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Original Article

Development of a local dose-response relationship for osteoradionecrosis within the mandible

Nienke D. Sijtsema [a,b,1,*], Gerda M. Verduijn [a], Kazem Nasserinejad [c,f], Yvette van Norden [a], Hetty Mast [d], Aad van der Lugt [b], Mischa S. Hoogeman [a,e], Steven F. Petit [a]

[a] Department of Radiotherapy, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands; [b] Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [c] Department of Hematology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [d] Department of Oral and Maxillofacial Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [e] Department of Medical Physics and Informatics, HollandPTC, Delft, The Netherlands; [f] Innovative Statistical Consulting, Therapeutics Development Team, Cytel Inc., Cambridge, MA, USA

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ABSTRACT

Purpose: Osteoradionecrosis (ORN) of the mandible is a severe complication following radiotherapy of the head and neck, but not all regions of the mandible may be equally at risk. Therefore our goal was to explore a local dose response relationship for subregions of the mandible.
Materials and methods: All oropharyngeal cancer patients treated at our hospital between 2009 and 2016 were reviewed. Follow-up was cut-off at 3 years. For patients that developed ORN, the ORN volume was delineated on the planning CT. Each mandible was divided into 16 volumes of interest (VOIs) based on the location of the dental elements and the presence of ORN in each was scored. Generalized estimating equations were used to build a model for the probability of developing ORN in an element VOI.
Results: Of the 219 included patients, 22 developed ORN in 89 element VOIs. Mean dose to the element VOI (odds ratio (OR) = 1.05 per Gy, 95% confidence interval (CI): (1.04,1.07)), pre-radiotherapy extractions of an element ipsilateral to element of interest (OR = 2.81, 95% CI: (1.12,7.05)), and smoking at start of radiotherapy (OR = 3.37, 95% CI: (1.29,8.78)) were significantly associated with an increased probability of ORN in the VOI.
Conclusion: The developed dose-response model indicates that the probability of ORN varies within the mandible and strongly depends on the local dose, the location of extractions, and smoking.

Osteoradionecrosis (ORN) of the mandible is a severe late complication after radiotherapy in the head and neck region. It can cause pain, oral skin fistulae, and even pathological fracture of the mandible requiring extensive reconstruction [1]. Although the incidence of ORN has declined in the era of intensity-modulated radiotherapy (IMRT), incidence rates varying between 4–10% are still reported [2–6]. Different studies have associated a variety of risk factors with the onset of ORN, including tumor location, size and stage, the presence of bone invasion, dose volume histogram (DVH) parameters of the entire mandible, radiotherapy technique, irradiated volume, smoking, alcohol use, oral hygiene, pre- and post-radiotherapy dental extractions, and several comorbidities [2–8].

A high dose to the mandible is related to an increased risk of ORN. However, there are indications that not all regions of the mandible are equally prone to develop ORN. For instance, ORN is most commonly observed in premolar, molar, and retro-molar areas of the mandible, but hardly in the incisor and canine area of the mandible [9]. Moreover, trauma to the mandible (i.e. due to teeth extractions) may affect the radio-sensitivity of the mandible in the vicinity of the trauma. Indeed, recent reviews investigating the relationship between teeth extractions and ORN show that in some cases their locations are linked, although often the relationship is unclear [10,11].

If differences in radio-sensitivity indeed exist *within* the mandible and could be identified, selective sparing of the more sensitive regions of the mandible could reduce the likelihood of ORN. However, to the best of our knowledge, studies investigating local differences in radio-sensitivity within the mandible are currently lacking. Therefore, the goal of the current study was to explore a local dose response relationship taking into account the location of ORN, the dose deposited locally to the ORN site, and the vicinity of teeth extractions.

