RESEARCH ARTICLE

Prognostic factors and long-term survival in oral squamous cell carcinoma: a cross-sectional study

Fatores prognósticos e sobrevida a longo prazo em carcinoma espinocelular bucal: um estudo transversal

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Abstract

Objective: this study aimed to evaluate long-term survival and prognostic factors in patients with oral squamous cell carcinoma (OSCC) in an economically poor region of Brazil.

Methods: the data were obtained from analysis of medical and mortality records of 210 patients with OSCC treated at an oncology hospital providing services to the Brazilian Unified National Health System in a State of northeastern Brazil between January 2006 and December 2008. Sociodemographic and clinical information, treatment performed, recurrence and evolution were collected. Survival curves were estimated by the Kaplan-Meier method and the log rank and Cox regression tests were used to compare the curves.

Results: the median survival in the study period was 47.4 months (95% CI = 38.2 - 56.7). The overall survival rates at 5 and 10 years were 29% and 19.8%, respectivelly. Individuals over 60 years of age (HR = 1.70; 95% CI = 1.06 - 2.73), presence of regional metastasis (HR = 2.51; 95% CI = 1.55 - 4.08), presence of recurrence (HR = 3.18; 95% CI = 1.88 - 5.39) and no surgical treatment (HR = 2.10; 95% CI = 1.31 - 3.35) had a worse prognosis.

Conclusions: advanced age, presence of regional metastasis, tumor recurrence and non-surgical treatment predict poorer survival in patients diagnosed with OSCC.

Keywords: prognosis, survival analysis, medical records, mouth neoplasms, carcinoma squamous cell.

Resumo

Objetivo: este estudo objetivou avaliar a sobrevida a longo prazo e fatores prognósticos de pacientes com carcinoma espinocelular bucal em uma região pouco desenvolvida economicamente do Brasil.

Métodos: os dados foram obtidos a partir da análise de registros médicos de 210 pacientes com carcinoma espinocelular bucal tratados em um hospital especializado em oncologia que presta serviços ao Sistema Único de Saúde em um estado do Nordeste brasileiro entre janeiro de 2006 e dezembro de 2008. Informações clínicas, sociodemográficas e referentes aos tratamentos realizados, recidivas e evoluções foram coletadas. As curvas de sobrevida foram estimadas pelo método de Kaplan-Meier, sendo utilizado o teste de Log-rank para comparar as curvas.

Resultados: a sobrevida média no estudo foi de 47.4 meses (95% IC = 38.2 - 56.7). As taxas de sobrevida global em 5 e 10 anos foram de 29% e 19.8%, respectivamente. Indivíduos com idade superior a 60 anos (RR = 1.70; 95% IC = 1.06 - 2.73), que apresentaram metástases regionais (RR = 2.51; 95% IC = 1.55 - 4.08), recidivas tumorais (RR = 3.18; 95% IC = 1.88 - 5.39) e que foram tratados apenas não cirurgicamente (RR = 2.10; 95% IC = 1.31 - 3.35) tiveram pior prognóstico.

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Conclusões: idade avançada, presença de metástases regionais, recidivas tumorais e tratamento apenas não cirúrgico foram preditores de pior sobrevida em pacientes diagnosticados com carcinoma espinocelular bucal.

Palavras-chave: prognóstico, análise de sobrevida, registros médicos, neoplasias bucais, carcinoma de células escamosas.

ABBREVIATIONS: OSCC, oral squamous cell carcinoma; OS, overall survival; SCC, squamous cell carcinoma.

Introduction

Oral cavity cancers correspond to about 30% of all head and neck tumors, around 90% of those tumors are histologically squamous cell carcinomas (SCC) (1). Approximately 15,000 new cases of oral SCC are expected in Brazil for each year of the 2020-2022 triennium (11,180 cases in men and 4,010 in women) (2). It corresponds to an estimated risk of 10.69 new cases per 100 thousand men and 3.71 for every 100 thousand women, occupying the fifth and the thirteenth position among the most frequent malignant tumors in men and women, respectively (2).

