PROGNOSTIC VALUE OF NON-SMOKING, NON-ALCOHOL DRINKING STATUS IN ORAL CAVITY CANCER

Running title: Non-smoking non-drinking oral cavity cancer

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Keywords: nonsmokers, nondrinkers, NSND, oral cavity cancer

ABSTRACT

Objectives

To compare the treatment response and prognosis of oral cavity cancer between non-smoking and non-alcohol-drinking(NSND) patients and smoking and alcohol drinking(SD) patients.

Methods

A total of 313 consecutively-treated patients from 2000 – 2019 were included. Demographic, clinicopathologic, treatment, and prognosis information were obtained. Relapse-free survival(RFS), disease-specific survival (DSS), and overall survival(OS) were compared between NSND and SD groups using Kaplan-Meier plots, log-rank test, and multivariate Cox regression analysis.

Results

Sample prevalence of NSND patients was 54.6%. These patients were predominantly females in their eighth decade with lower prevalence of floor of the mouth cancers compared to SD patients (1.8% vs 14.8%). No difference in the RFS and DSS between both groups were found following multivariable analysis, however, NSND patients had better OS (HR(95% CI) – 0.47 (0.29 – 0.75); p = 0.002). Extracapsular extension was associated with significantly poorer OS, DSS and RFS in this oral cavity cancer cohort.

Conclusion

Treatment response and disease-specific prognosis are comparable between NSND and SD patients with oral cavity cancer. However, NSND patients have better OS.

Clinical relevance

This study shows that oral cavity cancer in NSND is not less or more aggressive compared to SD patients. Although better survival is expected for NSND than SD patients, this is likely to be due to the reduced incidence of other chronic diseases in the NSND cancer patients.

INTRODUCTION

Oral cavity cancer is the most common malignancy of the head and neck ranking 15th among all-cancer incidence and mortality worldwide[1,2]. Tumor occurrence is often linked to risk habits including tobacco smoking, heavy alcohol consumption, smokeless tobacco use, betel nut consumption, poor dietary habits, immunodeficiency, and genetic predisposing conditions like Fanconi anemia, Li Fraumeni syndrome, and ataxia telangiectasia[3]. Recently, the decreasing influence of these putative factors have been well acknowledged and different cohorts without clear etiologic associations have been described, referred to as non-smoking non-alcohol drinking (NSND) patients[4-9].

Among all head and neck carcinomas reported in NSND patients, tumors often occur in the oral cavity[4,6,10]. Several studies describing the clinicopathologic and molecular characteristics of oral cavity cancer in NSND patients have proposed that these tumors are indeed a distinct entity[4-8,11-14]. Specifically, NSND oral cancers were suggested to be prevalent among females in their sixth and eighth decade with the predilection of lesions for the anterior tongue and gingivobuccal mucosa[4-8]. More so, these malignancies were found to be associated with increased expression of CD274 (programmed death-ligand 1) compared to oral cavity cancers in conventional smoking and alcohol drinking (SD) cohorts[11,15,16]. However, only few studies have compared treatment response and prognostic outcomes between NSND and SD oral cavity cancer cases in the absence of betel nut chewing habits due to the low prevalence of NSND oral cavity cancers in many centers. Even for available studies, most have included cases with oropharyngeal tumors due to high-risk human papillomavirus infection, cases with oral cavity adenocarcinomas as NSND cases, considered persons with mild tobacco and alcohol exposure with non-exposed individuals for analysis, considered a single survival outcome or failed to perform multivariable statistical analysis to generate robust conclusions[5,6,12,17-19]. Therefore, this aim of this study is to comprehensively compare the

treatment response and prognostic outcomes of NSND and SD patients with oral cavity squamous cell carcinomas.