* Corresponding author at: P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.
E-mail address: n.sijtsema@erasmusmc.nl (N.D. Sijtsema).
[1] Visiting address: Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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Materials and methods

Patients

The records of all patients with oropharyngeal squamous cell carcinoma who were treated with curative (chemo-)radiotherapy at our department between January 2009 and May 2016 and survived at least one year were reviewed. Exclusion criteria were as follows: diagnosis of another primary tumor within 6 months, previous oropharyngeal cancer, previous head and neck radiotherapy, tumor progression within 6 months, unavailability of dosimetric data or radiological data of ORN location, follow up of less than 3 years except for patients that developed ORN within three years. Patients not followed-up in our hospital were not actively approached. The study was approved by the institutional review board (protocol EMC17404).

Treatment

Patients were referred to either one of two treatment schedules in line with the standard clinical protocol. Patients with large cT3-T4N0-2 M0 and any cT1-4N3M0 tumors receivedIMRT of 70 Gy (35 fractions of 2 Gy) to the primary tumor and regions containing pathological neck nodes, and 46 Gy to the elective neck regions, with a sequential or simultaneously integrated boost. At least 98% of the PTV should be covered by 95% of the prescription dose (V95% > 98%). Chemotherapy was added to the treatment if indicated based on TNM stage (T3-4 or N+), and consisted of cisplatin (100 mg/m^2 on days 1, 22 and 43 of treatment) or cetuximab (400 mg/m^2 initial dose, followed by a weekly dose of 250 mg/m^2). The overall treatment time of this group was 6 weeks in case of accelerated treatment (6 fractions/week) and 7 weeks in case of non-accelerated treatment (5 fractions/week).

Patients with cT1-smallT3N0-2 cM0 tumors were treated with 46 Gy IMRT (23 fractions of 2 Gy) to the primary tumor and elective neck node regions, followed by a stereotactic body radiotherapy (SBRT) boost of 16.5 Gy to the primary tumor (3 fractions 5.5 Gy) delivered by the Cyberknife system (Accuracy Inc., Sunnyvale, CA, USA). The SBRT boost dose of 16.5 Gy was prescribed to the 80% isodose line, where the maximum dose was set to 100%. The overall treatment time for this group was 5 weeks. In the SBRT boost group, patients with an N+ neck underwent neck dissection after the boost.

Patients were routinely seen at the department of Oral and Maxillofacial surgery before the start of radiotherapy and dental extractions were performed according to national guidelines of the Dutch Association of Oral and Maxillofacial Surgeons [12]. During radiotherapy treatment, dentulous patients were seen weekly by a dental hygienist, and received fluoride treatment. Patients were followed by the head and neck multidisciplinary team. Follow-up visits were planned every 2 months for the first year following radiotherapy. Starting from the second year, the frequency gradually decreased to every 6 months for a minimum of 5 years. In case of suspicion or diagnosis of ORN, patients were referred to the ORN outpatient clinic at the department of Oral and Maxillofacial surgery.

Scoring and delineation of ORN

ORN was defined as clinically exposed bone following radiotherapy, without evidence of recurrent or residual tumor and no signs of healing for at least 3 months. ORN as late toxicity (>90 days after completion of radiotherapy) was scored according to CTCAE v5.0 by an experienced radiation oncologist. Predictors were scored independently, before knowing whether a patient had ORN, and were therefore blinded for outcome. Follow-up was cut off at three years. For patients with ORN grade 2 or higher within 3 years after treatment, regions of mandibular bone affected by ORN (ORN volumes of interest (VOIs)) were delineated by a radiation oncologist and an oral and maxillofacial surgeon (both experienced in ORN) on the planning CT, based on clinical and radiological examination of the mandible.

Scaling and accumulation of dose distributions to the mandible

All dose distributions were converted voxel-wise to the equivalent dose of 2 Gy (EQD2 Gy) based on α/β = 0.85 Gy for bone toxicity [13]. Patients in the IMRT boost group had one (simultaneous integrated boost) or two (sequential boost) treatment plan(s) planned on the same planning CT, that were accumulated for the purpose of the study.

