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Marion Renouf, Simon Auger, Loïc Champion, Grégory Delpon, Julie Longis, et al.. Prognostic Factors of Mandibular Osteoradionecrosis Including Accurate Colocalization of Avulsions and Dosimetric Dental Mapping Software, a Case-control Study. *International Journal of Radiation Oncology, Biology, Physics*, 2024, 120 (3), pp.783-795. 10.1016/j.ijrobp.2024.04.019 . hal-04725601

HAL Id: hal-04725601

<https://hal.science/hal-04725601v1>

Submitted on 15 Jan 2025

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CLINICAL INVESTIGATION

Prognostic Factors of Mandibular Osteoradionecrosis Including Accurate Colocalization of Avulsions and Dosimetric Dental Mapping Software, a Case-control Study



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Received Nov 6, 2023; Accepted for publication Apr 3, 2024

Purpose: Osteoradionecrosis (ORN) of the mandible remains a significant complication in the intensity modulated radiation therapy (IMRT) era. Dental dose cannot be predicted from heterogeneous IMRT dose distributions; mandibular dose metrics cannot guide dentist avulsion decisions in high-risk ORN situations. Using a mapping tool to report dental root dose, avulsions, and ORN sites, we re-examined ORN risk factors in a case-control study.

Methods and Materials: From 2008 to 2019, 897 consecutive patients with oral cavity/oropharynx or unknown primary cancer undergoing IMRT were analyzed to identify ORN cases. These were matched (1 ORN/2 controls) retrospectively for tumor location, surgery, and tobacco consumption in a monocentric case-control study. Univariate and multivariate analyses integrated ORN factors and accurate dental dose data (grouped into 4 mandibular sectors). Generalizability was investigated in a simulated population database.

Results: A total of 171 patients were included. The median follow-up was 5.2 and 4.5 years in the ORN and control groups, respectively. The median time to ORN was 12 months. In univariate analysis, post-IMRT avulsions at the ORN site (hazard ratio [HR] = 3.6; 95% confidence interval [CI] = 1.5-8.9; $P = .005$), tumor laterality (HR, 4.4; 95% CI, = 1.4-14, $P = .01$), mean mandibular dose (HR, 1.1; 95% CI, = 1.01-1.1; $P = .018$) and mean dose to the ORN site (HR, 1.1; 95% CI, = 1.1-1.2; $P < .001$) correlated with higher ORN risk. In multivariate analysis, mean dose to the ORN site (HR, 1.1; 95% CI, = 1.1-1.2; $P < .001$) and post-IMRT avulsions at the ORN site (HR, 4.6; 95% CI, = 1.5-14.7; $P = .009$) were associated with ORN. For each increase in gray in dental dose, the ORN risk increased by 12%. Simulations confirmed study observations.

Conclusions: Dental dose and avulsions are associated with ORN, with a 12% increase in risk with each additional gray. Accurate dose information can help dentists in their decisions after IMRT. © 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC license (<http://creativecommons.org/licenses/by-nc/4.0/>)

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Disclosures: None.

Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Acknowledgments—This work was partly carried out thanks to the support of the INCa (french national institute of cancer) as part of the call for projects SEQ-RTH22.

Introduction

Osteoradionecrosis (ORN) of the mandible is a rare but dreadful complication of cervicofacial irradiation for patients with head and neck cancer. It can lead to severe functional sequelae, such as chronic pain, phonation, and swallowing disorders. Although the dosimetric benefit of intensity modulated radiation therapy (IMRT) on parotid and mandible sparing is significant and toxicity profiles have substantially improved with IMRT, ORN remains an issue. Despite IMRT and strict prophylactic dental care, ORN incidence still ranges from approximately 4% to 8%.¹⁻⁵ There is a wide range of identified ORN risk factors in the literature, often determined from retrospective studies with no strong consensus. A few of them stand out, such as surgery before radiation therapy, tumor location (oral cavity/oropharynx [OC/OR]), dental avulsions after radiation therapy, higher mean dose to the mandible (with no consensual threshold), volume of the mandible receiving over 60 Gy (V60) > 14% to 25%,⁶⁻¹⁵ and maximal dose to the mandible (to 1 cm³ of the mandible) of 70 Gy.¹⁶ However, there is a failure to accurately prevent ORN in the context of avulsions after completion of IMRT. Global mandibular dose metrics are not appropriate when dental care in irradiated areas is needed. Dose-volume histograms of the whole mandible cannot fully summarize the geometric complexity of the IMRT dose distribution. IMRT relies on dose heterogeneities to preserve organs at risk close to the tumor volumes, with strong local gradients in the mandible. Therefore, developing tools and strategies to predict ORN and prevent such complications is crucial. Preliminary works have proposed atlases providing accurate dental root dose but have been limited in their applicability to routine practice by nonclinically relevant computational times.¹⁷ Considering the need for accurate dose reporting to each tooth unit with its surrounding periodontium in the mandible to assist dentists in their decisions and to better understand dose-ORN relationships, a semiautomatic ubiquitous scripting-based dental dose mapping tool for the individual segmentation of each tooth was designed.¹⁸ Using this specific semiautomatic dental dose mapping tool, we reassess dose-effect relationships to model the risk of ORN, integrating geometric information.

The aim of this study was 1) to identify patient, tumor, and dosimetric factors associated with ORN in a case-control study and (2) to establish geo-anatomic correlations between dose delivered to dental roots/mandibular dental sectors and ORN location using the dental dose mapping tool in a cohort of patients treated with IMRT for OC, OR, or unknown primary carcinoma (CUP).