MATERIALS AND METHODS

This is a retrospective report of 313 consecutively treated oral cavity cancer patients at the Queen Mary Hospital, Hong Kong between January 1, 2000, and October 1, 2019. Patients were identified through the Hospital Authority Clinical Management System (HA-CMS) based on a histologic diagnosis of squamous cell carcinoma involving the oral cavity. Disease identifiers were limited to the International Classification of Diseases (ICD-10) codes C02.0, C02.8, C02.9, C03, C04, C05.0, C05.8, C05.9, and C06. Only patients with a minimum follow-up time above 12 months were included. Cancers with non-squamous histology were excluded. All carcinoma involving the lips, palatal and lingual tonsils, tongue base, soft palate, oropharynx, salivary glands, and perioral sites were also not considered in this study. Further excluded were cases with oral cavity carcinoma-in-situ, high-risk human papillomavirus associated oral cavity cancers, recurrent oral cavity tumors with primary malignancies outside the collection timeframe, patients that chewed betel nuts regularly, and those without documentation of their tobacco or cannabis smoking and alcohol drinking status.

All patients in this study were treated via surgery with curative intent. Neck dissection was performed when indicated with the surgical approach and extent based on perioperative clinical, imaging, and histologic assessments of the patients. Adjuvant treatment included chemotherapy and radiotherapy administered in line with National Comprehensive Cancer Network (NCCN) recommendations for head and neck cancers[20]. When considered, platinum-based chemotherapy regimen (usually cisplatin or carboplatin when indicated) and intensity-modulated radiotherapy were the standard modalities for postoperative control.

Patients' demographic, clinicopathologic, surgical, and treatment records were obtained from the electronic database. Tumor staging was conducted according to the American Joint Committee on Cancer (AJCC) classification, 7th edition. To ensure standardization of study data, TNM staging records documented in the database with the most recent or older classification were converted to the 7th Edition AJCC Classification by the study authors with Stage I/II and Stage III/IV denoting early disease and advanced disease respectively. Likewise, the WHO classification was used to stratify the histologic tumor grades[21]. Detection of definite malignant features at or very close (< 2mm) to the resection margins was the basis for their classification as 'involved' or 'clear' margins in post-surgery histology assessment. Patients were classified and compared based on their smoking and alcohol drinking status as documented in the HA-CMS database. NSND cases were those who at the time of diagnosis had no previous or current history of tobacco smoking and alcohol consumption at any timepoint. All other patients in this study were categorized as SD patients based on their current or previous regular practice of one or both risk habits.

Outcomes considered in this study were the treatment relapse rates (locoregional and distant metastasis), relapse-free survival (RFS), overall survival (OS), and disease-specific survival (DSS) measured from the date of cancer diagnosis. Key dates recorded include the date of histologic diagnosis, date of pathologic diagnosis of recurrent disease, and the date of death for deceased patients. The censored date used in this study was December 20, 2020.

Statistical analysis

Descriptive statistics were computed for all variables and presented in tables, text, and figures. Normality of data distribution was assessed using Shapiro-Wilk's test and the Mann-Whitney U test was used to compare the median distribution of all continuous variables. Differences in proportions among categorical variables were determined using the Pearson's chi-squared test and Fisher's exact test when the statistical assumptions of the former were not fulfilled.

Bivariate comparisons of the relapse-free, disease-specific, and overall survival times based on independent variables were conducted using Kaplan-Meier survival analysis and log-rank test. Multivariable analysis was then conducted for statistically significant variables in bivariate analysis using the Cox regression model. Proportional hazards assumption was checked according to each survival outcome (i.e., RFS, DSS, and OS) using the goodness of fit method which evaluates whether Schoenfeld (partial) residuals were correlated with time. If uncorrelated ($p \geq 0.05$) , the regular Cox regression model was used, otherwise time-dependent covariate Cox model was performed. All comparisons were conducted at the 95% confidence level and probability value < 0.05 was used to denote statistical significance. Analyses were performed with SPSS v 26 (IBM Corp, Armonk, NY, USA) and R statistical software v 4.0.4.

