

Clinicopathological parameters of oral squamous cell carcinoma in Florianópolis: A 10-year study

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Abstract:

Oral squamous cell carcinoma (OSCC) is one of the most common cancers and presents the highest mortality rate of head and neck tumours. The aim of this study was to evaluate the clinical and histological features of patients with OSCC in Florianópolis, Santa Catarina, Brazil between 2006 and 2016. Demographic and clinical characteristics such as age, gender, tobacco and alcohol consumption, anatomical site, clinical stage, and treatment were retrospectively collected from histopathological and medical reports. Of 196 patients with OSCC, 82.14% were male with a mean age of 58.28 ± 10.45 years. Tobacco and alcohol consumption was reported in 88.76% and 75.9% of patients, respectively. The tongue was the anatomical site most affected (25.13%) and ulcers were the most prevalent clinical aspect (95.21%). A total of 103 (52.55%) patients were diagnosed with advanced stage (III/IV). Regarding treatment, 59.24% received more than one type of therapy, while 39.67% were treated exclusively with surgery. Regarding histological differentiation, 72.9% of the cases were moderately/poorly differentiated, 23.8% had vascular invasion, 17.9% had lymphatic invasion, and perineural invasion was observed in 29.5% of the patients. The survival rate showed a worse prognosis for patients diagnosed at stage III/IV and the primary tumour was located in the inferior level of the mouth in 80% of these cases. The results showed that the majority of cases were diagnosed at an advanced stage, compromising treatment and prognosis. Educational and preventive measures should be improved in an effort to allow for early diagnosis.

Keywords: Carcinoma, Squamous Cell; Head and Neck Neoplasms; Ulcer; Tongue.

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INTRODUCTION

Head and neck squamous cell carcinoma is the sixth most common cancer in the world, and most frequently involves the oral cavity. In Brazil, oral cancer is the seventh more frequent cancer¹; in the United States, it has been estimated that 49.670 new cases and 9.700 deaths occurred in 2017². Most patients have advanced disease at the time of diagnosis, with a poor prognosis and a 5-year survival rate less than 50%^{3,4}. Squamous cell carcinoma represents approximately 90% of all oral cancers, and treatment usually results in a high morbidity and mortality⁵.

Alcohol and tobacco consumption is strongly associated with oral squamous cell carcinoma (OSCC) and their cumulative effects decrease patient survival⁶. Recently, OSCC has been correlated with human papilloma virus (HPV), especially HPV-16 in oropharyngeal squamous cell carcinoma (OP-SCC)⁷. The survival outcomes are influenced by variable factors such as disease stage, primary tumour site, nodal metastasis, status of the surgical margins, histological grade, tumour thickness, and perineural invasion^{8,9}.

Epidemiological studies are necessary to clarify the incidence of oral cancer worldwide and the prevalence differs significantly among areas in which the influence of different risk factors must be considered. Knowledge of patient profiles of oral cancer will provide a better understanding of the disease and guide public health preventive measures. Although there is a high prevalence of oral cancer in southern Brazil, epidemiological studies in this location are scarce. The aim of the present study was to analyse the clinical and histological features of patients diagnosed with primary oral and oropharyngeal squamous cell carcinoma in Florianópolis, Santa Catarina, Brazil between 2006 and 2016, and to correlate the clinical reports with recurrence and survival rates.

MATERIALS AND METHODS

A total of 196 patients diagnosed with OSCC between 2006 and 2016 at the University Hospital of Federal University of Santa Catarina were evaluated through their medical records. This research was approved by the Ethics Committee on Human Research of Federal University of Santa Catarina, Florianópolis, Brazil (# 1.215.468).

Oral, lip, and oropharyngeal squamous cell carcinomas cases were included in the study. Sociodemographic characteristics including age,

gender, skin colour, occupation; habits such as smoking and alcohol consumption; clinical features such as anatomical site, presence of pain, evolution time, clinical aspects, TNM stage, treatment, tumour recurrence, and survival rates were obtained from medical records. Histological characteristics of biopsies and surgical specimens processed and fixed onto glass slides were reviewed by two expert pathologists. The lesions were classified according to histological differentiation (well differentiated or moderately/poorly differentiated), presence of vascular, lymphatic or perineural invasion, and status of the surgical margins¹⁰. Cases with insufficient clinical or microscopic information were excluded from the study.

