost, MD PhD. OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Dresden, Germany; Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany; National Center for Tumor Diseases (NCT), Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany, and; Helmholtz Association / Helmholtz-Zentrum Dresden - Rossendorf (HZDR), Dresden, Germany

Christian Richter, OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Dresden, Germany; Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany

Senior author

Jan Unkelbach, Department of Radiation Oncology, University Hospital Zürich, Zürich, Switzerland, jan.unkelbach@usz.ch

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding statement

This work was in part supported by the Swiss Cancer Research grant KFS-4528-08-2018 on combined proton-photon radiotherapy.

Acknowledgment

We thank Tony Lomax and our colleagues at the Paul Scherrer Institute (PSI) for providing feedback and comments on the project.

Data sharing statement

This study is based on the mean dose values in the contralateral parotid gland, oral cavity, and superior pharyngeal constrictor muscle from IMRT and IMPT plans for a cohort of 45 patients, which are made available at the following link 10.6084/m9.figshare.12977765. All the results in this paper can be reproduced using the mean dose values as input parameters for the different NTCP models.

Abstract

Purpose: Proton therapy is a limited resource, which is not available to all patients who may benefit from it. We investigate 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: To quantify differences in normal tissue complication probability (NTCP) between protons and photons, we consider a cohort of 45 head-and-neck cancer patients for which IMRT and IMPT 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 develop methods to optimally assign proton fractions in combined proton-photon treatments to minimize the average NTCP on a population level. Such combined treatments are compared to 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 over patient selection due to the nonlinearity of NTCP functions, i.e. 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 models considered, but may be larger if dose-response relationships are better known. In addition, when proton slots are limited, patient selection methods face a tradeoff 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 a better utilization 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 to conventional photon-based radiotherapy and its clinical value is being investigated in the context of clinical studies [1]. As a rule of thumb, protons allow reducing the integral dose to normal tissues by a factor of 2-3 [2], [3]. 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 [4]. This must be compared to more than 12'000 conventional radiotherapy units [5]. Consequently, only a small percentage of patients with an indication for radiotherapy is treated with protons [6] and not all patients who may benefit from proton therapy have access to it.

Strategies for selecting patients for proton therapy varies between institutions, countries, and health care systems. In most countries, several treatments are

considered standard indications for proton therapy, including pediatric patients and tumors in proximity of the base of skull or spinal cord, e.g., chordoma and chondrosarcoma. In addition, there are treatment sites that are not routinely referred to proton therapy, but planning studies comparing intensity-modulated proton therapy (IMPT) to photon-based intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) have demonstrated a potential advantage of proton therapy. One such treatment site is head and neck cancer squamous cell carcinoma (HNSCC). In 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 [7]–[9]. Dose reduction is expected to lower normal tissue complication probabilities (NTCP) for common side effects such as xerostomia and dysphagia [10]–[12].

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], [14]. In this approach, both photon and proton treatment plans are created and the dose difference between the two modalities is translated into an expected NTCP difference using agreed-upon NTCP models. Subsequently, patients in whom the NTCP reduction through protons exceeds a threshold are referred to proton therapy while 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 work, 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 HNSCC patients. As the measure of benefit, we aimed to minimize the expected total number of complications in a patient population. To that end, we investigated if there is a role for combined proton-photon treatments where several fractions are delivered with IMPT and the remaining fractions with IMRT/VMAT.

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

1. On the convex part of the NTCP curve, the first proton fractions are the most beneficial, i.e. the patient is on a steeper section of the NTCP curve. For an increasing number of proton fractions, the benefit of any additional proton fraction decreases. Thus, there may be a point of diminishing return and it may be more beneficial to give proton fractions to other patients.
2. Assume there is a given number of proton slots available each day to treat HNSCC patients. Then, any single-modality patient selection strategy faces a tradeoff between leaving a proton slot unused and blocking a proton slot for future patients who may have a larger benefit. Instead, flexible allocation of proton fractions in combined proton-photon treatments may make optimal use of all available proton slots.

Here, we present a methodology to optimally distribute a limited number of IMPT slots over a patient population to answer the question "How many proton fractions

should each patient receive?" rather than "Which patient should receive IMPT only and which IMRT only?". The methods benefit in a HNSCC population is compared to a patient-wise selection for single-modality treatment based on a $\Delta NTCP$ threshold.

Materials and Methods

Patient cohort and treatment plans

To quantify the dosimetric differences of proton and photon treatments, we consider a cohort of 45 patients with locally advanced HNSCC in different locations. This patient cohort was previously studied by Jakobi et al. [2] in the context of proton patient selection [2] and the dose escalation potential of proton therapy [15]. For all patients, IMPT and IMRT plans for a simultaneous integrated boost (SIB) treatment are available, which deliver 70 Gy(RBE) to a boost volume (GTV_{SIB}) and 54 Gy(RBE) to the remaining target volumes (PTV_{all}) in 30 fractions (see further details in Appendix A).

NTCP modeling

To calculate NTCP values for IMRT, IMPT, and combined treatments, we apply the NTCP models that have been agreed upon in the Netherlands for selecting patients for proton [16]. We consider NTCP models for xerostomia and dysphagia as described in [17], [18] but with updated parameters according to [16]. The general form of the NTCP model is the following:

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

For xerostomia, the model parameters are

- $a = 1.507,\ b = 0.052$;
- d is the mean dose to the contralateral parotid gland.

For dysphagia, the model parameters are

- $a = 3.303,\ b = 0.024$;
- d is the sum of the mean doses in the oral cavity and in the superior pharyngeal constrictor muscle (PCM).

Let ${d_j}^{\gamma}$ and ${d_j}^{p}$denote the photon and proton mean doses per fraction for patient *j* for a given organ. In a combined photon-proton treatment with ${n_j}^{p}$ proton fractions and ${n_j}^{\gamma}$photon fractions, the cumulative mean dose d_j in the organ is given by the sum of photon and proton doses:

$$d_j = {n_j}^{\gamma}{d_j}^{\gamma} + {n_j}^{p}{d_j}^{p} \quad (2)$$

where ${n_j}^{p} \in \{0,1,2\ldots,30\}$ and ${n_j}^{\gamma} = 30 - {n_j}^{p}$ throughout this work. In this formulation, the proton dose ${d_j}^{p}$ includes a constant RBE of 1.1.

