Difference in Clinical Presentation and Their Significance in Oral Squamous Cell Carcinoma – a Retrospective Analysis

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Research Article

Keywords: Oral Squamous Cell Carcinoma, buccoalveolar complex(BAC) , pathological factors

Posted Date: January 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1159763/v1

Abstract

Oral squamous cell carcinoma(OSCC) involving tongue and buccoalveolar complex(BAC) behaves differently. Clinical features of the two subsites and their influence on pathological factors remain least analysed.

Patients are divided into two groups i.e, tongue cancer and BAC cancer group, and various clinical parameters were compared.

Among 474 patients 232 had tongue cancer and 242 had BAC cancer. 30% of patients with OSCC were asymptomatic at presentation except for the ulcer. Compared to tongue cancers, lesions confined to BAC presents at an advanced stage(p=0.006). Multivariate analysis showed that dysphagia in tongue cancer(p=0.020) and external swelling or lesion in BAC cancers(p=0.002) were significant predictors of an advanced stage of disease. On histopathology perineural invasion was significantly associated tongue(p=0.008) and BAC cancers(P=0.015). Among tongue cancers, those with pain and referred otalgia had a statistically significantly high depth of invasion(DOI), compared to those without pain (DOI – no pain 6.9mm, pain 9.9mm and referred otalgia 11.4mm).

There is a delay in clinical presentation of OSCC. Among tongue cancers, clinical history of pain was significantly associated with depth of invasion and perineural invasion, the significance of which needs to be prospectively analysed. Clinical history in OSCC can be used as predicting factors for various pathological characters, which is subsite specific.

Introduction:

Oral cancer is the most common cancer in India, which commonly involves men of the elderly age group of lower socioeconomic status. Oral cancer is used synonymously for oral squamous cell carcinoma(OSCC) because 90% of oral cancers are squamous cell carcinoma (1, 2). In India, OSCC most frequently involves buccal mucosa and gingiva with the age-standardized incidence among men being 13.9 per 100,000(3, 4). The 5-year survival of a patient presenting with early OSCC is up to 80–90%, but once OSCC reaches an advanced stage, the survival is about 40%(5). Thus, there is a 50% drop in survival when the disease progresses to advanced stages. In India, 70% of the patients present in an advanced stage, thus leading to a major health concern(6). There is a recent change in the trend of presentation of OSCC which is mainly related to change in lifestyle, habits and awareness. All this had led to a change in the incidence of the disease with more patients affected being under 45 years (5–8).

Clinical history taking is an integral part of patient care but when it comes to oral cancer only few analytical articles are available. It should be worthy to note that, most OSCC, especially in the Indian scenarios, are diagnosed as a result of direct patient presentation to a doctor due to symptoms and not because of screening or incidental diagnosis. Though Kumar et al. showed 92% of the patient are aware of the link between tobacco products and cancer, symptoms of oral cancer have been poorly understood, leading knowledge gap resulting in a delayed presentation(9, 10).

One major concern regarding the evaluation of symptoms is an inter-individual variation in symptoms among patients. Studies based on symptoms to analyze OSCC are rare. This study would be the first to analyze the common symptoms of tongue and buccoalveolar complex(BAC) OSCC separately in detail along with other clinicopathological parameters. With currently available awareness and improved education among patients, it would be the right time to look at clinical symptoms with oral subsites separately and their association with the advanced stage of OSCC presentation.

Methodology:

This is a retrospective study conducted in a tertiary care center in South India between March 2017 to March 2020 after approval from the institutional review board, Christian Medical College, Vellore[IRB Min no: 137759]. The methods used for the study were all conducted according to relevant guidelines and regulations. We included 474 patients who underwent primary surgical management for oral OSCC from two subsites namely tongue and BAC. Patients with recurrent oral cancer, second primary and patients who had previous radiotherapy to the head and neck region were excluded from the study. The treatment plan of all the included patients was discussed in the multidisciplinary tumor board (MDT). Records of the included patients were retrieved from electronic medical records, the pathological staging was done according to the AJCC 8th edition staging system for cancer of the oral cavity. Demographic details were obtained. Clinical history findings included pain, referred otalgia, speech issues, dysphagia, bleeding from lesion, halitosis, burning sensation in mouth, external swelling or lesion in face/neck, tooth-related issues (sharp tooth excluded).

