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

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Chapter 4

Potential benefits of scanned intensity-modulated proton therapy versus advanced photon therapy with regard to sparing of the salivary glands in oropharyngeal cancer

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Abstract

Purpose: To test the hypothesis that scanned intensity-modulated proton therapy (IMPT) results in a significant dose reduction to the parotid and submandibular glands as compared with intensity-modulated radiotherapy with photons (IMRT), and 3-dimensional conformal radiotherapy (3D-CRT) for oropharyngeal cancer. In addition, we investigated if the achieved dose reductions would theoretically translate into a reduction of salivary dysfunction and xerostomia.

Materials and Methods: Ten patients with N0 oropharyngeal carcinoma were used. The intensity-modulated plans delivered simultaneously 70 Gy to the boost planning target volume (PTV2) and 54 Gy to the elective nodal areas (PTV1). The 3D-CRT technique, delivered sequentially 70 Gy and 46 Gy to PTV2 and PTV1, respectively. Normal tissue complication probabilities (NTCP) were calculated for salivary dysfunction and xerostomia.

Result: Planning target volume coverage results were similar for IMPT and IMRT. IMPT clearly improved the conformity. The 3D-CRT results were inferior to these results. The mean dose to the parotid glands by 3D-CRT (50.8 Gy), IMRT (25.5 Gy) and IMPT (16.8 Gy) differed significantly. For the submandibular glands no significant differences between IMRT and IMPT were found. The dose reductions obtained with IMPT theoretically translated into a significant NTCP reduction.

Conclusion: Compared with IMRT and 3D-CRT, IMPT improved sparing of the organs at risk, while keeping similar target coverage results. The dose reductions obtained with IMPT versus IMRT and 3D-CRT varied widely per individual patient. Intensity-modulated proton therapy theoretically translated into a clinical benefit for most of the cases, but this requires clinical validation.

Introduction

The objective of radiotherapy is to administer a sufficient radiation dose to the planning target volume (PTV), while sparing the normal surrounding tissues as much as possible. In particular in head and neck cancer (HNC), PTVs are generally large and complex, and surrounded by many critical structures. Hence, the dose that can be administered to the PTV is limited and generally results in considerable and clinically relevant acute and late side effects. The introduction of advanced photon radiation techniques, such as 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) enable better conformation of the radiation dose to the PTV and/or better sparing of critical structures [119,186].

In the case of HNC, radiation oncologists have mainly focused on prevention of radiation-induced xerostomia, as this is the most frequently reported side effect significantly affecting quality of life [87]. Many studies indicated that with IMRT, as compared with conventional techniques, the parotid gland dose can be reduced significantly resulting in higher salivary flow rates post-treatment and/or lower rates of xerostomia [95,186]. However, sufficient sparing of the parotid glands with IMRT below the threshold dose cannot be achieved in all patients. Moreover, sparing of the parotid glands alone does not always translate into a reduced probability of patient-rated xerostomia [95]. Therefore, further dose reduction to all relevant salivary glands, e.g., by using emerging radiation techniques such as protons, may be warranted.

Proton irradiation has important advantages compared with the currently used photon irradiation. Protons offer the greatest conformal delivery of radiation energy, because of their unique energy absorption profile. Proton beams are typically manipulated to generate a spread-out Bragg peak to yield a flat dose profile across the PTV, followed by a rapid fall to nearly zero dose. The Bragg peak is extremely useful when complex PTVs close to critical structures have to be irradiated, as frequently encountered in HNC. Currently, scanned intensity-modulated proton therapy (IMPT) is the most advanced proton technique available [112,140], and therefore most promising in HNC.

The aim of this planning comparative study was to test the hypothesis that scanned IMPT significantly reduces the dose to the parotid and submandibular glands as compared with IMRT, and 3D-CRT among patients with oropharyngeal carcinoma. In addition, we investigated if, and to what extent, dose reductions achieved with IMPT would theoretically translate into a reduction of salivary dysfunction and xerostomia by using existing normal tissue complication probability (NTCP) models.

Materials and Methods

Patients and computed tomography

The study included 10 patients with clinically N0 oropharyngeal squamous cell carcinoma with various T-stages (T2-T4N0). Planning computed tomography (CT)-scans were made with the patient in supine position. Slice separations were 4 or 5 mm. Target volume and organ at risk (OAR) delineation and photon radiation treatment planning were carried out at the department of Radiation Oncology of the UMCG. Proton treatment planning was performed at the Centre for Proton Therapy at the Paul Scherrer Institute (PSI) in Villigen, Switzerland.

