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Potential benefits of intensity-modulated proton therapy in head and neck cancer

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Chapter 6

Sparing the salivary glands with protons in oropharyngeal cancer: benefits of 6-beam split-field intensity-modulated proton therapy (IMPT) versus 3-beam IMPT

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Abstract

Background and purpose: To test the hypothesis that 6-beam split-field intensity-modulated proton radiotherapy (6B-SFIMPT) instead of 3-beam IMPT (3B-IMPT), further reduces the parotid and submandibular gland doses. Additionally, investigated was if the obtained dose reductions would theoretically translate into a reduction of normal tissue complication probabilities (NTCPs).

Materials and Methods: Ten patients with NO oropharyngeal cancer were used. The IMPT plans delivered simultaneously 70 Gy to the boost planning target volume (PTV) and 54 Gy to the elective nodal PTV. The 6B-SFIMPT technique avoided anterior beam directions passing through the oral cavity and posterior beams passing through the lung and shoulders. 3B-IMPT did not avoid those regions. NTCPs were calculated for salivary dysfunction and xerostomia.

Results: Target coverage was similar for both IMPT techniques. The parotid and ipsilateral submandibular gland mean doses did not differ significantly. 6B-SFIMPT reduced unnecessary normal tissue irradiation and significantly reduced the mean contralateral submandibular gland dose from 44.7 Gy, with 3B-IMPT, to 42.8 Gy.

Only the NTCP related to contralateral submandibular gland salivary dysfunction differed significantly.

Conclusions: 6B-SFIMPT improved sparing of the OARs, and avoided more adequately sources of density heterogeneity, while maintaining similar target coverage results. These findings require validation.

Introduction

The general objective in radiotherapy is to administer an adequate dose to the tumour while sparing the normal surrounding healthy tissues as much as possible. In the radiation of tumours of the head and neck region, the planning target volumes (PTVs) are generally large, complex-shaped and surrounded by many critical structures. Thus, optimization of the dose distribution in these cases may be challenging. The administered dose to the PTV and subsequent normal tissues will normally result in clinically relevant acute and late side effects that may adversely impair health-related quality of life.

In a previous study, we showed that scanned intensity-modulated proton therapy using 3 beams from standardized angles (3-beam IMPT) improves target conformity and organ at risk (OAR)-sparing as compared with the most advanced photon technique, i.e. intensity-modulated radiotherapy (IMRT) [181]. More specifically, we showed that 3-beam IMPT and 7-beam IMRT yielded similar target coverage, while 3-beam IMPT significantly reduced the dose to the parotid glands, which is in line with the results reported by other investigators [172,192]. It has been reported that patient-reported xerostomia not only depends on the dose in the parotid glands but also on the mean dose in the submandibular glands [86]. However, 3-beam IMPT did not allow for a reduction of the submandibular gland dose in the majority of patients, which indicates that there is still room for further improvement.

The three studies mentioned above used two anterior proton beams passing through the oral cavity and thus crossing regions that include density heterogeneities, such as bone-soft tissue and/or soft tissue-air interfaces. These density heterogeneities highly degrade the proton Bragg peak and result in variable ranges of the individual protons [115], which makes the shape of the resulting dose distributions very sensitive to positioning variations and density heterogeneity changes. Density heterogeneities are common in the head and neck region and the size and shape of some may vary from day to day. Hence, avoidance of regions with density heterogeneities is of high importance for proton therapy, and could

potentially be achieved by the use of posterior only beams. On the other hand, for the inferior (caudal) part of the target volumes, posterior beams are not ideal, as they pass through large amounts of normal tissue to reach the anterior-positioned target volume, and in particular through the apical lungs.

Consequently, the current planning comparative study was carried out to test the hypothesis that 6-beam split-field IMPT (6B-SFIMPT), using posterior beam directions superiorly to avoid the oral cavity and anterior beams inferiorly to avoid the lung apex and excessive normal tissue irradiation, allows for a further reduction of the dose to non-target tissues and relevant OARs compared with 3-beam IMPT (3B-IMPT) [181]. In addition, we used existing Normal Tissue Complication Probability (NTCP) models to investigate if dose reductions obtained with 6B-SFIMPT theoretically will translate into a reduction of salivary flow dysfunction and xerostomia.

It should be noted that this is a pure dosimetric comparison to study the clinical feasibility of such a split-field approach, and as such no effort has been made to study the relative robustness of this approach to anatomical changes, which will be the subject of further work.

Materials and Methods

Patients and computed tomography

This study cohort was composed of the same ten patients as used in our previous study [181], with clinically No oropharyngeal squamous cell carcinoma with various T-stages (T2-T4No), who had previously undergone 3D-conformal radiotherapy. Planning computed tomography (CT) scans were made with the patient in supine position. The scanned area was extended at least 4 cm beyond the PTVs and included anatomic structures from the level of the aortic arch until the eye balls (in some cases more caudal/cranial slices were included). Slice separations were 4 or 5 mm. Target volume and 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 report [181]. 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 PTV2 the primary tumour. The mean volumes of PTV1 and PTV2 were 506 cm³ (range: 354-658 cm³) and 164 cm³ (range: 25-353 cm³).

