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ORIGINAL ARTICLE

# Rates of osteoradionecrosis in resected oral cavity cancer reconstructed with free tissue transfer in the intensity-modulated radiotherapy era

**Shannon S. Wu BA**[1] | **Hanna Hong BS**[1] | **Michael Fritz MD**[2] | **Jamie Ku MD**[2] | **Brandon Prendes MD**[2] | **Natalie Silver MD**[2] | **Dane J. Genther MD**[2] | **Peter Ciolek MD**[2] | **Patrick Byrne MD, MBA**[2] | **Philip Brauer BA**[3] | **Chandana A. Reddy MS**[4] | **Neil Woody MD**[4] | **Shauna Campbell DO**[4] | **Shlomo A. Koyfman MD**[4] | **Eric D. Lamarre MD**[2]

[1]Cleveland Clinic Lerner, College of Medicine, Cleveland, Ohio, USA

[2]Cleveland Clinic, Head and Neck Institute, Cleveland, Ohio, USA

[3]Case Western Reserve, University School of Medicine, Cleveland, Ohio, USA

[4]Cleveland Clinic, Taussig Cancer Institute, Cleveland, Ohio, USA

**Correspondence**
Eric D. Lamarre, Head and Neck Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA.
Email: lamarre@ccf.org

## Abstract

**Background:** Resected oral cavity carcinoma defects are often reconstructed with osteocutaneous or soft-tissue free flaps, but risk of osteoradionecrosis (ORN) is unknown.

**Methods:** This retrospective study included oral cavity carcinoma treated with free-tissue reconstruction and postoperative IMRT between 2000 and 2019. Risk-regression assessed risk factors for grade ≥2 ORN.

**Results:** One hundred fifty-five patients (51% male, 28% current smokers, mean age 62 ± 11 years) were included. Median follow-up was 32.6 months (range, 1.0–190.6). Thirty-eight (25%) patients had fibular free flap for mandibular reconstruction, whereas 117 (76%) had soft-tissue reconstruction. Grade ≥2 ORN occurred in 14 (9.0%) patients, at a median 9.8 months (range, 2.4–61.5) after IMRT. Post-radiation teeth extraction was significantly associated with ORN. One-year and 10-year ORN rates were 5.2% and 10%, respectively.

**Abbreviations:** ALT, anterolateral thigh; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky performance status; ORN, osteoradionecrosis; RT, radiation therapy; SCC, squamous cell carcinoma.

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**Conclusions:** ORN risk was comparable between osteocutaneous and soft-tissue reconstruction for resected oral cavity carcinoma. Osteocutaneous flaps can be safely performed with no excess concern for mandibular ORN.

**KEYWORDS**

fibula flap, free tissue transfer, head and neck cancer, mandibular reconstruction, oral cancer, oral cavity, osteocutaneous flap, osteoradionecrosis, squamous cell carcinoma

## 1 | INTRODUCTION

Osteoradionecrosis (ORN) is a serious complication of radiation therapy (RT) characterized by exposed and devitalized bone, leading to pain, discomfort, and poor quality of life.[1] The advent of intensity-modulated radiotherapy (IMRT) may reduce the incidence of ORN due to the improved ability to contour radiation beams around critical structures.[2–4] Despite the ability to focus beams more precisely, reported incidence of ORN remains at 5%–35% of head and neck cancers following IMRT.[5,6] High radiation dose (>50–60 Gray [Gy]), oral cavity tumor site, mandibular surgery, poor dental hygiene, smoking, and alcohol use are known risk factors for the development of ORN.[7–14]

Fibular flap reconstruction has become a mainstay treatment of locally invasive oral cavity cancers involving the mandible. However, it is unknown whether reconstructed mandibles carry an elevated risk of ORN. Reconstructed mandibles must undergo a slow process of bone unionization and mineralization, a gradual process that is interrupted by the initiation of postoperative radiation. Hardware and plate exposure after mandibular reconstruction may induce chronic local inflammation that predisposes to ORN.[15] Flap loss, wound breakdown, and orocutaneous fistulas are complications after fibular flap reconstruction that may disrupt wound healing and create a hypoxic, hypovascular environment leading to bone necrosis.[16,17] To our knowledge, two prior studies have reported on ORN rates in this patient population. Among 74 patients with head and neck cancer undergoing osseous free flaps and postoperative RT not limited to IMRT, an ORN rate of 34% was reported.[18] Wang et al. reported a 47% incidence of ORN in 15 patients treated with osteocutaneous fibula flap who underwent postoperative RT.[19]

The incidence of ORN in reconstructed versus native mandibles and the identification of risk factors have not been formally evaluated. Prior studies have lacked a direct comparison group. Furthermore, published reports to date have included heterogeneous cancer types and multiple subsites, lack of long-term follow-up, and differences in classification systems.[3,9,14,20,21] Therefore, this study aimed to evaluate the risk factors for ORN in patients who underwent surgical resection of oral cavity squamous cell carcinoma (SCC) and free-tissue transfer with reconstructed versus native mandibles.

