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Planned dose of intensity modulated proton beam therapy versus volumetric modulated arch therapy to tooth-bearing regions

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ABSTRACT

Background: Intensity modulated proton beam therapy (IMPT) for head and neck cancer offers dosimetric benefits for the organs at risk when compared to photon-based volumetric modulated arch therapy (VMAT). However, limited data exists about the potential benefits of IMPT for tooth-bearing regions.
The aim of this study was to compare the IMPT and VMAT radiation dosimetrics of the tooth-bearing regions in head and neck cancer patients. Also, we aimed to identify prognostic factors for a cumulative radiation dose of ≥40 Gy on the tooth-bearing areas, which is considered the threshold dose for prophylactic dental extractions.
Methods: A total of 121 head and neck cancer patients were included in this retrospective analysis of prospectively collected data. We compared the average Dmean values of IMPT versus VMAT of multiple tooth-bearing regions in the same patients. Multivariate logistic regression analysis was performed for receiving a cumulative radiation dose of ≥40 Gy to the tooth-bearing regions (primary endpoint) in both VMAT and IMPT.
Results: A lower Dmean was seen after applying IMPT to the tooth-bearing tumour regions ($p < 0.001$). Regarding VMAT, oral cavity tumours, T3-T4 tumours, molar regions in the mandible, and regions ipsilateral to the tumour were risk factors for receiving a cumulative radiation dose of ≥40 Gy.
Conclusions: IMPT significantly reduces the radiation dose to the tooth-bearing regions.

Introduction

Pre-radiation dental screening of patients with head and neck cancer is carried out early in the diagnostic phase before commencing treatment. The treatment of dental foci has evolved from a strict approach where all the foci are eliminated to a more targeted approach where infectious foci are grouped into low-risk and high-risk areas, according to the localized radiation dose [1,2,3] Generally, when the area of interest is due to receive a cumulative dose of ≥40 Gy, tooth extraction is advised [3] If oral foci receive a cumulative dose of <40 Gy, more conservative treatment options, such as restoration, endodontic treatment and periodontal therapy, can be applied [4]. The goal of dental screening is to reduce the risk of post-radiation dental extractions, thereby reducing the risk of developing osteoradionecrosis (ORN) [3,5]. The incidence of ORN has declined in the last few years, most likely due to advances in radiotherapy techniques [6–11].

The risk of ORN increases with radiation exposures beyond 40 Gy, with a clear increase in risk when the dose delivered to the mandible is >60 Gy [7,8]. However, it is generally assumed that the development of ORN is a multifaceted process which also includes issues like tumour staging and localization, radiation dose and volume, patient-related factors such as tobacco/alcohol use, and post-radiation invasive bone procedures [9]. Multiple studies identified tooth extraction (pre- and post-radiotherapy) and periodontal decay as risk factors for osteoradionecrosis [12–14].

New radiation techniques, such as intensity modulated radiotherapy (IMRT) and volumetric modulated arch therapy (VMAT), offer the possibility to limit the radiation dose on multiple organs at risk (e.g., salivary glands, swallowing muscles, mandibular bone), resulting in a decrease in treatment-associated toxicities such as hyposalivation, xerostomia and dysphagia [15–17]. Tooth-bearing regions can also be considered to be organs at risk which can be helped by, for example, constraining the radiation dose to the anterior mandible in oropharynx tumors [18]. In January 2018, intensity modulated proton therapy

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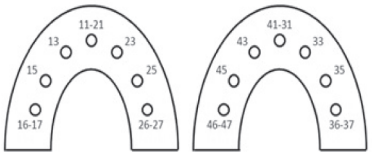
(IMPT) was introduced in our treatment centre as an option for head and neck cancer patients [19]. The superior physical beam properties of protons compared to photons offer the possibility of depositing their energy at a specific depth known as the Bragg peak. Distally from this peak, there is a rapid loss of energy, sparing the tissue behind the tumour without affecting target dose coverage [20–23]. Hence, for patients with oropharyngeal cancer, the use of IMPT results in a further dose reduction to organs at risk, potentially leading to a reduction in treatment-related toxicities [24–26]. However, as to how proton therapy can influence the decision-making processes still has to be determined for dental professionals undertaking pre-radiation dental screening, as the dosimetric differences between VMAT and IMPT for dental structures have not been studied widely. Therefore, the aim of this study was to compare the radiation dosimetrics of IMPT and VMAT on the tooth-bearing regions in head and neck cancer patients. Secondly, we aimed to identify the prognostic factors after applying a cumulative radiation dose of ≥40 Gy to the tooth-bearing areas, which is considered the threshold dose to reduce the risk of prophylactic dental extractions.