The following OARs were delineated: the parotid, submandibular and sublingual salivary glands, the soft palate, the oral cavity, the mandible body (the horizontal part of the mandible), the pharyngeal constrictor muscles, the larynx and the spinal cord. In order 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 [180].

For optimization of the 3B-IMPT and 6B-SFIMPT plans, the same delineated volumes were used.

Treatment planning techniques

IMPT planning was performed on a treatment planning system (TPS) developed at the Paul Scherrer Institute (PSI) for scanned proton beam therapy [140]. For both the 3-beam and 6-beam split-field techniques, the prescribed total dose to PTV1 and PTV2 was 54 Gy and 70 Gy, respectively, delivered in 35 fractions, using a simultaneous integrated boost. The dose per fraction was 1.54 Gy and 2 Gy, respectively. A relative biological effectiveness (RBE) of 1.1 relative to ⁶⁰Co was used for the dose calculations.

Initial proton energies varied from 138-177 MeV for each beam. Bragg peak positions (spots) were varied by automated insertion of multiple (4.6 mm water equivalent) range shifter plates into the beam [140]. 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. Only the Bragg peaks inside the target volume or within 5 mm distance from the target surface were taken into account for the optimization. A proton pencil beam model was used

[159] that included heterogeneity corrections [143,158], and allowed 3D-optimization of inhomogeneous (intensity-modulated) fields [112]. The dose grid resolution was $5 \times 5 \times 5 \text{ mm}^3$ or $5 \times 5 \times 4 \text{ mm}^3$ (depending on the CT-slice separation). For each initial beam energy, a Gaussian cross section of the pencil beam was assumed with a σ of 3.5 mm in air ($\sigma_x = \sigma_y$, full-width-at-half-maximum of $\sim 8 \text{ mm}$), without insertion of range shifter plates (similar to the σ clinically achieved at PSI [116]). Furthermore, a fixed air gap between the gantry nozzle and the patient was assumed for each beam direction, i.e., the gantry nozzle was able to adapt for patient contour variations during scanning at one specific beam angle. The dose calculation takes the effect of beam divergence across this gap (due to the scatter of protons in the range shifter) and in the patient into account.

3-beam IMPT. The fields of the 3B-IMPT plans irradiated the entire target volume in the cranial-caudal direction. Gantry angles were set to 180° (couch angle: 0° or $\pm 10^\circ$), $300^\circ - 310^\circ$ (couch angle: 0°) and $50^\circ - 60^\circ$ (couch angle: 0°) [181], Figure 1. Couch angles were applied for the 180° beam to avoid grazing the skull base.

6-beam split-field IMPT. The 6B-SFIMPT technique composed of split-beams for the inferior and superior portions of PTV1 and included 6 individual beams (Figure 1). Two anterior beams with gantry angles 30° and 330° (couch angles: 0°) irradiated the caudal part of the target volume up to the lower edge of the mandible (inferior beams). Three posterior beams with gantry angles 150° , 180° and 210° (corresponding couch angles were 0° , 0° or $\pm 10^\circ$ and 0° , respectively) and one lateral beam with a gantry angle of 70° or 290° (couch angle: 0°) irradiated the cranial part of the target volume (superior beams). The angles of the superior beams ensured that the oral cavity, the region with most anatomic variations, could be avoided, whilst the inferior-anterior beams avoided the lung apex and excessive normal tissue irradiation in the shoulders. Furthermore, the gantry angles 150° and 210° avoided the parotid glands, while the target was covered. The extra lateral superior beam ensured adequate coverage of the boost target. The gantry angle used (70° or 290°) was patient-specific and depended on the primary tumour

location. The inferior and superior fields overlapped for at least 20 mm. The boost target was always irradiated by the superior fields (ensuring good target coverage), therefore the size of the overlapping area depended on the extension of the boost target in caudal direction. The overlap equalled 20 mm in four cases, 44 – 48 mm in three cases and 70 – 80 mm in the remaining three cases.

