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Osteoradionecrosis after postoperative radiotherapy for oral cavity cancer: A retrospective cohort study

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ABSTRACT

Objective: Osteoradionecrosis (ORN) is a severe late complication after radiotherapy but current knowledge on ORN risks in the setting of postoperative radiotherapy (PORT) is limited. We studied the incidence and risk factors of ORN in patients with oral cavity cancers (OCC, treated with PORT.

Patients and Methods: A retrospective cohort study was conducted including OCC patients (mainly squamous cell) treated with postoperative intensity modulated radiotherapy between 2010 and 2018 with > 1 year disease-free survival. Cumulative incidences of ORN were computed using the Kaplan Meier method. Clinical and dosimetric risk factors for mandibular ORN were evaluated using Cox regression models.

Results: Within our cohort (N = 227, median follow-up 49 months) we observed 46 cases of ORN, mainly in the mandible (n = 41). The cumulative incidence of mandibular ORN was 15.9 % (SE 2.5 %) at three years and 19.8 % (SE 3.0 %) at five years. At univariable analysis, smoking, mandibular mandibulotomy or segment resection, mean dose to the mandible, and mandible volume (%) ≥ 60 Gy (V60) were significantly associated with increased ORN risks. At multivariable analysis, smoking (HR 2.13, 95 %CI 1.12–4.06) and V60 (HR 1.02 per 1 % increase, 95 %CI 1.01–1.04) remained predictive factors. For active smokers with a high V60 ≥ 40 % we observed rapid ORN development with a 1-year incidence of 29 % vs 6 % for others ($p < 0.01$).

Conclusion: OCC Patients treated with PORT are at high risk for mandibular ORN. We identified the mandibular volume receiving ≥ 60 Gy as the dominant risk factor, especially in active smokers. Limiting high-dose volumes at treatment planning may decrease ORN risks.

Introduction

Osteoradionecrosis (ORN) is a serious late complication of radiotherapy (RT) for head and neck cancer. Over the years several theories have emerged describing the pathophysiology of ORN. In 1983, Marx proposed the hypoxic, hypovascular, and hypocellular model (the three H principle), describing the changes in irradiated tissue that lead to ORN [1]. More recently, Delanian and Lefaix detailed the fibroatrophic theory, where fibroblast dysfunction leads to changes in tissue composition that allow for the development of ORN [2]. Both approaches describe radiation-induced changes to the tissue on a cellular and molecular level, leading to vascular injury and changes in tissue composition. These changes lead to the inability of the bone tissue to respond to the increased oxygen requirement and tissue repair demands after trauma (such as post-RT dental extractions or infections), or even to seemingly spontaneous breakdown of tissue [1–3]. The clinical presentation varies, ranging from stable small areas of asymptomatic exposed bone to severe progressive necrosis. In the more severe cases patients may experience severe pain, trismus, dysphagia, pathological fractures, or the formation of orocutaneous fistulas. Consequently, repeated hospital visits and

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sometimes extensive surgical reconstructions are needed to manage these sequelae. Depending on the severity, ORN can have a debilitating impact on patients' quality of life [4]. Treatment options may include pain medication, antibiotics, removal of sequesters, hyperbaric oxygen therapy, segmental resection of the maxilla/mandible, and free flap reconstruction.

Oral cavity cancer (OCC) is the most common type of head and neck cancer and may have a great impact on appearance and oral functions and therefore on quality of life[5,6]. The primary treatment for OCC is surgery combined with postoperative RT (PORT) when indicated, whereas for other head and neck tumors (chemo)radiation is the primary treatment of choice [7]. Patients with OCC are more likely to have tumor bone invasion, surgery of the mandible, and high-dose volumes in the mandible, all previously described risk factors for developing ORN [8–13]. Literature on ORN incidence and risk factors in OCC patients treated with PORT is limited, as most studies focus on cohorts of mixed head and neck cancers or oropharynx tumors, and provide little to no specific data on OCC patients [9,14–16]. Therefore, this study aims to describe ORN incidence in a cohort of OCC patients treated with PORT and to determine the incidence of ORN and relevant risk factors. To our knowledge, this is the first study providing data specifically about ORN development in a postoperative setting, and the first to assess dosimetric risk factors in a OCC population.