Materials and methods

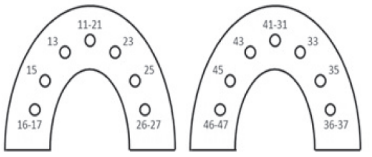
All the patients treated with radiotherapy for a head and neck malignancy between January 2018 and January 2020 were evaluated. At the time of the diagnosis, all the patients underwent the standard pre-radiation dental screening, including a panoramic x-ray and a periodontal pocket status. Intraoral periapical radiographs were made of all the endodontically treated teeth to enable a proper evaluation of the periapical region by an oral and maxillofacial surgeon, a dental hygienist and a maxillofacial prosthodontist. Pre-radiotherapy treatment consisted of extractions or apicoectomies. As the definite type of radiation therapy, i.e., VMAT or IMPT, had not been determined yet at the time of the pre-radiotherapy treatment, the patients receiving IMPT underwent similar preventive measures as the patients treated with VMAT. Patients were deemed eligible for IMPT through model-based selection [19,27,28]. This method utilises multivariable prediction models to determine the risk of radiation-induced side-effects (xerostomia, dysphagia, tube feeding dependence) as a function of radiation dose deliverance to organs at risk (OAR) and other risk factors [20,28]. A VMAT plan and an IMPT plan was composed for each patient (RayStation treatment planning system v6.1 and v8, RaySearch Laboratories AB, Stockholm, Sweden). Subsequently, the difference in dose between the VMAT and IMPT (ΔDose) was translated into an expected difference in the risk of a radiation-induced side effect (ΔNTCP), using the above mentioned prediction models. The patients who were expected to benefit significantly from IMPT in terms of the expected risk profiles, and who met the criteria of the National Indication Protocol for Proton therapy, would then receive IMPT, while the remaining patients were treated with VMAT. The patients received definitive radiation therapy or postoperative radiotherapy, with or without systemic treatment. When indicated, chemotherapy was given concurrently with the radiotherapy, consisting of cisplatin, carboplatin/5-fluorouracil (5-FU), or cetuximab intravenously.

The VMAT and IMPT plans from the planning software were translated by the radiation oncologist to dental maps, a symbolic representation of the radiation dose on the dental arch (Fig. 1), and were included in the patient file. Each number in the dental map is the result of a dose calculation for a cylindrical sample of 5 mm in diameter and 6 mm in height, and represents the localized radiation dose for two



Type of treatment: Photon / ~~Proton~~

Dose point	Dose (Mean Gy)
11-21	9.99
13	15.77
15	25.27
16-17	31.7
23	18.45
25	31.5
26-27	55.08
31-41	13.27
33	19.7
35	47.69
36-37	56.85
43	16.33
45	33.34
46-47	37.54



Type of treatment: ~~Photon~~ / Proton

Dose point	Dose (Mean Gy)
11-21	0.1
13	0.2
15	0.2
16-17	0.2
23	0.2
25	0.2
26-27	1.4
31-41	0.2
33	0.2
35	0.5
36-37	26.2
43	0.2
45	1.0
46-47	2.9

Fig. 1. Examples of dental maps provided by the department of radiotherapy for a patient with a T3N1M0 oropharyngeal tumour. Each point corresponds to a location in the upper and lower jaw.

adjacent teeth in the upper or lower jaw.

Inclusion and exclusion criteria

The inclusion criteria were dentate patients with a malignancy in the head and neck region who had undergone a pre-radiation dental screening and were eligible for VMAT and IMPT plan comparisons (Fig. 2). Edentulous patients, patients who had undergone pre-radiation dental screening at a different treatment centre, and patients with a missing radiation plan, were excluded. The patient characteristics, tumour characteristics, and radiotherapy data were retrieved from the patient files.

Plan comparison of the tooth-bearing regions

The cumulative VMAT and IMPT radiation doses were retrieved from the dental maps. The mean radiation dose levels (average Dmean), according to tumour location (nasopharynx, oral cavity, oropharynx, hypopharynx, larynx), tumour size and location relative to the tumour (contra- or ipsilateral), were calculated. The average subgroup Dmean values were analysed for the anterior (canine to canine) and posterior (premolar and molar) regions in the maxilla and mandible. The number of high-risk regions in the jaw, defined as regions in the jaw receiving a VMAT or IMPT radiation dose of $\geq$40 Gy, were identified.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the study population. To compare the radiation dose parameters between the VMAT and IMPT plans, a paired samples T-test or Wilcoxon Signed Rank Test was applied whenever appropriate, depending on the distribution (normal or non-normal) of the data. A p-value of $\leq$0.05 was considered statistically significant. The potential risk factors of receiving a radiation dose of $\geq$40 Gy, and thus becoming a high-risk region, were identified through multivariate logistic regression analysis with forward selection. The following covariates were included in the analysis: tumour location, T-status, N-status, tooth location in the jaw, tooth location in relation to the tumour (contralateral or ipsilateral) and applied radiation technique (VMAT or IMPT). The odds ratios, regression coefficients and predicted probabilities were calculated. Risk scores were reported by multiplying the regression coefficient by 5 and rounding off to the first integer. IBM SPSS statistics version 23 was used to execute the statistical analyses. Graphs were constructed with GraphPad Prism version 9.1.0.

