RISK FACTORS FOR SURVIVAL AFTER HEAD AND NECK CANCER: A COHORT STUDY IN THE SOUTH OF ESPIRITO SANTO STATE

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Palavras-chave: Carcinoma de Células Escamosas de Cabeça e Pescoço. Carcinoma de Células Escamosas de Cavidade Oral. Carcinoma de Células Escamosas de Laringe. Carcinoma de Células Escamosas de Orofaringe. Índice de Sobrevida. Prognóstico.

RESUMO

Introdução: O carcinoma de células escamosas (CCE) de cabeça e pescoço possui alta incidência na população brasileira e normalmente está associado a um prognóstico desfavorável. **Objetivo**: Avaliar os fatores de risco para sobrevida de pacientes diagnosticados com CCE de cabeça e pescoço e investigar a influência de fatores clínico-epidemiológicos no prognóstico do CCE. **Materiais e Métodos**: Foram selecionados prontuários de 211 pacientes com CCE de cabeça e pescoço diagnosticados e tratados entre 2010 e 2018 em um hospital de referência em oncologia. Foram coletadas as características clínico-patológicas no momento do diagnóstico e nos 5 anos de acompanhamento. A curva de Kaplan-Meier com o teste Log-Rank avaliou a sobrevivência e o modelo de regressão logística multivariada progressiva foram realizados para determinar os fatores que afetaram a sobrevivência do CCE. **Resultados**: A sobrevida global em 5 anos foi de 30,0%. O câncer de laringe foi o mais prevalente (34,1%), seguido de orofaringe (33,6%) e cavidade oral (24,2%). 64% dos pacientes apresentavam tumores localmente avançados (T3 e T4) e 75,4% dos pacientes foram diagnosticados em estádios clínicos avançados (III e IV). Na análise multivariada, os tumores localmente avançados (RC = 2,748; IC 95%: 1,310-5,765), quimioterapia paliativa (RC = 15,757; IC 95%: 5,868-42,309) e metástases durante o acompanhamento oncológico (RC = 11,602; IC 95%: 1,380-97,507) foram associados a um pior prognóstico. **Conclusão**: A taxa de sobrevida foi considerada baixa. Tumores localmente avançados, quimioterapia paliativa e aparecimento de metástases durante o seguimento foram considerados os fatores de risco mais importantes associados a uma baixa sobrevida.

Keywords: Squamous Cell Carcinoma of Head and neck. Oral Cavity Squamous Cell Carcinoma. Laryngeal Squamous Cell Carcinoma. Oropharyngeal Squamous Cell Carcinoma. Survival Rate. Prognosis.

ABSTRACT

Introduction: Head and check squamous cell carcinomas (HNSCC) affects the Brazilian population with a high incidence and usually has a poor prognosis. **Objective**: To evaluate the risk factors for survival of patients diagnosed with HNSCC and investigate the influence of epidemiological and clinical factors on the prognostic of HNSCC in southeastern Brazil. **Materials and Methods**: Clinical records of 211 patients with head and neck squamous cell carcinomas diagnosed and treated between 2010 and 2018 at a reference hospital for oncology, were selected. Clinical and pathological characteristics at diagnosis and for 5 years follow up were collected. The Kaplan-Meier Curve with the Log-Rank test assessed survival, and forward stepwise multivariate logistic regression model was performed to determine the factors affecting HNSCC survival. **Results**: The 5-year overall survival was 30.0%. Laryngeal cancer was the most prevalent (34.1%), followed by oropharynx (33.6%) and oral cavity (24.2%). About 64% of patients had locally advanced tumors (T3 and T4) and 75.4% of the patients were diagnosed as being in the advanced clinical stages (III and IV). In the multivariate analysis, the locally advanced tumors (OR=2.748; 95%CI:1.310-5.765), palliative chemotherapy (OR=15.757; 95%CI:5.868-42.309) and metastasis during oncological follow-up (OR=11.602; 95%CI:1.380-97.507) were associated with a poor prognosis. **Conclusion**: The survival rate was considered low when compared with the literature. Locally advanced tumors, palliative chemotherapy, and the appearance of metastases during follow-up were considered the most important risk factors associated with a low HNSCC survival.

