



Treatment outcomes and prognostic factors in oral tongue cancer: a 20-year retrospective study at the National Cancer Center, South Korea

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Abstract (J Korean Assoc Oral Maxillofac Surg 2022;48:192-200)

Objectives: This study aimed to analyze the treatment outcomes and to evaluate the clinicopathological prognostic factors of oral tongue cancer.

Patients and Methods: We retrospectively analyzed treatment results and prognostic factors in 205 patients with oral tongue squamous cell carcinoma who were admitted to the National Cancer Center, South Korea, between January 2001 and December 2020. The patients were treated with surgery and postoperative, definitive radiotherapy (RT) or chemoradiotherapy (CRT).

Results: Eighteen patients (8.8%) were treated with curative RT or CRT, while the rest (91.2%) were treated with surgery with or without postoperative RT or CRT. The median follow-up period was 30 months (range, 0-234 months). The 5-year overall survival (OS) and 5-year disease-free survival (DFS) were 72% and 63%, respectively. Multivariate analysis revealed that a positive neck nodal status (N1, N2-3) was significantly associated with poorer 5-year OS and DFS, while perineural invasion was associated with poorer 5-year DFS.

Conclusion: Cervical metastasis and perineural invasion are significant prognostic predictors, and combination treatments are necessary for improving OS and DFS in patients with these factors.

Key words: Tongue, Oral cancer, Treatment outcome, Prognostic factors

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I. Introduction

Oral cavity cancer is common, with an estimated 350,000 new cases and 170,000 deaths annually worldwide¹. The most common histological type of oral cavity cancer is squamous cell carcinoma (SCC), with the tongue being the most frequent site of occurrence^{2,3}. The standard treatment for oral cavity cancer is surgery. However, in locally or locoregionally advanced disease, combined-modality therapy with surgery followed by adjuvant radiotherapy (RT) or chemoradiotherapy (CRT) is indicated⁴. Despite a stable annual incidence of oral cavity cancer in South Korea, the incidence

of tongue cancer has increased significantly in both men and women, particularly in younger patients (≤ 40 years)⁵. Furthermore, there have been no improvements in 5-year overall survival (OS) and disease-free survival (DFS), which remain in the range of 50%-60%^{6,7}. Several factors that negatively affect the clinicopathological prognosis of oral tongue squamous cell carcinoma (OTSCC) have been identified, including pathological T-stage, N-stage perineural invasion (PNI), and extranodal extension (ENE)^{8,9}. Moreover, OTSCC is characterized by a high frequency of lymphatic metastasis, a high risk of recurrence, and the possibility of developing drug resistance to chemotherapy during treatment¹⁰. Since the incidence of OTSCC is on the rise and treatment outcomes in OTSCC are reportedly poorer compared to those of carcinomas arising in other oral cavity regions^{11,12}, it is important to identify the clinicopathological factors associated with carcinomas in this site. Therefore, this retrospective study aimed to assess the potential clinicopathological factors that could affect treatment outcomes in OTSCC with the goal of making recommendations for the management of tongue cancers.

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II. Patients and Methods

1. Patient selection

This study was a retrospective, monocentric, independent analysis of 205 patients with primary OTSCC who were treated and followed-up at the Oral Oncology Clinic of the National Cancer Center (Goyang, Korea) from January 2001 to December 2020. This study was reviewed and approved by the Institutional Review Board of the National Cancer Center, South Korea (NCC2022-0095). Demographic data, risk factors, histopathological features, and disease status were obtained from the medical records. The inclusion criteria involved patients with primary OTSCC, without second primaries other than mobile tongue cancer, and who had undergone primary surgical resection of the primary tumor and regional lymph nodes or definitive RT or CRT. The exclusion criteria included neoadjuvant chemotherapy administered prior to primary surgical resection, surgical resection performed with palliative or debulking intent, recurrent OTSCC, and a history of treatment including surgery or RT/CRT at another center. Although the seventh edition of the American Joint Committee on Cancer's (AJCC) staging manual was used for staging and management, the eighth edition was used for analyzing the prognostic factors in this study. Patients treated with definitive RT or CRT were staged clinically, while those treated with primary surgery were staged pathologically. Adjuvant RT was administered within 4-6 weeks of surgery depending on the high-risk features found on the histopathology of the resected specimen. As per institutional policy, pathological T3 or T4 stages, node positivity, and critical resection margins within 5.0 mm were considered indications for adjuvant RT based on the decision of the treating physician. Adjuvant CRT was administered to patients with positive resection margins or ENE.