Target volumes and OARs

An experienced radiation oncologist (H.B.) delineated the gross tumour volume (GTV) on the planning-CT scan. The GTV included the primary tumour as visible on the planning-CT scan. A clinical target volume (CTV), CTV1, was generated by adding a 3D-margin of 10 mm around the GTV and by extending this CTV with the elective nodal areas on both side of the neck (levels II-IV). These neck node levels were delineated according to consensus guidelines [73]. In addition, a CTV2 was generated by adding a 3D-margin of 5 mm around the GTV. The CTVs were adjusted based on anatomical boundaries such as air cavities. The corresponding planning target volumes PTV1 and PTV2 were created by adding a 3D-margin of 5 mm around CTV1 and CTV2, respectively. 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).

The following OARs were delineated: 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 [180].

For optimization of all treatment techniques used in this study, the same delineated volumes were used.

Treatment planning techniques

3D-CRT. The three-dimensional conformal radiotherapy plans were generated using the Pinnacle^3 treatment planning system (TPS) (version 8.0 h, Philips Radiation Oncology Systems, Fitchburg, WI, USA). All beams were 6 MV photon beams, assuming an Elekta SLi 15 linear accelerator equipped with a multi-leaf collimator consisting of 40 leave pairs of 10 mm thickness. The prescribed total dose to PTV1 and PTV2 was 46 Gy and 70 Gy, respectively, using a sequential boost and 35 fractions of 2 Gy. Two opposing lateral fields covered the cranial part of PTV1, and two opposing anterior-posterior fields covered the lower neck and supraclavicular region. If possible, central blocking was used to spare the larynx, oesophagus and spinal cord. PTV2 was irradiated using 2 opposed lateral fields with an oblique orientation to avoid the spinal cord. In some cases small beams were added to improve the radiation dose homogeneity in the target volume. Wedges were applied if necessary. All fields were shaped to cover the PTV and weighted manually such that the 3D-CRT plan satisfied the dose prescriptions as well as possible. Heterogeneity-corrected dose calculations were based on a collapsed cone algorithm (dose grid resolution: 4×4×4 mm^3).

IMRT. The prescribed total dose to PTV1 and PTV2 was 54 Gy and 70 Gy, using 1.54 Gy and 2 Gy per fraction in 35 fractions, respectively, using a simultaneous integrated boost (SIB). The total dose of 54 Gy instead of 46 Gy was chosen to

compensate for the lower fraction dose and the longer overall treatment time. This fractionation schedule is the current practice at our institution.
The plans consisted of 7 coplanar 6MV photon beams (gantry angles: 0°, 50°, 100°, 150°, 210°, 260° and 310°) delivered in a step and shoot mode by the same linear accelerator and the same TPS as used for the 3D-CRT plans. Direct machine parameter optimization (DMPO) was applied for each beam. The maximum number of segments per beam was set to 84 and the dose grid resolution to 4×4×4 mm^3.

IMPT. Intensity-modulated proton therapy planning used the same dose prescription as IMRT planning (using a relative biological effectiveness of 1.1 for protons) and was performed on a TPS developed at PSI for scanned proton therapy [140]. The plans consisted of three fields with gantry angles of 180° (couch angle: 0° or ±10°), -50° to -60° (couch angle: 0°) and 50 to 60° (couch angle: 0°). Couch angles were applied for the 180° beam to avoid grazing the skull base. Initial beam energies varied from 138-177 MeV for each field. Beam ranges were varied in the patient by automated insertion of multiple (4.6 mm water equivalent) range shifter plates into the beam [140]. For dose calculations a proton pencil beam model was used [159] that included heterogeneity corrections [143,158], and allowed 3D-optimization of inhomogeneous (intensity-modulated) proton fields [112]. The dose grid resolution was 5×5×5 mm^3 or 5×5×4 mm^3 (depending on the CT-slice separation). For each initial beam energy, a Gaussian cross section of the proton pencil beam was assumed with a σ of 3.5 mm in air ($\sigma_x = \sigma_y$, full-width-at-half-maximum of ~8 mm), without insertion of range shifter plates (similar to the σ clinically achieved at PSI [116]). Individual Bragg peaks were distributed over a regular grid covering the target volume. Only the Bragg peaks inside the target volume or within 5 mm distance from the target surface were taken into account for the optimization. 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) into account.

