Long-term outcomes of early stage oral tongue cancer: Main cause of treatment failure and second primary malignancy

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Abstract

Objective: We attempted to investigate the long-term outcomes, prognostic factors, treatment failures, second primary malignancies, and salvage therapies in early (pT1-2N0) oral tongue squamous cell carcinoma (OTSCC).

Methods: We retrospectively analyzed the medical records of 295 early stage OTSCC patients.

Results: Two hundred ninety-five patients were enrolled. The average follow-up period was 64.5 months (range, 1–190 months). Five-year recurrence-free survival rate was 84.8% and disease-specific survival rate was 91.2%. On multivariate analysis, only the depth of invasion (DOI) exhibited significant correlations with the disease recurrence. Patient’s age and DOI demonstrated a significant association with survival. A total of 53 recurrence and 35 death events occurred, with the main cause of treatment failure being regional or local recurrence. In recurrent cases, the success rate of salvage treatment was 42% at 5 years. During the follow-up period, second primary malignancy occurred in 13 patients, and 8 (61.5%) of those patients were successfully treated.

Conclusions: In pT1-2N0 OTSCC, regional or local recurrence is the main recurrence pattern, whereas age and DOI >5 mm are significant prognostic factors related to recurrence and survival. Since several patients experienced second primary malignancies in the head and neck, careful and thorough surveillance may be required to detect second primary lesions.

Level of Evidence: 4.

Keywords
long-term outcome, prognosis, recurrence, second primary cancer, tongue cancer

INTRODUCTION

Oral cavity cancer is the sixth most common malignant tumor in the world with the tongue being the most common site. Oral tongue squamous cell carcinoma (OTSCC) is often diagnosed at an early stage, but it has unfavorable prognosis compared to other oral cancers. In previous studies, early stage OTSCC exhibited a high loco-regional recurrence rate and poor overall survival and cancer-specific
survival compared to oral cancers of other sites. Surgical treatment is generally preferred for the treatment of early stage (pT1-2 N0) OTSCC, and adjuvant radiotherapy can be performed if adverse features, such as positive/close margin, lymphovascular invasion (LVI), perineural invasion (PNI), and node positivity, are observed in the permanent pathologic report after surgery. For tongue defects that occur after surgery, they can be healed secondarily and reconstruction can be performed using methods such as regional or free flap, depending on the size, location, and institutional policy. In the treatment of early stage OTSCC, elective neck dissection (END) can be decided according to the depth of invasion (DOI). For a depth greater than 4 mm, END is strongly recommended; and if the depth is less than 2 mm, a watchful policy can be implemented. For a depth of 2–4 mm, the surgeon decides whether to perform END based on clinical judgment.

Despite the standard treatment such as surgery on radiotherapy alone, some patients with early stage OTSCC may experience recurring disease and progress to death. In addition, in selected patients, a second primary malignancy occurred during a follow-up period, requiring additional treatment. In this study, the authors retrospectively explored the medical records of early stage (pT1-2N0) OTSCC patients who underwent surgery and analyzed their natural history during a long-term follow-up period. The treatment failure patterns, prognostic factors, salvage treatments, and second primary malignancies in early stage OTSCC patients were then investigated.

2 | MATERIALS AND METHODS

We retrospectively analyzed the medical records of 501 patients who were diagnosed with OTSCC and underwent surgery at the Severance Hospital from January 2005 to December 2019. The Institutional Review Board of Yonsei University approved this study, and since it was a retrospective study, the IRB waived the need for informed consent. Patients diagnosed with stage I-II (pT1-2N0) OTSCC were included in the study. The exclusion criteria were as follows: (1) patients who had previously undergone surgery or radiation therapy in the head and neck region, and (2) patients with lymph node metastasis or distant metastasis at the time of diagnosis. Among them, 329 patients with cN0 underwent END and 85 (25.8%) patients turned out to be pN+ on permanent pathologic report. On logistic regression analysis, only T classification showed a significant relationship with LNs metastasis in these patients. About 102 patients with cN+ underwent therapeutic neck dissection and 14 (13.7%) patients were found to have pN0. The remaining 70 patients did not undergo any neck dissection. Among them, only pT1-2N0 OTSCC patients (n = 295) were included in this study, and the remaining 206 patients were excluded.