2. Statistical analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata 17.0 (Stata Corp., College Station, TX, USA). The endpoints were OS and DFS, which were calculated through the Kaplan–Meier method. Univariate analysis was performed using demographic and clinicopathological factors, while multivariate Cox proportional hazard models were used to identify factors independently associated with OS and DFS. A *P*-value <0.05 was considered significant.

Table 1. Demographic and clinicopathological data of the cohort

Variable	Value
Sex	
Female	89 (43.4)
Male	116 (56.6)
Age	
≤40 yr	33 (16.1)
>40 yr	172 (83.9)
Smoking	
No	106 (51.7)
Yes	99 (48.3)
Drinking	
No	103 (50.2)
Yes	102 (49.8)
T stage	
T1 or T2	128 (62.4)
T3 or T4	77 (37.6)
N stage	
N0	124 (60.5)
N1	31 (15.1)
N2 or N3	50 (24.4)
pTNM stage	
Stage I or II (early)	100 (48.8)
Stage III or IV (advanced)	105 (51.2)
Treatment	
Surgery only	110 (53.7)
Surgery+RT/CT	77 (37.6)
RT/CT	18 (8.8)
Extranodal extension	
Absent	165 (80.5)
Present	40 (19.5)
Differentiation grade	
Well	97 (47.3)
Moderate	76 (37.1)
Poor	24 (11.7)
N/A	8 (3.9)
Depth of invasion	
≤5 mm	65 (31.7)
6-10 mm	37 (18.0)
>10 mm	71 (34.6)
N/A	32 (15.6)
Perineural invasion	
Absent	149 (72.7)
Present	38 (18.5)
N/A	18 (8.8)
Lymphovascular invasion	
Absent	144 (70.2)
Present	43 (21.0)
N/A	18 (8.8)
Resection status	
Close (<5 mm)	63 (30.7)
Safe (≥5 mm)	124 (60.5)
N/A	18 (8.8)
Recurrence	
No	145 (70.7)
Yes	60 (29.3)

(RT: radiotherapy, CT: chemotherapy, N/A: not available)

Values are presented as number (%).

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III. Results

1. Demographic characteristics

The median age of the patients was 57 years (range, 19-92 years), and the median follow-up period was 30 months (range, 0-234 months). Table 1 presents an overview of the demographic and clinicopathological data of the cohort. A total of 187 patients (91.2%) underwent primary surgical resection with or without adjuvant therapy (RT/CRT), while 18 patients (8.8%) were treated with definitive RT or CRT. Overall, disease control failed in 60 patients (29.3%) as observed during follow-up. The median duration of disease control failure was 6 months in this group. The most frequent type of recurrence was locoregional (25 patients, 41.7%). The most common site of distant metastasis was the lung.

2. Survival outcomes and prognostic factors associated with OS

The median duration of OS was 30 months. The 5-year OS was 72%. (Fig. 1) The univariate analysis revealed that the following factors were significantly associated with poor prognosis in terms of OS: increasingly positive pN stages (N1, N2-3); advanced-stage disease (III-IV); treatment modality (adjuvant RT or CRT, definitive RT/CRT); moderately (G2) to poorly differentiated (G3) tumors; depth of invasion (DOI) >10 mm; advanced T stage (T3-4); PNI, lymphovascular invasion (LVI), and ENE. However, the multivariate analysis revealed that pN1 (hazard ratio [HR], 4.684; 95% confidence interval [CI], 1.975-11.111; $P<0.001$) and pN2-3 (HR, 7.640;