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INTRODUCTION

Head and neck cancer (HNC) is considered a public health problem and includes lip, oral cavity cancer (OC), nasal cavities, pharynx and larynx cancer (LC).[1] HNC has a multifactorial etiology, and the most important risk factors are smoking, alcohol use, HPV infection, genetic polymorphisms, immunosuppression, low fruit and vegetables diet, excessive exposure to ultraviolet light (for lip carcinomas) and environmental factors.[2–4] According to a recent review of case-control studies,[5] there was consensus on the positive cause-effect relationship between pesticides and head and neck cancer, especially when the frequency of exposure occurred. In addition to risk factors, the epidemiological profile has changed over time, possibly associated with regional characteristics.[2–4]

Head and neck cancer cases have a major impact in low-middle-income countries, ranking sixth among the most incident cancer cases.[4,6] Current survival data about head and neck squamous cell carcinoma (HNSCC) are scarce in South America despite a multicenter case-control study that revealed a high incidence in four countries: Argentine, Brazil, Colombia, and Uruguay. Late stage and older age at diagnosis, alcohol use for LC/hypopharynx cancer (HC), male gender and low education level for oropharynx cancer, and mulatto skin color for LC/HC were associated with the worst prognosis. The HPV infection in oropharynx cancer has worst prognosis.[7]

Based on the growing number of cases in Brazil this study aimed to evaluate the risk factors for survival of patients diagnosed with HNSCC and investigate the influence of epidemiological and clinical factors on the prognostic of HNSCC in a reference oncology hospital.

MATERIALS AND METHODS

The Institutional Review Board of the Veiga de Almeida University (UVA), Rio de Janeiro, (RJ), Brazil approved the study (registration number 2.905.044) and complied with the Declaration of Helsinki (World Medical Association 1997).

The retrospective cohort study was developed with data from clinical records of patients with HNSCC diagnosed according to the International Classification of Diseases – WHO (ICD-10) C00-C14 to C32 and treated between 2010 and 2018 at the Evangelical Hospital of Cachoeiro de Itapemirim, Espírito Santo, Brazil.

All the sociodemographic data such as gender, skin color (white or non-white), age at diagnosis (≤40 and >40 years), education level (≤08 years and >08 years), profession, smoking and alcohol history (never, former or current), clinical staging (TNM system: I, II,III and IV),[8] tumor site (anatomical site), histopathological data (well, moderately and poorly differentiated),[8] treatment modality (single therapy or combination therapy) location of metastasis and/or appearance of a second tumor site or recurrence and date of death (or last follow-up) were collected from the clinical records. The 5-year overall survival was calculated from the date of diagnosis or primary HNSCC to the date of death or last follow-up.

The descriptive analysis of the distribution of cases and the analysis of the association between the qualitative variables was carried out using the 5^2 test considering a significance level of 5%. Survival curves were estimated using the Kaplan-Meier method and compared by the Log-Rank test. Multivariate logistic regression analysis was performed to determine the factors affecting survival with the use of forward stepwise method, calculating the odds ratio (OR) with a 95% confidence interval (95% CI).

RESULTS

A total of 289 clinical records were collected from patients with HNSCC. Patients who received treatment and follow-up in another hospital (n=42), cases not histologically classified as HNSCC (n=14) and patients with previous history of cancer (n=8) were excluded. A total of eleven patients with tumors in the paranasal sinuses (n=4), nasopharyngeal (n=4), parotid gland (n=2) and cervical region (n=1) were excluded from the study. Three patients given supportive care were excluded; specific oncological treatment was not initiated in poor performance status and/or to patients who refused any treatment. Analyses were based on 211 patients (95% from the public health system) followed for 5 years from the cancer diagnosis.

The mean age of patients was 59.9 years (±12.22). Most patients were men (86.7%) and non-white (46.9%), smokers (65.9%) and alcohol users (75.4% reported being an alcoholic, current or past). Regarding education level, 64.5% of the patients had less than 8 years of formal education. The baseline characteristics of the participants are listed in Table 1 and were not found to associate significantly with cancer survival ($p > 0.05$).