Oral squamous cell carcinomas (OSCC) results from a series of molecular and cellular events, resulting from intrinsic factors, such as genetic components, as well as lifestyle factors, including tobacco, alcohol and probably the human papilloma virus (1). OSCC is more common in men aged 50 or over, and tongue is the most common site for intraoral cancer (1). Its treatment usually includes surgical resection of the primary tumor and elective or therapeutic dissection of the neck (3, 4). Adjuvant radiotherapy and/or chemotherapy are usually indicated when there are pathological factors that increase the risk of tumor recurrence (3, 4).

An increase in global survival of 12% in the last two decades has been reported among patients with oral SCC treated at cancer centers around the world, which is attributed to recent advances in imaging and therapies (5). Despite this progress, the overall 5-year survival, even with wide variation in the literature, is around 50% (6). A worse prognosis has been pointed out with lower survival by oral SCC in developing countries (1, 7). In general, mortality rates tend to decrease with a higher mean number of years of study and increase with a higher proportion of people aged 16 years or more unemployed, confirming the existing evidence linking socioeconomic inequalities to cancer (8, 9).

There is still a great lack of data relative to its clinical outcome, especially in South America (10). Considering Brazil, the studies carried out generally represent data from the Southeast region, to the detriment of the other regions (11). The Northeast has historically presented an unfavorable situation in relation to the other regions of Brazil, as it is one of the poorest economically, with the highest rates of infant mortality and illiteracy (9, 12). Additionally, an increase in the trend of oral cancer mortality in the Northeast region has been described (13).

In this context, the present study aims to evaluate the survival of patients diagnosed with OSCC and the associated prognostic factors, in a cancer reference center providing services to the Brazilian Unified National Health System in a State of northeastern Brazil.

Methods

This retrospective, sectional study was based on analysis of medical records of patients with OSCC diagnosed and treated at a cancer referral center providing services to the Brazilian Unified National Health System in the State of Piauí, Northeast Brazil, between January 2006 and December 2008. The study protocol was conducted in full agreement with the Declaration of Helsinki and was approved by the local Research Ethics Committee (ethics committee's approval report number 2.645.858).

Sample size was estimated based on available data. It was assumed that the number of estimated cases of OSCC for Piauí is 130 per year (2). An OSCC survival rate of 50% (1, 6), 95% confidence interval and 5% sampling error were accepted. The minimum sample size consisted of 194 records, and an additional 10% was implemented, therefore a total of 215 records were analyzed. The sample size was calculated using the EpiInfo 3.5.3 software (Centers for Disease Control and Prevention, Atlanta, Ga., USA). The inclusion criteria for this study were:

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histologically proven SCC; at least 10 years of the initial diagnosis, to allow analysis of 10-year survival; medical records completely filled out; and any age at the time of diagnosis. The final sample of the present study consisted of 210 patients.

Sociodemographic and clinical information, treatment performed, recurrence and evolution were collected from patients' medical records. All patients were staged according to the American Joint Committee on Cancer staging system. The overall survival (OS) rate was the primary outcome (dependent variable), defined as the time interval in years between the date of diagnosis and the date of death from any cause. Date and cause of death were recorded based on the death records of patients in the Mortality Information System. The International Classification of Diseases (ICD-10) was used for registration.

IBM SPSS Statistics 25 was used to perform the analyses. Survival curves were calculated using the Kaplan-Meier method. The differences in survival curves were compared using a log-rank test. The hazard ratio (HR) as its corresponding 95% confidence interval (CI) was determined using a Cox regression model. Variables with p values ≤0.20 in the bivariate analysis were included in the adjusted model. A significance level of 5% was adopted.

