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Analysis of prognostic factors through survival rate analysis of oral squamous cell carcinoma patients treated at the National Cancer Center: 20 years of experience

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Abstract (J Korean Assoc Oral Maxillofac Surg 2022;48:284-291)

Objectives: This study aimed to analyze the clinicopathological prognostic factors affecting the survival of patients with oral squamous cell carcinoma (OSCC).

Materials and Methods: A retrospective study was conducted on patients with OSCC who received treatment at the Oral Oncology Clinic of the National Cancer Center (NCC) from June 2001 to December 2020. The patients' sex, age, primary site, T stage, node metastasis, TNM staging, perineural invasion (PNI), lymphovascular invasion (LVI), differentiation, surgical resection margin, smoking, and drinking habits were investigated to analyze risk factors. For the univariate analysis, a Kaplan–Meier survival analysis and log-rank test were used. Additionally, for the multivariable analysis, a Cox proportional hazard model analysis was used. For both analyses, statistical significance was considered when $P<0.05$.

Results: During the investigation period, 407 patients were received surgical treatment at the NCC. Their overall survival rate (OS) for five years was 70.7%, and the disease-free survival rate (DFS) was 60.6%. The multivariable analysis revealed that node metastasis, PNI, and differentiation were significantly associated with poor OS. For DFS, PNI and differentiation were associated with poor survival rates.

Conclusion: In patients with OSCC, cervical node metastasis, PNI, and differentiation should be considered important prognostic factors for postoperative survival.

Key words: Oral squamous cell carcinoma, Treatment outcome, Prognostic factor, Survival analysis

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I. Introduction

Oral cancer accounts for approximately 90% of oral squamous cell carcinoma (OSCC) and occurs anywhere in the oral cavity, such as the tongue, buccal mucosa, and gingiva. Approximately 377,000 new cases of oral cancer and 177,000 deaths occur annually worldwide[1,2]. However, patients with oral cancer have a relatively similar or poorer prognosis than those with other cancers, even though it occurs in a relatively easy-to-detect organ. Between 2015 and 2019, the five-year observed survival rate for all cancers in Korea was 65.6%. During the same period, the five-year observed survival rate for lip, oral, and pharyngeal cancers (C00-C14, ICD-10) was 64.3%[3]. The survival rate of cancers in the oral cavity is 48%-70%[4,5]. There are several prognostic factors after cancer therapy; however, the most widely used prognostic factor for patients with oral cancer is TNM staging according to the American Joint Committee on Cancer (AJCC). This prognostic factor relies on tumor size, metastasis to adjacent lymph nodes, and remote metastasis to other organs[6]. However, even if a cancer is classified at the same stage after treatment, post-treatment prognosis can vary for each patient. Therefore, other risk factors for prognosis should also be considered for these patients[7]. In this study, we retrospectively analyzed patients with OSCC who underwent surgical treatment at the Oral Oncology Clinic of the National Cancer Center (NCC) over a 20-year period between 2001 and 2020 to investigate

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the relative survival rate and risk factors affecting their survival.

II. Materials and Methods

A retrospective study was conducted on patients diagnosed with OSCC who underwent surgical treatment with or without adjuvant radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) at the Oral Oncology Clinic of the NCC in South Korea between June 2001 and December 2020. This study was reviewed and approved by the Institutional Review Board (IRB) of the NCC (IRB No. NCC2022-0214). Surgery was perfomed with wide excision of the primary site with or without neck dissection. Patients with clinically single node metastasis or negative nodal disease, where there is high risk of occult metastasis, underwent selective neck dissection, whereas patients with multiple node metastasis underwent modified radical neck dissection. The patients' clinicopathological data (sex, age, primary site, T stage, node metastasis, TNM stage, perineural invasion [PNI], lymphovascular invasion [LVI], differentiation, surgical resection margin, smoking, and drinking habits) were obtained from medical records, including surgical records, biopsy reports, and radiographic images. TNM classification was performed based on the AJCC 8th Oral Cancer Classification Criteria published in 2017, and pathological TNM (pTNM) data were used in this study. The criteria for postoperative RT included T3 or T4 tumors, multiple metastatic neck nodes, or a close resection margin within 5 mm. Adjuvant CCRT was considered when a positive resection margin or extra-nodular extension (ENE) was observed.

