Using a reduced spot size for intensity-modulated proton therapy potentially improves salivary gland-sparing in oropharyngeal cancer

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PHYSICS CONTRIBUTION

USING A REDUCED SPOT SIZE FOR INTENSITY-MODULATED PROTON THERAPY POTENTIALLY IMPROVES SALIVARY GLAND-SPARING IN OROPHARYNGEAL CANCER

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Purpose: To investigate whether intensity-modulated proton therapy with a reduced spot size (rsIMPT) could further reduce the parotid and submandibular gland dose compared with previously calculated IMPT plans with a larger spot size. In addition, it was investigated whether the obtained dose reductions would theoretically translate into a reduction of normal tissue complication probabilities (NTCPs).

Methods: Ten patients with N0 oropharyngeal cancer were included in a comparative treatment planning study. Both IMPT plans delivered simultaneously 70 Gy to the boost planning target volume (PTV) and 54 Gy to the elective nodal PTV. IMPT and rsIMPT used identical three-field beam arrangements. In the IMPT plans, the parotid and submandibular salivary glands were spared as much as possible. rsIMPT plans used identical dose–volume objectives for the parotid glands as those used by the IMPT plans, whereas the objectives for the submandibular glands were tightened further. NTCPs were calculated for salivary dysfunction and xerostomia.

Results: Target coverage was similar for both IMPT techniques, whereas rsIMPT clearly improved target conformity. The mean doses in the parotid glands and submandibular glands were significantly lower for three-field rsIMPT (14.7 Gy and 46.9 Gy, respectively) than for three-field IMPT (16.8 Gy and 54.6 Gy, respectively). Hence, rsIMPT significantly reduced the NTCP of patient-rated xerostomia and parotid and contralateral submandibular salivary flow dysfunction (27%, 17%, and 43% respectively) compared with IMPT (39%, 20%, and 79%, respectively). In addition, mean dose values in the sublingual glands, the soft palate and oral cavity were also decreased. Obtained dose and NTCP reductions varied per patient.

Conclusions: rsIMPT improved sparing of the salivary glands and reduced NTCP for xerostomia and parotid and submandibular salivary dysfunction, while maintaining similar target coverage results. It is expected that rsIMPT improves quality of life during and after radiotherapy treatment.

Intensity-modulated proton therapy, IMPT, Head and neck, Comparative treatment planning.

INTRODUCTION

In a previous publication, we showed that scanned intensity-modulated proton therapy (IMPT) improved organ at risk (OAR) sparing in advanced oropharyngeal cancer cases compared with an advanced photon technique, *i.e.*, intensity-modulated radiotherapy (IMRT) (1). This study showed that three-field IMPT yielded similar results as seven-field IMRT with regard to target coverage, whereas three-field IMPT significantly reduced the dose to the parotid glands, which is in agreement with the results reported by other studies (2, 3).

Of note is that patient-rated xerostomia, which is the most frequently reported radiation-induced side effect significantly affecting quality of life of head and neck cancer patients (4), depends not only on the parotid gland dose but also the submandibular gland dose (5). In addition, Murdoch-Kinch *et al.* (6) reported that preservation of the submandibular gland function depends on the mean dose to this gland. More specifically, when the mean dose remained below 39 Gy, stimulated and unstimulated flow rates recovered over time, whereas after a mean dose beyond 39 Gy, flow rates decreased over time. Unfortunately, three-field IMPT, as reported in our previous study (1), did not reduce the submandibular gland dose in the majority of patients. Moreover, most treatment-planning comparison studies that investigated the potential benefits of protons vs. photons in head and neck cancer took into account only the dose distribution in the parotid glands (2, 3, 7).

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These results indicate that there is still room for improvement of IMPT plans with regard to salivary gland sparing. It should be emphasized that in our previous study (1), a relatively wide proton pencil beam (lateral width) was assumed with an initial σ of 3.5 mm in air ($\sigma_x = \sigma_{y,}$, full-width-at-half-maximum [FWHM] of the Gaussian proton pencil beam is $2.35 \times \sigma$), which was degraded by range shifter plates, the gap to the patients surface, and the patient's tissue itself (see Fig. 1, left diagrams).

In general, the lateral pencil beam width depends on the initial beam width (initial phase space) in air and broadening due to multiple Coloumb scattering in traversed materials/tissues (8). Potential benefits of a smaller proton pencil beam spot size (lateral width, σ, at the Bragg peak) in head and neck cancer treatment was already investigated by Steneker *et al.* (7), who showed that parotid gland sparing could be improved while maintaining target homogeneity. However, in this study, the high-risk area did not receive a boost dose, which is unlikely to happen in real clinical practice (both the elective nodal areas and the high risk area received 54 Gy). Furthermore, the possible sparing of the submandibular glands was not investigated.