Results

The sociodemographic and clinical characteristics of the 210 patients diagnosed with oral SCC participating in this study are shown in **Table 1**. Most patients were male (73.3%), between 15 and 90 years old (mean age 62.86 ± 14.03 years). The tongue was the most prevalent location (34.8%). Regarding staging at diagnosis, 51.8% were in an advanced stage (IV), 42.9% with tumor size T4, 55.7% absence of lymph node metastasis (N0) and 92.9% absence of metastasis the distance (M0). As for the type of treatment, surgery was performed in 50% of cases, radiotherapy in 82.4% and chemotherapy in 47.1%. Most of the participants presented recurrence after treatment (54.9%). Of the total of 210 patients, 55.8% had confirmed death in the evaluated period, and in 66.4% the cause of death was OSCC (Table 1).

TABLE 1 – Sociodemographic and clinical features of patients with OSCC (n=210).

Features		N	%
Sex	Male	154	73.3
	Female	56	26.7
Age*, years	<40	11	5.3
	40-49	31	14.9
	50-59	44	21.2
	60-69	48	23.1
	>70	74	35.5
Ethnicity	Brown	171	81.4
	White	25	11.9
	Asian	8	3.8
	Black	5	2.4
	NI	1	0.5
Anatomical site	Tongue	73	34.8
	Mouth NE	53	25.2
	Lip	18	8.6
	Floor of the mouth	18	8.6
	Palate	18	8.6
	Gingival border	8	3.8
	Oral mucosa	5	2.4
	Retromolar area	3	1.4
	Mouth vestibule	3	1.4
	Others	11	5.2
General Staging	I	27	12.9
	II	31	14.8
	III	43	20.5
	IV	109	51.8
T staging	T1	31	14.8
	T2	32	15.2
	T3	53	25.2
	T4	90	42.9
	TX	4	1.9
N staging	N0	117	55.7
	N1	29	13.8
	N2	31	14.8
	N3	29	13.8
	NX	4	1.9
M staging	M0	195	92.9
	M1	2	1.0
	MX	13	6.1
Surgery	Yes	105	50.0
	No	97	46.2
	NI	8	3.8
Radiotherapy	Yes	173	82.4
	No	29	13.8
	NI	8	3.8
Chemotherapy	Yes	99	47.1
	No	103	49.1
	NI	8	3.8
Recurrence	Yes	79	37.6
	No	65	31.0
	NI	66	31.4
*Causa mortis**	OSCC	78	66.7
	Another cause	19	16.2
	NI	20	17.1
Current situation	Dead	117	55.8
	Alive	74	35.2
	NI	19	9.0

*Variable with loss of information; NI, not identified; NE, not specified; OSCC, Oral Squamous Cell Carcinoma.

The median survival time was estimated to be 47.4 months (95% CI = 38.2 - 56.7). The OS rate was 29% at 5 years and 19.8% at 10 years. Cox univariate and multivariate models for OSCC are described in **Table 2**. **Figure 1** shows the results of survival analysis by the Kaplan Meier method.

There was a significant low survival rate linked to advanced clinical staging (p = 0.001), larger tumor size (p = 0.002), presence of regional metastasis (N+) (p < 0.001), procedures without surgery (p < 0.001) and recurrence (p < 0.001). In the multivariate analysis, four variables independently reduced OS: age over 60 years (HR = 1.70; 95% CI = 1.06 - 2.73), regional metastasis (HR = 2.51; 95% CI = 1.55 - 4.08), recurrence (HR = 3.18; 95% CI = 1.88 - 5.39) and non-surgical treatment (HR = 2.10; 95% CI = 1.31 - 3.35) (Table 2).

TABLE 2 – Multivariate analysis of risk factors for overall survival of patients with OSCC using Cox regression

Variables	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Age (years)				
≤ 60	1		1	
> 60	1.28 (0.89 – 1.85)	0.186	1.70 (1.06 – 2.73)	0.026
Sex				
Female	1		1	
Male	1.41 (0.91 – 2.18)	0.121	1.01 (0.60 – 1.71)	0.956
Anatomical site				
Tongue	0.96 (0.65 – 1.41)	0.833	-	-
Others	1		-	
General Staging				
I - II	1		1	
III - IV	2.10 (1.35 – 3.25)	0.001	1.97 (0.23 – 4.06)	0.964
N Staging				
N0	1		1	
N1, N2, N3	2.51 (1.73 – 3.63)	<0.001	2.51 (1.55 – 4.08)	<0.001
T Staging				
T1 - T2	1		1	
T3 - T4	1.92 (1.26 – 2.92)	0.002	1.83 (0.22 – 3.17)	0.791
Recurrence				
Yes	3.46 (2.06 – 5.82)	<0.001	3.18 (1.88 – 5.39)	<0.001
No	1		1	
Surgical treatment				
Yes	1		1	
No	2.36 (1.62 – 3.43)	<0.001	2.10 (1.31 – 3.35)	0.002