Plan optimization

Table 1 specifies the dose acceptance criteria/dose prescriptions for the 3D-CRT, IMRT and IMPT plans. For all treatment techniques, similar target dose prescriptions were used. Furthermore, hotspots (dose >107% to >15 mm^3 or >2% of the volume (taking into account small OARs) of the prescribed PTV2 dose outside the target) were not allowed. For the 3D-CRT technique, only the spinal cord dose was limited (Table 1). The planning objectives for the IMRT and IMPT techniques 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 (Table 1) 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), without deteriorating satisfactory target coverage.

Table 1. Dose prescriptions and acceptance criteria per technique.

Volume of interest	3D-CRT	IMRT	IMPT
PTV	≥ 98% of volume ≥ 95% of dose	≥ 98% of volume ≥ 95% of dose	≥ 98% of volume ≥ 95% of dose
	≤ 2% of volume > 107 % of PTV2 dose	≤ 2% of volume > 107 % of PTV2 dose	≤ 2% of volume > 107 % of PTV2 dose
Spinal cord	≤2% of volume ≥ 50 Gy	≤2% of volume ≥ 54 Gy	≤2% of volume ≥ 54 Gy
Mean dose parotid glands		Minimized	Minimized
Mean dose submandibular glands		Minimized	Minimized
NTV	No hotspots	No hotspots	No hotspots

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy; IMRT = Intensity-modulated radiotherapy with photons; IMPT= intensity-modulated proton therapy; NTV = normal tissue volume.

To avoid conflicting objectives, the DVO to the parotid gland was only applied to the part of the gland outside the PTVs; 3. Finally, in a similar way, the mean dose to the submandibular glands was reduced as much as possible by adding extra DVOs to the submandibular gland part outside the PTVs. 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. For the optimization of the IMRT plans, additional structures were used to limit the dose outside the target volumes (i.e. a ring-like structure at a distance of 5-10 mm from the PTV surface; and a volume including the nontarget tissue outside the previously defined ring structure).

NTCP models

To estimate the clinical relevance of differences in dose distributions among the three radiation techniques, we used two existing NTCP models. The first model predicts the probability of a reduction in salivary flow to <25% of the baseline level 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.

Evaluation tools

Dose distributions obtained with the three planning techniques were evaluated by using dose-volume histograms (DVHs) and by checking the presence of hotspots in the 3D-dose distributions. Plans were compared by using the parameters as specified in Table 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.

Observed differences between the three techniques were tested for statistical significance ($p < 0.05$) using the sign test, for paired data. All tests were two-tailed.

Results

Target volume coverage

The 3D-CRT plans for some individual patients were clearly inferior to the plans of the other two modalities: 50% and 10% of the cases did not satisfy the acceptance criteria for PTV1 and PTV 2 coverage, respectively (Table 2). However, these results were considered acceptable for actual treatment, as satisfying the acceptance criteria with regard to the PTVs would have resulted in unacceptable spinal cord doses (Table 1).

The IMRT and IMPT dose distributions did satisfy the PTV coverage acceptance criteria in all cases (Table 2). IMPT clearly improved the conformity, whereas the target inhomogeneity was similar (Table 2).

Table 2. Planning target volume coverage.

Target coverage	Mean volume (SD)		
	3D-CRT	IMRT	IMPT
% PTV1 receiving ≥ 95% prescribed dose	97.8 (1.6)	99.0 (0.5)	98.1 (0.3)
% PTV2 receiving ≥ 95% prescribed dose	98.5 (2.3)	98.3 (0.3)	98.4 (0.4)
Conformity Index	2.61 (0.19)	1.63 (0.13)	1.40 (0.06)
Inhomogeneity index PTV1	0.49 (0.04)	0.27 (0.02)	0.26 (0.02)
Inhomogeneity index PTV2	0.06 (0.01)	0.08 (0.01)	0.07 (0.01)

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy; IMRT = Intensity-modulated radiotherapy with photons; IMPT= intensity-modulated proton therapy; PTV, planning target volume; SD, standard deviation.

Normal tissue and OAR-sparing

The dose distributions of all three modalities satisfied the acceptance criteria with regard to hotspots and the spinal cord dose. Reduction of ≥ 95% of the prescribed dose to PTV1 to the normal tissue volume (NTV), defined here as all non-target tissue, was most effective with IMPT (Table 3). IMPT significantly reduced the low dose NTV as compared with IMRT and 3D-CRT. An example is shown in Figure 1.