After treatment, follow-up procedures included neck enhanced computed tomography (CT), posteroanterior chest X-ray (Chest PA), and chest CT at intervals of three to six months, and positron emission tomography (PET)-CT at one-year intervals. Any case confirmed by imaging or biopsy during follow-up was considered recurrence. The patient's death was confirmed based on medical records. Causes of death included disease progression, other primary cancers, or underlying diseases. The overall survival rate (OS) was calculated as the proportion of patients who survived from the day of surgery. Furthermore, the disease-free survival rate (DFS) was defined as the proportion of patients who survived without any signs or symptoms of recurrence after surgery.

Prism 9 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. The univariate analysis of five-year OS and DFS were performed using the Kaplan–Meier survival analysis, and the survival rates according to clinicopathologic factors were compared respectively. The statistical significance of the survival rate by risk factor was investi-

Table 1. Distribution of oral squamous cell carcinoma among patients according to clinicopathological characteristics (n=407)

Variable	Value
Sex	
Male	261 (64.1)
Female	146 (35.9)
Age	
<40 yr	37 (9.1)
≥40 yr	370 (90.9)
Primary site	
Lip	9 (2.2)
FOM	28 (6.9)
Tongue	199 (48.9)
Lower gingiva	51 (12.5)
Upper gingiva	32 (7.9)
RMT	34 (8.4)
Buccal cheek	39 (9.6)
Palate	8 (2.0)
Others	7 (1.7)
T stage	
T1	101 (24.8)
T2	96 (23.6)
T3	114 (28.0)
T4	95 (23.3)
Node metastasis	
N0	250 (61.4)
N+	156 (38.3)
TNM stage	
Early (I+II)	146 (35.9)
Advanced (III+IV)	261 (64.1)
Perineural invasion (n=384)	
P–	322 (83.9)
P+	62 (16.1)
Lymphovascular invasion (n=396)	
L–	310 (78.3)
L+	86 (21.7)
Differentiation (n=405)	
Well	189 (46.7)
Moderate	162 (40.0)
Poor	54 (13.3)
Surgical resection margin (n=392)	
Clear (≥0.5 cm)	214 (54.6)
Close (<0.5 cm)	178 (45.4)
Treatment modality	
Surgery only	209 (51.4)
Surgery+PORT	173 (42.5)
Surgery+PO-CCRT	25 (6.1)
Smoking	
No	187 (45.9)
Yes	220 (54.1)
Drinking	
No	187 (45.9)
Yes	220 (54.1)
Recurrence	
No	269 (66.1)
Yes	138 (33.9)

(FOM: floor of mouth, RMT: retromolar trigone, PORT: postoperative radiotherapy, PO-CCRT: postoperative concurrent chemoradiotherapy)
Values are presented as number (%).

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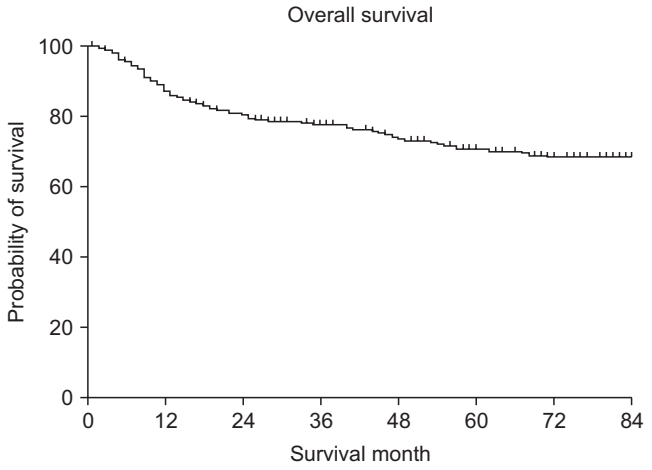

Fig. 1. Kaplan–Meier curve of overall survival.
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gated using the log-rank test. For the multivariable analysis, a Cox Proportional Hazard Model analysis was used. In both analyses, statistical significance was considered when $P<0.05$.

III. Results

A total of 407 patients received surgical treatment at the NCC during the study period. The distribution of the clinical and pathological data is shown in Table 1. The patients included 261 male patients (64.1%) and 146 female patients (35.9%). The most common primary site was the tongue (199 patients, 48.9%), followed by the lower gingiva, buccal cheek, retromolar trigone (RMT), upper gingiva, floor of mouth (FOM), lip, palate, and others. A total of 146 patients (35.9%) had early-stage disease, whereas 261 (64.1%) had advanced-stage disease. The disease recurred in 138 patients (33.9%), while 269 patients (66.1%) remained recurrence free.