Patients and methods

Study population

The study protocol was reviewed by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, the Netherlands (reference EMC17404), and we obtained permission for retrospective collection of anonymized clinical and dosimetric data. The retrospective cohort included all patients (≥18 years of age) treated for OCC (regardless of tumor type) with PORT with curative intent in the Erasmus Medical Center between January 2010 and December 2018. Patients with tumor progression, death, loss of follow-up within one year, or a history of RT in the head/neck region were excluded.

Treatment and follow-up

OCC treatment consisted of surgical resection, followed by PORT, indicated due to intermediate or high risk of recurrence (following national treatment guidelines [17]), as determined by a multidisciplinary tumor board. Surgical procedures ranged from local soft-tissue resections to commando procedures with (partial) resection of the mandible or maxilla, depending on several factors such as tumor size and location. Direct reconstruction with a free radial forearm flap, anterolateral thigh flap, or free vascularized fibula graft was performed in case of expected postoperative dysfunctioning. A neck dissection or RT of the ipsilateral neck levels I – III/IV was performed, in patients without lymph node disease (cN0) and level I-IV/V in patients with lymph node disease (cN1-3), with bilateral treatment if the tumor reached the midline of the oral cavity. Depending on the surgery, the surgical team varied from a single experienced head and neck surgeon, to a multidisciplinary team.

The applied RT technique was intensity modulated radiotherapy (IMRT). For high-risk patients, the standard PORT treatment schedule was 33x2Gy. The clinical target volume (CTV) encompassed the tumor bed (margin of 1 cm if resection margins < 1 mm) and all lymph node regions with affected nodes with extranodal growth (minimum margin of 1 cm around the lymph node). For intermediate-risk patients, standard protocol was 30x2Gy until 2017, when the protocol was adjusted to 28x2Gy, with the CTV defined as the tumor bed (1 cm margin) and all lymph node regions with lymph node disease. An accelerated RT schedule with six fractions per week was the standard procedure until 2015, when a five fraction a week schedule became the new standard.

Before the start of RT, all patients had a dental evaluation, including dental radiograph. When possible, any necessary dental extractions were performed during ablative surgery. During RT (and less frequently during follow-up), dentulous patients and patients with implants were monitored weekly by a dental hygienist and received fluoride treatments. Oncological follow-up visits were planned every-two months in the first year, alternating between the radiation oncologist and the maxillofacial or ear nose throat surgeon. Follow-up continued for at least five years, with the frequency of the visits gradually decreasing to every-six months after the first year. The surgery and radiotherapy clinical protocol did not differ between patients with oral squamous cell carcinoma and other tumor types, with the exception of less frequent treatment of the neck.

Osteoradionecrosis

The primary endpoint ORN was defined as the presence of a pathological mandibular fracture or exposed bone for $\geq$ 3 months, in an irradiated area without evidence of tumor recurrence, and/or requiring treatment for ORN (e.g., sequesterectomy, hyperbaric oxygen)[9,15]. Late surgical complications, such as primary failure of the fibular graft or infected osteosynthesis material, can lead to exposed bone [18]. These cases were only defined as ORN if determined as such by the treating head and neck surgeon, based on clinical presentation and imaging. Patients with (suspected) ORN were referred to a specialized outpatient clinic of the oral- and maxillofacial surgery department for monitoring and treatment, and further diagnostics if indicated.

Details on ORN were collected from correspondence, notes, and reports, (by MM) and all independently checked by a second researcher (WH). In case of incomplete or contradicting information, it was discussed with an experienced maxillofacial surgeon (HM). The ORN severity was graded using both the common terminology criteria for adverse events (CTCAE) 5.0 for osteonecrosis of the jaw[19] and Notani scores. Notani scores were collected from the patient files or (when not recorded prospectively) retrospectively assigned by the same maxillofacial surgeon (HM) based on imaging. The CTCAE 5.0 score was retrospectively assigned by two independent investigators (MM&WH), based on available data.

Dosimetric data

Dosimetric data was extracted from original RT treatment plans (physical dose), with automatic delineation of organs at risk with manual correction. The mandible was delineated retrospectively since it was not part of the original treatment plan optimization. Based on literature, dosimetric analysis was focused on mean RT dose to the mandible (Dmean) and the volume of the mandible receiving $\geq$ 60 Gy in % (V60), [9,10,15].

