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# Does intensity-modulated radiation therapy lower the risk of osteoradionecrosis of the jaw? A long-term comparative analysis

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*Abstract.* The aim of this study was to analyze the impact of different radiation techniques on the long-term incidence of osteoradionecrosis in head and neck cancer. Risk factors and the occurrence of osteoradionecrosis were analyzed in a retrospective, comparative, observational study. Medical files and radiological images of 109 patients treated with primary intensity-modulated radiation therapy (IMRT) and 129 patients treated with primary three-dimensional conformal radiotherapy (3D-CRT) were evaluated. Proportional hazards models were used to analyse the effects of the radiation modality and patient characteristics on the necrosis risk. Twenty-two patients developed osteoradionecrosis (9.2%) during a mean follow-up of 4.3 years. A numerical difference was observed, with more osteoradionecrosis after 3D-CRT ($n = 18$) than after IMRT ($n = 4$). After correction for group differences and confounders, no statistical difference in risk was observed between the two treatment groups ($P = 0.37$). Multivariate analysis showed evidence of a higher osteoradionecrosis risk for patients with a tumour of the oropharynx and for patients with tooth extraction after radiation therapy. Although the incidence of osteoradionecrosis tended to be lower after IMRT, due to the multifactorial aetiology it remains a severe problem and cannot be prevented by new radiotherapy techniques. Continuous efforts are necessary to control additional risk factors and avoid osteoradionecrosis.

Key words: osteoradionecrosis of the jaw; intensity-modulated radiation therapy; 3D conformal radiotherapy.

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Radiation therapy (RT) with or without concurrent chemotherapy has emerged as an important treatment modality for patients with locally advanced head and neck squamous cell carcinoma (HNSCC). Co-irradiation of the adjacent functional structures in the head and neck region can cause acute and late complications. Acute side effects (e.g., mucositis) are often debilitating but resolve with time. Late toxicity, such as trismus, xerostomia and subsequent caries, and osteoradionecrosis (ORN), can have a problematic and lifelong impact on quality of life[1]. However, much progress has been made in the field of RT over the last decades. The use of more conformal radiation techniques, such as intensity-modulated radiation therapy (IMRT), has allowed the dose to the surrounding normal tissue to be reduced by sculpting the dose more precisely around the target volume[2,3].

IMRT can provide dose gradients with narrow margins, making it ideal for treating complex treatment volumes and avoiding close functional organs at risk, such as the spinal cord, the optic apparatus, the salivary glands, and the mandible. This can reduce acute and long-term toxicity without affecting tumour control in HNSCC. Recent investigations have illustrated reduced acute and late toxicity (e.g., mucositis, xerostomia, and dysphagia) without an effect on tumour control and patient outcomes with the implementation of IMRT[4–7]. Although IMRT was initially assessed for its ability to exclude the parotid gland from the radiation field to reduce xerostomia, it also has the potential to reduce the incidence of ORN by excluding the mandible from the high-dosage radiation field[8].

This is an important finding, since ORN of the jaw is a late toxicity caused by irradiation of the mandibular/maxillary bone. The most accepted definition of ORN is an area of exposed bone that fails to heal after a period of 3 months, after the exclusion of all other diagnoses[9]. The incidence rate following radiotherapy for head and neck cancer varies widely and ranges from 4.7% to 37.5%[10,11]. Many factors such as smoking, alcohol use, tumour characteristics, oral hygiene, and traumatic events (e.g., surgery) can influence the risk of developing ORN[12]. This risk is strongly associated with the volume of the mandible or maxilla that received radiation and the radiation dose[10,12–14].

With the possibility of more conformal radiation delivery and consequent dosimetric advantages of IMRT, the potential to reduce the radiation dose and thus the risk of ORN could be expected. However, due to heterogeneity of RT regimens and other confounding factors, the benefit of IMRT in reducing the risk of ORN is still unclear. Previous studies on this subject are scarce and present conflicting results[15–19].

