Original

http://dx.doi.org/10.1590/1981-86372025001520240078

Revista Gaúcha de Odontologia

Clinical-pathological characteristics and risk factors for oral squamous cell carcinoma in young patients

Características clínico-patológicas e fatores de risco para o carcinoma epidermóide oral em pacientes jovens

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ABSTRACT

Objective: To evaluate the clinical-pathological characteristics and risk factors of patients with young oral squamous cell carcinoma at a referral service in oncology. **Methods**: A retrospective analysis of 12 patients diagnosed with squamous cell carcinoma in the oral cavity treated between 2006 and 2015 was performed, and the following data were collected: age, sex, habits, anatomical location of the lesion, clinical stage of the tumor, time of disease, clinical characteristics, histological gradation, comorbidities, family history of cancer, therapeutic modality and outcome. **Results**: The average age found was 39 years old (SD ± 5.3). Most of the sample consisted of male individuals (n=9; 75%), risk factors were present in 5 patients (41.6%) and the most affected site was the tongue (n=7; 58, 3%). Symptoms were present in most patients (n=7; 58.3%) studied, as well as clinical staging III and IV (n=9; 75%). Surgery associated with radio and/or chemotherapy was used in 5 cases (41.7%) and most patients died. **Conclusion**: Most of the patients had advanced clinical stage, leading

How to cite this article

Carlan LM, Morais MLSA. Clinical-pathological characteristics and risk factors for oral squamous cell carcinoma in young patients. RGO, Rev Gaúch Odontol. 2025;73:e20250015. http://dx.doi.org/10.1590/1981-86372025001520240078

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to high rates of recurrence and therapeutic failure, contributing to a negative prognosis and high mortality rates.

Indexing terms: Carcinoma, squamous cell. Mouth neoplasms. Neoplasms, squamous cell. Prognosis. Risk factors.

RESUMO

Objetivo: Avaliar as características clínico-patológicas e fatores de risco dos pacientes com carcinoma de células escamosas oral jovens em um serviço de referência em oncologia. **Métodos**: Foi realizada uma análise retrospectiva de 12 pacientes diagnosticados com carcinoma de células escamosas em cavidade oral tratados entre 2006 e 2015, sendo coletados os seguintes dados: idade, sexo, hábitos, localização anatômica da lesão, estadiamento clínico do tumor, tempo da doença, características clínicas, gradação histológica, comorbidades, histórico familiar de câncer, modalidade terapêutica e desfecho. **Resultados**: A idade média encontrada foi de 39 anos (SD ± 5,3). A maior parte da amostra era composta por indivíduos do sexo masculino (n=9; 75%), os fatores de risco estavam presentes em 5 pacientes (41,6%) e o sítio mais acometido foi a língua (n=7; 58,3%). A sintomatologia esteve presente na maioria dos pacientes (n=7; 58,3%) estudados, assim como o estadiamento clínico III e IV (n=9; 75%). A cirurgia associada a radio e/ou quimioterapia foi utilizada em 5 casos (41,7%) e a maioria dos pacientes evoluíram para óbito. **Conclusão**: Grande parte dos pacientes apresentaram estágio clínico avançado, levando altas taxa de recidiva e insucesso terapêutico, contribuindo para um prognóstico negativo e altas taxas de mortalidade.

Termos de indexação: Carcinomas de células escamosas. Neoplasias bucais. Neoplasias de Células Escamosas. Prognóstico. Fatores de risco.

INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) is the most common histological type of neoplasm affecting the oral cavity, accounting for approximately 90% of malignant neoplasms in this region [1,2]. It has a complex and multifactorial etiology, predominantly affecting men in their sixth and seventh decades of life, particularly smokers and alcohol consumers. OSCC is considered a public health issue due to its high morbidity and mortality rates [3,4].

Among young adults, the occurrence of OSCC is rare, accounting for less than 5% of all cases [5]. Nevertheless, a growing incidence of OSCC has been observed in this population, particularly among women with no history of tobacco and/or alcohol exposure [6]. Several authors have proposed that OSCC in this group of patients may constitute a distinct and heterogeneous biological entity, with underlying causes that remain largely unknown [7,8].

Evidence suggests that OSCC in younger patients exhibits greater aggressiveness compared to cases affecting older patients [9,10]. However, defining the prognosis remains challenging, and more precise prognostic markers are needed to assess the aggressiveness of OSCC in this population. Lymph node metastasis, tumor location, and TNM classification have been cited as clinical prognostic indicators [2]. Nevertheless, there are few studies worldwide on the clinical prognostic factors of OSCC in young patients.

In this context, the aim of the present study was to examine and describe a series of cases of oral squamous cell carcinoma in young patients diagnosed at a Reference Oncology Center in Northeast Brazil over a 10-year period. The study sought to assess the epidemiological profile of these patients and to correlate their clinical and pathological features.