Statistical analysis

Statistical analyses were performed using SPSS software (Version 25, IBM Corporation, Armonk, NY). We calculated follow-up from the first day of RT. Follow-up was censored at five years (end of standard follow-up), death, disease recurrence, or other head and neck RT (whichever came first). Cumulative incidences were computed using Kaplan Meier method to adjust for differences in follow-up. As ORN located outside the mandible is rare, we focused on evaluating risk factors for the endpoint of mandibular ORN only. Based on literature [9,10,12,14,15,20], we selected potential risk factors for assessment in uni- and multivariable analysis in Cox regression models. For the multivariable model all risk factors with $p < 0.1$ at univariable analysis were included, taking into account that we only selected the most significant variable of a set of variables with high correlation (i.e. mandible surgery variables, dose variables).

Results

A total of 357 patients were treated with RT for OCC between 2010 and 2018, of whom 227 were eligible for this study. Reasons for exclusion were: follow up < 1 year (due to death, loss of follow up, or tumor progression (N = 66)), brachytherapy (N = 33), primary RT without surgical intervention (N = 17), incomplete RT treatment (N = 9), and a history of head and neck RT (N = 5). Dosimetric data was retrieved for 224 patients.

Baseline characteristics

The median follow-up was 49.2 months (IQR 32.5–67.1 months, censored after 60 months in further analysis). Complete (5 years) follow-up was available for 94 patients. For 58 patients, the follow-up was ongoing, and in the remaining 75 patients, follow up ended early due to loss of follow up (N = 14), tumor progression (N = 3), other tumors (N = 6), or death (N = 52, caused by primary tumor N = 27, other tumors N = 16, other/unknown causes N = 9). The median age was 66 years (range 24–91).

Baseline characteristics are summarized in Table 1. The majority of patients (95.6 %) were treated for squamous cell carcinoma. For 43 % of the OCC patients, the primary surgical resection involved surgery to the mandible; 94 % of patients (N = 47) with a segmental mandible resection received direct reconstruction with a fibula graft. The time between surgery and start of RT was five to nine weeks for most patients (78 %). The majority (87 %) of patients had a prescribed dose of ≥ 60 Gy.

Incidence and development of osteoradionecrosis

We observed 46 cases of ORN (crude incidence 20.3 %); N = 41 in the mandible, N = 4 in the maxilla, and N = 1 in the zygomatic arch. The estimated cumulative incidence of ORN was 8.4 % (SE 1.8 %) at 1 year, 17.6 % (SE 2.7 %) at 3 years, and 23.4 % (SE 3.3 %) at 5 years (another 2 cases developed after 6.5 and 6.8 years). The cumulative incidence of mandibular ORN was 8.4 % (SE 1.8 %) at one year, 13.2 % (SE 2.3 %) at two years, 15.9 % (SE 2.5 %) at three years, 18.9 % (SE 2.8 %) at four years, and 19.8 % (SE 3.0 %) at five years (Figure 1). The median time to development of mandibular ORN was 13.6 months (range 3–81 months). Nine out of the 41 ORN cases (22 %) developed after post-RT dental extractions, 26/41 (63 %) had some type of complications (surgical or otherwise) in the months or years before the development of ORN, including 17 patients with infection (postoperative wound infection N = 5, infected osteosynthesis material N = 5, soft tissue infection N = 7, abscess formation N = 5), 6 patients with post-operative bleeding or hematoma's, 6 patients with surgical wound dehiscence, 5 patients with ulcers formation, 9 patients with late fistula formation, and 3 patients with primary reconstruction failure (soft tissue N = 2, Fibula N = 1). Overall, 70.7 % (29/41) of mandibular cases occurred in the first 2 years. The ORN outside the mandible developed later than the mandibular ORN, with the earliest case of maxilla ORN after 26.7 months (latest 59.8 months) and the ORN of the zygomatic arch after 37 months.