Therefore, the aim of this treatment planning study was to investigate whether three-field IMPT with a reduced spot size (three-field reduced spot IMPT, rsIMPT) allows for a further reduction of the dose to the salivary glands compared with three-field IMPT using a larger σ (1) among the same set of oropharyngeal cancer cases. In addition, existing normal tissue complication probability (NTCP) models were used to investigate whether dose reductions obtained with rsIMPT theoretically translate into a reduction of salivary flow dysfunction and xerostomia.

METHODS AND MATERIALS

Patients and computed tomography

The study cohort consisted of 10 patients with clinically N0 oropharyngeal squamous cell carcinoma with various T stages (T2–T4N0) (1) previously treated with three-dimensional conformal radiotherapy. Planning computed tomography (CT) scans were made with patients in supine position. The scanned area extended at least 4 cm beyond the planning target volumes (PTVs) in both directions. Slice separations were 4 or 5 mm. Target volume and organ at risk (OAR) delineation were carried out at the Department of Radiation Oncology of the University Medical Center Groningen.

Target volumes and OARs

Target volumes were defined on the planning CT scan by an experienced radiation oncologist (H.B.) as described in our previous article (1). Two planning target volumes, PTV1 and PTV2, were generated. PTV1 enclosed the elective nodal areas on both sides of the neck (levels II–IV) and the primary tumor, whereas PTV2 only enclosed the primary tumor. The mean volumes of PTV1 and PTV2 were 506 cm^3 (range, 354–658 cm^3) and 164 cm^3 (range: 25–353 cm^3), respectively.

The delineated OARs included the parotid, submandibular, and sublingual salivary glands, the soft palate, the oral cavity, and the spinal cord. To ensure consistent delineation, all OARs were delineated according to CT-based delineation guidelines for OARs in the head and neck region developed at our department (partly presented in van de Water *et al.*) (9).

For each patient, the same delineated volumes were used to optimize both IMPT plans.

Treatment planning and the dose delivery model

IMPT planning was performed on a treatment planning system (TPS) developed at the Paul Scherrer Institute (PSI) for parallel-scanned proton therapy (1, 10, 11, 12). For both the IMPT and rsIMPT plans, the prescribed total dose to PTV1 and PTV2 was 54 and 70 Gy, using 1.54 and 2 Gy per fraction in 35 fractions, respectively, using a simultaneous integrated boost. This fractionation schedule is the current clinical practice for head and neck cancer patients treated with photon IMRT at the Department of Radiation Oncology of the University Medical Center Groningen. A relative biological effectiveness of 1.1 relative to ^{60}Co was used for the dose calculations.

For the IMPT plans, delivery characteristics similar to those used in our previous publication (1) have been used. That is, that the Bragg peak range is modulated by a set of range shifter plates inserted immediately at the exit of the nozzle. This has the consequence that the shape of the Bragg peak in depth is invariant with energy but also that the beam in air after the range shifters broadens considerably (see Fig. 1, left diagram).

For modeling the rsIMPT plans, we assumed in contrast that energy changes would be performed upstream of the treatment gantry, as shown in the diagrams on the right side of Fig. 1. This is the configuration that we have on the new PSI gantry currently under development and is the configuration of all commercially available scanning proton systems. This means that after collimating the beam directly after the degradation step, a narrow pencil beam can be preserved over a wide energy range, with the consequence that the width of the Bragg peak in the depth direction will vary with energy. Because the TPS used for this work was specifically designed to support the PSI gantry 1, where energy variation is achieved through the insertion of range shifter plates at the nozzle exit (1, 10, 11), two simplifications had to be made to model such a system.

The first, and most relevant for this work, is that we had to model the beam width in air as being invariant as a function of energy. Although this is not strictly correct, the constant value of 3.5 mm sigma we have used in this work is a good average value based on measured values for the new gantry, in which the beam size in air has been measured to vary from 2.5 mm sigma for 240 MeV to 4.5 mm for 70 MeV beams. Thus, with a constant value of 3.5 mm we are somewhat overestimating the beam width in air for energies above about 110 MeV (equivalent to a range of about 10 cm in water) and slightly underestimating beam widths for energies below 110 MeV.