RESULTS

Patient demography

Three hundred and thirteen oral cavity cancer patients were included in this study, 171 (54.6%) of which were NSND cases. Compared to SD patients (10.6%), a significantly higher proportion of patients in the NSND group were females (73.7%) ($p<0.001$, Table 1). The median age of all patients was 62years with no statistically significant differences between the NSND and SD groups ($p=0.443$). No marked difference in the proportion of patients' age distribution based on their smoking and alcohol drinking status was observed ($p=0.141$), although fewer SD patients were above 70 years (33.9% vs 24.6%) (Figure 1). Further, 45 patients (14.4%) had a previous cancer history before oral cavity cancer diagnosis with no significant difference in the proportion of these patients between the NSND and SD groups ($p=0.138$) in this study.

Clinicopathologic characteristics

In this study, most patients had primary tumors involving the tongue (50.8%), gingiva (20.1%), and buccal mucosa (16.9%) (Table 1). On comparing both patient groups, we observed a lower prevalence of tumors involving the floor of the mouth in NSND patients (1.8%) compared to SD patients (14.8%) (p = 0.001). Although, a higher proportion of NSND than SD cases involved the tongue (52.6% vs 48.6%), gingiva (22.8 vs 16.9%), and buccal mucosa (18.7% vs 14.8%), the site predilection pattern was similar in both groups. When stratified by age, smoking, and alcohol drinking status, the prevalence of carcinomas involving the tongue was higher among young NSND patients (100%, n=14) than other patient groups (p=0.001; Appendix S1). Likewise, the occurrence of tumors involving the gingiva was higher among elderly NSND patients while buccal mucosa tumors were preponderant in NSND patients between 41 and 69 years.

More patients had late-stage disease (55.2%) in this study with no disparity in the pattern of presentation between NSND and SD patients (p=0.576). Majority of the patients also had tumors of moderate histologic differentiation (72.2%), with NSND patients having more well-differentiated tumors (26.5 vs 17.9), although this was not statistically significant (p=0.070). Similarly, the proportion of cases with positive histologic characteristics including median depth of invasion, perineural, lymphovascular, and infiltrative bony invasion did not differ between patient groups (p=0.439-0.610) (Table 1).

Intervention, Treatment response, and survival

All patients were treated with curative intent surgery with positive margins observed in 6.5% of cases (Table 1). Neck dissections were performed in 87.9% of patients with no significant difference in the proportion of the procedure between NSND and SD groups (p = 0.623). In total, 145 patients had adjuvant treatment, the majority of which involved only radiotherapy (25.6%). No difference was observed in the proportion of NSND and SD patients that received

adjuvant treatment (p=0.819) or had positive resection margins (p=0.409). One hundred and five patients (33.5%) had histologically-diagnosed tumor relapse following treatment and comparable proportions were observed between NSND and SD patients (32.2 vs 35.2; p=0.570).

Relapse-free survival

Survival analysis showed no difference in the 10-year relapse-free survival (RFS) for all patients when stratified by their gender, tobacco smoking, and alcohol drinking status (p=0.211 – 0.967) (Appendix S2). No difference in the RFS was also observed between NSND and SD patients even when categorized based on gender and age distribution (p=0.439 – 0.856). However, when stratified by the tumor stage, both early and advanced oral cavity cancers in NSND patients had better RFS than corresponding stages in the SD patient group (p=0.028). Among NSND patients, those with tumors involving the tongue and buccal mucosa had better RFS than tumors involving the gingiva and floor of the mouth (FOM) (p<0.001) while for SD patients tongue and FOM tumors had better RFS than buccal mucosa tumors (p=0.014). Altogether, patients with involved margins had poorer RFS than those with clear margins irrespective of their NSND or SD status (p<0.001) while different adjuvant treatments yielded no difference in the RFS in this cohort (p = 0.748).