The mean parotid and submandibular gland DVHs obtained with 3D-CRT were considerably worse compared with those obtained with IMRT and IMPT (Figure 2). In addition, the mean parotid gland DVHs obtained with IMPT were better than those obtained with IMRT (Figure 2a and 2b). Similar results were obtained for the sublingual glands and the oral cavity. However, the ispilateral sublingual gland DVH obtained with 3D-CRT was better than those obtained with IMRT and IMPT (Figure 2e). For the other OARs, the differences between the three techniques were less clear.

Table 3. Irradiated normal tissue volume.

	Mean volume (SD) [%]			Statistical significance *p*		
Normal tissue volume	**3D-CRT**	**IMRT**	**IMPT**	**3D-CRT vs. IMRT**	**3D-CRT vs.IMPT**	**IMRT vs. IMPT**
NTV receiving ≥ 95% PTV1 dose	8.7 (3.0)	3.3 (1.4)	2.5 (0.7)	< 0.01 *	< 0.01 *	0.021 *
NTV receiving > 107% of PTV2 dose (hotspots)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0	1.0	1.0
NTV receiving ≥ 40 Gy	12.5 (3.5)	8.7 (2.5)	6.0 (1.4)	< 0.01 *	< 0.01 *	< 0.01 *
NTV receiving ≥ 20 Gy	23.8 (5.2)	23.6 (4.7)	13.5 (2.8)	1.0	< 0.01 *	< 0.01 *

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy; IMRT = Intensity-modulated radiotherapy with photons; IMPT= intensity-modulated proton therapy; NTV = normal tissue volume; SD, standard deviation.

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

The mean parotid and submandibular gland doses reduced significantly ($p<0.01$) with IMRT compared with 3D-CRT (Figure 3). However, the mean ipsilateral sublingual gland dose was significantly lower with 3D-CRT as compared with IMRT. For the other OARs, no significant differences were found between 3D-CRT and IMRT.

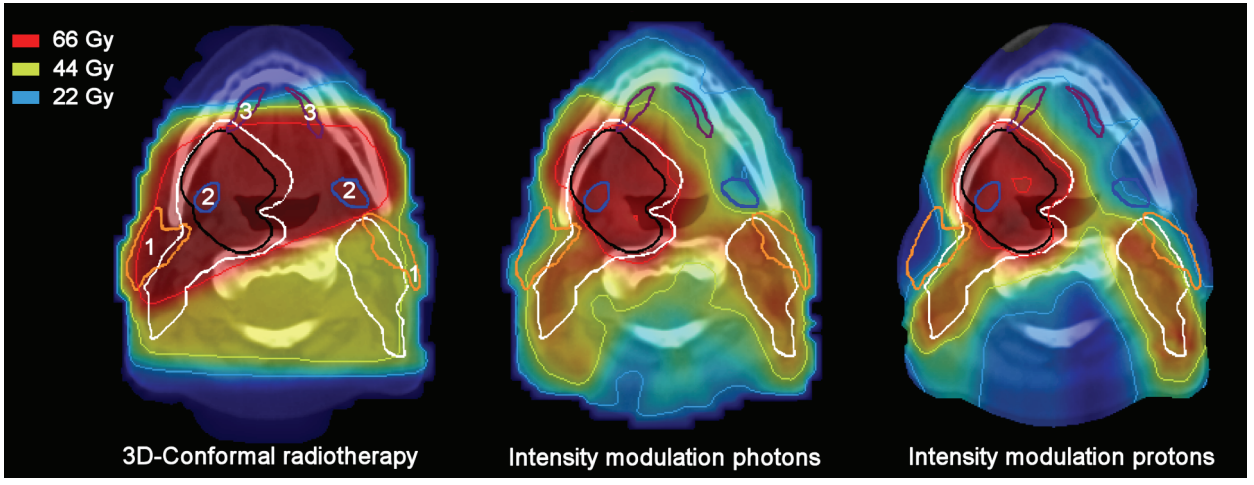

Figure 1. Dose distribution comparison example of case 2. The contours of the volumes of interest are thickened: elective target volume PTV1 (white contour); boost volume PTV2 (black contour); (1) parotid glands; (2) submandibular glands; (3) sublingual glands.

