



# Risk factors and treatment outcomes in osteoradionecrosis in head and neck cancer patients: a retrospective analysis

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**Abstract** (J Korean Assoc Oral Maxillofac Surg 2025;51:284-293)

**Objectives:** Osteoradionecrosis of the jaw (ORNJ) is a serious late complication in patients with head and neck cancer who have undergone radiation therapy. This study aimed to identify clinical and treatment-related risk factors associated with the development of ORNJ and to evaluate the therapeutic outcomes across various treatment modalities.

**Materials and Methods:** A retrospective analysis was performed on 80 patients diagnosed with ORNJ following radiotherapy (RT) for head and neck malignancies. Patient demographics, oncologic characteristics, and treatment histories were reviewed. Clinical outcomes of conservative therapy, sequestrectomy, and partial mandibulectomy were assessed. Ordinal logistic regression analysis was conducted to determine associations between treatment modality and disease course (improved, stable, or progressed).

**Results:** Most ORNJ cases developed spontaneously within 48 months post-RT. Surgical intervention was performed in 73.8% of patients, with sequestrectomy being the most frequently applied procedure. Overall outcomes were classified as improved in 26.3%, stable in 37.5%, and progressed in 36.3% of cases. Ordinal logistic regression revealed that conservative treatment (odds ratio [OR]=4.64,  $P=0.041$ ) and sequestrectomy (OR=4.92,  $P=0.022$ ) were significantly associated with poorer outcomes compared to partial mandibulectomy. This association remained significant in Stage III ORNJ, whereas no statistically significant differences were observed in Stages I and II, although trends varied depending on treatment type.

**Conclusion:** This study underscores the prognostic relevance of treatment modality in ORNJ management. Partial mandibulectomy appears to confer more favorable outcomes in advanced-stage ORNJ, although its invasive nature necessitates individualized treatment planning. Future prospective studies incorporating dosimetric parameters and long-term follow-up are warranted to establish evidence-based guidelines for ORNJ treatment.

**Key words:** Osteoradionecrosis, Head and neck neoplasm, Radiotherapy, Treatment outcome, Risk factors

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## I. Introduction

Osteoradionecrosis of the jaw (ORNJ) is a serious late complication of radiation therapy for malignant head and neck cancers. ORNJ is commonly defined as a region of exposed, irradiated bone that remains unhealed for a duration of 3-6 months in the absence of any local neoplastic recurrence<sup>1</sup>. Nonetheless, there have been reports of instances with intact

mucosa and radiological evidence of necrosis<sup>2</sup>.

Patients suffering from ORNJ commonly report persistent orofacial pain that is difficult to manage, along with chronic exposure of bone. Associated clinical manifestations include dysesthesia, halitosis, dysgeusia, and food impaction in the vicinity of the exposed sequestrum<sup>3</sup>. These symptoms can progress to pathological fractures, persistent nonunion accompanied by chronic infection, and the development of orotracheal or orocutaneous fistulas. These complications may adversely impact the patient's ability to swallow, breathe, and speak<sup>4</sup>.

The prevalence rate of ORNJ varies widely according to the literature, with the most frequently reported rates ranging from 5% to 15%<sup>5</sup>. Risk factors include the location of the original tumor, the radiation therapy technique employed, the extent and dosage of radiation exposure, dental condition, and associated injuries such as dental extractions or surgeries

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performed before or after radiation therapy<sup>6</sup>.

ORNJ treatment protocols are not clearly established, and there is a scarcity of research analyzing the outcomes of ORNJ based on various treatment approaches. Consequently, there are no definitive guidelines for selecting appropriate treatments. By identifying risk factors and evaluating treatment-specific prognoses, this study aimed to provide insights to guide clinicians in selecting the most appropriate therapeutic approaches for ORNJ, thereby contributing to the establishment of evidence-based treatment guidelines.

## II. Materials and Methods

### 1. Patients

A retrospective evaluation of the medical records of 80 individuals was conducted. These individuals were treated for head and neck cancer by either radiation therapy alone or with surgery and chemotherapy. Medical records were reviewed for the presence of osteoradionecrosis in the mandibular area. The clinical database of Seoul National University Dental Hospital was searched for cases of ORNJ from January 2019 to May 2024 seen in the Department of Oral and Maxillofacial to identify a group of patients appropriate for inclusion in this study. This research was performed under approval by the Institutional Review Board (IRB) of Seoul National University Dental Hospital (IRB No. ERI24033). The requirement for written informed consent was waived due to the retrospective nature of the study.