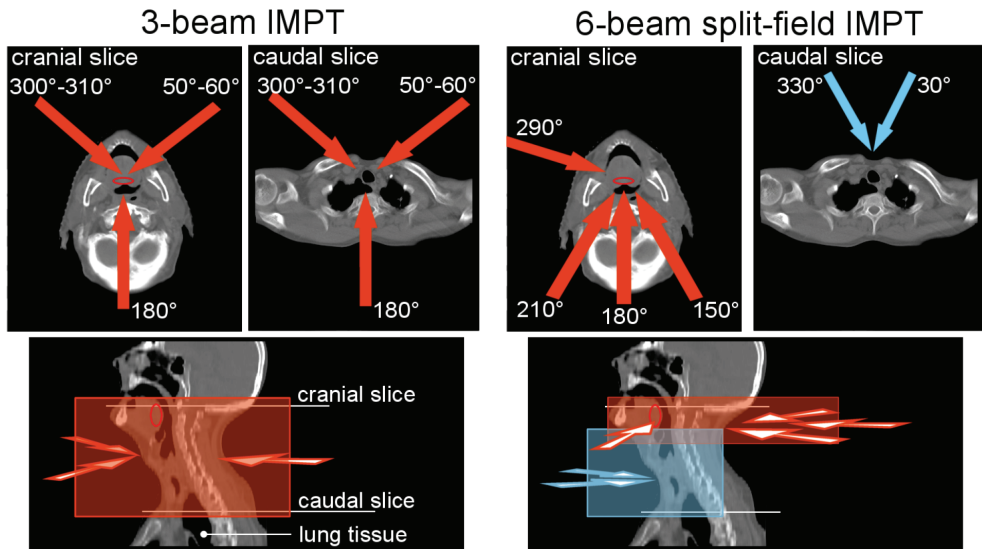


Figure 1. Schematic overview of the beam arrangement for 3-beam intensity-modulated proton therapy (3B-IMPT) and the 6-beam split-field IMPT. Couch angles used for the 180° beam are not shown. The red contour represents the boost target location.

IMRT. To illustrate the relevance of the differences in dose distribution obtained between the two IMPT techniques, results were also compared with the results obtained with photon IMRT from a recent planning comparative study [181]. Identical patient data, dose prescriptions, and plan acceptance criteria were used as in this study.

Plan optimization

Identical dose acceptance criteria/dose prescriptions were used for both IMPT techniques (Table 1). Hotspots were defined as a dose >107% to >15 mm³ or >2% of

the volume (taking into account small OARs) of the prescribed PTV2 dose outside the target, and were not allowed. Optimization strategies for both IMPT plans were similar. Optimization took place in 3 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 PTVs had to satisfy the planning goals as well as possible without exceeding the maximum dose to the spinal cord (54 Gy, Table 1); 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), without deteriorating the minimal requirements for target coverage. To avoid conflicting objectives, the DVO to the parotid gland was 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 when necessary to avoid dose values higher than the prescribed target dose.

Table 1. Dose prescriptions and acceptance criteria for both IMPT techniques.

Volume of interest	Dose prescriptions/acceptance criteria
PTV	$\geq 98\%$ of volume $\geq 95\%$ of dose $\leq 2\%$ of volume $> 107\%$ of PTV2 dose
Spinal cord	$\leq 2\%$ of volume ≥ 54 Gy
Parotid glands	Mean dose minimized
Submandibular glands	Mean dose minimized
NTV	No hotspots

Abbreviations: IMPT, intensity-modulated proton therapy; NTV, normal tissue volume; PTV, planning target volume.

Evaluation of the dose distributions

Dose distributions were evaluated by using dose-volume histograms (DVHs) and by checking the presence of hotspots. Plans were compared by using the parameters as specified in Table 1. Additionally, the conformity index (CI) ($[\text{volume} \geq 95\% \text{ PTV1 dose}]/[\text{PTV1}]$) and the heterogeneity index (HI) ($[(D_{5\%} - D_{95\%})/D_{\text{mean}}$,

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.

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

NTCP models

To estimate the clinical relevance of differences in dose distributions, we used three existing NTCP models. The first model predicts the probability of a reduction in salivary flow below 25% referenced to the baseline at ≤ 6 months after radiotherapy [164]. 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 [86] 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 below 25% referenced to the baseline (per gland) at 12 months after radiotherapy [128]. The input parameter is the mean submandibular gland dose.

Results

Target volume coverage

Both techniques satisfied the PTV coverage acceptance criteria in all cases (Table 2). Compared with 6B-SFIMPT, conformity was slightly better with 3B-IMPT, whereas target inhomogeneity was similar (Table 2 and Figure 2). IMRT also satisfied the PTV acceptance criteria, but the conformity was worse, while target inhomogeneity was similar to both IMPT techniques.

Table 2. Planning target volume coverage.

Target coverage	Mean volume (SD)		
	3-beam IMPT	6-beam split-field IMPT	IMRT
% PTV1 receiving \geq 95% prescribed dose	98.1 (0.3)	98.2 (0.3)	99.0 (0.5)
% PTV2 receiving \geq 95% prescribed dose	98.4 (0.4)	98.5 (0.5)	98.3 (0.3)
Conformity Index	1.40 (0.06)	1.50 (0.09)	1.63 (0.13)
Inhomogeneity index PTV1	0.26 (0.02)	0.27 (0.02)	0.27 (0.02)
Inhomogeneity index PTV2	0.07 (0.01)	0.07 (0.01)	0.08 (0.01)

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy with photons; PTV, planning target volume.

Table 3. Irradiated normal tissue volume.