## 2 | METHODS

### 2.1 | Study population

This retrospective study included patients with oral cavity SCC at a tertiary-care, academic institution. Patients were included if they underwent surgical resection involving free-tissue transfer, received IMRT at least 45 Gy in at least 20 fractions, and completed IMRT between January 2000 and December 2019. Exclusion criteria were cancer not limited to the oral cavity, non-conventional squamous cell carcinoma, re-irradiation, received a radiation modality other than IMRT, or had metastatic disease at diagnosis. This study received Institutional Review Board approval and written informed consent was waived.

### 2.2 | Data collection

Electronic medical records were reviewed to record patient-level data, tumor characteristics, treatment details, and clinical outcomes. Demographics included age at IMRT completion, sex, and Karnofsky performance status (KPS). Tumor characteristics included T classification, N classification, perineural invasion (PNI), and lymphovascular space invasion (LVSI). Treatment variables included duration of IMRT, total received dose in Gy and fractions, and days between surgery and IMRT initiation. ORN grading was established by the Schwartz and Kagan classification system: Stage 1, superficial involvement of mandible (only soft tissue ulceration with exposed cortical bone); Stage 2, Exposed cortical bone and underlying medullary bone necrotic; Stage 3, full diffuse involvement.[22] ORN diagnosis was established if the lesion failed to heal by 3 months from initial documentation in the electronic medical records.[23]

### 2.3 | Clinical treatment

Tumor subsite was determined by laryngoscopy and radiographic imaging (computed tomography [CT] and/or magnetic resonance imaging [MRI]). Midline tumors were characterized by oral (mobile) tongue or floor of mouth tumors. Lateral tumors were those that were located in the buccal mucosa, retromolar trigone, alveolar ridge, gingiva, or hard palate. The diagnosis of SCC was established by biopsy; non-conventional SCC pathology was excluded. Patients were typically prescribed 60 Gy in 30 fractions of IMRT. All patients were evaluated by laryngoscopy every 3 months in the first year after IMRT completion, every 6 months for the next 2 years, and every year thereafter for at least 5 years by a radiation oncologist and head and neck surgeon.

### 2.4 | Dose–volume histogram

IMRT contouring plans were de-archived, and dosimetric parameters were analyzed to compare radiation dose to the mandible and oral cavity between reconstructed versus non-reconstructed mandibular groups. Dose–volume histograms were available for 34 patients, including 11 patients with reconstructed mandibles and 23 patients without mandibular reconstruction. Mean dose to the oral cavity and maximum dose to the mandible were obtained. Other dosimetric parameters included: mandible volume receiving 40 Gy (V40), 50 Gy (V50), and 60 Gy (V60), and oral cavity receiving 30 Gy (V30), V40, and V50.

### 2.5 | Statistical analysis

Categorical variables were described as frequency rates and percentages and compared by chi-squared test. Continuous variables were summarized with medians and quartiles and compared by ANOVA. The primary endpoint was incidence of Grade ≥2 ORN, calculated from last date of IMRT. Competing risk regression, with death as a competing event, was used to assess risk factors for the development of Grade ≥2 ORN. Variables examined in univariate analysis were age at IMRT completion, sex, smoking status (current smoker vs. former or never smoker), mandibular reconstruction, oral cavity subsite (lateral vs. midline), pathologic T classification (pT4 vs. pT1–T3), radiation therapy dose, and teeth extraction. Cumulative incidence analysis was done to model the incidence of ORN over time. All statistical analyses were performed in SAS version 9.4 software with $p < 0.05$ considered statistically significant.

