




ORIGINAL RESEARCH

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

Young M. Park MD, PhD¹  | Jae-Yol Lim MD, PhD¹  | Yoon W. Koh MD, PhD² |
Se-Heon Kim MD, PhD²  | Eun C. Choi MD, PhD²

¹Department of Otorhinolaryngology, Yonsei University College of Medicine, Gangnam Severance Hospital, Seoul, South Korea

²Department of Otorhinolaryngology, Yonsei University College of Medicine, Seoul, South Korea

Correspondence

Young M. Park, MD, PhD, Department of Otorhinolaryngology, Yonsei University College of Medicine, Gangnam Severance Hospital, 211 Eonju-ro, Gangnam-gu, Seoul 06273, South Korea.
Email: autumnfe@daum.net

Funding information

National Research Foundation of Korea, Grant/Award Number: NRF-2021R1C1C1012004

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

1 | INTRODUCTION

Oral cavity cancer is the sixth most common malignant tumor in the world with the tongue being the most common site.^{1,2} Oral tongue

squamous cell carcinoma (OTSCC) is often diagnosed at an early stage, but it has unfavorable prognosis compared to other oral cancers.^{3,4} In previous studies, early stage OTSCC exhibited a high loco-regional recurrence rate and poor overall survival and cancer-specific

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC on behalf of The Triological Society.

survival compared to oral cancers of other sites.⁴⁻⁶ 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.⁷⁻¹¹ 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.

TABLE 1 Clinical information of all patients ($n = 295$) enrolled in the study

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, well differentiated.

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

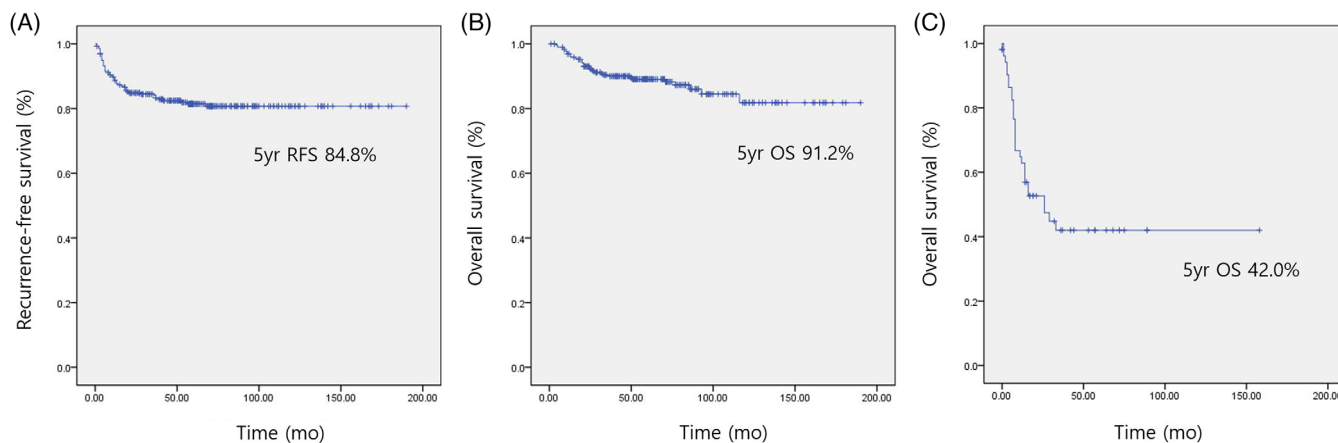


FIGURE 1 The 5-year recurrence-free survival rate was 84.8% (A) and the disease-specific survival rate was 91.2% (B). In recurrent cases, the 5-year survival rate after salvage treatment was 42.5% (C).

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).

3 | 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 due to postoperative pathological findings. Thirty-two patients were classified as cT2-3 before

surgery, but were down-staged to pT1 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

TABLE 2 Multivariate Cox regression analysis for recurrence-free and disease-specific survival on various factors

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.

