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Original research

The impact of treatment accuracy on proton therapy patient selection for oropharyngeal cancer patients

Tine Arts [a,*], Sebastiaan Breedveld [a], Martin A. de Jong [b], Eleftheria Astreinidou [b], Lisa Tans [a], Fatma Keskin-Cambay [a], Augustinus D.G. Krol [b], Steven van de Water [a], Rik G. Bijman [a], Mischa S. Hoogeman [a]

[a] Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam; and [b] Department of Radiation Oncology, LUMC, Leiden, The Netherlands

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ABSTRACT

Background and purpose: The impact of treatment accuracy on NTCP-based patient selection for proton therapy is currently unknown. This study investigates this impact for oropharyngeal cancer patients.
Materials and methods: Data of 78 patients was used to automatically generate treatment plans for a simultaneously integrated boost prescribing 70 Gy_{RBE}/54.25 Gy_{RBE} in 35 fractions. IMRT treatment plans were generated with three different margins; intensity modulated proton therapy (IMPT) plans for five different setup and range robustness settings. Four NTCP models were evaluated. Patients were selected for proton therapy if NTCP reduction was ≥10% or ≥5% for grade II or III complications, respectively.
Results: The degree of robustness had little impact on patient selection for tube feeding dependence, while the margin had. For other complications the impact of the robustness setting was noticeably higher. For high-precision IMRT (3 mm margin) and high-precision IMPT (3 mm setup/3% range error), most patients were selected for proton therapy based on problems swallowing solid food (51.3%) followed by tube feeding dependence (37.2%), decreased parotid flow (29.5%), and patient-rated xerostomia (7.7%).
Conclusions: Treatment accuracy has a significant impact on the number of patients selected for proton therapy. Therefore, it cannot be ignored in estimating the number of patients for proton therapy.

Radiation therapy (RT) combined with chemotherapy is frequently used to treat patients with head and neck cancer. RT is also associated with acute and late side effects that deteriorate quality of life (QoL) [1]. Intensity modulated proton therapy (IMPT) is a promising approach to reduce these adverse effects [2]. However, costs of IMPT exceed those of photon intensity modulated radiation therapy (IMRT) and world-wide IMPT capacity is limited. Therefore, IMPT should be applied to patients who are expected to benefit most.

Langendijk et al. proposed a model-based approach to select patients for proton therapy based on a reduction in normal tissue complication probability (ΔNTCP) calculated from a photon and a proton treatment plan. If ΔNTCP exceeds a pre-defined threshold level, e.g. 10% or 5% for a grade II or grade III complication respectively, IMPT is the treatment of choice [3]. This methodology gives rise to various concerns. One is that normal-tissue sparing also depends on the extra volume irradiated to mitigate errors in patient setup and proton range [4]. The impact of uncertainties and the measures to mitigate them, varies for IMRT and IMPT due to the physical differences between photons and protons. So while in photon therapy treatment uncertainties are typically compensated using safety margins, in IMPT they are increasingly dealt with using robust optimization. Recently, van der Voort et al. derived robustness recipes yielding the setup and range robustness settings for given distributions of systematic and random setup errors and systematic range errors [5]. However, the robustness settings that need to be used depend on the image-guidance procedures that will be applied. In addition, the IMRT margins are subject to change due to advances in image-guidance procedures. The aim of this study was to identify the impact of treatment accuracy on model-based IMPT patient selection for oropharyngeal cancer patients. To this purpose, IMRT and IMPT plans were automatically generated with various margins and robustness settings and the impact on patient selection was investigated for four IMRT-derived NTCP models for xerostomia, dysphagia, and tube feeding.

* Corresponding author at: Department of Radiation Oncology, Erasmus MC Cancer Institute, PO Box 5201, 3008 AE Rotterdam, The Netherlands.
E-mail address: t.arts-3@umcutrecht.nl (T. Arts).

