치의과학박사 학위논문

# Staging significance of bone invasion in small-sized (4 cm or less) oral squamous cell carcinoma as defined by the American Joint Committee on Cancer

# 구강편평세포암종에서 골침범 요소가 병기 결정에 미치는 영향에 관한 연구

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서울대학교 대학원
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이 논문을 치의과학 박사학위논문으로 제출함

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# Abstract

# Staging significance of bone invasion in small-sized (4 cm or less) oral squamous cell carcinoma as defined by the American Joint Committee on Cancer

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Objectives: The staging significance of bone invasion is controversial in oral squamous cell carcinoma (OSCC) cases with tumors measuring 4 cm or less according to the American Joint Committee on Cancer (AJCC). Our aim was to retrospectively examine a large group of patients with OSCC to determine the staging significance of bone invasion.

Materials and Methods: Three hundred and twenty-three patients with primary OSCC were classified based on tumor size. Mandibular bone invasion was categorized as absent, one side bone, and both buccal and lingual bones, and analyzed for association with disease progression. Regional lymph node

metastasis (N), perineural invasion, vascular invasion, surgical margin involvement, and adjuvant treatment were also analyzed.

Results: In all OSCC cases, bone invasion (p=0.007) with stage N, perineural invasion, and surgical margin involvement were significant independent prognostic factors of disease progression. However, in OSCC cases with tumors measuring 4 cm or less, bone invasion was not significantly associated with disease progression. Nevertheless, invasion of both buccal and lingual bones was significantly associated with disease progression (p=0.03). In multivariate analysis, both buccal and lingual bone invasion (p=0.04; hazard ratio=3.4; 95% confidence interval, 1.0–11.0), stage N2, and perineural invasion were also independent prognostic factors. Kaplan-Meier analyses indicated that OSCC cases with one sided bone invasion can be upstaged by one T stage.

Conclusion: Although OSCC bone invasion was an independent prognostic factor, bone invasion in small OSCC was not. The AJCC T system is of limited prognostic value for small OSCC with bone invasion. However, small OSCC with both buccal and lingual bone invasion had a significantly worse prognosis. Therefore, we recommend a revision of the T staging system such that tumors are classified as T1 to T3 based on size, and mandibular OSCCs with both buccal and lingual bone invasion should be defined as T4. The remaining groups should be upstaged by one T stage in the presence of bone invasion.

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**Keywords :** Oral cancer, Head and neck cancer, Squamous cell carcinoma, Bone invasion, Prognosis, Disease progression, Staging

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# Contents

# I. Introduction

According to the 2010 American Joint Committee on Cancer (AJCC) [1], primary oral squamous cell carcinoma (OSCC) patients with medullary bone invasion should be defined as T4a. Some studies show that OSCC bone invasion has a significant effect on survival in univariate analysis [2, 3]. Furthermore, infiltrative bone invasion was shown to be associated with patient prognosis after correcting for the effects of other variables [4].

Despite the fact that OSCC bone invasion is an independent prognostic factor, a revision of the 2010 AJCC T system was suggested for small-sized (≤4 cm) OSCC [5]. Ebrahimi et al. recommended a revision of the T system that included the classification of tumors as T1–T3 based on size and their upstaging by one T stage in the presence of medullary bone invasion [5]. This was supported by another study that showed that although bone invasion is a statistically significant factor for survival, bone invasion in OSCC ≤4 cm has no significant effect [6]. This issue remains controversial.

In the present study, we examined whether bone invasion in OSCC ≤4 cm is a significant factor using multivariate analysis with the inclusion of other important prognostic factors. Additionally, many cases of OSCC with tumors measuring >2 cm and ≤4 cm (T2) show bone

invasion without invasion of the maxillary sinus or nasal cavities [7]. In particular, certain cases show extensive destruction of both buccal and lingual bones among patients with mandibular OSCC. Here, we examined whether the prognosis of these patients differed from that of patients with minimal bone invasion. In addition, appropriate criteria for predicting the prognosis of patients with OSCC and bone invasion were investigated.

# II. Patients and methods

## Patients

Archival glass slides from 323 primary OSCC patients (144 with medullary bone invasion) who underwent surgery at Seoul National University Dental Hospital, Seoul, South Korea, between January 1999 and January 2013 were selected. All cases treated during this period were included in the study, except for patients who did not undergo surgery or had insufficient information or other malignancies before the diagnosis of OSCC. Based on the initial pathological and clinical data, patients were classified according to the 2010 AJCC staging system as T1, 83 cases; T2, 74 cases, T3, 17 cases; and T4, 149 cases (Table 1). The study protocol was approved by Seoul National University Dental Hospital Institutional Review Board (CRI14030).

## Clinicopathological data

Age, gender, tumor location, adjuvant therapy, regional lymph node metastasis and distant metastasis were included as retrospective analysis factors. The patients received postoperative adjuvant therapies at different institutions; therefore, the decision to use postoperative radiotherapy (RT) or concurrent chemotherapy and radiotherapy (CCRT) was made by each institution. As a result, the

patients with adverse risk features were not treated according to RT or CCRT guidelines defined by the National Comprehensive Cancer Network [8]. In the present study, the patients treated with RT had a positive surgical margin, bone invasion, perineural invasion, vascular invasion, or N2 nodal disease. The patients treated with CCRT showed a positive margin and extracapsular nodal spread or had multiple poor prognostic factors. In patients with tumors ≤2 cm (T1), 18 patients (18.7%) received RT with a radiation dose of 56–66 Gy targeted to the primary site and/or neck. In patients with tumors >2 cm and ≤4 cm (T2), 48 (32.7%) patients received postoperative RT (56–70 Gy) and four (2.7%) patients were treated with CCRT. In patients with tumors >4 cm (T3), 45 (56.3%) patients received RT (56–70 Gy) and seven (8.7%) patients received CCRT. Clinical endpoints referred to cases where patients were lost to follow-up, died, or were transferred to the department of hemato-oncology.