Inclusion criteria were patients who received radiation therapy for head and neck cancer, with or without surgical treatment, and had a confirmed clinical or radiographic diagnosis of ORNJ. Only cases involving the mandible were included in this study. ORNJ was defined as cases with spontaneous formation of a mucosal or skin fistula leading to bone exposure that did not heal for more than 3 months, or radiographic evidence of sequestrum or progressive bone destruction persisting for over 3 months<sup>7-9</sup>. Exclusion criteria were patients with bone necrosis caused by medication-related osteonecrosis of the jaw or patients with a recurrence of malignant lesions. Patients with less than 6 months of follow-up or those lost to follow-up before outcome evaluation were excluded from the analysis.

### 2. Data collection

#### 1) Patient demographics and medical history

Patient demographics, including age and sex, were recorded to assess overall population characteristics. Additionally, the presence of comorbidities such as hypertension and diabetes mellitus was documented to evaluate their potential impact on osteoradionecrosis development and outcomes.

#### 2) Primary tumor characteristics

The histopathological diagnosis of the primary tumor was noted, with cases categorized into types such as squamous cell carcinoma, mucoepidermoid carcinoma, and adenoid cystic carcinoma. Tumor staging was based on the American Joint Committee on Cancer (AJCC) 8th edition Cancer Staging System, and the anatomical location of the tumor, such as the maxilla, mandible, tongue, floor of the mouth, buccal mucosa, or nasopharynx, was recorded. Surgical interventions were categorized based on the extent of resection, distinguishing between soft tissue-only resections (e.g., partial glossectomy) and bone-involving resections (e.g., partial mandibulectomy or marginal mandibulectomy).

#### 3) Radiation therapy

The type of radiation therapy modality administered was recorded, including three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and proton therapy. Additionally, the total radiation dose, measured in grays (Gy), and the number of radiation sessions completed were documented to analyze their correlation with ORNJ development.

#### 4) ORNJ characteristics

This study focused on ORNJ cases affecting the mandible. The time interval between the completion of radiation therapy and the onset of ORNJ was calculated in months. The primary causes of ORNJ were also documented, including spontaneous occurrences, dental extractions, fractures, or other related factors.

ORNJ staging was classified according to the Notani classification, which categorizes ORNJ based on the anatomical extent of bone involvement as seen on clinical and radiographic examination. In this system, Stage I is confined to the alveolar bone, Stage II extends to the mandible above the inferior alveolar canal, and Stage III involves the mandible below the canal, or includes pathological fracture, skin fistula, or orocutaneous communication<sup>10</sup>. Patients were classified

according to their initial Notani stage at ORNJ diagnosis.

### 5) ORNJ treatment and outcomes

Treatment methods for ORNJ were categorized into conservative management, such as non-surgical wound care and antibiotic therapy, and surgical interventions, including sequestrectomy and partial mandibulectomy. Treatment modality for osteoradionecrosis was determined based on a multi-disciplinary assessment of clinical and radiographic findings. Conservative management included antibiotics (administered during infectious episodes), chlorhexidine mouth rinses, analgesics, and pentoxifylline-tocopherol therapy when indicated, and was primarily chosen for patients with limited bone exposure, absence of pathological fracture, and minimal symptoms. Sequestrectomy was considered for patients with localized necrotic bone and signs of infection or progression despite conservative care. Partial mandibulectomy, which specifically refers to segmental resection involving complete discontinuity of the mandible including the inferior border, was reserved for advanced cases with extensive necrosis, pathologic fractures, or failure of prior conservative or minor surgical interventions. Treatment decisions also accounted for patient comorbidities, performance status, and treatment goals.

Treatment outcomes were categorized into three groups based on clinical and radiographic findings assessed at six months from treatment initiation. The improved group was defined as a noticeable reduction in symptoms such as pain and purulent discharge, partial or complete re-epithelialization, or radiographic evidence of stabilization, without requiring further intervention for at least six months. The stable group referred to cases with persistent but non-worsening symptoms—such as mild discomfort or localized exposed bone—that showed no progression or need for additional surgical intervention over a six-month period. The progressed group indicated clinical or radiographic deterioration despite treatment, including worsening pain, expansion of necrotic bone, recurrent infection, or the development of complications such as fractures or abscesses, often necessitating escalation of care.

