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ORIGINAL ARTICLE

Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations

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ABSTRACT

Background: The project aimed at determining the incidence of mandibular osteoradionecrosis (ORN) after radiotherapy, possible risk factors, and mandibular dose-volume effects in a large cohort of head and neck cancer patients (HNC).

Methods: The cohort consisted of 1224 HNC patients treated with 66–68 Gy in 2007–2015 predominantly with IMRT. ORN cases were defined from clinical observations at follow-up and through hospital code diagnostics after oral-maxillofacial surgery and cross-checked with the national Danish Head and Neck Cancer database. In a nested case–control study, patients with ORN cases were matched with two controls (1:2) and pre-RT dental procedures including surgery to the mandible were documented. Multivariable Cox regression analysis was applied using demographic and treatment variables including dental procedures, smoking and tumor characteristics, and combined with dosimetric data. Mean mandibular dose (D_{mean}) was pre-selected for the multivariable model.

Results: ORN was recorded in 56 cases (4.6%) with a median time to event of 10.9 months (range 1.8–89.7) after RT, 90% occurred within 37.4 months. Median follow-up time was 22 months (0.3–95). Average D_{mean} was significantly higher in the ORN event cohort and significant dose-volume differences were observed for population mean DVH doses between 30 Gy and 60 Gy. In univariable analysis, smoking (HR = 1.69; CI 1.14–2.5), pre-RT surgery/tooth extraction (HR = 2.76; 1.48–5.14), and several dosimetric parameters including D_{mean} (HR = 1.05, 1.02–1.08) were all significantly associated with ORN. D_{mean} and surgery/tooth extraction remained significant predictors of ORN in multivariable analysis, HR = 1.04 (CI 1.01–1.07) and HR = 2.09 (CI 1.1–3.98), respectively, while smoking only retained its significance in an interaction analysis with pre-RT dental procedures.

Conclusion: The onset of ORN of the mandible was early (median 10.8 months) and the incidence low (4.6%) after IMRT in HNC cancer patients. Surgery to the mandible and pre-RT tooth extraction, tobacco smoking, and treatment dose were associated with the development of ORN.

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Introduction

Necrosis of the mandible is a debilitating complication to treatment after head and neck cancer (HNC) [1]. It may be related to bone erosion from the primary tumor or subsequent recurrent disease, or as sequelae from treatment, either surgery or radiotherapy (RT).

Osteoradionecrosis (ORN) is a condition with bone and mucosal breakdown after RT. Its occurrence may lead to a pronounced reduction in quality of life (QoL) [2] for which reason all prophylactic and therapeutic measures should be taken for its prevention. Various definitions of ORN have been proposed, but no current accepted standard of classification or grading exists. The most prevalent definition is exposed bone after RT that fails to heal over a period of three months without evidence of persisting or recurrent tumor [3,4].

A plethora of variables have been found to be associated with the development of ORN. These include patient-related factors such as smoking, dental hygiene, alcohol consumption and various comorbidities, as well as treatment-related factors of which pre-RT dental extraction and surgery and radiation treatment have been most intensively studied [5–11], in recent years with addition of dose-volume correlations of the irradiated mandible [12].

In the 1990s, incidence rates of ORN were reported as high as 21% in clinical controlled trials such as the DAHANCA 7 trial, but data from this century have shown somewhat lower rates, but highly variable values between 0 and 25% [9,11,13–16] depending on case-mix, surgical procedures, and inclusion of patients with recurrent disease. Thus, despite intensive dental guidance and introduction of intensity-modulated radiation therapy (IMRT), ORN seems to continue to be a significant side effect to radiotherapy even though prevalence rates in the modern era with IMRT may have declined to less than 5% [11,12,15–17].

The study aimed to report the incidence of mandibular ORN in a case–control design based on a large cohort of

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patients treated for head and neck cancer in the modern era of radiotherapy and to determine mandibular dose-volume correlates of ORN with proper consideration to other possible risk factors including pre-RT dental procedures.

Material and methods

The cohort was retrieved from patients undergoing radiation treatment for head and neck cancer at Odense University Hospital in 2007–2015. This period was selected to reflect the IMRT era and ensure sufficient observation time for ORN to occur. During the period, 1429 patients were registered as having RT for HNC. The study excluded patients with unknown primary tumor, patients receiving palliative treatment or re-irradiation, and patients with recurrent disease before experiencing ORN, the latter to exclude mandibular necrosis owing to tumor destruction and multiple treatments. A cohort of 1224 radically treated patients was then obtained comprising patients with cancer of the oral cavity, pharynx, or larynx.