Statistical analysis

The categorical variables were summarised as frequencies/percentages, and Pearson chi-squared and Kruskal–Wallis tests were performed. Spearman's correlation test was used to assess the clinical and microscopic variables. Kaplan–Meier cumulative survival curves were generated and compared using the log-rank test. The software used was SPSS version 18.0 and the level of statistical significance was set at 5% ($P < 0.05$).

RESULTS

Clinical findings

Among the 196 cases of OSCC, 161 (82.14%) occurred in males, and 61.48% of men affected were classified as advanced stage (III/IV), while 62.5% of women affected were classified as stage I/II ($p = 0.013$). The male:female ratio was 4.6:1. The mean age at time of diagnosis was 58.28 ± 10.45 years (range, 32–92 years). Regarding tobacco consumption, 88.7% of patients were smokers and 64.8% of these were classified as stage III/IV ($p = 0.007$); 75.9% reported alcohol consumption and the majority of these cases were classified as advanced stage ($p = 0.003$). Regarding the tumour size, 63.7% were described as T1/T2, and 36.3% as T3/T4. The majority of stage III/IV patients reported the evolution time of the disease in 0–3 months ($p = 0.011$), and painful symptomatology was reported by 44.3% of patients. The tongue was the anatomical site most affected (25.1%), followed by the lip (14.8%). The main clinical aspect presented was ulcer (95.2%), and 57.2% were characterised as advanced stage (TNM III/IV). Patient characteristics are summarised in Table 1.

Regarding treatment modality, 59.2% of the patients received more than one type of therapy, and

Table 1. Descriptive analysis of clinical and histological findings of patients with oral squamous cell carcinoma.

	Variable	Mean/SD	Min-Max
Age		58.28 ±10,45	32-92 years
		Absolute frequency (n)	Relative frequency(%)
Gender	Male	161	82.1%
	Female	35	17.9%
Skin Color	White	170	92.4%
	Black	9	4.9%
	Others	5	2.7%
	NA	12	
Occupation	Manual workers	85	48.2%
	Non-manual workers	42	23.7%
	Domestic workers/retired	50	28.1%
	NA	19	
Tobacco consumption	Smoker	158	88.8%
	Non-smoker	20	11.2%
	NA	18	
Alcohol consumption	Yes	126	75.9%
	No	40	24.1%
	NA	30	
Anatomic site	Tongue	49	25%
	Lip	29	14.9%
	Mouth floor	28	14.4%
	Multiple areas	30	15.4%
	Amygdala	21	10.2%
	Retromolar area	15	7.7%
	Palate	13	6.7%
	Gingiva	8	4.1%
	Oral mucosa	3	1.6%
Pain	Pain	87	44.4%
	Painless	109	55.6%
Evolution time	0-3 months	45	36.6%
	3-6 months	28	22.8%
	6-12 months	35	28.4%
	>12 months	15	12.2%
	NA	73	
Clinical Aspects	Ulcer/erythroplakia	159	95.2%
	Plaque/nodule/leucoplakia	8	4.8%
	NA	29	
Tumor Size	T1/T2	116	63.7%
	T3/T4	66	36.3%
	NA	14	
TNM Stage	I/II	77	42.8%
	III/ IV	103	57.2%
	NA	16	
Treatment	Surgery	73	39.7%
	Radiotherapy	2	1.1%
	Combination therapy	109	59.2%
	NA	16	

Treatment	Surgery	73	39.7%
	Radiotherapy	2	1.1%
	Combination therapy	109	59.2%
	NA	12	
Recidive	Yes	53	26.5%
	No	140	73.5%
Histologic differentiation	Well	35	27.1%
	Moderately/ Poorly	94	72.9%
	NA	67	
Vascular invasion	With vascular invasion	25	23.8%
	No vascular invasion	80	76.2%
	NA	91	
Lymphatic Invasion	With lymphatic invasion	19	17.9%
	No lymphatic invasion	87	82.1%
	NA	90	
Perineural Invasion	With perineural invasion	31	29.5%
	No perineural invasion	74	70.5%
	NA	91	