### 3. Statistical analysis

Data analyses were conducted using IBM SPSS Statistics (ver. 29.0; IBM). Additionally, ordinal logistic regression analysis was used to examine the impact of ORNJ treatment, sex, ages, and ORNJ stages on clinical outcomes. The Krus-

kal–Wallis test was employed to compare the onset time of ORNJ across different treatment modalities, as the data did not meet normality assumptions verified through the Shapiro–Wilk test. The Kaplan–Meier method was used to estimate the cumulative incidence of ORNJ over time. A *P*-value <0.05 was considered to indicate statistical significance.

## III. Results

### 1. Patient demographics

In this study, a total of 80 patients with ORNJ were analyzed. The demographic distribution included 43 males (53.8%) and 37 females (46.2%). Average age at the onset of ORNJ was 64.36 years, with the majority of cases occurring in the 60-69 age group (31.3%) and the 70-79 age group (31.3%). Comorbid conditions included hypertension in 33 patients (41.2%) and diabetes mellitus in 19 patients (23.7%). (Table 1)

### 2. Oncological data

The most prevalent type of cancer among patients was squamous cell carcinoma, accounting for 54 cases (67.5%). Predominant primary cancer sites were the tongue (36.3%) and mandible (26.3%). Tumor staging revealed that 31.3% of the patients had stage T4 tumors, and 26.3% tumors were classified as N0 in the nodal staging. The majority of patients had stage 4A (36.3%) cancer according to the TNM classification. (Table 2)

**Table 1.** Summary of patient demographics, including age, sex, and comorbid conditions at ORNJ onset (n=80)

Category	Sub-category	Number (%)
Sex	Male	43 (53.8)
	Female	37 (46.2)
Age (yr), onset of ORNJ	20-29	1 (1.2)
	30-39	3 (3.7)
	40-49	3 (3.7)
	50-59	18 (22.5)
	60-69	25 (31.3)
	70-79	25 (31.3)
	80-90	5 (6.3)
Hypertension	No	47 (58.8)
	Yes	33 (41.2)
Diabetes mellitus	No	61 (76.3)
	Yes	19 (23.7)
Osteoporosis	No	75 (93.8)
	Yes	5 (6.2)

(ORNJ: osteoradionecrosis of jaw)

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**Table 2.** Primary tumor characteristics: histologic type, site, and TNM staging (n=80)

Category	Sub-category	n (%)
Type of cancer	Adenoid cystic carcinoma	3 (3.8)
	Mucoepidermoid carcinoma	2 (2.4)
	Squamous cell carcinoma	54 (67.5)
	Others	8 (10.0)
	Unknown	13 (16.3)
Site of cancer	Buccal mucosa	6 (7.5)
	Floor of mouth	8 (10.0)
	Mandible	21 (26.3)
	Maxilla	2 (2.5)
	Pharynx	13 (16.2)
	Parotid gland	1 (1.2)
	Tongue	29 (36.3)
T stage	1	9 (11.2)
	2	15 (18.7)
	3	4 (5.0)
	4	25 (31.3)
	Unknown	27 (33.8)
N state	0	21 (26.3)
	1	7 (8.7)
	2	19 (23.8)
	3	3 (3.7)
TNM stage	Unknown	30 (37.5)
	1	2 (2.5)
	2	8 (10.0)
	3	5 (6.2)
	4A	29 (36.3)
	4B	6 (7.5)
	Unknown	30 (37.5)

(T stage: tumor stage, N stage: node stage, TNM stage: tumor-node-metastasis stage)

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### 3. Treatment modalities

The most common treatment modality was surgery followed by postoperative radiotherapy (PORT), which was utilized in 44 patients (55.0%). Surgery combined with postoperative concurrent chemoradiotherapy (POCCRT) was the next most frequent treatment, applied in 17 patients (21.3%). Concurrent chemoradiotherapy (CCRT) alone was administered to 13 patients (16.3%), while radiotherapy (RT) alone was used in 5 patients (6.2%). Proton therapy alone was employed in one patient (1.2%).