## 3 | RESULTS

### 3.1 | Patient characteristics

In total, 155 patients with oral cavity SCC were treated with free flap surgery and completed postoperative IMRT between January 2000 and December 2019 (Table 1). Of these, 61% of patients were male, and 93% were Caucasian. There were 43 (28%) current smokers, 71 (46%) former smokers, and 41 (26%) never smokers. History of heavy alcohol consumption was reported in 46 (30%) of the study cohort. The median age at IMRT completion was 62 years (range, 28–93 years). Oral cavity subsite was midline in 103 (67%) patients, which included 72 (47%) oral tongue and 33 (21%) floor of mouth tumors. Oral cavity subsites were lateralized in 52 (34%) patients; these included 19 (12%) buccal mucosa, 13 (8.4%) retromolar trigone, 9 (5.8%) alveolar ridge, 6 (3.9%) gingiva, and 3 (1.9%) hard palate. T classification was most frequently T2 and higher, and 61 (39%) patients had pathologic N0 nodal disease. Rates of perineural invasion and lymphovascular space invasion were 63% and 52%, respectively (Table 2).

### 3.2 | Primary treatment

In total, 38 (25%) patients received a fibular free flap for mandibular reconstruction, whereas 117 (75%) patients did not have mandibular reconstruction. Of the 117 patients without mandibular reconstruction, 63 (41%) received radial forearm free flap, 43 (28%) had anterolateral thigh, and 10 had latissimus dorsi free flap surgery at tumor resection. All patients had postoperative IMRT, with a median radiation dose of 60 Gy in a median of 30 fractions. Dosimetric parameters to the native mandible and oral cavity were not different between patients with and without mandibular reconstruction, with the exception of mandibular V60, which was higher in patients with reconstructed mandibles (44.9% vs. 19.2%, $p = 0.002$) (Table 3). Sixty (39%) patients received chemotherapy at any timepoint during their treatment. Surgical intervention in the oral cavity and/or neck for any indication other than ORN was performed in 70 (45%) patients after completion of IMRT, most commonly for flap debulking, flap revision, vestibuloplasty, and local tissue rearrangement.

### 3.3 | Osteoradionecrosis

Moderate to severe ORN occurred in 14 (9.0%) patients; these included 3 (1.9%) patients with Grade 2 and

**TABLE 1** Descriptive statistics for patients with resected oral cavity cancers treated with free flap surgery and intensity-modulated radiation therapy ($N = 155$).

| Patient characteristic | Alive without ORN ($n = 71$) | Dead without ORN ($n = 70$) | Grade 2 or 3 ORN ($n = 14$) | $p$-value |
|---|---|---|---|---|
| Mean age at RT completion ± SD, in years | 60.9 ± 10.0 | 65.4 ± 11.9 | 60.5 ± 9.7 | **0.035** |
| Sex | | | | |
| Female | 25 (35%) | 29 (41%) | 6 (43%) | 0.710 |
| Male | 46 (65%) | 41 (59%) | 8 (57%) | |
| Ethnicity | | | | NA |
| White | 63 (89%) | 68 (97%) | 13 (93%) | |
| Black or African American | 6 (8%) | 2 (3%) | 1 (7%) | |
| Asian | 2 (3%) | 0 (0%) | 0 (0%) | |
| Smoking | | | | 0.299 |
| Current | 24 (34%) | 16 (23%) | 3 (21%) | Current vs. |
| Former | 29 (41%) | 36 (51%) | 6 (43%) | Former/ |
| Never | 18 (25%) | 18 (26%) | 5 (36%) | Never |
| Heavy alcohol consumption | 17 (24%) | 26 (37%) | 3 (21%) | 0.179 |
| Median KPS (range) | 90 (60–100) | 80 (50–100) | 80 (70–90) | 0.256 |
| Location | | | | |
| Lateral | 28 (39%) | 17 (24%) | 7 (50%) | |
| Midline | 43 (61%) | 53 (76%) | 7 (50%) | |
| Pathologic T-Stage | | | | 0.956 |
| T1 | 5 (7%) | 6 (9%) | 3 (21%) | T1–T3 |
| T2 | 26 (37%) | 21 (30%) | 6 (43%) | vs. T4 |
| T3 | 12 (17%) | 15 (21%) | 0 (0%) | |
| T4 | 28 (39%) | 28 (40%) | 6 (36%) | |
| Pathologic N-Stage | | | | **<0.001** |
| N0 | 38 (54%) | 19 (27%) | 4 (29%) | N0 vs. |
| N1 | 10 (14%) | 16 (23%) | 3 (21%) | N1–N3 |
| N2 | 18 (25%) | 24 (46%) | 5 (36%) | |
| N3 | 5 (7%) | 3 (4%) | 2 (14%) | |
| Mean duration of follow-up ± SD, in months | 64.7 ± 39.9 | 20.0 ± 26.5 | 63.4 ± 33.8 | **<0.001** |

Abbreviations: ORN, osteoradionecrosis; RT, radiation therapy.