In all cases, data on histopathological factors, tumor size, regional lymph node metastasis, bone invasion, perineural invasion, vascular invasion, and surgical margin involvement were obtained from the original pathology reports and reviewed on slides by an oral pathologist. Bone invasion, which was defined based on the 2010 AJCC staging system, included cortical bone destruction with micro- and macro-medullary bone invasion and excluded superficial erosion

alone. Mandibular bone invasion was categorized into three groups as follows: absence, one sided bone invasion, and both buccal and lingual bone invasion. A close margin was defined as the distance from the invasive tumor front to a resected margin of less than 5 mm [8]. In cases with inadequate information, stored pathology slides and radiology images were blindly reviewed by an oral pathologist and an oral radiologist. The oral radiologist examined the results of computed tomography (CT), magnetic resonance imaging (MRI), and a panoramic radiograph of the OSCC patients [9].

## Statistics

Correlation analyses were performed using Pearson's Chi-square and Fisher's exact tests to investigate the relationship between tumor size, bone invasion, and various variables. Survival curves were generated using the Kaplan–Meier method, and comparisons were analyzed by the log-rank test. Cox proportional hazards regression analysis was performed to determine whether bone invasion was an independent prognostic factor. Statistical significance was defined as a *p*-value $<0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS software Version 18.0, SPSS Inc., Chicago, IL, USA).

# III. Results

## Patients and histopathological features

In the present study, 323 patients with primary OSCC treated by surgical resection, with 245 undergoing concurrent neck dissections, were analyzed. The average age of the patients was 60.2 ± 11.6 years (range, 22–91 years), and there were 203 men and 120 women. Pathologically proven bony medullary invasion was present in 144 patients. The clinicopathological data of patients are presented in Table 1. There were three T2 (>2 cm and ≤4 cm) and two T3 (>4 cm) cases without bone invasion but with invasion into the tongue's hyoglossus muscle, the masticator space, or the cheek skin that were defined as T4. Of 66 patients who showed disease progression, 19 had lymph node metastases, 27 had distant metastases, 18 showed recurrence and were upstaged, and two died. The median survival time of disease progression was more than five years in the study population. The median follow-up period of the patients who did not experience disease progression was 32 months.

The correlation between tumor size, bone invasion, and adverse histopathological features was reviewed. Tumor size was significantly correlated with bone invasion ($p < 0.001$), regional lymph node

metastasis ($p < 0.001$), and perineural invasion ($p = 0.006$). Regional lymph node metastasis also showed significant associations with tumor size, bone invasion ($p = 0.005$), and perineural invasion ($p = 0.002$). Bone invasion showed significant correlations with tumor size and regional lymph node metastasis. Perineural invasion had significant correlations with tumor size, regional lymph node metastasis, vascular invasion ($p = 0.003$), and surgical margin involvement ($p = 0.046$). Vascular invasion showed significant correlations with perineural invasion and surgical margin involvement ($p = 0.042$).

## Proportional hazards analysis according to bone invasion in all and small (≤4 cm) OSCC cases

Multivariate Cox analysis was performed for all 323 OSCC cases by including factors such as pathological N stage, bone invasion, perineural invasion, vascular invasion, surgical margin involvement, and adjuvant treatment. Pathological N stage (N1, $p = 0.012$; N2, $p = 0.001$), bone invasion ($p = 0.007$), perineural invasion ($p < 0.001$), and positive surgical margin ($p = 0.001$) were significantly associated with disease progression (Table 2).

Of 96 patients with tumors ≤2 cm (T1), 13 had bone invasion. Multivariate Cox analysis with various factors showed that the risk of

disease progression was not higher in patients with bone invasion than in those without bone invasion (Table 3). N2, perineural invasion, and positive surgical margin significantly affected the risk of disease progression in tumors ≤2 cm (Table 3). Of 147 patients with tumors >2 cm and ≤4 cm (T2), 70 had bone invasion. Among these, 15 patients had invasion into the maxillary sinus or nasal cavities and were classified as T4. In addition, three cases without bone invasion but with other T4 factors were defined as T4. In the multivariate Cox analysis these 18 T4 patients had a greater risk of disease progression than those without bone invasion ($p < 0.001$; hazard ratio [HR], 10.96; 95% confidence interval [CI], 3.42–35.10; Table 3). There was no statistically significant difference in the risk of disease progression between patients with or without bone invasion (Table 3). N2 and perineural invasion were significantly associated with disease progression (Table 3).

## Proportional hazards analysis according to the pattern of bone invasion in OSCC >2 cm and ≤4 cm

Among patients with tumors ≤2 cm (T1), 13 patients with bone invasion had no severe bone destruction. However, in patients with tumors >2 cm and ≤4 cm (T2), 13 of the 55 patients with bone invasion showed severe mandibular destruction with destruction of all buccal and lingual

bones. Disease progression-free survival was significantly longer in the two groups without bone invasion ($p = 0.047$, Fig. 1a) or one sided bone invasion ($p = 0.047$, Fig. 1b) than in the 13 patients with both buccal and lingual bone invasion. Furthermore, the prognosis of the T2 (>2 cm and ≤4 cm) cases with both buccal and lingual bone invasion did not differ significantly from that of the T3 (>4 cm) patients with bone invasion ($p = 0.35$, Fig. 2).

Univariate Cox analysis was performed in patients with tumors >2 cm and ≤4 cm including those without bone invasion, those with one sided bone invasion, and those with mandibular invasion of both buccal and lingual bones. There was no statistically significant difference in disease progression between patients with or without one sided bone invasion (Table 4). However, the analysis revealed an increased risk of disease progression when comparing patients with both buccal and lingual invasion to those without bone invasion ($p = 0.033$; HR, 3.54; 95% CI, 1.11–11.34; Table 4). N2 and perineural invasion also showed statistically significant results in univariate analyses (Table 4). On multivariate Cox analysis adjusted by these significant covariates, both buccal and lingual bone invasion, N2, and perineural invasion were negative predictors of disease progression (Table 4). Therefore, both buccal and lingual bone invasion should be considered an independent prognostic factor. Patients with disease progression had 3.37 times

more odds to have both buccal and lingual bone invasion (p = 0.044; 95% CI, 1.04–10.95; Table 4).