44 patients (55.0%) received a radiation dose greater than 60 Gy. The number of radiation treatment sessions varied, with an average of 28.9 sessions across the cohort, and 51 patients (63.8%) receiving 30 or fewer sessions.(Table 3)

### 4. Oncologic and reconstructive surgery

Oncologic surgery was categorized based on the extent of resection. Ablative surgery with bone resection was performed in 20 patients (25.0%), while 38 patients (47.5%) underwent ablative surgery without bone resection. Radiation-

**Table 3.** Treatment and radiation characteristics for primary cancer management in patients with osteoradionecrosis of the jaw (n=80)

Category	Sub-category	n (%)
Treatment modality	CCRT	13 (16.3)
	RT only	5 (6.2)
	Surgery and POCCRT	17 (21.3)
	Surgery and PORT	44 (55.0)
Oncologic surgery	Proton therapy	1 (1.2)
	Ablative surgery with bone resection	20 (25.0)
	Ablative surgery without bone resection	38 (47.5)
	Radiation-based treatment without surgery	19 (23.8)
Radiation dose	Unknown	3 (3.7)
	≤60 Gy	9 (11.2)
	>60 Gy	44 (55.0)
No. of irradiations	Unknown	27 (33.8)
	≤30	51 (63.8)
	>30	8 (10.0)
	Unknown	21 (26.2)

(CCRT: concurrent chemoradiotherapy, RT: radiotherapy, POCCRT: postoperative concurrent chemoradiotherapy, PORT: postoperative radiotherapy, Gy: grays)

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based treatment without surgery was performed in 19 patients (23.8%).(Table 3)

Among the patients who underwent surgical treatment, 33 received reconstructive surgery with free flaps. Of these, 14 patients had radial forearm free flaps, and 9 patients had fibular free flaps. Anterolateral thigh flaps were used in four patients, as were lateral arm free flaps. Additionally, latissimus dorsi flaps were used in two patients.

### 5. Characteristics of ORNJ

In accordance with our inclusion criteria, all cases involved mandibular ORNJ. ORNJ most commonly occurs spontaneously, with 49 cases (61.3%) presenting without an identifiable triggering event. Among the induced cases, dental extraction was the most frequent precipitating factor, accounting for 77.4%. Onset of ORNJ occurred within 48 months post-RT in 40 patients (50.0%), while 22 patients (27.5%) experienced ORNJ onset beyond 48 months.

Regarding the anatomical relationship with the primary lesion, ORNJ occurred ipsilaterally to the primary lesion in 63 patients (78.8%), while five patients (6.2%) exhibited contralateral involvement. 7 patients (8.8%) had ORNJ affecting

**Table 4.** Clinical characteristics of ORNJ, including causative factors, timing, lesion location, stage, and treatment outcomes (n=80)

Category	Sub-category	n (%)
Triggering factors	Spontaneous	49 (61.3)
	Induced	31 (38.7)
	Inducing factor	
	Dental extraction	24 (77.4)
	Dental implant	1 (3.2)
	Dental infection	3 (9.7)
	Exposed jaw plate	1 (3.2)
Timing of ORNJ	Pathologic fracture	2 (6.5)
	≤48 months	40 (50.0)
	>48 months	22 (27.5)
Anatomical relationship with the primary lesion	Unknown	18 (22.5)
	Contralateral	5 (6.2)
	Ipsilateral	63 (78.8)
	Ipsilateral+contralateral	7 (8.8)
	Unknown	5 (6.3)
Staging of ORNJ	Stage I	16 (20.0)
	Stage II	33 (41.3)
	Stage III	31 (38.7)
Treatment of ORNJ	Conservative therapy	21 (26.2)
	Sequestrectomy	45 (56.3)
	Partial mandibulectomy	14 (17.5)
Treatment outcome	Improved	21 (26.2)
	Stable	30 (37.5)
	Progressed	29 (36.3)

(ORNJ: osteoradionecrosis of jaw)

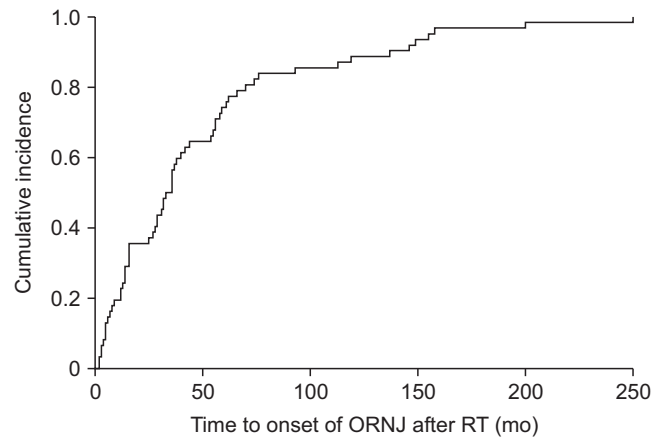
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both the ipsilateral and contralateral sides.(Table 4)

