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ORIGINAL ARTICLE

Radiation dose-painting with protons vs. photons for head-and-neck cancer

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ABSTRACT

Background: Dose-painting has recently been investigated in early-phase trials in head-and-neck cancer (HNC) with the aim of improving local tumor control. At the same time proton therapy has been reported as potentially capable of decreasing toxicity. Here, we investigate whether protons could be applied in a dose-painting setting by comparing proton dose distributions with delivered photon plans from a phase-I trial of FDG-PET based dose-painting at our institution.

Material and methods: Eleven oropharynx (5), hypopharynx (2) and larynx cancer (4) patients from the recently conducted phase I trial were used for comparison of proton and photon dose-painting techniques. Robust optimization (3.5%/3 mm) was used for proton plans. Plan robustness and difference in dose metrics to targets and organs at risk were evaluated.

Results: The proton plans met target dose constraints, while having lower non-target dose than photon plans (body-minus-CTV, mean dose 3.9 Gy vs 7.2 Gy, $p = .004$). Despite the use of robust proton planning for plan max dose, photon plan max doses were more robust ($p = .006$). Max dose to medulla, brainstem and mandible were lower in the proton plans, while there was no significant difference in mean dose to submandibular- and parotid glands.

Conclusion: Proton dose-painting for HNC seems feasible and can reduce the non-target dose overall, however not significantly to certain organs close to the target, such as the salivary glands. Max dose in proton plans had a lower robustness compared to photons, requiring caution to avoid unintended hot spots in consideration of the risk of mucosal toxicity.

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Introduction

Balancing treatment efficacy and toxicity is challenging in the treatment of head-and-neck cancer (HNC). To improve the toxicity profile, de-escalation protocols are being tested for patients with good prognosis, such as HPV-positive oropharynx patients [1]. At the same time, there is an interest in treatment intensification protocols using radiation dose-painting, to increase the treatment efficacy for patients with adverse risk factors [2,3]. Both strategies aim at optimizing the therapeutic ratio for specific patient risk groups, identified by specific inclusion/exclusion criteria or advanced risk models [4].

Dose-painting is a concept where a non-uniform dose is prescribed within the clinical target volume, in order to escalate the dose to regions of presumed high risk of local failure [5,6]. Proton therapy has the potential to widen the therapeutic window compared with photon therapy [7] and has been proposed as an interesting radiation modality also for dose-painting [8,9]. Studies have shown that lower organ at risk (OAR) doses are achievable in HNC proton plans, while maintaining the same dose to the target as in photon therapy [10–12]. Conversely, the physical properties of the proton beam might allow increasing the target doses, while maintaining the level of toxicity of standard photon therapy. Early-phase trials show promising results for both dose-painting and proton therapy in the treatment of HNC [13,14]. In the present work, these two promising ways forward are combined.

The 11 patients included in this study were head-and-neck squamous cell carcinoma (HNSCC) patients treated at Rigshospitalet, Copenhagen, as a part of a single-arm, phase I trial of 18-fluoro-deoxyglucose (FDG)-based dose-painting with photons (the CONTRAST trial). Tumor outcome and safety profile of the CONTRAST trial have been reported [3]. In the current study, the delivered photon plans were used as comparison to achievable proton plans for a retrospective in-silico study. The aim was to investigate whether the dose constraints/aims of the CONTRAST trial treatment plans could be better met using protons rather than the delivered photon therapy. Additionally, the robustness of both the photon and proton plans was studied.

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Supplemental data for this article can be accessed here

Material and methods

Patients

Fifteen patients were enrolled on the CONTRAST trial. For four of the patients, dental artifacts were very severe (example shown in Supplementary Figure S1). As we could not reconstruct the CTs with metal artifact reduction, the decision was made to exclude the patients due to potential inaccurate stopping power ratio. This left eleven patients eligible for proton/photon plan comparison and thus for inclusion in the current study. Five of these patients had oropharyngeal cancer, while four had tumors in the larynx and two in the hypopharynx. The CONTRAST trial was approved by the local ethics committee, approval number H-1-2013-024. No ethics approval was required for the retrospective plan comparison study.

Photon plans

The photon plans of the 11 patients were approved and delivered clinically in the CONTRAST trial. Dose-painting by contours [15] was used, and the prescribed doses were 79.7 Gy (in 34 fractions, 6 days/week) to PTV_{PET} (FDG-PET avid volume with a 4 mm margin), 73.1 Gy to PTV_{gross} (gross tumor volume (GTV) with a 4 mm margin), 69.7 Gy to PTV_1 (clinical target volume (CTV_1) with a 4 mm margin) and 52.8 Gy to PTV_3 (low-risk elective volume (CTV_3) with a 4 mm margin). The GTV and CTVs were delineated according to DAHANCA guidelines [16], and further detail on the FDG-PET delineation can be found in [3]. The prescription was given as mean dose to the targets, with the aim of reaching the prescription dose plus/minus one Gy [17]. Note, thus, that an inhomogeneous dose was allowed within each dose level, with an exception for a 95% dose coverage that was required for CTV1 and CTV3 (with 64.6 Gy and 46 Gy, respectively). The planning constraints to targets and organs at risk (OAR) are shown in Table 1. The dose was normalized to 100% at target mean (PTV_{PET}). In case of overlap between PTV_{PET} and the mandible, the dose constraint to the mandible was prioritized, and the dose was instead normalized to PTV_{PET} minus mandible. Planning risk volume (PRV) expansions of 4 mm were used for the spinal cord and brainstem to ensure that dose limits were not exceeded in case of positioning errors. Plans were optimized by an experienced dose planner and approved for treatment by head-and-neck oncologists and a physicist. Planning was performed in Eclipse version 11 (Varian Medical Systems, Palo Alto, California), using the AAA 11.0.31 algorithm. Volumetric arc therapy (VMAT) with two full arcs was used. Dental artifacts in the images were handled by manual contouring of artifact effected areas around the teeth, overriding the CT numbers with HU = 0 (water). The CT scans were performed with a single energy and without IV-contrast.