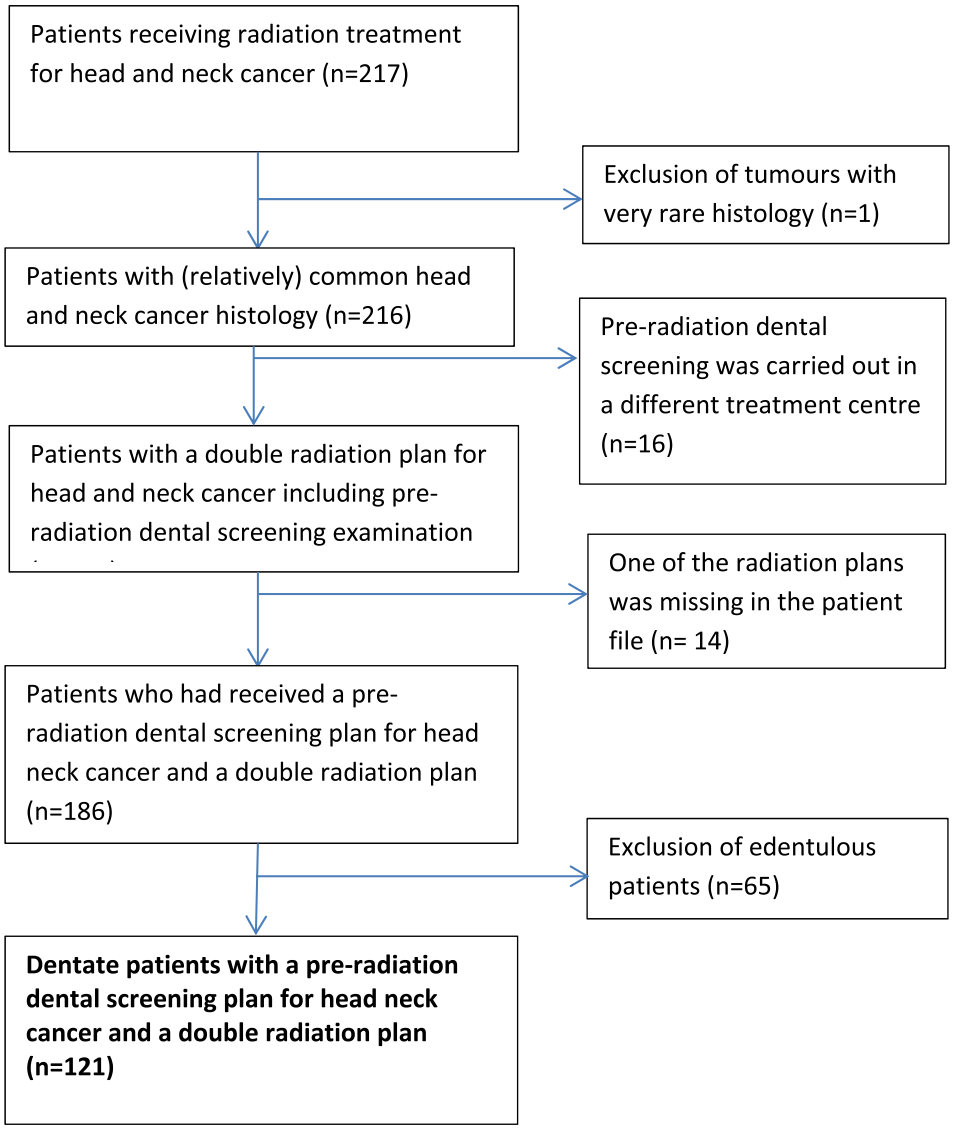


Fig. 2. Algorithm for the inclusion and exclusion of patients.

Results

Clinical data

The original study population consisted of 216 patients whereupon 95 patients were excluded due to various reasons, resulting in 121 eligible patients (Fig. 2). The patient demographics are given in Table 1. Among the 121 included patients, 2525 teeth were still in situ at the time of the dental screening (mean 21 teeth per patient, SD 7.9). Forty-eight patients (39.7%) were treated with definitive radiotherapy, while 52 patients (42.9%) received concurrent chemoradiotherapy (chemotherapy types: cisplatin (5-FU), carboplatin (5-FU)) and six patients (5%) were treated with radiotherapy and cetuximab. Fifteen patients (12.4%) initially underwent surgery followed by radiotherapy (with or without chemotherapy). After the model-based selection, 55 patients (45.5%) were ultimately treated with VMAT and 66 patients (54.5%) with IMPT.

Table 1
Patient demographics. (s.d. = standard deviation).

