Radiotherapy and Oncology 187 (2023) 109847

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

The extent of unnecessary tooth loss due to extractions prior to radiotherapy based on radiation field and dose in patients with head and neck cancer

Doke J.M. Buurman [a,b,*], Caroline M. Speksnijder [a,c,d], Marlies E. Granzier [e], Veronique C.M.L. Timmer [a,b], Frank J.P. Hoebers [b,e], Peter Kessler [a,b]

[a] *Maastricht University Medical Center, Department of Cranio-Maxillofacial Surgery, P.O. Box 5800 6202 AZ;* [b] *Maastricht University Medical Center, GROW School for Oncology and Reproduction, P.O. Box 616 6200 MD, Maastricht;* [c] *University Medical Center Utrecht Cancer Center, Department of Head and Neck Surgical Oncology;* [d] *University Medical Center Utrecht, Department of Oral and Maxillofacial Surgery and Special Dental Care, Utrecht University, P.O. Box 85500 3508 GA, Utrecht; and* [e] *MAASTRO, Department of Radiation Oncology, Doctor Tanslaan 12 6229 ET, Maastricht, the Netherlands*

ARTICLE INFO

Article history:
Received 11 April 2023
Received in revised form 1 July 2023
Accepted 31 July 2023
Available online 4 August 2023

Keywords:
Head and neck cancer
Radiotherapy
Oral foci of infection
Tooth extraction
Osteoradionecrosis
Masticatory system

ABSTRACT

Background and purpose: Prior to radiotherapy (RT), teeth with poor prognosis that pose a risk for post-RT osteoradionecrosis (ORN) are removed. To allow enough time for adequate wound healing prior to RT, decisions are made based on the estimated radiation dose. This study aimed to gain insight into (1) the overall number of teeth extracted and (2) the patient and tumor characteristics associated with the number of redundantly extracted teeth.

Materials and methods: Patients with head and neck cancer (HNC), treated with RT between 2015 and 2019, were included in this cross-sectional study. For each extracted tooth the radiation dose was calculated retrospectively. The cut-off point for valid extraction was set at $\geq$ 40 Gy in accordance with the national protocol. Potential factors for doses $\geq$ 40 Gy were identified, including age, sex, tumor location, tumor (T) and nodal stage (N), overall tumor stage and number of teeth extracted.

Results: A total of 1759 teeth were removed from 358 patients. Of these 1759 teeth, 1274 (74%) appeared to have been removed redundantly, based on the mean dose (D_{mean}) of < 40 Gy. Using the maximum dose (D_{max}) of < 40 Gy, 1080 teeth (61%) appeared to have been removed redundantly. Tumor location and N-classification emerged as the most important associative variables in the multivariable regression analysis.

Conclusion: To our knowledge this is the first study to provide insight into the amount of teeth redundantly extracted prior to RT and represents a step forward in de-escalating the damage to the masticatory system prior to RT.

Osteoradionecrosis (ORN) of the jaw is among the most feared late complications observed in patients with head and neck cancer (HNC) treated with radiotherapy (RT) [1].

Removal of teeth with a limited prognosis and identified as a potential cause of infection in the oral cavity prior to head and neck RT can be associated with a lower risk of developing ORN compared to performing tooth extractions after or during RT [2]. Therefore, it is important that the jaw areas receiving significant doses of radiation are free of potential sources of infection prior to RT. However, tooth extractions result in a decreased number of functional units and impair mastication and swallowing, contributing to a decreased health-related quality of life (QoL) [3–8]. In a recent study on patients with oropharyngeal squamous cell carcinoma (OPSCC), tooth extractions prior to therapy contributed to significant weight loss during RT combined with chemotherapy (CRT) or biotherapy (BRT) [9]. Since maintaining body weight is important for completion of planned RT and to support the

---

Abbreviations: BRT, Bioradiotherapy; CRT, Chemoradiotherapy; CTV, Clinical Target Volumes; D_{max}, Maximum Dose; D_{Mean}, Mean Dose; FDI, Fédération Dentaire Internationale; GTV, Gross Tumor Volume; HNC, Head and Neck Cancer; MUMC+, Maastricht University Medical Center; OAR, Organ At Risk; OPSCC, Oropharyngeal Squamous Cell Carcinoma; ORN, Osteoradionecrosis; PTV, Planning Target Volumes; QoL, Quality of Life; RT, Radiotherapy; VMAT, Volumetric-Modulated Arc Therapy.

* Corresponding Author at: Maastricht University Medical Center, Department of Cranio-Maxillofacial Surgery, GROW School for Oncology and Reproduction, P. Debyelaan 25 6229 HX, Maastricht, the Netherlands.