The aim of this study was to compare the incidence of ORN in a large cohort of patients with locally advanced HNSCC, treated with IMRT or three-dimensional conformal radiotherapy (3D-CRT). Further aims of this retrospective study with long-term follow-up were to gain further insight into the actual incidence rates of ORN according to the radiation modality, assess the possible advantages of IMRT, and analyze the current related risk factors.

## Materials and methods

### Patient population

A retrospective, comparative analysis was performed at a single, tertiary referral hospital. The research adhered to the tenets of the Declaration of Helsinki and approval was obtained from the local medical ethics committee. All patients diagnosed with locally advanced HNSCC from January 2003 to December 2010 were examined for eligibility. Staging was performed according to the 2009 TNM classification system of the American Joint Committee on Cancer (AJCC). Eligibility criteria were (1) pathologically proven HNSCC, of AJCC stage III or IV, without distant metastasis at the time of diagnosis, (2) treated with primary radiation therapy (IMRT or 3D-CRT) with or without concomitant targeted therapy or chemotherapy, and (3) minimum of 6 months follow-up. Patients with no invasive (in situ) head and neck cancer, cancer of unknown primary, incomplete medical records, previous or current treatment with bone resorption inhibitors (bisphosphonates or denosumab), or inadequate follow-up were excluded.

### Treatment protocol

All patients were imaged with computed tomography (CT) and/or magnetic resonance imaging (MRI) of the HNSCC region, and their cases were discussed in a meeting of the multidisciplinary team. Patients underwent a dental evaluation by a team of dentists and oral surgeons prior to the treatment. Patients with a good oral health status and regular dental evaluation had the option to be monitored by their regular dentist. Those with a poor oral health status were referred to the hospital dental clinic for oral rehabilitation, improvement of oral hygiene, and planning of dental extractions if necessary. Radiotherapy was withheld for at least 2 weeks following dental extraction, to allow for wound healing.

Patients were treated either with a 3D-CRT photon delivery technique as described by Maes et al.[20], or with parotid-sparing IMRT with photons. The spinal cord was delineated in all patients and the cumulative dose to the spinal cord was not to exceed 50 Gy. In those patients for whom parotid sparing was feasible, the mean dose to at least one parotid gland was kept below 26 Gy. The oral cavity, pharyngeal constrictor muscles, oesophagus, and mandible were outlined when appropriate and the dose to these structures was kept as low as reasonably possible without compromising the planning target volume (PTV) coverage. Both IMRT and 3D-CRT treatments were routinely performed for head and neck cancer at the study hospital, and assignment to one or the other was determined by machine availability. Both populations were treated within a short time frame (7 years); apart from the technique, little or no changes were made in fractionation schedule or indication setting during this period.

Following radiation treatment, all patients were enrolled in a multidisciplinary follow-up programme with regular visits according to a uniform schedule. Clinical charts were completed using a standardized form. Physical and endoscopic examinations were performed at each follow-up visit to detect recurrent disease. When ORN was clinically suspected (pain, bone exposure, chronic oral wounds, fistula), the patient was referred to the oral and maxillofacial department for appropriate diagnosis and treatment.

### Data collection

The clinical charts of the patients were reviewed and demographic data were collected (including sex, age, continuing smoking and alcohol intake). Other variables that could influence the risk of ORN were obtained: primary tumour characteristics (i.e., TNM staging, tumour localization, treatment modality) and dental assessment documentation (in-hospital dental screening, dental X-ray, dental status, time and localization of tooth extraction).

The primary endpoint of this study was clinical and/or radiological evidence of ORN after treatment with IMRT or treatment with 3D-CRT. ORN was defined as exposure of the bone for more than 3 months or radiological evidence without breach of the oral mucosa or cervicofacial

skin[9,11]. ORN lesions were graded retrospectively according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE, US Department of Health and Human Services)[21]. Follow-up was assessed up until January 2014. Ambiguous data were only included after discussion amongst the authors.