	N = 121
Mean age in years (s.d.)	60.5 (11.1)
Gender (%)	
Male	90 (74.4)
Female	31 (25.6)
Smoking (%)	
Current smoker	36 (29.8)
Never smoked	24 (19.8)
Previous smoker	54 (44.6)
Not reported	7 (5.8)
Tumour site (%)	
Oropharynx	62 (51.2)
Tonsillar region	44 (36.3)
Uvula	1 (0.8)
Base of tongue	17 (14)
Larynx	20 (16.5)
Oral cavity	13 (10.8)
Tongue	5 (4.1)
Floor of mouth	2 (1.7)
Maxillary gingiva or palate	2 (1.7)
Mandibular gingiva or retromolar region	4 (3.3)
Hypopharynx, piriform sinus	9 (7.4)
Nasopharynx	7 (5.8)
Lymph node metastasis of unknown primary	5 (4.1)
Sinonasal cavity	4 (3.3)
Parotid gland	1 (0.8)
Histology	
Squamous cell carcinoma	113 (93.4)
Other	8 (6.6)
T-classification	
T1	21 (17.4)
T2	25 (20.6)
T3	22 (18.2)
T4	48 (39.6)
Tx	5 (4.2)
N-classification	
N0	25 (20.7)
N1	30 (32)
N2	44 (36.3)
N3	20 (16.5)
Nx	2 (1.7)

Radiation dose comparison

The median prescribed radiation dose to the target was similar for both VMAT and IMPT (70 Gy for definitive radiotherapy; 66 Gy for postoperative radiotherapy). Fig. 3 compares the value of the individual VMAT dose points (left side of the graph) with the corresponding IMPT dose points in various tumour locations. Each point in the graph represents a specific tooth-bearing area in the jaw. The average Dmean of the specific tooth-bearing tumour areas was significantly lower for IMPT than for VMAT ($p < 0.001$). The intraoral tumour values show the highest average Dmean for the tooth-bearing areas (VMAT: 41.5 Gy, SD 19.3; IMPT 31.3 Gy, SD 24.7; $p < 0.001$). When analysing the influence of tumour size on radiation dose, the average Dmean for the VMAT of the larger (T3 and T4) tumours (26.8 Gy; SD 18.8) was not significantly different from the average Dmean of the smaller (T1 and T2) tumours (25.8 Gy; SD 14.8). However, the patients with larger tumours received a significantly higher average Dmean to the tooth-bearing areas with IMPT (12.9 Gy; SD 21.2) when compared to smaller tumours (8.0 Gy; SD 14.6; $p = 0.042$). The distributions of the average Dmean in the various anterior, premolar and molar tumour locations are presented in Tables 2 (maxillary regions) and 3 (mandibular regions), respectively. As depicted in Fig. 4, the high-risk areas for VMAT and IMPT were mostly located in the posterior regions of the lower jaw.

Logistic regression analysis and risk scores

From the multivariate logistic regression analysis, treatment with VMAT molars in the lower jaw, teeth ipsilateral to the tumour, patients with larger tumours, and patients with a tumour in the oral cavity were significantly associated with a higher risk of receiving a Dmean > 40 Gy (Table 4). Adding up the risk scores from Table 4 on the basis of clinical risk factors gives an estimate of the probability of a certain tooth receiving a radiation dose >40 Gy (Fig. 5).

Discussion

The results from this study illustrate a significant reduction in the Dmean regarding IMPT and VMAT of the tooth-bearing regions in head and neck cancer patients. The reduction in Dmean occurred for all the tumour locations. The difference in dosimetry between VMAT and IMPT was significant for all the tooth locations, except for the premolars and molars in the mandible and the molars in the maxilla of patients with intraoral tumours.

The dosimetric benefits of IMPT for organs at risk were published by an earlier study focusing on oropharyngeal cancer patients [20]. That study illustrated a Dmean of >40 Gy for VMAT of the oral cavity to <30 Gy for IMPT, which is comparable to our study's results where the average Dmean of the dentition in oropharyngeal tumours also dropped significantly for IMPT. Although it appears that IMPT has a significant dose-sparing effect on the dentition, we see that the single dose values are more relevant to the individual patient. Single radiation dosages exceeding 40 Gy were still observed in the mandibular regions of both groups' patients with nasopharyngeal, oral, oropharyngeal and hypopharyngeal tumours. An IMPT regimen can also result in high radiation dosages in the maxilla of patients with nasopharyngeal, oral, and oropharyngeal tumours. This is a finding clinicians need to be aware of when screening their patients before radiotherapy.

Undergoing VMAT instead of IMPT leads to a risk of the dentition being exposed to a radiation dose exceeding 40 Gy. Also, larger tumour sizes are risk factors for receiving radiation doses ≥40 Gy. The role of tumour size on the tooth-bearing regions was illustrated by one other study reviewing the radiation dose metrics in patients with a tongue tumour [29]. They also concluded that a larger tumour size is an important predictor of high radiation doses to the tooth-bearing regions. Tumour location also plays a role in the radiation dose on tooth-bearing regions. Patients with tumours located further away from the tooth-