Severity and treatment of osteoradionecrosis

Most (92.7 %) patients with ORN were symptomatic or required treatment (CTCAE grade ≥ 2)(Table 2). Thirteen patients with mandibular ORN developed mandibular fractures (53.8 % of whom had mandibular surgery, N = 1 marginal resection, N = 4 segment resection, N = 2 Mandibulotomy), and 15 patients developed orocutaneous fistulas. The median time between the first sign of ORN and mandibular fracture was 6.9 months (Range 0–5.1 years). Most fractures (61.5 %) developed within the first year after developing ORN, with 2 fractures being the first manifestation of ORN and another 3 developing within a month of the first exposed bone. In 3 cases (6.4 % of fibula

Table 1
Baseline characteristics.

	All patients (%)
Median age start RT (min–max)	66 (24–91)
Sex	
Female	94 (41.4 %)
Male	133 (58.6 %)
Smoker at diagnosis	
Current	105 (46.3 %)
Previous	77 (33.9 %)
Never	45 (19.8 %)
Alcohol use at diagnosis	
Current (>1 unit a week)	133 (58.5 %)
Previous	18 (7.9 %)
No/ seldom	76 (33.5 %)
Charlson comorbidity index	
0–1	112 (49.3 %)
2 or higher	115 (50.7 %)
Oral cavity tumor subsite	
Oral tongue	78 (34.4 %)
Floor of mouth	57 (25.1 %)
Hard palate	10 (4.4 %)
Buccal mucosa (cheek)	18 (7.9 %)
Gum	64 (28.2 %)
Tumor type	
Squamous cell carcinoma	217 (95.6 %)
-Poorly differentiated	59 (26 %)
-Moderately differentiated	145 (63.9 %)
-Well differentiated	13 (5.7 %)
Other tumor types	10 (4.4 %)
-Adenoid cystic carcinoma	4 (1.8 %)
-Adenocarcinoma	3 (1.3 %)
-Mucoepidermoid carcinoma	2 (0.9 %)
-Neuro endocrine carcinoma	1 (0.4 %)
T-stage(pathology)	
T1	52 (22.9 %)
T2	71 (31.3 %)
T3	18 (7.9 %)
T4A	81 (35.7 %)
T4B	5 (2.2 %)
N-stage	
N0	133 (58.6 %)
N1	34 (15 %)
N2A-C	59 (26 %)
N3	1 (0.4 %)
Bone-invasion (at pathology)	
Mandible	51 (22.5 %)
Maxilla	15 (6.6 %)
Both	1 (0.4 %)
No	160 (70.5 %)
Surgical resection bone	
Maxilla resection (partial)	18 (7.9 %)
Mandible surgery	95 (41.9 %)
Both	3 (1.3 %)
None	111 (48.9 %)
Type of mandible surgery performed	
Mandibulotomy (for surgical access)	17 (7.5 %)
Segment resection mandible	50 (22 %)
Marginal mandible resection or alveolotomy [a]	31 (13.7 %)
Neck dissection	
Yes, unilateral	153 (67.4 %)
Yes, bilateral	51 (22.5 %)
No	23 (10.1 %)
Highest prescribed radiotherapy schedule	
28x2Gy (56 Gy)	27 (11.9 %)
30x2Gy (60 Gy)	48 (21.1 %)
33x2Gy (66 Gy)	136 (59.9 %)
34x2Gy (68 Gy)	2 (0.9 %)
22-24x2.5 Gy (55–60 Gy)	3 (1.3 %)
25-26x2.5 Gy (62.5–65 Gy)	8 (3.5 %)
Another dose schedule	3 (1.3 %)
RT of the neck	
Yes, unilateral	59 (26 %)
Yes, bilateral	23 (10.1 %)
No	145 (63.9 %)
Accelerated RT	
Yes	114 (50.2 %)
No	113 (9.8 %)

[a] Resection with a minimum of 1 cm of mandibular height remaining.

reconstructions), the fibula reconstruction of the mandible was lost due to ORN (7 patients developed graft failure with graft loss without signs of ORN).

At the end of follow-up, 18 cases (43.9 %) of mandibular ORN were resolved entirely, with a median time between the first sign of ORN to curation of 12.9 months (range 1.4–82.1 months). Of the 23 ORN cases ongoing at last follow-up, 11 were still under active follow-up. Most patients (82.9 %) received treatment for ORN, see Table 2 for details.