Methods and Materials

Patient selection

We conducted a monocentric retrospective case-control study. Consecutive patients treated with curative intention with exclusive or adjuvant IMRT for carcinoma of the OC/

OR or CUP between 2008 and 2019 were included. Exclusion criteria were age <18, prior cervical radiation, and other head and neck cancer/tumor location.

This institutional review board approved the study, which was also general data protection regulation (GDPR)-compliant for the local ethics committee (RGPD CHU-MR004). The study involved patients selected on the basis of tobacco consumption, tumor location, and surgery before radiation to match controls without ORN and cases with ORN. Secondary matching criteria were age at diagnosis and gender.

Data collection

Data were retrospectively collected from patient charts and DICOM radiation therapy data.

Patient characteristics

Patients' demographic characteristics and comorbidities were collected, including age, gender (male/female), history of diabetes, cardiovascular disease, alcohol consumption, nutritional status prior/during radiation, long-term corticotherapy (>3 months), and bisphosphonate treatment. Alcohol misuse was quantified using the French national authority for health (Haute Autorité de la Santé, HAS) recommendations on alcohol consumption, defined as "2 alcohol units per day, and not every day." Smoking status at the time of treatment (yes or no) was a matching parameter, so that it would not be a confounding factor. Pack-year history was also collected.

Tumor characteristics (TNM 7th version, status, location, and P16 status) were also collected. Prior dental evaluation and posttreatment evaluation (at 3 months and every 6 months) were collected, as well as pre-IMRT dental avulsions (yes/no, mandible location, and time between avulsion and radiation therapy), post-IMRT dental avulsions (yes/no, mandible location, and time between radiation therapy and avulsion), fluoride prophylaxis (yes/no), and dental rehabilitation (prosthetics, yes/no).

Treatment characteristics

Prior surgery (with or without bone resection), type of reconstruction (ie, soft tissue, flaps, and/or osteosynthesis), and concomitant systemic treatment (concomitant chemotherapy [cisplatin] or cetuximab) data were collected.

All patients were treated with IMRT using helical or static IMRT. Definitive radiation therapy consisted of 70 Gy, delivered in 35 fractions to the tumor +/- nodal volume, and 56 Gy, delivered to elective prophylactic nodal regions. Patients treated with adjuvant radiation received 60 to 66 Gy in 30 to 33 fractions in the tumor bed, with 54 Gy (50 Gy EQD2) to prophylactic lymph node areas. Tumor and nodal clinical target volumes (CTVp and CTVn) were delineated using a combination of geometric approaches, with adjustments using the anatomic method to include microscopic extensions depending on each tumor location. The

dosimetric constraints used were mean dose (Dmean) to at least 1 parotid < 24 Gy. There was no specific constraint applied to the mandible owing to tumor location and stage.

Acute toxicity during and <3 months post-IMRT (mucositis, weight loss, radiation-induced dermatitis) and late toxicity (xerostomia) were graded using the Common Terminology Criteria of Adverse Events (CTCAE) v. 5.0 classification.¹⁹

ORN data

Osteoradionecrosis was defined as a lack of healing mucosa of >1 cm² appearing in an irradiated field of the mandible 3 months after radiation in the absence of cancer recurrence.^{6,20} The clinical diagnosis was completed with a computed tomography (CT) scan of the jaw if necessary. Time from end of IMRT to ORN diagnosis was also reported.

ORN grades were determined using the CTCAE and Radiation Therapy Oncology Group (RTOG) classifications. The CTCAE ORN grades were defined as follows: grade 1: asymptomatic, clinical or diagnostic observations only; grade 2: symptomatic, medical intervention indicated (eg, topical agents), limitations in the performance of instrumental activities of daily living; grade 3: severe symptoms, limitations in the performance of self-care ADLs, elective operative intervention indicated; grade 4: life-threatening consequences, urgent intervention indicated; and grade 5: death. RTOG grades were grade 0: no sign; grade 1: asymptomatic, bone density reduction; grade 2: moderate pain/tenderness; grade 3: severe pain/tenderness; grade 4: necrosis, spontaneous fracture; and grade 5: death.

Dosimetric data extraction

Dosimetric data were extracted from the treatment planning software Raystation (RaySearchLabs) using a semiautomatic Python script algorithm integrated into RayStation and serving as a dental dose mapping tool (possibly implemented in open-source solutions and other treatment planning software interfaces).¹⁸ Thirty-two dental regions of interest (ROIs) corresponding to 32 cylinders including each tooth and its surrounding periodontium were automatically created by linear interpolation on the mandible based on 3 points positioned manually. Dmean, maximum dose (Dmax), and minimum dose (Dmin) were extracted from each ROI and collected in a database, among other common dosimetric data, such as Dmean and Dmax to the mandible, volume of mandible receiving 35 Gy (V35), V44, V50, V58, and V60.^{12,14,15}

Anatomic correlation between ORN, dental avulsions, and dosimetric factors

ORN location was reported using the following mandibular dental sectors (based on the world dental federation notation): 31 to 34, 35 to 38, 41 to 44, and 45 to 48. This repartition determines anterior tooth sectors (31-34, 41-44) and molar sectors (35-38, 45-48). Anatomic dental location on dosimetry, avulsions, and ORN site were examined in dental

sectors. The 32 ROI were grouped into mandibular dental sectors, and mean dose was extracted in each sector for patients with ORN and compared with controls. To standardize dose analysis for case-match comparison, mandibular sectors were renamed as ipsilateral and contralateral sectors depending on ORN location.

For each triplet (1 case, 2 controls), the geoanatomic reference area for the 3 patients was the area where ORN occurred in the case. Thus, for the 2 controls, the absolute locations of the irradiation doses (31-48) were recoded into locations relative to the case as the same or different area from the case or ipsilateral or contralateral to the case.