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Materials and methods

Patient group and treatment plan generation

Anonymized CT data and structure sets of 78 consecutive oropharyngeal patients were used, of whom 24 patients were previously treated at the Leiden University Medical Center (LUMC) and 54 patients at the Erasmus MC Cancer Institute. Characteristics are listed in Table 1. All patients were planned using a simultaneously integrated boost scheme prescribing 70 Gy_{RBE} to the primary tumour and pathological lymph nodes (LUMC) or levels with pathological lymph nodes (Erasmus MC) and 54.25 Gy_{RBE} to the elective nodal areas in 35 fractions. For IMPT, "minimax" robust optimization (see section "Margins and robustness settings") was applied to the unmodified clinical target volumes (CTVs). For IMRT CTVs were expanded to planning target volumes (PTVs). The planning goal was that ≥95% of the prescribed dose should be received by ≥98% of the PTV (IMRT) or CTV of the worst-case robustness scenario (IMPT). A constant radiobiological effectiveness (RBE) of 1.0 and 1.1 was assumed for the IMRT and IMPT plans respectively [6]. All plans were generated using Erasmus-iCycle, an in-house developed optimizer [7,8]. This optimizer allows to efficiently generate treatment plans for a large cohort of patients in a fully automated fashion. Input for this optimizer is a user-defined wish-list, composed of constraints and prioritized objectives, where each objective is assigned a certain goal. Based on this wish-list, the multi-criterial optimizer optimizes the objectives one-by-one according to the set priorities. In contrast to the objectives, the constraints have to be met at all times. Separate wish-lists, but with similar intent, were used for IMRT and IMPT plans (see Supplementary material) [9,10]. Both wish-lists were constructed based on the same treatment objectives. However, due to the different physical characteristics between photons and protons, the used wish-lists are not identical. The wish-lists were designed in close collaboration with radiation oncologists. For the IMRT plans, we used a 23 equi-angular beam arrangement to simulate volumetric arc therapy (VMAT) dose distributions [9]. The dose was computed in CT-resolution ($0.98 \times 0.98 \times 2.5$ mm^3). For IMPT we used three equi-angular beams at 60°, 180° and 300°, as suggested by literature [11]. Available proton energies ranged from 69 to 250 MeV with corresponding spot widths ranging from 3.8 to 6.0 mm sigma (in air at the isocentre), respectively. To irradiate superficially located target regions, we assumed that a range shifter of 57 mm water equivalent thickness could be inserted during the delivery of a field. Pencil beams were selected and optimized using the resampling method described by van de Water et al. [12]. Final dose calculation was performed on a $2 \times 2 \times 2$ mm^3 grid and interpolated to CT-resolution. In case of minor violations in target coverage (<1%) after final dose calculation, the dose distribution was rescaled to again fulfil the constraint $V_{95\%} \geq 98\%$.

CT artefacts were present in 45 patients due to metal dental artefacts (e.g. fillings). The artefacts may impact IMPT treatment plan generation and subsequently the NTCP values. Therefore, IMPT treatment plans were generated before and after artefact reduction (Metal Deletion Technique v1.1, Revision Radiology) for five patients with the most severe artefacts.

Table 1
Patient and tumour characteristics.

Characteristics		Number	%
Sex	Male	58	74
	Female	20	26
Age	<65	47	60
	>65	31	40
T-classification	T1	4	5
	T2	42	54
	T3	12	15
	T4	20	26
Bilateral neck irradiation	Yes	71	91
	No	7	9
Weight loss	None	59	75
	Moderate	17	22
	Severe	2	3
Accelerated radiotherapy	Yes	38	49
	No	40	51
Radiotherapy plus Cetuximab	Yes	14	18
	No	64	82
Chemoradiation	Yes	22	28
	No	56	72

Margins and robustness settings

For IMRT, the CTV was isotropically expanded with a 0, 3, or 5 mm margin to account for geometrical uncertainties with a 5 mm retraction under the patient's skin [13]. For IMPT, robust optimization was used to account for uncertainties using setup robustness and range robustness. Nine scenarios were included: setup errors in the positive and negative direction along three axes (six scenarios), positive and negative range errors (two scenarios) and one nominal scenario (no errors). Erasmus-iCycle includes these nine scenarios simultaneously using a "minimax" optimization [14,15], and optimizes the worst-case scenario for each objective. Fractionation is not considered directly, but similar to margins robustness recipes can be used to determine for fractionated treatments the settings needed to ensure adequate CTV coverage in patients for given random and systematic error distributions [5]. Setup error scenarios were simulated by laterally shifting the pencil beams. The range error scenarios were generated by altering the proton energy. Hereto, we transformed the range error into an equivalent energy adjustment for each spot. The IMRT margins and IMPT robustness settings are summarized in Table 2. IMRT plans with 0 mm margins and IMPT plans with 0 mm setup robustness (SR = 0 mm) and 0% relative range robustness (RR = 0%) were included for a baseline comparison between IMRT and IMPT.

Plan evaluation

All IMRT plans were evaluated for meeting the clinical target goals ($V_{95\%} \geq 98\%$) for the low-dose as well as the high dose PTV and $V_{107\%} \approx 2\%$ and $V_{110\%} \approx 0\%$ for the high dose PTV. For IMPT, we evaluated the same parameters but then for the CTVs of the nominal and error scenarios. The dose to organs at risk (OARs) was checked for outliers and all IMRT and nominal IMPT dose distributions were evaluated visually.

NTCP models

Published NTCP models recently discussed for IMPT patient selection in the Netherlands were used to compare IMRT and IMPT plans and assess the impact of margins and robustness settings on

Table 2
Used margins and robustness settings for IMRT and IMPT plans. IMPT robustness settings were first sorted to setup robustness and second to range robustness as setup robustness has a larger impact on OAR dose than range robustness [9].

IMRT	IMPT	
Margin (mm)	Setup Robustness (SR) (mm)	Range Robustness (RR) (%)
0	0	0
3	3	3
5	3	5
	5	3
	5	5

Abbreviations: IMRT = intensity modulated radiation therapy; IMPT = intensity modulated proton therapy; OAR = organ at risk.

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