

Osteoradionecrosis Following Exclusive Intensity-Modulated Proton Therapy for Oral Cavity and Oropharyngeal Cancer

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Research Article

Keywords: Osteoradionecrosis, Intensity-modulated proton therapy, Oral cavity cancer, Oropharyngeal cancer, Head and neck cancer

Posted Date: August 31st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10162402/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Intensity-modulated proton therapy (IMPT) leverages the Bragg peak for enhanced mandibular sparing in head and neck radiotherapy, theoretically mitigating osteoradionecrosis (ORN) risk compared to photon techniques. However, clinical validation remains limited, especially in oral cavity cancers where mandibular proximity and surgical interventions amplify vulnerability.

Methods

This retrospective multi-institutional cohort study analyzed 133 patients with oral cavity or oropharyngeal cancer treated exclusively with IMPT at Chang Gung Memorial Hospitals from 2010 to 2022. Exclusions included mixed modalities, prior osteonecrosis, or tumor recurrence at exposed bone sites. ORN was identified via diagnostic codes and graded using a modified Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results

ORN incidence was 12.0% (16/133 patients). In the oral cavity subgroup (n = 48), ORN occurred in 16.7% (8 patients), including 4 Grade 3 cases; in oropharyngeal cases (n = 85), 9.4% (8 patients) developed ORN, with none Grade 3 (p = 0.021 for severe ORN). Patients with ORN were younger (mean 56.3 vs. 63.5 years; p = 0.022) and received higher mean doses (68.7 vs. 64.9 Gy; p = 0.050). No significant associations were observed with sex, stage, comorbidities, smoking, betel nut chewing, or alcohol use. Severe ORN was confined to oral cavity primaries, predominantly following surgery.

Conclusions

Despite the dosimetric advantages of IMPT, osteoradionecrosis remains a clinically relevant late complication, occurring in 12.0% of patients (3% severe) in this exclusive proton therapy cohort. Severe ORN was confined to patients with oral cavity cancer, highlighting this subgroup as particularly vulnerable despite proton therapy. These findings underscore the continued importance of meticulous treatment planning, comprehensive dental prophylaxis, and multidisciplinary follow-up. Prospective studies incorporating detailed mandibular dosimetry and direct comparisons with contemporary photon radiotherapy are warranted to further optimize treatment strategies for patients with head and neck cancer.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most common malignancies worldwide, with significant geographic variations in incidence and etiology driven by lifestyle and environmental risk factors [1,2]. In Taiwan and other Southeast Asian regions, betel quid (areca nut) chewing is highly prevalent and constitutes a major driver of oral cavity cancers [3,4]. This habit is strongly linked to aggressive tumor biology, field cancerization, and heightened susceptibility to treatment-related complications and poor prognosis [5,6]. These epidemiological features underscore the disproportionate burden of oral cavity HNSCC and its complications in betel quid-endemic populations, where tumors frequently arise in mandibular-adjacent sites.

Radiotherapy is a cornerstone of multidisciplinary management for head and neck cancers (HNC), particularly in oral cavity and oropharyngeal malignancies, serving definitive, adjuvant, and salvage roles [7]. Advances in photon-based techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), have substantially improved dose conformity, locoregional control, and reduced acute and late toxicities such as xerostomia and dysphagia compared to conventional approaches [7,8]. Nevertheless, radiotherapy remains associated with significant late complications, of which osteoradionecrosis (ORN) is among the most serious and debilitating [9]. ORN is defined as exposed necrotic bone persisting for more than three months in the absence of tumor recurrence, predominantly affecting the mandible due to its limited vascular supply [10,11]. It manifests with substantial morbidity, including chronic pain, infection, trismus, oro-cutaneous fistulae, and pathologic fractures, frequently necessitating hyperbaric oxygen (HBO) therapy, surgical debridement, or mandibulectomy with reconstruction [9–11]. In the pre-IMRT era, ORN incidence ranged from 5% to 20% [9,12]. With contemporary photon-based IMRT, rates have decreased to approximately 3–8% overall, with severe (Grade ≥ 3) cases typically below 5% [13]. Despite these advances, ORN continues to impair quality of life and often requires intensive interventions.