Statistical analysis such as mean and standard deviation was presented for all continuous variables whereas absolute number and percentage were reported for all categorical variables across the Composite Stage. Chi-square test was used to assess the association of all categorical variables with the composite stage and t-test was used to compare the continuous variable. To identify the independent risk factors that were associated with the composite stage, firth logistic regression was used to build up the models and adjust for confounders. All analysis was also carried out separately for both Tongue and Buccal Mucosa Site. A p-value <0.10 was considered as the statistically significant parameters. All statistical analysis was performed using STATA 16.

Results:

We included 474 patients(Table 1), among them, the first group included 232 patients with tongue cancer(49%) and the second group included 242 patients with BAC cancer (51%). 72% of OSCC involved patients who were above 45 years. The male to female ratio of OSCC was about 2.5:1. It was found that a significantly higher number of patients in BAC cancer(65.3%) presented in an advanced stage compared to tongue cancer(52.3%) (p=0.006). Majority of Tongue cancers (31.9%) affected younger(≤45 years) population compared to the BAC (23.6%)(p=0.042). The mean age of patients presenting with tongue cancer was 51.1 ± 11.7years and the mean age of patients with BAC cancer was 54.1 ± 12.2 years. Among the associated comorbidities, 18.6% had diabetes, 24.5% had hypertension and 6.5% had associated coronary artery disease with no difference between the two groups.

Table 1
Univariate analysis of factors predicting advanced stage disease in tongue and buccoalveolar complex OSCC

Variable	Tongue OSCC				Buccoalveolar complex OSCC			
	Composite stage		Univariate Analysis		Composite stage		Univariate Analysis	
	Early Stage (N=104)	Advanced Stage (N=128)	OR (95% - CI)	p - value	Early Stage (N=75)	Advanced Stage (N=167)	OR (95% - CI)	P - value
n (%)	n (%)	n (%)	n (%)					
BMI (Mean, SD)	24.54 ± 3.72	24.57 ± 5.28	1.00 (0.95 – 1.06)	0.974	23.92 ± 4.57	23.60 ± 3.94	0.98 (0.92 – 1.05)	0.565
Demography								
North India	66(47.47)	73(52.52)	1.00		47(32.19)	99(67.81)	1.00	
South India	23(44.23)	29(55.77)	1.14 (0.60 – 2.14)	0.695	14(35.00)	26(65.00)	0.87 (0.42 - 1.81)	0.713
Others	15(36.59)	26(63.41)	1.55 (0.76 – 3.14)	0.228	14(25.00)	42(75.00)	1.40 (0.70 – 2.79)	0.339
Age								
<=45	29(39.19)	45(60.81)	1.00		16(28.07)	41(71.93)	1.00	
>45	75(47.47)	83(52.53)	0.72 (0.41 – 1.25)	0.243	59(31.89)	126(68.11)	0.86 (0.44 – 1.62)	0.611
Sex								
Male	74(46.84)	84(53.16)	1.00		57(31.84)	122(68.16)	1.00	
Female	30(40.54)	44(59.46)	1.29 (0.74 – 2.24)	0.375	18(28.57)	45(71.43)	1.15 (0.62 – 2.16)	0.652
Diabetes mellitus	19(47.50)	21(52.50)	0.88 (0.44 – 1.72)	0.703	19(39.58)	29(60.42)	0.62 (0.32 – 1.18)	0.146
Hypertension	22(40.74)	32(59.26)	1.23 (0.67 – 2.30)	0.500	23(37.10)	39(62.90)	0.69 (0.38 – 1.26)	0.222