*NA: not available

39.7% were treated exclusively with surgery; 79.4% of those treated with surgery only were diagnosed as stage I/II and 88.8% of the patients that received more than one treatment modality were classified as stage III/IV ($p < 0.001$) (Table 2). Regarding recurrence, 26.5% of the patients experienced disease recurrence at some point during follow-up, and of these patients, 55.7% were diagnosed as stage III/IV, and the primary tumour was located in the inferior level of mouth in 61.5% of patients. However, recurrence was not correlated with clinical stage ($p = 0.238$) or histological differentiation of the tumour ($p = 0.837$).

Histological findings

Classification of histological differentiation was available in 129 patients (Table 1) and revealed that 72.9% were moderately/poorly differentiated, 23.8% presented vascular invasion, 17.9% presented lymphatic invasion, and 29.5% of patients exhibited perineural invasion. Most of the cases that exhibited vascular ($p < 0.001$) and perineural invasion ($p = 0.038$) were correlated with stage III/IV (Table 3). The absence of lymphatic invasion was observed mostly in cases of stage I and II ($p < 0.001$).

Survival rates

Regarding survival rates, at the end of the study, 94.9% were alive, with an average follow-up time of 41.4 ± 32.1 months (range, 7–127 months).

Stage III/IV had the worst prognosis ($p = 0.021$). In terms of risk factors and survival rates, non-smokers had a better survival at 25 months, although the difference was not statistically significant ($p = 0.587$); however, smokers had a better outcome. Alcohol use presented the worst survival, even if not statistically significant ($p = 0.161$).

The histological features did not present a statistically significant difference with survival rates ($p = 0.752$), although the cases described as moderately and poorly differentiated presented worse survival rates at 40 months compared to well-differentiated tumours. Patients with lymphatic invasion had a worse outcome at 37 months, similar to vascular invasion. Patients without perineural invasion had a better prognosis at 120 months, although this difference was not statistically significant ($p = 0.74$) (Figure 1).

DISCUSSION

OSCC is a disease with high morbidity and mortality, with a high incidence rate, making it a public health issue¹¹. Previous studies have shown that most of the patients affected by oral and oropharyngeal cancer are male, older than 45 years, and with the presence of risk factors such as alcohol and tobacco consumption. Our data collection revealed a higher prevalence of OSCC in males, with a mean age of 58.28 years, consistent with other epidemiological studies^{11,12}. Tobacco consumption continues to be a major risk factor

Table 2. Clinical aspects correlation with clinical stage

Clinical Stage	Clinical Stage i/ii	Clinical stage III/IV	<i>p</i> -value
Gender			
Male	57 (38.5%)	91(61.5%)	0.013
Female	20(62.5%)	12(37.5%)	
Tobacco consumption			
Smoker	55(38.2%)	89(64.8%)	0.007
Non-smoker	14(70%)	6(30%)	
Alcohol consumption			
Yes	39(33.6%)	77(66.4%)	0.003
No	23(60.5%)	15(39.5%)	
Anatomic area			
Tongue	21(44.6%)	26(55.4%)	<0.001
Mouth floor	12(48%)	13(52%)	
Lip	24(96%)	1(4%)	
Others	20 (24.4%)	62(75.6%)	
Evolution time			
0-3 months	12(28.5%)	30(71.5%)	0.011
3-6 months	10(38.4%)	16(61.6%)	
6-12 months	15(46.8%)	17(53.2%)	
>12 months	11(78.5%)	3(21.5%)	
Treatment			
Surgery	58(79.4%)	15(20.6%)	<0.001
Radiotherapy	2(100%)	0	
Combination therapy	17(16.2%)	88(83.8%)	
Neck dissection			
With neck dissection	32(35.5%)	58(64.5%)	<0.001
No neck dissection	22(80%)	3(20%)	

Table 3. Histologic features correlation with clinical stage.