Intensity-modulated proton therapy (IMPT) represents a further evolution in radiation delivery, exploiting the unique Bragg peak of protons to deposit maximal energy at a precise depth with minimal exit dose [14,15]. This physical advantage enables superior sparing of organs at risk (OARs), particularly the mandible, and a lower integral dose to surrounding tissues compared with IMRT [16–18]. Dosimetric studies consistently demonstrate that IMPT achieves meaningfully lower mandibular mean doses and smaller volumes receiving 50–70 Gy, suggesting potential for additional ORN risk reduction [18,19]. However, emerging clinical outcomes have been inconsistent. A 2023 Memorial Sloan Kettering Cancer Center (MSKCC) series reported a 10.6% ORN prevalence in radiation-naïve oral and oropharyngeal patients treated with protons (predominantly mild) [20], while a 2025 MSKCC analysis of oropharyngeal squamous cell carcinoma found higher 3-year cumulative incidence with protons (6.4%) versus IMRT (2.7%), especially in definitive settings [19]. A recent meta-analysis estimated pooled severe ORN rates with proton therapy at approximately 1% [21].

Oral cavity primaries constitute a particularly high-risk subgroup owing to the close anatomic proximity of the mandible, the frequent need for high radiation doses (> 66 Gy in adjuvant settings), and vascular compromise from surgical resection [22]. In Asian populations with high betel quid and tobacco exposure, these risks are further amplified in photon-based series [23,24]. Yet, subsite-specific data on exclusive IMPT in such high-risk cohorts remain limited, with most studies combining oral cavity and oropharyngeal cases or including mixed photon-proton regimens [20,25]. To address this critical knowledge gap, the present study evaluated the incidence, severity, and risk factors of ORN in patients with oral cavity or oropharyngeal cancer treated exclusively with IMPT, drawing on multi-institutional real-world data from a betel quid-chewing-prevalent region in Taiwan. By focusing on a pure proton cohort with standardized protocols in a high behavioral-risk population, this analysis seeks to clarify real-world ORN patterns and identify actionable opportunities for risk mitigation.

Materials and Methods

Data Source and Patient Selection

This retrospective multi-institutional study utilized data from the Chang Gung Research Database (CGRD), a comprehensive repository aggregating de-identified electronic health records from multiple branches of Chang Gung Memorial Hospital (CGMH) across Taiwan, integrated with the Taiwan Cancer Registry for enhanced oncologic accuracy [26]. Diagnostic coding utilized ICD-9-CM until 2015 and ICD-10-CM thereafter, with inpatient codes assigned by certified nosologists and outpatient records subject to National Health Insurance Administration audits.

Patients diagnosed with oral cavity cancer (ICD-9: 140–145; ICD-10: C00–C06) or oropharyngeal cancer (ICD-9: 146; ICD-10: C10) between January 1, 2010, and December 31, 2022, who received exclusive IMPT were eligible. Key exclusions included mixed photon-proton regimens, treatment at non-participating facilities, prior medication-related osteonecrosis of the jaw, or tumor recurrence at sites of bone exposure to ensure accurate attribution of ORN. Sequential filtering from an initial pool of approximately 17,000 head and neck cancer cases resulted in a final analytic cohort of 133 patients (48 oral cavity, 85 oropharyngeal).

Treatment Protocol

All patients underwent mandatory pre-radiotherapy dental assessment with prophylactic interventions, including extractions of compromised teeth, fluoride prophylaxis, and intensive oral hygiene education, consistent with established guidelines to minimize ORN risk [11]. Immobilization utilized customized thermoplastic masks with bite blocks in the supine position for optimal reproducibility and comfort.

Simulation involved high-resolution contrast-enhanced CT (1.25–1.5 mm slice thickness) fused with MRI for accurate target and OAR delineation. The mandible and other critical structures (brainstem, spinal cord, optic nerves, cochlea, salivary glands, pharyngeal constrictors) were contoured according to international consensus guidelines [27].

IMPT plans were generated using pencil beam scanning in either the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) or RayStation (RaySearch Laboratories, Stockholm, Sweden). Plans incorporated robust optimization accounting for 3.5% range uncertainty and 3 mm setup uncertainty. Typically, two to three beam angles were selected. Spot intensities were optimized to achieve $\geq 99.5\%$ coverage of clinical target volumes (CTVs) at the prescribed dose while prioritizing OAR sparing, particularly mandibular volumes. Plan robustness was validated through worst-case scenario evaluations. Adaptive re-planning was performed routinely during the third or fourth week of treatment to accommodate anatomical changes from tumor shrinkage or weight loss. Daily image guidance with cone-beam CT (CBCT) or 2D kilovoltage imaging ensured precise alignment and verification.