***Variables which are significant at 10% level were considered for the multivariate analysis**

Variable	Tongue OSCC				Buccoalveolar complex OSCC			
	Composite stage		Univariate Analysis		Composite stage		Univariate Analysis	
	Early Stage (N=104)	Advanced Stage (N=128)	OR (95% - CI)	p - value	Early Stage (N=75)	Advanced Stage (N=167)	OR (95% - CI)	P - value
Cardiac Issues	3(21.43)	11(78.57)	2.83 (0.83 – 9.66)	**0.095**	8(47.06)	9(52.94)	0.48 (0.18 – 1.25)	0.133
Pain	46(36.80)	79(63.20)	2.02 (1.20 – 3.41)	**0.008**	27(25.47)	79(74.53)	1.58 (0.91 – 2.80)	0.106
Referred Otalgia	9 (28.13)	23 (71.88)	2.23 (1.00 – 4.50)	**0.049**	3 (27.27)	8 (72.73)	1.10 (0.31 – 3.95)	0.879
Speech Disturbance	6(13.33)	39(86.67)	6.68 (2.80 – 16.10)	**<0.001**	0(0.00)	6(100.0)	6.07 (0.33 – 109.29)	0.221
Dysphagia	6(12.00)	44(88.00)	7.98 (3.33 – 19.10)	**<0.001**	2(8.70)	21(91.30)	4.31 (1.13 – 16.46)	**0.032**
Bleeding	9(33.33)	18(66.67)	1.68 (0.73 – 3.85)	0.218	8(24.24)	25(75.76)	1.42 (0.62 – 3.25)	0.409
Burning Sensation	9(34.62)	17(65.38)	1.58 (0.68 – 3.64)	0.285	6(26.09)	17(73.91)	1.24 (0.48 – 3.20)	0.651
Restricted Mouth opening	0(0.00)	2(100.00)	4.13 (0.19 – 86.98)	0.362	12(25.53)	35(74.47)	1.36 (0.67 – 2.77)	0.395
Halitosis	1(10.00)	9(90.00)	5.48 (0.96 – 31.31)	**0.055**	1(12.50)	7(87.50)	2.32 (0.39 – 13.68)	0.325
External swelling/lesion	0(0.00)	1(100.00)	2.45 (0.99 – 60.99)	0.583	9(13.04)	60(86.96)	3.93 (1.86 – 8.33)	**<0.001**

***Variables which are significant at 10% level were considered for the multivariate analysis**

Variable	Tongue OSCC				Buccoalveolar complex OSCC			
	Composite stage		Univariate Analysis		Composite stage		Univariate Analysis	
	Early Stage (N=104)	Advanced Stage (N=128)	OR (95% - CI)	p - value	Early Stage (N=75)	Advanced Stage (N=167)	OR (95% - CI)	P - value
Tooth Issues	7(63.64)	4(36.36)	0.47 (0.14 - 1.56)	0.217	9(19.57)	37(80.43)	2.01 (0.93 – 4.34)	**0.076**
Number of Symptoms								
<=3	92 (52.27)	84 (47.73)	1.00		68 (36.96)	116 (63.04)	1.00	
>3	12 (21.43)	44 (78.57)	3.90 (1.95 – 7.80)	**<0.001**	7 (12.07)	51 (87.93)	4.04 (1.77 – 9.19)	**0.001**
Smokeless Tobacco use	55(45.83)	65(54.17)	0.91 (0.55 - 1.54)	0.751	63(30.88)	141(69.12)	1.05 (0.50 – 2.19)	0.894
Smoking	29(46.03)	34(53.97)	0.93 (0.52 – 1.66)	0.818	21(29.58)	50(70.42)	1.10 (0.60 – 1.98)	0.779
Alcohol intake	21(47.73)	23(52.27)	0.87 (0.45 – 1.66)	0.663	15(26.79)	41(73.21)	1.28 (0.66 – 2.48)	0.462
Tobacco abuse								
Tobacco/Smoke	68(46.90)	77(53.10)	0.80 (0.47 – 1.37)	0.418	67(30.88)	150(69.12)	1.08 (0.45 – 2.58)	0.857
Others	36(41.38)	51(58.62)	1.00		8(32.00)	17(68.00)	1.00	
Habits								
All Habits	5(25.00)	15(75.00)	1.78 (0.61 – 5.17)	0.290	7 (24.14)	22 (75.86)	1.26 (0.37 – 4.32)	0.715
No Habits	32(38.55)	51(61.45)	1.00		6(28.57)	15(71.43)	1.00	
***Variables which are significant at 10% level were considered for the multivariate analysis**								