### 6. Onset of ORNJ

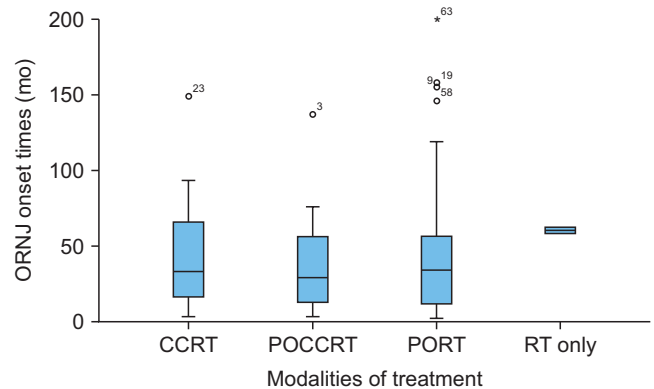
Overall mean onset time for ORNJ across all patients, regardless of treatment modality, was 49.6 months, with a median of 34.5 months. The cumulative incidence curve illustrates the time to onset of ORNJ following RT. The majority of cases occurred within the first 100 months, with a sharp increase during the initial 50 months. After approximately 150 months, the curve plateaued, indicating a reduced rate of new ORNJ cases over time.(Fig. 1)

Mean onset times (in months) after RT for each treatment modality were as follows: 46.3 months for CCRT, 60.0 months for RT only, 37.6 months for surgery with POC CRT, and 49.9 months for surgery followed by PORT.(Fig. 2) The RT-only group had the longest mean onset time, while the surgery with POC CRT group had the shortest. However, the Kruskal-Wallis test results revealed no statistically significant differences in onset times across treatment modalities (P=0.581).



**Fig. 1.** Cumulative incidence of osteoradionecrosis of the jaw (ORNJ) onset after RT (in months). This Kaplan–Meier curve shows the cumulative incidence of ORNJ over time following RT. The x-axis represents the time in months from RT to ORNJ onset, while the y-axis indicates the cumulative incidence. (ORNJ: osteoradionecrosis of jaw, RT: radiotherapy)

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**Fig. 2.** Comparison of onset time (in months) across different treatment modalities. Each box represents the distribution of onset times for the respective treatment group. (ORNJ: osteoradionecrosis of jaw, CCRT: concurrent chemoradiotherapy, POC CRT: postoperative concurrent chemoradiotherapy, PORT: postoperative radiotherapy, RT: radiotherapy)

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### 7. Treatment outcomes of ORNJ

Surgical intervention was the most common treatment approach for ORNJ, utilized in 59 patients (73.8%). Among the surgical interventions, sequestrectomy was performed in 45 patients (56.3%), while 14 patients (17.5%) required partial mandibulectomy. Conservative therapy was employed in 21 patients (26.2%). The median postoperative follow-up periods were 20 months (mean 25.9 months) for sequestrectomy

and 28 months (mean 29.0 months) for partial mandibulectomy. Outcomes of ORNJ treatment were improved in 21 patients (26.2%), stable in 30 patients (37.5%), and progressed in 29 patients (36.3%). Among the progressed patients, stage progression was observed in 10 patients, with 6 patients progressing from Stage II to Stage III, 3 patients from Stage I to Stage III, and 1 patient from Stage I to Stage II.

Treatment strategies for ORNJ varied by disease stage. In Stage I cases, sequestrectomy (56.3%) and conservative therapy (43.7%) were the only modalities used. In Stage II, sequestrectomy remained the most common approach (72.7%), while conservative therapy and partial mandibulectomy were used in 21.2% and 6.1% of cases, respectively. In Stage III, partial mandibulectomy was most frequently performed (38.7%), followed by conservative therapy (22.6%) and sequestrectomy (38.7%).(Table 5)

The distribution of treatment outcomes varied across treatment methods and ORNJ stages.(Fig. 3) In ordinal logistic regression, both conservative treatment (odds ratio [OR]=4.64,  $P=0.041$ ) and sequestrectomy (OR=4.92,  $P=0.022$ ) were associated with significantly worse outcomes compared to

partial mandibulectomy.

This association remained significant in the subgroup analysis of patients with Stage III ORNJ, where both conservative treatment (OR=8.22,  $P=0.038$ ) and sequestrectomy (OR=10.49,  $P=0.011$ ) were significantly associated with worse outcomes compared to partial mandibulectomy.