Survival plots obtained according to the histologic characteristics are depicted in Appendix S3. Only the presence of histologically-confirmed infiltrative bony invasion and extracapsular extension was significantly associated with poorer relapse-free survival (p≤0.001). Differences in the pattern and significance of these prognostic features were not observed between NSND and SD groups. Multivariable analysis of the RFS according to significant variables in the survival plots is shown in Table 2. In all patients, tumors involving the buccal mucosa (HR(95% CI) – 2.42 (1.36 – 4.29); p=0.003) and extracapsular extension (HR(95% CI) – 3.02 (1.78 – 5.14); p < 0.001) were predictors of poor RFS.

Disease-specific survival and overall survival

Disease-specific survival (DSS) and overall survival (OS) rates for NSND and SD patients were 80.1% vs 71.1% and 64.3% vs 49.3% respectively. Regarding the disease-specific prognosis of the entire cohort, males and smokers had worse survival, although this was not statistically significant (p = 0.250; 0.238). However, DSS was significantly lower among non-drinkers than ever-drinkers (p=0.008). Overall, NSND status was associated with better survival from censored data (p=0.048) which when further stratified by gender, was lower among NSND males compared to NSND females, although this did not reach statistical significance (p = 0.132) (Appendix S4). No significant difference in the DSS was observed when NSND patients were further stratified by their age and gender individually and collectively (p = 0.141 – 0.620). Advanced disease stage was associated with poorer DSS (p = 0.001) which when grouped according to NSND and SD status, both early and advanced NSND patients had better survival than corresponding SD patient subgroups at 10 years(p = 0.001). In NSND patients, based on the tumor sites, FOM and retromolar area cancers had worse survival which was not statistically significant (p = 0.061) while cancers involving the buccal and retromolar mucosa were significantly associated with worse survival in SD patients (p = 0.026). Also, those with involved resection margins following surgery had significantly lower survival than those with clear margins irrespective of their NSND or SD status (p = 0.001). Disease-specific survival did not differ in this cohort based on the modality of adjuvant treatment received (p = 0.131). All histologic characteristics assessed (i.e., infiltrative bony, perineural, and lymphovascular invasion as well as extracapsular extension) were associated with significantly lower DSS in this cohort (p < 0.001 – 0.005, Appendix S5). However, when stratified by the NSND and SD status, the presence of infiltrative bony invasion and lymphovascular invasion were significant prognostic factors only in the NSND group (p =

0.001, p = 0.002) with no difference in DSS observed irrespective of their status in the SD group (p = 0.177, p = 0.338).

Evaluating the overall survival of this patient cohort yielded no difference in the survival probability patterns or statistical significance from the DSS in most of the factors compared (Appendix S6, S7). However, elderly (>70 years) and SD patients had significantly poorer overall survival at 10 years in this study (p<0.001, p = 0.010). While NSND patients had significantly better overall survival, we found that NSND males and SD patients (irrespective of their gender) had comparable overall survival with both groups observing lower rates compared to NSND females (p = 0.034). In contrast to the DSS for NSND patients based on age distribution, poorer overall survival was observed among NSND elderly patients than other NSND patients and all SD patients (p<0.001). No significant difference was observed in the overall survival between NSND and SD elderly patients (p=0.321), however, when NSND patients were sub-categorized based on their gender, NSND elderly females had significantly better overall survival (p = 0.013). Based on the histologic characteristics, absence of lymphovascular invasion was associated with better overall survival in NSND patients (p = 0.006) which was not observed in the SD group (p = 0.110, Appendix S6).

Multivariate analysis showed that NSND status is not a significant predictor of disease-specific survival (HR(95% CI) – 1.14 (0.42 – 3.05; p = 0.799) but good overall survival (HR(95% CI) – 0.47 (0.29 – 0.75); p = 0.002). Regarding the OS, elderly patients had lower survival probability compared to patients below 70 years (HR(95% CI) – 3.03 (1.87 – 4.92); p < 0.001) while those with infiltrative bony invasion were also more likely to have poorer disease-specific survival (HR(95% CI) – 2.58 (1.14 – 5.84); p = 0.023). Like the RFS, extracapsular extension was associated with reduced disease-specific and overall survival in this patient cohort (Table 3 and 4).