### Statistical analysis

Comparisons of patient characteristics between the two groups were performed using the $\chi^2$ test for categorical variables and the two-sample *t*-test for continuous variables. Cox proportional hazards models were used for the analysis of the effect of treatment group or patient characteristics on the risk of necrosis. The time between the start of RT and necrosis was considered, while patients without necrosis were censored at the end of follow-up or at the time of death. In the analysis of a treatment group effect, correction for differences in group characteristics was performed by propensity score adjustment[22]. A propensity score is the chance that a patient, based on his/her characteristics, was assigned to either treatment group. Propensity scores or group membership probabilities were estimated by logistic regression model. The Cox model was then applied with both treatment groups and the propensity score as explanatory variables. All tests were two-sided, and a 5% significance level was assumed for all tests. All analyses were performed using SAS software, version 9.4 (SAS System for Windows; SAS Institute Inc., Cary, NC, USA).

## Results

### Patient characteristics

Between January 2003 and December 2010, 245 consecutive patients with pathologically proven, locally advanced HNSCC received primary (chemo)radiotherapy and were confirmed to be eligible for this study. Seven patients with incomplete medical records or inadequate follow-up were excluded; thus, 238 patients were included in the retrospective analysis: 129 patients (54.2%) were treated with 3D-CRT and 109 patients (45.8%) with-IMRT. The average follow-up was 4.3 years (range 6 months to 11 years): 4.8 years (range 6 months to 11 years) in the 3D-CRT group and 3.7 years (range 6 months to 8 years) in the IMRT group. Patient characteristics by group can be found in Table 1. The two treatment groups differed significantly in four probable ORN risk factors: tumour site ($P = 0.034$), in-hospital dental screening ($P = 0.004$), edentulous state ($P = 0.002$), and age ($P = 0.013$).

### Osteoradionecrosis

Twenty-two of the 238 patients (9.2%) eventually developed ORN: 18 (14.0%) following treatment with 3D-CRT and four (3.7%) after IMRT. The median interval from the end of RT to ORN diagnosis was 40 months (range 1.2–92.4) in the 3D-CRT group and 53 months (range 6.7–67.7) in the IMRT group (Table 2). Most ORN lesions were grade 1 or 2 (78.9% for 3D-CRT and 75% for IMRT), requiring no treatment or only conservative treatment. Three patients in the 3D-CRT group had lesions that evolved to grade 4, needing urgent intervention; these patients ultimately underwent a mandibulectomy. ORN was situated in the mandible in all affected patients; only one patient had additional ORN lesions in the maxilla. In both populations, the majority of ORN lesions were diagnosed following irradiation of an oropharyngeal tumour (83.3% for 3D-CRT and 75% for IMRT). ORN developed at the site where teeth had previously been extracted in 14 patients. In four of these patients, this occurred after prophylactic extractions (Table 3).

### Risk factors for osteoradionecrosis

Due to a limited number of events in the dataset, correction for confounders via a classical multivariable model was not possible. Correction for confounding was therefore performed using the propensity score approach. Variables used in the propensity score model were the factors for necrosis on which the two treatment groups were shown to differ (Table 1): tumour site, in-hospital dental screening, edentulous state, and age. The C-index or discriminative ability of the patient characteristics to predict group membership was 0.695 (95% confidence interval (CI) 0.63–0.76), with a moderate discrimination and a reasonable overlap of distributions. Without considering the group differences, patients who had received 3D-CRT tended to be at higher risk of necrosis than patients who had received IMRT (hazard ratio (HR) 3.01, 95% CI 1.00–9.05; $P = 0.05$). The same trend was observed when the risk of developing ORN 5 years after RT was estimated based on a Cox model (HR 14.4, 95% CI 6.7–21.6 for 3D-CRT vs. HR 5.1, 95% CI 0.0–9.8 for IMRT). However, after correction for group differences, there was no longer a significant difference between the two groups (HR 1.69, 95% CI 0.54–5.26; $P = 0.37$) (**Supplementary Material**, Table A).