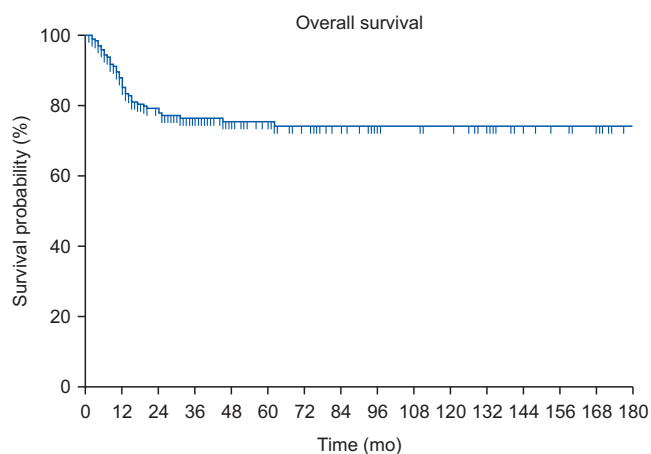


Fig. 1. Kaplan–Meier curve of overall survival. Min-Gyeong Kim et al: Treatment outcomes and prognostic factors in oral tongue cancer: a 20-year retrospective study at the National Cancer Center, South Korea. J Korean Assoc Oral Maxillofac Surg 2022

95% CI, 3.588-16.266; $P<0.001$) were significantly associated with poorer OS. (Table 2, Fig. 2) Unlike other studies, age, sex, and addictions (smoking and drinking) were not significant predictors of OS.

3. Survival outcomes and prognostic factors associated with DFS

The median duration of DFS was 25 months. The 5-year DFS was 63%. (Fig. 3) The univariate analyses revealed that the following factors were significantly associated with poor prognosis in terms of DFS: increasing pN stages (N1, N2-3), treatment modality (adjuvant RT or CRT, definitive RT/CRT), PNI, advanced disease stage (III-IV), DOI >10 mm, G3 tumors, ENE, advanced T stage (T3-4), and marginal status (close or involved). However, multivariate analysis revealed that pN1 (HR, 2.499; 95% CI, 1.148-5.442; $P=0.021$), pN2-3 (HR, 4.022; 95% CI, 2.124-7.614; $P<0.001$), and PNI (HR, 2.145; 95% CI, 1.192-3.860; $P=0.0109$) exhibited significant negative effects on DFS. (Table 3, Fig. 4, 5) Similar to OS, age, sex, and addictions (smoking and drinking) did not significantly affect DFS.

IV. Discussion

In this study, we aimed to ascertain OS and DFS rates in tongue cancer and to identify the clinicopathological factors predicting treatment outcomes in this disease. Our study of survival outcomes revealed 5-year OS and DFS of 72% and 63%, respectively. These results are encouraging given that the corresponding results in previous reports are in the range of 5%-60%^{6-8,11}. These results could be attributed to the post-operative treatment strategies, including adjuvant therapy (RT/CRT), implemented by a multidisciplinary team, as well as to surgical treatment with concomitant microvascular reconstruction, which enabled complete (R0) resection and improved patient quality of life. Moreover, it is believed that the relatively high frequency at which elective neck dissection was performed in this cohort also contributed to this favorable outcome.

Previous reports have discussed several clinicopathological parameters in relation to survival and disease progression in oral squamous cell carcinoma (OSCC), but only a few focused on tongue cancer. For patients with high-risk factors, multimodality treatments are mandatory for better prognoses^{6,13-15}. In the univariate analysis, factors significantly affecting prognosis included pN status (N1, N2-3), advanced