METHODS

This study is a retrospective 10-year analysis conducted using the medical records of young individuals diagnosed with OSCC between 2006 and 2015 at a Reference Oncology Center. The study received approval from the local Ethics and Research Committee under protocol number 2.445.452.

Patients with follow-up periods of five years or longer without signs of recurrence were classified as disease-free [11]. Young patients were defined as those aged 45 years or younger [12]. Exclusion criteria included other neoplasms occurring in the oral cavity, recurrent lesions, squamous cell carcinoma in other anatomical sites (such as the lip and oropharynx), and cases with insufficient diagnostic information.

Data on age, sex, tumor location, duration of symptoms, clinical features, histological grading, signs, treatment, follow-up, comorbidities, family history of cancer, therapeutic modality, and disease outcomes were collected. The data were analyzed descriptively based on absolute and relative frequencies, using Microsoft Office Excel® 2010.

RESULTS

Between 2006 and 2015, 164 patients were diagnosed with OSCC, of whom 12 (7.3%) were young patients. Ages ranged from 22 to 45 years, with a mean age of 39 years (SD ± 5.3). The majority were male, accounting for 9 cases (75%), while females comprised 3 cases (25%), resulting in a male-to-female ratio of 3:1. The duration of symptoms ranged from 2 to 12 months, with a mean of 4.4 months (SD ± 2.7). Risk factors (smoking and/or alcohol consumption) were identified in 5 cases (41.6%). The tongue was the most affected site (n=7; 58.3%). Most patients had no comorbidities (n=9; 75%) or family history of cancer (n=8; 66.6%). The most common clinical presentation was an exophytic lesion (n=6; 50%), while tumor-associated symptoms were present in 7 patients (58.3%) (table 1).

Table 1. Distribution of sociodemographic, clinical, and histopathological parameters.

PAC	SEX	ID	TD	COMOR	FR	HFC	LOC	CC	SIN	TNM	Estad. C.	Grad. H.
1	M	45	6	-	T + ET	-	Tongue	LE	+	T3N0M0	III	MD
2	M	39	2	O	-	-	Tongue	LE	-	T1N0M0	I	MD
3	F	31	3	-	-	+	Tongue	LE	+	T1N0M0	I	BD
4	M	43	2	H+TP	-	-	Tongue	LE	-	T3N2bM0	IV	MD
5	F	38	4	-	-	+	Tongue	LEX	-	T2N0M0	II	MD
6	M	37	5	-	T + ET	-	Tongue	LEX	+	T4N2M1	IV	MD
7	M	39	3	-	-	-	Palate	LEX	+	T4N0M0	IV	MD
8	M	44	5	-	T + ET	-	Palate	LEX	-	T2N3M0	IV	MD
9	M	41	2	-	T + ET	-	Tongue	LE	-	T4N2bM0	IV	MD
10	M	45	7	-	T + ET	-	Floor of mouth	LEX	+	T4N3M0	IV	MD
11	F	28	12	-	-	+	Gengival	LEX	+	T4N1M0	IV	MD
12	M	22	3	TP	-	+	Buccal mucosa	ER	+	T4N0M0	IV	FUSIF

Note: (-) = absent; (+) = present. BD: Well differentiated; CC: Clinical characteristic; COMOR: Comorbidities; ER: Erythroplakia; Estad. C.: Clinical staging; ET: Alcohol consumption; F: Female; FR: Risk factors; FUSIF: Spindle cell type SCC; Grad. H.: Histopathological grading [13]; H: Hypertension; HFC: Family history of cancer; ID: Age; LE: Endophytic lesion; LEX: Exophytic lesion; LOC: Tumor location; M: Male; MD: Moderately differentiated; O: Obesity; Pac: Patient; SIN: Symptoms; T: Smoking; TD: Duration of disease (months); TP: Psychological disorder.

Regarding clinical staging, 6 cases (50%) presented with tumor size classified as "T4," and an equal number had regional lymph node metastases. Consequently, advanced stages (III and IV) were observed in 9 patients (75%). The most prevalent histopathological grading was moderately differentiated tumors (n=10; 83.3%), with one case of a rare histopathological variant, spindle cell squamous cell carcinoma (Case 12) (table 1).

Initial treatment consisted of surgery combined with radiotherapy and/or chemotherapy in 5 patients (41.7%). Regarding survival outcomes, 6 patients (50%) died due to uncontrolled primary tumor progression, 3 patients (25%) experienced recurrence and subsequently died, 1 patient (8.3%) experienced recurrence but achieved disease-free status after treatment, and 2 patients (16.6%) had no recurrence and remained disease-free (table 2).

Table 2. Treatment and outcome of patients.