E-mail address: doke.buurman@mumc.nl (D.J.M. Buurman).

https://doi.org/10.1016/j.radonc.2023.109847
0167-8140/

recovery period, further weight loss caused by tooth extractions should be minimized or avoided as much as possible [10].

The original Dutch protocol which was re-evaluated in 2018 recommends comprehensive dental assessment of potential oral sources of infection at least 10 to 14 days prior to RT to allow adequate time for wound healing [11–13].

As described by Spijkervet et al., the risk of developing ORN starts at a RT dose of about 40 Gy and increases with increasing radiation dose [1]. It is therefore desirable to eliminate oral sources of infection where the radiation fields will achieve an expected cumulative radiation dose of $\geq$ 40 Gy [13,14]. However, some of the extracted teeth may be redundantly extracted, due to the fact that the estimated radiation dose prior to RT appeared to be lower after completion of RT planning. Considering the impact of pre-RT tooth extractions on patients with HNC and the advancements in RT techniques, there is a growing demand to adopt a less radical approach to pre-RT extractions [3,5,6,15,16]. The first objective of this study was to gain insight into the number of teeth not necessarily extracted prior to planned RT. The second objective was to determine which patient or tumor characteristics are associated with the number of redundantly extracted teeth prior to RT.

Materials and methods

Study design and population

This cross-sectional study included all patients who were treated by primary or adjuvant RT, CRT of BRT with curative intent for HNC at the Comprehensive Cancer Center of Maastricht University Medical Center (MUMC+) and Maastro Clinic between 2015 and 2019. Patients were excluded who were edentulous, did not need tooth extractions pre-RT, had a tooth extraction after RT instead of before, or neglected their teeth to such an extent that extraction of all remaining teeth was required. In addition, patients were excluded if they had previous head and neck RT, proton- or brachytherapy, or RT with palliative intent. Finally, patients with an unknown primary, centrally located, or bilateral proven tumor spread were excluded to allow for reporting of dose distributions in the jaws according to laterality: ipsi- versus contralateral. Data on age, sex, tumor location, tumor size (T), and lymph node status (N), as well as information on tooth extractions were extracted from the electronic health records by an experienced maxillofacial prosthodontist (DB). If a TNM classification was stated according to the 7th edition, it was converted to the TNM classification according to the 8th edition [17,18]. This study was approved by the medical ethics committee of the MUMC+ (METC 2019–1241). The institutional review board of MUMC+ allowed us to invoke the institutional "no objection regulation", so no patient informed consent was needed.

Tumor location

The patient cohort was divided into eight groups according to the anatomical region of the expected radiation fields: 1) larynx, 2) hypopharynx, 3) parotid region, 4) oropharynx, 5) oral cavity, 6) maxillary complex, 7) nasopharynx, and 8) other (Table 1). The group of patients with parotid gland tumors was supplemented with patients presenting with pre-auricular skin cancers with a radiation field including the parotid gland (due to metastasis or elective coverage) and formed the 'parotid region' group. Patients with a salivary gland tumor of the submandibular or sublingual gland were included in the 'oral cavity' group, because of the close anatomical relation with the mandible. Patients with a tumor in the maxillary region/hard palate were combined with patients with a nasal, paranasal sinus or nasal cavity tumor and formed: the 'maxillary complex' group.

Table 1
Baseline characteristics of the 358 patients.

	n = 358
Age (years)	
mean ± SD	63.6 ± 11.3
median (IQR)	60.0 (16)
Sex (n; %)	
Female	109 (30.4)
Male	249 (69.6)
Anatomical region of the expected radiation fields (n; %)	
Larynx	60 (16.8)
Hypopharynx	37 (10.3)
Parotid region	35 (9.8)
Oropharynx	117 (32.9)
Oral cavity	51 (14.2)
Maxillary complex	22 (6.1)
Nasopharynx	11 (3.1)
Other	25 (7.0)
Tumor stage (n; %)	
T0	6 (2)
T1	63 (18)
T2	93 (27)
T3	106 (30)
T4	81 (23)
Missing	9
Node stage (n; %)	
N0	148 (42)
N1	76 (22)
N2	87 (25)
N3	42 (12)
Missing	5
Tumor stage group (n; %)	
Stage 0 (cis)	1 (0)
Stage I	62 (18)
Stage II	63 (18)
Stage III	91 (26)
Stage IV	134 (38)
Missing	7
Type of tumor (n; %)	
Mucosal	289 (81)
Salivary gland	35 (10)
Skin, incl. Melanoma	22 (6)
Other types of tumor	12 (3)

Radiotherapy

RT was delivered using volumetric modulated arc therapy (VMAT) five days per week for six or seven weeks, to a total dose of 66 to 70 Gy in 33 to 35 fractions depending on the RT setting: adjuvant versus primary RT. Twenty-four patients underwent RT in a randomized trial on dose-escalation for the primary tumor (ARTFORCE, clinical.trial.gov ID NCT01504815) in which the FDG-avid part of the primary tumor was irradiated at a total dose of 84 Gy [19]. If indicated, RT was combined with systemic therapy, including cisplatin (CRT) or cetuximab (BRT) [20].