TABLE 3 Univariate analysis of variables for predicting survival in recurrent cases

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.

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

TABLE 4 Multivariate Cox regression analysis for predicting survival in recurrent cases

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.

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.

4 | DISCUSSION

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.¹²⁻¹⁶ In this study, the recurrence rate of early stage OTSCC patients was 18%.^{17,18} 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 \geq 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 \geq 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.¹⁹⁻²³ 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 \geq 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.²⁴

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.²⁵ 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.^{26,27} In particular, patients with oral cancer on the tongue are known to develop second primary tumors more frequently than patients with other oral cancers.²⁸ 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.²⁹⁻³¹ 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.³²⁻³⁴ Through additional research on these

genetic or radiomics biomarkers, 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.

ACKNOWLEDGMENT

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT) (NRF-2021R1C1C1012004).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Young M. Park  <https://orcid.org/0000-0002-7593-8461>

Jae-Yol Lim  <https://orcid.org/0000-0002-9757-6414>

Se-Heon Kim  <https://orcid.org/0000-0002-6407-5859>

REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
- Kim YJ, Kim JH. Increasing incidence and improving survival of oral tongue squamous cell carcinoma. *Sci Rep*. 2020;10(1):7877.
- Rusthoven K, Ballonoff A, Raben D, Chen C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. *Cancer*. 2008;112(2):345-351.
- Farhood Z, Simpson M, Ward GM, Walker RJ, Osazuwa-Peters N. Does anatomic subsite influence oral cavity cancer mortality? A SEER database analysis. *Laryngoscope*. 2019;129(6):1400-1406.
- Rusthoven KE, Raben D, Song JI, Kane M, Altoos TA, Chen C. Survival and patterns of relapse in patients with oral tongue cancer. *J Oral Maxillofac Surg*. 2010;68(3):584-589.
- Jerjes W, Upile T, Petrie A, et al. Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. *Head Neck Oncol*. 2010;2:9.
- Ganly I, Goldstein D, Carlson DL, et al. Long-term regional control and survival in patients with "low-risk," early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumor thickness. *Cancer*. 2013;119(6):1168-1176.
- Almangush A, Bello IO, Coletta RD, et al. For early-stage oral tongue cancer, depth of invasion and worst pattern of invasion are the strongest pathological predictors for locoregional recurrence and mortality. *Virchows Arch*. 2015;467(1):39-46.
- Almangush A, Bello IO, Keski-Säntti H, et al. Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. *Head Neck*. 2014;36(6):811-818.
- Subramaniam N, Balasubramanian D, Low TH, et al. Role of adverse pathological features in surgically treated early oral cavity carcinomas with adequate margins and the development of a scoring system to predict local control. *Head Neck*. 2018;40(11):2329-2333.
- Wilson JM, Lumley C, Tan X, et al. Clinical outcomes of patients with pT1-T2N0 oral tongue squamous cell carcinoma. *Am J Clin Oncol*. 2021;44(5):200-205.
- Yanamoto S, Yamada S, Takahashi H, et al. Predictors of locoregional recurrence in T1-2N0 tongue cancer patients. *Pathol Oncol Res*. 2013;19(4):795-803.
- Al-Rajhi N, Khafaga Y, El-Husseiny J, et al. Early stage carcinoma of oral tongue: prognostic factors for local control and survival. *Oral Oncol*. 2000;36(6):508-514.
- Brennan S, Corry J, Kleid S, et al. Prospective trial to evaluate staged neck dissection or elective neck radiotherapy in patients with CT-staged T1-2 N0 squamous cell carcinoma of the oral tongue. *Head Neck*. 2010;32(2):191-198.
- Mücke T, Mitchell DA, Wagenpfeil S, Ritschl LM, Wolff KD, Kanatas A. Incidence and outcome for patients with occult lymph node involvement in T1 and T2 oral squamous cell carcinoma: a prospective study. *BMC Cancer*. 2014;14:346.
- Whitehurst JO, Droulias CA. Surgical treatment of squamous cell carcinoma of the oral tongue: factors influencing survival. *Arch Otolaryngol*. 1977;103(4):212-215.
- Jones KR, Lodge-Rigal RD, Reddick RL, Tudor GE, Shockley WW. Prognostic factors in the recurrence of stage I and II squamous cell cancer of the oral cavity. *Arch Otolaryngol Head Neck Surg*. 1992;118(5):483-485.
- Fridman E, Na'ara S, Agarwal J, et al. The role of adjuvant treatment in early-stage oral cavity squamous cell carcinoma: an international collaborative study. *Cancer*. 2018;124(14):2948-2955.
- Anderson CR, Sisson K, Moncrieff M. A meta-analysis of margin size and local recurrence in oral squamous cell carcinoma. *Oral Oncol*. 2015;51(5):464-469.
- Smits RW, Koljenović S, Hardillo JA, et al. Resection margins in oral cancer surgery: room for improvement. *Head Neck*. 2016;38(Suppl 1):E2197-E2203.
- Bernier J, Dommengue C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350(19):1945-1952.
- Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2004;350(19):1937-1944.
- Pfister DG, Spencer S, Adelstein D, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). *Head and Neck Cancers*. Version 3.2021. Fort Washington; 2021.
- Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006;102(1):67-76.