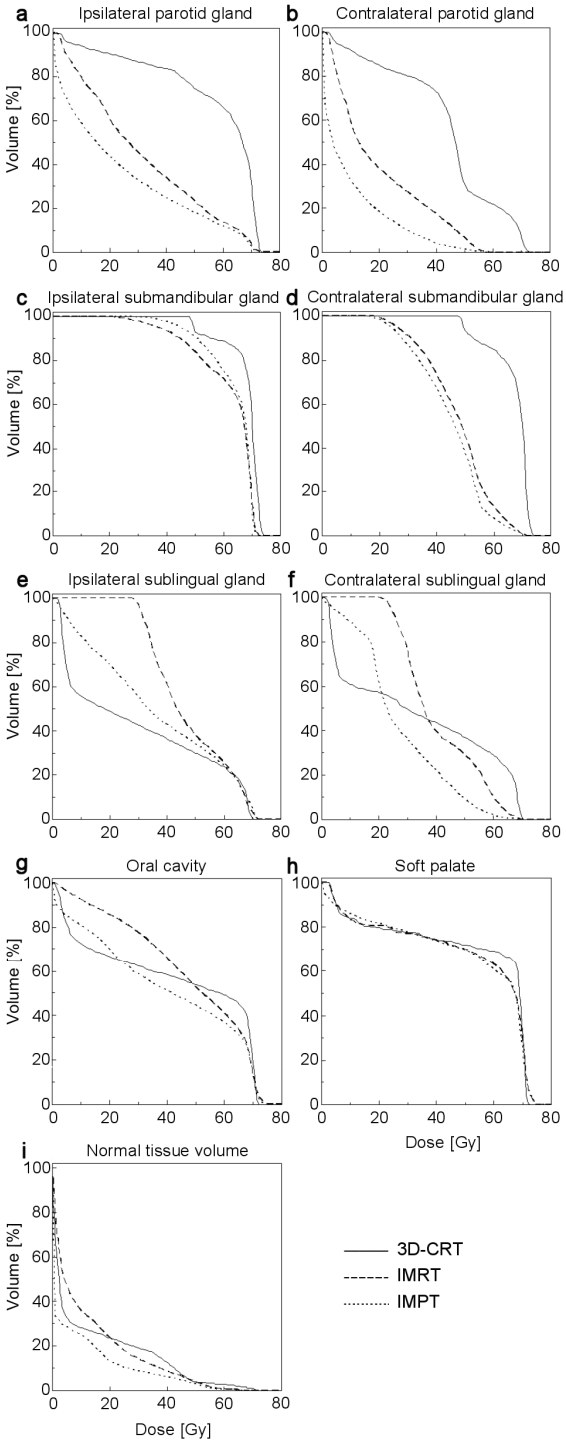

Figure 2. Cumulative dose-volume histograms, averaged over all ten cases, of the delineated organs at risk and the normal tissue volume for all treatment planning techniques. 3D-CRT, three–dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy with photons; IMPT, intensity-modulated proton therapy.

IMPT further reduced the mean dose to both the ipsilateral and contralateral parotid glands (Figure 3). However, no significant differences between IMRT and IMPT were found for the mean submandibular gland doses. Although no specific constraints were defined for the sublingual glands and the oral cavity, the mean dose values to these structures were significantly lower with IMPT.

An important finding was that the reduction in mean dose values obtained with IMPT versus IMRT varied widely among patients (Figure 4).

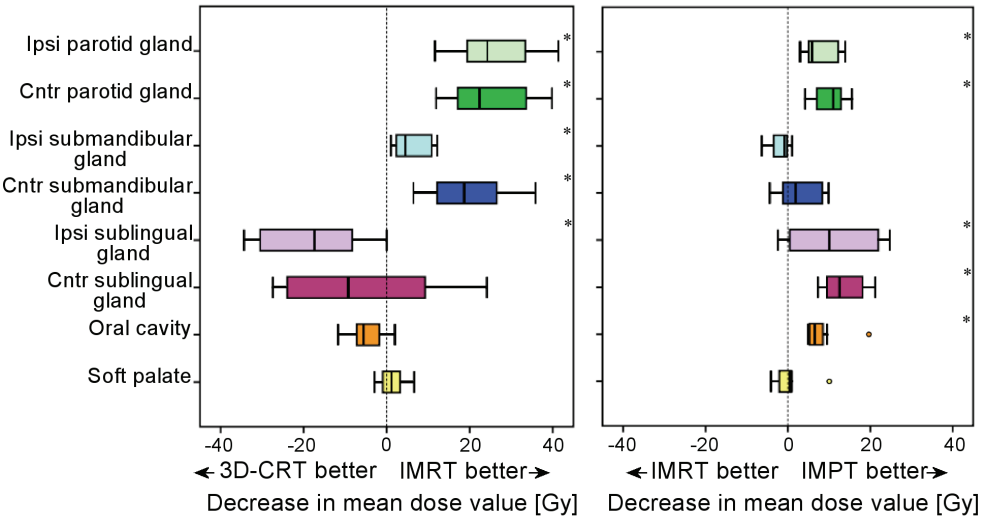

Figure 3. Decrease in mean dose value obtained by application of intensity-modulated radiotherapy with photons (IMRT) as compared with three-dimensional conformal radiotherapy (3D-CRT) (left) and intensity-modulated proton therapy (IMPT) as compared with IMRT (right). Per specific volume of interest, 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 and the soft palate structure. The asterisk, *, indicates significant differences.