The associations between patient characteristics and ORN risk are illustrated in Table 4. The results showed evidence of a higher necrosis risk for patients with localization in the oral cavity/oropharynx compared to nasopharynx/larynx (HR 5.20, 95% CI 1.21–22.44; $P = 0.027$), a higher risk for patients with in-hospital dental screening ($P = 0.023$), a higher risk for patients with tooth extraction post-RT (HR 3.60, 95% CI 1.51–8.60; $P = 0.004$), and a higher risk for patients with continuing alcohol use (HR 4.30, 95% CI 1.00–18.41; $P = 0.049$). The necrosis risk was found to increase with younger age (age +1 year, HR 0.95, 95% CI 0.91–1.00; $P = 0.049$). This study did not show an increase in ORN risk when concurrent chemotherapeutic agents were administered, or for higher T stages. Dental extractions before the start of radiotherapy did not decrease the risk of ORN development.

## Discussion

Historically, the incidence of ORN following radiotherapy for head and neck cancer reported in the literature has varied widely, from 4.7% to 37.5%[10,11]. These large variations can be explained by the heterogeneity of reported study populations, with large differences in tumour characteristics, variable lengths of follow-up, and different radiation techniques. Recent data have shown a declining trend in ORN risk[11,18]. Improved radiation techniques could be one possible factor explaining this observation. With the introduction of organ-preserving radiation techniques such as IMRT, large parts of the facial skeleton can be spared, thereby theoretically reducing the risk of ORN[8,23]. Several recent studies have reported a rate of 0% to 14% of ORN when using IMRT for head and neck cancer[8,14–17,19,24,25]. The results of the present study are in agreement with this observed decreased tendency of ORN after treatment with IMRT. However, following correction for group differences, the results did not reach statistical significance for the difference between the 3D-CRT group and the IMRT group.

In contrast to most studies, in which ORN lesions were reported to occur at an early stage (between 6 months and 2 years after RT)[25–27], the present study demonstrated a long interval from termination of

*Table 1*. Patient characteristics by treatment group[a].