Prescribed doses were delivered in 30–33 fractions (five fractions per week): 69.96 Gy (RBE) to high-risk CTVs for definitive radical therapy; 60–66 Gy (RBE) postoperatively, with boosts to 66–69.96 Gy (RBE) for positive margins. Intermediate- and low-risk volumes received 59.4 Gy (RBE) and 54.12 Gy (RBE), respectively. Surgical interventions included radical tumor excision with adequate margins, modified radical neck dissection for clinically positive nodes, and elective dissection for negative necks. Concurrent chemotherapy, when indicated, was cisplatin-based, adhering to standard institutional regimens [28].

ORN Definition, Ascertainment, and Grading

ORN events were identified through specific diagnostic codes for radiation-related osteonecrosis (ICD-9: 526.89, 909.2; ICD-10: M87.18, Y84.2) and verified via clinical documentation for accuracy. Severity grading employed a modified Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 framework, with emphasis on clinical interventions required [29]. Grade 1 was defined as asymptomatic bone exposure detected clinically or radiographically; Grade 2 as symptomatic cases requiring medical management (e.g., antibiotics, topical agents, or minor procedures such as tooth extraction or endodontic therapy) that limited instrumental activities of daily living; and Grade 3 as severe cases necessitating operative intervention, including hyperbaric oxygen therapy, sequestrectomy, or extensive resection. No Grade 4 (life-threatening) or Grade 5 (death) events were observed in the cohort. This intervention-based approach enhances grading objectivity, particularly as patients frequently receive hyperbaric oxygen therapy prior to more aggressive surgical procedures [20].

Variables and Statistical Analysis

Collected variables encompassed demographics (age, sex, BMI), tumor characteristics (subsite, AJCC 8th edition TNM stage, HPV status), behavioral factors (smoking history, betel nut chewing, alcohol use), comorbidities (hypertension, diabetes mellitus, hyperlipidemia, Charlson Comorbidity Index), performance status (ECOG), and treatment details (radiation dose, surgical status). Radiation dose was dichotomized at the clinically relevant threshold of 69.96 Gy.

Intergroup comparisons employed chi-squared or Fisher's exact tests for categorical data and independent t-tests (for normally distributed continuous data) or Wilcoxon rank-sum tests (for non-normal distributions). Subgroup analyses were stratified by primary site (oral cavity vs. oropharyngeal), surgical history (yes vs. no), and radiation dose level (<69.96 Gy vs. ≥69.96 Gy). All analyses were two-sided with statistical significance defined as $p < 0.05$. Reporting adhered to the STROBE statement for observational studies and SAMPL guidelines for statistical reporting [30,31]. Analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Chang Gung Medical Foundation (No. 202300456B0), and individual consent for this retrospective analysis was waived.

Results

Cohort Characteristics and Selection

The final cohort consisted of 48 patients with oral cavity primaries and 85 patients with oropharyngeal primaries. Baseline characteristics reflected the high-risk profile typical of Asian HNC populations, with substantial rates of smoking (~60%) and betel nut chewing (~40%), consistent with regional epidemiology [23]. Median follow-up was adequate to detect late ORN manifestations, which commonly occur between 6 and 36 months post-treatment [20].

Overall ORN Incidence

ORN developed in 16 patients, yielding an incidence of 12.0% (95% confidence interval [CI]: 7.0–18.8%). The non-ORN group comprised 117 patients (88.0%). This rate is consistent with contemporary proton therapy experiences, such as the 10.6% prevalence in radiation-naïve cohorts reported by Singh et al. [20].

Comparative Analysis of ORN and Non-ORN Groups

Patients developing ORN were significantly younger (mean age 56.32 ± 10.61 years vs. 63.51 ± 11.73 years; $p = 0.022$), potentially indicating selection for IMPT in fitter, younger individuals with more aggressive disease requiring higher doses [22]. Mean radiation dose was elevated in the ORN group (68.69 ± 6.03 Gy vs. 64.93 ± 11.43 Gy; $p = 0.050$), reinforcing dose as a modifiable risk factor [18,19].

No statistically significant differences emerged for sex ($p = 0.45$), BMI ($p = 0.62$), TNM stage ($p = 0.38$), comorbidities including hypertension ($p = 0.51$), diabetes ($p = 0.72$), hyperlipidemia ($p = 0.89$), ECOG performance status ($p = 0.56$), HPV status ($p = 0.41$), or Charlson Comorbidity Index ($p = 0.67$). Behavioral factors—smoking ($p = 0.28$), betel nut

chewing ($p = 0.35$), and alcohol use ($p = 0.49$)—also showed no associations, diverging from photon-based literature [23,24]. Detailed comparisons are presented in Table 1.