Dental assessment

According to national standard procedures, dental assessment of potential oral sources of infection was performed by oral and radiographic examination (e.g. orthopantomography), at least 14 days before the start of RT. Teeth with a poor prognosis due to extensive caries, advanced periodontal disease, and non-restorable teeth were considered a potential source of infection. Radiographic abnormalities such as apical radiolucency, (partially) impacted teeth, residual root apices, root resorption, and dental cysts were also considered as potential source of infection [11–13]. Teeth with poor prognosis were treated by extraction if the expected radiation dose to the jaws was $\geq$ 40 Gy [1,13].

Radiation dose calculations

All RT dose planning was performed in Eclipse (Aria version 15.5; Varian Medical Systems Inc, Palo Alto, California, United States) [21] in which the targets (gross tumor volume (GTV), clinical target volumes (CTV) and planning target volumes (PTV)) were delineated according to international guidelines [22] and the organs at risk (OAR's) according to the Brouwer's Atlas [23]. The radiation dose for each extracted tooth was calculated retrospectively: An experienced RT technologist (MG) delineated the location of the extracted teeth on the planning CT. First, the window level was set to bone density. Second, for each extracted tooth a new structure was created and named according to the Fédération Dentaire Internationale (FDI) World Dental Federation notation [24]. If the maxilla and/or mandible had received a maximum dose (D_{max}) of less than 25 Gy (defined as: the 25 Gy isodose line not touching the bone of the mandible/maxilla), this particular extracted tooth was not delineated, but was recorded as < 25 Gy. To delineate the location of the extracted tooth, the contouring tool was converted to a high-resolution segment and a 6 mm wide brush was selected. For each extracted tooth, the position on each CT slice (3 mm slice thickness) where the bone was visible was delineated (Fig. 1). After all locations of the extracted teeth were delineated, the mean dose (D_{mean}) and the D_{max} in these locations were exported. All exported data were converted to ipsilateral or contralateral, according to the laterality of the primary tumor region. RT dose was converted to a binary variable comparing sites that received $\geq$ 40 Gy with sites that received < 40 Gy, including sites recorded as < 25 Gy. To calculate the mean values, standard deviations and ranges of D_{mean} and D_{max}, the sites recorded as < 25 Gy were not included.

Statistical analyses

Descriptive statistics were reported as numbers and percentages, means with standard deviations (SDs), medians with interquartile ranges (IQRs), and total radiation dose ranges in Gy. Univariable logistic regression analyses was used to test the association between different demographic and clinical variables with dose $\geq$ 40 Gy, for both D_{mean} and D_{max}. These factors included: age at first dental assessment, sex, tumor location, tumor (T) and nodal stage (N), overall tumor stage (I, II, III, IV), early vs. advanced tumor stage, and number of teeth extracted. Factors with $p < 0.05$ were selected as potentially relevant associative variables and subsequently tested using multivariable logistic regression analyses. Data were analysed using SPSS (IBM version 28 for Windows, Armonk, New York, USA). A p-value of less than 0.05 was considered statistically significant.

Results

One thousand six hundred and sixteen patients were seen for dental assessment prior to RT of whom 1251 were excluded (Fig. 2). In total, 358 patients were included, 249 males (69.6%) and 109 females (30.4%). The mean age was 63.6 years (SD 11.3). Baseline characteristics are presented in Table 1. A total of 1759 teeth were removed from these 358 patients. Of these 1759 teeth, 1274 teeth (74%) appeared to have been removed redundantly, based on the D_{mean} of < 40 Gy. Using the D_{max} of < 40 Gy, 1080 teeth (61%) appeared to have been removed redundantly (Table 2).

Of the potential factors contributing to teeth receiving a cumulative RT dose $\geq$ 40 Gy, tumor location and N-classification