Normal tissue volume	Mean volume [l] or mean dose [Gy] (SD)			Statistical significance <i>p</i>		
	3-beam IMPT	6-beam split-field IMPT	IMRT	3-beam IMPT vs. 6-beam split-field IMPT	IMRT vs. 3-beam IMPT	IMRT vs. 6-beam split-field IMPT
NTV receiving \geq 95% PTV1 dose [l]	0.22 (0.04)	0.27 (0.06)	0.29 (0.10)	< 0.01 *	0.020 *	0.492
NTV receiving > 107% of PTV2 dose (hotspots) [l]	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.0	1.0	1.0
NTV receiving \geq 60 Gy [l]	0.04 (0.02)	0.05 (0.03)	0.06 (0.04)	< 0.01 *	0.010 *	0.08
NTV receiving \geq 40 Gy [l]	0.55 (0.09)	0.60 (0.11)	0.80 (0.21)	< 0.01 *	< 0.01 *	0.004 *
NTV receiving \geq 20 Gy [l]	1.25 (0.24)	1.24 (0.24)	2.20 (0.49)	0.77	< 0.01 *	< 0.01 *
NTV receiving \geq 10 Gy [l]	2.32 (0.48)	1.64 (0.35)	3.35 (0.77)	< 0.01 *	< 0.01 *	< 0.01 *
NTV mean dose [Gy]	7.3 (1.4)	6.3 (1.3)	12.1 (2.5)	< 0.01 *	< 0.01 *	< 0.01 *

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy with photons; NTV, normal tissue volume; PTV, planning target volume.

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

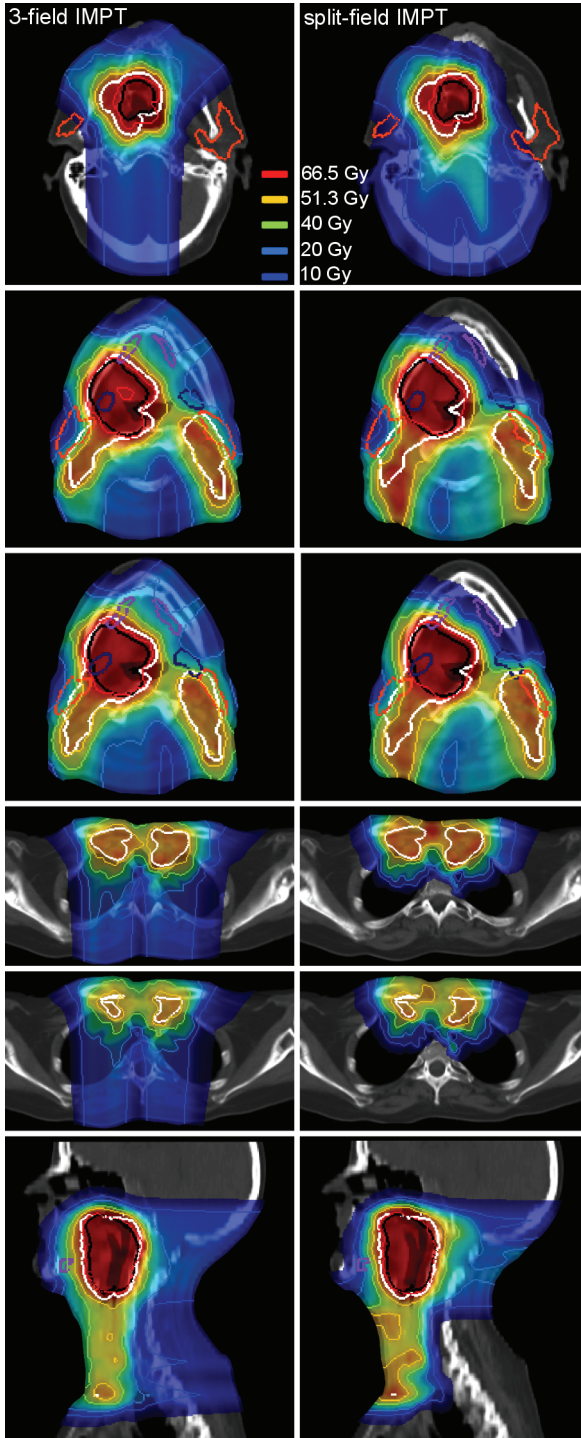


Figure 2. Dose distribution comparison of Case 2 in one sagittal and five transversal planes. Volumes of interest' contours are thickened: elective planning target volume (PTV), PTV1 (white); boost volume, PTV2 (black); parotid glands (orange); submandibular glands (blue); sublingual glands (purple).