Laryngeal cancer was the most prevalent (34.1%) tumor, followed by oropharynx (33.6%) and oral cavity (24.2%). Nearly 64% of the patients had locally advanced tumors (T3 and T4) and 55.9% presented affected lymph nodes at the cancer diagnosis. Thus, 75.4% of the patients were diagnosed at stages III and IV (Table 2). Most patients (77.3%) received chemoradiotherapy treatment. Seventy-seven patients (36%) underwent palliative chemotherapy in a second step. Of the total, 10.9% of the tumors relapsed, 6.6% of the patients had a second primary site, of which 50% were located in the esophagus, and 9.5% were metastatic

tumors (70% pulmonary metastasis) during the follow-up.

The 5-year overall survival was 30% (Figure 1A), with an average time of 31 months (95% CI 27.51–33.79). There was a positive association between death within 5 years and tumor size (T), the presence of compromised lymph nodes (N), staging, use of palliative chemotherapy in a second step and the presence of metastatic tumors after oncotherapeutic treatment (pd" 0.05) (Table 2). The Log-Rank test showed that there was a significant decrease in survival with increase of tumor size, affected lymph nodes, metastases at the time of diagnosis, clinical staging, use of palliative chemotherapy in a second step and occurrence of metastatic tumors during follow-up (Figures 1B, 1C and 1D).

In the forward stepwise multivariate logistic regression, the risk factor was confirmed for the locally advanced tumors (OR=2.748; 95%CI:1.310-5.765), palliative chemotherapy (OR=15.757; 95%CI:5.868-42.309) and metastasis during oncological follow-up (OR=11.602; 95%CI:1.380-97.507) (Table 3).

***Table 1**: Patient Characteristics for HNSCC at the Evangelical Hospital of Cachoeiro de Itapemirim, Espírito Santo, Brazil (Total Cases=211 and Death= 130).*

Charactheristics	CasesN (%)	Death*N (%)	p-value**
Sex			0.175
Female	28 (13.3)	14 (50.0)	
Male	183 (86.7)	116 (63.4)	
Skin color			0.577
White	88 (41.7)	52 (59.1)	
Not White	99 (46.9)	61 (61.6)	
NI	24 (11.4)	17 (70.8)	
Age at diagnosis			0.560
≤40 years old	13 (6.2)	9 (69.2)	
>40 years old	198 (93.8)	121 (61.1)	
Education level			0.495
≤08 years	136 (64.5)	83 (61.0)	
>08 years	13 (6.2)	10 (76.9)	
NI	62 (29.4)	37 (59.7)	
Profession			0.116
Farmer	50 (23.7)	28 (56.0)	
Repair, maintenance and installation	44 (20.9)	34 (77.3)	
Others	104 (49.3)	60 (57.7)	
NI	13 (6.2)	8 (61.5)	
Smoking history			0.118
Never smoked	16 (7.6)	10 (62.5)	
Former smoker	56 (26.5)	28 (50.0)	
Current smoker	139 (65.9)	91 (65.9)	
Alcohol history			0.240
Never drank	43 (20.4)	22 (51.2)	
Former user	59 (28.0)	34 (57.6)	
Current user	100 (47.4)	68 (68)	
NI	9 (4.3)	6 (66.7)	

*Note: Cohort participants who died within 5 years. **x^2. $p<0.05$. NI: Not informed.*

***Table 2**: Clinical Characteristic and therapeutic modalities for HNSCC at the Evangelical Hospital of Cachoeiro de Itapemirim, Espírito Santo, Brazil (Total Cases = 211 and Death = 130).*