Proton plans

The proton plans were optimized according to the same dose constraints as the photon plans (Table 1), but instead of using PTVs, robust optimization (3 mm/3.5%, in total 12 uncertainty scenarios) on the CTVs was performed for the target dose coverage constraints ($D_{98\%}$ for CTV1 and CTV3) and for the max doses to the spinal cord and brainstem (instead of the PRVs used in the photon plans). Robust optimization is a built-in option in the Eclipse TPS [18], and was also used for the maximum dose constraint. Plans were made by two physicists in collaboration (KH and BS). Planning was performed for a spot scanning technique in Eclipse version 13 (Varian Medical Systems, Palo Alto, California), using beam data from Maryland Proton Treatment Center (Varian ProBeam), the NUPO optimization algorithm with multi-field optimization and a proton convolution superposition (PCS, version 13.7.14) volume dose algorithm. Dose was normalized to 100% at target mean (PTV_{PET}), i.e., the same as for the photon plans. The doses reported for proton plans are given in Gy, after scaling with a constant, endpoint-independent RBE-factor of 1.1. Four fields were used: two oblique anterior fields with the possibility of covering all of PTV_3 except contralateral parts above the chin, while two oblique posterior fields added dose to one side each of the target between the shoulders and the skull base (Figure 1). The areas around the targets where beam spots were allowed were laterally set to 10 mm, while proximal and distal margins for beam spots were set to 3–4 mm and 6.5 mm, respectively, based on the water equivalent depth between energy layers in the direction of the beam. The Body structure was expanded by 1 cm from patient skin to

Table 1. Dose constraints for target volumes and organs at risk used in the CONTRAST study.

Target/OAR	Mean Dose	D_{max}	Dose volume limits
PTV_{PET}	79.7 Gy	85.3 Gy (plan maximum)	–
PTVgross only	73.1 Gy (± 1 Gy)	–	–
PTV1 only	69.7 Gy (± 1 Gy)	–	–
PTV3 only	52.8 Gy (± 1 Gy)	–	–
CTV1	–	–	$D_{98\%} > 64.6$ Gy
CTV3	–	–	$D_{98\%} > 46$ Gy
Medulla	–	45 Gy	–
Brainstem	–	54 Gy	–
Mandible	–	70 Gy (72.5 can be accepted in certain circumstances)	–
Inner ear	$\leq$ 45 Gy	–	$D_{95\%} \leq 55$ Gy
Parotis	$\leq$ 26 Gy (ipsilateral) $\leq$ 20 Gy (contralateral)	–	–
Larynx	–	–	$V_{50Gy} \leq 33\%$
Submandibularis	$\leq$ 35 Gy (only if level I and II is not in the target)	–	–