CI, confidence interval; HR, hazard ratio; OSCC, Oral Squamous Cell Carcinoma.

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The 5-year survival rates for patients with TNM I-II and TNM III-IV were 41% and 24.1%, respectively (Figure 1). Considering the size of the tumor, the OS rates for T 1-2 and T 3-4 patients were 39.1% and 24.6%, respectively. When comparing patients without regional metastasis (N0) with those with regional metastasis (N +), OS rates were 40.5% and 14%, respectively.
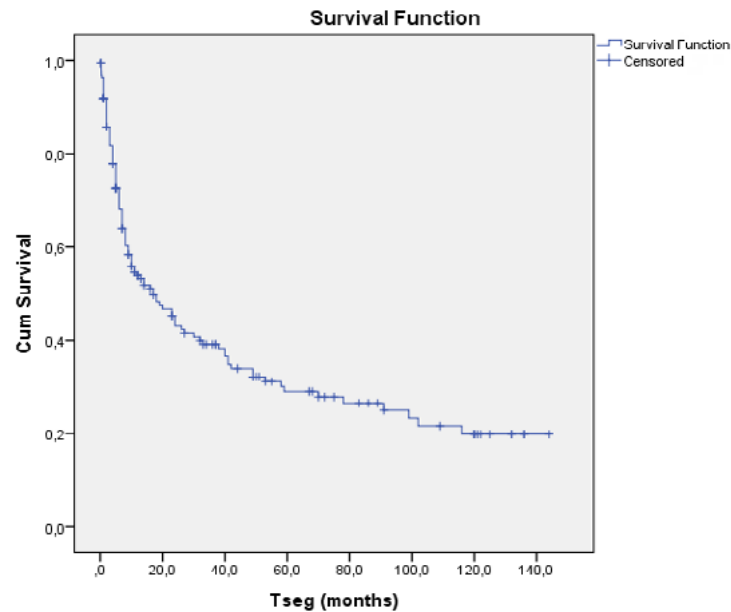
Figure 1 – Kaplan-Meier overall survival curve for oral SCC patients. Cum Survival, cumulative survival; OSCC, Oral Squamous Cell Carcinoma; Tseg: follow-up time.

Discussion

The last few years have shown considerable improvements in the diagnosis and treatment of OSCC, associated to the higher quality of imaging exams, technical advances in tumor resection, new methods of reconstruction, rigorous case selection, more effective radiotherapy and chemotherapy, use of targeted therapy against specific recipients and wide cooperation of multidisciplinary clinical teams (5). Such resources have made it possible to increase the survival rate of patients in the past two decades (5). However, OSCC remains a lethal disease in more than 50% of cases diagnosed annually worldwide (1). This is largely reflected by the advanced stage at the time of detection of the disease in most patients, despite the easy accessibility of the oral cavity for regular examinations (1).