DISCUSSION

Oral cavity cancer is often associated with tobacco and cannabis use, heavy alcohol consumption, and betel nut chewing according to the geographic preponderance of these risk habits. Less commonly, malignant lesions can develop in NSND patients with reports on specific cohorts across Australia, Europe, and the USA proposing clinicopathologic and molecular distinction of tumors in these patients compared to conventional smoking and alcohol drinking patients. Nonetheless, our hypothesis on the regional variation in this profile as well as the paucity of comprehensive studies evaluating treatment response and prognosis of NSND oral cavity cancer compared to their SD counterparts necessitated this research endeavor.

The sample prevalence of NSND patients with oral cavity cancer in our cohort is 54.6% which is higher than previously reported from most institutional cohorts describing the demography and clinical characteristics of these patients. Studies describing these individuals have observed that NSND patients constitute between 1.8 – 55.5% of oral cavity or head and neck cancer cases with reports on the high end of this range emanating from East Asia [4-6,8,11-13,15-17,19,22-26]. This may reflect the pattern of patients' presentation in this region based on their risk factor profile. Our study found NSND patients with oral cavity cancer to be predominantly females often in their eighth decade of life. While this gender and age distribution is in agreement with most studies describing NSND cohorts previously[4,6,12,23], the single peak age prevalence obtained contradicts some reports of bimodal peak occurrence in the 5th - 6th decade and 8th decade in other centers [5,7,11,14]. Additionally, this study confirms the site predilection of NSND oral cavity cancers for the anterior tongue and gingivobuccal mucosa with a distinctly lower incidence of tumors involving the floor of the mouth[4-7,12,13,24]. However, we observed a unique variation in the site predilection according to the age group of the patients. Young NSND patients were more likely to develop malignancies in the anterior tongue than middle-aged (41

– 69 years in this study) or elderly NSND patients. Gingival carcinomas were observed more commonly among elderly patients while buccal carcinomas were more prevalent among middle-aged NSND patients. Furthermore, our study found a comparable prevalence of early and advanced tumors between NSND patients and their SD counterparts which contrasts with many reports suggesting an early disease presentation trend among NSND patients[4-6,8,23,24]. Nonetheless, this may be reflective of the overall TNM stage at presentation for all oral cancer patients in our center and a peculiarity of the pattern of NSND presentation in the East Asian region[22,27,28].

Regarding the disparities in treatment response measures between patient groups, our study corroborates earlier-reported recurrence and distant metastasis rates as well as relapse-free survival which were comparable among NSND and SD patients even when stratified by their age and gender[6,12,18,22]. Notably, the classification of both cohorts according to their TNM stage revealed better RFS in early and advanced NSND than corresponding SD cases. This is in line with the concept of field cancerization in the oral cavity of smokers and drinkers with malignant lesions which predispose them to develop recurrent disease and second primary tumors[29]. Although FOM carcinomas were less common among NSND patients, these malignancies were associated with poorer RFS in this group than SD patients. While this may be an incidental finding given that there were few cases in this study, data pooling across centers in the future will be invaluable to corroborate this finding and guide future tumor biology and behavior investigations. We also observed that oral cavity cancers involving the buccal mucosa which have been associated with worse RFS were significantly pertinent to the SD than NSND cases[30,31]. This may likewise be adduced to an advanced-stage presentation of most buccal mucosa tumors known to involve the buccinator, buccal fat pad, and upper and lower alveolus combined with the increased tendency for infiltrative bony invasion of the latter among smokers and drinkers due to reduced bone density[31-34].