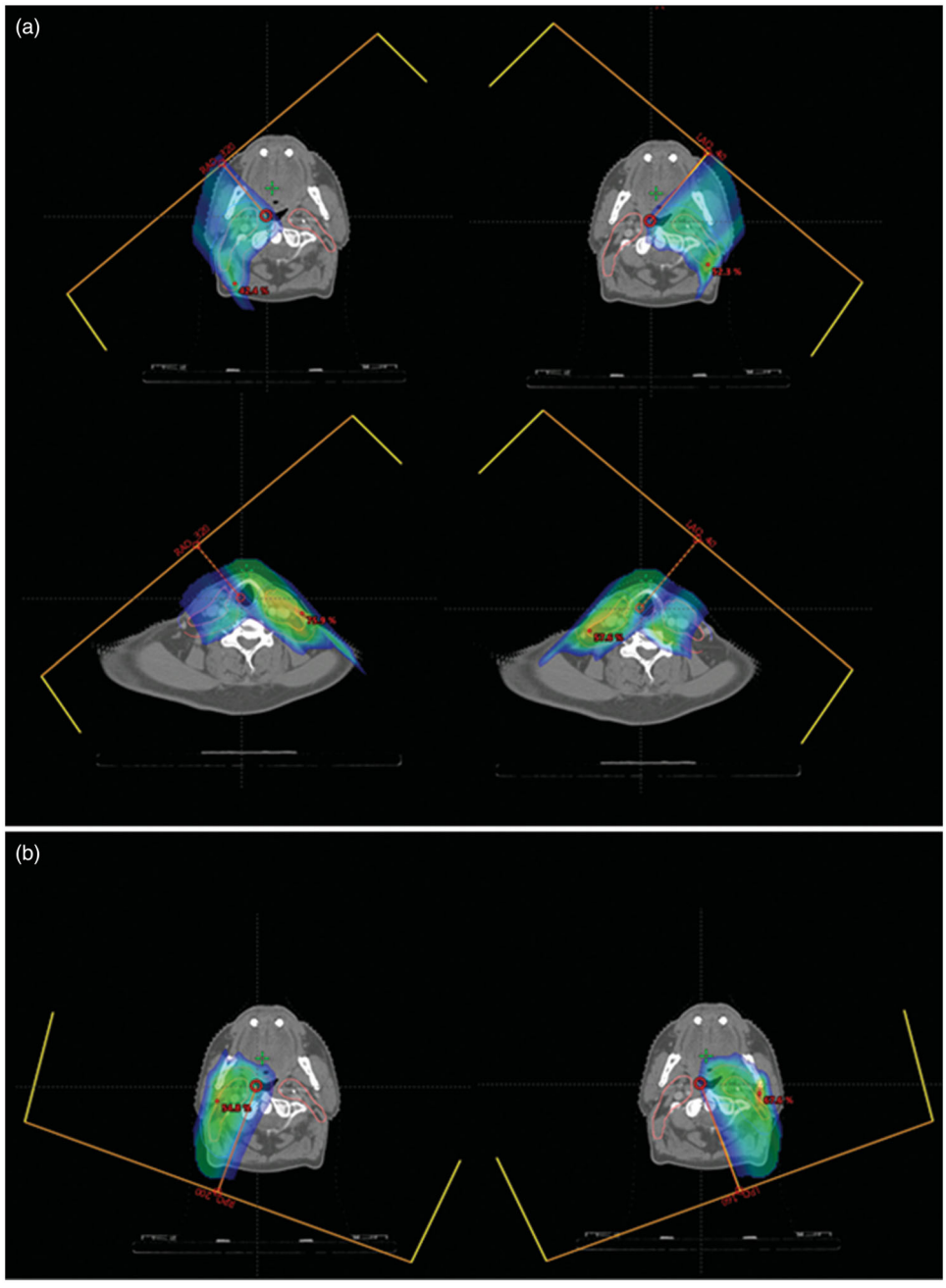

Figure 1. Proton plan field arrangement: there are four fields; (a) two oblique anterior fields with the possibility of covering all of PTV3, except the contralateral side of the target above the chin and (b) two oblique posterior fields added dose to one side each of the PTV3, between the shoulders and skull base.

allow the optimizer to put spots at the surface of the patient and to improve accuracy of dose calculation to the skin. Optimally, the fixation equipment should be included in the Body structure; however, due to proton incompatible fixation equipment this could not be accomplished here. The minimum air gap between snout (including range shifter) and body structure was set to 8 cm for oblique anterior fields and 15 cm for oblique posterior fields, according to Maryland Proton Therapy Center clinical practice. Dental artifacts in the images were handled by manual contouring of artifact effected areas around the teeth, overriding the CT numbers with HU = 0 (water). As the anterior beams were not allowed to cover contralateral parts of the target above the chin, no beams traveled directly through the dental implants.

Plan comparison

Dose-volume histograms (DVH) were calculated for all nominal photon and proton plans, and additionally for 12 different uncertainty scenarios: a range uncertainty of ± 3.5% (protons) and 3 mm setup error in six translational directions. The PTV margin of 4 mm in our clinic corresponds to 3 mm uncertainty accepted for pretreatment positioning and 1 mm added to account for an observed TPS error in PTV structure formation when slice thickness is 2 mm and PTV margin is 3 mm. As a sensitivity analysis, the proton plan of one patient was re-optimized using 4 mm positioning uncertainty instead of 3 mm in the settings for robust planning. Results are reported in the Supplementary material (Table S1).

In the plan comparison, robustness was defined from the above-mentioned uncertainty scenarios, and was reported by giving a range for the dose metrics, corresponding to the highest and lowest values among the different scenarios:

$$Robustness = abs(D_{highest} - D_{lowest})$$

Target dose was additionally evaluated by calculating quality (Q)-values, defined as planned dose normalized to prescribed dose in each voxel, and plotted in a quality-volume histogram (QVH) [15]. The root-mean-squared distance to $Q = 1$ (Q_{rms}) was used to compare the QVH steepness between photon and proton plans [17]. The Wilcoxon signed rank test was used to test for paired differences in dose metrics, in Q_{rms} and in robustness between photon and proton plans.

Normal tissue complication probability

Estimations of normal tissue complication probability (NTCP) for grade >2 xerostomia [19] and grade >2 dysphagia [20] were performed for both treatment modalities. Delta-NTCP values were calculated following Langendijk et al. [21]. In the model for xerostomia, the dose to the contra-lateral parotid gland was the predictor. In the model for dysphagia, the dose to the superior pharyngeal constrictor muscle (PCM) and the oral cavity were the predictors. As the PCM and oral cavity were not part of the planning constraints in the CONTRAST trial, these structures were retrospectively contoured and not included in the plan optimization. For one patient, a re-optimization of both photon and proton plans was performed with the PCM and oral cavity included in the optimization, to estimate the potential impact on NTCP/delta-NTCP.