## Analysis of T staging in small (≤4 cm) OSCC cases

In addition to the mandibular group with both buccal and lingual bone invasion, T1 (≤2 cm) and T2 (>2 cm and ≤4 cm) OSCC cases with one sided bone invasion were examined to determine the appropriate criteria of the T staging system. To confirm the staging of T1 (≤2 cm) OSCC with one sided bone invasion, Kaplan–Meier curves were generated in comparison with T2 (>2 cm and ≤4 cm) with no bone invasion and T3 (>4 cm) OSCC cases. T1 (≤2 cm) OSCC with one sided bone invasion did not differ significantly from T2 (>2 cm and ≤4 cm) OSCC with no bone invasion (p = 0.88, Fig. 3a). However, T1 (≤2 cm) OSCC with one sided bone invasion differed significantly from T3 (>4 cm) OSCC (p = 0.043, Fig. 3b). To confirm the staging of T2 (>2 cm and ≤4 cm) OSCC with one sided bone invasion, Kaplan–Meier curves were generated in comparison with T3 (>4 cm) OSCC with no bone invasion and with bone invasion. T2 (>2 cm and ≤4 cm) OSCC with one sided bone invasion did not differ significantly from T3 (>4 cm) OSCC with no bone invasion (p = 0.63, Fig. 4a). However, T2 (>2 cm and ≤4 cm) OSCC with one sided bone invasion differed significantly from T3 (>4 cm) OSCC with bone invasion (p = 0.001, Fig. 4b). As a

result, T1 (≤2 cm) OSCC and T2 (>2 cm and ≤4 cm) OSCC with one sided bone invasion can be upstaged by one T stage in the presence of one sided bone invasion.

# IV.Discussion

The present study showed that bone invasion with stage N, perineural invasion, and positive surgical margin were significantly associated with disease progression in all OSCC cases analyzed (Table 2). This is consistent with the findings of a previous report showing that bone invasion is an independent predictor of survival [10]. However, in T1 (<2 cm) and T2 (>2 cm and ≤4 cm) patients, bone invasion was not an independent prognostic factor in the present study (Table 3). This is in agreement with a report that the prognosis of small mucosal lesions with bone invasion is not worse than that of larger lesions without bony invasion [11]. In addition, particularly in small tumors, the detection of bone invasion may not be critical to surgical planning [12]. However, the possible existence of a subgroup with a different prognosis should be considered even in patients with small tumors ≤4 cm.

Despite our findings that bone invasion was not a significant risk factor in small OSCC (≤4 cm), our results identified a subgroup with a worse prognosis. Patients with severe mandibular destruction were found among those with tumors >2 cm and ≤4 cm (T2). These cases were characterized by both buccal and lingual bone invasion, which were among the independent prognostic indicators in the multivariate analysis ($p = 0.044$; HR, 3.37; 95% CI, 1.04–10.95; Table 4). Therefore,

a subgroup with a higher risk of disease progression, which should be defined as T4, exists even among patients with small tumors ≤4 cm. Our study suggests that the recommendation by Ebrahimi et al. [5] that all T2 patients with bone invasion should be upstaged by one T stage may not be valid. However, other than the mandibular group with both buccal and lingual bone invasion, T1 (≤2 cm) and T2 (>2 cm and ≤4 cm), OSCC cases can be upstaged by one T stage in the presence of bone invasion.

There are several possible reasons to explain the differences in prognosis among patients with similar tumor size (>2 cm and ≤4 cm). One of the primary reasons is that the extent of bone destruction is associated with the number of tumor cells invading the bone marrow. This may lead to the spread to other areas through lymphovascular channels. However, the depth of mandibular invasion is not correlated with OSCC prognosis [4]. Another possible explanation is that OSCC with mandibular bone erosion and infiltration shows a different cellular and molecular mechanism [13]. Similarly, OSCC with a higher degree of cortical bone destruction may have a different cellular and molecular mechanism than that showing destruction of one cortical bone. However, further study is necessary to confirm whether OSCC with more cortical bone invasion has a more aggressive potential.

The present multivariate analysis indicated that perineural invasion is an independent prognostic factor, underscoring the importance of perineural invasion, which is in agreement with recent studies [14, 15]. However, Chen et al. reported that perineural and lymphovascular invasion in stages I and II do not affect prognosis [16]. The reason why our results were different is that the multivariate analyses of T1 (<2 cm) and T2 (>2 cm and ≤4 cm) cases included the T4 cases with bone invasion and other T4 factors. Microvascular invasion was shown to be an independent prognostic factor in a large OSCC patient cohort [17]. In the present study, 3 of 96 patients in the T1 group, 3 of 147 in the T2 group, and 1 of 80 in the T3 group had vascular invasion. Because of the small number of cases, the influence of vascular invasion on disease progression could not be confirmed.

Among the 323 cases analyzed, positive surgical margin was an independent prognostic factor, whereas a close (<5 mm) surgical margin was not. This result was in agreement with the report by Ch'ng et al., which showed that close margins do not affect local control and survival [18]. Another study reported a close association between 5 year survival and a positive surgical margin [19]. In the present study, 21 did not undergo further resection after confirmation of a positive surgical margin. Four of these cases did not receive further treatment, and all showed disease progression. Thirteen cases received RT, of

which seven (54%) showed disease progression. Of four cases treated with CCRT, one (25%) showed disease progression. This is in agreement with a report that suggested CCRT as an effective treatment in high-risk patients with positive surgical margins [20].