Patients were treated to 66–68 Gy (95% dose to 98% of the PTV) with five to six fractions of 2 Gy per week, either with three-dimensional conformal RT (CRT) or IMRT, depending on treatment year. CRT was given as 48 Gy to elective lymph node regions with a final boost, while IMRT used simultaneous integrated boost, i.e., 60 Gy to CTV2 and 50 Gy to CTV3 (elective regions). Concomitant weekly cisplatin and the radiosensitizer nimorazole were prescribed as indicated according to the DAHANCA 2004 guidelines [18].

Patients were routinely seen at the Department of Oral and Maxillofacial Surgery before commencing treatment, and pre-RT dental extraction was performed if indicated as judged by the dental surgeon. Guidelines for pre-dental management follow national guidelines. During radiotherapy, dentulous patients were followed weekly at the Department of Oral and Maxillofacial Surgery with appropriate dental prophylactic management and guidance by a dental assistant, including fluoride treatment.

Follow-up after RT was performed every third month for two years, then every sixth month until five years. Normal tissue reactions were generally scored on an ordinal scale from 0–4 according to DAHANCA criteria, however, ORN was scored categorically as either 0 or 1 with no grading.

ORN cases were defined from hospital recordings and database records. Diagnosis codes related to dental procedures registered with patients from the cohort in the Department of Oral and Maxillofacial Surgery were obtained through local hospital code diagnostics (Cosmic Intelligence). Patients with a surgical procedure after the last recorded radiation treatment date were independently screened in the electronic hospital records. ORN was defined if reported as such by an oral-maxillofacial surgeon irrespectively of the extension. No grading of ORN was attempted. In addition, patients were cross-checked with the DAHANCA database for additional ORN cases that had been registered with DAHANCA, but missed from the local hospital registration. Time to ORN was described by actuarial incidence estimates.

In a nested case–control setting, cases were matched with two controls (1:2 matching) based on treatment year and subsite with no constraints on observation time to allow for the occurrence of ORN. All patients were immobilized with face masks and had CT-based dose planning performed in Pinnacle, and for dosimetric purposes, the mandible bone including sockets was delineated on all axial slices in cases and controls.

Dosimetric data related to mandibular irradiation was extracted from the dose planning system, and dose-volume differences between cases and controls were compared for all dose levels. This was done by calculating the population mean DVHs for each dose-volume to visualize the average dose distribution (Figure 1) indicating dose regions of significant differences [19].

The number of case–control matching factors was limited to retain the possibility to compare multiple (predictive) variables. Since the dosimetric variables may be mutually correlated, a single dosimetric covariate was preselected for the final multivariable regression model, namely mean mandibular dose (D_{mean}). A recent study had shown that maximum mandibular dose was not correlated with the risk of ORN [12] and therefore, D_{mean} was chosen alongside demographic and pretreatment variables which had been selected as a result of an observed association with ORN in univariate analysis defined by a p value below .2. Chi-square test was used for comparison between proportions.

In an exploratory data analysis, various fixed dose-volume parameters, besides D_{mean}, were also analyzed in relation to ORN. Univariable and multivariable Cox regression was performed. To investigate the association between pre-RT dental procedures and ORN, a combined covariate of mandibular surgery/tooth extraction was formed.

Permission to record and handle data was granted by the Danish Data Protection Agency and the Danish Patient Safety Authority.

Results

Patient characteristics for cases and controls are shown in Table 1. Follow-up time for the whole cohort was 22.8 months (0.3–115.5). A total of 56 patients out of 1224 were documented with ORN (4.6%) with a median time to event of 10.9 months (1.8–89.7). ORN had occurred in 90% within 37.4 months.

Dental extraction before radiotherapy was performed in 100 patients (60%), half of them with five or more teeth removed. At the start of radiation treatment, significantly more current smokers (63%) had dental extraction compared with former smokers (28%) or never smokers (34%), $p < .001$. The majority of cases and controls were treated with IMRT (94%). Only 10 patients received conformal radiation treatment.