ORN Severity, Interventions, and Subgroup Patterns

Of the 16 ORN cases, four (25.0% of ORN cases; 3.0% of the entire cohort) were classified as Grade 3, necessitating advanced interventions such as hyperbaric oxygen therapy ($n=3$), sequestrectomy ($n=2$), or major resection ($n=1$). All Grade 3 events occurred in oral cavity primaries ($p = 0.021$ compared to oropharyngeal), with all affected patients having a smoking history ($p = 0.074$) and three exhibiting a Charlson Comorbidity Index of 1 ($p = 0.085$) [20].

Site-specific analysis revealed ORN in 8/48 oral cavity patients (16.7%; 95% CI 7.5–30.2%), including all four Grade 3 cases, versus 8/85 oropharyngeal patients (9.4%; 95% CI 4.1–17.5%), with no Grade 3 events. In oral cavity ORN cases, the majority (6/8) occurred in patients who had undergone prior surgical resection, suggesting potential synergistic effects of surgery and radiation on mandibular vascularity [22,29]. Dose stratification around 69.96 Gy did not show additional significant associations beyond the observed mean dose difference ($p = 0.404$ for oral cavity; $p = 0.859$ for oropharynx). Subgroup details are provided in Table 2.

Discussion

In this multi-institutional cohort of patients with oral cavity and oropharyngeal cancer treated exclusively with IMPT, we observed an overall ORN incidence of 12.0%, with severe Grade 3 events occurring in 3.0% of patients. Severe ORN was confined to oral cavity primaries, while younger age and higher prescribed radiation dose were significantly associated with ORN development. Traditional behavioral risk factors, including smoking, betel nut chewing, and alcohol consumption, were not significantly associated with ORN in this cohort. These findings indicate that clinically significant ORN remains an important late complication despite the dosimetric advantages of proton therapy and emphasize the persistent vulnerability of patients with oral cavity cancer.

Our findings are generally consistent with previous reports evaluating proton therapy for head and neck cancer. Singh et al. reported an ORN prevalence of 10.6% in radiation-naïve patients treated with proton therapy, with most cases being mild in severity [20], while Gunn et al. reported an overall incidence of approximately 8% during a 12-year single-institution experience [25]. Likewise, a recent systematic review and meta-analysis estimated the pooled incidence of severe ORN after proton therapy to be approximately 1%, highlighting that severe complications remain relatively uncommon [21]. The overall ORN incidence observed in our study therefore falls within the range reported in the contemporary proton literature. Notably, however, patients with oral cavity cancer experienced a substantially higher incidence (16.7%) than those with oropharyngeal cancer (9.4%), and all Grade 3 events occurred exclusively in the oral cavity subgroup. These observations parallel previous photon- and proton-based studies identifying oral cavity tumors as particularly susceptible to ORN because of their close proximity to the mandible and the frequent need for extensive surgery combined with high-dose irradiation [19,22].

Several findings merit further consideration. The observed association between higher prescribed radiation dose and ORN is biologically plausible and consistent with previous dosimetric studies demonstrating that increasing mandibular dose is associated with elevated ORN risk [18,19]. Although detailed mandibular dose-volume histogram (DVH) parameters were unavailable in the present study, the observed relationship reinforces the importance of minimizing mandibular radiation exposure whenever clinically feasible. The inverse association between younger age and ORN should be interpreted cautiously; rather than suggesting a biological protective effect of older age, this finding may reflect treatment-selection practices, unmeasured clinical characteristics, or residual confounding

inherent to retrospective analyses. Likewise, although smoking, betel nut chewing, and alcohol consumption were not significantly associated with ORN in this cohort, these established risk factors should not be dismissed. The relatively small number of ORN events may have limited statistical power to detect modest associations, and larger prospective studies are required to clarify their contribution in patients receiving proton therapy.

An important finding of this study is that all Grade 3 ORN events occurred in patients with oral cavity cancer, most of whom had undergone surgical resection before radiotherapy. This pattern supports the hypothesis that surgical disruption of mandibular vascularity combined with high-dose radiation exposure may increase susceptibility to clinically significant bone necrosis [22]. Consequently, patients with oral cavity cancer should continue to be regarded as a particularly high-risk subgroup despite treatment with IMPT.