Patients in the SBRT boost group had at least two planning CT scans and treatment plans: one corresponding to the IMRT and one corresponding to the SBRT part of the treatment. Therefore, dose accumulation required registration between the CT scans. The following procedure was used. First, the mandible was automatically delineated in both scans using ADMIRE 3.7.7 (Elekta AB, Stockholm, Sweden) with employment of STAPLE [14]. The delineations were assessed qualitatively before being used in the registration procedure. Subsequently, the rigid registration (rotation and translation) was performed based on the delineations of the mandible. After registration, the EQD2 Gy SBRT and IMRT dose distributions to the mandible were accumulated.

For patients that had adaptive treatment plans, i.e. patients that showed considerable anatomical changes during treatment requiring a new treatment plan, dose was accumulated according to the same methods used for the SBRT boost group.

Transforming all dose distributions and delineations to one reference patient

To investigate the effect of anatomical location on the risk of ORN, the accumulated dose distributions and ORN delineations of all patients were projected on top of a reference patient using deformable image registration (ADMIRE 3.7.7 (Elekta AB, Stockholm, Sweden)). The accuracy of the deformable registration was assessed by comparing the mandible delineation of the reference patient with the transformed mandible delineations.

Next, the mandible of the reference patient was divided into different subvolumes based on the location of the dental elements. For that purpose all dental elements of the mandible were delineated on a patient with full dentition (including third molars and without severe crowding), since it was not feasible to accurately manually delineate these subvolumes in patients with partial or no dentition. To cover as much of the mandible as possible, the delineations were extended in caudal direction up to the caudal edge of the mandible. These regions were referred to as element VOIs and were numbered according to the WHO ISO dental notation system (left: 3.1 – 3.8, right: 4.1 – 4.8), where .1 refers to the central incisor and .8 to the third molar. The element VOIs were subsequently transformed to the reference patient. ORN at an element was scored if there was any overlap between the ORN VOI and the element VOI.

Statistical analysis

The probability of ORN at three years was modeled using a generalized estimating equations (GEE) model. GEE is an extension of generalized linear models for the analysis of clustered data, such as multiple measurements per patient, in our case multiple VOIs per patient [15,16]. GEE is based on a quasi-likelihood function and provides population-averaged estimates of the model coefficients. A first-order autoregressive (AR1) working correlation matrix was

chosen to capture the inherent correlation between dental elements within the subjects. The AR1 assumes the correlation between any two elements is equal to ρ for adjacent elements, ρ^2 for elements that are separated by one element, and so on. This structure is suitable for the purpose of the study since it acknowledges that if a certain element contains ORN, neighboring and nearby elements may have an increased risk of having ORN too. To tackle the potential misspecification of the covariance structure, the robust (sandwich) estimator [15] was used to produce unbiased standard error estimators for regression coefficients.

For selection of the patient level variables, the variables age, gender, WHO performance status (0 vs 1 and 2), alcohol use (yes/no), smoking at the start of therapy (yes/no), pretreatment teeth extractions (yes/no), T stage (1 and 2 vs 3 and 4), HPV status (positive/negative), treatment acceleration (5 vs 6 fractions per week), boost type (IMRT vs SBRT), concurrent systemic therapy, neck dissection and tumor subsite (tonsil vs other) were first separately tested on a patient level in univariate logistic regressions.

All patient level variables with a $p < 0.05$ in the univariate analysis were taken into account in the GEE model, which accounted for ORN on the element level. The following element VOI variables were taken into account in the GEE model: (1) The mean dose to the element VOI, and (2) whether the element was a molar (yes/no), or a (3) premolar (yes/no) to account for the anatomical location. Teeth extractions (in case univariable significant) were taken into account locally through the following three variables: (1) whether the element of the element VOI was extracted pretreatment (yes/no), (2) any pretreatment extractions ipsilateral to the element VOI including extractions of the element of interest itself (yes/no) and (3) any pretreatment extractions on the contralateral side of the mandible (yes/no).