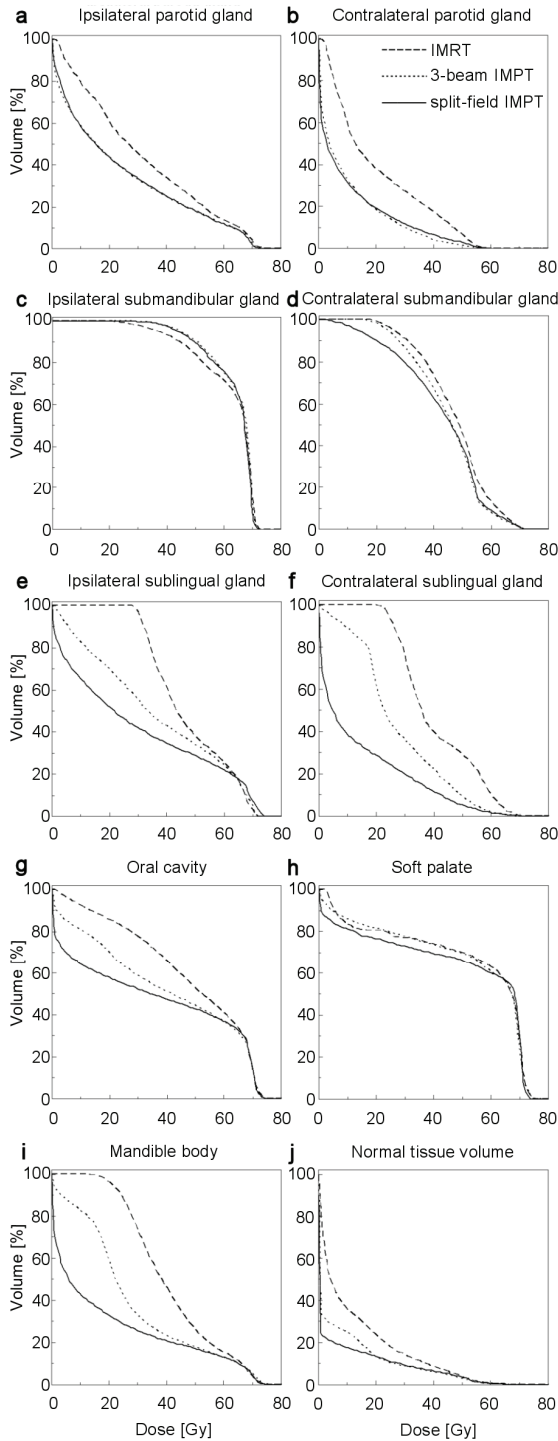


Figure 3. Comparison of the cumulative dose-volume histograms, averaged over all ten cases, of the delineated organs at risk and the normal tissue volume. Results of intensity-modulated radiotherapy with photons (IMRT) are presented as reference. IMPT, intensity-modulated proton therapy.

Normal tissue and OAR-sparing

The dose distributions of all techniques satisfied the acceptance criteria with regard to hotspots and the spinal cord dose. Compared with 3B-IMPT, 6B-SFIMPT substantially reduced the normal tissue volume (NTV), defined as all scanned nontarget tissue, irradiated below 20 Gy (Table 3, Figures 2 and 3j). Although, 3B-IMPT reduced the NTV receiving ≥ 40 Gy compared with 6B-SFIMPT, the absolute differences were small compared with the differences found at low dose values (also see Figure 3j). Figures 2 and 3 clearly display the effect of the split-field set-up on the dose distribution: no dose was administered to the left anterior NTV part, including the mandible body. Additionally, at the level of the shoulders and lungs, 6B-SFIMPT markedly reduced unnecessary normal tissue irradiation. However, cranially, on the posterior side, target conformity was worse with 6B-SFIMPT (shown by less steep dose gradients in Figure 2).

The mean DVHs and mean doses of the parotid glands and ipsilateral submandibular glands did not differ between the two IMPT techniques (Figure 3). However, with 6B-SFIMPT, the mean DVH of the contralateral submandibular gland could be improved compared with 3B-IMPT and IMRT (Figure 3d), which resulted in a lower mean contralateral submandibular gland dose (Figure 4). Although no specific constraints were defined for the sublingual glands, the oral cavity and the mandible body, the mean DVHs and mean doses of these structures were significantly lower with 6B-SFIMPT (Figures 3 and 4).

Except for the ipsilateral submandibular gland, mean IMRT OAR DVHs were always worse compared with IMPT.

In our previous study [181], no significant differences were found for the mean contralateral submandibular gland dose between 3B-IMPT (44.7 Gy, SD: 7.1Gy) and IMRT (47.2 Gy, SD: 8.7 Gy). In contrast, with 6B-SFIMPT, the mean contralateral submandibular gland dose (42.8 Gy, SD: 7.9 Gy) could be reduced significantly compared with IMRT.

Compared with 3B-IMPT, 6B-SFIMPT reduced the volume of the pharyngeal constrictor muscles receiving a medium-to-low dose (ranging from about 10-50 Gy) (Figure 5a). Differences between the two IMPT techniques with regard to the mean

larynx DVH were less clear. Although no dose constraints were defined for these structures, 6B-SFIMPT reduced the mean pharyngeal constrictor muscles dose (mean: 54.3 Gy, range: 41.4– 63.7 Gy) compared with 3B-IMPT (mean: 56.1 Gy, range: 43.7–65.7 Gy) for all ten cases ($p < 0.001$). However, these dose reductions never exceeded the 5 Gy level (Figure 5b).