In the subgroup analysis of patients with Stage II ORNJ, no statistically significant differences in treatment outcomes were observed among treatment groups. However, sequestrectomy showed a trend toward better outcomes compared to both partial mandibulectomy (OR=0.34,  $P=0.459$ ) and conservative treatment (OR=0.20,  $P=0.117$ ). Conversely, partial mandibulectomy was associated with higher odds of poor outcomes relative to conservative treatment (OR=12.84,  $P=0.115$ ), though none of these differences reached statistical significance.

In the Stage I subgroup, sequestrectomy was associated with higher odds of poor outcomes compared to conservative treatment (OR=5.34,  $P=0.181$ ), although this finding was not statistically significant.

#### IV. Discussion

Radiation therapy of the head and neck region accelerates cell death and collagen breakdown, leading to fibroatrophic and necrotic bone changes. In later phases, these mechanisms exacerbate tissue vascularization, impeding efficient healing<sup>11,12</sup>. The jaw’s exposure to oral microbes and continuous occlusal stresses can exacerbate the progression of ORNJ<sup>13</sup>.

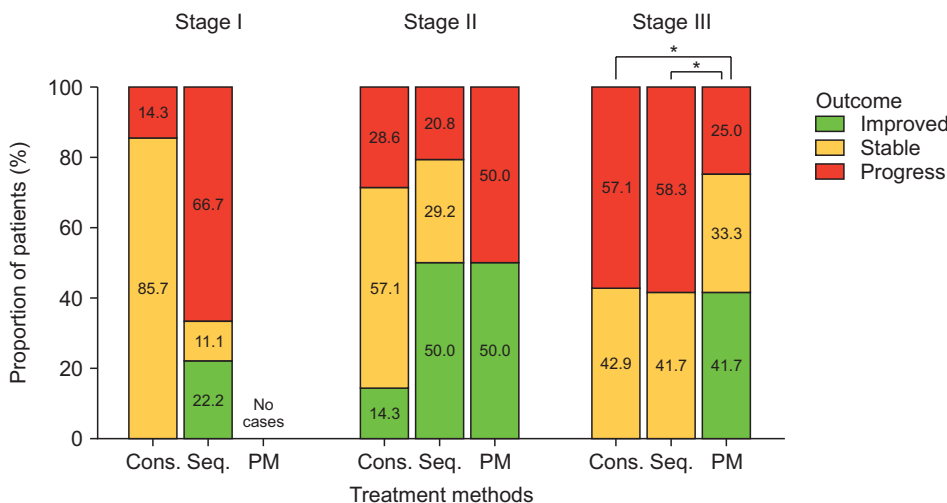
In patients with ORNJ, squamous cell carcinoma is the most common primary tumor, accounting for 65% of cases. This predominance is due to the fact that the majority of oral cavity cancers originate from epithelial cells as squamous

**Table 5.** Distribution of ORNJ treatment modalities by disease stage

ORNJ treatment	Stage		
	Stage I	Stage II	Stage III
Conservative therapy	7 (43.7)	7 (21.2)	7 (22.6)
Sequestrectomy	9 (56.3)	24 (72.7)	12 (38.7)
Partial mandibulectomy	0 (0.0)	2 (6.1)	12 (38.7)
Total	16 (100.0)	33 (100.0)	31 (100.0)

(ORNJ: osteoradionecrosis of jaw)  
Values are presented as number (%).

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**Fig. 3.** Outcome distribution across treatment methods within each ORNJ stage. In Stage III, conservative treatment and sequestrectomy were significantly associated with worse outcomes compared to partial mandibulectomy (\* $P<0.05$ , ordinal logistic regression). (ORNJ: osteoradionecrosis of the jaw, Cons.: conservative, Seq.: sequestrectomy, PM: partial mandibulectomy)  
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cell carcinoma<sup>14</sup>. The tongue and mandible were the most prevalent tumor locations of the ORNJ patients, indicating that when the jaw is exposed to radiation, the chance of developing ORNJ increases dramatically<sup>15,16</sup>. This association emphasizes the significance of careful treatment planning, since including the mandible in radiation therapy will likely result in significant challenges in controlling post-treatment problems.