Dose to the mandible

The average Dmean to the mandible was 37.1 Gy (SD 9.5) and the average V60 was 25.9 % (SD 20.3). Patients treated with surgery to the mandible had a higher overall Dmean (42 Gy, SD 7.0) and V60 (35 %, SD 20.4) compared to patients without mandibular surgery (DMean 34 Gy, SD 9.6, V60 19 %, SD 17.4). Segmental resection of the mandible was associated with the highest average DMean (42 Gy, SD 7.1) and V60 (38 %, SD 21.2). Similarly, patients who received neck RT had a higher average Dmean and V60 (Dmean 42 Gy, SD 6.8, V60 33 %, SD 19.8) than patients without neck RT (DMean 34 Gy, SD 9.6, V60 22 %, SD 19.3).

Oral cavity subsites

Highest ORN incidences and dosimetric values for the mandible were observed for floor of mouth tumors (5 year incidence 31 %, Dmean 41 Gy, V60 33 %), and buccal mucosa (5 year incidence 26 %, Dmean 36 Gy, V60 31 %). Lowest risks were observed for hard pallate (5 year incidence 0 %, Dmean 23 Gy, V60 5 %) and the gums of the maxilla (5 year incidence 0 %, Dmean 21 Gy, V60 7 %). Intermediate risks were found for the subsites gums of mandible (5 year incidence 20 %, Dmean 41 Gy, V60 35 %), and oral tongue (5 year incidence 16 %, Dmean 37 Gy, V60 19 %). Overall, incidences were not significantly different between the subsites (Log Rank p = 0.11).

Risk factors for osteoradionecrosis

In univariable analysis, we identified Dmean and V60 of the mandible as significant risk factors (Table 3). Notably, 97.6 % of patients with ORN had prescribed RT doses of 60 Gy or higher (40/41). In patients with V60 > 20 %, the incidence of mandibular ORN was 17.8 % at 2 years and 29.4 % at 5 years (versus 7.5 % at 2 and 5 years for < 20 %). Being an active smoker at diagnosis was also a significant risk factor for ORN development. We found that mandibular ORN developed earlier in smokers compared to non-smokers. In active smokers, the median time to ORN development was 9.3 months (range 3.2 months- 78 months), while for non-smokers, the median time to ORN was 21.4 months (range 8.5–81.2 months). Furthermore, mandibulotomy or segment resection of the mandible was significantly associated with ORN risk.

Multivariable analysis

Based on p < 0.10, four variables were selected for the multi-variable analysis: smoking, mandibulotomy or segment resection, neck RT and V60. Active smoking and higher V60 remained statistically significant with a hazard ratios of 2.15 and 1.02 (per 1 % increase in V60), respectively. We found that ORN developed particularly early in patients were active smoking was combined with a large high-dose volume