11 (7.1%) patients with Grade 3 ORN. There were 11 (7.1%) patients with Grade 1 ORN. As of last follow-up, 71 (46%) patients were alive without ORN, and 70 (45%) deceased without development of ORN. Among the 14 patients who developed Grade ≥2 ORN, mean time to ORN onset was 18.7 ± 17.3 months (range, 2.4–61.5) after IMRT completion. The 1-year rate of Grade ≥2 ORN was 5.2% (95% CI 2.4%–9.6%), and the 2-year rate was 6.6% (95% CI 3.4%–11.3%) (Figure 1). Cumulative incidence reached 10% (95% CI 5.7%–16.2%) at 5 years after IMRT completion, and did not increase thereafter.

On univariate analysis, age, smoking status, alcohol consumption, KPS, oral cavity subsite, T-stage classification, margin status, received dose of radiation therapy, and time from surgery to IMRT completion were not associated with Grade ≥2 ORN (Table 4). Patients who were alive without ORN were more likely to have N0 disease ($p < 0.001$). Three (7.9%) of 38 patients with mandibular

**TABLE 2** Treatment characteristics.

| Treatment characteristic | Alive without ORN ($n = 71$) | Dead without ORN ($n = 70$) | Grade 2 or 3 ORN ($n = 14$) | $p$-value |
|---|---|---|---|---|
| Use of chemotherapy | 28 (39%) | 24 (34%) | 8 (57%) | 0.273 |
| Mean received dose of RT ± SD, in Gy | 61.0 ± 3.6 | 61.5 ± 4.7 | 62.5 ± 2.9 | 0.419 |
| Mean duration of RT ± SD, in days | 41.7 ± 4.3 | 43.1 ± 7.2 | 43.2 ± 5.9 | |
| Mean time from surgery to RT Completion ± SD, in months | 3.1 ± 0.4 | 3.4 ± 1.3 | 3.0 ± 0.3 | 0.071 |
| Reconstructed mandible | | | | 0.951 |
| No | 53 (75%) | 53 (76%) | 11 (79%) | |
| Yes | 18 (25%) | 17 (24%) | 3 (21%) | |
| Margin status | | | | 0.580 |
| Close (<5 mm) | 25 (35%) | 21 (30%) | 3 (21%) | Negative/ |
| Negative | 38 (54%) | 39 (56%) | 8 (57%) | Close vs. |
| Positive | 8 (11%) | 10 (14%) | 3 (21%) | Positive |
| Perineural invasion | 41 (58%) | 50 (71%) | 6 (43%) | NA |
| Lymphovascular space invasion | 34 (48%) | 38 (54%) | 9 (64%) | NA |
| Pre-radiation teeth extraction | 42 (59%) | 31 (44%) | 6 (43%) | 0.172 |
| Post-radiation teeth extraction | 9 (13%) | 4 (6%) | 5 (36%) | **0.006** |
| Non-ORN head and neck surgery after completion of RT | 31 (44%) | 31 (44%) | 8 (57%) | 0.638 |

Abbreviations: ORN, osteoradionecrosis; RT, radiation therapy.

**TABLE 3** Dosimetric parameters compared between patients with and without reconstructed mandibles.

| Variable | Reconstructed mandible[a] ($n = 11$) | No reconstructed mandible[a] ($n = 23$) | $p$-value |
|---|---|---|---|
| Mandibular dose[a] | | | |
| Max dose | 65.50 [65.15, 68.00] | 65.10 [64.30, 66.55] | 0.473 |
| Dose at 0.03 cc | 65.10 [64.50, 67.60] | 64.70 [63.85, 66.20] | 0.450 |
| V40 | 68.72 [55.33, 74.70] | 63.22 [50.89, 73.06] | 0.581 |
| V50 | 61.53 [44.62, 67.50] | 47.09 [41.54, 55.32] | 0.136 |
| V60 | 44.89 [38.35, 47.92] | 19.21 [12.69, 28.49] | 0.002 |
| Oral cavity dose[a] | | | |
| Mean dose | 49.46 [37.93, 54.49] | 52.97 [38.97, 58.09] | 0.329 |
| V30 | 79.74 [58.95, 88.57] | 86.44 [58.56, 97.21] | 0.393 |
| V40 | 67.66 [45.38, 81.41] | 80.15 [49.09, 94.08] | 0.255 |
| V50 | 58.37 [34.30, 71.27] | 69.87 [41.58, 83.84] | 0.329 |
| Developed ORN | 6 (26.1%) | 4 (36.4%) | 0.692 |