In the present study, adjuvant therapy was not identified as an independent prognostic factor. A recent report showed that postoperative RT or CCRT is strongly correlated with a favorable prognosis [21]. However, in our Chi-square tests, adjuvant therapy was significantly correlated with tumor size, regional lymph node metastasis, and bone invasion ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Because only the patients with adverse risk features received postoperative RT or CCRT, these patients could not have a good prognosis. As suggested by Brown et al. [22], the lack of significance of adjuvant therapy in our study could be attributed to the limitations of the retrospective study. Therefore, the association between postoperative RT or CCRT and disease progression could not be confirmed in our cohort.

The present study has several limitations of retrospective studies. Because of long commuting distances and personal reasons, the postoperative adjuvant treatment of patients was performed at different institutions. Although the patients were followed up with clinical and

radiological information under consultation with these institutions, the decision to use adjuvant therapies was made by each institution. Therefore, some patients with adverse risk features received RT or CCRT, whereas others did not. Additionally, patients with similar risk factors were treated with different adjuvant therapy methods. However, if local recurrence or regional lymph node metastasis occurred, re-diagnosis and re-surgery were performed at our institution.

# V. **Conclusion**

Although OSCC bone invasion was an independent prognostic factor, our results showed that in small primary OSCC (≤4 cm), bone invasion was not significantly associated with disease progression. The current AJCC T staging system that defines small-sized (≤4 cm) OSCC with bone invasion as T4 has a prognostic limitation. However, higher risk subgroups, which should be defined as T4, can exist even among patients with small tumors with bone invasion. In the present study, the mandibular group (>2 cm and ≤4 cm) with both buccal and lingual bone invasion showed a statistically significantly worse prognosis than the other groups with or without bone invasion. In addition, we identified a group with one sided bone invasion that can be upstaged by one T stage. This is consistent with previous studies [5, 6] and suggests that the current AJCC T system, which has a prognostic limitation, should be revised. Therefore, we recommend the classification of OSCC cases as T1–T3 based on size. The mandibular group with both buccal and lingual bone invasion should be defined as T4, even among patients with small tumors ≤4 cm. The remaining groups should be upstaged by one T stage in the presence of bone invasion.

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# VII. Tables and Figures

Table 1. Patients' clinicopathological data

| Pathological T, size only Variable | T1(≤2cm) | T2(>2and≤4cm) | T3(>4cm) | |
|---|---|---|---|---|
| | No. (%) | No. (%) | No. (%) | Total (%) |
| **No. of patients** | 96 (29.7) | 147 (45.5) | 80 (24.8) | 323 |
| **Age (yrs.)** | | | | |
| <65 | 57 (59.4) | 80 (54.4) | 49 (61.3) | 186 (57.6) |
| ≥65 | 39 (40.6) | 67 (45.6) | 31 (38.7) | 137 (42.4) |
| **Sex** | | | | |
| Male | 56 (58.3) | 94 (63.9) | 53 (66.3) | 203 (62.8) |
| Female | 40 (41.7) | 53 (36.1) | 27 (33.7) | 120 (37.2) |
| **Tumor site** | | | | |
| Tongue | 45 (46.9) | 35 (23.8) | 6 (7.5) | 86 (26.6) |
| Mandible | 20 (20.8) | 64 (43.5) | 53 (66.3) | 137 (42.4) |
| Maxilla | 11 (11.5) | 36 (24.5) | 14 (17.5) | 61 (18.9) |
| Buccal mucosa | 12 (12.5) | 10 (6.8) | 7 (8.7) | 29 (9.0) |
| Floor of mouth | 5 (5.2) | 2 (1.4) | 0 | 7 (2.2) |
| Lip | 3 (3.1) | 0 | 0 | 3 (0.9) |
| **Concurrent neck dissection** | | | | |
| Surgery | 46 (47.9) | 27 (18.4) | 5 (6.2) | 78 (24.1) |
| Surgery + neck dissection | 50 (52.1) | 120 (81.6) | 75 (93.8) | 245 (75.9) |
| **AJCC T stage** | | | | |
| T1 | 83 (86.5) | 0 | 0 | 83 (25.7) |
| T2 | 0 | 74 (50.3) | 0 | 74 (22.9) |
| T3 | 0 | 0 | 17 (21.3) | 17 (5.3) |
| T4 | 13 (13.5) | 73 (49.7) | 63 (78.7) | 149 (46.1) |
| **AJCC N stage** | | | | |
| N0 | 75 (78.1) | 95 (64.6) | 36 (45.0) | 206 (63.8) |
| N1 | 9 (9.4) | 23 (15.7) | 14 (17.5) | 46 (14.2) |

| | | | | |
|---|---|---|---|---|
| N2 | 12 (12.5) | 29 (19.7) | 30 (37.5) | 71 (22.0) |
| **Bone invasion** | | | | |
| Absent | 83 (86.5) | 77 (52.4) | 19 (23.8) | 179 (55.4) |
| Present | 13 (13.5) | 70 (47.6) | 61 (76.2) | 144 (44.6) |
| **Perineural invasion** | | | | |
| Absent | 91 (94.8) | 133 (90.5) | 64 (80.0) | 288 (89.2) |
| Present | 5 (5.2) | 14 (9.5) | 16 (20.0) | 35 (10.8) |
| **Vascular invasion** | | | | |
| Absent | 93 (96.9) | 144 (98.0) | 79 (98.7) | 316 (97.8) |
| Present | 3 (3.1) | 3 (2.0) | 1 (1.3) | 7 (2.2) |
| **Surgical margin involvement** | | | | |
| Negative | 41 (42.7) | 63 (42.8) | 27 (33.8) | 131 (40.6) |
| Close (<5 mm) | 53 (55.2) | 72 (49.0) | 46 (57.5) | 171 (52.9) |
| Positive | 2 (2.1) | 12 (8.2) | 7 (8.7) | 21 (6.5) |
| **Treatment modality** | | | | |
| Surgery | 78 (81.3) | 95 (64.6) | 28 (35.0) | 201 (62.2) |
| Surgery + RT | 18 (18.7) | 48 (32.7) | 45 (56.3) | 111 (34.4) |
| Surgery + CCRT | 0 | 4 (2.7) | 7 (8.7) | 11 (3.4) |

Abbreviations: AJCC, American Joint Committee on Cancer; RT, radiotherapy;

CCRT, concurrent chemotherapy and radiotherapy.