The second, and less relevant simplification for this work, is that the Bragg peak shape and width are also invariant with delivered proton energy. Although physically incorrect, we believe that for the purposes of this study, this is sufficient for the following reasons: (*1*) we are primarily interested in the quality of plans that will be achievable if *laterally* narrower pencil beams can be delivered. As such, the shape of the Bragg peak *in depth* will have little influence on this. (*2*) The modeling of the beams using a fixed Bragg peak derived from the maximum energy required for a field gives a worse-case approximation of the distal falloff, because it always models the broadest Bragg peak in depth. Therefore, any benefits we see from the use of narrower pencil beams is solely from the

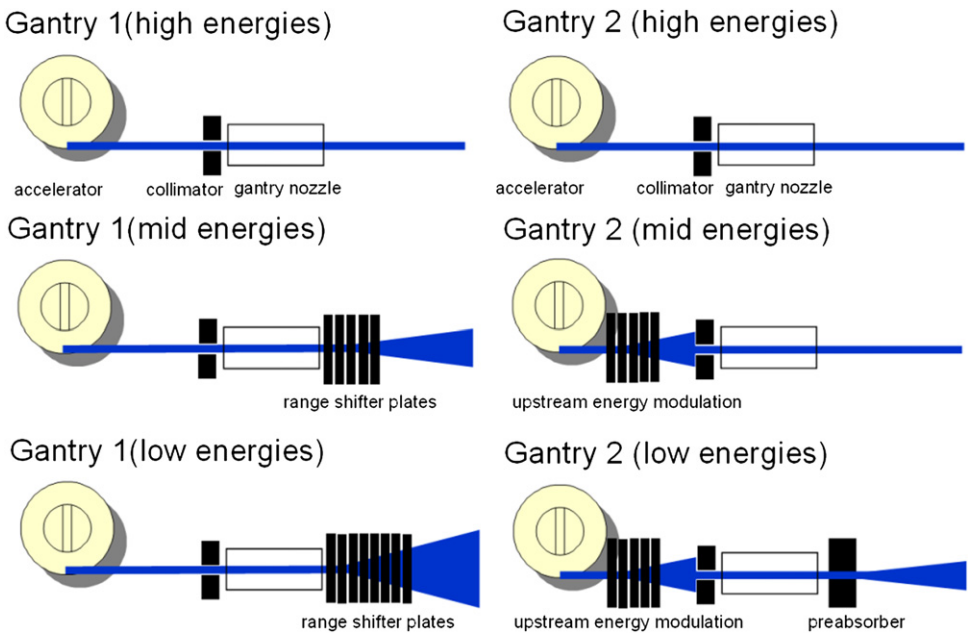

Fig. 1. Sketch of the differences in beam-broadening elements between the Gantry 1 and Gantry 2 beam line.

lateral width of the pencil beams and not due to the delivery of potentially narrower Bragg peaks.

Finally for the rsIMPT plans, we have also assumed that a single preabsorber can automatically be inserted into the beam at the nozzle exit to help deliver superficial (low-energy) Bragg peaks. Preabsorbers will always be required in practice to deliver superficial pencil beams because of the extreme sharpness of the Bragg peak for low energies and the problem of very low transmitted intensity due to the energy degrader and subsequent collimation before the beam enters the gantry beam line. In this work, we have assumed that a single preabsorber of 6 cm water equivalent thickness will be automatically placed in the beam for delivering all pencil beams of a field with a water equivalent residual range in the patient of less than 6 cm. Beam broadening due to multiple Coulomb scattering in this preabsorber has been modeled.

For both IMPT and rsIMPT, individual Bragg peaks were distributed over a regular grid covering the target volume with a 5 mm spot separation in the plane perpendicular to the field direction and with a separation in depth of 4.6 mm (water equivalent). Only Bragg peaks inside the target volume or within 5 mm from the target surface were taken into account for the optimization. A dose calculation algorithm was used (13) that included heterogeneity corrections (12, 14) and allowed simultaneous three-dimensional optimization of inhomogeneous (intensity-modulated) fields (15). The dose grid resolution was $5 \times 5 \times 5$ mm^3 or $5 \times 5 \times 4$ mm^3 (depending on the CT slice separation). Furthermore, identical beam arrangements were used for three-field IMPT and three-field rsIMPT with gantry angles of 180° (couch angle: 0° or ± 10°), –50° to –60° (couch angle: 0°) and 50 to 60° (couch angle: 0°) (1). Couch angles were applied for the 180° beam to avoid grazing the skull base.