Results

A dose color wash image of a patient illustrated the typical qualitative difference in dose distribution between photon and proton dose-painting plans (Figure 2). Large normal-tissue volumes in the proton plans could be spared from the low dose bath of the photon plans, while the high dose region in the proximity of the target was slightly more conformal in the photon plans.

Target dose

The constraints for target coverage ($D_{98\%}$ for CTV1 and CTV3) were reachable with both photons and protons, with the

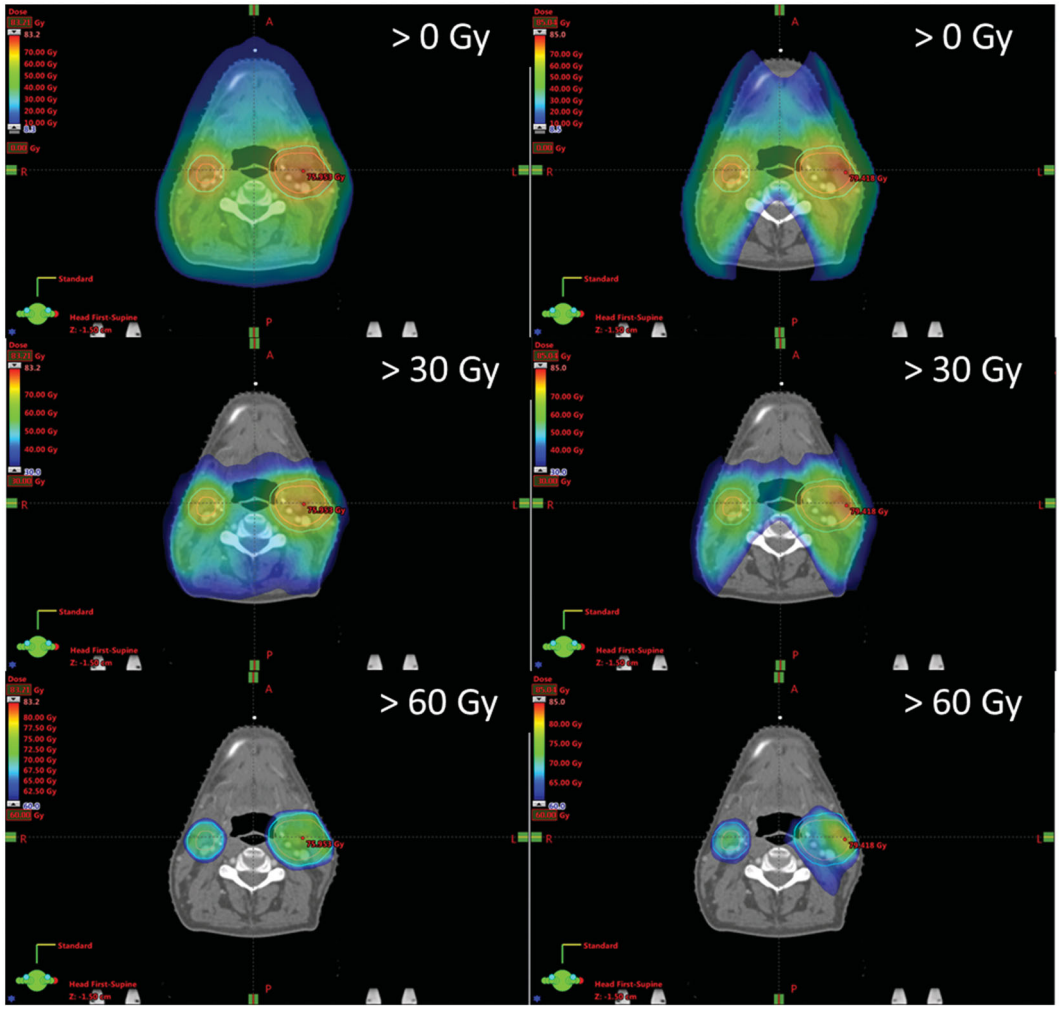

Figure 2. Dose color wash example showing a photon (left) and proton (right) dose-painting plan. Lower cutoff values for dose display were set to 0 Gy, 30 Gy and 60 Gy. The contours displayed are CTV1 and PTV1.

median target coverage doses being higher for photons than for protons ($p = .005$ for both CTV1 and CTV3) (Table 2(a)). None of the trial patients had a CTV_2. The robustness of the CTV coverage was higher in the photon plans (Table 2(b)). All target structures (GTV-PET, GTV, CTV1 and CTV3) additionally had mean dose constraints (mean dose to PTV should equal the prescribed dose ± 1 Gy). Both photon and proton plans were generally in the high end of the interval, but protons were closer to the required mean dose. The difference was, however, only significant for CTV1 (Table 2(a)). The target mean doses were more robust in the photon plans (Table 2(b)). The QVH analysis showed that the plan target doses were more homogeneous in the photon plans, and thus closer to the prescribed doses (Q_{rms}=0.074 for photons and 0.096 for protons, $p = .003$) (Supplementary Figure S2). There was no difference in max dose (D_{1cc}) between the two modalities, but the robustness of the max dose was higher in the photon plans ($p = .025$) (Table 2(b)).