Table 2. Multivariate Cox analysis of the risk factors for 5 year disease progression in all oral squamous cell carcinoma cases analyzed (N = 323)

| Variables | HR | 95.0% CI | *P* |
|---|---|---|---|
| **Pathological N stage** | | | |
| N1 vs N0 | 2.34 | 1.21-4.55 | .012 [a] |
| N2 vs N0 | 3.00 | 1.56-5.75 | .001 [a] |
| **Bone invasion** | 2.03 | 1.22-3.39 | .007 [a] |
| **Perineural invasion** | 4.18 | 2.12-8.26 | <.001 [a] |
| **Vascular invasion** | .69 | 0.16-3.07 | .63 |
| **Surgical margin involvement** | | | |
| Negative vs Close (<5 mm) | .73 | 0.42-1.28 | .27 |
| Negative vs Positive | 3.49 | 1.70-7.13 | .001 [a] |
| **Treatment modality** | | | |
| Surgery vs Surgery + RT | .63 | 0.33-1.18 | .15 |
| Surgery vs Surgery + CCRT | .86 | 0.28-2.68 | .80 |

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CCRT, concurrent chemotherapy and radiotherapy. [a]$p<0.05$

Table 3. Multivariate Cox analyses of the risk factors for 5 year disease progression in T1 (<2 cm) and T2 (>2 cm and ≤4 cm) oral squamous cell carcinoma (n = 96 and 147, respectively)

| **Pathological T, size only** | **T1 (≤2cm)** | | | **T2 (>2cm and ≤4cm)** | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95%CI** | ***P*** | **HR** | **95%CI** | ***P*** |
| **Bone invasion** | | | | | | |
| Bone invasion vs No bone invasion | .91 | 0.18-4.63 | .91 | 1.43 | 0.50-4.04 | .50 |
| Other T4 factors[b] vs No bone invasion | - | - | - | 10.96 | 3.42-35.10 | <.001[a] |
| **Pathological N stage** | | | | | | |
| N1 vs N0 | .42 | 0.04-4.05 | .45 | 2.30 | 0.73-7.26 | .15 |
| N2 vs N0 | 19.67 | 1.38-280.47 | .028[a] | 4.50 | 1.51-13.44 | .007[a] |
| **Perineural invasion** | 7.40 | 1.13-48.58 | .037[a] | 5.88 | 1.70-20.36 | .005[a] |
| **Vascular invasion** | 3.13 | 0.18-53.25 | .43 | 1.38 | 0.13-14.98 | .79 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Surgical margin involvement** | | | | | | |
| Negative vs Close (<5 mm) | 1.15 | 0.37-3.65 | .81 | 0.36 | 0.13-1.01 | .051 |
| Negative vs Positive | 21.05 | 1.94-228.64 | .012 [a] | 2.93 | 0.89-9.61 | .076 |
| **Adjuvant treatment** | | | | | | |
| Surgery vs Surgery + RT | .09 | 0.01-1.07 | .056 | 0.47 | 0.16-1.39 | .17 |
| Surgery vs Surgery + CCRT | - | - | - | 1.16 | 0.12-11.10 | .89 |

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CCRT, concurrent chemotherapy and radiotherapy. [a]$p<0.05$.

[b]Other T4 factors included invasion into deep muscle of tongue, maxillary sinus, skin of face, or masticator space.

Table 4. Univariate and multivariate Cox analyses of the risk factors for 5 year disease progression in oral squamous cell carcinoma tumors >2 cm and ≤4 cm (T2) (n = 129) Bone invasion was categorized into three groups: absence, one sided bone invasion, and both buccal and lingual bone invasion.

| **T2 (>2cm and ≤4cm)** | **Univariate analysis** | | | **Multivariate analysis** | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95%CI** | ***P*** | **HR** | **95%CI** | ***P*** |
| **Bone invasion** | | | | | | |
| One side bone invasion vs No bone invasion | 1.09 | 0.34-3.48 | .88 | 1.23 | 0.37-4.06 | .74 |
| Both buccal and lingual bone invasion vs No bone invasion | 3.54 | 1.11-11.34 | .033 [a] | 3.37 | 1.04-10.95 | .044 [a] |
| **Pathological N stage** | | | | | | |
| N1 vs N0 | 1.77 | 0.46-6.89 | .41 | 1.94 | 0.47-7.99 | .36 |
| N2 vs N0 | 3.85 | 1.35-11.02 | .012 [a] | 3.42 | 1.15-10.18 | .027 [a] |
| **Perineural invasion** | 5.11 | 1.79-14.57 | .002 [a] | 4.96 | 1.63-15.04 | .005 [a] |
| **Vascular invasion** | 2.17 | 0.29-16.45 | .45 | - | - | - |
| **Surgical margin involvement** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Negative vs Close (<5 mm) | 0.38 | 0.12-1.21 | .10 | - | - | - |
| Negative vs Positive | 2.65 | 0.73-9.68 | .14 | - | - | - |
| **Adjuvant treatment** | | | | | | |
| Surgery vs Surgery + RT | 2.59 | 0.97-6.91 | .06 | - | - | - |
| Surgery vs Surgery + CCRT | 2.94 | 0.36-23.68 | .31 | - | - | - |

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CCRT, concurrent chemotherapy and radiotherapy. [a]p<0.05.