[a]Median [IQR] values shown.

reconstruction developed Grade ≥2 ORN, compared to 11 (9.4%) of 117 patients with no mandibular reconstruction, and these rates were not significantly different ($p = 0.813$) (Figure 2). Post-IMRT surgical interventions for indications other than ORN was not significantly associated with Grade ≥2 ORN ($p = 0.435$). While pre-radiation teeth extractions were not associated with ORN, there was a significantly higher rate of post-IMRT teeth extractions in patients who developed ORN (36% in ORN vs. 12% for entire cohort) ($p = 0.006$). On competing risk regression analysis for ORN, post-radiation teeth extraction had a fourfold increased risk (HR = 4.53, $p = 0.007$) (Table 4).

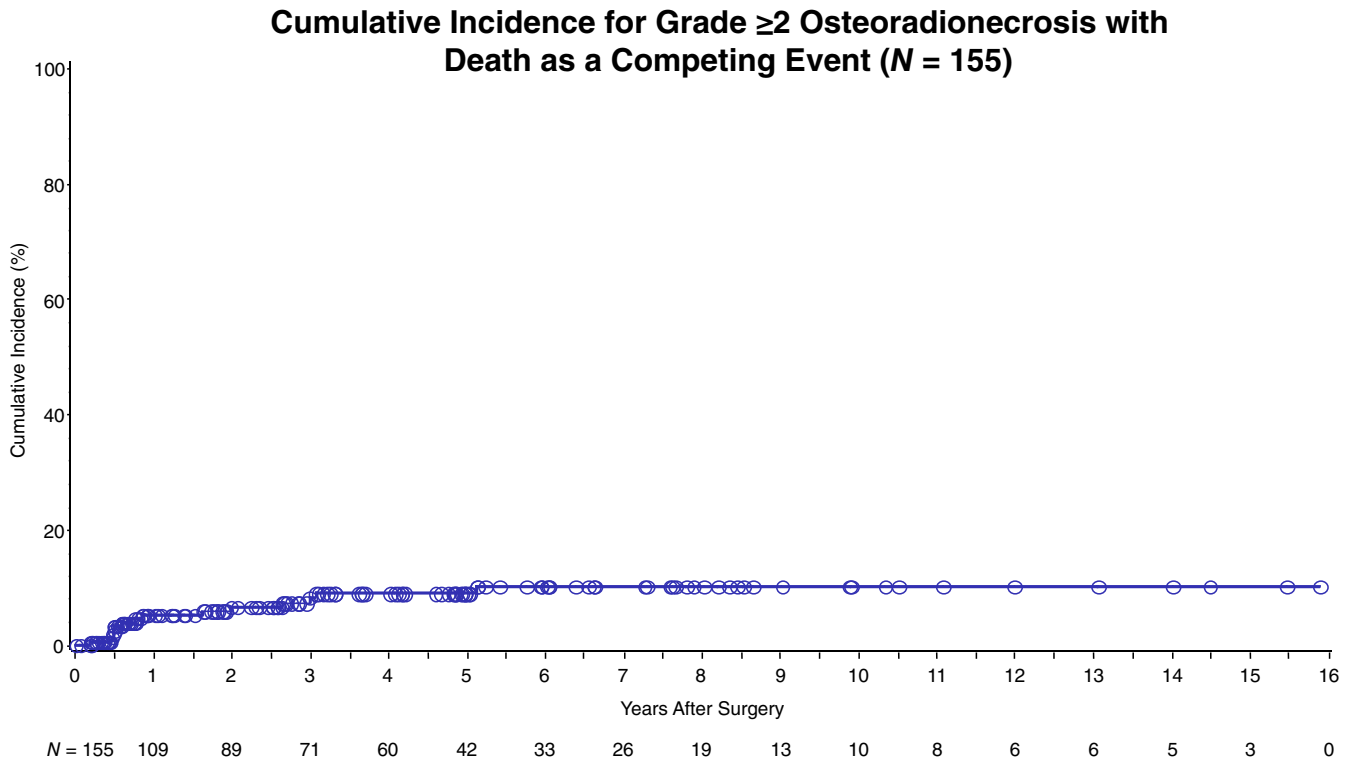


**FIGURE 1** Kaplan–Meier curve for cumulative incidence for Grade 2 or Grade 3 osteoradionecrosis with death as a competing event ($n = 155$). [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** Competing risk regression for Grade ≥2 osteoradionecrosis, univariate analysis.