Follow-up

Clinical follow-up of patients was performed quarterly by the physician and the surgeon for the first 2 years, then half-yearly for up to 5 years. A first CT scan was performed at 3 months, then annually. Patients were referred for dental evaluation every 6 months.

Statistical analysis

Categorical variables were described as the number (%) of each modality, and continuous variables, as the median (interquartile range [IQR]).

The univariable determination of relationships between the occurrence of osteoradionecrosis and the various variables of interest (biologic and clinical variables on the one hand, dosimetric variables on the other hand) was carried out using univariate conditional logistic regression.

The evolutionary variable (occurrence of ORN) was defined as the time between the start of radiation therapy and the date of diagnosis of ORN or censored at the date of the most recent news without ORN. It was described using Kaplan-Meier curves. The median of the whole population follow-up was calculated using the inverse Kaplan-Meier method.

For the multivariate step, the model included biologic and clinical parameters with a significant univariate relationship ($P < .10$), as well as a single dosimetric variable (only the one with the strongest univariate relationship to ORN). From the multivariable conditional logistic regression, the adjusted conditional odds ratios were calculated with their 95% confidence interval (95% CI). Missing data for variables selected for multivariable analysis were imputed by multiple imputation if they contained less than 20% missing data.

If necessary in post hoc analyses, subgroups of interest were compared using Pearson's χ^2 test (or Fisher's test if necessary) for categorical variables and Student's t test (or Mann-Whitney test if necessary) for continuous variables with 2 modalities (or Analysis of variance (ANOVA)/Kruskal-Wallis if more than 2 modalities).

We needed to assess estimated predictions of ORN as a function of the 3 independent factors found in the

multivariate analysis using conditional logistic regression, in a population of the same size as the whole population ($n = 897$), and in a robust and unbiased way. To do this, we created by simulation 100 samples of 897 patients with the 57 original cases, the 114 original controls, and 726 simulated controls with the same characteristics as the 114 original controls. Unconditional logistic regression was applied to these samples, allowing us to estimate the predictions that could not be made using conditional logistic regression.

All analyses were performed with a final significance level set at 5% (2-tailed formulation) using SAS software version 9.4 (SAS Institute Inc) and Stata SE 17 (StataCorp LLC, College Station).

Results

Patient characteristics

From 2008 to 2019, 897 patients were treated with IMRT for carcinoma of the OC/OR or CUP. Of them, 63 patients had ORN; 57 patients were included (6 patients were excluded, 3 had ORN associated with cancer recurrence, 1 had maxillary ORN, and 2 had salvage surgery after radiation therapy). A total of 114 controls were matched to the 57 cases. The median follow-up was 5.2 years in the ORN group (95% CI, 4-5.6) and 4.8 years in the control group (95% CI, 3.9-5.2). [Table 1](#) shows the patients' characteristics. Matching criteria are marked with an asterisk. General nonmatching criteria were well-balanced between cases and controls. More than 80% of patients had pre-IMRT dental evaluation. Two-thirds of cases and controls had pre-IMRT dental avulsions; 66.8% of ORN cases had post-IMRT dental avulsions versus 29.8% in controls ($P < .001$). One-third of patients continued smoking after radiation. Of the patients treated with surgery, there was slightly more invasive surgery (with bone effraction) in the ORN arm than in controls (31.5% vs 23.8%).

ORN

The relative frequency of ORN was 6.4%, and cumulative incidence in the total predictive population at 5 years was 10.9% (95% CI, 8.2-14.4). [Figure 1](#) shows time to ORN in the population of patients with ORN; 75% of cases appeared in the first 2 years, and the median time to ORN was 12.0 months (5.6; 25.3) ([Table 2](#)). More than two-thirds of ORN cases were grade 3 or higher in both RTOG and CTCAE classifications, but with more grade 4 cases in the RTOG classification (40.4% versus 5.3%). ORN was mainly located in molar mandibular sectors (43.9% in 35-38, 42.1% in 45-48), and nearly 80% of ORN cases were ipsilateral to the tumor location when the tumor was located laterally. The Dmean in ORN dental sectors was 60.8 Gy (35.4-70.6).

ORN risk factors

[Tables 3 and 4](#) show the results from uni- and multivariate analyses of the case-matching study for clinical and dosimetric factors associated with ORN.

In univariate analysis, tumor laterality (central vs sided, hazard ratio [HR], 4.4; 95% CI, 1.4-14; $P = .011$) and post-IMRT dental avulsions in the same site as the ORN (HR, 3.6; 95% CI, 1.5-8.9; $P = .005$) were significantly associated with a diagnosis of ORN. Diabetes (HR, 2.6; 95% CI, 0.9-7.4; $P = .07$), lymph node involvement (HR, 1.9; 95% CI, 0.8-4; $P = .11$), surgery with bone effraction (HR, 2.9; 95% CI, 1-8.4; $P = .051$), and post-IMRT alcohol use (HR, 2.1, 95% CI, 0.8-5.4; $P = .139$) showed a trend suggesting a risk of ORN ([Table 3](#)).

Among treatment-related potential factors, chemotherapy use did not increase the risk of ORN, but for patients who did not have concomitant chemotherapy, ORN appeared significantly earlier ($P = .008$).

Regarding dosimetric data analysis, mean dose to mandible (HR, 1.1; 95% CI, 1.01-1.1; $P = .018$), mean dose to the same dental sector as ORN (HR, 1.1; 95% CI, 1.1-1.2; $P < .001$), mean dose to the ipsilateral parotid (HR, 1.1; 95% CI, 1.0-1.1; $P = .004$), and all of the mandible dose-volume relations analyzed were significantly associated with ORN in univariate analysis. With regard to dosimetric variables, only the "mean dose to the same dental sector as ORN" variable was introduced for testing into the multivariate analysis ([Table 4](#)).