Figure 1. Kaplan–Meier curves of 5 year disease progression-free survival according to both buccal and lingual bone invasion compared with (a) no bone invasion (p = 0.047 and n = 87) and (b) one sided bone invasion (p = 0.047 and n = 55) in oral squamous cell carcinoma >2 cm and ≤4 cm.

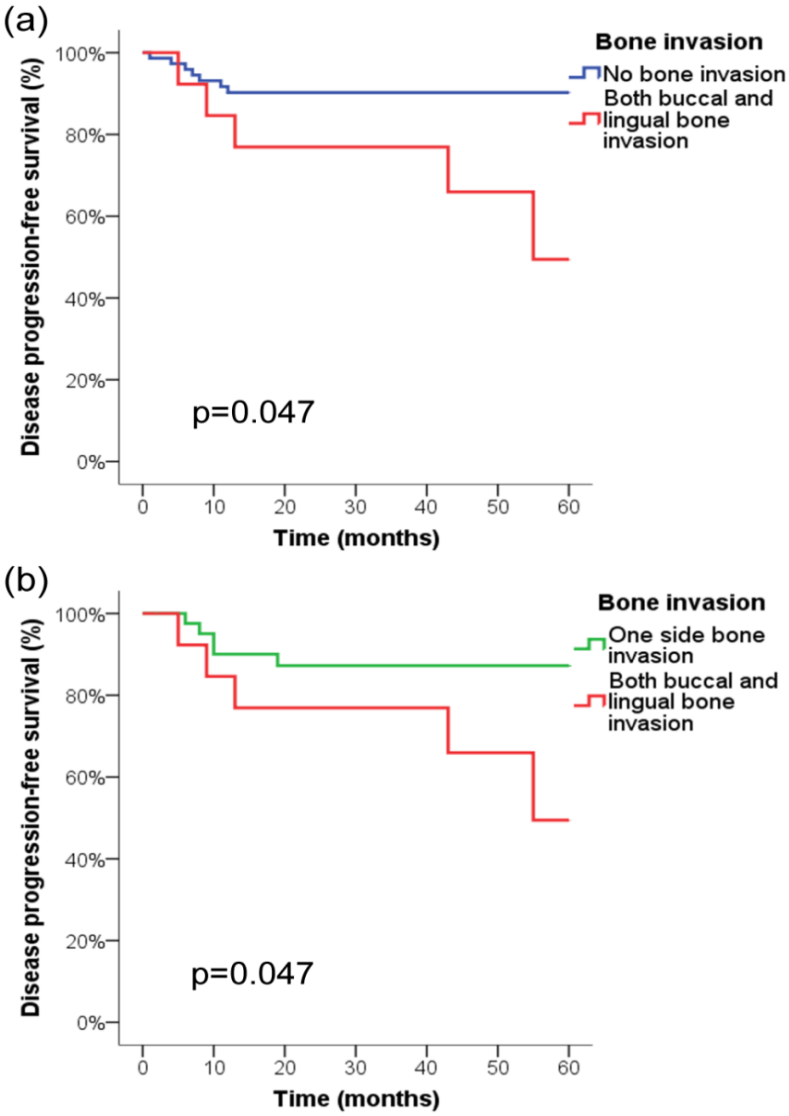


Figure 2. Kaplan–Meier curves of 5 year disease progression-free survival according to both buccal and lingual bone invasion in tumors >2 cm and ≤4 cm (T2), compared with those according to bone invasion in oral squamous cell carcinoma >4 cm (T3) (p = 0.35 and n = 74).

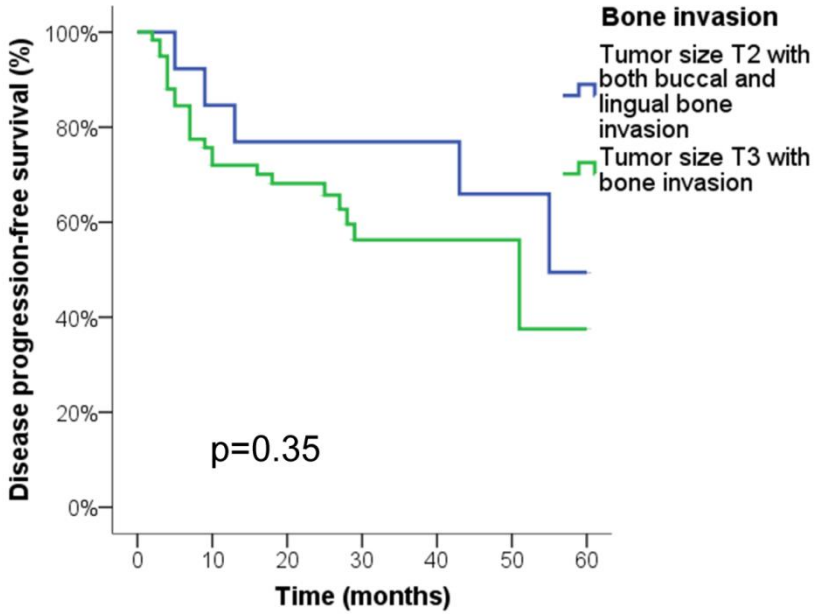


Figure 3. Kaplan–Meier curves of 5 year disease progression-free survival according to one sided bone invasion in tumors ≤2 cm (T1) compared with (a) no bone invasion in tumors >2 cm and ≤4 cm (T2) (p = 0.88 and n = 87) and (b) oral squamous cell carcinoma >4 cm (T3) (p = 0.043 and n = 93).