Let $NTCP_j({n_j}^{p})$ denote the NTCP value for patient *j* as a function of the number of proton fractions ${n_j}^{p}$. Let further $NTCP_{jk} = NTCP_j({n_j}^{p} = k)$ denote the NTCP value for patient j if the patient receives exactly k proton fractions and $30 - k$ photon fractions. In this work, the NTCP values refer to either xerostomia ($NTCP^{Xero}$) or dysphagia ($NTCP^{Dys}$), or to an equally weighted sum of both complication risks ($NTCP^{Sum} = NTCP^{Xero} + NTCP^{Dys}$). 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 the supplementary materials, Appendix I.

To quantify the benefit of proton therapy at a population level, we consider the average NTCP over a patient cohort:

$$< NTCP > = \frac{1}{M} \sum_{j=1}^{M} NTCP_j\left(n_j{}^p\right) \quad (3)$$

where M is the number of patients in the cohort.

Optimal proton slot allocation for a given patient cohort

First, we consider an idealized scenario, in which all the 45 HNSCC patients are known at the time of distributing the proton slots. Although this is a hypothetical situation, it allows us to investigate if 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, due to limited resources, only a percentage of the total number of fractions can be delivered with protons, i.e. a total number of N_{avail} proton slots are available, which is smaller 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:

$$\underset{n_j{}^p}{\text{minimize}} \qquad \frac{1}{M} \sum_{j=1}^{M} NTCP_j\left(n_j{}^p\right) \quad (4)$$

$$\text{subject to} \quad \sum_{j=1}^{M} n_j{}^p \leq N_{avail} \tag{5}$$

$$n_j{}^p \in \{0, 1, 2, \ldots, 30\} \ \forall j \tag{6}$$

This optimization problem can be solved to optimality by reformulating the problem as a linear binary integer programming problem as described in supplementary materials, Appendix B.

Combined proton-photon treatments with optimal allocation of proton fractions are compared to 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, newly diagnosed HNSCC patients continuously start radiotherapy throughout the year. Instead of allocating a total number of proton fractions over a given patient cohort, one has to decide for every incoming patient whether the patient receives protons or photons. We now consider a radiotherapy department in which both protons and photons are available, but the number of proton slots available for the treatment of HNSCC patients is smaller than the average number of HNSCC patients under treatment at a given time.

For this situation, we compare combined proton-photon treatments to a threshold-based proton patient selection strategy. More specifically, we compare the following two 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 under treatment. In this case, a patient may receive proton fractions on some days and photon fractions on other days, depending on the other patients that are under treatment. To assign proton slots on a given day, we determine the patients under treatment which 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:

$$\Delta NTCP_{kj} = NTCP_{kj} - NTCP_{(k+1)j} \quad (7)$$

which quantifies the benefit of receiving an additional proton fraction today, 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 above daily proton slot reassignment strategy is compared to 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 over pure IMRT ($\Delta NTCP_j$) of the incoming patient j exceeds a threshold (e.g. 5%, 10%, 15%);
- 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 radiotherapy department over a long period of time. As an example, we assume that the department treats on average 100 head & neck cancer patients per year, meaning that on average 2 newly diagnosed patients per week start treatment. For a 30-fraction treatment scheme, patients are under treatment for 6 weeks, meaning that on average 12 patients are under treatment on any given day. We assume here that a constant number of proton slots is available each day, which is smaller than what would be needed to treat all patients with protons.

Each iteration of the simulation corresponds to one working day and the following steps are executed:

1. We randomly decide if a new patient starts treatment on that day. In this work, we assume a 40% probability for a new HNSCC patient every 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 function[1]. The mean and covariance matrix of the Gaussian are calculated from the doses of the 45 HNSCC patients. The new patient is considered to be under treatment from now on.

3.1. For the daily slot reallocation strategy, the available proton slots are distributed among the patients under treatment as described above.

3.2. For the threshold-based single-modality patient selection, it is decided whether or not a new patient (if present) is assigned a proton slot for the next 30 days (if available today).

4. All patients under treatment receive one 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 any effects resulting from initial and ending conditions. Based on the remaining patients, the average NTCP value $< NTCP >$ is calculated.

Results

Optimal proton slot allocation for the given patient cohort

[1] Samples in which the mean dose in one organ exceeds the GTV_{SIB} prescription dose of 70 Gy(RBE) and/or in which the proton dose exceeds the photon dose in one of the organs are discarded.

For the patient cohort considered, IMPT reduces the NTCP values compared to IMRT for both xerostomia and dysphagia for all 45 HNSCC patients (Figure 1a), i.e. for every single patient a single modality IMPT treatment would have been optimal. The average NTCP values for xerostomia/dysphagia are 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 ($\Delta NTCP^{Sum}$) is expected. The individual $\Delta NTCP^{Sum}$ values vary between 4.8% and 23.8% (Figure 1b).

Figure 1c 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 while 29 patients receive only photons. 12 patients receive a combined proton-photon treatment. Patients with higher $\Delta NTCP^{Sum}$ 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 has 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 to treating all patients with photons (65.78% vs. 69.79%), as summarized in Table 1a. For the optimal patient selection strategy (where the 9

patients with the highest $\Delta NTCP$ are treated with protons only and the remaining patients with photons only), the average summed NTCP is 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 one randomly selected 20% of patients for proton therapy (without any NTCP modeling), one would, in expectation, realize 20% of the 15.49% benefit of protons over photons. Patient selection based on $\Delta NTCP$ increases this benefit to 25.5% ((69.79-65.84)/(69.79-54.30)). Combined proton-photon treatments with optimal proton fraction allocation increase the realized benefit to 25.9%. If 60% of all fractions are delivered with protons, combined proton-photon therapy can realize 67.8% of the possible benefit, compared to 67.7% for patient selection (Table 1a).

The optimal proton slot allocation for minimizing the average NTCP for xerostomia and dysphagia individually rather than the sum is investigated in Appendix C. When considering the two 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 the patients in whom the dose to the oral cavity and the PCM may be lowered. However, in all cases, only a small improvement in average NTCP is observed for combined proton-photon therapy over patient selection for single-modality treatment.

Proton slot allocation during the continuous operation of a clinic

Figure 2 illustrates the simulation of daily allocation of proton fractions assuming 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 while on average 12 patients are under treatment. Figure 2a 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 (e.g. patients 13, 15, 48, 55, 77). Similarly, patients may start with photons but switch to protons when patients with larger benefit finish treatment (e.g. patients 88, 94, 95). When two patients with very similar benefits from protons are under treatment at the same time, a proton slot may alternate between patients (e.g. patients 8, 9). Further details are provided in Appendix D.