Dosimetric data was available for all 56 cases and 112 controls. Figure 1 shows the population mean mandibular dose-volume estimates for cases and controls with the complementary line of p values from a continuous comparison between dose-values of the two groups. Statistically

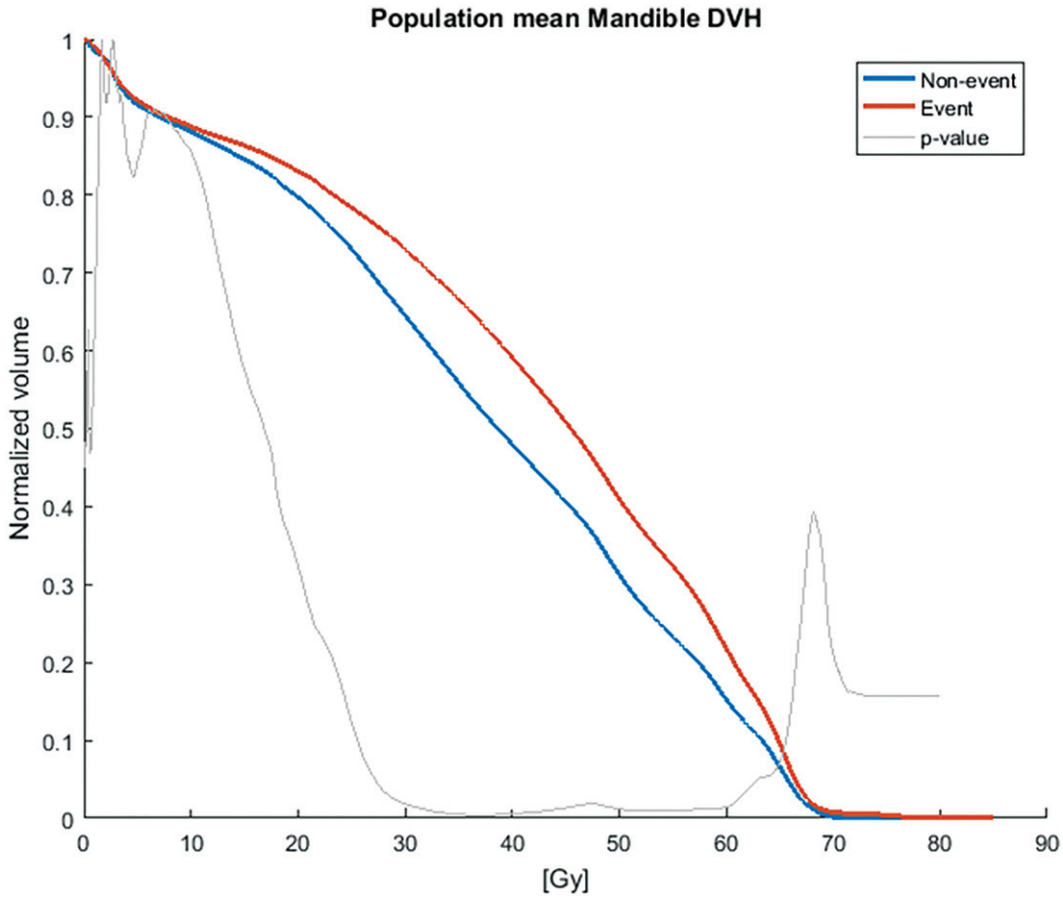

Figure 1. Mean DVHs of the mandible of 56 cases (red) and 112 controls (blue). *p* values (dotted) were derived from a paired two-sided Wilcoxon-signed rank test. The figure indicates significant dose-volume differences between cases and controls for mean doses between 30 Gy and 60 Gy.

Table 1. Characteristics of 56 patients with osteoradionecrosis and 112 matched controls.

	Cases (%)	Controls (%)	*p*-value
Tumor site			
Oral cavity	24	48	
Oropharynx	31	62	
Larynx	1	2	
Gender			.24
Male	42 (75.0)	74 (66.1)	
Female	14 (25.0)	38 (33.9)	
Median age at start of RT (years, range)	57.5 (38–76)	59.5 (30–83)	.17
T-classification			.38
T1	13 (23.2)	34 (30.4)	
T2	26 (46.4)	44 (39.3)	
T3	10 (17.9)	13 (11.6)	
T4	7 (12.5)	21 (18.8)	
Primary surgery	24 (42.8)	40 (35.7)	.47
Primary surgery/tooth extraction	43 (76.8)	57 (50.1)	.002
Cisplatin			.80
Yes	41 (73.2)	84 (75.0)	
No	15 (26.8)	28 (25.0)	
Smoking history			.09
No	17 (30.4)	51 (45.5)	
Yes	39 (69.6)	61 (54.5)	
D_{mean} of mandible (Gy)	41.7	37.7	.02

significant differences were noted between doses of 30 Gy to 60 Gy.