Plan optimization

IMPT plans. Good coverage of the PTVs (satisfying the dose prescriptions), without violating the dose constraint to the spinal cord, had the highest priority. With exception of the parotid and submandibular glands (as specified below), for both treatment techniques, identical target and OAR dose prescriptions and acceptance criteria were used as specified in our previous study (1). For both plans, hotspots, a dose >107% to >15 mm^3 or >2% of the volume, of the prescribed PTV2 dose in the normal tissue volume (NTV, all scanned nontarget tissue) were not allowed. For three-field IMPT, optimization took place in three steps, each optimizing the dose distribution for one of the planning goals, without deteriorating the results obtained in the previous step: 1. The dose to the PTV had to satisfy the planning goals as well as possible without exceeding the maximum dose to the spinal cord (54 Gy). 2. The mean dose to the parotid glands was reduced as much as possible by trial-and-error adjustment of the planning optimization dose–volume objectives (DVOs) while maintaining adequate target coverage. To avoid conflicting objectives, DVOs were only applied to the part of the gland outside the PTVs. 3. Finally, the mean dose to the submandibular glands was reduced as much as possible in the same way as described for the parotid glands. In some cases, extra maximum DVOs to the entire salivary glands were applied to avoid dose values higher than the prescribed target dose.

rsIMPT plans. Reduced spot IMPT and IMPT used identical dose acceptance criteria and dose prescriptions for the PTVs and myelum (1). More specifically, for the purpose of this study, rsIMPT plans used the same DVOs for the PTVs, myelum and parotid glands as used for the IMPT plans. Only the submandibular gland DVOs were tightened to investigate whether rsIMPT allowed a further reduced submandibular gland dose without compromising target coverage.

Evaluation tools

Dose distributions were evaluated by using dose–volume histograms (DVHs) and by checking the presence of hotspots. Plans were compared by using the acceptance criteria as specified in our previous study for the PTVs and spinal cord (1). Additionally, the conformity index (CI) ([volume ≥95% PTV1 dose] / [PTV1]) and heterogeneity index (HI) ([$D_{5\%}$ – $D_{95\%}$] / D_{mean}, with $D_{x\%}$ and D_{mean} being the dose level at which the cumulative PTV DVH intersects with x% of volume and the mean PTV dose, respectively) were calculated.

Table 1. Planning target volume coverage

Target coverage	Mean volume or mean index value (range) IMPT	rsIMPT
% PTV1 receiving ≥95% prescribed dose	98.1 (97.9–98.9)	98.1 (97.9–99.0)
% PTV2 receiving ≥95% prescribed dose	98.4 (98.0–99.3)	98.5 (98.0–99.9)
Conformity index	1.40 (1.32–1.48)	1.23 (1.13–1.41)
Inhomogeneity index PTV1	0.26 (0.22–0.28)	0.25 (0.21–0.28)
Inhomogeneity index PTV2	0.07 (0.06–0.09)	0.06 (0.05–0.07)

Abbreviations: IMPT = intensity-modulated proton therapy; PTV = planning target volume; rsIMPT = reduced spot IMPT.

Observed differences between the techniques were tested for statistical significance ($p < 0.05$) using the Wilcoxon signed-rank test, for paired data, that takes into account the magnitude of the differences and assumes the differences come from a symmetric population. All tests were two-tailed.

NTCP models

We used three existing NTCP models to estimate the clinical relevance of the differences in dose distributions among the two IMPT techniques. The first model predicts the probability of a reduction in parotid salivary flow below 25% referenced to the baseline at ≤6 months after radiotherapy (16). The input parameter in this model is the mean dose to both parotid glands. The second model predicts the probability of moderate to severe patient-rated xerostomia at 6 months after radiotherapy (5) based on the mean dose to both parotid glands and both submandibular glands. The third model predicts the probability of a reduction in stimulated submandibular salivary flow per gland below 25% referenced to the baseline at 12 months after radiotherapy (6), based on the mean submandibular gland dose.

RESULTS

Target volume coverage

The IMPT and rsIMPT dose distributions satisfied the PTV coverage acceptance criteria (1) in all cases (Table 1). Target inhomogeneity was similar for both IMPT techniques, whereas rsIMPT clearly improved target conformity (Table 1 and Fig. 2).