For the threshold-based patient selection scheme (Figure 2c), 24 patients receive IMPT and 76 patients receive IMRT for a 14% $\Delta NTCP^{Sum}$ threshold. 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 presented.

The daily slot allocation strategy for combined proton-photon treatments leads to a reduction of the average $NTCP^{Sum}$ values compared to the threshold-based patient selection for any number of available proton slots and for any threshold, as shown in

Figure 3a. For the patient selection strategy and 3 available proton slots per day, a 14% threshold yields the smallest average $NTCP^{Sum}$ value (Figure 3b). For this optimal threshold, the patient selection reduces the average $NTCP^{Sum}$ to 64.22% compared to 68.06% for pure IMRT treatments for all patients. The daily slot allocation strategy lowers the average $NTCP^{Sum}$ to 63.16%. The main reason for this improvement is 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 yields an average $NTCP^{Sum}$ of 52.35% (Table 1b). Further discussion on the patient selection threshold (Figure 3b) is provided in Appendix E.

Dependence of the benefit of combined proton-photon treatments on the NTCP model

The reduction of the average $NTCP$ for combined treatments compared to single-modality treatments depends on the shape of the NTCP curve. To demonstrate this, we investigate three $NTCP$ models illustrated in Figure 4:

1. The Dutch xerostomia model described in section 2 (Dutch model),
2. The xerostomia model published by Houweling et al. [19] (Houweling model), 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.

3. A hypothetical model that shows a larger benefit of combined treatments (Favorable model), with the same functional representation as the Houweling model but with parameters $D_{50} = 28\ Gy$ and $m = 0.3$.

In Figure 5 we consider the allocation of limited proton fractions over the given cohort of 45 HCSCC patients based on the three models. For the dutch model, there is only a very small benefit of combined proton-photon treatments for any number of available proton slots. The reason for this is that 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, i.e. 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, there is a benefit of combined proton-photon treatments over patient selection that arises from the non-linearity of the NTCP curve. The benefit for the Houweling model is in between the dutch model and the favorable model.

The average NTCP reductions for treating all 45 patients with protons only instead of photons only are 11.3%, 10.5%, and 25.7% for the Dutch, Houweling, and favorable

model, respectively. If 20% of all fractions are delivered with protons, 28.4%, 33.8%, 35.1% of that maximum improvement is realized through single-modality patient selection compared to 28.7%, 35.9%, 37.9 % for combined proton-photon treatments.

The favorable model also yields a larger improvement of combined proton-photon treatments over patient selection in the simulation of slot allocation during the continuous operation of a clinic (Appendix F). For example, for 3 available slots per day, combined treatments realize 38.0% of the maximum benefit of treating all patients with protons only, while patient selection with an optimal threshold realizes only 26.2%.

Discussion

Currently, concepts for selecting radiotherapy patients for proton therapy based on NTCP models are being developed, promoted, and implemented in individual countries [20], [21]. The goal of such patient selection schemes is to maximize the benefit of limited proton therapy resources for the healthcare system as a whole. In this work, we investigated if one can further increase the benefit of proton therapy for a population of patients 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 [22]–[25]. The main difference in our work is that we consider the optimal use of limited proton resources for a population of patients. Previous works

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 works on combined proton-photon treatments is provided in Appendix G.

First, we investigated if there is an advantage of combined treatments due 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 head & neck patient cohort considered in combination with the NTCP models proposed in the Netherlands. However, the advantage of combined proton-photon treatments would increase if the dose differences between proton and photon plans spanned a larger, non-linear section of the NTCP curve. This may become the case if a) dose-response relations become better known (e.g. by discovering additional biomarkers), resulting in steeper NTCP curves, and b) dosimetric differences between protons and photons become larger through further improvements in IMPT planning and delivery. In this work, we used step&shoot IMRT plans with 7 beams and IMPT plans with 3 beams. It can be expected that both plans can 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 radiotherapy clinic assuming a limited number of available proton slots for treating head & neck cancer patients. In that situation, an NTCP threshold-based patient selection method faces the tradeoff 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. Combined proton-photon treatments with daily slot allocation have the advantage that all proton slots are used effectively. If a new patient starts treatment who has a larger benefit from proton therapy than the other patients currently under 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 (due to word limitations) in Appendix H.

In 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.

References

[1] R. Mohan and D. Grosshans, “Proton therapy – Present and future,” *Adv. Drug Deliv. Rev.*, vol. 109, pp. 26–44, Jan. 2017, doi: 10.1016/j.addr.2016.11.006.

[2] A. Jakobi *et al.*, “Identification of Patient Benefit From Proton Therapy for Advanced Head and Neck Cancer Patients Based on Individual and Subgroup Normal Tissue Complication Probability Analysis,” *Int. J. Radiat. Oncol. • Biol. • Phys.*, vol. 92, no. 5, Art. no. 5, Aug. 2015, doi: 10.1016/j.ijrobp.2015.04.031.

[3] H. Paganetti, *Proton therapy physics*. CRC press, 2018.

[4] “PTCOG - Facilities in Operation,” Apr. 22, 2020. https://www.ptcog.ch/index.php/facilities-in-operation (accessed Apr. 22, 2020).

[5] E. Rosenblatt *et al.*, “Radiotherapy capacity in European countries: an analysis of the Directory of Radiotherapy Centres (DIRAC) database,” *Lancet Oncol.*, vol. 14, no. 2, Art. no. 2, Feb. 2013, doi: 10.1016/S1470-2045(12)70556-9.

[6] T. R. Bortfeld and J. S. Loeffler, “Three ways to make proton therapy affordable,” *Nat. News*, vol. 549, no. 7673, Art. no. 7673, Sep. 2017, doi: 10.1038/549451a.

[7] L. Cozzi, A. Fogliata, A. Lomax, and A. Bolsi, “A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced head and neck tumours,” *Radiother. Oncol.*, vol. 61, no. 3, Art. no. 3, Dec. 2001, doi: 10.1016/S0167-8140(01)00403-0.

[8] S. Kandula *et al.*, “Spot-scanning beam proton therapy vs intensity-modulated radiation therapy for ipsilateral head and neck malignancies: A treatment planning comparison,” *Med. Dosim.*, vol. 38, no. 4, Art. no. 4, Dec. 2013, doi: 10.1016/j.meddos.2013.05.001.