OAR dose and normal tissue complication probability

The proton plans had lower doses to the medulla (median D_{max} 30.8 Gy vs 44.0 Gy, $p = .001$), brainstem (4.4 Gy vs 33.6 Gy, $p = .001$) and mandible (70.1 Gy vs 71.2 Gy, $p = .006$) (Table 2(a)). The dose to all non-tumor tissue (body minus CTV_3) was on average 3.3 Gy lower in the proton plans (median D_{mean} 3.9 Gy vs 7.2 Gy, $p = .02$). No significant difference could be seen for the doses to the larynx, parotid- and submandibular glands (Table 2(a)). The robustness of the OAR doses was generally higher in the photon plans, the

Table 2. Dose/volume metrics from photon and proton dose-painting plans (a) and metrics from the robustness uncertainty analysis (b).

Structure (a)	Dose/volume metric	Photon dose Median (range)	Proton dose Median (range)	*p*-Value
PTVPET	Mean dose	79.7 (79.5–79.7)	79.7 (79.3–79.7)	.371
PTVgross only	Mean dose	74.1 (73.7–75.0)	73.7 (73.4–74.8)	.118
PTV1 only	Mean dose	70.7 (70.2–71.4)	**70.3 (68.7–70.7)**	**.014**
CTV1	$D_{98\%}$	**69.2 (67.8–70.1)**	66.7 (65.8–69.1)	**.005**
PTV3 only	Mean dose	54.4 (51.9–54.7)	53.5 (52.8–53.9)	.056
CTV3	$D_{98\%}$	**50.4 (47.5–51.9)**	47.2 (46.8–50.8)	**.005**
Whole target (CTV3)	Mean dose	64.1 (61.6–68.2)	64.1 (60.5–67.2)	.053
Medulla	Max dose ($D_{0.1\ \%}$)	44.0 (43.5–45.5)	**30.8 (16.2–37.8)**	**.001**
Brainstem	Max dose ($D_{0.1\ \%}$)	33.6 (1.3–50.6)	**4.4 (0.0–43.5)**	**.001**
Mandible	Max dose ($D_{0.1\ \%}$)	71.2 (53.2–72.9)	**70.1 (50.5–70.8)**	**.006**
Larynx	V_{50Gy} (%)	30.6 (2.2–100)	22.3 (1.0–100)	.554
Parotid glands	Mean dose	27.1 (13.0–69.1)	25.9 (17.1–72.2)	.745
Submandibular glands	Mean dose	58.0 (37.3–75.8)	61.6 (41.0–77)	.314
Non-tumor tissue (body minus CTV3)	Mean dose	7.2 (3.8–12.6)	**3.9 (2.3–7.7)**	**.004**
Body (not extended)	Max dose	84.4 (82.5–85.8)	84.6 (82.3–85.9)	.894
Body (not extended)	Max dose (1 cm^3)	82.7 (81.6–83.8)	82.6 (81.1–83.7)	.265
Inner ear	$D_{5\%}$	23.7 (2.3–46.7)	**13.6 (0.0–44.2)**	**.002**
	Mean dose	18.7 (2.0–35.3)	**7.7 (0.0–24.3)**	**.002**

(b)