Finally, a total of 295 patients consisting of 172 men and 123 women were included in the study. The age of the patients ranged from 20 to 79 years, and the mean age was 51.9 years. Tumor staging was classified according to the eighth American Joint Committee on Cancer Staging system (AJCC). Pathological findings, such as resection margin, DOI, histologic grade, LVI, and PNI, were analyzed.

| Characteristics | Patients, n (%) |
|-----------------|----------------|
| Sex             |                |
| Male            | 172 (58.3)     |
| Female          | 123 (41.7)     |
| Age, years      |                |
| <60             | 226 (76.6)     |
| ≥60             | 69 (23.4)      |
| Histologic grade|                |
| WD              | 88 (29.8)      |
| MD              | 80 (27.1)      |
| PD              | 10 (3.4)       |
| Unknown         | 117 (39.7)     |
| Surgical margin |                |
| Negative        | 291 (98.6)     |
| Positive        | 4 (1.4)        |
| LVI             |                |
| Yes             | 22 (7.5)       |
| No              | 273 (92.5)     |
| PNI             |                |
| Yes             | 28 (9.5)       |
| No              | 267 (90.5)     |
| pT classification|               |
| 1               | 201 (68.1)     |
| 2               | 94 (31.9)      |
| DOI             |                |
| <5 mm           | 220 (74.6)     |
| ≥5 mm           | 75 (25.4)      |
| Elective neck dissection |       |
| Yes             | 218 (73.9)     |
| No              | 77 (26.1)      |
| Adjuvant Tx     |                |
| Surgery alone   | 279 (94.6)     |
| RTx             | 10 (3.4)       |
| CCRTx           | 6 (2.0)        |

Abbreviations: CCRTx, concurrent chemoradiotherapy; DOI, depth of invasion; LVI, lymphovascular invasion; MD, moderately differentiated; PD, poorly differentiated; PNI, perineural invasion; RTx, radiotherapy; Tx, treatment; WD, welldifferentiated.

Cases where cancer cells were not observed in the surgical margin were defined as negative margins, and the range (mm) of the safety margins was further analyzed. Partial glossectomy or hemi-glossectomy was performed depending on the size and extent of the tumor. All operations were performed using a transoral approach. When it comes to END, it was decided according to the DOI of primary tumor. Ipsilateral END was performed in cases of DOI >4 mm, and END was omitted in cases of DOI <2 mm. For DOI of 2–4 mm, the surgeon decided whether to
perform END based on clinical judgment. Adjuvant therapy was considered if there were any findings such as positive margins, extracapsular nodal spread, metastatic lymph nodes, LVI, or PNI in the pathologic examinations.

Patient demographics, clinical records, postoperative pathology, recurrence, date of recurrence, site of recurrence, death, date of death, and cause of death were collected and analyzed. Univariate and multivariate analyses were performed to determine the prognostic factors affecting patient survival. Chi-square or Fisher’s exact test was used to evaluate the differences in categorical variables between the two independent groups. An independent two-sample t-test was used to assess the differences in continuous variables between the two independent groups. The multivariate Cox proportional hazards regression model was used to evaluate the simultaneous effect of several factors on distant metastasis and patients’ survival. The Kaplan–Meier curve was used to analyze disease-free survival, and the survival outcomes were assessed using a log-rank test. A p value < .05 was considered statistically significant. Statistical analyses were performed using SPSS 18.0 for Windows (SPSS).

### RESULTS

The 295 patients included in this study underwent surgery with curative intention as the initial treatment. Among them, 280 (94.9%) patients underwent partial glossectomy, whereas the remaining 15 (5.1%) patients underwent hemi-glossectomy. Seventy-seven patients did not undergo END, and the remaining 218 patients underwent END including levels I–III. In total, 279 (94.6%) patients received no adjuvant treatment after surgery, whereas 16 (5.4%) patients received adjuvant radiation or chemotherapy. According to the pathologic T classification, 201 (68.1%) cases were T1 and 94 (31.9%) cases were T2. The clinicopathological information of the other patients is summarized in Table 1. Thirty-two patients were classified as cT1 before surgery, but were up-staged to pT2 after surgery. Of the 295 patients enrolled in this study, 14 (4.7%) patients had suspected lymph node metastasis on preoperative imaging, but were ultimately diagnosed as pN0 after neck dissection. The mean follow-up period of the patients was 64.5 months (range of 1–190 months). The 5-year recurrence-free survival rate was 84.8% and the disease-specific survival rate was 91.2% (Figure 1). Fifty-three relapses occurred during the study period, and 35 patients died during the study period due to disease progression.