Variable selection for the final GEE model was done using five-fold selection. To that end, the group of ORN and non-ORN patients were first separately divided into five-folds. Next, the folds of the ORN and non-ORN patients were combined. In this way, the original distribution of ORN and non-ORN patients was maintained in each of the folds. Next, five models were built, each on four out of the five folds, leaving out a different fold for each model (leave one out approach), and backward selection was performed for variable selection for each of the models. If a variable was significant in the majority (at least three) of the five models after backward selection, the variable was included in the final model. In the final step, the final model coefficients of the selected variables were determined by fitting the GEE model to all data. To demonstrate the size of the effects, the model coefficients and odds ratios (ORs) are presented along their confidence intervals.

To study the robustness of the model stratified cluster bootstrapping (500 times) was performed. In stratified cluster bootstrapping the percentage of ORN and non-ORN patients included in each bootstrapping sample was the same as the percentage of ORN and non-ORN patients in the original data. The bootstrapping confidence intervals of the coefficients are reported. The receiver-operator characteristic (ROC) curve was calculated and reported with its corresponding confidence interval (based on 2000 bootstrap samples) to assess discrimination of the model. A calibration plot was made to assess the calibration of the model. All statistical analyses were performed using R Statistical Software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) using geepack (version 1.3–2), pROC (version 1.18.0) and rms (version 6.2–0) packages. A p-value < 0.05 was considered statistically significant.

Results

Patient and treatment characteristics are summarized in Table 1, as well as the results from the patient level univariate analysis. In total, 334 patients were reviewed, of which 219 were selected after applying the exclusion and follow-up criteria. One ORN patient was excluded due to unavailability of radiological data on the site of ORN. 120 patients (54.8%) were treated with the SBRT boost protocol and 99 patients (45.2%) with the IMRT boost protocol. For these patients there were no missing data for all predictors and outcomes. Twenty-two patients developed ORN CTCAE v5.0 grade 2 or higher within three years (11 grade 2, 11 grade 3). One patient developed bilateral ORN. The median volume of the ORN VOIs was 6.8 cc (range 0.6–43.2 cc). On average the ORN VOI covered 10.9% of the mandible (range 1.1–44.5%). The average symmetric distance between mandible delineations after registration of the IMRT CT and the SBRT CT was on average 1.0 mm (range 0.6 – 2.0 mm), indicating sufficiently accurate registrations.

Out of 3504 dental element VOIs in 219 patients, 89 element VOIs contained ORN. For the patients with ORN, on average 4 dental element VOIs (range 2–13) were affected. ORN was most frequently found in the molars, followed by the premolars and more often on the right side than the left side (Fig. 1a and b). The voxel-wise mean dose to the mandible for the group with and without ORN is shown in Fig. 1c and 1d, respectively, and the difference in mean dose in Fig. 1e. The average dose on the right side of the mandible was higher for patients with ORN, compared to without ORN, which was in line with a higher incidence of ORN on the right compared to the left side of the mandible.

From the univariate patient-level analysis, smoking at the start of radiotherapy, accelerated treatment and teeth extractions were significant (Table 1). After parameter selection, the final multivariate model contained mean dose to the element VOI (OR = 1.05 per Gy, 95% CI: (1.04,1.07)), pre-radiotherapy extractions ipsilateral to the element of interest (including extractions of the element of interest itself) (OR = 2.81, 95% CI: (1.12,7.05)), and smoking at the start of radiotherapy (OR = 3.37, 95% CI: (1.29,8.78)). Table 2 contains the details of the final model. The estimated correlation coefficient ρ was 0.61. Supplementary materials Figure S1 shows the ROC curve of the final model. Supplementary materials Figure S2 contains a calibration plot and several calibration measures. Please note that both the ROC curve and calibration measures were based on the same data as used for model development, and that the estimated risks were population average probabilities rather than patient individual probabilities. The corresponding population average dose response relations are shown in Fig. 2.

Discussion

ORN is a severe complication following radiotherapy of the head and neck. ORN mainly manifests in the posterior mandible (molars and premolars) [8,9] (supported by the current study) and teeth extractions are an important risk factor. This suggests that not all regions of the mandible are equally prone to ORN. Therefore, in this study we derived a local dose-response relationship of the mandible, corresponding to the location of dental elements. We found that the dose to dental element VOIs, extractions of and/or near the elements of interest and smoking at the start of treatment were strong predictors of ORN at the element of interest.