The five-year OS was 70.7%.(Fig. 1) In the univariate analysis, T stage, node metastasis, TNM stage, PNI, LVI, differentiation, surgical resection margin, and smoking were significantly associated with a poor prognosis.(Table 2) In particular, node metastasis showed differences of 80.5% and 54.7% for N0 and N+, respectively ($P<0.001$).(Fig. 2) PNI also showed a significant difference in survival rates of 75.6% and 41.9% for P– and P+, respectively ($P<0.001$).(Fig. 3)

The five-year DFS was 60.6%.(Fig. 4) Factors indicating a significant difference in DFS were T stage, node metastasis, TNM stage, PNI, LVI, differentiation, and surgical resec-

Table 2. Univariate analysis for overall survival

Variable	5-year overall survival			
	%	Hazard ratio	95% CI	*P*-value
Total	70.7			
Sex				0.447
Male	69.8			
Female	72.2			
Age				0.331
<40 yr	62.4			
≥40 yr	71.4			
Primary site				0.404
Lip	100.0			
FOM	70.0			
Tongue	72.0			
Lower gingiva	69.5			
Upper gingiva	52.3			
RMT	69.9			
Buccal cheek	76.0			
Palate	60.0			
Others	44.4			
T stage (missing 1 case)				<0.001
T1	84.5			
T2	74.9	2.006	1.024-4.095	
T3	62.3	2.969	1.614-5.818	
T4	60.7	3.408	1.842-6.704	
Node metastasis (missing 1 case)				<0.001
N0	80.5			
N+	54.7	3.108	2.107-4.637	
TNM stage (missing 1 case)				<0.001
Early (I+II)	87.2			
Advanced (III+IV)	60.8	3.835	2.317-6.781	
Perineural invasion (missing 23 cases)				<0.001
P–	75.6			
P+	41.9	3.029	1.962-4.580	
Lymphovascular invasion (missing 11 cases)				<0.001
L–	75.8			
L+	49.2	2.528	1.675-3.758	
Differentiation (missing 2 cases)				<0.001
Well	81.5			
Moderate	66.2	1.841	1.185-2.885	
Poor	34.5	3.835	2.257-6.423	
Surgical resection margin (missing 15 cases)				0.025
Clear (≥0.5 cm)	75.7			
Close (<0.5 cm)	65.2	1.570	1.056-2.348	
Treatment modality				<0.001
Surgery only	81.4			
Surgery+PORT	57.9			
Surgery+PO-CCRT	77.0			
Smoking				0.020
No	75.7			
Yes	66.5	1.601	1.080-2.413	
Drinking				0.939
No	70.4			
Yes	71.1			
Recurrence				<0.001
No	89.5			
Yes	40.0			

(CI: confidence interval, FOM: floor of mouth, RMT: retromolar trigone, PORT: postoperative radiotherapy, PO-CCRT: postoperative concurrent chemoradiotherapy)
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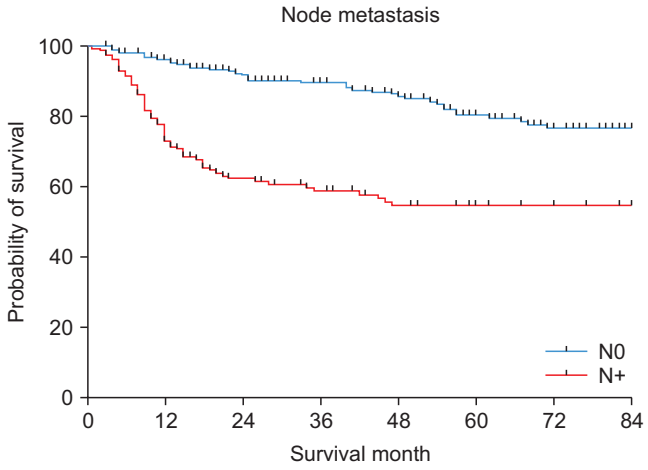