The median duration of clinical presentation of OSCC was 6 months (Interquartile range 4month and 10 months). Fig. 1 explains the various symptoms and habits, their prevalence among tongue cancer and BAC cancer groups. Although all patients presented with complaint of lesion in the oral cavity, 34.1%(79 of 232 patients) of tongue cancer and 25.6% BAC cancer(62 of 242 patients) did not have any other symptoms. Among patients with tongue

cancer the common symptoms(Fig. 1) includes pain(53.9%), dysphagia(21.6%) and speech-related issues(19.4%). The pain remained the most common symptom (43.8%) among patients with BAC cancer as well, followed by external swelling or lesion (28.5%), difficulty in mouth opening(19.4%) and tooth-related complaints(19%).

In the comparison of various substance abuse(Fig. 1,2) among subsites, it was noted that 84% of BAC cancer patients used smokeless tobacco($p<0.001$). On the contrary, 35.8% of patients who developed tongue cancer($p<0.001$), did not have any habits. Univariate analysis(Table 1) did not find any association between substance use and disease stage at presentation.

There was a significant correlation between pain and depth of invasion among tongue cancer. It was noted patient in patients with tongue cancer, depth of invasion (DOI) was significantly high in those with pain ($p<0.001$) and otalgia ($p=0.001$) compared to those without pain [mean(SD) DOI - painless 6.9mm(5.1mm), painful 9.9mm(6.2mm) and with referred otalgia 11.4mm(6.3mm)]. But the same association was not found in BM OSCC($p=0.96$).

Sixty-one percent (76/125) patients with tongue OSCC who had pain were found to have perineural invasion(PNI) compared to 43%(46/107) of patients with no pain. Thus, the patient with pain had a 2.06 times higher risk of having PNI compared to those without pain(95% CI, 1.2 to 3.5; $P = 0.008$). Similarly in BAC OSCC 45.2%(48/106) patients with pain had PNI compared to 30.1%(41/136) with no pain and patients with pain had a 2 times higher risk of PNI (95% CI, 1.2 to 3.4; $P = 0.015$). Although PNI was noted in 65.6% of patients(21/32) with otalgia among tongue OSCC and in 50%(5/10) of patients with BAC OSCC, it was not statistically significant.

Univariate analysis(Table 1) was done to find clinical, demographic factors associated with the advanced composite stage of the disease. It was found that pain, referred otalgia, speech issues, dysphagia and a cumulative symptom score of >3 were associated with advanced tumor stage. Univariate analysis among BAC OSCC subsites showed advanced stage was associated with dysphagia, external swelling or lesion, tooth-related issues and a cumulative symptom score of >3. Multivariate analysis(Table 2) showed that in tongue OSCC, dysphagia had a significant association with advanced-stage disease($p=0.020$) and in BAC SCC external swelling or lesion($p=0.002$) was significantly associated with advanced-stage disease.