The incidence of ORN in our cohort was similar to De Maesschalck et al. [4] who found 10% incidence of ORN in a cohort treated with IMRT. Though, other recent studies have reported slightly lower incidence values (4.6–7.5%) [2,3,5,17]. Previous studies that looked into risk factors for ORN focused on the *patient level* variables, and found high doses to the mandible (e.g. mean dose), the presence of teeth extractions anywhere in the mandible (yes/no) and smoking as relevant risk factors [2,3,5,7,8,17,18]. However, none of these studies have investigated whether the exact location

Table 1
Patient and treatment characteristics. ORN was scored according to CTCAE v5.0. ORN - osteoradionecrosis; WHO - World Health Organization; HPV - human papilloma virus; SBRT - Stereotactic Body RadioTherapy; IMRT - Intensity Modulated Radiotherapy.

Characteristics	All patients	Non ORN	ORN (≥grade 2)	p-value
N	219	197	22	
Age (median, interquartile range)	61 (55, 67)	60 (54, 67)	62 (58, 68)	0.47
Gender				0.90
Male	148 (54.8%)	133 (67.5%)	15 (68.2%)	
Female	71 (45.2%)	64 (32.5%)	7 (31.8%)	
WHO performance status				0.84
0	136 (62.1%)	125 (63.5%)	11 (50.0%)	
1–2	83 (37.9%)	72 (36.5%)	11 (50.0%)	
Alcohol				0.27
No/ previous	57 (26.0%)	54 (27.4%)	1 (4.5%)	
Current	162(74.0%)	143 (71.6%)	21 (95.5%)	
Smoking				**0.041***
No/ previous	116 (53.0%)	109 (55.3%)	2 (9.1%)	
Current	103 (47.0%)	88 (44.7%)	20 (90.9%)	
Teeth extraction				**0.022***
No/ edentulous	139 (63.5%)	132 (67.0%)	7 (31.8%)	
Partly/ completely	80 (36.5%)	65 (33.0%)	15 (68.2%)	
Time (days) extr – RT (median)	20	20	17	
T stage				0.73
T1-T2	132 (60.3%)	121 (61.4%)	11 (50.0%)	
T3-T4	87 (39.7%)	76 (38.6%)	11 (50.0%)	
HPV (P16) status				0.16
Negative	24 (11.0%)	20 (10.2%)	4 (18.2%)	
Positive	73 (33.3%)	69 (35.0%)	4 (18.2%)	
Unknown	122 (55.7%)	108 (54.8%)	14 (63.6%)	
Fractions per week				**0.036***
5	46 (21.0%)	44 (22.3%)	2 (9.1%)	
6	173 (79.0%)	153 (77.7%)	20 (90.9%)	
RT boost				0.47
SBRT	120 (54.8%)	110 (55.8%)	10 (45.5%)	
IMRT	99 (45.2%)	87 (44.2%)	12 (54.5%)	
Concurrent systemic therapy				0.80
No	135 (61.6%)	122 (61.9%)	13 (59.1%)	
Yes	84 (38.4%)	75 (38.1%)	9 (40.9%)	
Neck dissection (pre-/ post RT)				0.74
No	145 (66.2%)	130 (66.0%)	15 (68.2%)	
Yes	74 (33.8%)	67 (34.0%)	7 (31.8%)	
Tumor subsite				0.95
Tonsil	103 (47.0%)	94 (47.7%)	9 (40.9%)	
Other	116 (53.0%)	103 (52.3%)	13 (59.1%)	

of dose deposition and of the teeth extractions is related to the location (and presence) of ORN or not. If there would be a location effect, sparing complication prone regions of the mandible (for instance where extractions took place) may reduce the risk of ORN. However, if there would be no effect of location, selective sparing of certain mandible regions would not be effective. In the current study we demonstrate that a local dose effect relation in the mandible does exist and that the effect depends on whether dental elements in the vicinity are extracted and, on a patient level, whether the patient smoked or not.