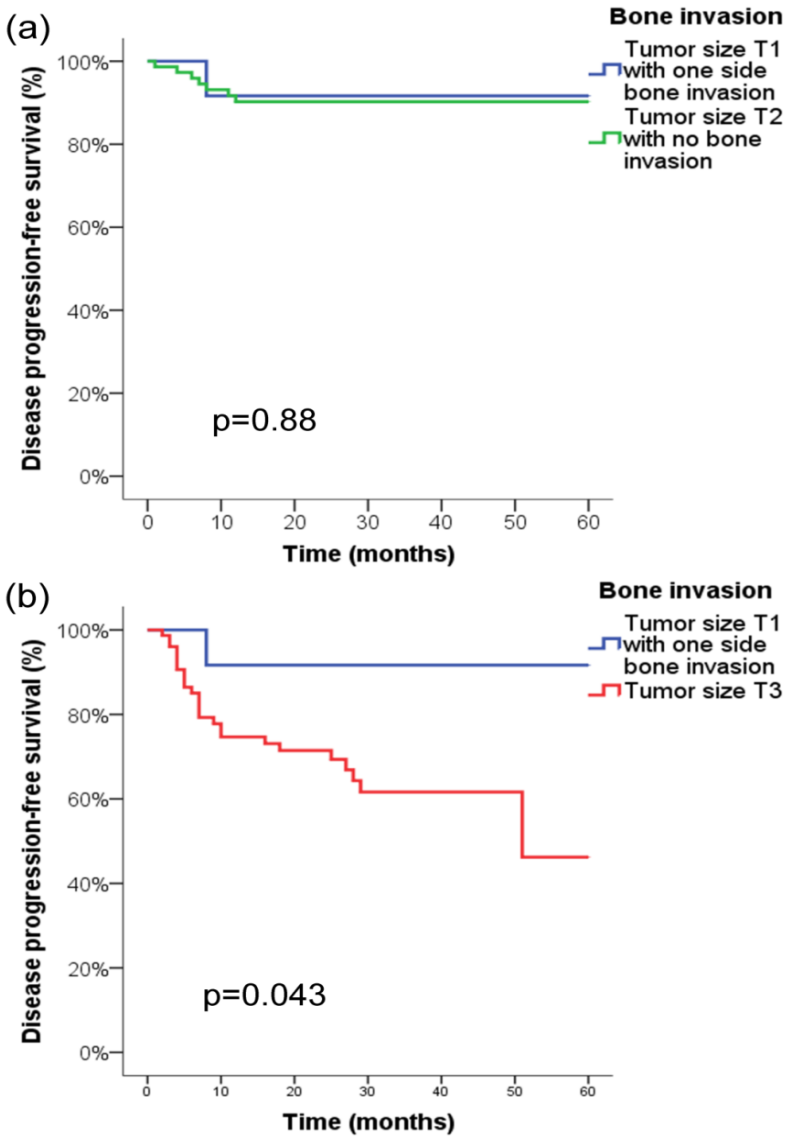
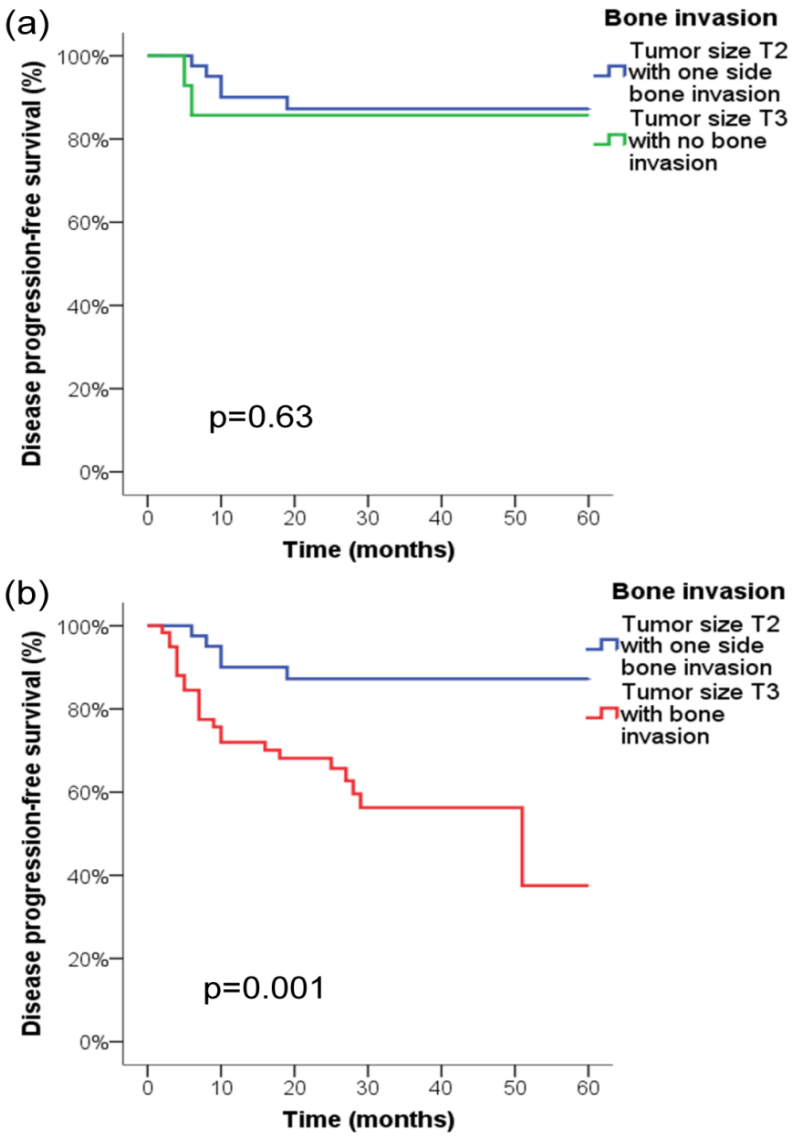


Figure 4. Kaplan–Meier curves of 5 year disease progression-free survival according to one sided bone invasion in tumors >2 cm and ≤4 cm (T2) compared with (a) no bone invasion (p = 0.63 and n = 59) and (b) bone invasion (p = 0.001 and n = 103) in oral squamous cell carcinoma >4 cm (T3).