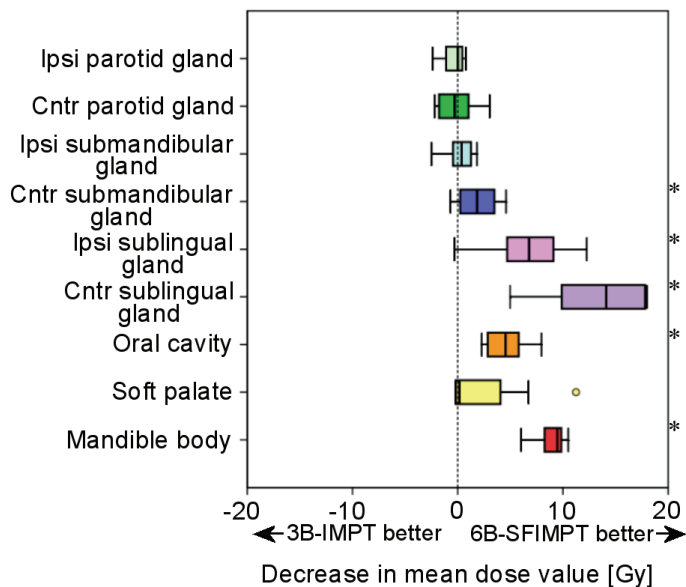
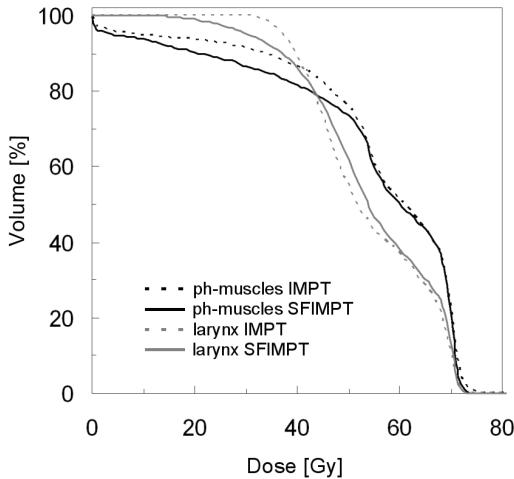


Figure 4. Decrease in mean dose value obtained by application of 6-beam split-field intensity-modulated proton therapy (6B-SFIMPT) as compared with 3-beam IMPT (3B-IMPT). For each OAR, results of all ten cases are presented in a box plot. The considered OARs are: all ipsilateral (Ipsi) and contralateral (Cntr) major salivary glands, the oral cavity, the soft palate and mandible body. The * indicates that the Wilcoxon signed rank test is statistically significant ($p < 0.05$).

Of note is that the reduction in mean dose values obtained with 6B-SFIMPT varied among patients and OARs (Figure 6): while the reduction in the mean contralateral submandibular gland dose varied from -0.7 to 4.6 Gy, the reduction obtained in mean contralateral sublingual gland dose varied from 5.0 to 18.0 Gy.

a Pharyngeal constrictor muscles and larynx dose volume histograms



b Differences in mean dose values for the pharyngeal constrictor muscles and larynx

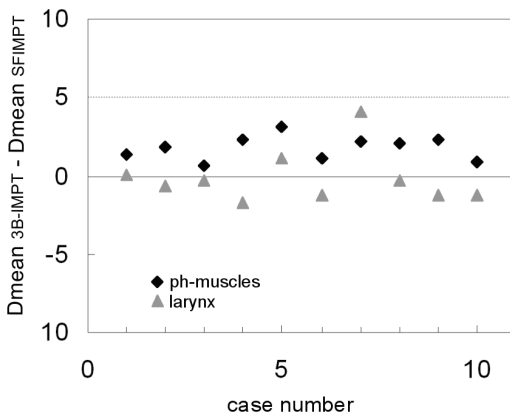


Figure 5. Differences between 3-beam intensity-modulated proton therapy (3B-IMPT) and split-field IMPT (SFIMPT) for the pharyngeal constrictor muscles (ph-muscles) and the larynx mean dose-volume histograms (a) and mean dose (b).