The average mean mandibular dose (D_{mean}) for the whole cohort was 39.0 Gy (range 0.8–61.6) and the average "near maximum dose" $D_{2\%}$ and average D_{1cc} were 63.0 Gy (7.2–78.6) and 63.4 Gy (9.1–78.8), respectively. Cases had a significantly higher D_{mean} than controls, 41.7 Gy vs. 37.7 Gy ($p = .02$).

Demographic and pretreatment factors and results of univariable and multivariable analysis of the relation to the development of ORN are shown in Table 2. Pre-RT dental procedure and smoking were used for the multivariable analysis. An interaction-term of the two covariates was applied as well, due to the smoking-tooth extraction relationship described above, however, this term did not significantly change the results ($p = .11$) and was omitted from the final analysis.

In the exploratory analysis, all tested dosimetric variables were mutually related and associated with the risk of ORN. D_{mean} as a continuous variable was significantly associated with the development of ORN in the multivariable analysis (HR 1.04; CI 1.01–1.07), and pre-RT dental procedure remained significant as well (HR = 2.09; CI 1.1–3.98), however, smoking was not statistically significant with a *p* value of .06 (HR = 1.45; CI 0.99–2.14) (Table 2, bottom).

Discussion

Several recent investigations have documented a low risk of mandibular necrosis after radiation treatment of head and neck cancer in the modern era of radiotherapy [11,12,17]. This is supported by the results from the present

Table 2. Univariable and multivariable analysis of demographic and pretreatment factors for risk of ORN.

	HR	95% CI	*p*-value
Univariable analysis			
Pre-RT dental procedure[a]	2.76	1.48–5.14	.001
Smoking	1.69	1.14–2.5	.009
T-classification	1.12	0.87–1.45	.37
Cisplatin	0.97	0.53–1.75	.91
Performance status	1.06	0.87–1.47	.74
D_{mean} of mandible (Gy)	1.05	1.02–1.08	.001
Multivariable analysis			
Pre-RT dental procedure (no, yes)	2.09	1.1–3.98	.02
Smoking (never, former, active)	1.45	0.99–2.14	.06
D_{mean} of mandible (Gy)	1.04	1.01–1.07	.02

For the multivariable analysis, covariates with $p < .2$ were entered, and only terms with $p < .10$ were kept in the backward selection.
[a]Joint factor of surgery involving the mandible and/or pre-RT tooth extraction.

case–control study that demonstrated an incidence rate of 4.6% in a population of more than 1200 patients. IMRT may be part of an explanation for this finding. A clear reduction in incidence rate of ORN was observed here compared with previous findings in Danish studies such as the prospective DAHANCA 7 trial where 21% of patients experienced ORN after conformal treatment of the supraglottic larynx, pharynx, and oral cavity.

In the present study, it is anticipated that only few cases may have been missed out since a very large cohort was obtained by retrieving data from the national DAHANCA database and cross-checked with hospital data, including diagnostic coding, to provide an extensive cohort and supposedly, a reliable number of events. The study showed that pre-RT dental management, either mandibular surgery or dental extractions, were significantly correlated with the development of ORN, and since cases comprised necrosis of the whole oral cavity, also outside high-dose volumes, it may be inferred that the study included additional cases not likely related to radiation treatment as such, but rather to other causes. It may thus be anticipated that the present low incidence rate of ORN has not been underestimated and that the rate of ORN below 5% seems valid and in accordance with other international reports.

The median time to the onset of ORN was short, namely 10.9 months. This is in line with other publications [9,11,16,20] which showed median ranges between 8 and 19 months. An appropriate follow-up time was ensured in this study by including patients no later than 2015 to allow for adequate observation time, and cases and controls were matched by site and by treatment year. The follow-up time of the whole cohort was more than twice as long, indicating that most of the events were to be picked up. Also, patients had routine follow-up at the hospital according to national guidelines to enable a proper registration of late side effects to treatment.