Table 2
Multivariate analysis of significant univariate factors influencing advanced staging in tongue and buccoalveolar complex OSCC

Tongue OSCC				
Variable	**p - value**	**Hazards ratio**	**95.0% confidence interval**	
			Lower	**Upper**
Cardiac Issues	0.054	3.43	0.98	12.0
Pain	0.398	1.30	0.71	2.40
Referred Otalgia	0.258	2.03	0.60	6.89
Speech Disturbance	0.968	1.05	0.12	9.42
Dysphagia	**0.020**	14.73	1.54	141.46
Halitosis	0.166	5.03	0.51	49.44
Number of Symptoms more than 3	0.146	0.29	0.06	1.54
Buccolalveolar complex OSCC				
Variable	**P - value**	**Hazards ratio**	**95.0% confidence interval**	
			Lower	**Upper**
Dysphagia	0.095	3.46	0.81	14.82
External swelling/lesion	**0.002**	3.36	1.54	7.35
Tooth Issues	0.224	1.67	0.73	3.82
Number of Symptoms more than 3	0.208	1.83	0.72	4.66

Discussion:

The major reason behind the delayed diagnosis of OSCC is considered to be the asymptomatic nature of disease presentation(1, 11). Although some patient fails to recognize the symptoms especially in early-stage disease, most tend to ignore the symptoms(5). Prevalence of OSCC among elderly men of lower socioeconomic status is another important factor for late diagnosis. To add to this, in India facilities to treat OSCC are not widely available(12). In addition, factors like the ongoing pandemic overwhelming the health care system will also contribute to the delayed diagnosis. People tend to underestimate the risk of premature mortality and morbidity associated with the use of tobacco products and OSCC(13).

The importance of early detection of OSCC has been well recognized especially in India, Srilanka, Bangladesh, Pakistan and Southeast Asian countries where the prevalence of malignancy is very high(6, 8, 14, 15). Self-examination of the oral cavity might be helpful in high-risk groups(16). However, screening is extremely difficult in highly populous countries like India. Hence, most often patients present to a primary care physician before being referred to a higher center leading to undue delay in treatment initiation. The median duration of symptoms when a patient presents to a referral center to receive definitive treatment was 6 months in our study. This was similar to a

study done by Joshi et al.(7months) in India, but it is much higher when compared to the study by McGurg et al(3months), which was on a different population(17, 18).

Like in other studies it was noted OSCC involves BAC more commonly compared to tongue, with an average age of incidence being the fifth decade. Patients with tongue OSCC were younger, similar to other reported literature(19).

About 34% of tongue OSCC and 26% of BAC OSCC were asymptomatic. Other than the lesion in the oral cavity, the most common symptom was pain, which was noted in about half of the patients. The same has also been noted in previous studies(1, 5). It was noted that OSCC involving tongue and BAC has different symptom characteristics. Next to pain, the most common symptoms of tongue OSCC were dysphagia(21.6%) and speech-related issues(19.4%). Whereas in BAC OSCC the common symptoms were external swelling or lesion in the face and neck(28.5%) followed by difficulty in mouth opening(19.4%).

Pain in OSCC are related to nerve involvement, infection, or it is also related to endothelin-1 (ET-1) and nerve growth factor which have nociceptive effects in the tumor microenvironment(20). PNI is a well-known histological factor, which influences the disease outcome. PNI denotes tumor cells invading the perineural tissue or tracking along the nerves or surrounding one-third circumference of the nerve.

The study by Hechler on tongue OSCC noted a significant association between pain(39.8%, p=0.006) and otalgia(56%, p<0.001) with PNI(21). We have noticed a similar result, in our study, especially for tongue subset where 61% of patients with pain had PNI(p=0.008) and 65.6% with otalgia had PNI. However, the latter did not meet statistical significance (p=0.129), which might be because of a fewer number of cases in referred otalgia group. To add a step further it was noted that pain was also significantly related to DOI. In tongue OSCC it was noted that patients with pain(average DOI 9.9mm) had a higher DOI compared to the patient with no pain(average DOI 6.9mm) which was further increased in patients with referred otalgia(average DOI 11.4mm). This may favor a compartmental resection of tongue OSCC in patients especially in those who have pain(22). The same couldnot be replicated in BAC cancer.