Patient	Initial TT	Recurrence	Recurrence type	Recurrence TT	Survivel
1	C+RT	-	-	-	LDD
2	C	3 months	M. linfonodal	C + RT + QT	LDD
3	C+RT+QT	14 months	M. linfonodal	C + RT + QT	DE (17 meses)
4	C+RT+QT	-	-	-	LDD
5	C+RT	9 months	Local	C + RT + QT	DE (15 meses)
6	-	-	-	-	DE (5 meses)
7	QT	-	-	-	DE (1 meses)
8	-	-	-	-	DE (1 meses)
9	QT	-	-	-	DE (6 meses)
10	QT	-	-	-	DE (5 meses)
11	C +RT	5 months	Local	C + RT	DE (9 meses)
12	QT	-	-	-	DE (19 meses)

Note: (-) = absent. C: Surgery; DE: Death; Initial TT: Initial treatment; LDD: Disease-free; Lymph node M.: Lymph node metastasis; N: None; QT: Chemotherapy; Recurrence TT: Treatment of recurrence; RT: Radiotherapy.

When comparing patients exposed to risk factors with those not exposed, it was observed that smokers and/or alcohol consumers had a higher mean age (42.4 years, SD ± 3 years). Additionally, this group exhibited a male predominance (n=5; 100%), advanced clinical staging (n=5; 100%), and a high mortality rate (n=4; 80%). In contrast, the second group had a mean age of 34.2 years (SD ± 6.9), with 3 patients (43%) presenting less severe clinical stages (table 3).

Table 3. Differences between smoking and/or alcohol-consuming patients and non-smoking, non-alcohol-consuming patients (n=12).

1 of 2

Variable	Smoking and/or alcohol consumption		No risk habits	
	n	%	n	%
Sex				
M	5	100	4	57
F	0	0	3	43

Table 3. Differences between smoking and/or alcohol-consuming patients and non-smoking, non-alcohol-consuming patients (n=12).

Variable	Smoking and/or alcohol consumption		No risk habits	
	n	%	n	%
Primary tumor site				
Tongue	3	60	4	58
Palate	1	20	1	14
Floor mouth	1	20	0	0
Buccal mucosa	0	0	1	14
Gum	0	0	1	14
Clinical staging				
I/II	0	0	3	43
III/IV	5	100	4	57
Histological grading				
BD	0	0	1	14
MD	5	100	5	72
O	0	0	1	14
Initial treatment				
C + RT	1	20	2	28.6
C + RT + QT	0	0	2	28.6
C	0	0	1	14
RT	0	0	0	0
QT	2	40	2	28.6
N	2	40	0	0
Outcome				
Cure	1	20	1	16.6
Recurrence + cure	0	0	2	40.6
Recurrence + death	0	0	3	50
Death	4	80	1	16.6

Note: BD: Well differentiated; C+RT: Surgery + radiotherapy; C+RT+QT: Surgery + radiotherapy + chemotherapy; F: Female; Initial TT: Initial treatment; M: Male; MD: Moderately differentiated; N: None; O: Other; QT: Chemotherapy; RT: Radiotherapy; T+E: Smoking and alcohol consumption; X: No habits.

DISCUSSION

Although OSCC is recognized as a malignant neoplasm primarily affecting elderly patients, its incidence in individuals under 45 years of age has increased substantially in recent years [9,12]. According to the analysis of this study, 7.3% of OSCC cases, occurring over a 13-year period in a city in Northeast Brazil, were diagnosed in young patients. However, higher prevalences have been reported in other studies, with rates ranging from 12% to 14% [14-16]. Regional, socioeconomic, and cultural characteristics of different

populations, along with methodological variations in the studies found in the literature, may explain the discrepancy observed in the reported prevalence of OSCC in this group [2,17].

In general, OSCC primarily affects males, regardless of age group. The results of this study align with those found in the literature, as 75% of OSCC cases in young adults occurred in men [3,14-16]. In contrast, some studies have reported a higher prevalence of this neoplasm in young women [18-20]. According to these authors, different population characteristics such as genetic predisposition, immune modulation, hormonal changes, and HPV infections may explain the differences in prevalence between sexes.

Regarding tumor location, OSCC can affect any site of the oral mucosa, with the tongue being the most commonly involved [21,22]. The tongue was also the most affected anatomical site in the present study, in agreement with the results of studies by Iamaroon et al. [11] and Udeabor et al. [23]

It is well-established that tobacco and alcohol consumption are significant risk factors for the development of OSCC in elderly patients. However, in young patients, the role of these risk factors in OSCC development remains questionable due to the short exposure time [17,24]. In the present study, smoking and/or alcohol consumption habits were present in about 42% of the cases, reflecting a sociocultural habit common in early adulthood in developing countries, such as Brazil. This finding was also confirmed in the study by Amorim et al. [2], where a predominance of smokers and alcohol consumers was observed in a sample of 35 patients under 45 years of age [2,14].