Table 2. Cox regression for overall survival

Variable	No. of patients	No. of events	Univariable Cox regression		Multivariable Cox regression (backward selection)	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Sex						
Female	89	22	1 (ref.)			
Male	116	25	0.962 (0.543-1.707)	0.8959		
Age						
≤40 yr	33	11	1 (ref.)			
>40 yr	172	36	0.685 (0.349-1.347)	0.2727		
Addictions						
Absent	83	16	1 (ref.)			
Present	122	28	1.313 (0.720-2.394)	0.3739		
T stage						
T1 or T2	128	17	1 (ref.)			
T3 or T4	77	30	3.302 (1.820-5.993)	<0.0001		
N stage						
N0	124	10	1 (ref.)		1 (ref.)	
N1	31	11	5.316 (2.256-12.528)	0.0001	4.684 (1.975-11.111)	0.0005
N2 or N3	50	26	8.616 (4.148-17.896)	<0.0001	7.640 (3.588-16.266)	<0.0001
TNM stage						
Stage I or II (early)	100	6	1 (ref.)			
Stage III or IV (advanced)	105	41	7.925 (3.361-18.686)	<0.0001		
Treatment						
Surgery only	110	10	1 (ref.)			
Surgery+RT/CT	77	32	5.433 (2.668-11.063)	<0.0001		
RT/CT	18	5	5.219 (1.778-15.319)	0.0026		
Differentiation (missing 8 cases)						
Well	97	14	1 (ref.)		1 (ref.)	
Moderate	76	21	2.233 (1.133-4.399)	0.0203	1.932 (0.972-3.840)	0.0604
Poor	24	12	4.220 (1.946-9.149)	0.0003	2.181 (0.981-4.852)	0.0558
Depth of invasion (missing 32 cases)						
≤5 mm	65	6	1 (ref.)			
6-10 mm	37	7	2.005 (0.674-5.968)	0.2113		
>10 mm	71	26	4.653 (1.913-11.315)	0.0007		
Lymphovascular invasion (missing 18 cases)						
Absent	144	27	1 (ref.)			
Present	43	15	1.980 (1.053-3.724)	0.0339		
Perineural invasion (missing 18 cases)						
Absent	149	23	1 (ref.)			
Present	38	19	3.951 (2.146-7.276)	<0.0001		
Extranodal extension						
Absent	165	22	1 (ref.)			
Present	40	25	5.701 (3.209-10.126)	<0.0001		
Resection status (missing 18 cases)						
Close (<5 mm)	63	21	1 (ref.)			
Safe (≥5 mm)	124	21	0.508 (0.278-0.931)	0.0283		

(HR: hazard ratio, CI: confidence interval, ref.: reference, RT: radiotherapy, CT: chemotherapy)

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disease stage (III-IV), treatment modality (adjuvant RT or CRT, definitive RT/CRT), moderately (G2) to poorly differentiated (G3) tumors, DOI >10 mm, advanced T stage (T3-4), PNI, ENE, and close marginal status. Multivariate analysis also revealed that the pN status (N1, N2-3) was the most important predictor of both OS and DFS. Moreover, PNI had a significant negative effect on DFS.

Cervical metastasis is reportedly a significant predictor of poor survival in OTSCC. Both univariate and multivariate analyses revealed that nodal metastasis with increasing pN stages significantly affected OS and DFS. In locoregionally

advanced disease, the survival rate decreased by <50%¹¹. Our study showed that nodal metastasis decreased 5-year OS and DFS from 93.7% to 50.7% and 85.1% to 47%, respectively, confirming these findings. Considering that approximately 60% of the instances of disease control failure occurred locoregionally and regionally in this study and considering the high rate of occult metastasis at this site^{8,16-18}, active management of regional lymphatics with elective neck dissection should be considered. In the present study, occult nodal metastasis was observed in 17.3% of patients, including patients with T1-2 tumors. The 5-year DFS was better in patients who

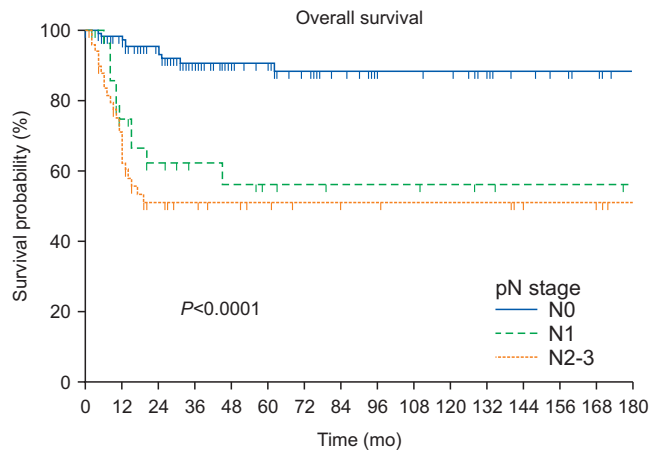


Fig. 2. Kaplan–Meier curve of overall survival by neck status. Min-Gyeong Kim et al: Treatment outcomes and prognostic factors in oral tongue cancer: a 20-year retrospective study at the National Cancer Center, South Korea. J Korean Assoc Oral Maxillofac Surg 2022