Results of the multivariate analysis are shown in [Tables 3 and 4](#). In multivariate analysis, only Dmean to the ORN site (HR, 1.1; 95% CI, 1.1-1.2; $P < .001$) and post-IMRT dental avulsions in the same dental sector as the ORN (HR, 4.6; 95% CI, 1.5-14.7; $P = .009$) were significantly associated with ORN. For each Gy increase to the ORN dental site, the risk of ORN increased by 12%.

ORN predictive factors

To determine the effect of identified ORN risk factors in the general population and their potential predictive value, predictive curves of ORN were generated in a global simulated population with significant ORN risk factors in multivariable conditional logistic analysis. [Figure 2](#) shows ORN occurrence simulated in the general population in relation to Dmean to the same dental sector in patient subpopulations exposed to diabetes and post-IMRT dental avulsions. Patients with avulsions had a high risk of developing ORN at a lower mean dose to the mandibular sector (up to 6.3% when the dose exceeded 30 Gy), with a 20.9% risk of ORN when the mean dose exceeded 60 Gy. The same observation could be made with diabetes, except the risk of ORN increased at a higher mean dose (the risk was 2.1% at 30 Gy, rising to 7.2% at 50 Gy). Patients with diabetes who underwent post-IMRT dental avulsions were prone to developing ORN at a lower mean dose in the same dental sector: the

Table 1 Characteristics of osteoradionecrosis (ORN) cases and controls

	ORN Cases (N = 57)	Controls (N = 114)	Wilcoxon or Fisher P value
Age*			.803
Median (Q1, Q3)	59.0 (52.0, 65.0)	59.0 (52.0, 66.0)	
Gender*			1.000
Male	46 (80.7%)	91 (79.8%)	
Female	11 (19.3%)	23 (20.2%)	
Body mass index classes			.372
18.5-25	34 (60.7%)	66 (57.9%)	
<18.5	3 (5.4%)	14 (12.3%)	
25-30	15 (26.8%)	22 (19.3%)	
>30	4 (7.1%)	12 (10.5%)	
Missing	1	0	
ECOG status			.954
0	39 (70.9%)	76 (68.5%)	
1	14 (25.5%)	30 (27.0%)	
2	2 (3.6%)	5 (4.5%)	
Missing	2	3	
Smoking status*			1.000
No	5 (8.8%)	9 (7.9%)	
Yes	52 (91.2%)	105 (92.1%)	
Missing	0	0	
Smoking pack-years			.650
Mean (SD)	35.4 (13.9)	36.8 (18.8)	
Persistent smoking after IMRT			.467
No	35 (63.6%)	60 (69.8%)	
Yes	20 (36.4%)	26 (30.2%)	
Missing	2	28	
Alcohol misuse			.496
No	17 (29.8%)	40 (35.4%)	
Yes	40 (70.2%)	73 (64.6%)	
Missing	0	1	
Diabetes			.100
No	47 (83.9%)	106 (93.0%)	
Yes	9 (16.1%)	8 (7.0%)	
Missing	1	0	
Weight loss			.256
<5%: grade 0	26 (45.6%)	65 (57.0%)	
5-10%: grade 1	21 (36.8%)	37 (32.5%)	
10-20%: grade 2	10 (17.6%)	12 (10.5%)	
>20%: grade 3	0	0	
Missing	0	0	

(Continued)

Table 1 (Continued)			
	ORN Cases (N = 57)	Controls (N = 114)	Wilcoxon or Fisher P value
Tumor location*			.271
Oral cavity	28 (51.9%)	54 (47.4%)	
Oropharynx	26 (48.1%)	54 (47.4%)	
Cancer of unknown primary	0 (0.0%)	6 (5.3%)	
Missing	3	0	
Bone invasion			.402
No	49 (86.0%)	89 (80.2%)	
Yes	8 (14.0%)	22 (19.8%)	
Missing	0	3	
Tumor laterality			.030
Lateral	34 (69.4%)	92 (85.2%)	
Central	15 (30.6%)	16 (14.8%)	
Missing	8	6	
cT stage			.939
1	3 (5.4%)	7 (6.1%)	
2	14 (25.0%)	34 (29.8%)	
3	18 (32.1%)	30 (26.3%)	
4	18 (32.1%)	37 (32.5%)	
X	3 (5.4%)	6 (5.3%)	
Missing	1	0	
cN stage			.047
0	13 (23.2%)	41 (36.0%)	
1	20 (35.7%)	30 (26.3%)	
2	21 (37.5%)	29 (25.4%)	
3	2 (3.6%)	14 (12.3%)	
Missing	1	0	
Dental hygiene			.829
Poor	28 (71.8%)	47 (69.1%)	
Healthy	11 (28.2%)	21 (30.9%)	
Missing	18	46	
Pre-IMRT dental evaluation			.256
No	6 (10.7%)	19 (18.6%)	
Yes	50 (89.3%)	83 (81.4%)	
Missing	1	12	
Edentulous			.382
No	54 (94.7%)	94 (89.5%)	
Yes	3 (5.3%)	11 (10.5%)	
Missing	0	9	
Pre-IMRT dental avulsions			.582
No	15 (28.3%)	31 (33.3%)	
Yes	38 (71.7%)	62 (66.7%)	

(Continued)