| Variable | Statistic | 3D-CRT | IMRT | *P*-value |
|---|---|---|---|---|
| Age (years) | *N* | 129 | 109 | 0.013* |
| | Mean | 57.3 | 60.2 | |
| | SD | 9.01 | 9.09 | |
| | Median | 56.0 | 59.0 | |
| | IQR | (51.0–63.0) | (53.0–67.0) | |
| | Range | (38.0–87.0) | (41.0–84.0) | |
| Sex | | | | |
| Male | *n*/*N* (%) | 110/129 (85.3%) | 93/109 (85.3%) | 1.000 |
| Female | *n*/*N* (%) | 19/129 (14.7%) | 16/109 (14.7%) | |
| Tumour site | | | | |
| Oral cavity | *n*/*N* (%) | 5/129 (3.9%) | 4/109 (3.7%) | 0.034* |
| Oropharynx | *n*/*N* (%) | 74/129 (57.4%) | 42/109 (38.5%) | |
| Nasopharynx | *n*/*N* (%) | 2/129 (1.5%) | 5/109 (4.6%) | |
| Hypopharynx | *n*/*N* (%) | 22/129 (17.0%) | 31/109 (28.4%) | |
| Larynx | *n*/*N* (%) | 26/129 (20.2%) | 27/109 (24.8%) | |
| Stage | | | | |
| III | *n*/*N* (%) | 29/129 (22.5%) | 20/109 (18.3%) | 0.520 |
| IV | *n*/*N* (%) | 100/129 (77.5%) | 89/109 (81.7%) | |
| T-stage | | | | |
| 1 | *n*/*N* (%) | 7/129 (5.4%) | 6/109 (5.5%) | 0.896 |
| 2 | *n*/*N* (%) | 28/129 (21.7%) | 19/109 (17.4%) | |
| 3 | *n*/*N* (%) | 43/129 (33.3%) | 39/109 (35.8%) | |
| 4 | *n*/*N* (%) | 50/129 (38.8%) | 45/109 (41.3%) | |
| x | *n*/*N* (%) | 1/129 (0.8%) | 0/109 (0.0%) | |
| N-stage | | | | |
| 0 | *n*/*N* (%) | 16/129 (12.4%) | 13/109 (11.9%) | 0.063 |
| 1 | *n*/*N* (%) | 29/129 (22.5%) | 12/109 (11.0%) | |
| 2a | *n*/*N* (%) | 7/129 (5.4%) | 3/109 (2.8%) | |
| 2b | *n*/*N* (%) | 40/129 (31.0%) | 33/109 (30.3%) | |
| 2c | *n*/*N* (%) | 35/129 (27.1%) | 41/109 (37.6%) | |
| 3 | *n*/*N* (%) | 2/129 (1.6%) | 6/109 (5.5%) | |
| x | *n*/*N* (%) | 0/129 (0.0%) | 1/109 (0.9%) | |
| Concurrent systemic treatment | | | | |
| No | *n*/*N* (%) | 25/129 (19.4%) | 21/109 (19.3%) | 1.000 |
| Yes | *n*/*N* (%) | 104/129 (80.6%) | 88/109 (80.7%) | |
| Nicotine | | | | |
| No | *n*/*N* (%) | 14/129 (10.9%) | 15/109 (13.8%) | 0.283 |
| Yes | *n*/*N* (%) | 112/129 (86.8%) | 94/109 (86.2%) | |
| Unknown | *n*/*N* (%) | 3/129 (2.3%) | 0/109 (0.0%) | |
| Alcohol | | | | |
| No | *n*/*N* (%) | 31/129 (24.0%) | 29/109 (26.6%) | 0.330 |
| Yes | *n*/*N* (%) | 95/129 (73.6%) | 80/109 (73.4%) | |
| Unknown | *n*/*N* (%) | 3/129 (2.3%) | 0/109 (0.0%) | |
| Edentulous before diagnosis | | | | |
| No | *n*/*N* (%) | 122/129 (94.6%) | 92/109 (84.4%) | 0.002* |
| Yes | *n*/*N* (%) | 4/129 (3.1%) | 16/109 (14.7%) | |
| Unknown | *n*/*N* (%) | 3/129 (2.3%) | 1/109 (0.9%) | |
| In-hospital dental screening | | | | |
| No | *n*/*N* (%) | 18/129 (14.0%) | 32/109 (29.4%) | 0.004* |
| Yes | *n*/*N* (%) | 111/129 (86.0%) | 77/109 (70.6%) | |
| Dental extractions before radiotherapy | | | | |
| No | *n*/*N* (%) | 54/122 (44.3%) | 40/92 (43.5%) | 0.748 |
| Yes | *n*/*N* (%) | 65/122 (53.3%) | 51/92 (55.4%) | |
| Unknown | *n*/*N* (%) | 3/122 (2.4%) | 1/92 (1.1%) | |
| Dental extractions after radiotherapy | | | | |
| No | *n*/*N* (%) | 84/122 (68.8%) | 67/92 (72.8%) | 0.679 |
| Yes | *n*/*N* (%) | 35/122 (28.7%) | 24/92 (26.1%) | |
| Unknown | *n*/*N* (%) | 3/122 (2.5%) | 1/92 (1.1%) | |

3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; SD, standard deviation.

*$P < 0.05$.

[a] Variables presented with percentages were analyzed using Fisher's exact test. Variables summarized as the mean or median were analyzed using the independent *t*-test. All reported *P*-values are two-sided.