Clinical Stage	I/II	III/IV	<i>p</i> -value
Histologic Differentiation			
Well differentiated	20(48.8%)	21(51.2%)	0.095
Moderately/poorly differentiated	33(38.4%)	53(61.6%)	
Vascular invasion			
With vascular invasion	3(13.6%)	19(86.4%)	< 0.001
No vascular invasion	36(70.5%)	15(29.5%)	
Lymphatic invasion			
With lymphatic invasion	1(6.2%)	15(93.8%)	< 0.001
No lymphatic invasion	35(70%)	15(30%)	
Perineural invasion			
With perineural invasion	10(38.4%)	16(61.6%)	0.038
No perineural invasion	24(64.8%)	13(25.2%)	

for oral and oropharyngeal cancer, and its risk appears to be dose-dependent with cumulative effects. In addition, alcohol consumption acts synergistically with tobacco, increasing the risk of OSCC¹³. In our study, 88.8% of the patients affected by OSCC were smokers and 75.9%

reported daily consumption of alcohol; this data is consistent with previous reports^{11,14,15}.

Another risk factor that has been described for oral and oropharyngeal squamous cell carcinoma is HPV infection. Although HPV is present in considerable

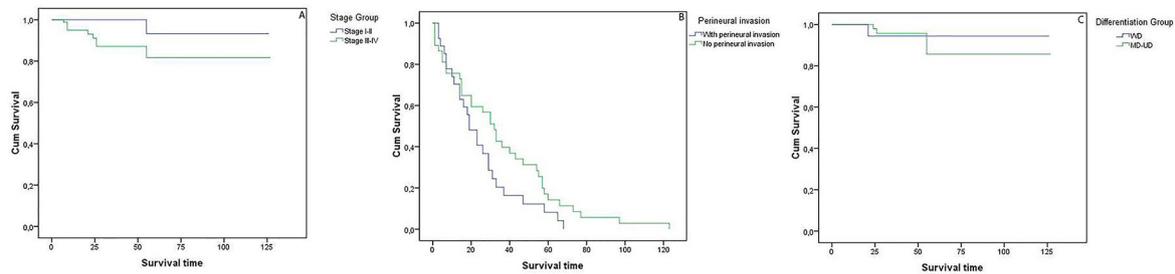


Figure 1. A- Kaplan–Meier survival rates in months by stage of disease. Stage III/IV was correlated with a low survival rate ($P=0.021$). B- Kaplan–Meier survival rates in months by histologic differentiation. The moderately/undifferentiated group was correlated with a worse survival rate at 50 months ($P=0.752$). C- Kaplan–Meier survival rates in months in patients with perineural invasion. Perineural invasion presented a worse prognosis ($P=0.074$).

subgroups of cancers, not all HPV-positive tumours can be considered etiologically driven by HPV¹⁶. Recent reports have presented data indicating a discrepancy in HPV DNA positivity and oncogene activity. The majority of the cases of HPV-positive OSCC are negative for p16INK4A overexpression, which is also true in HPV-negative tumours^{17,18}. Expression of E6/E7 in HPV DNA-positive OSCC could detect expression of viral oncogenes in only 6–7% of cases, supporting the notion that HPV is not biologically active in most cases of OSCC^{17,18}.

Recently, an increase in the incidence of OSCC in young patients has represented approximately 4–13% of all cases of OSCC¹⁹. In our study, 6.12% of patients were less than 45 years old and half of these patients were women that did not report alcohol and tobacco consumption. The OSCC aetiology in these patients is still poorly understood, and usually diagnosed at a late stage of the disease, leading to more aggressive treatment. Some hypotheses regarding the aetiology have been suggested over the years, such as environmental factors, family history of head and neck cancer, HPV, and genetic alterations^{20,21}.

The clinical aspect most observed in oral cancer is ulcers, as described by Oliveira et al.¹¹, and in our study, 95.2% of patients experienced an ulcer or erythroplakia. Several epidemiological studies have revealed that the tongue is the anatomical site most commonly affected by oral cancer^{11,12,15}. As noted in this study, the tongue was the location of the primary tumour in 25% of patients. In addition, the tongue and floor of the mouth have a worse prognosis and higher possibility of developing node metastasis, requiring aggressive treatment^{22,23}.