Normal tissue and OAR-sparing

The plan acceptance criteria with regard to hotspots and the spinal cord dose were satisfied in all cases for both IMPT techniques. Table 2 and Fig. 2 (and Fig. 3d to a lesser extent) show that sparing of the NTV was most effective with rsIMPT.

rsIMPT yielded significantly lower mean doses to both parotid glands (14.7 Gy; range, 9.3–25.2 Gy) and both submandibular glands (46.9 Gy; range, 39.9–58.8 Gy) compared with IMPT (16.8 Gy; range, 10.1–27.8 Gy and 54.6 Gy; range, 48.1–63.0 Gy, respectively). Although mean dose reductions were significant (Fig. 4), the mean DVHs of the parotid glands and the ipsilateral submandibular gland were only slightly lower with rsIMPT (Fig. 3).Nevertheless, the

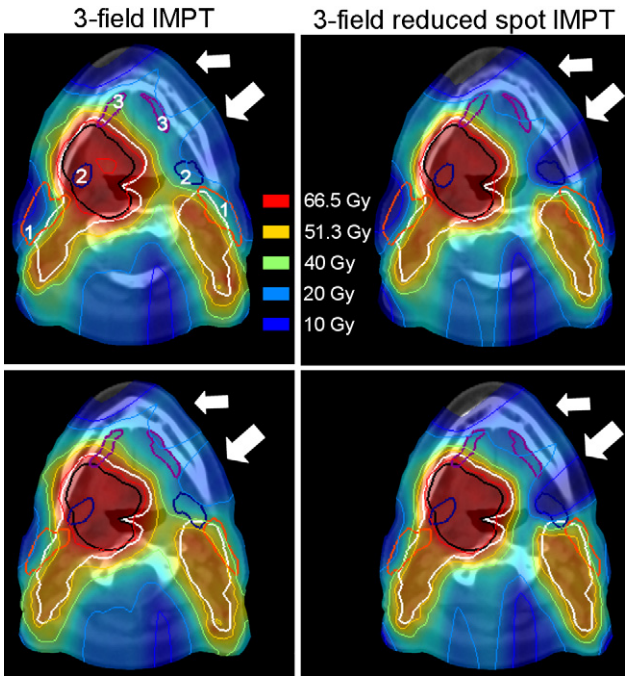

Fig. 2. Dose distribution for both intensity-modulated proton therapy (IMPT) plans in Case 2 for two subsequent CT slices. Thick lines indicate the volumes of interest: elective planning target volume, PTV1 (white); boost volume PTV2 (black); parotid glands (1); submandibular glands (2); and sublingual glands (3). Arrows indicate the most important differences.

mean DVH of the contralateral submandibular gland was clearly improved with rsIMPT (Fig. 3b), resulting in a substantial mean dose reduction (Fig. 4). In addition, although no constraints were applied to the sublingual glands, the soft palate and oral cavity, the mean dose to these structures were also significantly lower with rsIMPT (Fig. 4), as a result of lower mean DVHs (Fig. 3).

Figure 5a clearly shows that the dose reduction obtained with rsIMPT compared with IMPT varied between cases. Whereas the mean parotid gland dose reductions remained

Table 2. Irradiated normal tissue volume

NTV	Mean volume [L] or mean dose [Gy] (SD) IMPT	rsIMPT	Statistical significance *p*
NTV receiving ≥95% PTV1 dose	0.22 (0.04)	0.13 (0.03)	<0.01*
NTV receiving >107% of PTV2 dose (hotspots)	0.00 (0.00)	0.00 (0.00)	1.0
NTV receiving ≥60 Gy	0.04 (0.02)	0.01 (0.01)	<0.01*
NTV receiving ≥40 Gy	0.55 (0.09)	0.36 (0.06)	<0.01*
NTV receiving ≥20 Gy	1.25 (0.24)	1.01 (0.18)	<0.01*
NTV receiving ≥10 Gy	2.32 (0.48)	2.08 (0.41)	<0.01*
NTV mean dose	7.3 (1.4)	6.0 (1.1)	<0.01*

Abbreviations: IMPT = intensity-modulated proton therapy; NTV = normal tissue volume; PTV = planning target volume; rsIMPT = reduced spot IMPT.

* Wilcoxon test statistically significant ($p < 0.05$).