| Variable | Hazard ratio | 95% CI | *p*-value |
|---|---|---|---|
| Age at radiation therapy completion | 0.979 | 0.94–1.02 | 0.313 |
| Smoking status (current vs. never/former) | 0.754 | 0.21–2.71 | 0.665 |
| Sex (female vs. male) | 1.162 | 0.41–3.32 | 0.779 |
| Reconstructed mandible (yes vs. no) | 0.854 | 0.23–3.14 | 0.813 |
| Location (lateral vs. midline) | 2.056 | 0.73–5.82 | 0.174 |
| Margin status (positive vs. negative/close) | 1.775 | 0.51–6.18 | 0.367 |
| Pathologic T-stage (T4 vs. T1–T3) | 0.883 | 0.30–2.61 | 0.822 |
| Radiation therapy dose | 1.082 | 0.98–1.20 | 0.124 |
| Post-radiation teeth extraction (yes vs. no) | 4.530 | 1.52–13.49 | **0.007** |

Abbreviation: CI, confidence interval.

### 3.4 | Treatment of osteoradionecrosis

Among the 14 patients with Grade ≥2 ORN, 12 required surgical intervention for treatment. Four patients had mandibular resection and fibular free flap reconstruction for treatment of ORN, and none had prior mandibular reconstruction. Five patients were treated with an antero-lateral thigh flap, four of whom had previous fibular flap mandibular reconstruction. Two patients underwent debridement, one patient had radial forearm free flap, and one patient had a transposition flap for treatment of ORN. Ten (83%) of 12 patients had complete resolution of their ORN following surgery at a mean time of 8.9 ± 6.3 months.

## 4 | DISCUSSION

This is the first study to evaluate the risk of ORN in reconstructed versus native mandibles in patients with oral cavity SCC in the IMRT era. All patients underwent free flap surgery, with reconstructed mandibles defined by those who had fibular free flap, and native mandibles defined by those who had any non-osseous free tissue

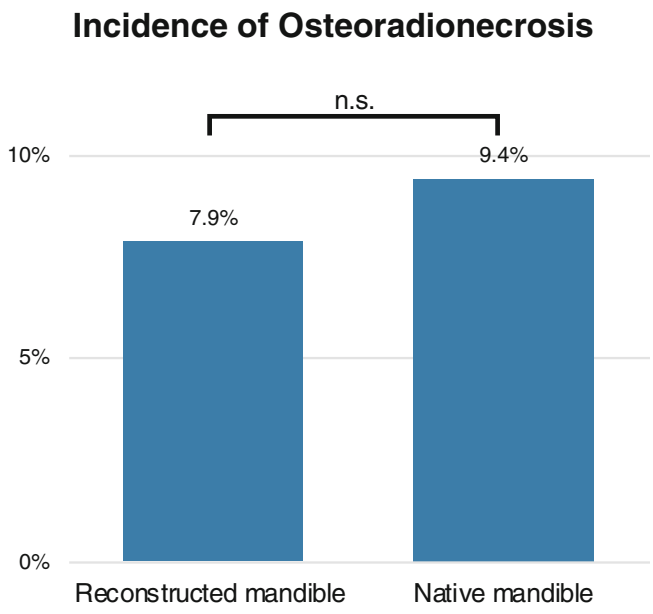


**FIGURE 2** Incidence of osteoradionecrosis (ORN) compared between reconstructed and native mandibles. Out of 38 mandibles reconstructed with fibular free flap, three developed ORN. Out of 117 patients with native mandibles, 11 developed ORN. n.s., non-significant. [Color figure can be viewed at wileyonlinelibrary.com]

transfer. The overall incidence of Grade ≥2 ORN for the cohort was 9.0%, which is substantially lower than two studies specifically analyzing fibular flap reconstruction,[18,19] but consistent with those reported by other prior studies.[6,9,24–29] The incidence of ORN between reconstructed and native mandible cohorts was not significantly different (7.9% vs. 9.4%, respectively). Eight (57%) of 14 patients with ORN were diagnosed at 5 years or longer after IMRT completion.