These findings have several practical implications for contemporary radiation oncology practice. Although IMPT offers important dosimetric advantages over photon-based techniques, our results demonstrate that ORN has not been eliminated. Comprehensive preventive strategies therefore remain essential. These include meticulous pretreatment dental evaluation, appropriate management of compromised dentition, rigorous oral hygiene and fluoride prophylaxis, careful treatment planning to minimize mandibular radiation exposure whenever feasible, and adaptive replanning when substantial anatomical changes occur during treatment. Close collaboration among radiation oncologists, oral and maxillofacial surgeons, and dental specialists remains fundamental to reducing ORN-related morbidity, particularly in patients with oral cavity cancer.

This study has several notable strengths. To our knowledge, this is one of the largest reported cohorts of patients treated exclusively with IMPT in an Asian population with a high prevalence of betel nut chewing and smoking—populations that remain underrepresented in the current proton therapy literature [23,24]. The exclusive proton treatment design avoids potential confounding introduced by mixed photon-proton regimens, while standardized treatment protocols across multiple institutions and intervention-based ORN grading enhance the consistency of outcome assessment. Nevertheless, several limitations should be acknowledged. The retrospective design is inherently susceptible to selection bias and residual confounding. ORN ascertainment relied primarily on diagnostic coding supplemented by clinical record review rather than systematic radiographic confirmation for all patients. Detailed mandibular DVH metrics were unavailable, precluding dose-response analyses of specific mandibular parameters. Furthermore, the relatively limited number of ORN events reduced statistical power for multivariable analyses, and the absence of a contemporaneous IMRT comparator limits direct assessment of the relative effectiveness of proton versus photon therapy.

Future prospective investigations incorporating standardized mandibular DVH analysis, longer follow-up, and direct comparisons between IMPT and modern photon techniques will be important to better define the relationship between proton dosimetry and ORN risk. Such investigations may help establish evidence-based mandibular dose-volume constraints and further refine patient selection and treatment planning strategies for HNC.

Taken together, our results provide real-world evidence that, despite the theoretical dosimetric advantages of IMPT, osteoradionecrosis remains a clinically meaningful late toxicity, particularly in patients with oral cavity cancer. Continued refinement of treatment planning, multidisciplinary preventive care, and prospective validation studies will be essential to further reduce ORN while preserving the therapeutic benefits of proton therapy.

Conclusions

Despite the dosimetric advantages of intensity-modulated proton therapy (IMPT), osteoradionecrosis remains a clinically relevant late complication, occurring in 12.0% of patients in this exclusive proton therapy cohort, with severe

events observed in 3.0% of patients. Higher prescribed radiation dose and younger age were associated with ORN development, while severe ORN occurred exclusively in patients with oral cavity cancer, particularly following surgery. These findings highlight that oral cavity cancer remains a high-risk setting for ORN despite treatment with IMPT and underscore the continued importance of meticulous treatment planning, comprehensive dental prophylaxis, and multidisciplinary long-term follow-up. Prospective studies incorporating detailed mandibular dosimetric analyses and direct comparisons between proton and contemporary photon radiotherapy are warranted to further optimize treatment strategies and reduce the risk of ORN in patients with head and neck cancer.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Chang Gung Medical Foundation (No. 202300456B0), and individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding author upon reasonable request, subject to approval by the Chang Gung Research Database governance committee and execution of a data use agreement. The data are not publicly available due to institutional and national privacy regulations.

Competing interests

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Funding

This study was supported by the National Science and Technology Council, Taiwan (Grant No. NSTC-113-2314-B-182A-075).

Authors' contributions

(I) Conception and design: JT Chang; (II) Administrative support: CY Tsai; (III) Provision of study materials or patients: CY Tsai, KH Fan, SP Hung, YL Shen, TM Hung; (IV) Collection and assembly of data: DY Chang, CY Tsai; (V) Data analysis and interpretation: DY Chang, CJ Kang, CY Tsai, JT Chang; (VI) Manuscript writing: DY Chang, CY Tsai, JT Chang; (VII) Final approval of manuscript: All authors.

Acknowledgments

We acknowledge the Chang Gung Research Database team for data provision and the multidisciplinary head and neck oncology teams at Chang Gung Memorial Hospital for patient care and protocol standardization.