Clinical Factors	Cases N(%)	Death* N(%)	p-value**
Tumour site			0.135
Larynx	72 (34.1)	38 (52.8)	
Oropharynx	71 (33.6)	43 (60.6)	
Oral cavity	51 (24.2)	37 (72.5)	
Hypopharynx	17 (8.1)	12 (70.6)	
Degree of differentiation			0.462
Well	32 (15.2)	17 (53.1)	
Moderately	96 (45.5)	57 (59.4)	
Poorly	19 (9.0)	12 (63.2)	
NI	64 (30.3)	44 (68.8)	
T			**<0.001**
T1 + T2	59 (28.0)	25 (42.4)	
T3 + T4	135 (64.0)	97 (71.9)	
NI	17 (8.1)	8 (47.1)	
N			**0.018**
N0	84 (39.8)	42 (50.0)	
N+	118 (55.9)	82 (69.5)	
NI	9 (4.3)	6 (66.7)	
M			0.175
M0	200 (94.8)	122 (61.0)	
M1	5 (2.4)	5 (100)	
NI	6 (2.8)	3 (50.0)	
Stage at diagnosis			**0.005**
I	18 (8.5)	5 (27.8)	
II	23 (10.9)	11 (47.8)	
III	54 (25.6)	37 (68.5)	
IV	105 (49.8)	72 (68.6)	
NI	11 (5.2)	5 (61.6)	
Treatment			0.257
Surgery + adjuvant	10 (4.7)	6 (60.0)	
Radiotherapy	38 (18.0)	19 (50.0)	
Chemoradiotherapy***	163 (77.3)	105 (64.4)	
Palliative chemotherapy			**<0.001**
No	135 (64.0)	59 (44.7)	
Yes	76 (36.0)	71 (93.4)	
Tumour Recurrence			0.082
No	188 (89.1)	112 (59.6)	
Yes	23 (10.9)	18 (78.3)	
Second primary site			0.177
No	197 (93.4)	119 (60.4)	
Yes	14 (6.6)	11 (78.6)	
Metastasis			0.001
No	191 (90.5)	111 (58.1)	
Yes	20 (9.5)	19 (95.0)	

*Note: Cohort participants who died within 5 years. **x^2. ***01 patient treated only with chemotherapy. p<0.05. NI: Not informed.*

***Table 3**: Multivariate logistic regression for the factors influencing overall survival.*

Variables	OR (CI 95%)	p-value
T		**0.018**
T1 + T2	1	
T3 + T4	2.748 (1.310-5.765)	
NI	1.117 (0.310-4.029)	
Palliative chemotherapy		**<0.001**
No	1	
Yes	15.757 (5.868-42.309)	
Metastasis	**0.024**	
No	1	
Yes	11.602 (1.380-97.507)	

Note: OR: Odds ratio, 95% CI: 95% confidence interval. p<0.05.