Lip cancer has been described by some authors as one of the most common head and neck cancers, compromising approximately 25–35% of all cases in this region²⁴. In this study, lip cancer was the second most frequent, affecting

14.8% of all cases, which might be explained by our geographic region, skin colour, and frequent sun exposure, as one of the main aetiological factors of lip cancer is long-term exposure to ultraviolet (UV) radiation and fair skin²⁵. Chronic cheilitis appears as one of the most frequent precancerous lesions²⁵, and when diagnosed early can prevent the onset of oral cancer. In this study, 96% of lip cancers were classified as stage I/II ($p<0.001$). Males were more affected (72%) by lip cancer than women, which may be explained by the higher number of men working under sun exposure or the fact that women apply lipstick, which is known to protect against the effects of UV radiation.

OSCC is detected in the late stages in the majority of cases²⁶, as observed in this study with 61.5% of the men diagnosed at stage III/IV, whereas 62.5% of the women were diagnosed at stage I/II ($p=0.013$). This difference might be explained by women attending medical appointments more regularly than men, favouring early diagnosis of the disease. Stage III/IV was also correlated with an evolution time of less than 3 months ($p=0.011$), tobacco consumption ($p=0.007$), alcohol use ($p=0.003$), application of multiple therapies ($p<0.001$), and a poor prognosis ($p=0.021$).

In this study, all of the patients who died were diagnosed with stage III/IV, as described in other studies correlating an advanced stage with a poor prognosis^{11,26}. Moreover, 78 patients presented an evolution time greater than 3 months, demonstrating a delayed diagnosis. This may have been a result of several factors, such as lack of oral health care by the patients, professionals unprepared to detect early stage cancer and/or precancerous lesions, insufficient information of the risk factors related to oral cancer, or an increase in the incidence of OSCC in the Brazilian population.

The modality of treatment of oral cancer is determined according to the clinical stage, tumour location, and the patients' physical conditions. Surgical

treatment is recommended for small tumours²⁷; in this study, 77.6% of the patients in stage I and II were treated with surgery only, while advanced stage cancers were treated with combination therapy.

Several tools have been studied for determining prognostic factors of OSCC, such as histological differentiation of the tumour and stage of the disease^{4,9}. In this study, 72.9% of the tumours were classified as moderately or poorly differentiated and 61.6% of the patients were in stage III or IV, as has been described by other studies⁴. Lymphatic invasion has been correlated with a higher recurrence rate and a poor prognosis²³ as revealed in the current study. Perineural invasion is correlated with a poor outcome in salivary gland malignancies and colorectal carcinomas, but in oral cancer its importance as a tool for prognosis remains unclear. Jardim et al.⁹ demonstrated a correlation between perineural invasion and decreased overall survival. Our data showed that patients without perineural invasion had a better prognosis. This report suggests that histological features such as poor differentiation and lymphatic and perineural invasion should be considered to determine the therapy modality; aggressive treatment should be offered once these characteristics are correlated with poor prognosis and lower survival rates.

Epidemiological studies are important for a better understanding of the disease in the population. The lack of information in some medical records was an important limiting factor in our work; we believe that retrospective analysis not only contributes to the prevention and early detection of cancer, but also to a better understanding of treatment modalities and their impacts on survival rates. This work highlights that patients are diagnosed at an advanced stage in the vast majority of cases and campaigns providing information about the clinical aspects and risk factors of oral cancer are important in early detection of the disease.

CONCLUSIONS

After analyses of 196 patients with oral and oropharyngeal cancer in Florianópolis, Santa Catarina, Brazil, was observed that this disease is frequently diagnosed at stage III/IV. It is relevant to mention that risk factors identification is an important tool for oral cancer prevention. Public strategies focused on education and preventive actions should be implemented to allow for early detection of oral cancer. Further well-structure epidemiological studies in south of Brazil are necessary for better oral health promotion strategy.

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