We found that the anatomical location (molar vs premolar vs teeth) was not significant in our analysis. This suggests that the higher frequency of ORN observed in the molars is not due to its anatomical location, but most likely due to the dose that is often higher in the posterior mandible compared to the other mandible regions. We found ORN more frequently on the right side of the mandible, which was in line with the fact that most tumors in the group of patients that developed ORN were located also on the right side (13 out of 22) which led to on average a higher dose on the right side.

Previous studies have proposed dose constraints for the entire mandible, implicitly assuming no differences in radio-sensitivity within the mandible. For instance, Owosho et al. [8] suggested a maximum dose of 60 Gy on the mandible in a group of patients that developed ORN with very few pre-radiotherapy extractions (2/44 patients). Due to tumor location, in our dataset for only 2% of the patients a maximum dose lower than 60 Gy was achieved (without setting constraints for the mandible). So, a 60 Gy dose constraint does not seem feasible for the majority of our oropharyngeal cancer patients. Mohamed et al. [5] suggested V44 Gy < 42% and V58 Gy < 25% as constraints for the mandible, which according to a recent paper by Lee et al. [19] was feasible in the majority of their OPC patients. While such a DVH constraint will diminish high dose areas within the mandible, the remaining high dose being delivered close to teeth extractions might still lead to increased risk of ORN. So, a DVH constraint of the whole mandible disregards that the location of teeth extractions could play an important role in the risk of ORN.

Indeed, our results suggest that the risk on ORN does depend on the location of the extractions. Having extractions on the contralateral side did not increase the risk compared to no extractions (OR non-significant), while extractions on the ipsilateral side or of the element of interest did increase the likelihood developing of ORN (OR = 2.81, 95% CI: (1.12,7.05)). The ORs from GEE can be interpreted the same way as in a logistic regression model. The model therefore suggests that steering away high doses from areas with extractions would reduce the risk of ORN.

While GEE appropriately accounts for the correlation between dental elements of a patient, a limitation of GEE is that it allows for population average predictions only. Since estimating only population average effects is computationally easier than estimating both population average (fixed) and patient random effects, GEE