Despite the controversies surrounding the etiological factors involved in the development and biological behavior of OSCC in young populations, it is believed that smoking and alcohol consumption alone are not the primary determinants of carcinogenesis in this age group due to the limited exposure [25,26]. Therefore, other factors, such as genetic instability, are likely to play a role in the initiation and progression of carcinogenesis. The accumulation of genetic alterations is influenced by the level of exposure to carcinogenic agents and the ability of each organism to efficiently repair DNA damage [3].

An analysis of the clinical course revealed a high proportion of patients diagnosed with OSCC in stages III and IV (75%), resulting in a correspondingly high mortality rate. This finding highlights that, in the present sample, OSCC is an aggressive cancer with a poor prognosis, consistent with other studies [15,27]. Research conducted in developed countries such as France [28], South Korea [18], Germany [29] and China [20] has reported lower frequencies of advanced-stage diagnoses (20–42%). These findings suggest that greater awareness of oral cancer and improved access to healthcare services could facilitate the early detection of OSCC.

It was also observed in this study that smokers and alcohol consumers were diagnosed at older ages and presented tumors at more advanced clinical stages compared to those without these habits. This observation suggests that OSCC in this group differs in clinical and behavioral aspects from the group of smokers and alcohol consumers. These results were also found in other studies, which reported that smokers and alcohol consumers have a more unfavorable prognosis when compared to the group with neither smoking nor alcohol consumption [2,5,6,21].

Furthermore, a higher prevalence of the conventional histopathological type was observed, according to the grading system parameters proposed by the World Health Organization (WHO), with only one case presenting the fusiform cell histological variant (Case 12), in agreement with other studies [26,27,30]. However, well-differentiated tumors are also frequently reported in young patients [20,21,24]. According to Vered et al. [31] well-differentiated tumors are generally associated with a more favorable prognosis. However, the histological grade does not seem to have any influence on the clinical progression of the disease, as some cases of well-differentiated tumors report high recurrence rates, along with low disease-free survival rates [20,27].

Given the discrepancies in published outcome data, the appropriate management of young patients with OSCC has been the subject of much debate. In most cases, it is treated with surgical removal, which may be complemented by radiotherapy and/or chemotherapy, especially when the tumor exhibits high-risk pathological characteristics (positive margins, perineural invasion, lymphovascular invasion, multiple nodules, extracapsular invasion, and advanced T stage) [5,14,23,24,29,30]. Additionally, Dubray-Vautrin et al. [7] report that biomarkers such as a high Neutrophil-to-Lymphocyte Ratio (NLR), mutations in p53, cyclin D1, and increased Vascular Endothelial Growth Factor (VEGF) expression are associated with reduced survival. In the present sample, there was a predominance of surgical treatment combined with radiotherapy and/or chemotherapy, in agreement with most recently published studies. The high frequency of radiotherapy and chemotherapy reflects a high proportion of young adults diagnosed at advanced stages of the disease. However, it is important to highlight that these adjuvant therapies may compromise the general health status and quality of life of patients, contributing to an unfavorable clinical outcome and, thus, increasing the morbidity of OSCC [17].

Given the results presented, it is suggested that oral SCC in young patients is being diagnosed at later stages, making it necessary to implement more effective preventive measures and increase the focus on early diagnosis, considering the identified risk factors. However, the findings presented here should be viewed with caution, as the data are derived from a small patient group, using information collected retrospectively from medical records. Additionally, the presence of Human Papillomavirus (HPV) infection was not analyzed, and further data regarding smoking and/or alcohol habits, such as the age of onset and daily consumption amounts, were not available. Therefore, a prospective, multicenter, and well-designed study would be necessary to obtain a sufficient number of patients and generate more reliable data.

CONCLUSION

Oral SCC in young patients predominantly affects men, who exhibited associated risk factors. The most common site was the tongue, with advanced clinical staging, and the majority were histologically classified as moderately differentiated. The predominant treatment of choice was surgery combined with adjuvant chemotherapy and/or radiotherapy. However, even with this approach, mortality in these patients was high. Despite few recurrences, clinical staging and associated habits of smoking and alcohol consumption may serve as negative prognostic factors for this age group.

Conflicts of interest: The authors declare that there are no conflicts of interest.

Collaborators

LM Carlan, conceptualization, data curation, formal analysis, investigation, methodology, development, writing – original draft. MLSA Morais, resources, supervision, visualization, Writing – original draft, Writing – review & editing.

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Received on: 4/11/2024
Approved on: 17/12/2024

Assistant editor: Luciana Butini Oliveira