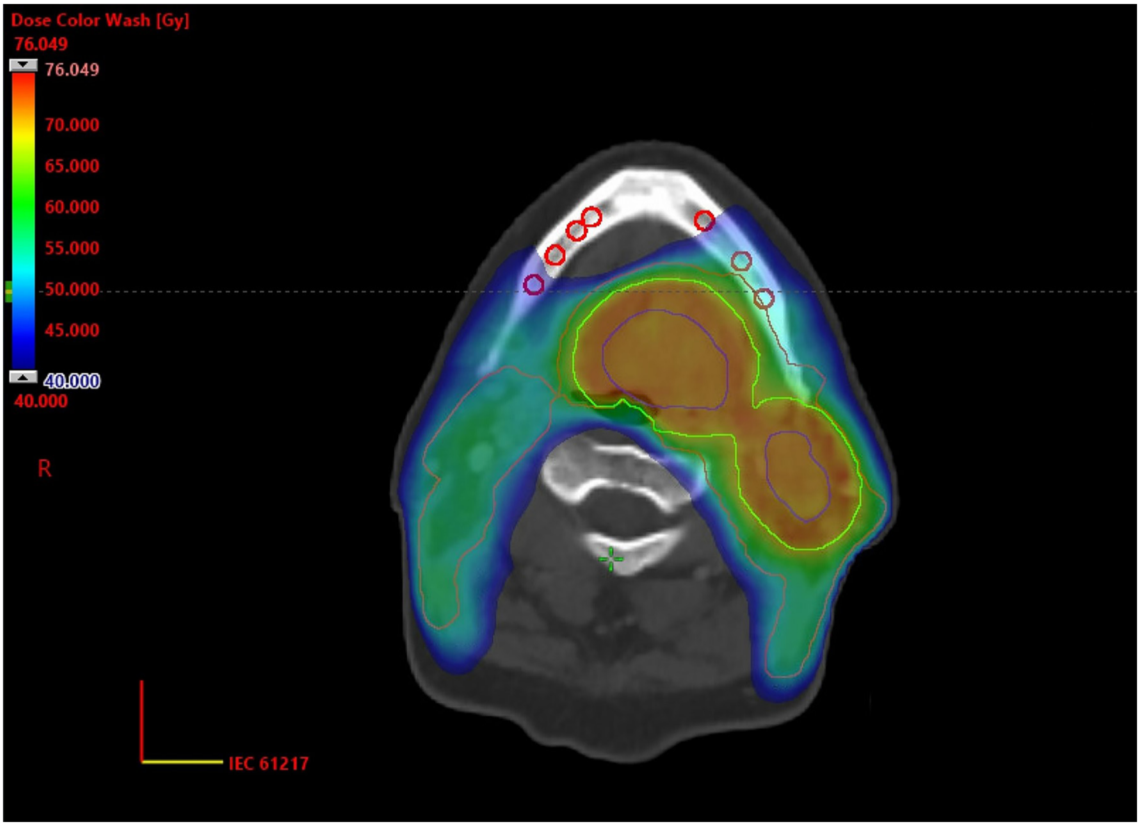

Fig. 1. Delineation of the location of the extracted teeth.

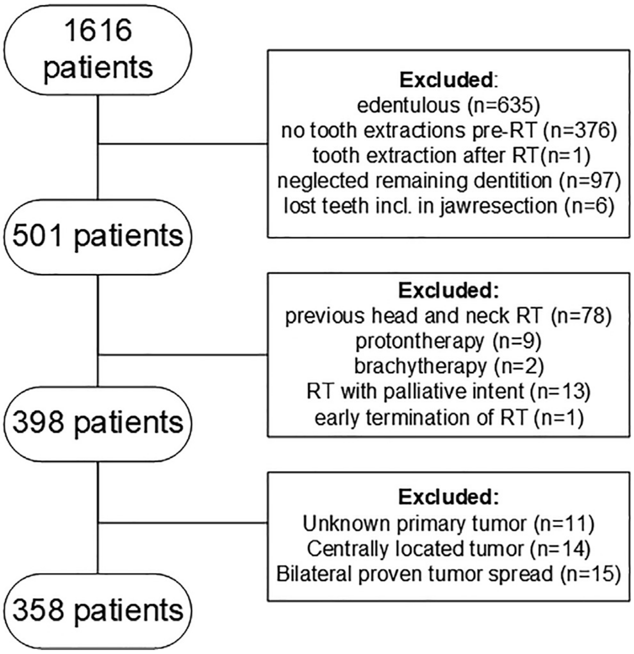

Fig. 2. Exclusion criteria.

emerged as the most important factors in the multivariable regression analysis (Fig. 3). Logistic regression outcomes for each factor per individual tooth in Fig. 3 can be found in Supplementary Table 1.

The highest percentages of redundantly removed teeth were found in the patients with tumors in the laryngeal (94–96%), hypopharyngeal (78–89%) and 'parotid region' (77–86%) (Table 2). In all but one of these 132 patients, the regions that received a dose of ≥ 40 Gy were the mandibular molar and mandibular second premolar regions on both sides in the hypopharyngeal and laryngeal group. In patients from the 'parotid region' group, this affected only the ipsilateral side. Detailed information on the doses for each tooth and the number and percentage of redundantly removed teeth can be found in Supplementary Tables 2A1-2H2.