The results of the present study showed an OS rate of 29% at 5 years, which is in agreement with that observed in the literature. The 5-year survival rates of patients with OSCC vary worldwide, from 26% to 72,5% (5, 10, 14-18). In South America, 3-year OS rate for OSCC was 54.7%, however more than half of the participants of the study were treated at private hospitals (10). Among Brazilian studies, the 5-year OS may vary regionally from 24% to 51.7% (6, 7, 20-26), and it was 30% for patients with OSCC undergoing outpatient cancer treatment by Brazilian Unified National Health System (27). Differences in presentation, clinical course and evolution showed a worse prognosis for patients with OSCC in developing countries, when compared to patients seen in developed countries (7). Treatment in public or private institutions has also impacted in survival (6). Though, a study carried out comparing institutions from developed and developing countries showed that after controlling for stage, site, and treatment, there was no statistically significant survival between the two institutions. Only clinical stage and treatment were impacted on survival on multivariate analysis (19). Additionally, factors such as year of diagnosis

and initial treatment, epidemiological and clinical characteristics, experience of the surgical team, quality of radiotherapy and use of adjuvant treatment have been described as related to variations in the survival of patients with oral SCC (3, 16).

Analyzing the regions of Brazil, in the Southeast, 5-year OS rates were 43% (19) and 51,7% (6) in São Paulo, and it was even possible to observe an increase in survival between the 1950s and 1990s, from 28.7% to 43.2% (7). OS rates were 27.9% in Rio de Janeiro (20). In the South of Brazil, 5-year and 10-year OS rates were respectively: 42% and 38% in Rio Grande do Sul (21); 33.3% and 26.9%, in Santa Catarina (22). Data from the Northeast region show that the 5-year OS rates were 27.8% in Alagoas (23), 39% in Paraíba (24), 42.61% in Rio Grande do Norte (25) and 15-year OS rate was 46.8% in Ceará (26). The survival rates presented above seem do not reflect the socioeconomic inequalities present among the different regions of the country, with higher survival rates expected in the South and Southeast regions, due to their better economic and social indicators, when compared to the Northeast region (9, 12). However, this result should be interpreted with caution, considering the influence of regional inequalities in recording mortality data, in addition to methodological differences between the various studies presented. For example, some studies with longer survival had only tongue SCC patients (25), a lower percentage of patients with advanced disease (6,24,26) or had patients with private health plans assistance (6, 7, 19, 26). Additionally, despite the best of our efforts, we have not found OSCC survival studies in the Central West and North regions, which highlights the need for more scientific evidence on the topic in Brazil.

A differential of this study was the long evaluation period, which also allowed the analysis of the 10-year survival, while the majority of the studies presented the survival only in a period up to 5 years. Two findings draw attention to the survival curve. First, an abrupt drop until the second year was observed, when the survival rate reached 43%. The increased risk of death in the early years has been associated with early tumor

recurrences. About 63% of recurrences occur usually within a year of initial treatment (28) and when there is no recurrence within 30 months, the subsequent risk becomes minimal (18). Second, there was a curve stabilization tendency after 5 years: the OS rates of 5 and 10 years were 29% and 19.8%, respectively. Similar event is also described in the literature, and only a small difference of 4 to 9% has been reported between 5 and 10-year OS (1, 15, 21). This suggests that after 5 years of survival, deaths may be more likely due to other causes, such as age-related comorbidities, and less associated with oral SCC.

It was observed that the patients were predominantly male, over the age of 60 years, which probably results from greater exposure to risk factors throughout life, such as alcohol and tobacco (1, 2, 16, 17, 27). Most individuals were of mixed race, the result of the region's typical miscegenation (23, 26). The tongue was the site most affected, confirming itself as the most predisposed SCC intraoral site in most populations (1 ,2, 16, 17, 21). In the present study, patients over the age of 60 years had lower survival. Several authors describe these findings and suggest a higher prevalence of comorbidities and treatment toxicity as probable causes (16, 17, 20, 26, 27). The variables sex, skin color (ethnicity) and tumor location did not show a significant relationship with survival rates. Similar results regarding sex (10, 14, 21, 23) and ethnicity (21, 23) are described in the literature. Regarding the tumor location, there are authors who observed a lower survival rate associated with tongue tumors (27) while for others, as seen in the present study, the location did not influence significantly the prognosis (14, 19).