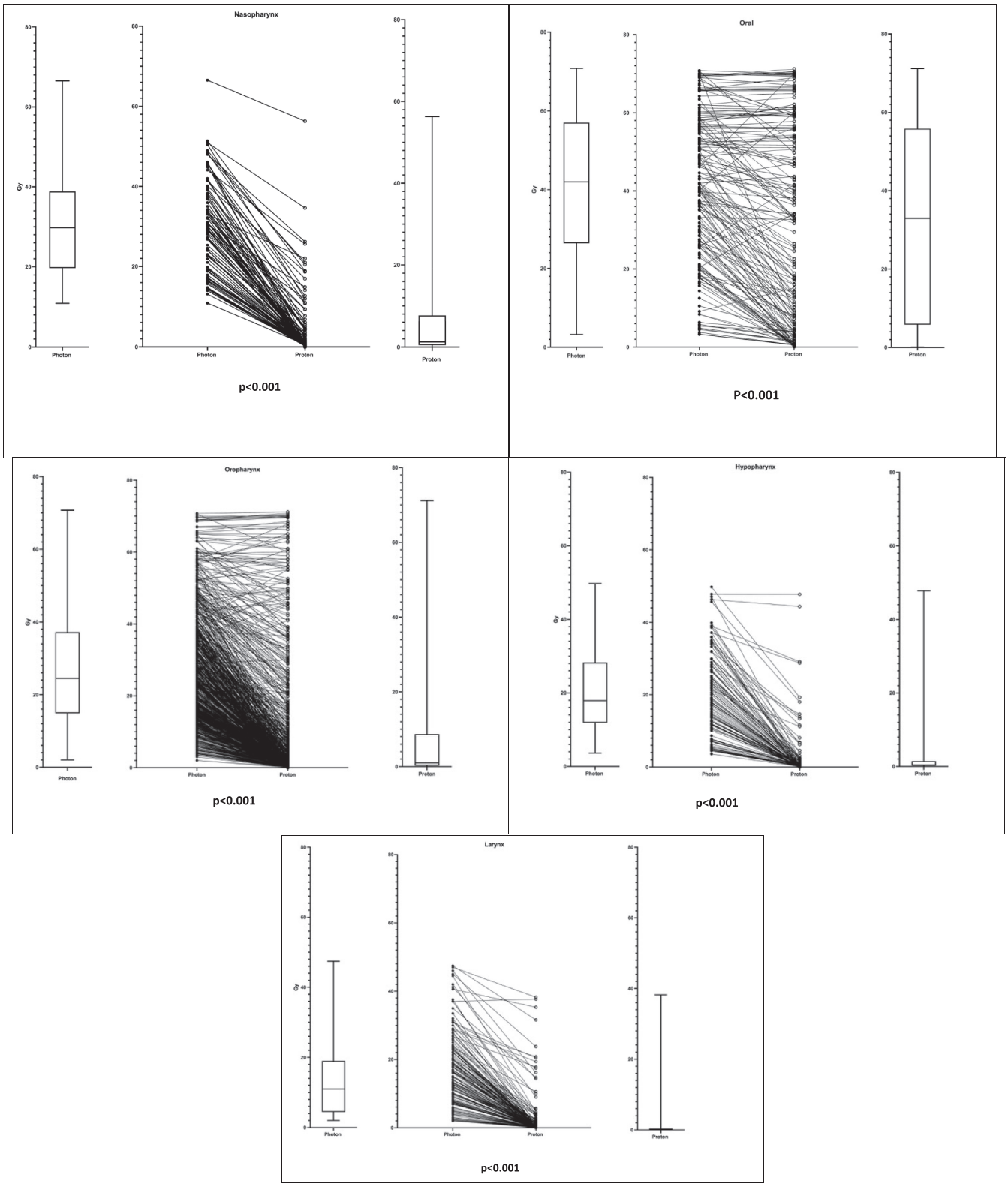


Fig. 3. Display of individual dose points in the upper and lower jaw for photon therapy (VMAT) on the left side of the graph. The points on the right side of the graph depict the corresponding dose points for proton therapy (IMPT). Each graph represents a certain tumour location.

bearing regions benefit the most from the dose-sparing effect of IMPT; when the distance between the tumour location and the oral cavity is shorter, the tooth-bearing regions will receive more radiation [30]. Consequently, the difference between VMAT and IMPT is less striking for patients with oral tumours. The relationship between tumour location and radiation dose was also clearly observable in our study population where the maxillary molars in the nasopharyngeal tumour patients and the mandibular molars in the oropharyngeal tumour patients were most likely to become high-risk regions, which is also in line with the findings of others [31–34].

Table 2
Dosimetry (average Dmean) of maxillary teeth in the anterior region, ipsilateral and contralateral to the tumour (VMAT = volumetric modulated arch therapy, IMPT = intensity modulated proton beam therapy).

	VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT	
	Ipsilateral molar	Ipsilateral molar	p	Ipsilateral premolar	Ipsilateral premolar	p	Anterior	Anterior	p	Contralateral premolar	Contralateral premolar	p	Contralateral molar	Contralateral molar	**p**
Nasopharynx															
Mean (s.d.)	52.1 (9.1)	27.2 (18.5)	0.01	41.6 (8.1)	5.6 (6.1)	0.07	27.5 (10.6)	0.6 (0.8)	<0.01	33.9 (3.8)	4.4 (3.7)	0.06	40.5 (8.5)	13.8 (5.9)	
Min-max	44.8–66.5	11.0–56.3		30.2–48.4	1.0–14.1		13.9–37.5	0–2.2.0		31.0–39.6	0.6–9.3		29.0–51.4	5.5–18.9	0.01
Oral															
Mean (s.d.)	45.1(18.6)	42.4 (20.7)	0.27	38.9 (20.7)	31.8 (20.8)	0.02	32.3 (20.8)	23.6 (23.2)	<0.01	25.9 (17.2)	13.0 (19.8)	<0.01	26.1 (13.2)	8.8 (12.5)	<0.01
Min-max	5.8–68.3	0.9–69.0		4.7–69.1	0.5–63.9		3.3–69.9	0.1–70.5		3.4–67.6	0.3–68.2		3.8–53.5	0.62–46.9	
Oropharynx															
Mean (s.d.)	33.2(16.8)	17.4 (20.5)	<0.01	25.3 (14.1)	6.7 (12.6)	<0.01	16.5 (10.6)	2.7 (8.9)	<0.01	17.3 (10.9)	2.9 (10.8)	<0.01	20.9 (11.8)	4.7 (12.5)	<0.01
Min-max	5.0–70.7	0.1–71.2		3.0–63.2	0.0–60.9		2.0–50.0	0.0–55.1		3.0–57.0	0.0–65.1		4.0–60.0	0.0–67.8	
Hypopharynx															
Mean (s.d.)	26.9(11.9)	1.06 (1.1)	<0.01	18.4 (9.4)	0.3 (0.2)	<0.01	11.8 (6.4)	0.2 (1.3)	<0.01	13.1 (6.9)	0.2 (0.1)	<0.01	15.8 (9.7)	0.5 (0.8)	<0.01
Min-max	7.0–39.9	0.2–3.9		5.0–29.0	0.0–0.6		3.6–21.2	0.0–0.4		5.2–24.0	0.0–0.5		5.2–32.0	0.1–2.3	
Larynx															
Mean (s.d.)	6.6 (6.3.)	0.1 (0.1)	<0.01	5.6 (5.7)	0.1 (0.1)	<0.01	4.2 (3.0)	0.1 (0.1)	<0.01	5.1 (3.8)	0.1 (0.1)	<0.01	6.0 (4.6)	0.1 (0.2)	<0.01
Min-max	2.0–25.0	0.0–0.4		2.0–21.0	0.0–0.4		2.0–15.0	0.0–0.4		2.0–16.0	0.0–0.4		2.0–20.0	0.0–0.6	

Table 3
Dosimetry (average Dmean) of mandibular teeth in the anterior region, ipsilateral and contralateral to the tumour (VMAT = volumetric modulated arch therapy, IMPT = intensity modulated proton beam therapy).

	VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT		VMAT	IMPT	
	Ipsilateral molar	Ipsilateral molar	p	Ipsilateral premolar	Ipsilateral premolar	p	Anterior	Anterior	p	Contralateral premolar	Contralateral premolar	p	Contralateral molar	Contralateral molar	**p**
Nasopharynx															
Mean (s.d.)	38.4 (6.4)	15.1 (9.8)	0.01	29.1 (1.6)	3.5 (2.9)	0.06	22.2 (8.7)	0.3 (0.23)	<0.01	23.4 (5.3)	1.4 (1.1)	0.07	26.9 (3.4)	6.2 (5.8)	0.01
Min-max	33.0–47.9	4.5–26.2		27.2–31.0	0.4–6.8		10.9–34.0	0.0–0.6		16.5–28.0	0.3–2.8		23.0–30.5	0.7–14.9	
Oral															
Mean (s.d.)	60.7 (9.7)	54.4 (19.1)	0.30	57.5(12.7)	50.7(24.5)	0.84	52.1 (16.4)	35.8 (23.7)	<0.01	42.2(11.8)	27.1(19.2)	<0.01	43 (7.1)	25.1(15.8)	<0.01
Min-max	36.0–69.8	8.3–70.2		29.3–70.1	9.3–70.6		18.6–70.8	0.1–69.9		20.7–62.0	0.2–56.3		35.2–57.0	3.2–56.7	
Oropharynx															
Mean (s.d.)	48.7 (13.5)	32.8 (21.6)	<0.01	37.4(12.8)	13.1(17.3)	<0.01	25.6 (13.2)	4.5(13.7)	<0.01	27.6(12.2)	5.8(14.0)	<0.01	31.7(12.6)	9.8 (16.6)	<0.01
Min-max	18.0–70.5	1.7–69.9		14.1–68.8	0.0–69.7		5.3–69.6	0.0–70.2		10.2–68.9	0.0–70.8		11.0–68.5	0.0–70.1	
Hypopharynx															
Mean (s.d.)	35.7 (8.1)	14.1 (9.9)	<0.01	25.3(6.7)	3 (2.6)	<0.01	18.4(8.4)	1.4(2.6)	<0.01	23.5(12.1)	6.3(14.5)	<0.01	27.1(13.6)	9.0 (15.5)	<0.01
Min-max	20.6–47.1	0.4–29.1		14.9–34.7	0.3–6.8		7.5–35.9	0.1–11.2		10.9–46.3	0.1–44.3		14.0–49.7	0.3–47.7	
Larynx															
Mean (s.d.)	23.6 (10.2)	4.1 (9.5)	<0.01	18.9 (8.0)	1.9 (4.6)	<0.01	13.8(5.4)	0.9(2.0)	<0.01	21.3(10.1)	2.9 (5.8)	<0.01	26.6(12.2)	9.1(13.9)	<0.01
Min-max	12.0–46.0	0.1–37.6		8.0–37.0	0.0–19.3		7.0–26.1	0.0–10.0		8.0–44.4	0.0–20.4		11.3–47.4	0.0–38.2	