In patients with an oropharyngeal tumor the percentages of redundantly removed teeth were 57–72%, with the areas of the four incisors, the two canines and the two contralateral premolars of the maxilla all exposed to a RT dose < 40 Gy. For other regions of the maxilla and for the entire mandible, the radiation dose for each tooth varied widely, resulting in percentages of redundantly removed teeth from 0% to 100% (Supplementary Tables 2D1-2D2).

In the 'oral cavity group' the number of redundantly removed teeth was the lowest. Eleven percent of the mandibular teeth on the ipsilateral side and 40% on the contralateral side were extracted redundantly due to a D_{mean} of < 40 Gy. Considering the

Table 2
Number of removed teeth per location.

Region	Nr. of extracted teeth	D_{mean} < 40 Gy N (%)	$D_{mean} \geq 40$ Gy N (%)	D_{max} < 40 Gy N (%)	$D_{max} \geq 40$ Gy N (%)
Larynx	217	209 (96)	8 (4)	204 (94)	13 (6)
Hypopharynx	163	145 (89)	18 (11)	127 (78)	36 (22)
Parotid region	94	81 (86)	13 (14)	72 (77)	22 (23)
Oropharynx	667	480 (72)	187 (28)	383 (57)	284 (43)
Oral cavity	378	177 (47)	201 (53)	139 (37)	239 (63)
Maxillary complex	87	52 (60)	35 (40)	43 (49)	44 (51)
Nasopharynx	72	62 (86)	10 (14)	54 (75)	18 (25)
Other	81	68 (84)	13 (16)	58 (72)	23 (28)
Total	1759	1274 (72)	485 (28)	1080 (61)	679 (39)

Fig. 3. Factors potentially contributing to RT dose ≥ 0 Gy.

D_{max} of < 40 Gy, 5% of the ipsilateral and 23% of the contralateral mandibular teeth were redundantly extracted. For maxillary teeth it was 89% and 81% for D_{mean} and D_{max} < 40 Gy, respectively (Supplementary Tables 2E1-2E2).

Patients with a tumor in the 'maxillary complex' were at risk of receiving a radiation dose of $\geq$ 40 Gy for all maxillary teeth and ipsilateral mandibular molars. The percentage of redundantly removed teeth in this group was 60% for D_{mean} and 49% for D_{max} (Table 2 and Supplementary Table 2F1-2F2).

In the nasopharyngeal group, the only jaw regions that ultimately received a dose of $\geq$ 40 Gy were the molar regions in the maxilla and ipsilateral mandible and the second premolar on the contralateral side of the mandible. This resulted in a percentage of redundantly extracted maxillary teeth of 76% for D_{mean} and 61% for D_{max}. For mandibular teeth the percentages were 95% for D_{mean} and 87% for D_{max} (Supplementary Tables 2G1-2G2).

All but one of the 25 patients from group "other" consisted of skin tumors located in the face, scalp and or neck region, treated with radiation. The percentage of redundantly removed teeth ranged from 84% for the D_{mean} to 72% for the D_{max} (Table 2 and Supplementary Tables 2H1-2H2).

Discussion

The results of this study show that up to 61% of teeth were unnecessarily extracted at D_{max} < 40 Gy and up to 74% at the D_{mean} < 40 Gy. To our knowledge, this is the first study to provide insight into the amount of teeth redundantly extracted prior to RT. It therefore provides arguments to drastically reduce the number of tooth extractions prior to RT for HNC. This de-escalation can help maintain the masticatory system and reduce the loss of functional units, which has a direct effect on food intake [3–9]. Not only the crushing of food, the maintenance of body weight, but also a person's social integration is often linked to the presence of functional teeth [25]. Patients suffer not only from the underlying oncological diseases, but also from the demands of therapy. The removal of teeth is generally negatively connoted [7,8]. The procedure itself and the expected pain can lead to a deterioration in the patient's general situation before the start of oncological therapy. For these reasons, de-escalation in the sensitive area of the oral cavity is extremely desirable.

Tumor location had a high association with unnecessarily extracted teeth. In patients with tumors located in the laryngeal, and hypopharyngeal region, only the mandibular molars and the second mandibular premolar received a dose of $\geq$ 40 Gy. In these regions the primary tumor is relatively further away from the teeth. In the oral cavity, oropharynx and 'maxillary complex' group the number of redundantly extracted teeth was less due to the closer proximity of the primary tumor to the mandible or maxilla. This led to a higher radiation dose in the jaw bones, consistent with the delineation of GTV, CTV and PTV according to international guidelines [22].

N-state was also associated with unnecessarily extracted teeth. The presence of positive lymph nodes located near the mandible (high level II or retropharyngeal), and submandibular lymph nodes of level Ib of the neck included in the clinical (elective) target volume resulted in a higher RT dose in the mandible.