The study did not intend to grade ORN. ORN has been scored binary as no/yes in the DAHANCA follow-up for years and accordingly, a diagnostic code of oral-maxillary treatment of ORN was recorded as an event. This will inherently categorize even small lesions as ORN such as mucosal dehiscence, a procedure that was also followed in the very large SEER-analysis using ICD-9 classification codes to identify jaw complications [13]. The SEER-study found more low-grade complications than expected from the literature indicating that not only are rates of ORN declining, perhaps also the severity.

Recent publications on ORN have mainly included oropharyngeal cancer patients. However, this selection also favors a population with HPV-induced carcinomas reflecting patients in good performance status, nonsmokers, and younger patients different from the typical tobacco and alcohol-affected patients. This study included all HNC sites where events were observed, in oropharynx and oral cavity cancer as well, and few larynx. The advantage in this setting is that bias may be reduced by including the whole spectrum of head and neck patients and thus avoid interaction mechanisms related to predictive clinical and patient-associated factors detached from radiation dose-volume effects. In essence, patients with ORN and low radiation doses to the mandible may carry important predictive biological information to the data analysis.

Tobacco exposure increases surgical complications after head and neck surgery resulting in impaired local wound healing [21] adding to the risk of necrosis after surgery and RT. Active smoking and poor dental hygiene have been associated with ORN in previous publications [7,8,10], the two factors being mutually related. In this study, both smoking and pre-RT dental procedures were significantly correlated with the risk of ORN, smoking only borderline in the multivariable analysis, and it could be inferred that one or the other factor would be a pseudo-covariate for the other. Clearly, tobacco consumers were twice as likely to have pre-RT tooth extraction compared to former smokers or never smokers.

The risk of ORN was just below 5% in this large study cohort after a median of almost two years of follow-up, and of those experiencing ORN, 90% occurred within three years.

The average D_{mean} was 39 Gy. Treatment dose was not surprisingly associated with ORN. In the literature, only few studies have dealt with dose-volume correlation analyses, and it still remains to be determined which dose constraints should be recommended for optimal dose planning in HNC. Generally, various dosimetric factors have been correlated to ORN, and in this study, all intended analytic dosimetric covariates were interrelated. Patients with ORN had higher dose levels to mandibular volumes compared to the control group. Thus, any covariate could be selected for the regression analysis. D_{mean} was pre-selected in this study from the argument that maximum dose to the mandible had been shown in a recent study not to correlate well with the risk of ORN [12]. The average D_{mean} was significantly higher in cases than in controls, and D_{mean} retained its predictive effect on ORN in the multivariable regression analysis. D_{mean} may reflect a general damaging mechanism in a parallel organ such as the mandible, and from this study, D_{mean} seems an appropriate parameter to consider in dose planning and to be included without a threshold. Doses should be kept as low as possible to reduce the risk of ORN.

The aim of this study was to generate more insight into which factors that were associated with the development of

ORN and to predict which patients who are at a higher risk of developing ORN. The ultimate goal would be to optimize radiation treatment plans and offer patients appropriate counseling for dental management to decrease the risk of ORN.

Despite the variability in the nature of published ORN studies, preradiation dental procedures (surgery or tooth extraction) are constantly reported as explainable factors for the development of ORN [6,7,10,11]. In this study, and the large SEER study [13], as significantly higher rate of ORN was observed after postoperative/adjuvant radiotherapy. Beech et al. [22] studied postoperative radiotherapy in 190 HNC in two independent hospitals. Two-thirds had dental extraction, which was equal to the 60% observed in the present study. They found that 75.9% of ORN were in sites of pre-RT extraction, and pre-RT dental extractions significantly increased the risk of developing ORN. It was concluded that pre-RT dental extractions do not protect against the development of ORN.

Dental extraction is often considered in patients with head and neck cancer before radiotherapy as part of the management plan to prevent dental complications such as osteoradionecrosis. It must be recalled, though, that the occurrence of ORN is perhaps less than that 5% in large cohorts of HNC patients and that the bony structures outside the radiation volume, including the upper jaw [1], are rarely involved in necrotic pathology. While statistical associations do not explain causal relationships, it ought to be considered that with the clear and constant correlation found between pre-RT dental procedures and the occurrence of mandibular necrosis after radiation treatment, pre-RT dental extractions guidelines, as recommended today, should perhaps consider more conservative measures.

Disclosure statement

No potential conflict of interest was reported by the authors.

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