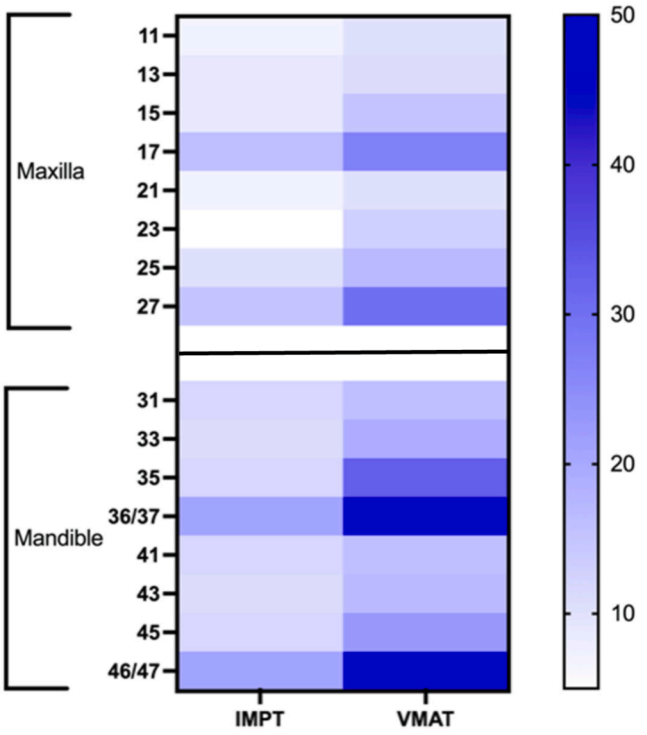


Fig. 4. Heatmap of the number of high-risk regions defined as teeth receiving ≥40 Gy during IMPT and VMAT.

Possible consequences for the clinician

When performing a pre-radiation dental screening, the definitive irradiated volumes and radiation technique (VMAT or IMPT) are often still unknown. This puts clinicians in a difficult situation regarding the decision of whether or not a dental focus of infection needs to be extracted as the data is still unknown. The risk scores and probability curve from Table 4 and Fig. 5, respectively, can be used as a tool to make a rough estimate of whether or not a tooth will be exposed to high radiation doses. However, communication between the dental clinician and radiation oncologist in this stage of the treatment process is of utmost importance and can prevent dental foci of infection being unnecessarily or unjustifiably extracted before radiation treatment. Previously, when patients were treated with conformal radiotherapy, a more aggressive approach, whereupon all the dental foci were removed before the radiotherapy, was preferred. When considering VMAT, a more tailored approach is advised because more dental foci will be located outside irradiated volumes. As the irradiated volumes are even smaller for IMPT, we expect that fewer pre-radiation extractions will be carried out in the future. This is an important consequence as pre-radiating tooth extractions can have a significantly negative impact on the quality of life and is considered a risk factor for weight loss in oropharyngeal cancer patients [35,36]. It needs to be stated that these dental foci still have to be attended to after radiation treatment in order to achieve a healthy dental status. A recent study on the value of radiotherapy dose mapping for tooth-bearing regions illustrated that the teeth which were exposed to ≥40 Gy were significantly more at risk of being extracted in the future than teeth located outside the irradiated volumes or receiving <40 Gy [37]. This illustrates that tooth loss is not only the result of the indirect effect of radiation-induced hyposalivation caused by salivary gland damage, but is also directly caused by the individual dose values on the teeth. Nonetheless, further prospective studies are needed in order to demonstrate the effects of IMPT on salivary gland function and the development of late radiation-induced toxicities such as radiation-induced caries.

Table 4
Factors associated with a Dmean of 40 Gy or higher based on a multivariate regression analysis. The risk score was derived from the regression coefficient multiplied by 5 and rounded off at the first integer. The risk score varies from −4 to 54. The probability of a dose > 40 Gy per element was derived from Figure 5. (OR = odds ratio).