In this study, a cut-off point of $\geq$ 40 Gy was chosen as the threshold as indication for tooth extraction [12,13]. Studies focusing on vascular changes at microscopic level after RT showed changes in tissue structure that occur at much lower doses [26,27]. Studies dealing with radiation doses in typical anatomical locations of the head and neck skeleton showed average doses of 24.4 and 28.2 Gy, which can be sufficient to trigger an ORN. The maximum doses measured at these specific ORN-sensitive regions were 44.3 and 48.4 Gy [28,29]. The choice of 40 Gy as the threshold dose for the risk of developing ORN as described in the Dutch National Protocol is empirical [12,13]. Several other studies suggest using 50 Gy or 60 Gy for the mandible or even 70 Gy for the maxilla as a reference value for the development of ORN [28–32], with only one Delphi study discussing a critical radiation threshold for prophylactic removal of teeth [33]. While the Canadian Dental Oncology Network seems to accept a certain risk of developing ORN, the Dutch guidelines prefer minimizing this risk as much as possible.

There are previous publications describing radiation doses to portions of the mandible and maxilla [34–37]. One study retrospectively delineated each tooth within the radiation fields in 18 HNC patients and used a D_{mean} cut-off point of > 50 Gy to assess the need for pre-RT extractions or similarly invasive procedures [34]. Two studies did not report the doses in ipsi- and contralateral which made it difficult to compare the results [35,36]. Another study looked at the mandibular volume percentages receiving > 55 Gy for 28 patients with base of tongue malignancies [37].

The strength of our study includes the large sample size (358 patients with 1759 precisely delineated extraction sites) and the detailed information on radiation doses (mean and maximum dose). Another strength of this comprehensive study is the fact that all extraction sites were delineated by a single experienced radiation technician (MG) in close collaboration with an experienced prosthodontist (DB). This contributes significantly to the consistency of the results.

A limitation of the present study is that the exact diagnosis for tooth extraction is missing. For some teeth, the prognosis might have been so poor that extraction would be the treatment of choice regardless of planned radiotherapy. Tooth extractions in these patients is also partly triggered by the insurance system in the Netherlands. The treatment of possible oral infection sites and the resulting prosthetic rehabilitation are covered by the national insurance system in the Netherlands. This opportunity leads to acceptation of more frequent tooth extractions in order to favorably access standardized prosthetic denture rehabilitation. This means that the actual percentage of redundantly removed teeth for reasons of planned radiotherapy is probably lower.

Another limitation is the indication of the location of the radiation field at the time of the comprehensive dental assessment. This can lead to a bias in judgement, especially since the guidelines for the expected dose still date from the early days of IMRT and have not yet been adapted to the much more appropriate VMAT-RT.

Extrapolation of the results described here is difficult since it is linked to the RT technique used (3D RT, IMRT or VMAT) and to the local experience in aspects of treatment planning with consequent differences in sparing of normal tissues. Therefore, in addition to properly assessing the tumor location and the location of the positive lymph nodes, good consultation with the radiation-oncologist remains of great clinical importance.

Future research to define a true radiation dose cut-off point for ORN in the head and neck area is needed to achieve a potential further de-escalation in preventive measures with the result of a functional destruction of the masticatory organ. Thereby, it is important that it is clearly described whether the mean or the maximum dose must be used. Artificial intelligence (AI) algorithms using Deep Learning (DL) may be able to accurately predict the radiation dose for new patients, based on an input of cohorts of previously treated cases with imaging and dose to the teeth available. This would allow a fast and reliable dose-prediction based on CT imaging, without the need to await the results of the labor-intensive manual treatment planning process [38,39].

In conclusion, this study represents insights in how to de-escalate damage to the masticatory system before RT without neglecting the risk of developing ORN. Especially in patients undergoing RT for cancer of the larynx, the hypopharynx or the 'parotid region', guidelines have been given to support decision making during comprehensive dental assessment. To prevent redundant tooth loss and functional damage close cooperation between all specialists involved in head and neck cancer therapy is of great importance. Guidelines must be adapted where appropriate.

Author contributions

All authors contributed to the conception and design of the study. Material preparation, data collection and analysis were performed by Doke JM Buurman, Caroline M. Speksnijder, Marlies E. Granzier and Frank J.P.Hoebers. The first draft of the manuscript was written by Doke J.M. Buurman, Caroline M. Speksnijder, Veronique C.M.L. Timmer, Frank J.P.Hoebers and Peter Kessler and all authors have commented on earlier versions of the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Illustration by Keisuke Koyama, Maastricht University Medical Center.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109847.

References

[1] Spijkervet FKL, Brennan MT, Peterson DE, Witjes MJH, Vissink A. "Research frontiers in oral toxicities of cancer therapies: Osteoradionecrosis of the jaws". J Natl Cancer Inst Monogr Aug 1 2019;2019. https://doi.org/10.1093/jncimonographs/lgz006.