*Table 2*. Description of osteoradionecrosis sites by radiation modality.

| Variable | | 3D-CRT | IMRT |
|---|---|---|---|
| Interval to ORN (months) | Median (range) | 40 (1.2–92.4) | 53 (6.7–67.7) |
| ORN grade (CTCAE v4.0) | 1 | 10 | 2 |
| | 2 | 5 | 1 |
| | 3 | 1 | 1 |
| | 4 | 3 | 0 |
| ORN location | Posterior mandible | 17 | 2 |
| | Anterior mandible | 1 | 2 |
| | Maxilla | 1 | 0 |
| Radiation dose to ORN site | Median (range) | 72 Gy (50–72) | 65 Gy (60–72) |
| Tumour site | Oropharynx | 15 (83.3%) | 3 (75%) |
| | Oral cavity | 0 | 0 |
| | Nasopharynx | 0 | 0 |
| | Hypopharynx | 1 (5.6%) | 1 (25%) |
| | Larynx | 2 (11.1%) | 0 |

3D-CRT, three-dimensional conformal radiotherapy; CTCAE v4.0, Common Terminology Criteria for Adverse Events version 4.0; Gy, Gray; IMRT, intensity-modulated radiation therapy; ORN, osteoradionecrosis.

*Table 3*. Osteoradionecrosis event at the site of tooth extraction. Characteristics are presented for each radiation modality.

| Variable | 3D-CRT | IMRT |
|---|---|---|
| ORN lesions related to tooth extraction, *n*/*N* (%) | 11/18 (61.1%) | 3/4 (75%) |
| Extraction *before* RT start | 3/11 | 1/3 |
| Extraction *after* RT start | 8/11 | 2/3 |
| Median radiation dose on extraction site (range) | 72 Gy (50–72) | 70 Gy (60–72) |

3D-CRT, three-dimensional conformal radiotherapy; Gy, Gray; IMRT, intensity-modulated radiation therapy; ORN, osteoradionecrosis; RT, radiation therapy.

*Table 4*. Association between patient characteristics and osteoradionecrosis risk.

| Variable, test | HR (95% CI)[a] | *P*-value |
|---|---|---|
| IMRT vs. 3D-CRT | 1.685 (0.540–5.263) | 0.3691 |
| Oral cavity/oropharynx vs. nasopharynx/larynx | 5.204 (1.207–22.435) | 0.0269* |
| T3/4 vs. T1/2 | 0.898 (0.366–2.206) | 0.8149 |
| In-hospital dental screening[b] | | 0.0226* |
| Edentulous[b] | | 0.2463 |
| Extraction before RT: yes vs. no | 2.012 (0.819–4.939) | 0.1272 |
| Extraction after RT: yes vs. no | 3.599 (1.506–8.603) | 0.0040* |
| Alcohol: yes vs. no | 4.300 (1.004–18.413) | 0.0494* |
| Nicotine yes vs. no | 1.744 (0.407–7.468) | 0.4533 |
| Concurrent chemo: yes vs. no | 0.585 (0.213–1.605) | 0.2983 |
| Sex: female vs. male | 1.411 (0.520–3.826) | 0.4987 |
| Age: +1 year | 0.954 (0.909–1.000) | 0.0490* |

3D-CRT, three-dimensional conformal radiotherapy; CI, confidence interval; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

* $P < 0.05$.

[a] Binary variables: HR >(<)1: higher (lower) necrosis risk for first level. Continuous variables: HR >(<)1: higher (lower) necrosis with increasing variable level.

[b] HR cannot be estimated.

RT to ORN diagnosis. Comparable results were reported by Chen et al.[24], who identified 105 ORN cases in 2103 patients receiving IMRT for oral cancer, with an average duration to diagnosis of ORN of 29.8 months. Late-stage ORN can be observed several years following radiotherapy, at lower radiation doses, and is probably more related to trauma within the radiated bone[10]. Indeed, the greater part of events reported in the current study followed tooth extraction after RT. The fact that the median interval to the development of ORN exceeded the average follow-up period in the IMRT group confirms the indefinite risk and stresses the importance of continuing long-term monitoring of patients who have received head and neck RT.