Postoperative pathological findings showed positive surgical margins in four (1.4%) cases, and the remaining 291 (98.6%) patients exhibited negative margins in their findings. The resection margins of the 291 patients with negative margins were analyzed. Safety margins ≤3 mm were observed in 158 (53.6%) patients, whereas margins ≥3 mm were detected in 133 (45.1%) patients. When the patient groups were divided based on 3-mm safety margins, no significant difference was observed in either the 5-year recurrence-free rate or disease-specific survival rate between the two patient groups. When the safety margin was divided based on 5-mm margins, 217 (73.6%) cases were ≤5 mm and 78 (26.4%) cases were ≥5 mm. When the patient groups were divided based on 5-mm safety margins, no significant differences were observed in either the 5-year recurrence-free rate or disease-specific survival rate between the two patient groups.

Clinico-pathologic factors related to recurrence and death were evaluated by univariate analysis. Only DOI exhibited a significant correlation with disease recurrence, whereas age, T classification, and DOI findings revealed a significant correlation with patient death. Multivariate Cox proportional hazard regression analysis was performed including variables with a p value of .3 or less in univariate analysis. On multivariate analysis, only DOI showed a significant correlation with disease recurrence, whereas patient age and DOI exhibited a statistically significant correlation with patient death (Table 2).

A total of 53 recurrences occurred during the study period, including 20 cases of local recurrence, 27 cases of regional recurrence, two cases of distant metastasis, and four cases of multiple-site
recurrence. Regional recurrence was the main cause of treatment failure. Among 27 patients with regional recurrence, 18 patients received END and 9 patients received watchful policy without END. In our study, 218 (73.9%) patients received END and 77 patients received watchful policy. However, no statistically significant difference was observed when comparing the incidence of regional recurrence according to END ($p$ value = 0.365). The 5-year recurrence-free survival rate was 79.3% in the observed necks and 82.1% in the dissected necks. The 5-year disease-specific survival rate was 91.8% in the observed necks and 88.1% in the dissected necks. No significant differences were found in recurrence-free and disease-specific survival rates. The mean period from initial treatment to recurrence was 14.4 months (range, 1–68 months). Among the relapsed patients, 16 (30.2%) patients had a history of smoking, whereas 44 (83%) patients received salvage surgery with/without chemotherapy and radiotherapy. Of these patients, 14 eventually died due to disease progression, and the 5-year survival rate after salvage treatment was 42.5% (Figure 1C). We analyzed the prognostic factors regarding the outcomes of salvage treatment and determined that age (>60 years) and the presence of necrotic lymph nodes exhibited a statistically significant correlation with poor prognosis (Tables 3 and 4).

Second primary malignancy was defined as the occurrence of a malignant tumor 5 years after initial treatment or at a site more than 2 cm away from the index tumor. During the follow-up period, there were 13 cases of second primary malignancies in the head and neck region in eight males and five females who were all under 60 years of age. Three patients (23.1%) had a history of smoking, whereas 10 patients (76.9%) had no smoking history. One patient (7.7%) had a history of radiation therapy to the head and neck region, whereas the remaining 12 patients (92.3%) had no history of radiation therapy. The most common site of second primary malignancy was the oral cavity ($n = 9$). In some cases, second primary malignancy occurred in the oropharynx ($n = 1$) and, hypopharynx ($n = 1$), and presented as multiple lesions ($n = 2$). The lesion was diagnosed within 5 years in three cases, within 5–10 years in six cases, and after 10 years in four cases. Of these patients, eight survived after curative treatment for the lesion, three died due to progression of the second primary malignancy, and the remaining two patients survived with disease during the study period.

| Variables | Recurrence-free survival | Disease-specific survival |
|-----------|--------------------------|---------------------------|
|           | HR  | 95% CI     | P value | HR  | 95% CI     | p Value |
| Sex       | 1.364  | 0.725–2.566  | 0.336 | -  | -          | -       |
| Age       | 0.666  | 0.365–1.216  | 0.186 | 0.319  | 0.154–0.661  | 0.002  |
| Smoking   | 1.402  | 0.707–2.778  | 0.333 | -  | -          | -       |
| PNI       | -     | -           | -     | 0.711  | 0.447–1.130  | 0.149  |
| T         | -     | -           | -     | 0.994  | 0.435–2.274  | 0.989  |
| DOI       | 0.502  | 0.287–0.877  | 0.016 | 0.344  | 0.152–0.780  | 0.011  |