		Photon robustness		Proton robustness		
		Robustness min values (median (min-max))	Robustness max values (median (min-max))	Robustness min values (median (min-max))	Robustness max values (median (min-max))	
PTVPET	Mean dose	**78.9 (78.5–79.3)**	**79.7 (79.5–80.0)**	77.7 (76.7–79.2)	80.5 (79.7–81.1)	**.013**
PTVgross only	Mean dose	**73.6 (73.0–74.8)**	**74.6 (74.1–75.6)**	72.6 (71.7–72.9)	75.1 (73.7–76.1)	**.010**
PTV1 only	Mean dose	**69.9 (69.2–70.6)**	**70.7 (70.2–71.4)**	68.5 (67.7–69.0)	71.4 (69.3–72.0)	**.004**
CTV1	$D_{98\%}$	**68.3 (67.0–69.1)**	**69.2 (68.0–70.1)**	65.1 (62.0–66.5)	67.0 (66.1–69.2)	**.003**
PTV3 only	Mean dose	**54.0 (51.5–54.3)**	**54.5 (52.1–55)**	52.4 (52.0–53.1)	54.0 (53.1–54.5)	**.004**
CTV3	$D_{98\%}$	49.9 (47.3–51.6)	50.5 (47.6–51.9)	46.7 (46.4–49.4)	47.4 (47.1–51.1)	.365
Whole target (CTV3)	Mean dose	**63.6 (61.2–67.8)**	**64.3 (61.7–68.3)**	62.5 (60.0–66.0)	64.7 (60.8–68.1)	**.004**
Medulla	Max dose ($D_{0.1\%}$)	**43.8 (42.6–44.9)**	**46.7 (45.3–48.8)**	23.0 (12.2–31.7)	40.2 (23.8–44.8)	**.001**
Brainstem	Max dose ($D_{0.1\%}$)	30.7 (1.2–48.2)	36.2 (1.5–54.1)	3.1 (0.0–30.4)	9.1 (0.0–56.4)	.638
Mandible	Max dose ($D_{0.1\%}$)	70.5 (51.0–72.0)	74.8 (54.2–78.1)	67.6 (48.4–70.5)	72.8 (51.7–78.4)	.185
Larynx	V_{50Gy} (%)	21.6 (1.5–98.6)	39.5 (3.9–100)	13.25 (0.1–100)	32.2 (2.5–100)	.353
Parotid glands	Mean dose	**24.6 (9.6–66.8)**	**29.8 (17.0–70.7)**	22.7 (13.4–70.3)	28.7 (21.1–73.8)	**<.001**
Submandibular glands	Mean dose	53.3 (32.7–73.6)	62.5 (41.7–77.9)	57.6 (37.0–73.9)	64.9 (44.5–79.5)	.455
Non-tumor tissue (body minus CTV3)	Mean dose	**7.2 (3.8–12.5)**	**7.3 (3.9–12.7)**	3.7 (2.2–7.4)	4.1 (2.4–8.0)	**.004**
Body (not extended)	Max dose	**83.8 (82.2–85.7)**	**85.1 (82.9–86.5)**	83.5 (82.3–84.9)	87.0 (84.7–89.4)	**.006**
Body (not extended)	Max dose 1 cm^3	**82.5 (81.1–83.5)**	**83.0 (81.9–84.2)**	82.3 (80.2–83 .0)	83.9 (82.2–85 .0)	**.025**
Inner ear	$D_{5\%}$	17.1 (2.0–40.9)	29.4 (2.7–54.7)	8.8 (0.0–33.4)	25.8 (0.0–55.0)	.492
	Mean dose	12.3 (1.8–31.9)	22.9 (2.3–39.2)	4.3 (0.0–17.2)	12.5 (0.0–32.5)	.557

Wilcoxon signed rank test *p*-values between photons and protons are displayed for dose difference (a) and for difference in robustness (range between min and max values among the uncertainty scenarios) (b). Values that are significantly better/closer to the aim than for the other modality (photons or protons) are displayed as bold.