Fig. 2. Kaplan–Meier curve of overall survival by node metastasis.
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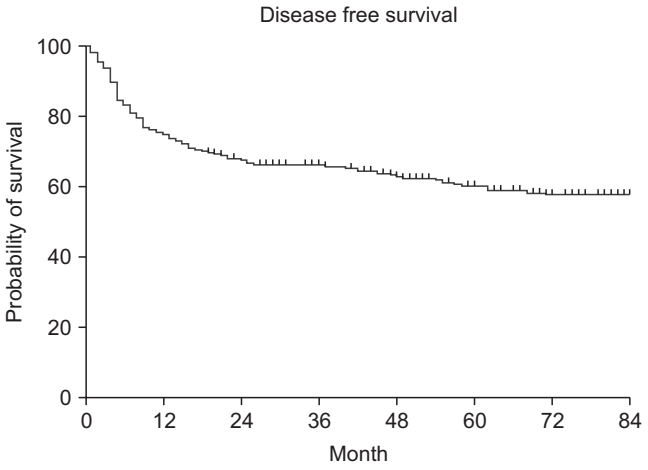

Fig. 4. Kaplan–Meier curve of disease free survival.
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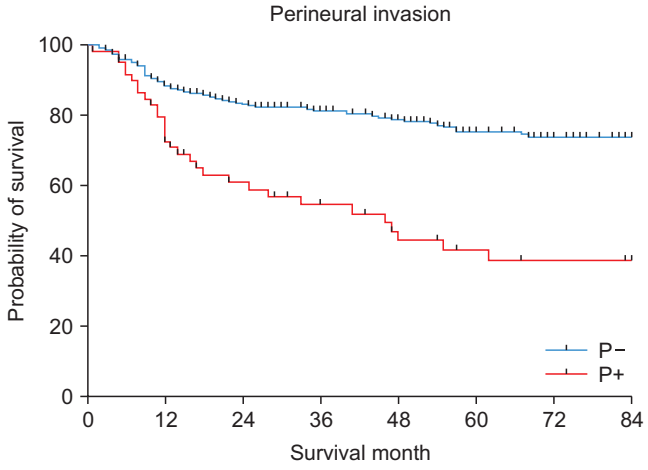

Fig. 3. Kaplan–Meier curve of overall survival by perineural invasion.
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tion margin.(Table 3) Interestingly, there was no statistically significant difference for smoking and DFS, but there was a significant difference in OS (*P*=0.307).

We performed a multivariable analysis on node metastasis, TNM stage, PNI, LVI, differentiation, surgical resection margin, and smoking, which were associated with poor prognosis in the univariate analysis of OS. Among these, node metastasis (*P*=0.013), PNI (*P*=0.007), and differentiation (*P*=0.004) were statistically significant.(Table 4) Moreover, the multivariable analysis revealed that PNI (*P*=0.022) and differentiation (*P*=0.025) had a significant negative effect in DFS.(Table 5)

IV. Discussion

According to the 8th AJCC classification, the factors affecting OSCC staging are tumor size, depth of invasion, number of metastatic nodes, location of the node (ipsilateral/contralateral), ENE, and distant metastasis[6]. In this study, the OS for each T stage was T1 (84.5%), T2 (74.9%), T3 (62.3%), and T4 (60.7%), with statistically significant differences (*P*<0.001). Additionally, for node metastasis, N0 (80.5%) and N+ (54.7%) showed a significant difference in OS (*P*<0.001). In TNM staging, there was a significant difference (*P*<0.001) in the univariate analysis (87.2% in the early stage and 60.8% in the advanced stage). Nonetheless, no difference was noted in the multivariable analysis (*P*=0.505). These data suggest that predicting the prognosis of OSCC patients based on stage alone is challenging, and other factors should be considered in the prognosis analysis.

Therefore, in this study, in addition to the TNM classification of OSCC, survival analysis was conducted based on sex, age, primary site, PNI, LVI, differentiation, surgical resection margin, smoking, and drinking to identify prognostic factors.