Tobacco remains the top officially permitted substance that remains in the market. As per the Global Adult Tobacco Survey estimate, 10.7% (99.5 million) of adults currently smoke Tobacco and 21.4%(199.4 million) of adults use the smokeless form of Tobacco(23). Although in our study these habits did not directly influence the stage of disease, we noted a high usage of smokeless tobacco products(84.3%) among patients who developed BAC OSCC. On the contrary, 35.8% of patients with tongue OSCC had not used tobacco products or consumed alchohol.

The staging of cancer plays a crucial role in cancer management as it directs the treating clinicians for making the right decision and further proceeding with management(24). We have noticed, in clinical history symptoms, that presence of dysphagia in tongue OSCC is associated with hazards ratio of 14.73 to have an advanced stage disease (95% CI, 1.54 -141.46; P = 0.02) and external swelling or lesion in BAC SCC has a hazards ratio of 3.36 to have an advanced stage disease(95% CI, 1.54-7.35; P = 0.002). It also expands the corridor to understand various factors related to OSCC. Detection of OSCC in an advanced stage, in addition to the poor disease survival, also, has various direct and indirect impacts on the patients and caregivers. A study by Epstein et al. noted that the cost of care for early-stage OSCC is 36% less than the advanced stage(25). Advanced stage OSCC will require a more complex surgery with higher morbidities and would invariably require radiotherapy or chemoradiotherapy. Ultimately, the quality of life and functional impairment of such patients will be worse compared to early-stage disease(26). To take it to a next level, few in the advanced group cannot be treated and they end up in palliative treatment(1). Globally neoplasm stands second only next to cardiovascular diseases in Years of Life Lost (YLLs) and disability-

adjusted life year(DALYs)(27). Still, the majority of patients present in an advanced stage of disease especially among those with BAC OSCC (65.3%) and they tend to face the above-mentioned issues. A study by Chandrana et al. noted 61% of patients presenting in advanced stage disease(12).

The study will help people to be aware of the early symptoms of OSCC and also to warn patients regarding the advanced nature of the disease especially the high-risk individuals. Moreover, we could understand the difference in the clinical pattern of two distinct subsites of OSCC and its significance. PNI is not consistently visualized radiographically(28). Pain may be used as a preoperative tool to predict PNI and DOI. The need for aggressive treatment especially concerning pain and its clinic-radiological correlation, needs further prospective evaluation. The drawbacks of the study is clinical symptoms are subjective and the study is retrospective. A prospecitve study of pain with especially tongue subsite will further add to the understanding on this subject.

Conclusion:

There appears to be a serious delay among patients with OSCC to get definitive treatment care. Belligerent screening and awareness should be undertaken to overcome the above problem. Clinical symptoms, especially dysphagia (consider better terminology, dysphagia in tongue SCC and external swelling or lesion in BAC SCC were strong predictors of an advanced stage of disease. Pain especially in tongue OSCC had a significant correlation with PNI and DOI so the need for an aggressive treatment approach in this group needs further prospective evaluation. Smokeless tobacco had a strong relation with development of BAC cancer and majority of which presented in an advanced stage in this study.

Declarations

AUTHORS CONTRIBUTION:

Author name	Research and Study design	Data collection & analysis	Interpretation and conclusion	Preparation of Manuscript	Review of Manuscript	Guide and critical revision	Technical Support
JR	√	√	√	√	√		√
AJT	√		√	√	√	√	
MB	√	√	√	√	√	√	
RA		√			√		√
AMB	√				√		
KV					√		√
MA					√		√

Competing interests:

Nil.