Our study corroborates reports suggesting a lack of disparity based on the cancer-related survival between NSND and SD patients. This is quite paradoxical as molecular studies have observed increased levels of CD8+ T cells (which are indicative of favorable prognosis in head and neck cancers) in oral cavity cancers of NSND than SD patients[11,35,36]. Nonetheless, we found that overall survival was better in the NSND group which may be as a result of the higher mortality from other malignancies or systemic comorbid conditions associated with tobacco smoking and alcohol consumption[37]. Alternatively, this may reflect the propensity of SD patients to develop life threatening complications from interventional cancer management modalities; thus, contributing to an increased all-cause mortality in this group[38]. In contrast, we did not observe a disparate pattern in the DSS when stratified by age distribution and sex, and overall, this study did not corroborate reports in an Australian cohort suggesting an aggressive OSCC variant among NSND elderly females than other NSND and SD patients[5,7]. Nonetheless, NSND tumor behavior in this patient subgroup may exhibit regional variation and more studies are required to confirm or refute this proposition. More so, this study showed a better overall survival for NSND females than NSND males which may reflect the increased overall likelihood of chronic diseases among males than females irrespective of their risk habit status in our city-state[39]. Among all elderly patients, NSND females also had better overall survival.

Comparing the findings of this study with recent summary reports on oral cancer prognostic factors, corroborates the choice of extracapsular extension as a putative predictor influencing patients' relapse-free, disease-specific, and overall survival following surgical intervention[40]. However, based on the findings of our study, the combined smoking and alcohol consumption status at diagnosis may be considered as an additional relatively-influential to influential prognostic feature with regards the overall patient prognosis. Though this study uniquely presents a comprehensive evaluation of the prognosis of NSND oral cavity cancer patients not

associated with betel nut chewing or genetic predisposition, it is not without limitations. First, some patients were excluded from selection based on missing details, especially regarding their smoking and alcohol drinking status. Likewise, this may have contributed to the high sample prevalence of NSND patients in this study on the assumption that most of the excluded patients could have been smokers and/or alcohol drinkers. Nonetheless, to our knowledge, this study comprises one of the largest cohorts of NSND oral cavity cancer patients with no betel nut chewing habits comparing their clinicopathologic characteristics and prognostic predictors with a balanced subset of smoking and alcohol-drinking patients. Second, our inclusion of prognostic factors based on patient records may be biased due to potential documentation errors by the multidisciplinary managing teams. However, most of the variables collected were duplicated across multiple platforms on the electronic database, and information obtained for this study were correlated across those platforms. Third, all patients were treated primarily via surgery with curative intent and adjunctive chemoradiation; hence, the prognosis information may not be generalizable to patients that receive chemoradiation as the main treatment or as neoadjuvant therapy.

CONCLUSION

Overall, while oral cavity cancer in NSND patients may have a distinct demographic and anatomic site presentation, it does not pose a distinct treatment response challenge compared to smoking and alcohol-drinking patients based on recurrence rate and time-to-recurrence evaluation. Although cancer-specific survival was not different between NSND and SD patients, NSND patients had better overall survival than SD patients.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest

JA declares that he has no conflict of interest. LH declares that she has no conflict of interest. JYT declares that she has no conflict of interest. MK-M declares that he has no conflict of interest. S-WC declares that she has no conflict of interest. PT declares that he has no conflict of interest.

Funding

The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Approval

Approval to conduct this study was granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number UW- 19-704). All clinical data were anonymized by the researchers, and all potential patient identifiers were removed before data analysis.

Informed Consent

For this type of study, formal consent is not required.

FIGURE LEGENDS

Figure 1: Age distribution of oral cavity cancer patients stratified by smoking and drinking status.

Table 1: Demographic and clinicopathologic characteristics of NSND and SD patients