[2] Normando AGC et al. "To extract or not extract teeth prior to head and neck radiotherapy? A systematic review and meta-analysis". Support Care Cancer Jun 17 2022. https://doi.org/10.1007/s00520-022-07215-y.

[3] Parahoo RS, Semple CJ, Killough S, McCaughan E. The experience among patients with multiple dental loss as a consequence of treatment for head and neck cancer: A qualitative study. J Dent Mar 2019;82:30–7. https://doi.org/10.1016/j.jdent.2019.01.010.

[4] de Groot RJ et al. Masticatory function and related factors after oral oncological treatment: A 5-year prospective study. Head Neck Jan 2019;41:216–24. https://doi.org/10.1002/hed.25445.

[5] Brahm CO et al. "Patients with head and neck cancer treated with radiotherapy: Their experiences after 6 months of prophylactic tooth extractions and temporary removable dentures". Clin Exp Dent Res Mar 23 2021. https://doi.org/10.1002/cre2.418.

[6] Clough S, Burke M, Daly B, Scambler S. The impact of pre-radiotherapy dental extractions on head and neck cancer patients: a qualitative study. Br Dent J Jul 13 2018;225:28–32. https://doi.org/10.1038/sj.bdj.2018.442.

[7] Kanatas A et al. Issues patients would like to discuss at their review consultation: variation by early and late stage oral, oropharyngeal and laryngeal subsites. Eur Arch Otorhinolaryngol Mar 2013;270:1067–74. https://doi.org/10.1007/s00405-012-2092-6.

[8] Rogers SN et al. Variations in concerns reported on the patient concerns inventory in patients with head and neck cancer from different health settings across the world. Head Neck Mar 2020;42:498–512. https://doi.org/10.1002/hed.26027.

[9] Buurman DJM et al. "Tooth extractions prior to chemoradiation or bioradiation are associated with weight loss during treatment for locally advanced oropharyngeal cancer". Support Care Cancer Mar 12 2022. https://doi.org/10.1007/s00520-022-06942-6.

[10] Willemsen ACH et al. Disease-induced and treatment-induced alterations in body composition in locally advanced head and neck squamous cell carcinoma. J Cachexia Sarcopenia Muscle Feb 2020;11:145–59. https://doi.org/10.1002/jcsm.12487.

[11] Jansma J et al. Protocol for the prevention and treatment of oral sequelae resulting from head and neck radiation therapy. Cancer Oct 15 1992;70:2171–80. https://doi.org/10.1002/1097-0142(19921015)70:8<2171::aid-cncr2820700827>3.0.co;2-s.

[12] Schuurhuis JM et al. Patients with advanced periodontal disease before intensity-modulated radiation therapy are prone to develop bone healing problems: a 2-year prospective follow-up study. Support Care Cancer Apr 2018;26:1133–42. https://doi.org/10.1007/s00520-017-3934-y.

[13] Spijkervet FKL, Schuurhuis JM, Stokman MA, Witjes MJH, Vissink A. Should oral foci of infection be removed before the onset of radiotherapy or chemotherapy? Oral Dis Jan 2021;27:7–13. https://doi.org/10.1111/odi.13329.

[14] Schuurhuis J.M, Spijkervet F.K.L, Vissink A and Stokman M.A, "[A PhD completed 9. The value of oral foci screening in oncology patients]," *Ned Tijdschr Tandheelkd*, vol. 124, pp. 279-281, May 2017, doi: 10.5177/ntvt.2017.05.17125. Hora est 9. De waarde van tandheelkundig focusonderzoek bij oncologiepatienten.

[15] Ben-David MA et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. Int J Radiat Oncol Biol Phys Jun 1 2007;68:396–402. https://doi.org/10.1016/j.ijrobp.2006.11.059.

[16] Studer G, Graetz K.W, Glanzmann C, "In response to Dr. Merav A. Ben-David et al. ("Lack of osteoradionecrosis of the mandible after IMRT," Int J Radiat Oncol Biol Phys 2007:In Press)," *Int J Radiat Oncol Biol Phys*, vol. 68, pp. 1583-4, Aug 1 2007, doi: 10.1016/j.ijrobp.2007.04.030.

[17] Edge S.B and Compton C.C, "The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM," *Ann Surg Oncol*, vol. 17, pp. 1471-4, Jun 2010, doi: 10.1245/s10434-010-0985-4.

[18] Huang S.H and O'Sullivan B, "Overview of the 8th Edition TNM Classification for Head and Neck Cancer," *Curr Treat Options Oncol*, vol. 18, p. 40, Jul 2017, doi: 10.1007/s11864-017-0484-y.