[9] A. C. Moreno *et al.*, “Intensity modulated proton therapy (IMPT) – The future of IMRT for head and neck cancer,” *Oral Oncol.*, vol. 88, pp. 66–74, Jan. 2019, doi: 10.1016/j.oraloncology.2018.11.015.

[10] T. A. van de Water *et al.*, “Potential Benefits of Scanned Intensity-Modulated Proton Therapy Versus Advanced Photon Therapy With Regard to Sparing of the Salivary

Glands in Oropharyngeal Cancer," *Int. J. Radiat. Oncol.*, vol. 79, no. 4, Art. no. 4, Mar. 2011, doi: 10.1016/j.ijrobp.2010.05.012.

[11] T. A. van de Water, H. P. Bijl, C. Schilstra, M. Pijls-Johannesma, and J. A. Langendijk, "The Potential Benefit of Radiotherapy with Protons in Head and Neck Cancer with Respect to Normal Tissue Sparing: A Systematic Review of Literature," *The Oncologist*, vol. 16, no. 3, Art. no. 3, Mar. 2011, doi: 10.1634/theoncologist.2010-0171.

[12] L. V. van Dijk *et al.*, "Robust Intensity Modulated Proton Therapy (IMPT) Increases Estimated Clinical Benefit in Head and Neck Cancer Patients," *PloS One*, vol. 11, no. 3, Art. no. 3, 2016, doi: 10.1371/journal.pone.0152477.

[13] J. A. Langendijk, P. Lambin, D. De Ruysscher, J. Widder, M. Bos, and M. Verheij, "Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach," *Radiother. Oncol.*, vol. 107, no. 3, Art. no. 3, Jun. 2013, doi: 10.1016/j.radonc.2013.05.007.

[14] J. Widder *et al.*, "The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine," *Int. J. Radiat. Oncol.*, vol. 95, no. 1, Art. no. 1, May 2016, doi: 10.1016/j.ijrobp.2015.10.004.

[15] A. Jakobi *et al.*, "Increase in Tumor Control and Normal Tissue Complication Probabilities in Advanced Head-and-Neck Cancer for Dose-Escalated Intensity-Modulated Photon and Proton Therapy," *Front. Oncol.*, vol. 5, 2015, doi: 10.3389/fonc.2015.00256.

[16] "Landelijk Indicatie Protocol Protonen Therapie", 2017, *private communication*.

[17] M. E. M. C. Christianen *et al.*, "Predictive modelling for swallowing dysfunction after primary (chemo)radiation: results of a prospective observational study," *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 105, no. 1, Art. no. 1, Oct. 2012, doi: 10.1016/j.radonc.2011.08.009.

[18] I. Beetz *et al.*, "NTCP models for patient-rated xerostomia and sticky saliva after treatment with intensity modulated radiotherapy for head and neck cancer: the role of dosimetric and clinical factors," *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 105, no. 1, Art. no. 1, Oct. 2012, doi: 10.1016/j.radonc.2012.03.004.

[19] A. C. Houweling *et al.*, “A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients,” *Int. J. Radiat. Oncol. Biol. Phys.*, vol. 76, no. 4, Art. no. 4, Mar. 2010, doi: 10.1016/j.ijrobp.2009.07.1685.

[20] S. Teoh, F. Fiorini, B. George, K. A. Vallis, and F. Van den Heuvel, “Proton vs photon: A model-based approach to patient selection for reduction of cardiac toxicity in locally advanced lung cancer,” *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, Aug. 2019, doi: 10.1016/j.radonc.2019.06.032.

[21] P. Blanchard *et al.*, “Toward a model-based patient selection strategy for proton therapy: External validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort,” *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 121, no. 3, Art. no. 3, 2016, doi: 10.1016/j.radonc.2016.08.022.

[22] S. C. M. Ten Eikelder, D. den Hertog, T. Bortfeld, and Z. Perkó, “Optimal combined proton-photon therapy schemes based on the standard BED model,” *Phys. Med. Biol.*, vol. 64, no. 6, Art. no. 6, 12 2019, doi: 10.1088/1361-6560/aafe52.

[23] H. Gao, “Hybrid proton-photon inverse optimization with uniformity-regularized proton and photon target dose,” *Phys. Med. Biol.*, vol. 64, no. 10, Art. no. 10, May 2019, doi: 10.1088/1361-6560/ab18c7.

[24] J. Unkelbach, M. Bangert, K. De Amorim Bernstein, N. Andratschke, and M. Guckenberger, “Optimization of combined proton-photon treatments,” *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 128, no. 1, Art. no. 1, Jul. 2018, doi: 10.1016/j.radonc.2017.12.031.

[25] S. Fabiano, P. Balermpas, M. Guckenberger, and J. Unkelbach, “Combined proton-photon treatments - A new approach to proton therapy without a gantry,” *Radiother. Oncol. J. Eur. Soc. Ther. Radiol. Oncol.*, vol. 145, pp. 81–87, Jan. 2020, doi: 10.1016/j.radonc.2019.12.013.

[26] D. L. Schwartz, “Current Progress in Adaptive Radiation Therapy for Head and Neck Cancer,” *Curr. Oncol. Rep.*, vol. 14, no. 2, pp. 139–147, Apr. 2012, doi: 10.1007/s11912-012-0221-4.

[27] Q. Wu, Y. Chi, P. Y. Chen, D. J. Krauss, D. Yan, and A. Martinez, “Adaptive Replanning Strategies Accounting for Shrinkage in Head and Neck IMRT,” *Int. J. Radiat. Oncol.*, vol. 75, no. 3, pp. 924–932, Nov. 2009, doi: 10.1016/j.ijrobp.2009.04.047.

Figure captions

Figure 1: (a) Cumulative $NTCP$ and (b) $\Delta NTCP$ values for the 45 HNSCC patients for the IMRT and IMPT 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 $\Delta NTCP^{Sum}$.

Figure 2: (a) Example for the allocation of 3 daily available proton slots to 100 consecutive HNSCC patients for combined proton-photon treatments corresponding to the time period of approximately one year (281 working days), extracted randomly from the simulation. 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. If the patient receives a photon fraction, the element is white.; (b) Number of proton fractions received by each patient; (c) patients selected for protons based on a $\Delta NTCP$ threshold of 14% for the same sequence of patients as in (a/b).

Figure 3: (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 $\Delta NTCP^{Sum}$ thresholds. (b) Average $NTCP^{Sum}$ for threshold-based patient selection with 3 proton slots per day as function of the $\Delta NTCP^{Sum}$ threshold.