Informed consent:

Informed consent was Exempted from ethics committee/IRB of Christian Medical College, Vellore[IRB Min no: 137759], due to retrospective study design.

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Figures

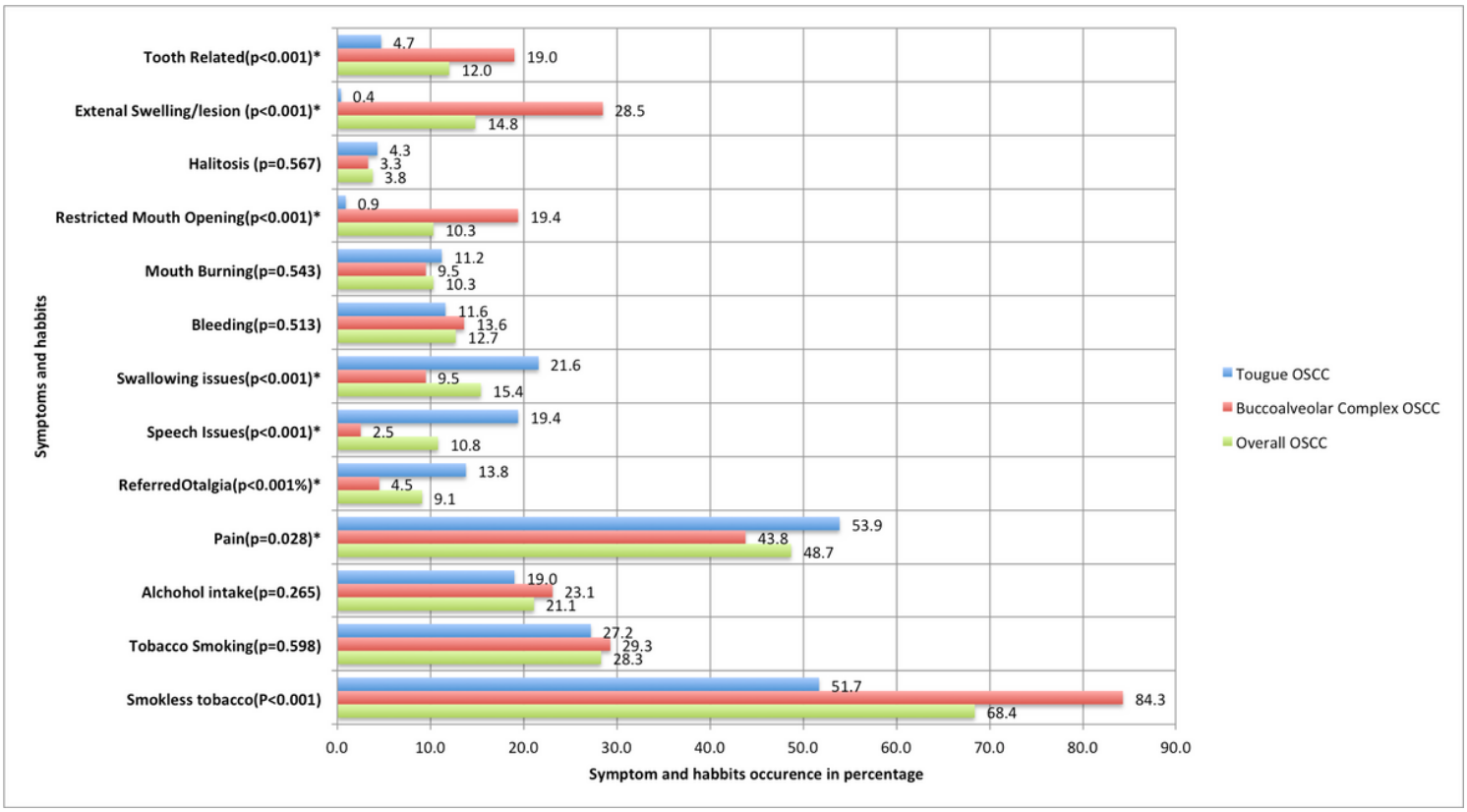

Figure 1

Bar diagram showing various symptoms and habits, occurrence in percentage based on specific sub sites and combined. Tongue cancer and BAC cancer groups compared to obtain p-value.