[19] Heukelom J et al. Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE); a randomized controlled phase II trial for individualized treatment of head and neck cancer. BMC Cancer Feb 22 2013;13:84. https://doi.org/10.1186/1471-2407-13-84.

[20] Bonner JA et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med Feb 9 2006;354:567–78. https://doi.org/10.1056/NEJMoa053422.

[21] Saw CB, Li S, Battin F, McKeague J, Peters CA. External beam planning module of Eclipse for external beam radiation therapy. Med Dosim Summer 2018;43:195–204. https://doi.org/10.1016/j.meddos.2018.03.003.

[22] Gregoire V et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Radiother Oncol Jan 2018;126:3–24. https://doi.org/10.1016/j.radonc.2017.10.016.

[23] Brouwer CL et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol Oct 2015;117:83–90. https://doi.org/10.1016/j.radonc.2015.07.041.

[24] ISO, ISO 3950:2016 Dentistry — Designation system for teeth and areas of the oral cavity. https://www.iso.org/standard/68292.html (accessed 07-04-2023).

[25] Pereira LJ, van der Bilt A. The influence of oral processing, food perception and social aspects on food consumption: a review. J Oral Rehabil Aug 2016;43:630–48. https://doi.org/10.1111/joor.12395.

[26] Poort LJ et al. The histological and histomorphometric changes in the mandible after radiotherapy: An animal model. J Craniomaxillofac Surg May 2017;45:716–21. https://doi.org/10.1016/j.jcms.2017.02.014.

[27] Patel V et al. The impact of intensity-modulated radiation treatment on dento-alveolar microvasculature in pharyngeal cancer implant patients. J Oral Rehabil Nov 2020;47:1411–21. https://doi.org/10.1111/joor.13084.

[28] Kubota H et al. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. Radiat Oncol Jan 5 2021;16:1. https://doi.org/10.1186/s13014-020-01701-5.

[29] Owosho AA et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The Memorial Sloan Kettering Cancer Center experience. Oral Oncol Jan 2017;64:44–51. https://doi.org/10.1016/j.oraloncology.2016.11.015.

[30] Hoebers F.J.P, Ferguson P.C and O'Sullivan B, "Bone," in *Human Radiation Injury*, D. C. Shrieve and J. S. Loeffler Eds., 2010, ch. 43.

[31] Studer G et al. Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). Strahlenther Onkol May 2006;182:283–8. https://doi.org/10.1007/s00066-006-1477-0.

[32] Caparrotti F et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. Cancer Oct 1 2017;123:3691–700. https://doi.org/10.1002/cncr.30803.

[33] Watson E, Dorna Mojdami Z, Oladega A, Hope A, Glogauer M and G. Canadian Dental Oncology Network Consensus, "Clinical practice guidelines for dental management prior to radiation for head and neck cancer," *Oral Oncol*, vol. 123, p. 105604, Dec 2021, doi: 10.1016/j.oraloncology.2021.105604.

[34] Polce S et al. Dental radiation dosimetric maps from intensity-modulated radiation therapy planning for head and neck cancers. Head Neck May 2021;43:1428–39. https://doi.org/10.1002/hed.26611.

[35] Bak SY et al. Dosimetric distribution to tooth-bearing areas in intensity-modulated radiation therapy for head and neck cancer: a pilot study. Oral Surg

Oral Med Oral Pathol Oral Radiol Jan 2016;121:43–8. https://doi.org/10.1016/j.oooo.2015.10.007.

[36] Parahyba CJ, Ynoe Moraes F, Ramos PA, Haddad CM, da Silva JL, Fregnani ER. Radiation dose distribution in the teeth, maxilla, and mandible of patients with oropharyngeal and nasopharyngeal tumors who were treated with intensity-modulated radiotherapy. Head Neck Nov 2016;38:1621–7. https://doi.org/10.1002/hed.24479.

[37] Hansen HJ, Maritim B, Bohle 3rd GC, Lee NY, Huryn JM, Estilo CL. Dosimetric distribution to the tooth-bearing regions of the mandible following intensity-modulated radiation therapy for base of tongue cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Aug 2012;114:e50–4. https://doi.org/10.1016/j.oooo.2012.01.024.

[38] Chan JW et al. ''Artificial Intelligence-Guided Prediction of Dental Doses Before Planning of Radiation Therapy for Oropharyngeal Cancer: Technical Development and Initial Feasibility of Implementation''. AdvRadiat Oncol Mar-Apr 2022;7:. https://doi.org/10.1016/j.adro.2021.100886100886.

[39] Thariat J et al. Dentalmaps: automatic dental delineation for radiotherapy planning in head-and-neck cancer. Int J Radiat Oncol Biol Phys Apr 1 2012;82:1858–65. https://doi.org/10.1016/j.ijrobp.2011.03.035.