In our study, there were no significant differences in OS and DFS according to sex. Funk et al.[8] and Leite and Koifman[9] reported a higher OS for women with oral cancer, and Oh et al.[10] reported that the OS of men and women was 61.51% and 81.86%, respectively. The OS of women was higher by approximately 20%, which was statistically significant[8-10]. However, in a study investigating patients treated surgically for OSCC, OS was 68.9% in men and 54.5% in women, although the difference was not statistically signifi-

Table 3. Univariate analysis for disease free survival

Variable	5-year disease free survival			
	%	Hazard ratio	95% CI	*P*-value
Total	60.6			
Sex				0.220
Male	63.1			
Female	55.8			
Age				0.730
<40 yr	60.0			
≥40 yr	60.5			
Primary site				0.334
Lip	75.0			
FOM	57.0			
Tongue	63.8			
Lower gingiva	58.1			
Upper gingiva	32.7			
RMT	62.1			
Buccal cheek	51.4			
Palate	60.0			
Others	45.7			
T stage (missing 1 case)				0.018
T1	72.6			
T2	61.3	1.716	1.052-2.800	
T3	53.4	1.976	1.260-3.099	
T4	52.1	2.118	1.324-3.390	
Node metastasis (missing 1 case)				<0.001
N0	68.8			
N+	45.6	1.950	1.413-2.693	
TNM Stage (missing 1 case)				<0.001
Early (I+II)	74.8			
Advanced (III+IV)	51.2	2.095	1.532-2.865	
Perineural invasion (missing 23 cases)				<0.001
P–	63.7			
P+	34.3	2.118	1.340-3.348	
Lymphovascular invasion (missing 11 cases)				<0.001
L–	64.3			
L+	42.2	1.921	1.291-2.859	
Differentiation (missing 2 cases)				<0.001
Well	68.1			
Moderate	57.1	1.419	1.000-2.013	
Poor	33.4	2.995	1.734-5.173	
Surgical resection margin (missing 15 cases)				0.005
Clear (≥0.5 cm)	66.8			
Close (<0.5 cm)	52.5	1.556	1.131-2.141	
Treatment modality				<0.001
Surgery only	70.5			
Surgery+PORT	49.1			
Surgery+PO-CCRT	51.7			
Smoking				0.411
No	60.3			
Yes	59.3			
Drinking				0.655
No	59.8			
Yes	59.9			

(CI: confidence interval, FOM: floor of mouth, RMT: retromolar trigone, PORT: postoperative radiotherapy, PO-CCRT: postoperative concurrent chemoradiotherapy)

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Table 4. Multivariable analysis for overall survival

Variable	Hazard ratio	95% CI	*P*-value
T stage	1.088	0.820-1.454	0.565
Node metastasis	2.010	1.178-3.569	0.013
TNM stage	1.363	0.548-3.421	0.505
Perineural invasion	1.888	1.181-2.964	0.007
Lymphovascular invasion	1.422	0.882-2.257	0.141
Differentiation	1.543	1.147-2.068	0.004
Surgical resection margin	0.828	0.536-1.272	0.390
Smoking	1.251	0.819-1.941	0.307

(CI: confidence interval)

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Table 5. Multivariable analysis for disease free survival

Variable	Hazard ratio	95% CI	*P*-value
T stage	0.987	0.782-1.251	0.911
Node metastasis	1.501	0.973-2.357	0.071
TNM stage	1.227	0.611-2.456	0.564
Perineural invasion	1.595	1.058-2.362	0.022
Lymphovascular invasion	1.396	0.934-2.058	0.097
Differentiation	1.309	1.031-1.654	0.025
Surgical resection margin	0.742	0.527-1.044	0.087

(CI: confidence interval)

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cant[11]. Arduino et al.[12] and Mosleh-Shirazi et al.[13] reported no difference in OS according to sex. In this study, young age (<40 years) showed lower OS and DFS than older age (≥40 years), although the difference was not statistically significant. Research on similar age groups demonstrated that the survival rate (61%-72.7%) in older patients was higher than that in young patients (55%-66.6%)[14-16]. In contrast with our data, Pytynia et al.[17], Ho et al.[18], and Udeabor et al.[19] reported higher survival rates in young patients. Further research is required considering the inconsistent data on survival rates according to sex and age.

The oral cavity is composed of various sublocations, such as the tongue, FOM, cheek mucosa, alveolar gingiva, and lip, which have different functions and histological structures[20]. There is a large difference in the incidence of cancer according to its sublocation in the oral cavity. In the United States, oral cancer incidence occurs in the following order: tongue (31.9%), FOM (28.4%), retromolar area (9.3%), palate (7.7%), cheek mucosa (6.7%), lower gum (6.1%), and upper gum (2.8%)[8]. In this study, OSCC incidence occurred in the following order: tongue, lower gingiva, buccal cheek, RMT, upper gingiva, FOM, lip, and palate. Additionally, there was no significant difference in OS and DFS between the two groups. Similar results were found in previous studies, in which the sublocation of OSCC did not appear to affect the survival of OSCC patients[8,21].