Despite high reported rates of ORN in two prior studies specifically evaluating fibular free flaps (34%–47%),[18,19] the present findings found that mandibular reconstruction did not escalate risk of ORN. The incidence of ORN in reconstructed mandibles was 7.9%, which was slightly lower than that of native mandibles (9.4%), and the difference was not statistically significant. Dziegielewski et al. reported on 38 patients, in which the mandible was reconstructed by fibular flap in 36 patients and scapula flap in 2 patients. Their high ORN incidence of 34% may be due to a heterogeneous patient population, as SCC, adenoid cystic carcinoma, mucosal melanoma, and juvenile ossifying fibroma were included in their cohort. Postoperative radiation in their study was not limited to IMRT, and three-dimensional radiation therapy without the ability to contour beams may have contributed to higher ORN rates. Furthermore, high radiation doses were received in their patient cohort, ranging from 60 to 74.4 Gy; in fact, more than half their cohort received at least 70 Gy of radiation. These findings suggest that other tumor-level and treatment-related factors may have contributed to the high ORN rate rather than osseous flap reconstruction. Wang et al. reported that the ORN incidence among 15 patients with head and neck cancer who received osteocutaneous fibula flap as 47%. This study did not report on radiation dose, cancer type, or method of defining ORN, and, thus, conclusions concerning risk factors for the high observed incidence of ORN were difficult to draw. Overall, our findings support the conclusion that mandibles reconstructed with fibular flaps are not inherently more vulnerable to ORN than native mandibles.

Post-RT teeth extraction was significantly associated with ORN, with a hazard ratio of 4.53. In contrast, pre-RT teeth extraction was not significantly associated with ORN. This divergent finding is supported by prior findings in the literature. Wang and colleagues assessed 23 527 patients with head and neck cancer and concluded that pre-RT teeth extraction was not a risk factor for ORN (HR 1.069, $p = 0.25$), whereas post-RT teeth extraction was a risk factor (HR = 1.593, $p < 0.001$).[30] Similarly, Iqbal et al. assessed 17 patients with head and neck cancer between 2005 and 2017 and found that ORN incidence after post-RT dental extraction was 35%.[6] Willaert and colleagues evaluated 109 patients with head and neck cancers, and identified that post-RT tooth extraction was associated with ORN (HR = 4.300, $p = 0.049$) whereas pre-RT extraction was not (HR = 2.012, $p = 0.13$). Liao et al. assessed 8000 patients with oral cavity cancer and identified post-RT tooth extraction as a risk factor.[8] However, other studies have identified pre-RT tooth extractions as independent risk factors for ORN.[5,31,32] Our findings suggest that prophylactic tooth extraction must be carefully evaluated prior to treatment initiation to minimize post-RT disturbances.

Post-RT surgical manipulation of the oral cavity or neck was not associated with ORN. Notably, all surgical procedures were performed at least 4 months following completion of postoperative RT. Nearly half of patients underwent flap debulking, flap revision, local tissue rearrangement, or surgery for other indications following free flap surgery, without an observed increase in ORN incidence. Ten of 70 patients with any surgical manipulation had mandibular surgery specifically, and the incidence of ORN in these patients was not different from those who had non-mandibular surgery. In contrast to our findings, Iqbal et al. and Lee et al. reported that post-RT mandibular surgery was a significant risk factor for ORN,[4,6] perhaps due to insufficient healing time between IMRT completion and surgery, which was not reported. In our cohort, median time between IMRT completion and post-RT surgical intervention was 7.7 (IQR 4.1–53.6) months,

and waiting at least 4 months prior to subsequent surgical intervention may be protective. Similarly, Owosho et al. reported that ORN occurred spontaneously, without history of trauma or dentoalveolar procedures, in 83% of patients.[20] Together, these findings suggest that further surgical manipulation following an adequate window for initial wound healing did not predispose to ORN.

In contrast to many prior studies,[6,7,9,13,20,26,27] received-dose of RT was not significantly associated with ORN. A possible explanation for this finding is that most patients received the standard RT dose of 60 Gy in 30 fractions, as is standard practice at our institution, and there were few treatment regimens that deviated from this either on the high or low end. There were only 7 (4.5%) patients who received >70 Gy, and one of these patients developed ORN. IMRT allows precise contouring of high-dose radiation beams around normal tissue, thus the low incidence of ORN observed that is consistent with prior studies. Dosimetric parameters obtained from dose–volume histograms showed no difference in mandibular or oral cavity dosages, with the exception of V60 which was higher in the reconstructed mandible cohort. Thus, despite higher radiation dosages in the neo-mandible, these were no more likely to develop ORN.