Table 1 (Continued)			
	ORN Cases (N = 57)	Controls (N = 114)	Wilcoxon or Fisher P value
Missing	4	21	
Post-IMRT dental follow-up			1.000
Yes	48 (84.2%)	72 (63.2%)	
No/missing	9 (15.8%)	42 (36.8%)	
Post-IMRT dental avulsions			<.001
No	18 (31.6%)	62 (54.4%)	
Yes	38 (66.7%)	34 (29.8%)	
Missing	1 (1.8%)	18 (15.8%)	
Pre-IMRT surgery*			.738
No surgery	20 (35.1%)	44 (38.6%)	
Surgery without BE	17 (31.5%)	43 (37.7%)	
Surgery with BE	17 (31.5%)	27 (23.7%)	
Missing	3	0	
Surgery with reconstruction†			.418
No surgery	20 (39.2%)	44 (38.6%)	
Surgery without reconstruction	11 (21.6%)	35 (30.7%)	
Surgery with reconstruction	20 (39.2%)	35 (30.7%)	
Missing	6	0	
Surgery with osteosynthesis			.423
No surgery	20 (39.2%)	44 (39.3%)	
Surgery without osteosynthesis	22 (43.1%)	56 (50.0%)	
Surgery with osteosynthesis	9 (17.6%)	12 (10.7%)	
Missing	6	2	
Concurrent chemotherapy			.599
No	19 (33.3%)	33 (28.9%)	
Yes	38 (66.7%)	81 (71.1%)	
Missing	0	0	
IMRT type			.321
Helical IMRT	31 (54.4%)	72 (63.2%)	
Static IMRT	26 (45.6%)	42 (36.8%)	
Missing	0	0	
Total IMRT dose			.852
Mean in Gy (SD)	67.75 (2.00)	67.61 (2.36)	
Median (Q1, Q3)	66.0 (66.0, 70.0)	66.0 (66.0, 70.0)	
Min, Max	66.0, 70.0	54.0, 70.0	
Missing	0	0	
Uni/bilateral IMRT			1.000
Cervical unilateral RT	12 (21.1%)	24 (21.1%)	
Cervical bilateral RT	45 (78.9%)	90 (78.9%)	
Missing	0	0	

* Matching criteria for case-control study.

† Reconstruction: Soft tissue with/without flap and/or all types of bone effraction (osteosynthesis and mandible interruption or bone plate without mandible interruption).

Abbreviations: BE = bone effraction; ECOG = Eastern Cooperative Oncology Group; IMRT = intensity modulated radiation therapy.

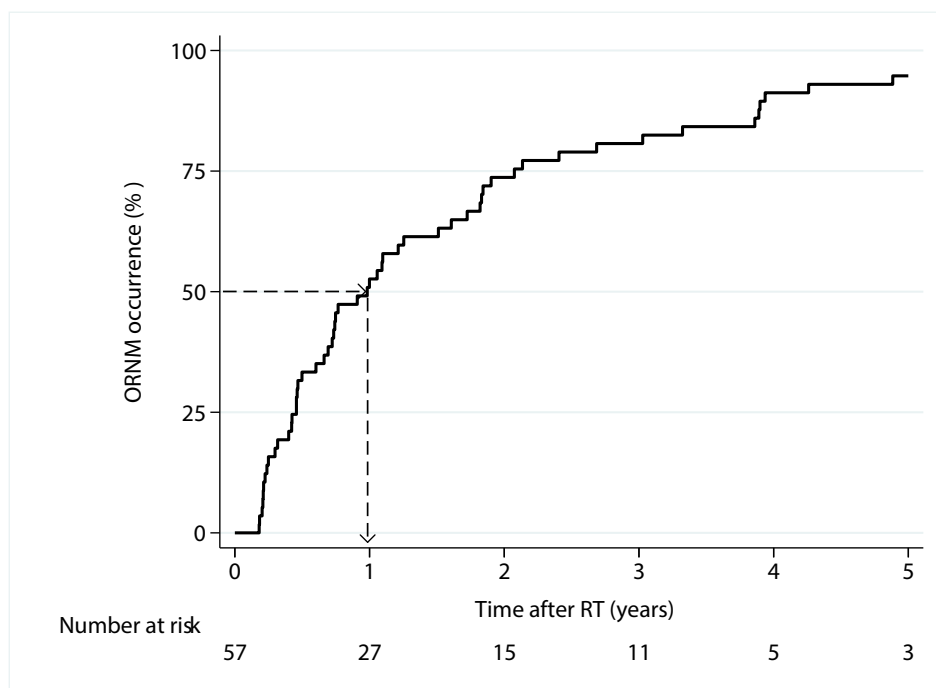


Fig. 1. Time to ORN diagnosis in the population of cases.

risk of ORN rose to 8.2% when the Dmean exceeded 30 Gy. Theoretical ORN recurrence rates increased to 37.3% at 60 Gy.

Discussion

This study is one of the largest case-control cohorts analyzing ORN in patients treated exclusively with IMRT, and it used an accurate dental root—dose mapping tool. In our study, the relative frequency of ORN was 6.4%; 75% of ORN cases occurred in the first 2 years after completion of IMRT, with 50% 2-year overall survival, which is consistent with data from recent literature establishing its incidence at approximately 4% to 8% in the IMRT era.^{12-15,21} Here, the ORN cumulative incidence (determined in the whole population by extrapolation) was 10.9%, with a higher ORN incidence in surviving patients.¹⁰ Follow-up is therefore essential for long-surviving patients.