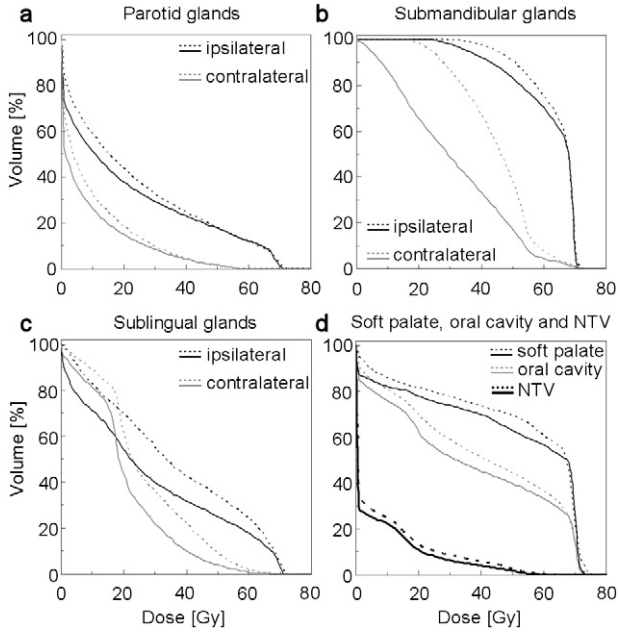

Fig. 3. Cumulative dose volume histograms averaged over all ten cases for the intensity-modulated proton therapy (IMPT; dotted line) and reduced spot IMPT (solid line) plans. NTV = normal tissue volume.

below 5 Gy, the corresponding values for the contralateral submandibular glands were always higher than 5 Gy, with a maximum of 23.7 Gy.

NTCP values

rsIMPT significantly reduced the NTCP values estimated by the parotid and contralateral submandibular salivary flow models and the patient-rated xerostomia model (Fig. 5 and Fig. 6, $p < 0.01$). The average decrease of the NTCP was

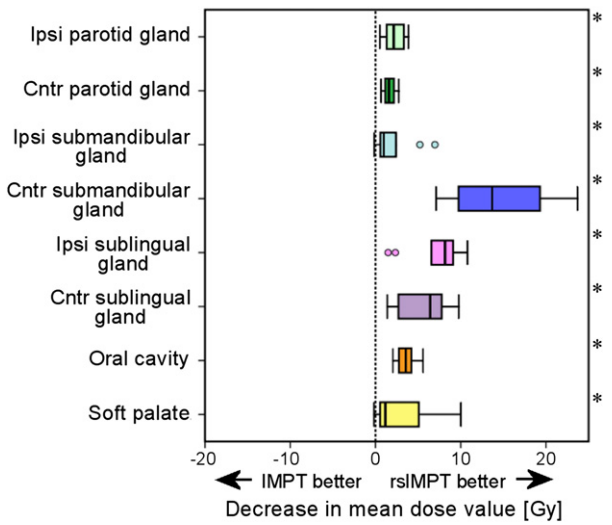

Fig. 4. Reduction in mean dose value obtained by application of reduced spot intensity-modulated proton therapy (rsIMPT) compared to IMPT. For each OAR, the results of all ten cases are displayed by a box plot. * Wilcoxon signed rank test is statistically significant. Cntr = contralateral; Ipsi = ipsilateral.

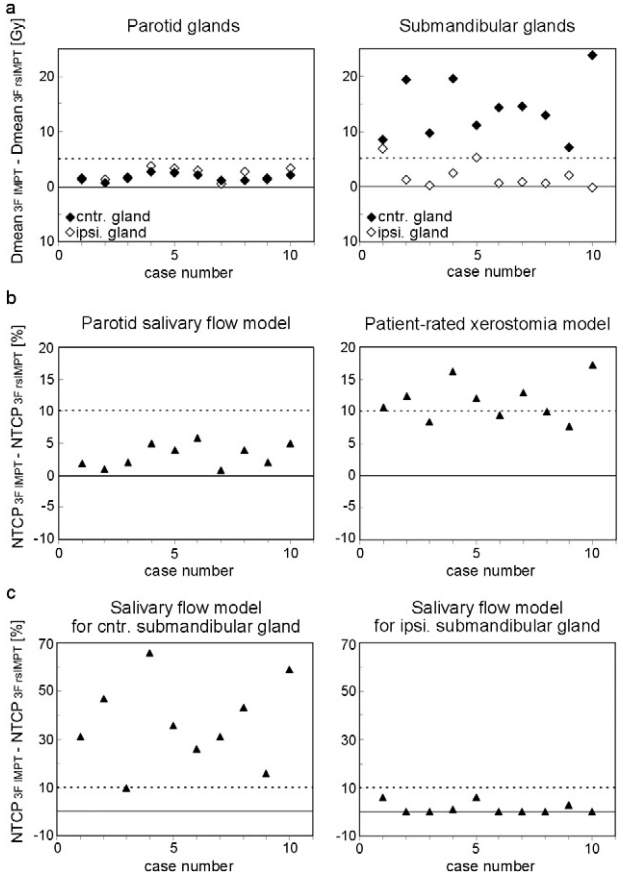

Fig. 5. (a) Differences in mean dose (Dmean) for the submandibular and parotid glands and (b) and (c) differences in normal tissue complication probability (NTCP) obtained between three-field IMPT and rsIMPT plans for all 10 cases. Cntr = contralateral; Ipsi = ipsilateral.