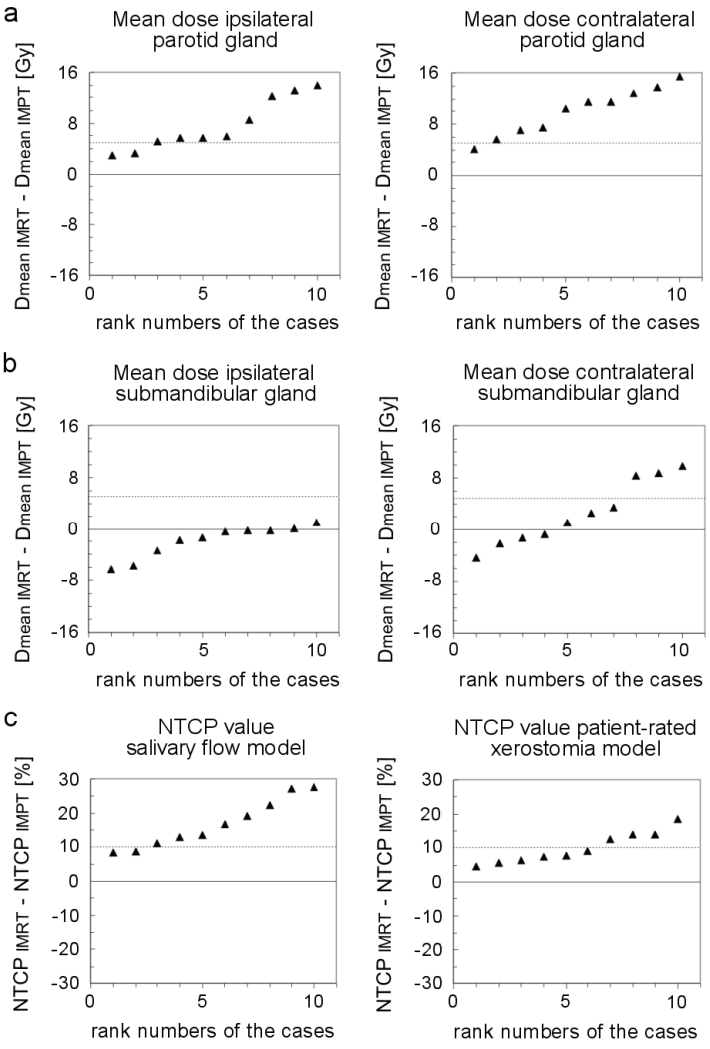

Figure 4. Reduction in mean dose (Dmean) value for the parotid glands (a), the submandibular glands (b), and the reduction in normal tissue complication probability (NTCP) value (c), obtained by application of intensity-modulated proton therapy (IMPT) as compared with intensity-modulated radiotherapy with photons (IMRT) for all ten cases. The ten cases are ranked such that the values are arranged from low to high values.

NTCP estimates

IMRT reduced the NTCP significantly, for salivary flow dysfunction as well as for patient-rated xerostomia compared with 3D-CRT ($p < 0.01$) (Figure 5). IMPT

significantly reduced the NTCP even more. As compared with IMRT, IMPT decreased the NTCP on average by 16.8% and 9.9% for salivary flow dysfunction and patient-rated xerostomia, respectively ($p < 0.01$). The estimated reduction in NTCP varied widely among patients (Figure 4c). When applying a threshold of 10% NTCP reduction, 80% and 40% of the patients in this cohort would benefit from IMPT with regard to salivary flow dysfunction and patient-rated xerostomia, respectively.