Variables		NSND	SD	All cases	p-value
		N(%)	N(%)	N(%)	
Median age (IQR)		63 (53 – 74)	62 (55 – 69)	62 (55 – 73)	0.443[a]
Gender	Female	126(73.7)	15(10.6)	141(45.0)	***<0.001*** [b]
	Male	45(26.3)	127(89.4)	172(55.0)	
Positive cancer history		20(11.7)	25(17.6)	45(14.4)	0.138 [b]
Tumor site	Tongue	90(52.6)	69(48.6)	159(50.8)	***0.001*** [c]
	Gingiva	39(22.8)	24(16.9)	63(20.1)	
	Buccal mucosa	32(18.7)	21(14.8)	53(16.9)	
	Floor of the mouth	3(1.8)	21(14.8)	24(7.7)	
	Retromolar area	4(2.3)	4(2.8)	8(2.6)	
	Hard palate	3(1.8)	3(2.1)	6(1.9)	
Tumor stage	Stage I/II	71(43.3)	66(46.5)	137(44.8)	0.576 [b]
	Stage III/IV	93(56.7)	76(53.5)	169(55.2)	
Tumor grade	Well	44(26.5)	25(17.9)	69(22.5)	0.070 [b]
	Moderate	111(66.9)	110(78.6)	221(72.2)	
	Poor	11(6.6)	5(3.6)	16(5.2)	
Positive histologic characteristics	PNI	38(33.0)	32(28.3)	70(30.7)	0.439 [b]
	LVI	30(21.0)	32(23.7)	62(22.3)	0.585 [b]
	BNI	42(25.9)	32(23.9)	74(25.0)	0.510 [b]
	ECE	32(19.0)	21(15.1)	53(17.3)	0.363 [b]
Median DOI (IQR)		0.86(0.36 – 1.28)	0.9(0.43 – 1.35)	0.9(0.36 – 1.30)	0.610 [a]
Resection margin	Involved	9(5.4)	11(7.7)	20(6.5)	0.409 [b]
	Clear	157(94.6)	131(92.3)	288(93.5)	
Neck dissection done		152(88.9)	123(86.6)	275(87.9)	0.541[b]
Adjuvant therapy	Chemotherapy	1(0.6)	1(0.7)	2(0.6)	0.819 [c]
	Radiotherapy	45(26.3)	35(24.6)	80(25.6)	
	Both	31(18.1)	22(22.5)	63(20.1)	
Recurrence	Yes	55(32.2)	50(35.2)	105(33.5)	0.570 [b]
	No	116(67.8)	92(64.8)	208(66.5)	
Death due to any cause		61(35.7)	72(50.7)	133(42.5)	***0.007*** [b]
Death due to disease		34(19.9)	41(28.9)	75(24.0)	0.064 [b]

[a]Mann-Whitney U test; [b]Pearson Chi-Square test; [c]Fisher's exact test

NSND – Nonsmoker nondrinker; SD – Smoker drinker; IQR – Interquartile range lower and upper limits; PNI – Perineural invasion; LVI – Lymphovascular invasion; BNI – Bone invasion (infiltrative); ECE – Extracapsular extension; DOI – Depth of invasion
Texts in bold and *italics* are statistically significant

Table 2: Multivariable relapse-free survival analysis for tumor sites, staging, positive histological characteristics, and resection margin status

Variables		Events[a] (n)	**Relapse-free survival**		
			Hazard Ratio	95% Confidence Interval	p-value
Tumor sites	Tongue	38	1.00	Reference	
	Hard Palate	2	1.00	0.13 – 7.90	0.996
	Buccal mucosa	27	2.42	1.36 – 4.29	***0.003***
	Gingiva	26	1.39	0.69 – 2.80	0.350
	FOM	9	1.48	0.70 – 3.16	0.306
	Retromolar area	3	1.10	0.29 – 4.19	0.891
Tumor stage	Early (Stage I and II)[a]	37	1.00	Reference	
	Advanced (Stage III and IV)	63	1.25	0.74 – 2.14	0.405
Infiltrative bony invasion (BNI)	BNI-	64	1.00	Reference	
	BNI+	33	1.39	0.76 – 2.55	0.281
Extracapsular extension (ECE)	ECE-	76	1.00	Reference	
	ECE+	26	3.02	1.78 – 5.14	***<0.001***
Resection Margin	Clear	90	1.00	Reference	
	Involved	11	1.69	0.80 – 3.55	0.168