In our study, post-IMRT dental avulsions in the same dental sector as ORN were associated with a risk of ORN in the multivariate analysis ($P = .009$). These results are consistent with previously published literature, mainly retrospective studies with small cohorts and scarce information on the location of extraction compared with ORN.^{11,22-24} In 1970, Meyer²⁵ suggested that bone trauma in a previously irradiated territory of the mandible could induce ORN. Other studies found that postradiation therapy dental avulsions were associated with a higher risk of ORN, possibly because of the local induced trauma.^{24,26} These data suggest the importance of preventive care and close life-long dental follow-up after radiation therapy. On the other hand, the

role of preradiation therapy dental avulsions in ORN occurrence is more debated.²⁷⁻²⁹ In our study, there was no influence of pre-IMRT dental avulsions on ORN.

Numerous retrospective studies have evaluated the dosimetric factors associated with ORN, without any clear consensus emerging. Mohamed et al¹² and Aarup Kristensen et al¹³ found that mean dose to the mandible was associated with a higher risk of ORN. In our study, Dmean to the mandible was not correlated with a risk of ORN in multivariate analysis. In other studies, the volume of the mandible exposed to a radiation dose is frequently used as a determinant factor: Kubota et al¹⁴ found V60 Gy > 14% to be associated with ORN; Mohamed et al¹² found that 81% of ORN cases appear when V44 > 42% and V58 > 25%. Tsai et al¹⁵ found higher V50 and V60 values in patients with ORN compared with ORN-free patients. Based on this literature, V35, V44, V50, V58, and V60 were analyzed and found to be significantly associated with ORN in univariate analysis, but this association lost significance in multivariate analysis. IMRT induces very steep gradients, and the local dose to the mandible depends greatly on tumor location and laterality. Therefore, using dosimetric data based on mandible volume does not take into account high gradients of doses delivered to subparts of the mandible and thus may not accurately predict ORN risks.

Past studies have evaluated the dose distribution to dentate portions of the mandible during head and neck irradiation: the dose delivered in tooth-bearing areas was associated with tumor location, laterality, and lymph node involvement, with high gradients between posterior and anterior teeth. Bak et al³⁰ retrospectively reviewed the dosimetry of tooth-bearing areas in 54 patients treated with

Table 2 Characteristics of osteoradionecrosis (ORN) of the mandible in cases

	Total (N = 57)
RTOG/EORTC classification (0, 1, 2, 3, 4, 5) (n = 57)	
1	3 (5.3%)
2	12 (21.1%)
3	19 (33.3%)
4	23 (40.4%)
CTCAE classification (0, 1, 2, 3, 4, 5) (n = 57)	
1	3 (5.3%)
2	13 (22.8%)
3	38 (66.7%)
4	3 (5.3%)
Time after IMRT (days)	
Mean (SD)	599.74 (640.57)
Median (Q1, Q3)	359.0 (167.0, 758.0)
Min, Max	66.0, 2919.0
Time between post-IMRT avulsions and ORN (d)	
Median (Q1, Q3)	132.0 (90.0, 381.0)
Min, Max	20.0, 1756.0
ORN location in dental sectors	
31-34	4 (7.0%)
35-38	25 (43.9%)
41-44	4 (7.0%)
45-48	24 (42.1%)
ORN location according to tumor location	
Ipsilateral	27 (79.4%)
Contralateral	7 (20.6%)
Mean dose (Dmean) (SD) in ORN sectors (Gy)	60.8 (8.6)
	Range = 35.4-70.6
ORN in avulsion sites	
Yes vs No vs NK	26/29/2
<p><i>Abbreviations:</i> RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; CTCAE = Common Terminology Criteria for Adverse Events, version 4.0; NK = not known; IMRT = intensity modulated radiation therapy; SD = standard deviation.</p>	

IMRT for head and neck cancer. Teeth were individualized as molars, premolars, and anterior teeth. Mandibular molar regions received a Dmean of 50 to 60 Gy in tumors of the base of the tongue or tonsils, with an anteroposterior gradient of 10 to 20 Gy in tumors of the OC or OR. Polce et al

generated 18 dosimetric scenarios of head and neck IMRT.³¹ For advanced tumors of the oral cavity and level 1b lymph node involvement, the Dmean to posterior thirds of the mandible was greater than 50 Gy. Even though these data represent valuable information on dose repartition to dentate portions of the mandible during IMRT, to our knowledge, our study is the first linking an anatomic sub-unit of the mandible to the risk of ORN.

The Dmean was significantly higher in the dental sector in which ORN was diagnosed: for each increase in gray, the risk of ORN rose by 12%. These results are in line with those of Owosho et al, which is the most comparable study to ours in the published literature. In this case-control analysis of patients treated with IMRT for OC/OR cancer between 2004 and 2013, 44 out of 1023 patients developed ORN (4.3%).³² ORN sites were delineated, and the Dmax and Dmean to the ORN site were analyzed retrospectively: the Dmean to the ORN site was significantly higher than that to the ipsilateral molar region in ORN-free patients. For each increase in gray, there was a 7% increase in the risk of ORN. In the ORN population, the Dmean and Dmax to the ORN site were significantly higher than that to the contralateral non-ORN site. The main difference with our study is that in the prior study, ORN was retrospectively delineated by a radiation oncologist at the ORN site and compared with dosimetry, while we used a semiautomatic delineation technique and data extraction of dosimetry, which was independent of the ORN occurrence event.