Figure 4: Dutch (blue), Houweling (red), and favorable (yellow) NTCP models for xerostomia. The vertical lines show the mean of the contralateral mean doses ± 1 standard deviation for photons (black) and protons (green) over the 45 HNSCC patients.

Figure 5: Average NTCP values as a function of the number of available proton fractions N_{avail} for combined proton-photon treatments (x) and patient selection (+) treat all 45 patients with only protons.

Table caption

Table 1: Comparison of the average $NTCP^{Sum}$ values for the patient selection, combined proton-photon treatments, and the case that all patients are treated with photons and protons. Numbers in parentheses indicate the percentage of the benefit relative to what is achievable when treating all patients with protons. (a) for proton slot allocation over the given cohort of 45 patients; (b) for the simulation of the continuous operation of a department for 4499 patients.

Table 1

(a)

Only photons	Only protons	Patient selection		Combined proton-photon RT	
69.79%	54.30% (100%)	20% protons	60% protons	20% protons	60% protons
		65.84% (25.5%)	59.31% (67.7%)	65.78% (25.9%)	59.29% (67.8%)

(b)

Only photons	Only protons	Patient selection with 14% threshold		Daily slot reallocation strategy	
68.06%	52.35% (100%)	3 proton slots per day	6 proton slots per day	3 proton slots per day	6 proton slots per day
		64.22% (24.4%)	60.67% (47.0%)	63.16% (31.2%)	59.05% (57.4%)