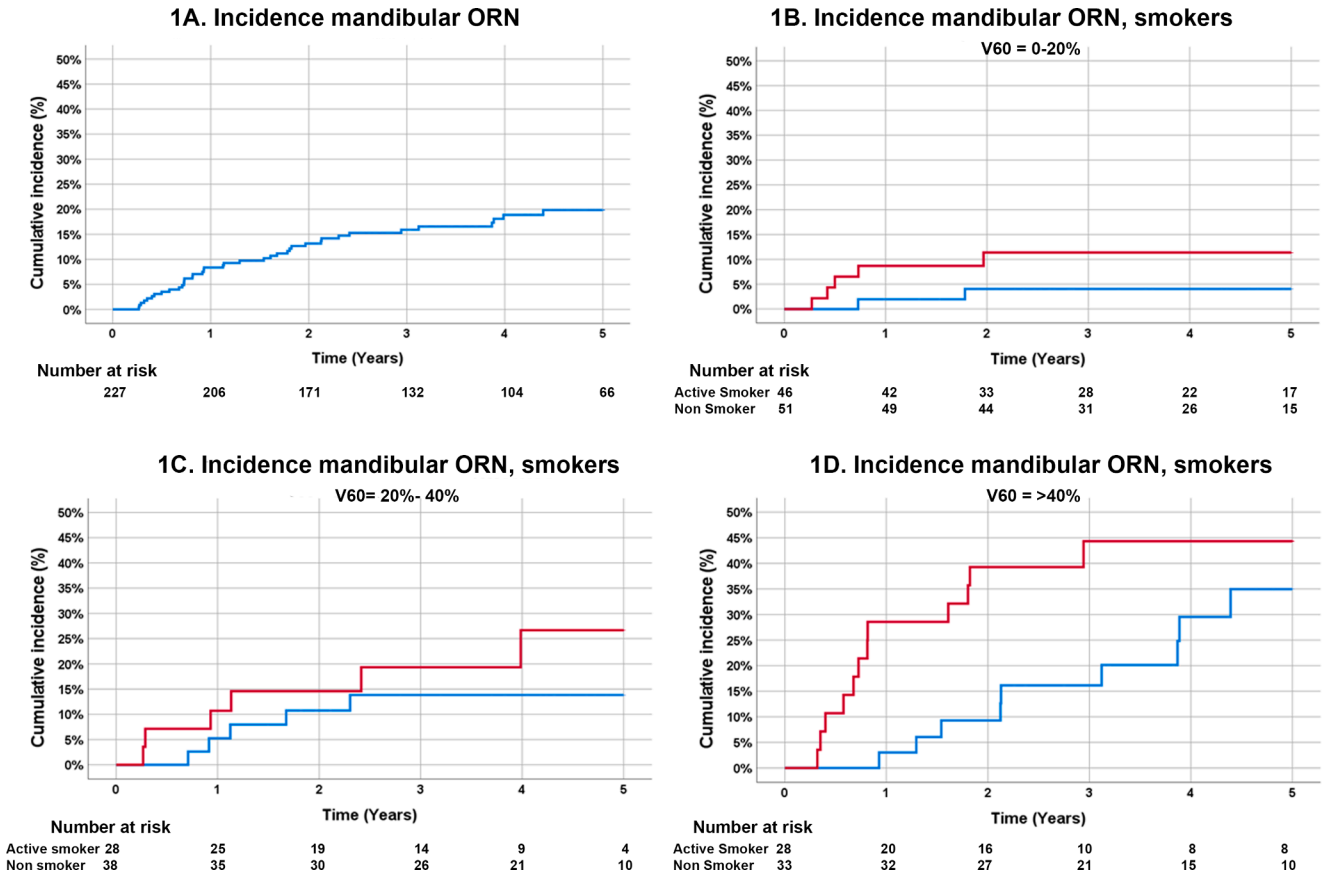

Figure 1. Estimated cumulative incidence of ORN over time. **1A**. Incidence of mandibular ORN. **1B-D**. active smoking at diagnosis (Red) vs non active smoker (Blue), within patient subgroups with small mandibular volumes receiving >=60 Gy (V60 < 20 %, N = 97), intermediate volumes receiving >=60 Gy (20–40 %, N = 66), and high volumes receiving >=60 Gy (>40 %, N = 61).

Table 2
Severity and treatments of mandibular ORN.

ORN	N (% within ORN groupN=41)
Severity	
Notani	
-Notani grade 1	7 (17.1 %)
-Notani grade 2	10 (24.4 %)
-Notani grade 3	20 (48.8 %)
-Notani score unavailable	4 (9.7 %)
CTCAE 5.0	
-Grade 1 (asymptomatic/no intervention)	3 (7.3 %)
-Grade 2 (symptomatic/intervention)	11 (26.8 %)
-Grade 3 (severe symptoms/ limiting self care/ surgery)	27 (65.9 %)
Loss of teeth/dental implants due to ORN	10 (24.4 %)
Opiates prescribed for severe pain	8 (19.5 %)
Feeding tube started due to ORN	4 (9.8 %)
Mandible fracture	13 (31.7 %)
Orocutaneous fistula	15 (36.6 %)
Treatment	
Removal of sequester or protruding bone in outpatient clinic	19 (46.3 %)
Surgery for ORN, primary closure [a]	10 (24.4 %)
Surgery for ORN, requiring free soft tissue flap reconstruction[b]	7 (17.5 %)
Surgery for ORN, requiring fibular free flap reconstruction[c]	4 (9.8 %)
Hyperbaric oxygen therapy	15 (36.6 %)

[a] Sequestrectomy, segment resection or another surgical debridement, primary closure defect.
[b] Sequesterectomy, segment resection, removal of avital fibula reconstructions, requiring reconstruction with free flap (for instance nasolabial flap or pectoralis major flap).
[c] Surgical reconstruction with fibula reconstruction after mandibular fracture. It should be noted some patients received a combination of these treatments.