The main drawback of studies evaluating doses to tooth-bearing areas was the technique used for tooth delineation, which was often manual by a radiation oncologist time-consuming and could be impaired by artifacts and missing teeth. With improvements in radiation treatment software, it is now possible to extract dosimetric data from new ROIs with more accurate organ-at-risk delineation during patient treatment planning. Thariat et al¹⁷ generated multiatlas-based tooth-by-tooth segmentation to extract maximum dose per tooth. The aim was to facilitate dosimetric information transmission to dentists as part of routine care, but it was difficult to implement because of redhibitory computer set-up times at this time. Chan et al³³ developed an artificial intelligence-based Clinical Decision Support tool to predict which subregions of the mandible would be exposed to a Dmean > 50 Gy from the gross tumor volume determined on diagnostic CT scans before treatment planning, with high precision and accuracy. Our dental dose mapping tool extracts dosimetric data (mean dose, maximum dose, minimum dose) from semiautomatically generated cylinders comprising each tooth with surrounding periodontium in a quick and reproducible way without any training or validation cohorts. This dental dose map is given to each patient for their dentists, with 3 levels of risk identified: mean dose < 35 Gy, based on the recommendations of the French-speaking Association of Oncological Support Care (AFSOS); mean dose between 35 and 50 Gy; and mean dose > 50 Gy. Using such tools in routine practice would help identify patients at risk as early as at the treatment planning stage.

Table 3 Univariate and multivariate analyses of patient and tumor osteoradionecrosis (ORN) risk factors

Univariate analysis of ORN risk factors				Multivariate conditional logistic regression			
	HR	95%CI	P value		HR	95%CI	P value
Body mass index classes							
18.5-25	ref						
<18.5	0.40	0.11-1.50	0.177				
25-30	1.41	0.64-3.14	0.395				
>30	0.69	0.21-2.29	0.545				
OMS ECOG status							
1-2 vs 0	0.77	0.37-1.62	0.493				
Alcohol misuse							
Yes vs No	1.44	0.61-3.40	0.407				
Diabetes				Diabetes			
Yes vs No	2.58	0.90-7.39	0.077	Yes vs No	3.39	0.88-13.01	.075
Bone invasion							
Yes vs No	0.65	0.26-1.59	0.342				
Tumor laterality				Tumor laterality			
Central vs Lateral	4.44	1.41-13.95	0.011	Central vs lateral	2.71	0.69-16.61	.153
cT stage							
cT2 vs cT1	1.05	0.24-4.49	0.950				
cT3 vs cT1	1.48	0.33-6.70	0.610				
cT4 vs cT1	1.26	0.28-5.81	0.760				
cN stage							
1-2-3 vs 0	1.85	0.86-3.97	0.113				
Dental hygiene							
Healthy vs Poor	0.88	0.33-2.38	0.802				
Pre-IMRT dental evaluation							
Yes vs No	1.67	0.62-4.53	0.310				
Pre-IMRT dental avulsions							
Yes vs No	1.24	0.61-2.52	0.548				
Pre-IMRT dental avulsions in same dental sector as ORN							
Yes vs No	1.63	0.80-3.33	0.180				
Post-IMRT dental avulsions							
Yes vs No	1.37	0.69-2.75	0.371				
Post-IMRT dental avulsions in same dental sector as ORN				Post-IMRT dental avulsions in same dental sector as ORN			
Yes vs No	3.60	1.46-8.86	0.005	Yes vs No	4.64	1.46-14.73	.009

Multivariate conditional logistic regression was performed on covariates with $P < .10$.
Abbreviations: Ref = reference; HR = hazard ratio; CI = confidence interval; OMS = organisation mondiale de la santé; ECOG = eastern cooperative oncology group; IMRT = intensity modulated radiation therapy.

As ORN remains a life-long risk in long-term follow-up of head and neck cancer patients, and as patients' survival increases, it has become crucial to predict the potential risk of ORN. Predictive curves of ORN were established according to mean dose to dental sectors, therefore determining

patients' risk profiles for developing ORN. Patients with diabetes who experience post-IMRT dental avulsions are exposed to a risk of developing ORN of up to 37.3% if the dose exceeds 60 Gy. We were able to identify a high-risk profile for patients with post-IMRT dental avulsions, with a

Table 4 Univariate and multivariate analyses of treatment osteoradionecrosis (ORN) risk factors

	Univariate analysis of ORN risk factors			Multivariate conditional logistic regression		
	HR	95%CI	P value	HR	95%CI	P value
Surgery with bone effraction						
Yes vs No	2.89	0.99-8.40	0.051			
Concurrent chemotherapy						
Yes vs No	0.80	0.39-1.63	0.539			
Total IMRT dose						
≥ 66 Gy vs < 66 Gy	1.23	0.26-5.75	0.790			
IMRT type						
Tomo vs Static	1.39	0.75-2.58	0.293			
Uni/bilateral IMRT						
Unilateral vs Bilateral	1.00	0.42-2.38	0.999			
Post-IMRT alcohol use						
Yes vs No	2.06	0.79-5.39	0.139			
Post-IMRT smoking status						
Yes vs No	1.44	0.66-3.15	0.358			
Mean dose to same dental sector as ORN	1.099	1.053-1.146	<0.001	Mean dose to same dental sector as ORN (for 1 Gy)	1.12	1.07-1.19 <.0001
Mean dose to contralateral dental sector as ORN	0.991	0.969-1.014	0.447			
Mean dose to ipsilateral parotide	1.033	1.010-1.056	0.004			
Mean dose to mandible	1.053	1.009-1.099	0.018			
V35 mandible	1.033	1.007-1.059	0.014			
V44 mandible	1.029	1.004-1.055	0.025			
V50 mandible	1.032	1.006-1.058	0.017			
V58 mandible	1.035	1.006-1.064	0.016			
V60 mandible	1.034	1.004-1.065	0.024			
Mean dose to oral cavity	1.011	0.983-1.039	0.439			
D2% PTV high risk	0.982	0.964-1.001	0.067			
Multivariate conditional logistic regression was performed on covariates with P < .10. Abbreviations: HR = hazard ratio; CI = confidence interval; IMRT = intensity modulated radiation therapy; Vx mandible (%) = volume of mandible receiving x Gy; D2% PTV high risk = minimum dose covering 2% of the planned target volume at high risk.						