Figure1

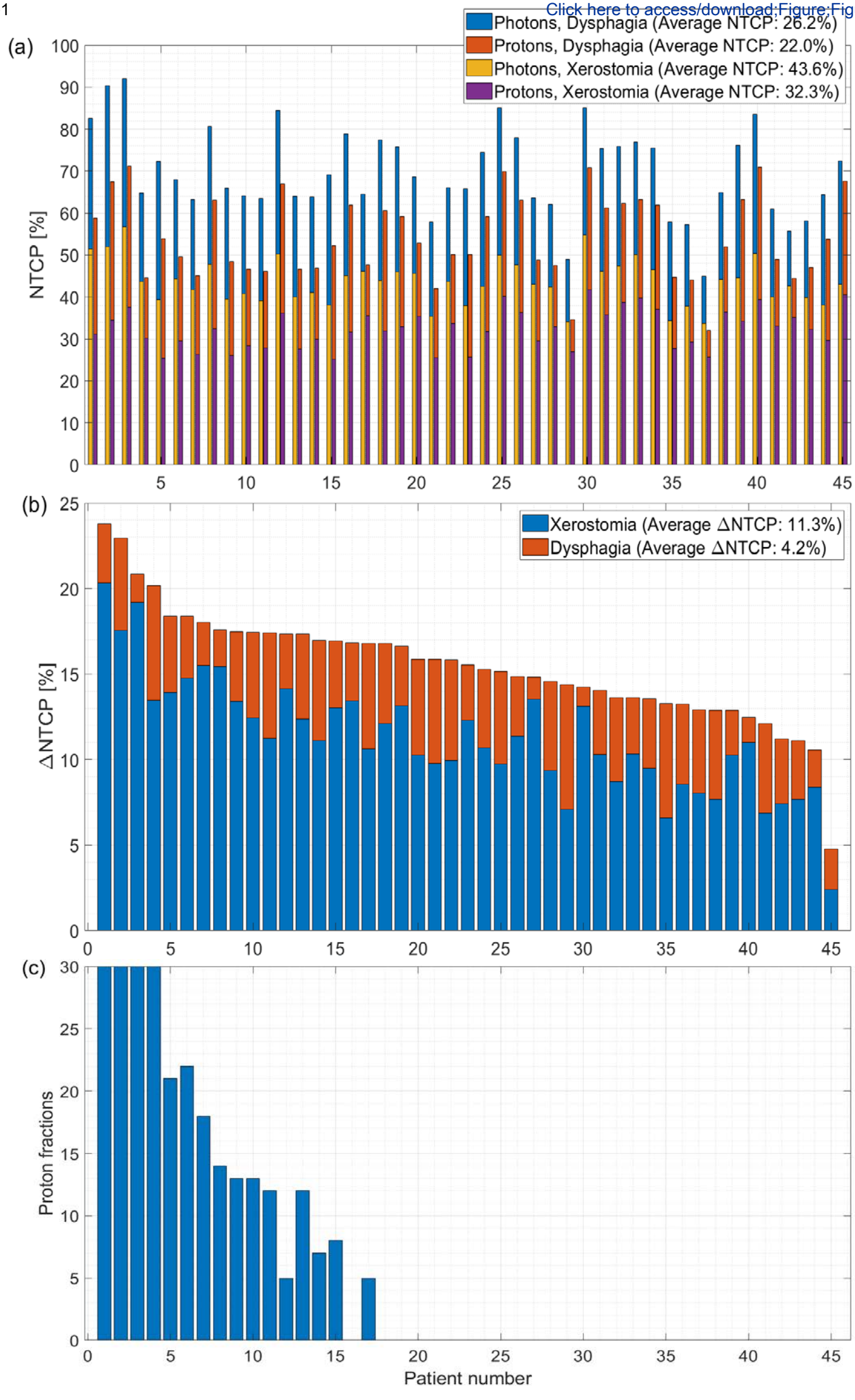
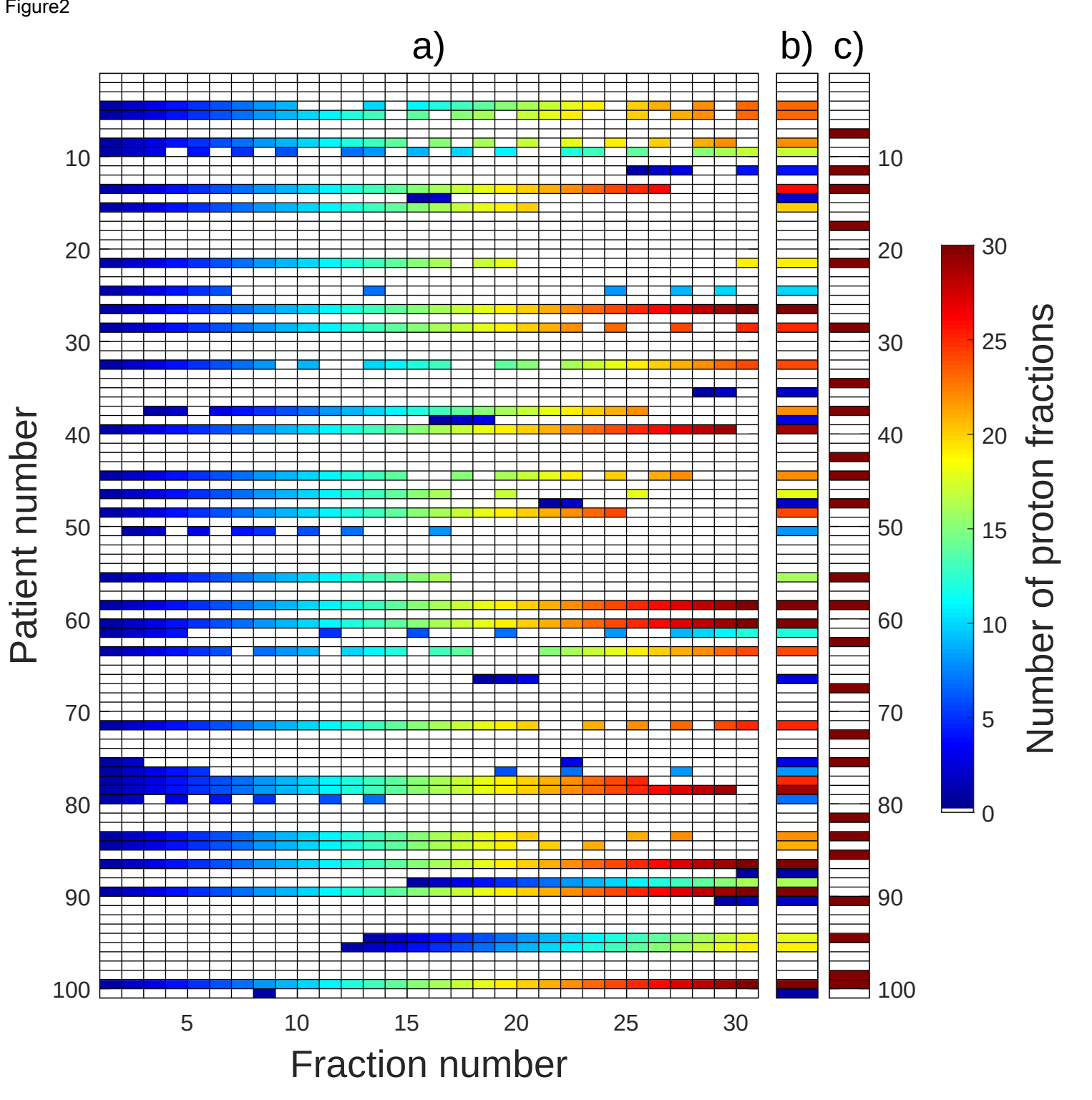