The most prevalent tumor stage of the underlying tumor was Stage IV, suggesting that an advanced tumor stage may be related to an increased risk of developing ORNJ. A previous study reported that the risk of ORNJ development was greater in patients with advanced-stage tumors<sup>17</sup>. Higher T stage tumors often involve the mandible, increasing the likelihood of direct radiation exposure to these areas. Also, a higher T stage often necessitates the use of radiation treatment, which explains why advanced-stage patients are more likely to develop ORNJ.

Surgery was the most common treatment method for the primary tumor, followed by PORT or POCRT. The likelihood of ORNJ increases with surgery due to damage to blood vessels caused by the ablative surgery, which impairs blood supply to the mandible, or as a result of bone resection surgery, which directly damages the bone. Previous studies have shown that people who have had mandibulectomy surgery are more likely to acquire ORNJ after radiation therapy<sup>18,19</sup>. However, another study suggested that the occurrence of ORNJ was not influenced by whether surgery was performed or not, but rather by the level of aggressiveness of the surgery or RT<sup>15</sup>.

One previous study reported that patients who received CCRT had a shorter onset time of ORNJ than those who received RT alone because chemotherapy has the potential to significantly weaken the local immune response, primarily by compromising the cellular immune system<sup>20</sup>. However, in our study, although the RT-only group showed the longest mean onset time, no statistically significant difference was observed between the various treatment modality groups.

While previous studies have suggested that radiation doses >60 Gy may represent a threshold for ORN risk, our study was limited by incomplete dosimetric data, preventing meaningful analysis of dose-response relationships in our cohort<sup>9,21</sup>. Therefore, we cannot draw conclusions about radiation dose thresholds based on our findings. The mandible appears to be a distinct organ at risk. Therefore, when planning radiation therapy, mandibular dosages must be carefully considered. Advanced radiation techniques such as IMRT can reduce the

radiation dose delivered to the mandible. IMRT minimizes unnecessary radiation exposure by precisely targeting the tumor while sparing surrounding healthy tissues, particularly the jawbone, thereby potentially lowering the risk of ORNJ. Previous studies have reported a lower incidence of ORNJ in patients treated with IMRT compared to conventional radiation techniques such as 3D-CRT, supporting its advantage in preserving mandibular integrity<sup>22</sup>. However, in our study, most patients had undergone IMRT, and due to the retrospective design and uneven distribution of radiation modalities, a direct comparison of ORNJ incidence between IMRT and 3D-CRT groups was not feasible. This limitation underscores the need for future prospective studies with balanced modality representation to better evaluate the differential impact of radiation techniques on ORNJ risk.

Our study focused exclusively on mandibular ORNJ, which is consistent with the well-documented higher susceptibility of the mandible compared to the maxilla. Prior research indicates that the mandible's reduced blood supply relative to that of the maxilla makes it more vulnerable to radiation-induced necrosis<sup>23</sup>. The stress induced by physiologic flexure may contribute to the mandible's accelerated bone turnover, which may play a part in the increased prevalence of ORNJ<sup>24</sup>. Furthermore, the mandibular molar region, particularly the posterior portion, has dense bone with a high mineral content, making it more likely to absorb more radiation during RT. Increased radiation absorption increases the chance of developing ORNJ in this location<sup>25</sup>. One study proposed that the increased frequency of ORNJ development in the mandible compared to the maxilla may be due to the mandible being more frequently included within the radiation field than the maxilla<sup>26</sup>.

ORNJ can occur spontaneously or be triggered by induced factors. Radiation-induced fibrosis leads to dysregulation of collagen metabolism and thrombosis in small vessels, creating a hypoxic and hypocellular environment. This compromised setting paves the way for the development of ORNJ<sup>27</sup>.

The average duration between radiation and onset in our research was about 49 months, although prior investigations found that the average onset time of ORNJ to be between 12 and 24 months<sup>6</sup>. The longer onset time in our study is likely due to improvements in oral hygiene care and radiation therapy techniques, such as IMRT.

When treating ORNJ, a conservative approach should be used at first, involving medications in conjunction with local wound care. Basic conservative treatments include chlorhexidine mouthwash and antibiotics. Pentoxifylline and tocoph-

erol-based therapies have been developed to counteract the effects of reactive oxygen species, which ultimately cause radiation-induced fibrosis and ORNJ<sup>28</sup>. Surgical intervention may be required to treat advanced ORNJ, but it should be performed with caution. When compared to primary malignant tumor reconstruction, ORNJ reconstruction has significantly greater risk of flap failure and postoperative morbidity. The presence of fibrotic, avascular tissue, which increases vulnerability to breakdown and infection, and restricted available blood vessels for microvascular surgery are two major challenges<sup>29</sup>. ORNJ therapy should begin conservatively, with surgery reserved for severe instances due to increased risks of complications in fibrotic tissues.