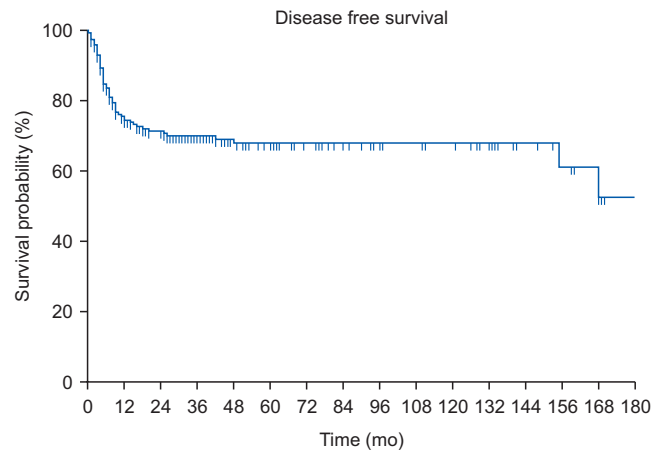


Fig. 3. Kaplan–Meier curve of overall disease-free survival. Min-Gyeong Kim et al: Treatment outcomes and prognostic factors in oral tongue cancer: a 20-year retrospective study at the National Cancer Center, South Korea. J Korean Assoc Oral Maxillofac Surg 2022

underwent neck dissections compared to those who did not undergo the procedure, even with early-stage disease (I, II).

PNI and LVI have been reported to adversely affect treatment outcomes in OSCC. However, a high level of heterogeneity exists in the detection criteria among studies. PNI is classified as tumor cells invading nerve sheaths or surrounding at least one-third of the circumference of the nerve, while LVI is defined as the presence of tumor cells within or adjacent to the vessels. Both of these factors can involve subjectivity in the diagnosis¹⁹. Several studies have confirmed that PNI and LVI possess a high prognostic value for decreased survival in OTSCC^{8,20,21}. The results of the univariate analyses in our study were consistent with such findings. However, the results of the multivariate analysis, apart from those related to PNI in DFS, were not significant in terms of OS and DFS. The identification of PNI as an independent prognosticator in our study supports the finding that the perineural space acts as a low-resistance route for progression of SCC within connective tissue-innervating peripheral nerves²².

Regarding the effect of tumor grade on OS and DFS, it is widely accepted that well-differentiated tumors (G1) have a better prognosis in OSCC compared with moderately to poorly differentiated tumors (G2-3)¹⁸. However, most studies do not consider the histological grade to be a significant predictor of treatment outcomes^{9,14,20,23}. Our study showed that OS and DFS decreased with increasing tumor grade (from G1 to G3). This finding was significant only in the univariate analysis. Further randomized multi-institutional prospective studies are necessary to ascertain the effect of tumor grade on prognosis.

Age and sex have been suggested to be possible risk factors affecting treatment outcomes. Some studies have reported that the prognosis in younger patients (≤ 40 years of age) is poorer compared to the elderly, justifying more aggressive treatment in this subgroup²³⁻²⁵. However, other studies have highlighted the role of aging in poor prognosis and the negative effect of comorbidities in the elderly^{26,27}. Likewise, regarding sex as a prognostic factor, various studies have produced varying results, ranging from those indicating that female sex is associated with better survival^{28,29} to those exhibiting no significant difference between the sexes³⁰. The current study revealed no significant effects of age and sex on OS and DFS, in line with the findings of the latter studies. Therefore, further well-defined studies are warranted to elucidate the prognostic effects of age and sex on OTSCC.

Many studies have shown that smoking and alcohol consumption are prognostic predictors in head and neck cancers^{16,31,32}. However, many other studies have presented conflicting results, revealing no significant association between survival time and habitual factors such as smoking and alcohol consumption^{33,34}. Upon examining OTSCC cases, no association was observed between these habits and an increased risk of reduced survival time^{20,21}. Similar to the findings in the latter studies, these habits were not identified as prognostic factors in our study. However, the high number of cases in which the association with these habits was falsely classified as negative has to be considered.