The development of ORN has a multifactorial aetiology, which was confirmed by this study. Tumour irradiation in the oropharyngeal region results in an increased incidence of ORN due to the greater chance of including the mandible in the radiation field[11,14,24,27]. However, RT for cancers arising from the hypopharynx or larynx can also be a risk factor for ORN due to tumour extension or radiation of the lymph nodes close to the mandible (e.g., level 2). Continuing smoking and alcohol intake have been linked to ORN occurrence in previous reports[13], and this was also illustrated in the present study cohort. The association between chemotherapy and the risk of ORN remains unclear in the literature[10,11], and could not be clarified by the present study findings. Elderly patients have previously been reported to have an increased risk of ORN[28]. However, the results of this study indicate that the ORN risk increases with younger age. The same finding was reported by Chen et al.[24]. It is hypothesized that the longer life expectancy, and thus increased time to develop ORN, could explain the increased risk when RT is administered at a younger age.

Many articles have associated dental extractions after RT with a higher incidence and more severe ORN[10,27,28], which was confirmed by the study results. Whether dental extraction before RT reduces the risk of ORN is still being debated. This study found no decrease in necrosis risk when extractions were performed before radiotherapy. De Felice et al.[26] reported that in most cases (79%), ORN arose in the pre-RT extraction site. After reviewing 413 patients, Chang et al.[29] concluded that extractions before RT do not appear to reduce the risk of ORN, regardless of whether the teeth are in relatively good condition or not. This is in contrast with the finding that edentulous patients are at lower risk of developing ORN, because less traumatic dental events are to be expected[30]. The most plausible reason could be that bony remodelling after a tooth extraction will continue for a long time after initial healing[29], implying that a longer period (compared to the usual 2 weeks) may be needed before the start of RT after extractions. This argument could also explain the presence of in-hospital dental screening as a significant risk factor for ORN development. Patients who are treated in the hospital dental clinic (often with a poor dental status) probably have a higher rate of tooth extractions a short time before the start of RT. These findings illustrate that one should be very cautious when indicating and performing these extractions. Future research on this topic should clarify when and how 'prophylactic' tooth extractions play a role in the prevention of ORN.

The enrolment of a large population of patients with locally advanced head and neck cancer, all treated with primary radiation therapy and with long-term follow-up, is a considerable strength of this study. The risk of developing ORN probably lasts indefinitely, so a sufficient follow-up period is essential to provide valid results. There were some limitations to this study. Missing data and selection bias are inherent in a retrospective case comparison study. Only patients with AJCC stage III or IV carcinoma treated with primary (chemo)radiotherapy were included. Patients receiving primary surgical treatment were excluded to avoid clinical heterogeneity, which explains the low number of patients with oral cavity cancers included. It is possible that differences in the outcome of ORN incidence would be noticed if patients with AJCC stages I and II and those undergoing RT adjunctive to primary surgery were included. The toxicity of various chemotherapeutic agents can differ, but this was not taken into account in the current analysis. This could perhaps have influenced the outcome and should be addressed in future studies. A multitude of scoring systems (e.g., Notani, Lyons) are used in reporting ORN lesions[1,9,13]. Every scoring system has specific advantages and deficiencies, possibly affecting the reporting rates. In this study, ORN was graded retrospectively using the CTCAE v4.0. These criteria specify osteonecrosis of the jaws as a separate category, also consider radiological information, and can be used to score the severity of the lesion. However, this information must be interpreted carefully, as no statistical analysis on treatment modality and severity of the lesion can be performed.

In conclusion, osteoradionecrosis remains a severe problem due to a complex multifactorial aetiology. Although IMRT showed a tendency to lower the risk, ORN cannot be avoided yet. Robust and continuous follow-up while reducing additional risk factors is essential to prevent the development of ORN.

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## Competing interests

There are no competing interests to disclose.

## Ethical approval

Ethical approval was obtained from the Ethics Committee of the University Hospitals Leuven, Leuven, Belgium (S59013-mp 11764).

## Patient consent

Not required.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijom.2019.04.018.

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