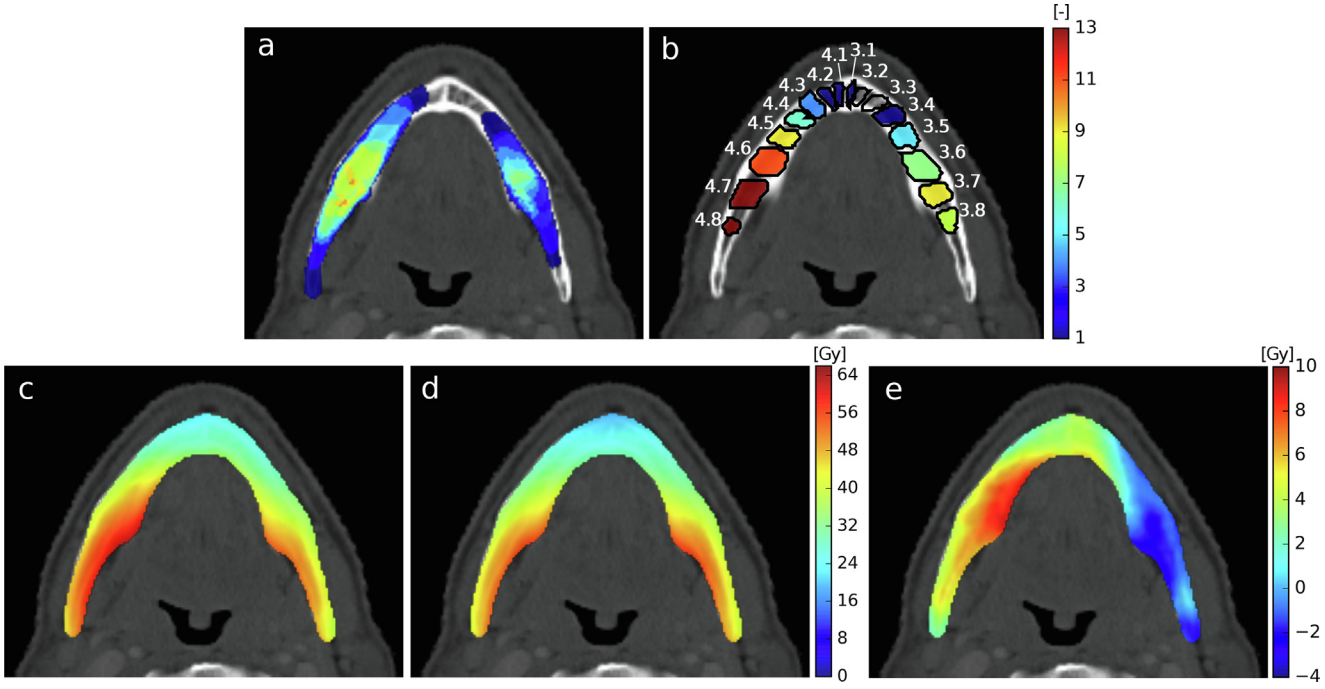

Fig. 1. Population map of the number of voxels with ORN and average dose distributions, deformed to and projected on the reference patient. (a) Total number of ORN cases depicted voxel-wise. (b) The number of ORN cases per delineated dental element VOI, the delineations of each dental element and their corresponding number. Note that none of the patients had ORN in element 3.2 and 3.3. Average dose maps [EQD2 Gy] of the mandible of (c) patients with ORN and (d) patients without ORN. The asymmetry of average dose map of patients with ORN (c) is most likely due to the majority (13 out of 22) of tumors being located on the right side of the mandible in the group of patients that developed ORN. In (e) the difference in average dose (ORN – no ORN) [EQD2 Gy] is shown.

Table 2
Intercept and coefficients for the final model including mean dose to the element VOI, extraction of the element of interest, and extraction of elements on the same side of the mandible (referred to as neighboring extractions) as variables. CI – Confidence interval, EQD2 Gy – equivalent dose of 2 Gy, OR – Odds ratio.

	Coefficient (95% CI)	OR (95% CI)	p-value	Bootstrapped Coefficient CI	Bootstrapped OR CI
Intercept	−7.01 (-8.04, −5.99)		$< 10^{-3}$		
Mean dose to element VOI [EQD2 Gy]	0.050 (0.040 0.063)	1.05 (1.04, 1.07)	$< 10^{-3}$	(0.037, 0.069)	(1.04, 1.07)
Ipsilateral extraction(s)	1.03 (0.11, 1.95)	2.81 (1.12, 7.05)	0.028	(-0.13, 2.01)	(0.88, 7.43)
Smoking at start RT	1.21 (0.25, 2.17)	3.37 (1.29, 8.78)	0.013	(0.40, 2.47)	(1.49, 11.85)

is better capable of dealing with smaller datasets than, for example, mixed-effect models. An additional implication of the fact that GEE only estimates population average effects is that it does not provide a way to translate the probability of ORN for each of the elements into a probability of ORN on a patient level. The correlation between elements in one patient ($\rho = 0.61$) suggests that ORN in these elements can indeed not be regarded independently, which implies that the element level probabilities are also not additive. To be able to use these results in the clinic, for example in treatment planning, it would be necessary to fit a multi-level mixed-effect model (i.e. a model that includes both random and fixed effects) to enable patient specific predictions followed by external validation of the model. Such a multi-level mixed-effect model would require considerably higher number of patients and events compared to the current study with 219 patients, and is therefore a topic for future research. What can be concluded from the GEE model is that further (multi-center) studies into ORN should acknowledge the location of extractions, the location of ORN within the mandible and the locally deposited dose, and not simply consider the mandible as one structure as most studies have done up to this point.