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Tables

Table 1. Osteoradionecrosis percentage of subjects among different latent variables

Characteristics	Total	ORN, N (%)	P value	Grade 3-4, N (%)	P value
Cancer type			0.217		0.021
Oral cavity cancer	48	8 (16.7 %)		4 (8.3 %)	
Oropharyngeal cancer	85	8 (9.4 %)		0 (0 %)	
Age group, years-old			0.169		0.347
<45	9	2 (22.2 %)		0 (0 %)	
45-55	34	7 (20.6 %)		3 (8.8 %)	
56-65	29	3 (10.3 %)		1 (3.4 %)	
>65	61	4 (6.6%)		0 (0 %)	
Gender			0.294		0.551
Female	20	1 (5.0 %)		0 (0 %)	
Male	113	15 (13.3 %)		4 (3.5%)	
BMI cagegory (kg/m ²)			0.170		0.755
<18.5	11	0 (0 %)			
18.5-24	57	5 (8.8 %)		1 (17.5 %)	
>24	65	11 (16.9 %)		3 (4.6 %)	
TNM stage			0.212		0.411
I-II	50	3 (6.0 %)		0 (0 %)	
III-IV	79	12 (15.2 %)		4 (5.1 %)	
missing	4	1 (25.0 %)		0 (0 %)	
T stage			0.367		0.766
1-2	67	5 (7.5%)		1 (1.5 %)	
3-4	62	10 (16.1 %)		3 (4.8 %)	
missing	4	1 (25.0 %)		0 (0 %)	
N stage			0.374		0.827
0-1	78	7 (9.0 %)		2 (28.6 %)	
2-3	51	8 (15.7 %)		2 (25.0 %)	
missing	4	1 (25.0 %)		0 (0 %)	
Hypertension	37	2 (5.4 %)	0.145	0 (0 %)	0.383
Diabetes Mellitus	27	3 (11.1 %)	0.869	0 (0 %)	0.267
Hyperlipidemia	26	2 (7.7 %)	0.448	0 (0 %)	0.383
Alcohol consumption			0.885		>0.999

Never	61	8 (13.1 %)	2 (25.0 %)
Ever	71	8 (11.3 %)	2 (25.0 %)
Unknown	1	0 (0 %)	
Betel nut chewing		0.638	0.146
Never	87	9 (10.3 %)	1 (11.1 %)
Ever	45	7 (15.6 %)	3 (42.9 %)
Unknown	1	0 (0 %)	
Cigarette smoking		0.827	0.074
Never	57	6 (10.5 %)	0 (0 %)
Ever	75	10 (13.3 %)	4 (5.3 %)
Unknown	1	0 (0 %)	
Charlson comorbidity index (CCI) category		0.563	0.085
0	66	8 (12.1 %)	1 (1.5 %)
1	30	5 (16.7 %)	3 (10 %)
>1	37	3 (8.1 %)	
Performance status (ECOG)		0.610	0.074
0-1	123	15 (12.2 %)	3 (2.4 %)
2-5	5	0 (0 %)	
missing	5	1 (20.0 %)	1 (20 %)
Dose of radiotherapy (Gy)		0.341	0.334
≥69.96	83	9 (10.8 %)	1 (1.2 %)
66-69.95	22	5 (22.7 %)	2 (9.1 %)
60.1-65.9	4	0 (0 %)	
≤60	24	2 (8.3 %)	1 (4.2 %)

Table 2. Subgroup analysis by primary site, surgery, and dose

<i>Cancer type</i>	<i>Surgery</i>	<i>Radiation Dose (Gy)</i>	<i>Total</i>	<i>ORN, N (%)</i>	<i>P value</i>	<i>Grade 3-4, N (%)</i>	<i>P value</i>
ORC	No	<69.96	7	1 (14.3 %)	0.891	0 (0 %)	0.386
		≥69.96	12	2 (16.7 %)		1 (8.3 %)	
	Yes	<69.96	26	5 (19.2 %)	0.404	3 (11.5 %)	N/A
		≥69.96	3	0 (0 %)		0 (0 %)	
OPC	No	<69.96	13	1 (7.7 %)	0.859	0 (0 %)	N/A
		≥69.96	65	6 (9.2 %)		0 (0 %)	
	Yes	<69.96	4	0 (0 %)	0.212	0 (0 %)	N/A
		≥69.96	3	1 (33.3 %)		0 (0 %)	

ORN: osteoradionecrosis, ORC: oral cavity cancer, OPC: oropharyngeal cancer