Abbreviations: CI, confidence interval; DOI, depth of invasion; HR, hazard ratio; PNI, perineural invasion.

| Variables | No of pts | Death events | p Value |
|-----------|-----------|--------------|---------|
| Sex       |           |              | .999    |
| Male      | 26 (49.1) | 14           |         |
| Female    | 27 (50.9) | 14           |         |
| Age       |           |              | .002    |
| <60       | 38 (71.7) | 15           |         |
| ≥60       | 15 (28.3) | 13           |         |
| Smoking   |           |              | .550    |
| Yes       | 16 (30.2) | 7            |         |
| No        | 37 (69.8) | 21           |         |
| Surgery   |           |              | .148    |
| Yes       | 44 (83.0) | 21           |         |
| No        | 9 (17.0)  | 7            |         |
| Recur site|           |              | .226    |
| Local     | 20 (37.7) | 6            |         |
| Regional  | 27 (50.9) | 18           |         |
| Distant   | 2 (3.8)   | 2            |         |
| Loco-regional | 4 (7.5) | 2 | |
| Necrotic LN|          |              | .005    |
| Yes       | 8 (15.1)  | 8            |         |
| No        | 45 (84.9) | 20           |         |

Abbreviations: LN, lymph node; No, number, pts, patients.

| Variables | HR  | 95% CI     | p Value |
|-----------|-----|------------|---------|
| Age       | 0.197  | 0.083–0.465  | <.001  |
| Surgery   | 2.026  | 0.676–6.072  | .207   |
| Site      |       |             | .618   |
| Site (1)  | 0.476  | 0.082–2.753  | .407   |
| Site (2)  | 0.909  | 0.182–4.537  | .908   |
| Site (3)  | 1.504  | 0.156–14.524 | .724   |
| Necrotic LN| 0.281  | 0.099–0.797  | .017   |

Abbreviations: CI, confidence interval; HR, hazard ratio; LN, lymph node.
In this study, 295 patients who underwent surgery for pT1-2N0 OTSCC were followed for an average of 64.5 months. The 5-year recurrence-free survival of the patients was 84.8% and the disease-specific survival was 91.2%. It can be observed that these treatment results were comparable to the treatment results from other studies. In this study, the recurrence rate of early stage OTSCC patients was 18%. A total of 53 recurrences occurred, with 20 (37.7%) local recurrence, 27 (50.9%) regional recurrence, 4 (7.5%) loco-regional recurrence, and 2 (3.8%) distant metastasis cases. The only factor that exhibited a statistically significant correlation with disease recurrence was DOI (>5 mm). When the characteristics of each patient group were analyzed based on the DOI of 5 mm, the number of cases with PNI findings was determined to be statistically significantly higher in the patient group with a DOI ≥ 5 mm. However, among the 20 patients who showed recurrence, only one case was accompanied by PNI findings. In this study, 73.9% of the patients underwent ENDS, and 5.4% underwent adjuvant therapies (radiation or chemoradiotherapy). Since the number of patients who received adjuvant therapies was small, it is difficult to determine its effect in the patient group with a DOI > 5 mm. If the disease occurred in early stage OTSCC patients, the success rate of 5-year salvage treatment was only 42.0%. If a DOI ≥ 5 mm is observed in early stage OTSCC patients, active follow-ups should be implemented to detect and treat disease recurrence at an early stage. Further research is needed to investigate the effects of adjuvant therapy for preventing disease recurrence in these patients.