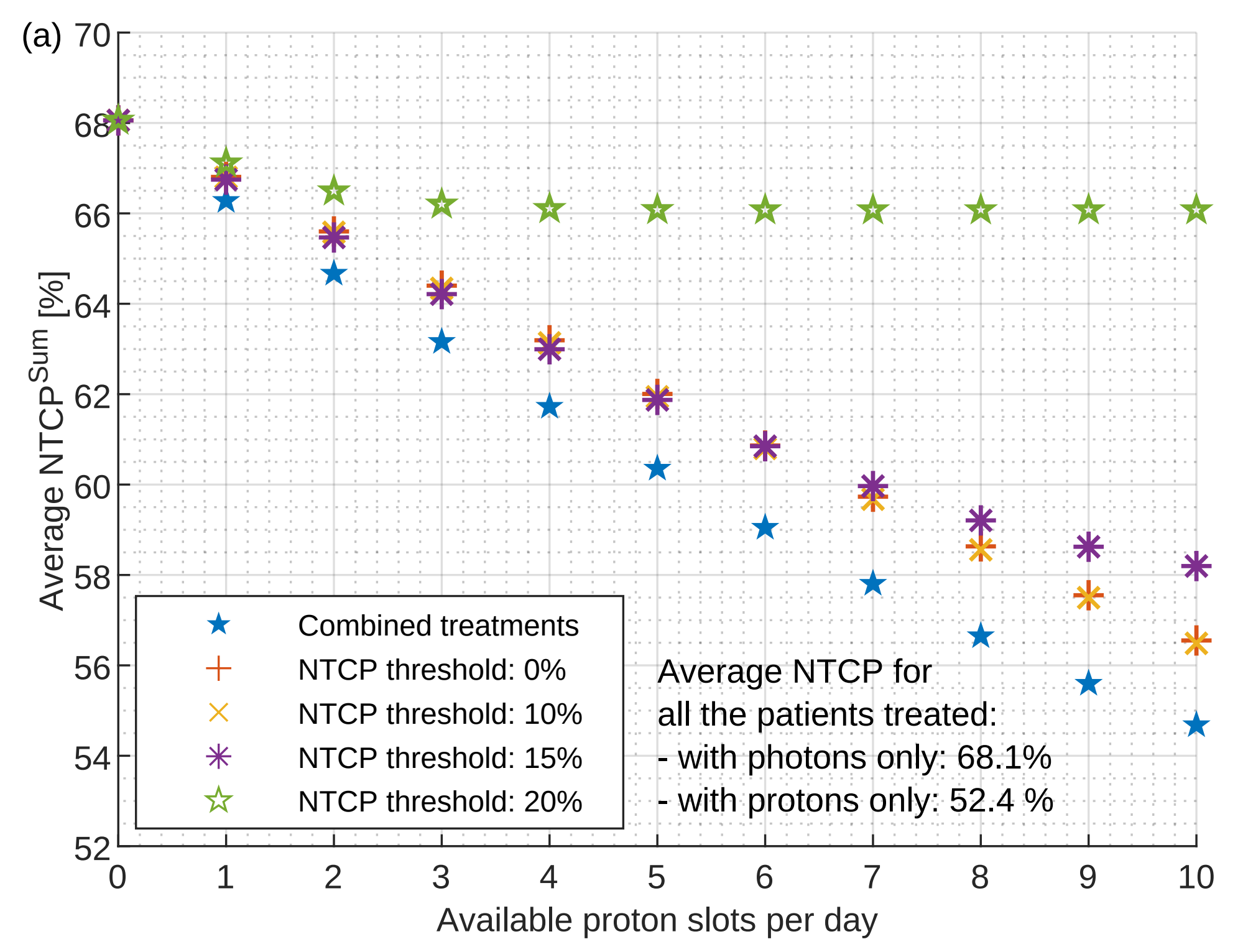
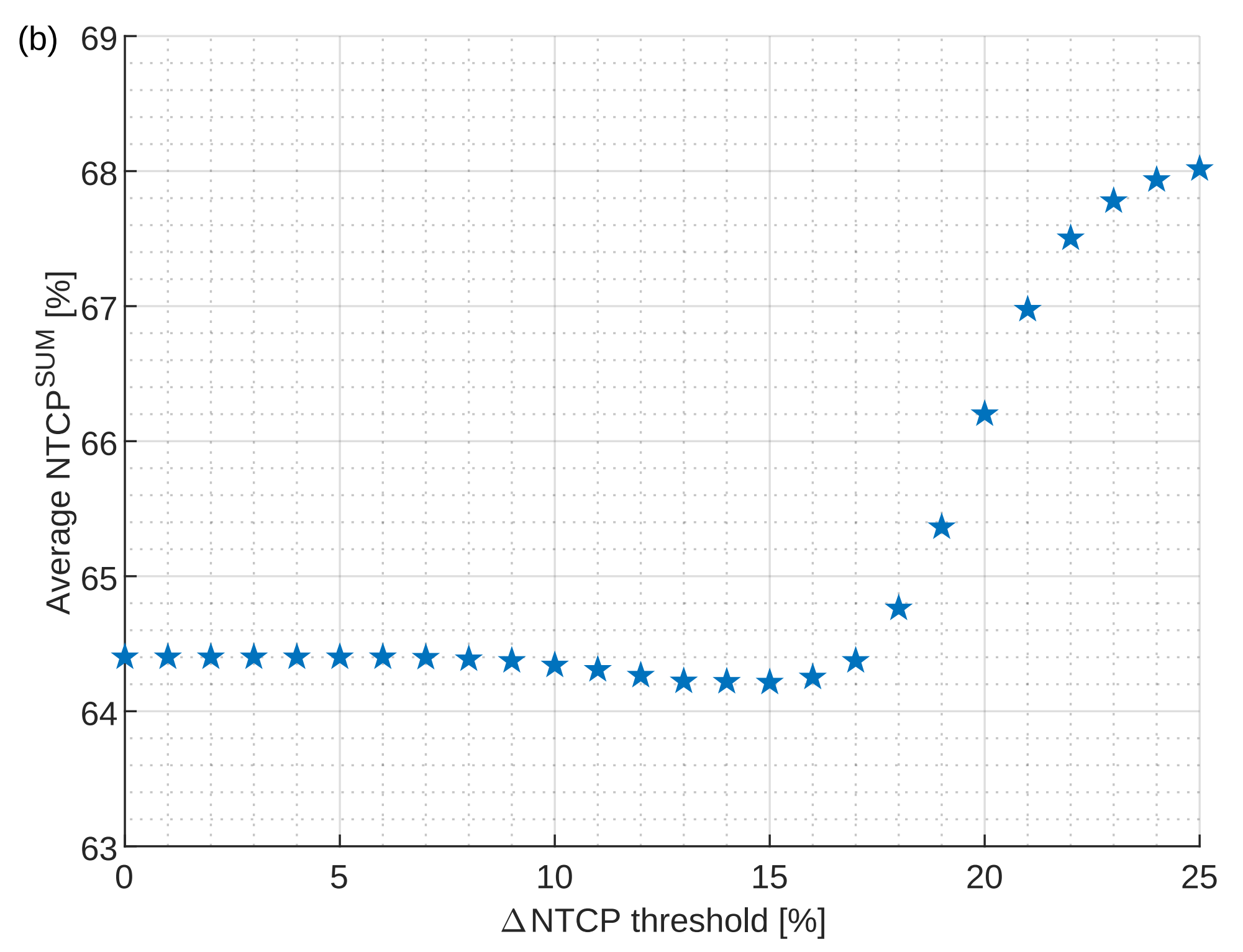
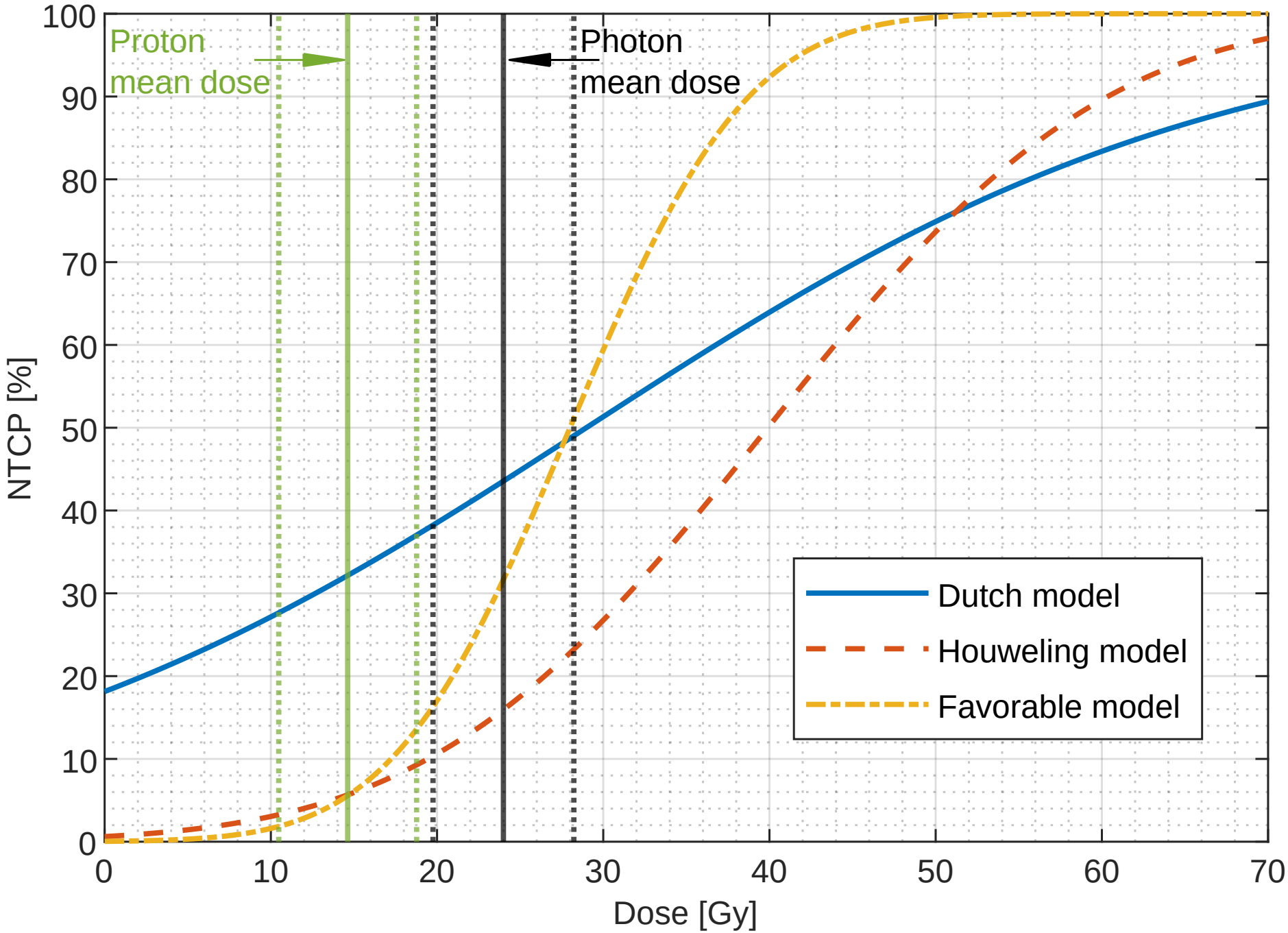