risk of developing ORN > 5% when the Dmean to the dental sector exceeds 30 Gy. If patients who undergo post-IMRT dental avulsions suffer from diabetes, the risk of ORN increases significantly when the Dmean to the same dental sector reaches at least 40 Gy. For patients with diabetes but no post-IMRT dental avulsions, the risk of ORN rises to more than 5% when the Dmean to the dental sector exceeds 45 Gy. For patients without diabetes with no need for dental care, the risk of ORN reaches 5% at around 50 to 55 Gy, as previously published in the literature. With our prediction data, we will be able to adapt dose thresholds on dental maps in relation to patients' medical history to guide dentists in their decision to perform conservative care when possible, or avulsions at a private clinic or at a tertiary center under strict protocols.

Our study has limits. First, the study was conducted in a single institution and may present selection bias due to its retrospective nature. The choice was made to include only patients with cancer of the OC/OR or CUP, which means that ORN may be underestimated in the whole population of patients treated for head and neck cancer. Patients with CUP were included because it is known that head and neck CUP are, for the most part, linked to a potential oropharyngeal origin.³⁴ Therefore, treatment typically involves prophylactic radiation of the whole oropharyngeal mucosa of at least 50 Gy. Moreover, human papilloma virus status was not available for patients treated before 2016. In addition, ORN is rather marginal after subhyoid tumor treatments.¹⁴ During data collection, we had to deal with significant amounts of missing data, especially on oral hygiene and

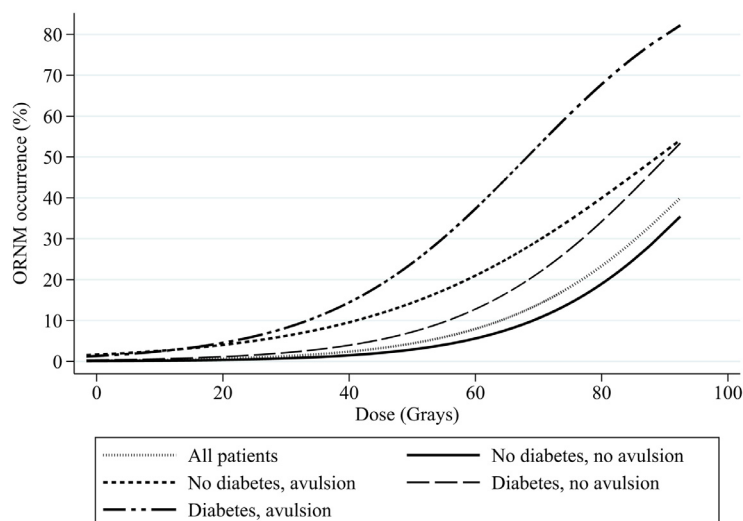


Fig. 2. Theoretical ORN prediction according to mean dose in the same dental sector (in Gy) depending on post-IMRT dental avulsions, diabetes, and dosimetry.

The small dotted line represents the dose-dependent prediction of osteoradionecrosis in the overall population – n=897 (without taking diabetes or avulsion into account). The dash/dotted line represents patients with diabetes and post-IMRT dental avulsions (1%), the dotted line represents patients without diabetes who had post-IMRT dental avulsions (9%), the large dashed line represents patients with diabetes but no post-IMRT dental avulsions (7%), the straight line represents patients with neither diabetes nor post-IMRT dental avulsions (83%).

dental follow-up, and after radiation therapy. These data were treated with multiple imputation when the missing data did not exceed 20%. Moreover, our study suggests that post-IMRT avulsion is a risk factor for the occurrence of ORN, according to the clinical definition used. However, it cannot be excluded that a subclinical ORN may exist before this avulsion. Because of the lack of compliance with dental follow-up and specific missing data in dental evaluation, it was not possible to analyze the effect of oral hygiene on the risk of ORN, which may be a major confounding factor. This bias is nevertheless common in the published literature, probably because of the retrospective nature of most studies. Moreover, data on the use of fluoride trays are missing, which would be useful information, especially on ORN prevention. Lack of compliance with custom trays and dental hygiene after head and neck irradiation can be frequent.³⁵ The decision to group dental cylinders into dental sectors was made in agreement with dentists, as posterior tooth removal can induce more severe trauma to the mandible. The dental dose mapping tool will also need validation with prospective data, which is the subject of an ongoing prospective study in all patients treated for head and neck cancer at our facility. Finally, our predictive curves are based on a simulated population; we were not able to determine the cumulative incidence of ORN stratified by risk factor. Despite these limitations, our study is one of the largest cohorts studying ORN of the mandible in the IMRT era, and the first to identify an anatomic correlation between the mean dose delivered in semiautomatically determined subunits of the mandible comprising teeth and periodontium,

post-IMRT dental avulsions in the dental sector, and the risk of ORN.

Conclusion

In this retrospective case-control study of patients treated with IMRT for cancer of the OC/OR or CUP, the ORN rate was 6.4%. Post-IMRT dental avulsions and mean dose to the same dental sector as the ORN were associated with a high risk of ORN. For each increase in gray, the risk of ORN in the same dental sector of the mandible increased by 12%. ORN predictive curves identify a high-risk profile: patients with diabetes who undergo post-IMRT dental avulsions. The risk of ORN exceeds 5% when the mean dose to the same dental sector exceeds 30 Gy for these patients. Using a dental dose mapping tool, this information can be transmitted to patients and help dentists in their dental care decisions.

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