In OTSCC, the T and N stages were independent indicators of prognosis even though they are interrelated. A higher T stage leads to an increase in the rate of occult metastas-

Table 3. Cox regression for disease-free survival

Variable	No. of patients	No. of events	Univariable Cox regression		Multivariable Cox regression (backward selection)	
			HR (95% CI)	P-value	HR (95% CI)	P-value
Sex						
Female	89	34	1 (ref.)			
Male	116	34	0.762 (0.474-1.227)	0.2638		
Age						
≤40 yr	33	13	1 (ref.)			
>40 yr	172	55	0.867 (0.472-1.592)	0.6456		
Addictions						
Absent	83	21	1 (ref.)			
Present	122	39	1.337 (0.796-2.246)	0.2718		
T stage						
T1 or T2	128	32	1 (ref.)			
T3 or T4	77	36	2.072 (1.285-3.341)	0.0028		
N stage						
N0	124	23	1 (ref.)		1 (ref.)	
N1	31	14	2.956 (1.519-5.753)	0.0014	2.499 (1.148-5.442)	0.0210
N2 or N3	50	31	4.553 (2.645-7.836)	<0.0001	4.022 (2.124-7.614)	<0.0001
TNM stage						
Stage I or II (early)	100	18	1 (ref.)			
Stage III or IV (advanced)	105	50	3.150 (1.834-5.412)	<0.0001		
Treatment						
Surgery only	110	19	1 (ref.)			
Surgery+RT/CT	77	39	3.357 (1.932-5.833)	<0.0001		
RT/CT	18	10	4.899 (2.271-10.566)	<0.0001		
Differentiation (missing 8 cases)						
Well	97	25	1 (ref.)			
Moderate	76	27	1.626 (0.942-2.808)	0.0812		
Poor	24	13	2.486 (1.270-4.864)	0.0078		
Depth of invasion (missing 32 cases)						
≤5 mm	65	12	1 (ref.)			
6-10 mm	37	11	1.625 (0.716-3.693)	0.2459		
>10 mm	71	32	2.894 (1.488-5.628)	0.0017		
Lymphovascular invasion (missing 18 cases)						
Absent	144	40	1 (ref.)			
Present	43	18	1.612 (0.924-2.814)	0.0926		
Perineural invasion (missing 18 cases)						
Absent	149	35	1 (ref.)		1 (ref.)	
Present	38	23	3.375 (1.987-5.732)	<0.0001	2.145 (1.192-3.860)	0.0109
Extranodal extension						
Absent	165	41	1 (ref.)			
Present	40	27	3.836 (2.345-6.274)	<0.0001		
Resection status (missing 18 cases)						
Close (<5 mm)	63	27	1 (ref.)			
Safe (≥5 mm)	124	31	0.547 (0.326-0.918)	0.0224		

(HR: hazard ratio, CI: confidence interval, ref.: reference, RT: radiotherapy, CT: chemotherapy)

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ses^{20,21,35}, while a higher N-stage is associated with the development of distant metastases, particularly with multiple organ involvement or ENE³⁶. Our study found that the prognostic value of a higher T stage is high in predicting decreased OS and DFS in cases when the T stage increases from early (T1-2) to advanced (T3-4) stages. This result is consistent with those of other studies^{20,21,37}. However, this factor was not a significant independent predictor in multivariate analysis.

Since DOI was a significant prognostic predictor and was included in the AJCC tumor-node-metastasis system (eighth edition), the staging system was redefined based on the DOI

cut off values of 5 and 10 mm. A DOI greater than 10 mm was significantly associated with decreased 5-year survival and increased risk of occult metastasis¹⁷. In this cohort, increasing DOI was significantly associated with poor prognosis in terms of decreased 5-year OS and DFS in the univariate analysis. However, in multivariate analysis, this finding was not significant. This result could be attributed to the inconsistency and subjectivity in histopathological reporting by different pathologists.

ENE is associated with poor prognosis in terms of locoregional failure and distant metastasis in OSCC, indications for

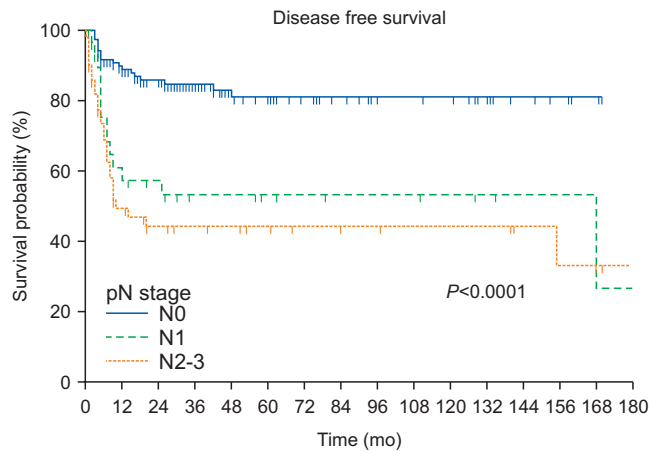


Fig. 4. Kaplan–Meier curve of disease-free survival by neck status. *Min-Gyeong Kim et al: Treatment outcomes and prognostic factors in oral tongue cancer: a 20-year retrospective study at the National Cancer Center, South Korea. J Korean Assoc Oral Maxillofac Surg 2022*