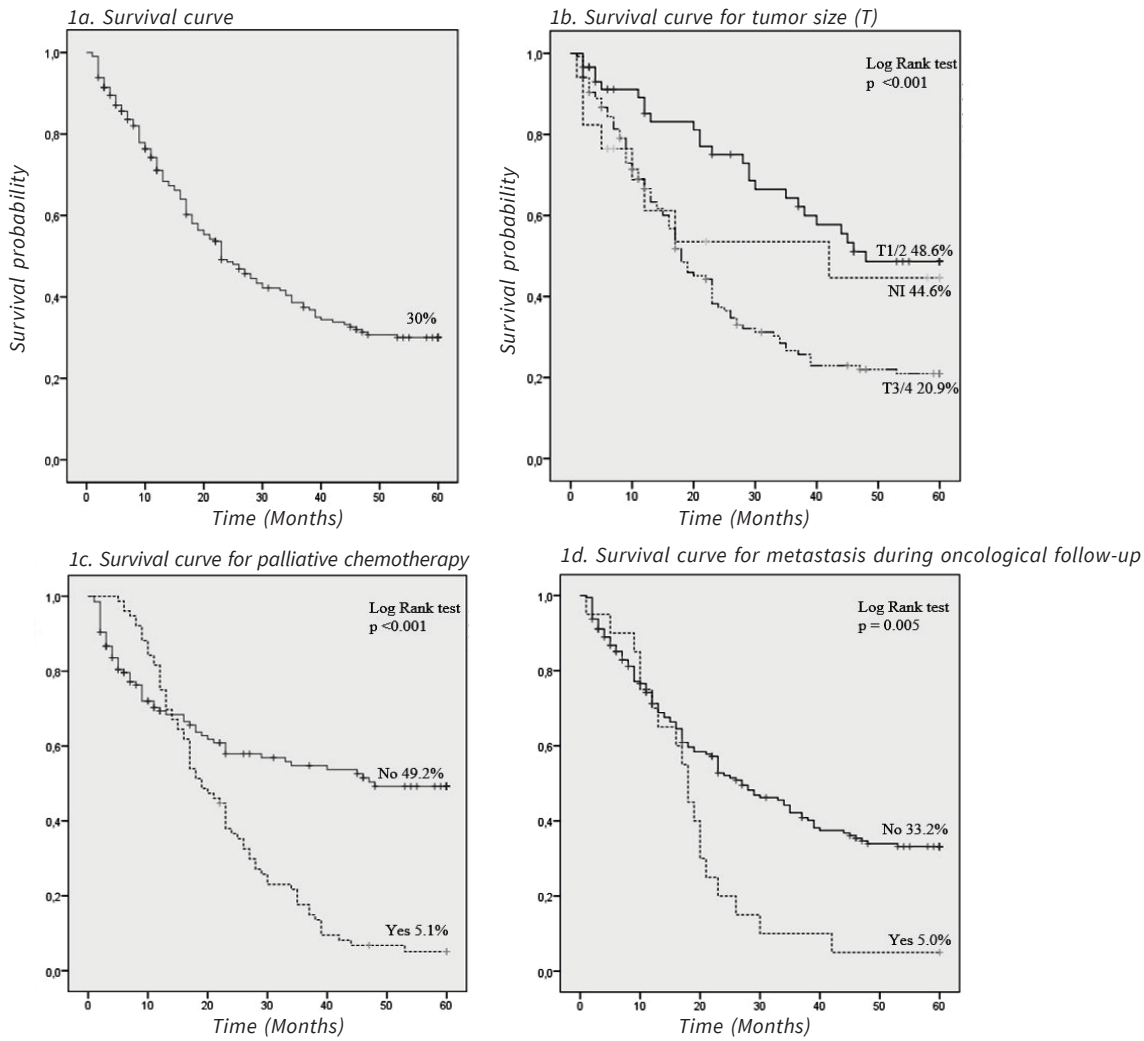

***Figure 1**: (a) Survival curve of patients with Head and Neck Squamous Cell Carcinoma estimated by Kaplan-Meier method. (b) Survival curve for tumor size of patients with Head and Neck Squamous Cell Carcinoma estimated by Kaplan-Meier method. (c) Survival curve for palliative chemotherapy of patients with Head and Neck Squamous Cell Carcinoma estimated by Kaplan-Meier method. (d) Survival curve for metastasis during oncological follow-up of patients with Head and Neck Squamous Cell Carcinoma estimated by Kaplan-Meier method. NI: Not informed*

DISCUSSION

The cohort in the current study included patients with HNSCC treated at a reference oncology hospital located in a macro-region in Espírito Santo state, Brazil. To our knowledge, there are no studies on survival of patients with head and neck cancer in Espirito Santo state. It is a state with a sustainable gross domestic product per capita and human development index, its economic growth was grounded in the European colonization and family-based farming still active to date[9]. Typically, the Caucasians who emigrated to the state were outdoor farming workers, mostly UV rays unprotected and exposed to pesticides. Patients with locally advanced tumors, who submitted to palliative chemotherapy in a second step and diagnosed with metastasis during follow-up had low survival and high mortality rate as the results showed. All the conditions were related to late diagnosis and probably could explain the low survival rate detected.

A substantial part of the study sample consisted of farmers, followed by professionals working in repair, maintenance, and installation, the latter had the lowest survival rate. Because of the small portion of farmers in the sample, a clear limitation the cohort, no association between this group and death within 5 years, was found. A recent case-control review[7] revealed a positive association between exposure to pesticides and different head and neck cancer sites, based on high quality studies. According to the authors, the increase in risk was correlated with the higher level of exposure and lower level of education of the individuals exposed to pesticides.[7]

Car mechanics who worked for more than 10 years had higher risk of cancer in the oral cavity and oropharynx in comparison with farmers who did not present significant risk of tumor development. Mechanics, repair, maintenance, and installation professionals are constantly exposed to engines combustion vapors, anhydrous alcohol, solvents, asbestos fibers, aldehydes, and countless other carcinogenic agents.[10,11]

Current data do not support clear evidence of an association between some chemicals exposure and HNSCC. The heterogeneity observed between the studies, in association with confounding factors already known in the genesis of cancer, keeps the relationship between chemicals as a causal factor open.[5,11,12]

Still considering the risk factors for cancer, many patients reported tobacco and alcohol use. A recent multicenter study concluded that current and former drinkers with LC or HC had approximately 2-fold higher mortality than never-drinkers. The authors concur with this study that a reduction of alcohol use is essential to decrease the high burden of HNSCC in South America.[7] It seems that improving the education level of individuals exposed to cancer risk factors can lead to a change of posture in the use of compounds. In relation to these risks, public health policies should prioritize the care to the exposed population, aiming wider protection, conscious use of pesticides, strategies against smoking and alcoholism, disclosure of health information, and early cancer screening.