[a]Events represent the occurrence of local or regional tumor recurrence.
FOM – Floor of the mouth
Text in bold and italics are statistically significant

Table 3: Multivariable analysis for the disease-specific survival according to the alcohol status, patient category, tumor sites, TNM stage, and resection margin status

Variables		Events[a] (n)	**Disease-specific Survival**		
			Hazard Ratio	95% Confidence Interval	p-value
Alcohol status	Non-drinker	43	1.00	Reference	
	Ever-drinker	32	1.73	0.64 – 4.66	0.278
Patient category	SD	41	1.00	Reference	
	NSND	34	1.14	0.42 – 3.05	0.799
Tumor sites	Tongue	29	1.00	Reference	
	Buccal mucosa	20	1.45	0.56 – 3.74	0.441
	Gingiva	14	0.94	0.34 – 2.57	0.904
	FOM	7	0.86	0.26 – 2.78	0.795
	Retromolar area	4	2.16	0.46 – 10.07	0.329
Tumor stage	Early (Stage I and II)	24	1.00	Reference	
	Advanced (Stage III and IV)	50	0.99	0.43 – 2.27	0.976
Resection Margin	Clear	63	1.00	Reference	
	Involved	11	1.47	0.45 – 4.89	0.525
Infiltrative bony invasion (BNI)	BNI-	46	1.00	Reference	
	BNI+	26	2.58	1.14 – 5.84	***0.023***
Lymphovascular invasion (LVI)	LVI-	45	1.00	Reference	
	LVI+	20	1.08	0.52 – 2.24	0.843
Perineural invasion (PNI)	PNI-	24	1.00	Reference	
	PNI+	24	2.02	0.99 – 4.12	0.054
Extracapsular extension (ECE)	ECE-	48	1.00	Reference	
	ECE+	27	5.09	2.41 – 10.75	***<0.001***

[a]Events represent death due to disease progression.

NSND – Non-smoker non-drinker; SD – Smoker drinker; FOM – Floor of the mouth

Text in bold and italics are statistically significant

Table 4: Multivariable overall survival analysis for age group, patient categories, tumor sites, TNM stage, histologic characteristics, and resection margin status.

Variables		Events[a] (n)	**Overall Survival**		
			Hazard Ratio	95% Confidence Interval	p-value
Age group	<70 years	74	1.00	Reference	
	≥70 years	59	3.03	1.87 – 4.92	***<0.001***
Patient category	SD	72	1.00	Reference	
	NSND	61	0.47	0.29 – 0.75	***0.002***
Tumor sites	Tongue	56	1.00	Reference	
	Hard Palate	4	1.82	0.34 – 9.64	0.482
	Buccal mucosa	28	1.25	0.59 – 2.65	0.558
	Gingiva	30	0.75	0.34 – 1.67	0.487
	FOM	10	0.57	0.23 – 1.43	0.235
	Retromolar area	5	0.82	0.22 – 3.11	0.769
Tumor stage	Early (Stage I and II)	42	1.00	Reference	
	Advanced (Stage III and IV)	89	1.78	0.98 – 3.24	0.059
Resection Margin	Clear	117	1.00	Reference	
	Involved	15	1.73	0.71 – 4.21	0.227
Infiltrative bony invasion (BNI)	BNI-	84	1.00	Reference	
	BNI+	42	1.81	0.90 – 3.62	0.094
Lymphovascular invasion (LVI)	LVI-	83	1.00	Reference	
	LVI+	33	1.20	0.69 – 2.10	0.520
Perineural invasion (PNI)	PNI-	56	1.00	Reference	
	PNI+	35	1.23	0.71 – 2.11	0.456
Extracapsular extension (ECE)	ECE-	95	1.00	Reference	
	ECE+	37	2.92	1.67 – 5.13	***<0.001***

[a]Events represent death due to any cause.

NSND – Non-smoker non-drinker; SD – Smoker drinker; FOM – Floor of the mouth

Text in bold and italics are statistically significant

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Figure

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