concurrent CRT^{19,38}. This was observed in several retrospective studies on OTSCC^{6,8,9,11}, including our cohort. Most patients with ENE in this cohort, along with involved resection margins, underwent CRT. Although the univariate analysis revealed a strong association between ENE and poor outcomes in terms of both OS and DFS in our cohort, the same association was found only in relation to OS in the multivariate analysis.

Surgery with or without adjuvant RT or CRT is the standard treatment for resectable OTSCC, with a high survival rate of up to 70% in the early stages³⁸. The importance of clear surgical margins has been the main focus of surgical oncology, considering that positive and close margins have a strong negative effect on survival. Several studies have shown the benefit of clear margins in OTSCC⁸. The results of our univariate analysis indicated that clear margins exhibited a significant effect on OS and DFS compared to close (5 mm) margins. The multivariate analysis did not demonstrate a significant effect of surgical margins on OS and DFS.

This study had several limitations. A potential bias could have resulted from its retrospective study design. Although our clinic adopted standardized treatment guidelines, differences may have arisen depending on the individual experiences of the treating oncologists. Since the histopathological characteristics of the analyzed samples were recorded by different pathologists over an extended period of time, standardization of pathologic assessments should be a subject for future studies.

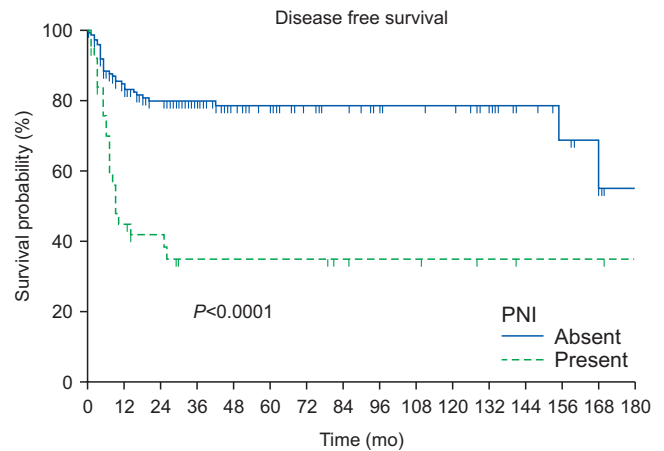


Fig. 5. Kaplan–Meier curve of disease-free survival by presence of perineural invasion (PNI). *Min-Gyeong Kim et al: Treatment outcomes and prognostic factors in oral tongue cancer: a 20-year retrospective study at the National Cancer Center, South Korea. J Korean Assoc Oral Maxillofac Surg 2022*

V. Conclusion

In conclusion, the univariate analyses in this study revealed that survival outcomes in OTSCC were affected by increasing T stage, pN status, ENE, moderately to poorly differentiated tumors, LVI, PNI, and marginal status. These factors were reported in previous studies^{30,31,38}. However, our multivariate analysis revealed that pN status (N1, N2-3) is significantly associated with poor prognosis in terms of OS and DFS and with PNI in terms of DFS. The rate of primary cervical metastases in this cohort was greater than 39%, while that of occult metastases was 17%. These results advocate the importance of regional control along with the need for elective neck dissection and postoperative adjuvant therapy in patients with neck node positivity.

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Authors' Contributions

M.G.K. and Y.S.C. participated in data collection and wrote the manuscript. S.M.Y., J.H.K., and H.J.O. participated in the design of the study. J.H.L., J.Y.P., and S.W.C. participated in the study design, coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was conducted after obtaining approval from the Institutional Review Board of the National Cancer Center, South Korea (NCC2022-0095), and informed consent was waived.

Conflict of Interest

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

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