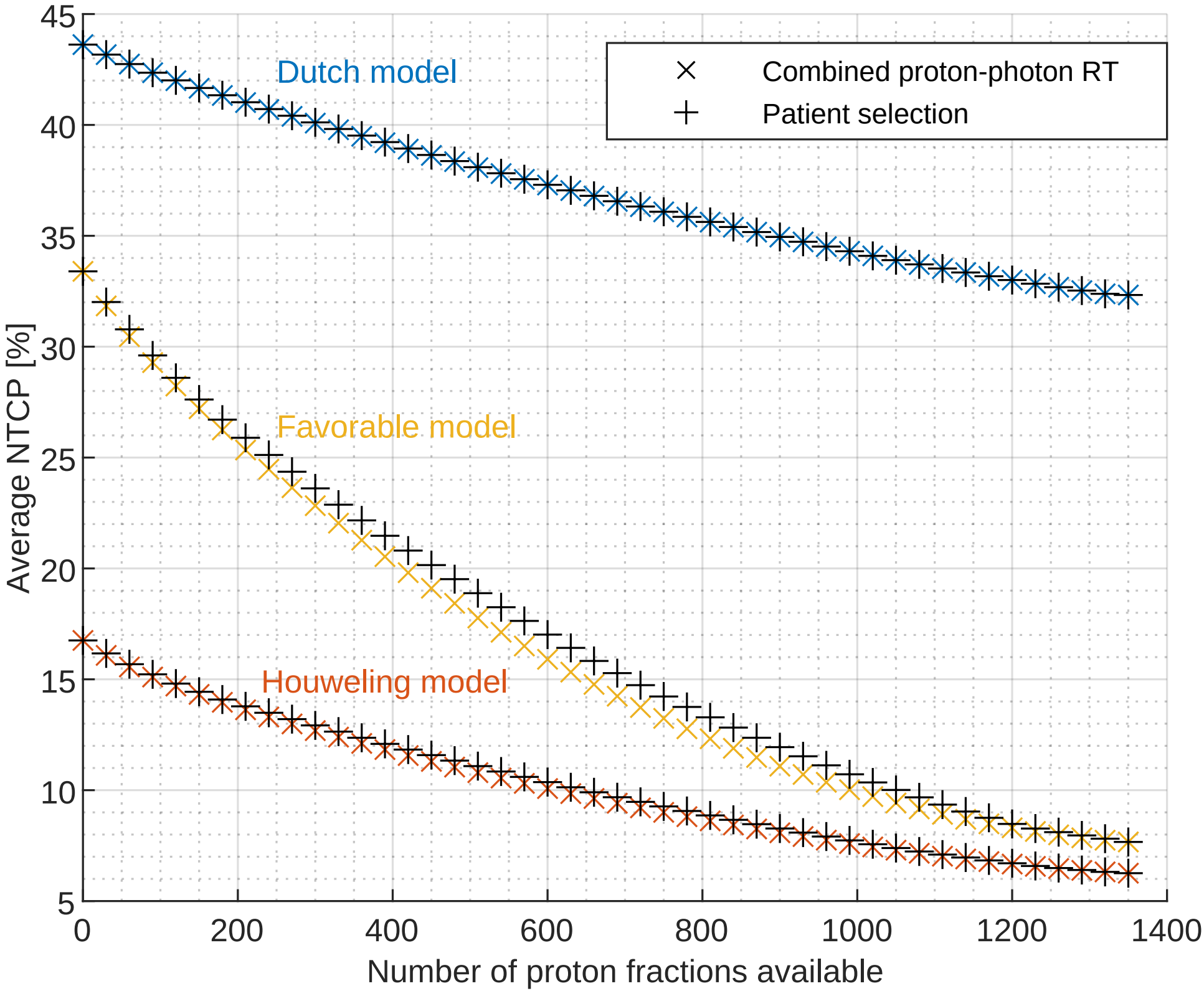
Figure2


a)
b)
c)
Patient number
Fraction number
Number of proton fractions
10
20
30
40
50
60
70
80
90
100
5
10
15
20
25
30
0
5
10
15
20
25
30


(a)
70
68
66
64
62
60
58
56
54
52
Average NTCP^Sum [%]
0
1
2
3
4
5
6
7
8
9
10
Available proton slots per day
Combined treatments
NTCP threshold: 0%
NTCP threshold: 10%
NTCP threshold: 15%
NTCP threshold: 20%
Average NTCP for
all the patients treated:
- with photons only: 68.1%
- with protons only: 52.4 %


(b)
69
68
67
66
65
64
63
Average NTCP^SUM [%]
0
5
10
15
20
25
ΔNTCP threshold [%]


Proton
mean dose
Photon
mean dose
Dutch model
Houweling model
Favorable model
NTCP [%]
Dose [Gy]
0
10
20
30
40
50
60
70
80
90
100


Dutch model
Favorable model
Houweling model
Combined proton-photon RT
Patient selection
Average NTCP [%]
Number of proton fractions available
45
40
35
30
25
20
15
10
5
0
200
400
600
800
1000
1200
1400