PNI is closely related to recurrence of OSCC, locoregional

and distant metastasis, and overall survival[22-25]. In this study, PNI was also found to significantly affect survival in both the univariate and multivariable analyses. In the presence of PNI, the five-year OS rate was 41.9%, which was lower than that in the absence of PNI (75.6%). Conversely, some studies showed that the presence or absence of PNI had no significant effect on survival in stage I-II early disease or N0 disease[26,27]. Therefore, PNI can be considered a factor that significantly affects survival in advanced stage OSCC.

The role of LVI as a prognostic marker remains controversial[28]. LVI is observed in 4.9%-36.9% of OSCC cases, although conflicting results exist as to whether it significantly affects survival[29-32]. In this study, LVI was found in 21.7% of patients, and the results were consistent with previous studies. The univariate analysis of the overall OS and DFS showed statistical significance. However, it was not significant in the multivariable analysis; therefore, LVI was not considered a factor directly affecting survival.

In terms of tumor grade, a well-differentiated tumor (grade 1) has improved prognosis compared to moderately or poorly differentiated tumors (grade 2-3)[33,34]. In addition, Wang et al.[35] reported that tumor grade was significantly associated with recurrence. However, previous research showed no statistical significance between tumor differentiation and survival rate[36]. In our study, as tumor grade increased, OS and DFS decreased, which was significant in both the univariate and multivariable analyses. These divergent results may be due to inter-observer and intra-observer variation, which may limit generalizability and reproducibility[37]. Nevertheless, patients with grade 3 tumors in this study showed a very low survival rate. Therefore, close observation and adjuvant therapy should be considered whenever biopsy results confirm grade 3.

The surgical resection margin was the only factor determined by the surgeon. In oral cancer, the distance from the resection margin to the tumor cells is divided into clear margin and close margin based on 5 mm, which has been accepted as a universal standard by most clinicians treating oral cancer[38]. In particular, the close margin or involved margin confirmed after surgery has been considered one of the factors contributing the implementation of adjuvant therapy[39]. However, there is controversy as to whether a 5 mm close margin predicts a poor prognosis[40,41]. In this study, there were significant differences in the univariate analysis for OS and DFS, but not in the multivariable analysis. This finding is consistent with other studies suggesting that the close margin threshold should be reconsidered. The quality of life of patients can be improved if the extent of resection is reduced or additional adjuvant therapy is not required. Therefore, further research and consideration is required on the criteria for close margins.

Alcohol and tobacco use are known risk factors for oral cancer[42]. In the oral cavity, there was no significant difference in the case of a small amount of alcohol consumption. However, the relative risk increased as the amount of alcohol consumption increased[43]. Nonetheless, no correlation was noted between alcohol consumption and prognosis[44]. In this study, there was little difference in OS and DFS between alcohol consumers and non-consumers. Therefore, alcohol itself is not a prognostic factor. Smoking had a significant effect on lowering the survival rate in the univariate analysis; however, the correlation was low in the multivariable analysis. Other studies also reported no significant effect between smoking and survival[11,21,45]. Although carcinogens increase the risk of cancer, they do not affect prognosis after treatment.

Our study has several limitations. A potential bias may have arisen in the retrospective study design. Our clinic follows standardized guidelines, although these may vary based on the experience of the surgeons. The histopathological characteristics of the analyzed specimens have been documented over a long period by several pathologists. Therefore, standardization of pathological evaluation should be considered in future research.

V. Conclusion

In this study, we retrospectively analyzed prognostic factors of OSCC patients after surgery. In multivariable analysis, PNI and differentiation were associated with poor OS and DFS. Node metastasis showed a statistically significant difference only in DFS. According to univariate analysis, LVI, surgical resection margin and smoking habit affected poor prognosis. Therefore, if these findings are observed pre or postoperatively, it is necessary to consider close observation and adjuvant therapy to increase the survival rate.

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Authors' Contributions

Y.S.C. participated in design of the study and statistical analysis, and wrote the manuscript. M.G.K. participated in data collection. 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 reviewed and approved by the IRB of the NCC (IRB No. NCC2022-0214), and the informed consent was waived by the IRB.

Conflict of Interest

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

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