Late diagnoses evolve into a generally mutilating treatment, with aggressive surgeries and more complex cancer treatments with a doubtful prognosis.[13] The data showed a large number of patients with locally advanced tumors, who probably had insufficient information and resources and consequently with difficulties to access the healthcare system. 30 months after the initial treatment, approximately 70% of patients with T3/4 tumors had died, compared with only 35% of T1/2 tumor patients in a similar period, which highlights the association between tumor size and survival.

All the patients with metastasis at the time of diagnosis had died within 18 months. Also, patients who did not receive treatment died within 2 months after the first consultation with an oncologist. The results reinforced previous findings: the late stage at diagnosis was the strongest predictor of HNSCC survival.[7]

Santos et al (2019)[14] found a 5-year survival rate of 24.8% in a sample containing only T3/4 tumors. In other studies carried out in Brazil, overall survival ranged from 27.8% (oral cavity, oropharynx),[14] 30% (oral cavity)[13] to 42% (oral cavity, oropharynx).[16] Apparently, Brazilian authors who attributed late diagnosis to absence of initial symptoms, lack of knowledge about the disease and the fear of diagnosis were correct.[17]

The clinical characteristics of patients are primarily responsible for the therapy adopted, with surgery as the first choice, sometimes associated with chemoradiotherapy. Le Campion et al (2017)[15] observed a survival rate of 59% in patients undergoing surgical treatments with adjuvant chemotherapy for oral and oropharyngeal cancer, showing a difference regarding non-surgical treatment ($p<0.001$), however this fact was not observed in this study.

Studies in recent decades have shown an increase in the use of chemotherapy combined with radiotherapy, revealing locoregional benefits for overall and disease-free survival, but with an increase in the toxicity rate[15]. Chemoradiotherapy was the treatment of choice for the majority of the study patients. According to the Kaplan-Meier graph, survival curves that cross the variable "palliative chemotherapy" in concurrence with the mean time of recurrence, second primary sites or distant metastases, are

the main reasons why patients are submitted to this therapy during follow-up. This also applied to patients who underwent palliative chemotherapy in a second step and presented metastasis during cancer follow-up. Moreover, it was revealed that patients who submitted to palliative chemotherapy have 5-fold more odds of dying in the first 5 years of follow up. Another cohort study conducted in northeastern Brazil showed that age < 40 years and a single therapeutic modality were associated with lower survival rates compared with older patients and use of combined therapies.[15]

The retrospective design and the use of secondary data from medical charts are the study limitations. A relevant number of these charts were incomplete or with incorrect data which diminished the sample. However, it is unlikely that a loss-related bias would have affected the results, given that a large proportion of the population was followed up until their death or for 5 years. Likewise, knowing that almost 65% of the cases were locally advanced, a major influence of anticipation bias is not expected. In addition, a multivariate logistic regression investigation was conducted to determine the factors affecting survival with the use of the Forward Stepwise method. This model was used to identify the independent risk factors associated with death. If there are a large number of factors of interest and there is relatively few information about their prognostic influence, automated selection techniques such as stepwise methods can be used.[18]

CONCLUSION

The 5-year survival rate was 30.0%. The prognostic factors for this poor survival rate were related to delayed prognosis. The study highlights the fact that this population has a low education level that probably influences lifestyle and access to the healthcare system. Locally advanced tumors, palliative chemotherapy in a second step and metastasis during follow-up were associated with a poor prognosis. It is known that the study does not reflect the national reality of HNSCC and portray the macro-region of Espírito Santo during a long period of observation and may be useful to support strategies of prevention programs for this population.

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