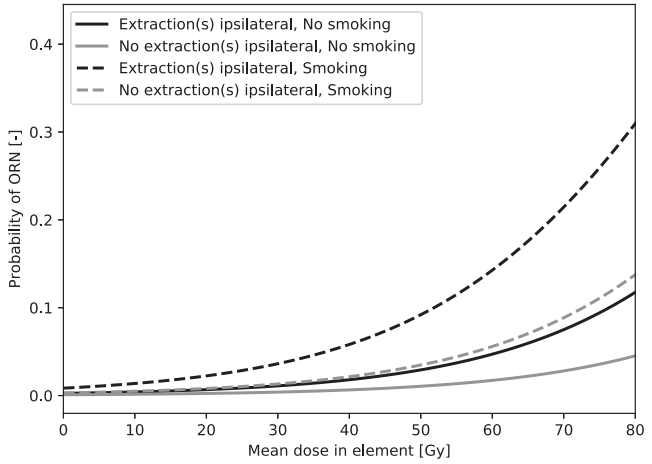

Fig. 2. Plots of the population average probability of ORN as function of the mean dose in the element VOI [EQD2 Gy]. The different curves represent situations with (black) and without (grey) extractions on the ipsilateral side of the element for non-smokers (solid) and smokers (dashed). The confidence intervals for the model coefficients can be found in Table 2.

This study has a couple of additional limitations that need to be addressed. First, the bootstrapping confidence intervals of the coefficients are generally slightly broader than those calculated based on the robust standard error. This was expected due to the limited data size. A clustered, stratified bootstrap was done to ensure the percentage of patients with ORN would be the same in all bootstrap samples. However, no stratification with regard to the

distribution of the extractions or smoking over the bootstrap sample was deployed. Since for smoking only two patients that developed ORN were non-smokers in our dataset, it is unlikely that the bootstrap sample contained only non-smokers or only very few smokers that developed ORN. In the case of extractions, it is possible that some bootstrap samples contained none or almost no patients with ORN and extractions ipsilateral, since around 33% of the patients that developed ORN did not have extractions pre-radiotherapy. This could explain why the resulting bootstrap coefficient CI included OR = 1 for extractions.

Second, a follow-up cut-off was chosen instead of time-to-event analysis. This was due, to the best of our knowledge, to the unavailability of a method that combined GEE with an AR1 working correlation matrix with time-to-event analysis.

Third, in this study we used the mean dose instead of the maximum dose to each dental element VOI as the mean dose is generally more robust than the maximum dose to deviations between planned and delivered dose. Also any treatment adaptations were fully accounted for in the dose accumulation. However, there still may be deviations between the planned and delivered dose. Fifth, even though post-radiotherapy extractions are a known risk factor for development of ORN, they were not taken into account in the analysis, since they are generally not known at the time of treatment planning, and can therefore not be accounted for to selectively spare regions at risk.

Finally, since patients with previous head and neck radiotherapy, as well as patients with previous oropharyngeal cancer were excluded from this study, the model does not apply for these two groups of patients. Additionally, one ORN patient was excluded because no radiological data on ORN location was available, which could have led to a slight underestimation of the ORN incidence.

In conclusion, we derived a local dose-response relationship on the level of the dental elements. Elements with ipsilateral extractions had 2.81 (95% CI: (1.12,7.05)) times higher odds of developing ORN than elements without ipsilateral extractions. Smoking at the start of radiotherapy (OR = 3.37, 95% CI: (1.29,8.78)), and mean dose to the element (OR = 1.05 per Gy, 95% CI: (1.04,1.07)) also significantly increased the odds of developing ORN. Our results indicate that regions of the mandible with pre-treatment extractions are locally more susceptible to ORN, than regions further away from the extractions. In future work, the local variation in radio-sensitivity should be taken into account in a larger dataset allowing for modelling of both fixed (population average) and patient random effects. Once independently validated, the dose response relations could help to selectively spare sensitive regions of the mandible to reduce the risk of ORN for patients with pre-radiotherapy extractions.

Conflict of interest statement

This research was funded by Elekta AB, Stockholm, Sweden. The department of radiotherapy also has a research collaboration with Accuray Inc., Sunnyvale, CA, USA and Varian, a Siemens healthineers company, Palo Alto, CA, USA.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109736.

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