26. Cianfriglia F, Di Gregorio DA, Manieri A. Multiple primary tumours in patients with oral squamous cell carcinoma. *Oral Oncol.* 1999;35(2): 157-163.
27. van der Waal I, de Bree R. Second primary tumours in oral cancer. *Oral Oncol.* 2010;46(6):426-428.
28. Levi F, Te VC, Randimbison L, Maspoli M, La Vecchia C. Second primary oral and pharyngeal cancers in subjects diagnosed with oral and pharyngeal cancer. *Int J Cancer.* 2006;119(11):2702-2704.
29. Alsofyani AA, Dallol A, Farraj SA, et al. Molecular characterisation in tongue squamous cell carcinoma reveals key variants potentially linked to clinical outcomes. *Cancer Biomark.* 2020;28(2):213-220.
30. Xiao F, Dai Y, Hu Y, Lu M, Dai Q. Expression profile analysis identifies IER3 to predict overall survival and promote lymph node metastasis in tongue cancer. *Cancer Cell Int.* 2019;19:307.
31. Tian T, Zhang L, Tang K, et al. SEMA3A exon 9 expression is a potential prognostic marker of unfavorable recurrence-free survival in patients with tongue squamous cell carcinoma. *DNA Cell Biol.* 2020;39(4): 555-562.
32. Alfieri S, Romanò R, Bologna M, et al. Prognostic role of pre-treatment magnetic resonance imaging (MRI)-based radiomic analysis in effectively cured head and neck squamous cell carcinoma (HNSCC) patients. *Acta Oncol.* 2021;60(9):1192-1200.
33. Peng Z, Wang Y, Wang Y, et al. Application of radiomics and machine learning in head and neck cancers. *Int J Biol Sci.* 2021;17(2): 475-486.
34. Min Park Y, Yol Lim J, Woo Koh Y, Kim SH, Chang Choi E. Prediction of treatment outcome using MRI radiomics and machine learning in oropharyngeal cancer patients after surgical treatment. *Oral Oncol.* 2021;122:105559.

How to cite this article: Park YM, Lim J-Y, Koh YW, Kim S-H, Choi EC. Long-term outcomes of early stage oral tongue cancer: Main cause of treatment failure and second primary malignancy. *Laryngoscope Investigative Otolaryngology.* 2022; 7(6):1830-1836. doi:[10.1002/liv.2.943](https://doi.org/10.1002/liv.2.943)