Table 3
Univariable and multivariable analysis risk factors for mandibular osteoradionecrosis.

Variable	Hazard ratio	95 % CI	P-value
Univariable			
Age[a]	0.99	0.96–1.01	0.22
Active alcohol user at diagnosis (yes vs no)	1.18	0.62–2.24	0.62
Active smoker at diagnosis (yes vs no)	1.90	1.00–3.60	**0.05**
Charlson comorbidity index (2 + vs 0–1)	1.34	0.71–2.53	0.36
Diabetic at diagnosis (yes vs no)	1.09	0.53–2.25	0.82
T stage (T3-4 vs T1-2)	0.81	0.43–1.53	0.51
Bone-invasion tumor in mandible (yes vs no)	1.15	0.56–2.36	0.70
Any surgery to mandibular bone (yes vs no)	1.80	0.95–3.38	0.07
Mandibulotomy or segment resection (yes vs no)	1.90	1.01–3.59	**0.05**
Segment resection mandible (yes vs no)	1.57	0.80–3.10	0.06
Accelerated RT (yes vs no)	1.17	0.62–2.22	0.63
RT prescribed dose ≥ 60 gy (yes vs no) [b]	5.49	0.75–40.05	0.09
RT of neck (yes vs no) [c]	1.80	0.96–3.37	0.07
DMean Mandible (for each increase of 1 Gy)	1.06	1.02–1.10	**0.004**
V60 (% of mandible that received 60 Gy, in steps of 1 %)	1.03	1.01–1.04	**<0.001**
Multivariable			
Active smoker at diagnosis (yes vs no)	2.13	1.12–4.06	**0.02**
Mandibulotomy or segment resection (yes vs no)	1.38	0.76–3.14	0.38
RT of neck (yes vs no)	1.45	0.75–2.78	0.27
V60 (% of mandible that received 60 Gy, in steps of 1 %)	1.02	1.01–1.04	**0.005**

[a] Age tested as a continuous variable,
[b] Highest prescribed dose (either tumor bed or neck dose) [c] Radiotherapy of the neck (uni or bilateral) yes vs *no*.

(Figure1).

Discussion

In this study, we established ORN risks for patients who received PORT for OCC and we identified relevant risk factors. At five years, the cumulative incidence was 23.4 % for all ORN and 19.8 % for mandibular ORN. ORN may occur months to years (even decades) after RT [21–23]. In our study, most cases of mandibular ORN (34/41) occurred within 3 years of follow-up.

Two previous studies reported incidences of mandibular ORN over time specifically for OCC patients. Monnier et al.[11] reported a 50 % cumulative incidence of mandibular ORN after 5 years in a small retrospective cohort of 43 OCC patients mainly treated with 66–70 Gy. They included all late necrosis of transplanted bone as ORN. When including all mandibular fibula graft failure as ORN as well, our number goes up from 19.8 % to 24.6 % at 5 years. Liao et al. [21] used a nationwide medical database based on insurance data, and reported a 5 year ORN incidence of 4–9 % depending on oral cavity subsite. The use of insurance data is a very different approach compared to using hospital records and therefore a valid comparison with our data is not possible.

In other recent literature, ORN incidences for OCC are limited to crude incidences in OCC subgroups of mixed cohorts. Kubota et al.[9] reported an 11.1 % ORN incidence in a 161 patient OCC cohort (median follow-up 40 months), including ORN with CTCAE scores ≥ 2 only. We observed a 16.7 % crude ORN incidence when only including CTCAE ≥ 2. Owosho et al.[14] described a 4.1 % incidence of mandibular ORN for their OCC subgroup who received maximum dose levels of 60 Gy after surgery. We observed an 6.4 % incidence (5/78) of ORN in patients treated with ≤ 60 Gy. Moon et al.[20] found a crude mandibular ORN incidence of 10.3 % (7/68) in their OCC subgroup, with a median follow-up of only 25 months, comparable to our crude incidence of 12.8 % at two years of follow-up. Kuhnt et al.[24] observed a 13.6 % incidence of ORN requiring surgical intervention for their OCC subgroup; higher than the 7.9 % incidence of ORN requiring surgical intervention within our study. In conclusion, our results are in reasonable agreement with these studies, taking into account the differences that exist between studies e.g. with respect to variations in follow-up, applied ORN definitions, and dose prescriptions.