The findings of this study emphasize the need for careful selection of treatment methods for managing ORNJ, as different approaches are associated with different disease stability outcomes. Sequestrectomy was the most commonly performed intervention; however, patients who underwent sequestrectomy had a higher likelihood of ORNJ progression than those who received conservative therapy. This suggests that sequestrectomy may not always lead to long-lasting disease control, even though its goal is to stabilize the illness by removing necrotic bone. Notably, in both Stage I and Stage III subgroups, sequestrectomy was associated with poorer outcomes compared to conservative treatment and partial mandibulectomy, respectively. A surgical approach has typically been reserved for advanced stages of necrosis, which highlights the importance of carefully evaluating the risks and benefits of this intervention based on disease stage before proceeding<sup>30</sup>.

We observed that none of the Stage I patients who received conservative treatment achieved ‘improved’ outcomes. This observation requires careful interpretation within the context of existing literature. Previous studies have reported variable success rates for conservative management in ORNJ. Oh et al.<sup>17</sup> reported that 47 of 114 patients (41.2%) achieved resolution with conservative treatment alone. Tadokoro et al. found that patients with asymptomatic ORN affecting bone length >2.5 cm were unresponsive to conservative treatment, suggesting that the effectiveness of conservative management may be limited even in cases without significant symptoms<sup>31</sup>. Several factors may explain our findings. First, our outcome criteria may have been stringent in defining ‘improved,’ requiring not only symptom reduction but also evidence of re-epithelialization or radiographic stabilization. Early-stage ORNJ may demonstrate slower healing process that require longer observation periods to detect meaningful improve-

ment. Second, the primary benefit of conservative treatment in Stage I disease may be prevention of progression rather than active improvement of existing pathology. These findings suggest that treatment expectations for Stage I ORNJ should focus on disease stabilization and prevention of progression, with active improvement being a secondary endpoint.

In contrast, partial mandibulectomy demonstrated better disease stability rates, with most patients achieving disease stability and only a small portion experiencing progression. Although partial mandibulectomy may offer more definitive disease control, its invasive nature—often necessitating free flap reconstruction—makes it a more complex option with significant potential morbidity. Due to its high invasiveness and requirement for advanced reconstructive techniques, partial mandibulectomy may not be appropriate for all cases. Treatment selection should carefully balance disease control benefits against surgical morbidity, functional outcomes, and patient quality of life considerations. While achieving wide resection with a safety margin may reduce the risk of residual necrotic tissue and disease recurrence<sup>31</sup>, the decision for partial mandibulectomy requires individualized assessment considering patient preferences, functional status, and overall treatment goals rather than disease progression rates alone.

This study has several limitations that may affect interpretation of its findings. As a retrospective study, incomplete radiation dosimetric data significantly limited our ability to analyze dose-response relationships and perform detailed multivariate risk analysis of radiation-related factors. In addition, data regarding the extent of resection or margin width in patients undergoing partial mandibulectomy were not consistently available, as surgical decisions were made based on intraoperative judgment rather than standardized criteria. This may limit the reproducibility of our findings regarding the effectiveness of partial mandibulectomy. Furthermore, since ORNJ can remain stable for a period before progressing, longer follow-up is needed to capture late-stage disease progression and recurrence. Prospective, multi-center studies with extended follow-up and detailed surgical and dosimetric data are necessary to develop standardized and evidence-based guidelines for ORNJ management.

## V. Conclusion

ORNJ management requires individualized approaches that consider both risk factors and disease severity. Key risk factors such as tumor stage, radiation dose, and location of

radiation exposure should guide treatment choices. While conservative therapies may be effective in milder cases, partial mandibulectomy may offer more stable outcomes for advanced disease. Further research is essential to establish clear treatment guidelines, optimizing patient outcomes by addressing both prevention and intervention strategies in ORNJ management.

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## Authors' Contributions

K.J.L. contributed to collecting data and writing the manuscript. H.M. was responsible for conceptualization and supervision. S.M.K. conceptualized and designed the study. M.H.S. contributed to writing, review, editing and conceptualization. All authors have read and approved the manuscript.

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## Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of Seoul National University Dental Hospital (IRB No. ERI24033). The requirement for written informed consent was waived due to the retrospective nature of the study.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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