Worse survival was associated with advanced clinical staging (TNM III and IV), larger tumor size (T3 and T4) and N+ in the univariate analysis, however among theses variables, only regional metastasis was related to lower survival after multivariate analysis. Worse prognosis for patients in clinical advanced stages is a consensus in head and neck cancer (1, 10, 16, 18, 20, 24, 27, 29). Tumor size has also been described as a factor that significantly affects overall survival

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(14, 16, 25, 26). Nevertheless, as observed in the present study, regional metastasis is one of the most important predictors for survival, which can reduce the chances of cure by half and increase the risk of local recurrence after resection (14, 16, 18). Distant metastasis was seen in the present study in only 1% of patients. It is not a common event in oral SCC (1, 26), which justifies the lack of specific association with worse survival.

The 5-year survival rate for patients with TNM I-II was 41%, although the proportion of these patients was less than 28% of the total patients diagnosed with OSCC, whereas among TNM III-IV patients, which corresponded to more than 70% of cases, survival was 24.1%. The distribution of cases according to clinical stage at the time of diagnosis, with a predominance of cases in advanced stages, is very similar to that observed in studies conducted in Brazil (22, 23, 25, 27) and in developing countries (10, 15, 18). It reflects the influence of socioeconomic factors on access to health. A multicenter study in South America listed as multifactorial the reasons for the late diagnosis of OSCC, including lack of knowledge of the signs and symptoms of cancer (in patients and health professionals), lack of access to adequate health care and scarcity of medical resources as a result of fragmentation of health systems (10).

A period of delay in diagnosis or even the start of treatment, around 11 months, may be enough for a patient in the initial clinical stage to progress to an advanced stage; 8 months may result in changes in the T or N classification at advanced stages; about 4 months, so that an advanced clinical stage becomes intractable; and another 4 months would be sufficient for the patient's death (30). It is evident that the diagnosis in earlier stages would increase the chances of cure and survival (6), and this should be a clear objective in terms of OSCC prevention.

Longer survival was observed in patients undergoing surgical treatment, which is described in the literature (5, 6, 15, 17, 18, 20, 23, 27). Surgical resection of the primary tumor and when necessary of the neck, in order to address regional metastases is often the first treatment for OSCC

(16). Recent evidence suggests that selective elective neck dissection offers longer rates of disease-free survival compared to therapeutic neck dissections (14). Adjuvant radiotherapy with or without chemotherapy is offered when there is a high risk of recurrence and after considering several factors, including the patient's age and comorbidities, pathological stage, margin status, extent of nodal involvement and other histopathological characteristics of the primary tumor (4, 16). In this study, the most commonly used modality was radiotherapy, which was associated to more advanced disease. It is possible to explain the greater survival in patients who underwent surgery due to the preferred adoption of this method for tumors of earlier stages (18, 27). Although this study does not demonstrate an association between radiotherapy and survival, it is known that this adjuvant modality has been significantly associated with longer OS (4).

In addition, more than half of the patients evaluated exhibited recurrence, which showed a significant correlation with lower OS rates. Local and neck recurrences are frequent failures in the treatment of OSCC (3). Recurrence rates usually vary according to the TNM stage and initial treatment, and can be found in more than 50% of patients with tumors diagnosed in advanced clinical stages III and IV (30).

The present study had some limitations that must be considered: the use of secondary data collected retrospectively, with restrictions concerning the availability and content of the medical records; the national Mortality Information System has been implemented over the years, but still have coverage below 100%, especially in the Northeast region of Brazil (12, 13). Nevertheless, regarding the reliability of the data of mortality by causes, it is believed that the Brazilian data are trustworthy as those from any other country with a long tradition in the outlining of these statistics (9). Additionally, the data were recorded and analyzed carefully in order to minimize such limitations and provide important evidence of factors associated with the prognosis of OSCC patients, which is a crucial field of study in public health.

Conclusions

In summary, OSCC was diagnosed in advanced stages and low survival rates were observed in this study. Patients diagnosed over the age of 60, with regional metastasis, who had not undergone surgical treatment and with locoregional recurrence throughout the disease had a poorer prognosis. These findings reinforce the crucial importance of more effective programs for the prevention and early diagnosis in order to improve OSCC survival.

Notes

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

All the authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

All the authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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