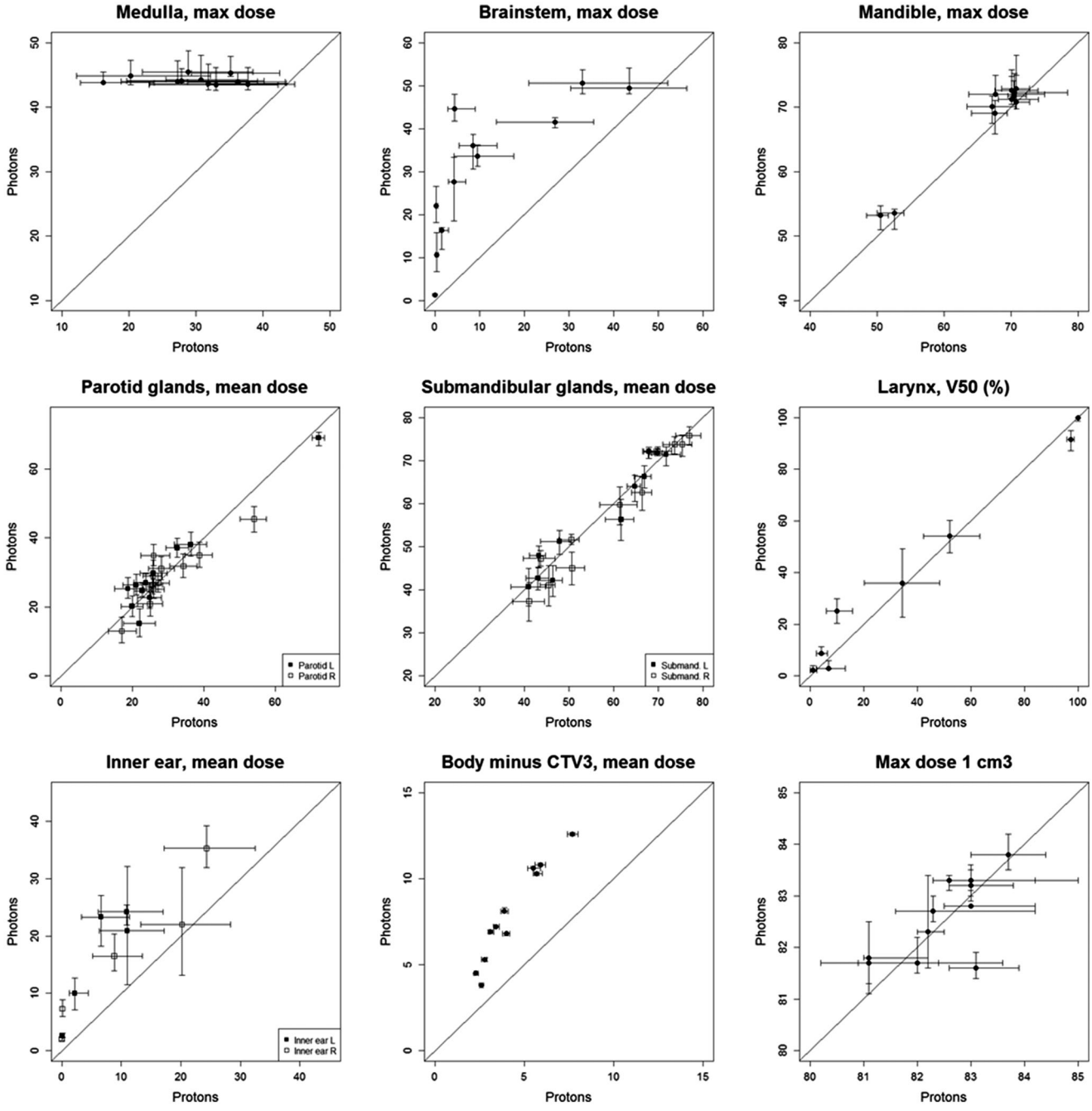

Figure 3. Doses to organs at risk for proton (y-axis) and photon (x-axis) dose-painting plans. Error bars represent the highest and lowest values from robustness analysis of 3 mm (photons) and 3 mm/3.5% (protons). Note that the plots have different axes scaling.

difference being statistically significant for twelve out of 22 dose metrics (Table 2(b)). The OAR dose metrics for all plans can be seen in the scatter plots of Figure 3, where the identity lines represent equal dose in photon and proton plans and the error bars show the robustness range ('worst case' metrics among the uncertainty scenarios). Large individual differences could, as expected, be seen (Figure 3). For the retrospectively contoured structures that were not included in the optimization, the dose to the oral cavity was lower in the proton plans (median D_{mean} 20.3 Gy vs 36.6 Gy, $p = .002$), while the difference for the superior PCM was non-significant. Re-optimization of one patient with the two structures included in the optimization showed similar sparing potential for both modalities (Supplementary Table S2). The difference in NTCP between photon and proton plans for each of the patients are shown in Figure 4. Overall, the NTCP for dysphagia was statistically significantly lower in proton plans (median 20.1% vs 27.3%, $p = .007$), while the difference for NTCP for xerostomia was not significant (median 43.3% vs 46.7%, $p = .24$). For detailed results on NTCP, see Supplementary Table S2.

Discussion

Proton dose-painting for HNC was suggested already in 2008, when a single in-silico case of hypoxia (cu-ATSM) based dose-painting was described [8], and a comparison of

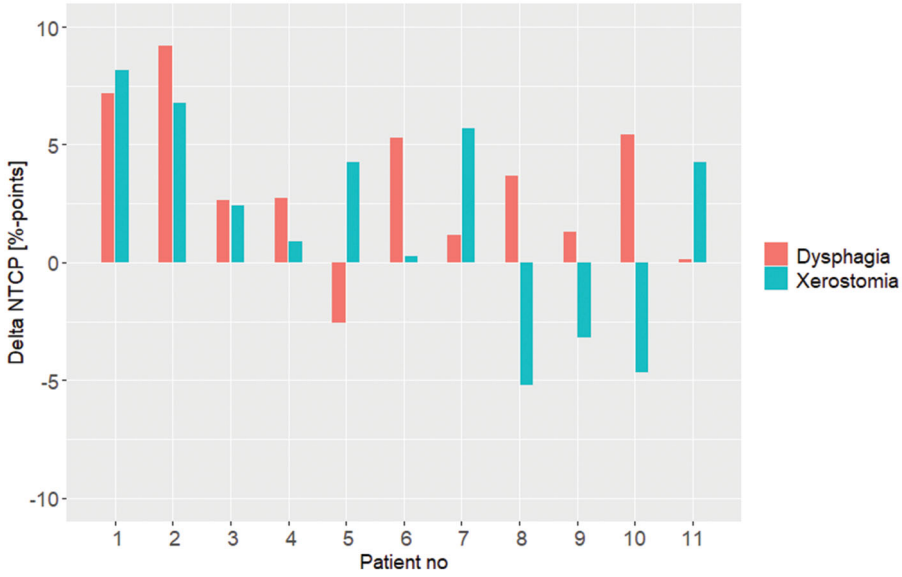

Figure 4. Difference between normal tissue complication probability (NTCP) between photon and proton dose-painting plans (photon NTCP minus proton NTCP) for grade >2 xerostomia and grade >2 dysphagia. Note that the structures in the dysphagia model (superior pharyngeal constrictor muscle and oral cavity) were retrospectively contoured and not included in the plan optimization constraints of the trial.

dose-painting with IMRT, helical tomotherapy and IMPT in three patients has been published [9]. Since then, studies have been scarce. In 2015, a study including two patients showed the importance of robustness analysis for proton dose-painting [22]. To our knowledge, the current study is the largest dose-painting proton study that includes robustness analysis.