3.1% and 37% for parotid and contralateral submandibular salivary flow dysfunction, respectively, and 11.6 % for patient-rated xerostomia. The NTCP reductions varied widely among patients (Fig. 5b and 5c). When an NTCP reduction of 10% was defined as clinically relevant, none of the patients in this study cohort would benefit from rsIMPT with regard to parotid salivary flow dysfunction. However, 100% and 70% of the included patients would benefit from rsIMPT with regard to contralateral submandibular salivary dysfunction and patient-rated xerostomia, respectively.

DISCUSSION

With this planning comparative study, we showed that rsIMPT significantly reduced the mean dose to the major salivary glands, the oral cavity and the soft palate, compared with IMPT with a larger spot size while maintaining adequate target coverage, yielding a potential clinical benefit. Hence, these results could theoretically lead to relevant clinical benefits with regard to parotid and submandibular gland salivary dysfunction and patient-rated xerostomia.

There are two important issues that should be taken into account while evaluating these results. First, we did not focus on further tightening of the parotid gland DVOs with

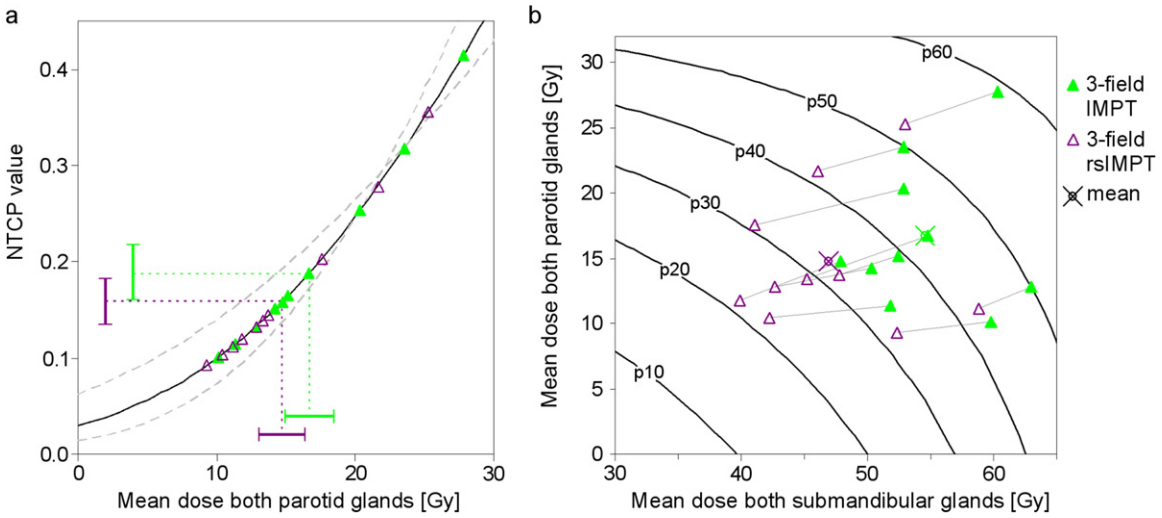

Fig. 6. (a) Normal tissue complication probability (NTCP) model for parotid salivary flow (solid curve) with corresponding 95% confidence interval (dashed curve). The NTCP value represents the probability that the salivary flow is <25% of the pretreatment flow at ≤6 months after radiotherapy. The mean parotid gland dose averaged over all 10 cases (dotted vertical line) ± standard error of the mean is displayed for both intensity-modulated proton therapy (IMPT; green) and reduced spot IMPT (rsIMPT; purple) with corresponding NTCP value ranges. (b) NTCP-model for patient-rated xerostomia (curves). P10 denotes the 10% probability of moderate to severe xerostomia at 6 months after radiotherapy. The mean gland dose values per case are plotted. The mean dose values averaged over all 10 cases are also displayed (mean). The obtained reductions are visualized by the lines connecting the corresponding cases.