The goal of OTSCC surgical treatment is to complete tumor extirpation with sufficient safety margins. Histologically, a complete excision is defined as when safety margins of at least 5 mm are observed. On the other hand, if a safety margin of 1–4 mm is obtained, it is classified as a “close” margin, and if the margin is less than 1 mm, the tumor extirpation result is classified as “involved” margins. Close or involved surgical margins are considered high-risk surgical margins, and adjuvant radiotherapy can be performed to reduce local recurrence. However, in the case of pT1-2N0 OTSCC, the concept of high-risk surgical margins should be set differently by reflecting the characteristics of the disease. According to previous reports, a significant difference in survival outcome was observed in cases with a resection margin of 1 mm or less, and there was no significant difference in local recurrence-free survival or disease-free survival even in cases with close margins (<5 mm) or dysplasia at the margins. Also, in this study, no significant difference was observed in recurrence-free survival or overall survival when the treatment results of patients with safety margins <3 mm and patients with safety margins≥3 mm were analyzed. When resecting a tumor that occurs in the tongue, it is necessary to excise a sufficient amount of tissue for the purpose of curative treatment while at the same time excising the least amount possible to preserve function. Even if the head and neck surgeon takes special care to achieve the two conflicting goals, close margins of 5 mm or less are often reported after surgery. Although the National Comprehensive Cancer Network (NCCN) Head and Neck Cancer recommend adjuvant treatment in cases of such close margins, in cases of pT1-2N0 OTSCC patients, if there are no other adverse features in consideration of the characteristics of the disease, adjuvant radiotherapy could be omitted and a wait and see approach could be implemented. Second primary tumors observed in patients with head and neck cancer are caused by neocarcinogenesis and occur in new anatomical sites distinct from the index tumor. They are considered to be one of the major causes of treatment failure in oral cancer patients, and an incidence of 10%–18.4% has been reported in previous studies. In particular, patients with oral cancer on the tongue are known to develop second primary tumors more frequently than patients with other oral cancers. The risk of developing a second primary tumor is high in patients with heavy tobacco consumption, and the 5-year survival rate of patients is poor when a second primary tumor occurs regardless of the index tumor. However, little is known about the incidence and related factors of second primary tumors in early stage OTSCC patients. In this study, if the secondary tumor occurred at a distance of 2 cm or greater from the index tumor or with a time difference of 5 years or more, it was defined as a second primary lesion. A total of 13 cases (4.4%) of second primary tumors were observed during the study period, demonstrating a lower frequency compared to previous reports. All patients with second primary tumors were under the age of 60 years, and nonsmokers accounted for 76.9% of the patients with second primary tumors. Most of the patients had not previously received radiotherapy to the head and neck area. The high incidence of second primary tumors in patients without risk factors such as old age, smoking, and radiation therapy is presumed to be related to demographic factors or the molecular biological mechanism of early stage OTSCC. The most common cases occurred in the oral cavity in the oropharynx, hypopharynx, or esophagus. In the present study, 69% of cases occurred within 10 years, whereas 30.7% of cases occurred after 10 years. Therefore, it can be theorized that even in patients who have been treated for early stage OTSCC, periodic and long-term surveillance of the entire head and neck region including the oral cavity is essential.

Currently, adjuvant radiotherapy for the treatment of head and neck cancer is determined based on traditional clinical and pathological prognostic factors. However, existing prognostic factors alone do not provide a complete guideline for adjuvant therapy decision-making. Depending on the stage or location of the tumor, the existing prognostic factors may not match the treatment results or prognosis of the actual patients. If adjuvant radiation therapy is administered to all patients with relevant prognostic factors, the recurrence rate and mortality of the disease can be reduced, but some patients will inevitably receive unnecessary radiotherapy, which could lead to morbidity and complications. Recently, with the rapid development of sequencing technology, gene mutations related to OTSCC and genetic biomarker candidates related to poor prognosis have been reported. In addition, with the development of radiomics and machine learning techniques, radiomics signatures related to the prognosis of head and neck cancer have been developed, and prognostic prediction models have been reported. Through additional research on these
genetic or radiomics markers, the development of a predictive model that can more precisely predict the disease risk of pT1-2N0 early stage OTSCC patients and select high-risk patients in need of active treatment is necessary.

Since this study was conducted retrospectively, selection bias should be considered in the interpretation of results. Most of the patients participating in this study received surgery alone and only a minority received adjuvant radiotherapy, limiting the analysis of the effects of adjuvant radiotherapy. However, compared to other studies, a relatively large number of pT1-2N0 OTSCC patients were included and a sufficient follow-up period was provided; therefore, the findings of this study provide relevant insight into the treatment of OTSCC.

5 | CONCLUSION

In pT1-2N0 OTSCC, local or regional recurrences were the main recurrence pattern, and age and DOI > 5 mm were determined to be significant prognostic factors for recurrence or death. In relapsed patients, the 5-year treatment success rate after salvage treatment was low at 42.5%. The occurrence of secondary primary tumors was observed in relatively young patients, nonsmokers, and patients without a history of radiotherapy, and it was also one of the major factors affecting treatment failure in early stage OTSCC.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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