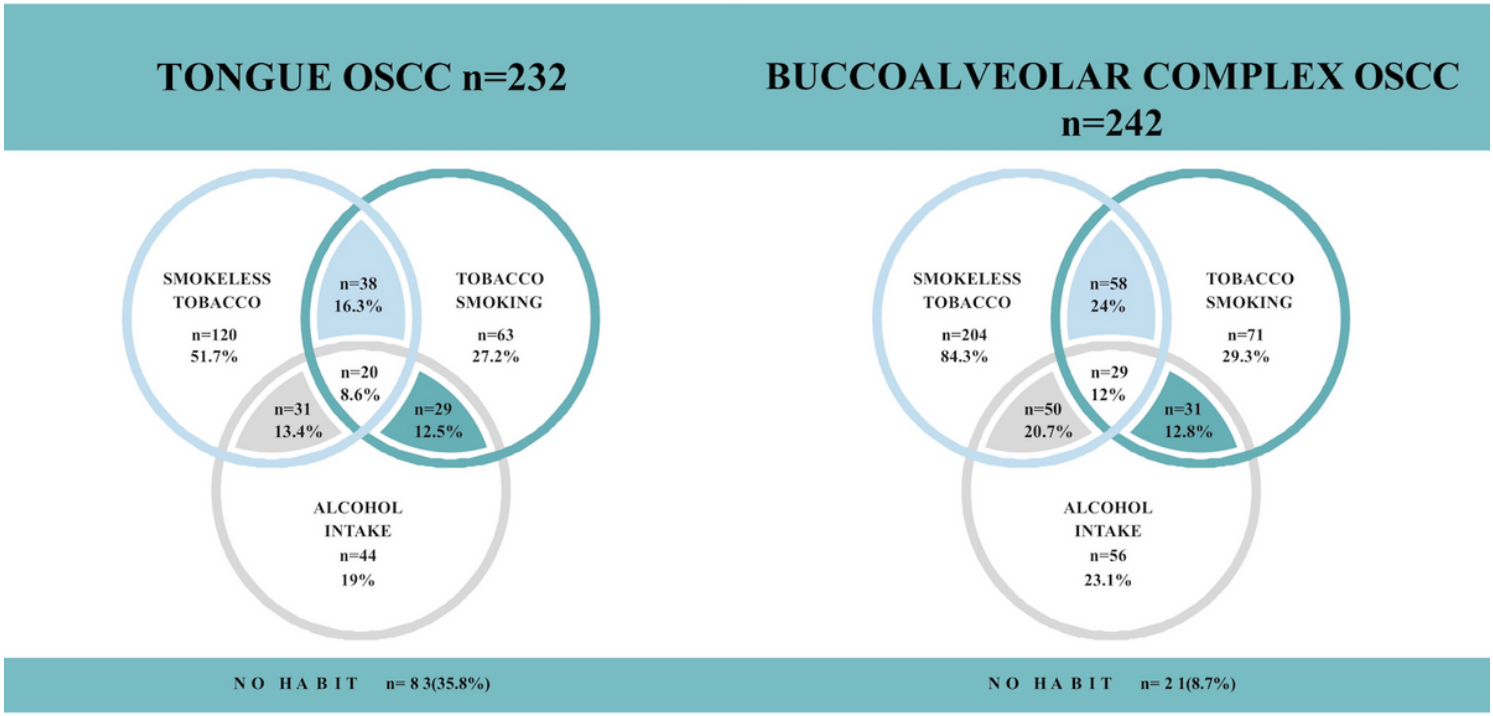

Figure 2

Venn diagram showing comparison of substance abuse.