# VIII.국문초록

**연구목적:** 2010 년도 미국공동암위원회의 TNM 병기 체계에 의하면 골수 침범을 보이는 모든 구강편평세포암 환자는 T4a 단계로 정의한다. 그러나 최근 몇몇 연구에서 4cm 이하의 작은 구강편평세포암 환자에서는 골 침범이 발견 되도 T4a 로 정의하는 현재의 T 체계는 예후 예측에 한계가 있고 수정이 필요하다는 주장이 있다. 골 침범을 보인 4 cm 이하 작은 암 환자의 T 병기를 어떻게 정의해야 할지는 아직도 논란이 되고 있다. 따라서 구강편평세포암 환자를 대상으로 골 침범이 T 병기를 결정함에 있어 어떻게 반영되어야 할지에 관한 연구를 하고자 한다. 이를 위해 우선 전체 환자 집단과 4 cm 이하의 암 환자 집단 각각에서 골 침범이 예후에 유의한 위험 요소인지 확인이 필요하다. 또한 암 크기 T2 (>2 cm 그리고 ≤4 cm) 증례들에서는 골 침범을 보이는 경우가 많은데, 이들 중 하악의 협측과 설측 골 모두 파괴된 증례들의 경우 예후에 의미 있는 차이를 보이는지 확인하고자 하였다.

**연구방법:** 서울대학교 치과병원에서 구강편평세포암으로 진단과 수술을 받은 323 명의 환자를 대상으로 연구하였다. 나이, 성별, 암의 위치, 항암 치료, 국부 림프절 전이와 원격 전이에 관한

정보를 의무 기록지에서 확인하였다. 또한 병리 보고서에서 암의 크기와 국부 림프절 전이의 병기 (N), 골수 침범 여부, 신경 침범 여부, 혈관 침범 여부, 수술 절제면 암조직 잔존 여부와 같은 조직병리학적 요소들을 정리하였다. 구강편평세포암 환자에서 암이 진행되어 악화된 경우의 사건에 관해서는 미국공동암위원회의 TNM 병기 체계에 근거하여 정의를 하였다. 암 크기 4 cm 이하의 하악 증례들에서는 골 침범의 정도를 침범이 없는 경우와 한 측면만 골 침범을 보인 경우, 협측과 설측 골 모두 침범한 경우의 세 집단으로 구분을 하였다. 골 침범을 보인 경우 암 진행의 예후에 어떤 차이가 있는지 확인하기 위해 Kaplan-Meier 생존 분석을 시행하였다. 추가로 국부 림프절 전이의 병기 (N) 와 신경 침범 여부, 혈관 침범 여부, 수술 절제면 암조직 잔존 여부, 항암 치료 여부와 함께 다변량 Cox 분석을 하였다.

연구결과: 전체 집단에서는 골 침범 여부 ($p = 0.007$) 가 국부 림프절 전이의 병기 (N) 와 신경 침범 여부, 수술 절제면 암조직 잔존 여부와 함께 독립적으로 암 진행 예후를 예측하는 유의한 인자임을 확인하였다. 그러나 4cm 이하의 암 증례들에서는 골 침범 여부가 암 진행 예후와 유의한 관련성을 보이지는 않았다. 그러나 하악의 협측과 설측 골 모두 파괴된 증례들 경우에는 암 진행의 예후와 유의한 관련성을 보였다 ($p = 0.03$). 다변량

분석에서도 협측과 설측 골 모두 파괴된 경우 (p = 0.04; 위험률, 3.4; 95% 신뢰 구간, 1.0–11.0) 는 N2 림프절 전이와 신경 침범된 경우와 함께 독립적으로 암 진행 예후를 예측하는 유의한 위험 인자임을 확인하였다. 그리고 한 측면만 골 침범을 보인 경우 어떻게 T 병기를 결정해야 할지를 확인하기 위해 분석을 시행하였다. 크기 T1 (≤2 cm) 암에서 한 면만 파괴된 경우 크기 T2 (>2 cm 그리고 ≤4 cm)의 골 침범이 없는 집단과 예후에 큰 차이는 없었으나 크기 T3 (>4 cm) 집단과는 유의한 예후적 차이(p = 0.043)를 보였다. 크기 T2 (>2 cm 그리고 ≤4 cm) 암에서 한 면만 파괴된 경우 크기 T3 (>4 cm)의 골 침범이 없는 집단과 예후에 큰 차이는 없었으나 크기 T3 (>4 cm)의 골 침범을 있는 집단과는 유의한 예후의 차이(p = 0.001)를 보였다. 결국 한 측면만 골 침범을 보이는 경우 한 단계만 T 병기를 높여 정의를 하여도 된다.

결론: 비록 전체 구강편평세포암 증례들에서는 골 침범 여부가 독립적인 위험 인자이기는 하지만 4cm 이하의 작은 증례들에서는 골 침범이 예후와 유의한 관련성을 보이지는 않았다. 현재 미국공동암위원회의 T 병기가 작은 암 증례에 골 침범이 있는 경우 예후를 예측하는 면에서 한계가 있다. 그러나 작은 크기의 암 증례들에서도 하악의 협측과 설측 골 모두가 파괴 된 경우에는

예후에 유의하게 나쁜 결과를 보였다. 따라서 구강편평세포암 환자에서 골 침범을 보인 경우 우선 암의 크기에 따라 T 병기를 구분하고, 하악의 협설측 모두 파괴된 경우에는 T4 로 정의를 해야 한다고 생각한다. 그리고 그 외의 증례들에서는 골 침범을 보인 경우 한 단계만 T 병기를 높여야 할 것으로 사료된다.

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**주요어 :** 구강암, 구강편평세포암, 골 침범, 암의 예후, 암의 병기

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