NTCP estimates

On average, no significant differences were found between the NTCP values estimated with the models of Semenenko et al. [164] and Jellema et al. [86] ($p > 0.05$). For parotid salivary flow dysfunction, the average NTCP value was 20.3% (range: 10.2–38.1%) with 6B-SFIMPT compared with 20.0% (range: 10.1–41.4%)

with 3B-IMPT. For patient-rated xerostomia these values were 37.5% (range: 28.7–55.5%) and 38.5% (range: 27.1–56.2%), respectively. Reductions in estimated NTCP values between 3B-IMPT and 6B-SFIMPT varied among patients but were relatively low. In none of the cases, the estimated NTCP value reduction was $\geq 5\%$. With IMRT, the average NTCP value for parotid salivary flow was 36.7% (range: 21.3–58.0%) and for patient-rated xerostomia 48.4% (31.8–62.4%) [181]. Hence, 3B-IMPT and 6B-SFIMPT significantly reduced these NTCP values compared with IMRT.

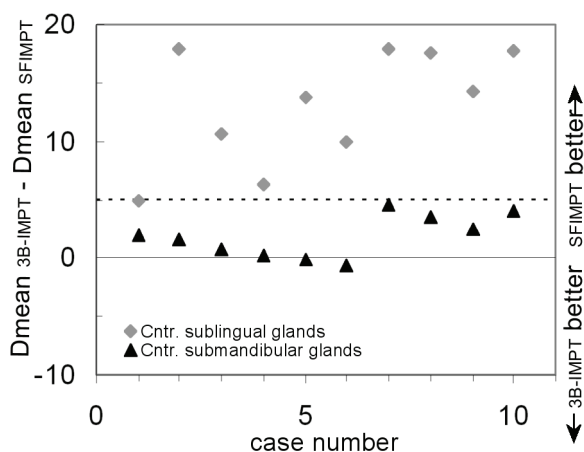


Figure 6. Differences in mean dose (Dmean) for the contralateral submandibular and contralateral sublingual glands between split-field intensity-modulated proton therapy (SFIMPT) and 3-beam IMPT (3B-IMPT) for all ten cases.

Significant differences were found for the NTCP values estimated with the model of Murdoch-Kinch et al. [128] for submandibular salivary flow dysfunction. For the contralateral submandibular salivary flow dysfunction, the average NTCP value significantly reduced from 79% (range: 53–96%) with 3B-IMPT to 74% (range: 41–95%) with 6B-SFIMPT ($p < 0.05$). More specifically, in 40% of the patients reductions in estimated NTCP were $\geq 5\%$. In two cases, reductions were 16 and 17% (which for patient-rated xerostomia corresponded to NTCP value reductions of 2.8 and 2.6%, respectively). However, estimated NTCP values for the ipsilateral submandibular gland did not differ significantly between 3B-IMPT

(average NTCP: 99%, range: 91–100%) and 6B-SFIMPT (average NTCP: 99%, range: 93–100%). Differences between IMRT and 3B-IMPT or 6B-SFIMPT were not significant. The IMRT [181] NTCP values were 83% (range: 53–100%) for the contralateral gland and 97% (range: 84–100%) for the ipsilateral gland. Nevertheless, when comparing IMRT with IMPT, in specific cases the contralateral submandibular gland NTCP values reduced substantially. More specifically, compared with IMRT, 6B-SFIMPT reduced this NTCP on average by 9% (range: -10–46%), while 3B-IMPT reduced this NTCP on average by 4% (range: -10–30%).

Discussion

In the present study, we showed that 6B-SFIMPT significantly reduced the mean dose to the contralateral submandibular gland, the oral cavity, the sublingual glands and the mandible body, and improved the avoidance of density heterogeneities. The ipsilateral submandibular gland dose and the parotid gland doses were not reduced. Based on the NTCP model results, the obtained dose reductions are not expected to result in clinically relevant benefits with regard to parotid gland salivary flow dysfunction or patient-rated xerostomia, though the probability of contralateral submandibular salivary flow dysfunction is expected to be reduced with 6B-SFIMPT.

Due to the beam arrangements chosen, 6B-SFIMPT significantly reduced the NTV receiving less than 20 Gy, while small differences were observed for the NTV receiving higher doses. In addition, although the oral cavity, the sublingual glands and mandible body overlapped with the PTVs in 100%, 40% and 100% of the cases, respectively, and although no dose constraints were applied to these structures, 6B-SFIMPT significantly reduced the doses to these OARs (also compared with IMRT). However, the clinical relevance of reducing the dose to the oral cavity and sublingual glands is less clear. In one paper, the mean oral cavity dose was significantly associated with patient-rated xerostomia [53], but not in another paper [86]. No data is currently available on the association between the sublingual gland dose and patient-rated or physician-rated xerostomia. However, these glands

produce about 7-8% of the total salivary flow [43] and they secrete similar amounts of mucins per time fraction as the submandibular glands [184]. Therefore, it is not unlikely that the dose to these salivary glands is clinically relevant. The clinical meaning of reducing the dose to the mandible will differ among patients and might help to reduce the probability of osteoradionecrosis [89,108] in individual cases. However, it should be stressed that sparing these structures was not the aim of this study.

6B-SFMPT, despite using mainly anterior beams to irradiate the inferior part of the target volume, did not increase the dose to the larynx and pharyngeal constrictor muscles. Sparing of these structures was not the aim of the current study but may be relevant in reducing the risk of radiation-induced swallowing dysfunction [53,109].