The relationship between RT dose and ORN has been quantified in several previous studies, using cohorts with mixed or oropharyngeal cancer patients. Kubota et al.[9] reported that V60 is an important risk factor (particularly V60 ≥ 14 %). The MD Anderson group[16] reported V44 ≥ 42 % and a V58 ≥ 25 % as relevant cutoffs. Aarup-Kristensen et al.[10] reported Dmean of the mandible as an important dose factor. Likewise, Caparrotti et al.[15] suggests limiting V50 and V60 to reduce ORN rates. The relationship between dose volume parameters and ORN probability might be different in an OCC cohort. To our knowledge, Lang et al. is the only study describing dose factors in a postoperative OCC cohort. They reported mandibular Dmean > 45 Gy, Dmax > 60 Gy and a > 40 % overlap between mandible and PTV as significant risk factors. We identified a higher V60 as risk factor for developing mandibular ORN, especially when combined with active smoking, with a cumulative incidence of 29 % at 1 year and 45 % at 5 years for active smokers with V60 > 40 %. Smoking has been reported to increase the risk of different types of late radiation tissue injuries [25,26], and is a well-known risk factor for developing ORN with hazard ratios between 1.7 and 3.1 described in recent mixed and oropharynx cohorts[10,15,20]. Notably, we observed ORN development much earlier in smokers (median time of 9.3 vs 21.4 months). This effect was strongest when in active smoking combined with a relatively high V60. To our knowledge, this phenomenon has not been reported in other ORN studies.

Surgery to the mandible has been described as an important risk

factor for developing ORN[9,11,24,27]. We found an increased risk of ORN in patients with mandibulotomy or segment resections. However, this effect did not remain significant in multivariable analysis when RT dose to the mandible was included. We hypothesize that this may be due to the correlation between mandible surgery and dose to the mandible. A tumor requiring segmental resection (or other surgery) of the mandible will often imply that the target volume for RT is located in or near the mandible and therefore will receive a relatively high dose. Kubota et al. [9] also found that pre-RT mandible surgery did not remain significant in multivariable analysis when correcting for high-dose volumes. Liao et al. [21] found that tumors located in the floor of the mouth, gums of buccal mucosa were associated with a significantly increased risk of ORN. We also found these locations to have the highest ORN risk and found these locations to, on average, receive the highest mandibular Dmean and V60. While patients with mandibular gum tumors often received a segment resection of the mandible (75 %), patients with tumors of the floor of mouth and buccal mucosa did not have mandibulotomies or segment resection at the same rate (14 % and 22 % respectively). We therefore hypothesize that for ORN risk, tumor sublocation within the oral cavity serves as a proxy for mandibular radiotherapy dose. RT of the neck may similarly be correlated with increased mandibular dose.

A strength of this study is that it focuses specifically on a homogeneous cohort of patients receiving PORT for OCC. This gives more insight into specific features and risk factors concerning ORN development in this population. One of the limitations is the retrospective design. This may have led to incomplete ORN information for patients with limited follow-up, possible underreporting of asymptomatic ORN, and may therefore influence the accuracy of assigned scores. Furthermore, minor (surgical) complications, dental health or problems like peridontitis (as a potential risk factor for ORN) could not be evaluated in this retrospective setting. Consequently, we aim to validate these outcomes in a prospective cohort study. Though previously described as risk factors in literature[13], we did not include post- operative chemoradiation or Pre-RT dental extractions in our analysis, due to very limited numbers of patients treated with chemoradiation, and the limited amount of Pre-RT extractions as most extractions were performed during surgery. Due to varying compositions of surgical teams we did not asses individual surgeon experience as a potential risk factor.

In conclusion, patients treated with postoperative RT for oral cavity cancers are at considerable risk for ORN, with a 5-year cumulative incidence of 19.8 % for mandible ORN. We identified he volume of the mandible receiving high dose levels ($\geq$60 Gy) as a dominant risk factor, especially when combined with smoking. Limiting these high-dose volumes may decrease the incidence of ORN, especially in active smokers.

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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.

Data availability statement:

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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