rsIMPT and effort was only made to improve submandibular gland sparing by tightening only those DVOs. The reason for this is that the dose to both parotid glands was already low with IMPT (except for one case, the mean dose to both glands was always far below 26 Gy; range, 10.1–27.8 Gy), whereas the mean dose to both submandibular glands was still high (range, 48.1–63.0 Gy) (1), and it is known that significant dose–effect relationships exist between the submandibular gland dose and salivary flow dysfunction and patient-rated xerostomia (5, 6). Nonetheless, a smaller spot size automatically improved target dose conformity and therefore parotid gland sparing. This effect also caused significant dose reductions in the sublingual glands, oral cavity, and soft palate (OARs to which no dose constraints were applied). However, to investigate whether rsIMPT can further reduce the dose in the parotid glands, the parotid gland DVOs have to be tightened as well. Consequently, there may still be room for improvement with regard to parotid gland sparing. Second, only the contralateral submandibular gland dose reductions lead to a clinically relevant reduction in predicted salivary flow dysfunction. For the ipsilateral submandibular gland, at least similar or reduced NTCP values were expected with rsIMPT compared with IMPT (Fig. 4c). This can be explained by the fact that, compared with the contralateral gland, the ipsilateral gland always overlapped more with the PTVs. Hence, reducing the dose in this gland was more difficult. (Dose reductions were always <2 Gy when the ipsilateral submandibular gland overlapped for more than 87% with the PTVs.).

Steneker *et al.* (7) also showed that a smaller spot size improved sparing of the parotid glands while maintaining target homogeneity in head and neck cancer patients. However, only the low dose PTVs were taken into account, which makes this treatment not state of the art. Additionally, submandibular gland-sparing was not considered.

In a previous planning study, we showed that IMPT (identical to the three-field IMPT plans used in this study) did not allow for a significant submandibular gland dose reduction, compared with photon IMRT (1). Dose reductions for the contralateral and ipsilateral gland were 2.5 Gy (range, –4.4 to 9.9 Gy) and –1.8 Gy (range, –6.4 to 1.0 Gy), respectively. The current study, however, shows that compared with IMRT, rsIMPT does allow for a substantial contralateral submandibular gland dose reduction (mean, 16.6 Gy; range, 6.6 to 22.9 Gy) and, on average, a similar ipsilateral gland dose (mean reduction, 0.2 Gy; range, –4.0 to 5.7 Gy). Additionally, with IMRT in only 20% of the cases the contralateral submandibular gland dose could be reduced below 39 Gy, whereas this percentage was 30% with IMPT and 80% with rsIMPT.

Other studies investigated the feasibility of submandibular gland sparing with IMRT (17, 18) and reported that it reduced the probability of xerostomia. These studies achieved submandibular gland sparing by compromising the target coverage (17) or by surgical transfer of the submandibular gland (18). The current study shows that rsIMPT, in contrast to IMRT, allows for a substantial contralateral submandibular gland dose reduction without surgical transfer of the gland or by compromising target coverage.

In general, compared with photons, the penumbra of protons is narrower up to a certain penetration depth, about 17–18 cm (depending on the used proton energy) (19). Goitein (20) reported that great care should be taken to optimize

the proton penumbrae and that beam sizes should be at the most 10-mm FWHM in air at isocenter (20). During the past decade, in addition to the gantry available at PSI, multiple proton therapy facilities allowing for gantry-based scanned proton therapy have been developed or are under construction (21). However, producing small proton beams remains a challenge. With the current gantry at PSI ∼8 mm FWHM in air can be achieved (10), but this is without the effect of the range shifter plates used to modulate energy that degrade the beam size considerably. As previously discussed, with the second-generation gantry at least similar spot sizes in air and improved spot sizes in the patient can be achieved, yielding clinical benefits.

It is possible that application of a smaller proton beam spot size (more steep dose gradients) results in IMPT plans that are more sensitive to range and dose calculation uncertainties, thus decreasing plan robustness (22). However, whether this effect occurs depends on the exact location of the steep dose gradients within the patient. Lomax *et al.* (22) suggested that the application of fields containing mixed spot sizes, with larger spots in the field center and smaller spots at the edges (where the glands are located in our case), could minimize this possible effect. However, it was beyond the scope of this study to analyze the differences between the rsIMPT and IMPT plans for these uncertainties.

CONCLUSION

IMPT applied with a smaller spot size results in a significant reduction of the mean parotid and submandibular gland doses. According to NTCP models for parotid and submandibular salivary flow dysfunction and patient-rated xerostomia, these dose reductions result in significant clinical benefits in most of the cases. Therefore, it is expected that rsIMPT improves quality of life during and after radiotherapy treatment. Further clinical validation is needed to confirm these outcomes.

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