It should also be noted that the benefit of 6B-SFIMPT over 3B-IMPT in terms of OAR dose reductions varied among individual patients. In general, 6B-SFIMPT significantly reduced the contralateral submandibular dose (reductions ranged from -0.7 to 4.6 Gy). However, only minor differences were observed with regard to the mean dose to both parotid glands (ranging from -2.2 to 1.5 Gy) and the mean dose to the ipsilateral submandibular glands (ranging from -2.5 to 1.8 Gy).

Murdoch-Kinch et al. [128] showed a significant dose-effect relationship between the mean dose to the contralateral submandibular gland and submandibular salivary flow. However, using the predictive model of Jellema et al., the reductions in contralateral submandibular gland dose are not expected to substantially reduce the risk for patient-rated moderate to severe xerostomia [86]. In particular, while in one specific case a NTCP reduction of 17% was achieved using the model for salivary flow, the corresponding reduction obtained assuming the model for patient-rated xerostomia was only 2.6%. Of note is that the NTCP model of Jellema et al. used the mean dose to both submandibular and both parotid glands as input parameters. In our study, the significant dose reduction obtained in the contralateral submandibular gland did not result in a significant reduction of the mean dose to both glands. On the other hand, for the parotid glands it is suggested that the gland's function should be modelled per individual

gland as they function independently. Moreover, sparing only one of the two glands resulted in a relatively high salivary flow rate after radiotherapy [44]. Such independent responses also occurred for the submandibular glands [128].

In the current study, we tried to translate the benefit in terms of dose reduction into estimated clinical benefits using existing NTCP models [86,128,164]. However, these translations should be interpreted with some caution. First, the NTCP model for patient-rated xerostomia was based on 3D-conformal radiotherapy with photons. It remains unclear as to whether these NTCP models can be extrapolated to patients treated with protons, as spatial dose distributions obtained with protons differ widely from those obtained with photons. As shown by Dijkema et al. [46], single dose parameter-based NTCP models differ for 3D-CRT and IMRT-irradiated parotid glands at ≤ 6 months after radiotherapy.

To our knowledge, 6B-SFIMPT, as presented in the current study, has not been used in earlier planning comparative studies. Other studies that compared photon IMRT with IMPT used beams passing superiorly through the oral cavity [172,192] and inferiorly through the lung [172], the regions in which anatomic variation are most likely to occur. These studies found similar results as presented in a recently performed study [181] that used the same 3B-IMPT technique as used in the current study. Compared with IMRT, IMPT allowed for similar (or improved [172]) target coverage results, while OAR-sparing (including the parotid glands) was significantly improved, resulting in lower NTCP values [181,192]. Despite the fact that patient-rated xerostomia depends on the submandibular gland dose as well, these studies [172,192] did not consider submandibular gland sparing. In contrast to our earlier results with 3B-IMPT [181], the 6B-SFIMPT technique as used in the current study allowed for a further reduction of the contralateral submandibular gland dose.

Due to the relatively wide proton pencil beam currently used (initially $\sigma=3.5$ mm in air and further degraded by the range shifter plates, the air gap, and the patient), the parallelism of the proton beams, the relative large overlapping field area (including at least 4 spots), and the accurate table translations achieved at PSI (positioning precision better than 0.1 mm [140]), the administered dose in the

overlapping field area is expected to be smooth. However, this should be validated in a subsequent study.

Despite the discussed advantages of 6B-SIMPT, we recognize that in this set-up Bragg peaks could still be placed at the border of target tissue and a distal/proximal air gap (we did not avoid the presence of air gaps in general). However, this will occur to a lesser extent in 6B-SFIMPT compared with 3B-IMPT. To determine whether 6B-SFIMPT yields more robust plans than 3B-IMPT, robustness analyses should be performed. However, these kinds of analyses were beyond the scope of the current study.

Nevertheless, we believe the 6B-SFIMPT technique would be more robust as the beams avoided irradiation of the lung and shoulders and reduced excessive normal tissue irradiation inferiorly (Figure 2). In addition, the 6B-SFIMPT beams have to pass through air cavities to a lesser extent compared with those of 3B-IMPT. Air cavities in the head and neck region may vary resulting from tumour regression, tongue movements and mucosal swelling due to radiation. To investigate the importance of these changes on the dose distributions, an additional study with repeated CT scans is required. This will be the subject of a subsequent study at our department.

Conclusion

Six-beam split-field IMPT significantly reduced the mean dose to the contralateral submandibular gland, the oral cavity, the sublingual glands and the mandible but did not improve dose distribution to the ipsilateral submandibular gland and the parotid glands. The clinical relevance of these differences remains to be determined. From a theoretical point of view, the main advantage is a better salivary flow function of the contralateral submandibular gland and the avoidance of air cavities which may contribute to improved robustness of proton therapy in head and neck cancer.