The expected advantage of proton therapy compared to photon therapy is not necessarily a higher tumor control probability, unless it enables a higher prescription [23]. Nor can it be expected to decrease the probability of mucosal ulcerations in the high-dose regions that were observed in some of the patients in the CONTRAST study and in the Ghent dose-painting studies [3,24]. Instead, proton therapy has the ability to reduce dose to important OARs, and thus reduce known toxicities related to radiation therapy of HNC, e.g., dysphagia and xerostomia, which if persistent can severely affect the patients´ quality of life. For example, Jakobi et al. have published work on normal tissue complication probability (NTCP) modeling for HNC dose-painting [25], showing that the NTCP could be lowered by dose-painting with protons as compared to photons, and that about 50% of the patients in the study would be chosen for protons when applying the >10% NTCP reduction criterion of Langendijk et al. [21]. It should be mentioned, however, that the plans of that study were not optimized nor analyzed for uncertainty scenarios. In the current study, the lower OAR and non-tumor tissue doses in the proton plans were promising, and would be expected to lead to lower levels of toxicity for the effected organs. Note, however, that some target-near OARs, such as the salivary glands, were not, in contrast to the Jakobi study, spared by using protons. We believe that the tradeoff between dose to target-near OARs and target dose robustness have influenced the lack of salivary gland sparing. On the other hand, no OARs received significantly higher doses in the proton plans.

In the present work, we used intensity-modulated proton therapy with a multi-field optimization (MFO) technique, deemed deliverable at a large, modern proton facility (the Maryland Proton Therapy Center in Baltimore). MFO has previously been shown to be the technique preferred for standard (non-dose-painting) proton therapy for HNC [26]. We also applied robust optimization and analysis based on the method of McGowan et al. [27]. As for the photon dose-painting plans, we used the plans that were delivered to the patients in the CONTRAST trial. While this obviously ensured final approval of plan quality at a large academic institution, it did, however, cause a limitation, as some OARs that are of interest for NTCP modeling were not delineated and used in plan optimization in the trial. For example, the oral cavity and the PCMs were not a part of the planning constraints in the trial – these structures were retrospectively contoured in the current work in the already optimized plans. This needs to be taken into consideration in the evaluation of these organ doses, as well as the of the NTCP estimates for dysphagia. The potential for further sparing of the oral cavity and the PCM was investigated separately in one patient, and the sparing potential was similar for protons and photons, leading to a very small difference in delta-NTCP (Supplementary Table S2). Overall, the dose to non-tumor tissue (body-minus-CTV) was reduced by about 40% in the proton compared with photon dose-painting plans, while the photon plans had a higher robustness for many dose metrics. Note, that the superiority of photon plan robustness might be overestimated in the present study, as the photon plans were optimized with 4 mm PTV margins but evaluated with 3 mm setup error (for explanation of this discrepancy see Materials and Methods). Securing fair comparison of photon and proton dose plans in terms of target coverage

probability in the presence of clinically relevant uncertainties is a general issue in dose plan comparisons. Results from the sensitivity analysis, where the proton plan of one patient was re-optimized using a 4 mm positioning uncertainty in the robust optimization settings, do however imply that the effect of this discrepancy is relatively small (Supplementary Table S1). The PTV/robustness settings do adhere to our institution's current clinical planning practice for the two modalities.

The target coverage doses ($D_{98\%}$ to CTV1 and CTV3) were higher in the photon plans, and the photon plans also had a higher robustness for the coverage of CTV1. Also, although this was not significant for all structures, the mean doses to the PTVs were slightly higher in the photon plans. Higher target doses were, however, not necessarily strived for – the trial was designed by a re-distribution rather than a dose-escalation strategy, and the mean target doses should be as close to the prescription as possible [28]. It is important to note that all proton plans had the required dose coverage of CTV3 (46 Gy) in all uncertainty scenarios considered. The same was the case for CTV1, except in one patient lacking coverage of CTV1 in one uncertainty scenario (Table 2(b)).

A strength of the present study is that the photon plans have been used for treatment, and the outcome and toxicity they led to are known. As was described in the trial report [3], the loco-regional control was promisingly high, while at the same time, there was concerning toxicity in form of ulcerations in the high-dose regions for some of the patients. This kind of toxicity is different from conventionally considered HNC radiotherapy side effects, as it is not related to the dose to OARs but to normal structures within the target volume itself. In the current study, there was no difference in the max doses between proton and photon plans, and in fact, the max dose was less robust in proton plans despite using robust optimization. If robust optimization was not used, the max doses for the worst-case uncertainty scenarios were in the range of 90–95 Gy (data not shown). The combination of the observed ulcerations and the sensitivity of proton max doses to anatomical changes, urge for great care if pursuing proton dose-painting for HNC. Daily imaging, preferably in 3 D, would be warranted, as well as robust optimization and adaptive strategies during the course of treatment. Additionally, it would be useful to analyze the linear energy transfer distribution in dose-painting proton plans, as this is related to the relative biological effect. Such an analysis was beyond the scope of the current study.

In conclusion, this study showed that proton dose-painting plans can be optimized with a quality comparable to photon dose-painting plans delivered in a phase I trial at our institution, but with different merits. The results are in line with expectations considering the physical properties of the photon- and proton beams. While the robustness was generally higher in the photon plans, proton plans led to lower doses to many OARs and non-tumor tissue compared with photons. There was, however, no difference in dose to OARs close to the target, such as the salivary glands, which we believe is due to the tradeoff necessary to obtain robust coverage of target structures.

Disclosure statement

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