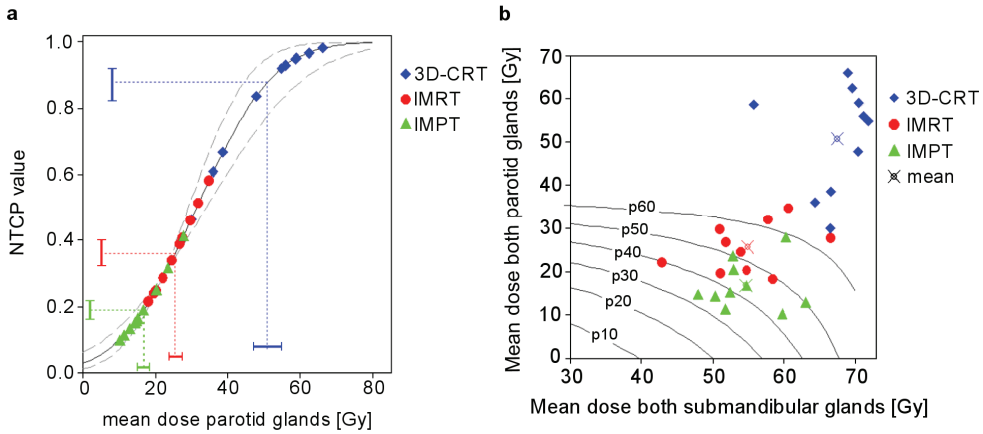

Figure 5. (a): Normal tissue complication probability (NTCP) model for parotid salivary flow (solid curve) with corresponding 95% C.I. interval (dashed curve). The NTCP value denotes the probability of a reduction in salivary flow to <25% of the pre-treatment flow at ≤6 months after RT. The mean parotid gland dose averaged over all ten cases (dotted vertical line) ± 1 standard error of the mean is displayed per technique with corresponding NTCP value ranges. (b) NTCP model for patient-rated xerostomia (solid lines). p10 denotes the 10%-probability of moderate or severe xerostomia at 6 months after radiotherapy. The mean gland dose values per case are plotted. The mean dose value averaged over all ten cases is also displayed (mean). 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy with photons; IMPT, intensity-modulated proton therapy.

Discussion

The present study showed that, on average, scanned IMPT results in a significant reduction of the parotid gland dose as compared with IMRT and 3D-CRT, while maintaining similar PTV coverage. Therefore, IMPT theoretically leads

to clinical benefits with regard to salivary dysfunction and xerostomia. As compared with 3D-CRT, IMPT significantly reduced the submandibular gland dose. However, no significant results were obtained for the submandibular glands, when IMPT was compared with IMRT.

Taking these results into consideration, there are three important issues that should be pointed out. First, in this study, spinal cord sparing had the highest priority, as in clinical practice we would not accept a spinal cord dose that exceeds the set constraint. In some patients the spinal cord was near the concave-shaped target. Hence, very steep dose gradients were required to preserve good target coverage, while satisfying the spinal cord constraint. The 3D-CRT technique did not always satisfy both the target and spinal cord constraints, and therefore was clearly inferior to the intensity-modulated techniques. Second, the benefit from IMPT over IMRT in terms of dose distribution varied widely among individual patients, ranging from 3 Gy to 16 Gy in the mean parotid dose and from -6 Gy to 10 Gy in the mean submandibular dose. Third, the same difference in mean dose to the parotid and submandibular glands will not always result in similar NTCP reductions. This will highly depend on the baseline value obtained with the reference technique and the shape of the NTCP curve. In addition, it should be emphasized that the 10% threshold was chosen on a purely arbitrary basis. These results illustrate that reporting only population-based mean differences in dose distributions between two radiation delivery techniques will not be sufficient to explore the full potential or possible disadvantages of emerging radiation techniques. Recently, Goitein stated that the dose distributions achieved with protons are in almost all cases superior to those possible with x-rays [70] and that with very few exceptions, there is little clinical reason to argue against the use of protons for almost any patient or disease site [68]. However, our results showed that these statements require some differentiation. It is probably true that for each disease site there will be a certain percentage of patients that will benefit from protons over photons, but the degree of this benefit in terms of reduction in the probability of side effects will vary among individual patients. The currently available data do not allow for a clear distinction (e.g., based on tumour characteristics) between patients that will

significantly benefit from protons and those who will not. Therefore, the most adequate methodology to select the proper patients for proton radiotherapy will probably be to compare different techniques by planning comparative evaluations for each individual patient.