Predictors	Multivariate analysis				Risk score
	Regression coefficient	OR (95% CI)	95% of OR	p-value	
Radiation technique					
IMPT reference	1.00				0
VMAT	1.08	2.94	2.48 – 3.49	<0.001	5
Tumor location					
Larynx reference	1.00				0
Hypopharynx	1.14	3.14	1.61 – 6.13	<0.001	6
Oropharynx	2.95	19.07	11.92 – 30.51	<0.001	15
Nasopharynx	3.01	20.26	10.96 – 37.44	<0.001	15
Oral	5.14	171.23	103.5 – 283.2	<0.001	25
T-classification					
T1-T2 reference	1.00				0
T3-T4	0.79	2.21	1.85–2.64	<0.001	4
N-classification					
N0 reference	1.00				0
N1	−0.77	0.47	0.36 – 0.61	<0.001	−4
N2	−0.47	0.62	0.49 – 0.79	<0.001	−2
N3	−0.36	0.70	0.51 – 0.95	0.02	−2
Tooth location					
Upper incisor or cuspid reference	1.00				0
Lower incisor or cuspid	1.19	3.29	2.37 – 4.58	<0.001	6
Upper premolar	0.59	1.81	1.23 – 2.65	<0.001	3
Lower premolar	1.85	6.34	4.51 – 8.92	<0.001	9
Upper molar	1.33	3.77	2.72 – 5.23	<0.001	7
Lower molar	2.54	12.65	9.21 – 17.36	<0.001	13
Laterality					
Contralateral reference	1.00				0
Ipsilateral	1.35	3.85 (3.23 – 4.59)	3.23 – 4.59	<0.001	7

Strengths and limitations

This is the first study comparing radiation dose levels to tooth-bearing regions for VMAT and IMPT within the same patient. The availability of both radiation plans clearly illustrates the dosimetric benefits of IMPT for the dentition. The potential tissue-sparing abilities of IMPT on the tooth-bearing regions were illustrated by another study [5]. However, the latter study was relatively small and they did not compare VMAT and IMPT plans from the same patient [5]. Our study also has several limitations. First, when calculating our results, certain radiation dosage assumptions had to be made for the tooth-bearing

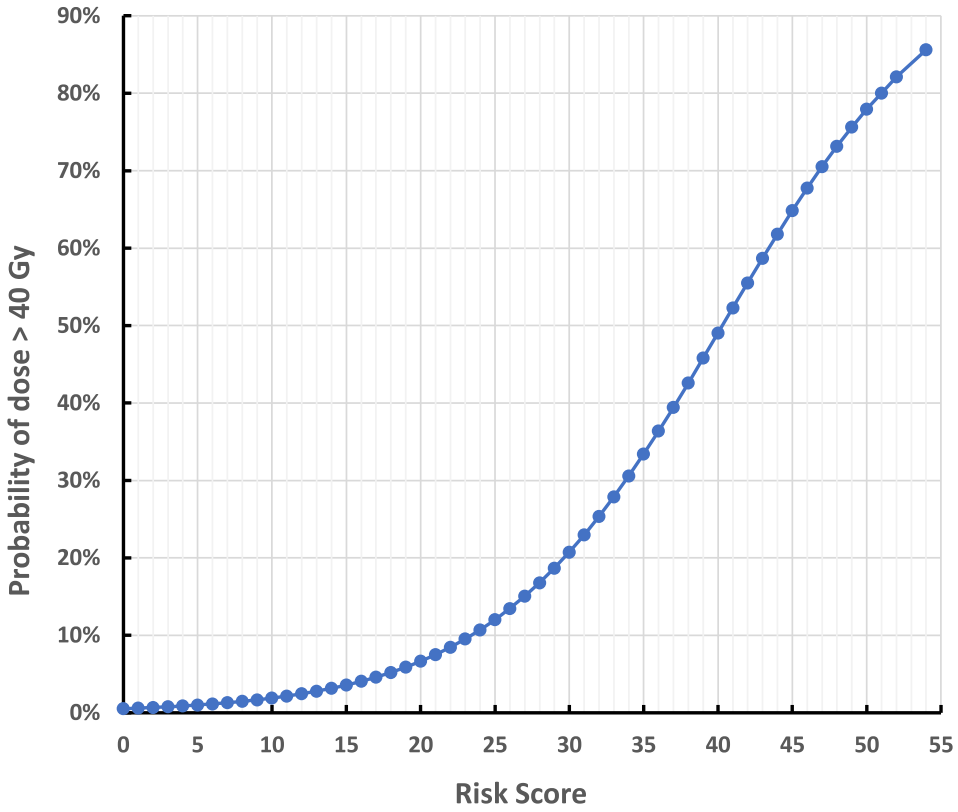


Fig. 5. The probability of a dose of >40 Gy to tooth elements was estimated from the Risk Scores derived from Table 4.

regions: the dental maps provided the exact dose for 2 adjacent teeth (e.g., 11, 13, 15, 16–17). Thus, the exact radiation dose for the teeth in the 12 and 14 locations were unknown. Regarding these locations, we assumed the same radiation dose as the highest adjacent value. Second, the threshold of 40 Gy for high-risk regions was rather 'conservative' as some studies applied a threshold of 50–60 Gy [12,38]. This could have led to an overestimation of the number of high-risk regions.

Conclusion

Compared to VMAT, applying IMPT to head and neck cancer patients leads to less cumulative radiation doses on the tooth-bearing regions of the upper and lower jaw. Treating a patient with IMPT can lead to a reduction in the number of pre-radiation dental extractions.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare that they have no conflict of interest. J.A. Langendijk is a member of the IBA Global Advisory Board. An honorarium was paid to the UMCG Research BV. The department of Radiation Oncology received research funding from the IBA.

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