Neither smoking nor alcohol use was significantly associated with ORN, differing from prior studies. Caparrotti et al. reported that in 1196 cases of oropharyngeal SCC treated with IMRT, smoking was significantly associated with ORN.[26] Owosho et al. showed that in oral cavity carcinoma and oropharyngeal carcinoma patients, alcohol use was predictive.[20] The negative findings may be attributable to proper patient counseling on perioperative smoking and alcohol use cessation. Furthermore, tumor characteristics such as grade, PNI, and LVSI were not associated with ORN, similar to the prior study findings.[18] Positive margins were higher in the ORN group (21% vs. 14% for the entire cohort), but this did not achieve statistical significance.

Among the 14 patients with Grade 2 or Grade 3 ORN, a high rate (83%) of resolution was achieved through surgical intervention. Fibula free flap reconstruction is the workhorse for treatment of ORN, although postoperative complications occur in up to 40% in the literature.[33–35] None of the four patients with fibula flaps for ORN treatment had previously reconstructed mandibles. However, patients who undergo a second fibular flap reconstruction for treatment of ORN are shown to achieve similar functional outcomes and safety profile.[36] Soft-tissue flaps including anterolateral thigh and radial forearm free flaps, along with adequate debridement led to resolution in our series. Newer surgical techniques such as anterolateral thigh fascia lata rescue flaps have been demonstrated to be promising alternatives to mandibular resection.[37]

### 4.1 | Limitations

Although the strengths in this study lie in the large sample size, dosimetric parameter data, and long-term follow-up to allow for accurate determination of ORN incidence, several limitations exist. Preoperative dental care was not consistent among patients and could not be adjusted for. Dose–volume histograms were available for 34 patients, showing higher dose to the neo-mandible yet no increased rate of ORN. However, future studies of larger sample size are needed to validate this. Furthermore, as no consensus on defining ORN has been universally established, we chose to define ORN using the Schwartz and Kagan classification given its widespread use and objective nomenclature.[22] Not all patients had radiological imaging available at time of ORN diagnosis, and, therefore, clinically asymptomatic cases or cases with intact mucosa but with radiologic signs of bone devitalization or demineralization may have been missed. Grade 1 ORN cases were excluded from the analysis due to the subjective nature of these observations and inconsistent documentation of soft-tissue ulceration in the electronic medical records. However, the outcome of Grade 2 and Grade 3 ORN constitutes only moderate to severe cases, of which 12 of 14 of these required surgical reinterventions. Thus, the present study findings are more relevant to clinically actionable and more severe, symptomatic cases of ORN.

## 5 | CONCLUSION

Fibula free flap mandibular reconstruction was not associated with increased risk of developing mandibular ORN compared to native mandibles in patients with oral cavity cancer treated with surgical resection followed by IMRT. Post-RT tooth extraction was identified as a significant predictor of ORN. Larger prospective studies are needed to definitively identify risk factors for the development of ORN in patients with mandibular reconstruction.

### AUTHOR CONTRIBUTIONS

**Shannon S. Wu**: Data acquisition, interpretation, analysis, drafting, revisions. **Hanna Hong**: Data acquisition, revisions. **Michael Fritz**: Interpretation, revisions. **Jamie Ku**: Interpretation, revisions. **Brandon Prendes**: Interpretation, revisions. **Natalie Silver**: Interpretation, revisions. **Dane J. Genther**: Interpretation, revisions. **Peter Ciolek**: Interpretation, revisions. **Patrick Byrne**: Interpretation, revisions. **Philip Brauer**: Interpretation, revisions. **Chandana A. Reddy**: Interpretation, analysis. **Neil Woody**: Interpretation, revisions. **Shauna Campbell**: Interpretation,

revisions. **Shlomo A. Koyfman**: Conception, design, interpretation, revisions. **Eric Lamarre**: Conception, design, interpretation, revisions.

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## CONFLICT OF INTEREST STATEMENT

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## DATA AVAILABILITY STATEMENT

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

## ORCID

*Shannon S. Wu* https://orcid.org/0000-0002-0809-9143
*Philip Brauer* https://orcid.org/0000-0002-6304-6909
*Neil Woody* https://orcid.org/0000-0003-4507-6167
*Eric D. Lamarre* https://orcid.org/0000-0001-9384-8470

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