From a theoretical point of view the use of NTCP models seems sound. However, the results should be interpreted with some caution. The model of Semenenko et al. [164] was based on a combined analysis of multi-institutional toxicity data. The model of Jellema et al. [86] was based on single institutional data. The patients included in all these studies were treated with either 3D-CRT or IMRT. It is hard to justify the use of any of the many published parameter estimates for different NTCP models obtained at individual institutions, for the purposes of biologically based treatment planning. In addition, as the spatial dose distributions obtained with protons differ from photons due to the differences in beam characteristics, the question arises as to whether NTCP models obtained with photon radiotherapy populations can be extrapolated to patients treated with protons. Recently, Dijkema at al. [46] illustrated that NTCP curves based on single parameters may differ for different photon-radiation delivery techniques. NTCP models should be validated in properly designed clinical studies. This is now subject to investigation in the currently ongoing ALLEGRO-project.

The results of the present study were only based on *in silico* comparisons of radiotherapy treatment planning. It is currently not completely clear whether these results will be realized when patients are actually treated using IMRT or IMPT. In clinical practice, set up errors may cause degradation of the dose distributions obtained with all techniques, but IMPT is generally more sensitive to heterogeneity changes (due to anatomic changes or geometric changes of the patient) as compared with photon irradiation. However, robustness analyses for IMRT and IMPT plans were beyond the scope of this study. The sensitivity of IMPT to treatment uncertainties is discussed in other papers [113,114]. Overall, the clinical introduction of IMPT should be accompanied by high quality image guidance during treatment, well-defined set-up correction protocols and adaptation of

treatment planning when necessary. In addition, it is of major importance that the estimated clinical benefit will be validated in well-designed clinical trials.

A number of other planning studies reported that with protons, the parotid gland dose could be reduced as compared with IMRT [40,92,170,192]. Notably, Widesott et al. [192] compared helical tomotherapy with IMPT among patients with nasopharyngeal carcinoma. They found similar results as found in the current study, with excellent PTV coverage and dose homogeneity within the PTVs, while IMPT allowed for better sparing of most OARs at medium-to-low doses, including the parotid glands and the mucosal areas, resulting in lower NTCP values. However, the results of some other studies should be interpreted with caution. In two of these studies [40,170], only the low dose PTVs (total dose: 54 Gy) were taken into account. This dose level should be considered insufficient for curatively intended radiation of squamous cell HNC. In addition, in some studies, no DVOs were applied to the parotid glands for either of the techniques [40,92] and therefore, the true additional value of IMPT over IMRT could not be evaluated with regard to parotid gland sparing. In addition, one study employed a single beam providing a nearly homogeneous dose to the target, instead of IMPT [40,92]. None of the previously mentioned studies considered sparing of the submandibular glands (which is important to reduce radiation-induced xerostomia) or NTCP models, if considered, based on patient-rated xerostomia.

An important finding in the current study was that, on average, the presented IMPT technique could not reduce the dose to the submandibular glands significantly as compared with IMRT. Moreover, in some patients, the mean dose to the ipsilateral submandibular gland was inferior with IMPT as compared with that obtained with IMRT. A number of explanations for this finding could be hypothesized. First, the lateral fall-off (penumbra) was larger for the proton beams than for the photon beams. Compared with the parotid glands, the submandibular glands were substantially smaller and always overlapped relatively more with the PTVs. Therefore, steeper dose gradients than currently used would be necessary to spare the non-target submandibular gland part compared with those necessary to spare the non-target parotid gland part. The disadvantage of the wider penumbra is

apparently larger than the benefit of the rapid fall of the Bragg peak for this particular organ. In this study, a relatively wide proton pencil beam was assumed. The initial σ of 3.5 mm in air was degraded by the range shifter plates, the air gap, and the tissue in the patient itself (all taken into account for dose calculations). In a subsequent study, the benefits of a smaller proton beam size will be analyzed. Second, inhomogeneities along the proton path could be of influence. In the current study, we used 3-field IMPT plans as target homogeneity and OAR-sparing results were similar with 3, 5 and 9-field IMPT [170]. However, the anterior-lateral beams (50-60°) propagate through the oral cavity, and thus possibly are affected by density transitions between bone, air and soft tissue. Such inhomogeneities may result in degradation of the sharp distal edge of the Bragg peak [68,113] leading to degradation of the dose distribution. In another subsequent study the influence of the IMPT beam set up is analyzed in more detail.

Conclusion

Intensity-modulated proton therapy significantly reduces the mean dose to the parotid glands, but not to the submandibular glands. However, these dose reductions vary widely among individual patients. Using existing NTCP models for salivary flow reduction and patient-rated xerostomia, it is expected that IMPT will yield significant clinical benefit for most of the cases. These findings require further clinical validation.