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PREVALENCE OF METASTASES IN PATIENTS WITH HEAD AND NECK TUMORS IN A PUBLIC RADIOTHERAPY SERVICE

PREVALÊNCIA DE METÁSTASE EM PACIENTES COM TUMORES DE CABEÇA E PESCOÇO EM UM SERVIÇO PÚBLICO DE RADIOTERAPIA

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ABSTRACT

Purpose: To evaluate the prevalence of metastasis and survival rate of patients diagnosed and treated with head and neck cancer and associate them with possible risk factors.
Methods: Medical records (June 2013 to April 2020) of patients diagnosed with head and neck tumors treated in the radiotherapy department of a public hospital were retrospectively evaluated. Three hundred and fifty-one patients were selected, and data regarding the patient, disease and treatment were collected and analyzed descriptively. The association between the independent variables and outcomes was determined by univariate analysis using crude odds ratios. Variables with a p-value <0.20 in the univariate analysis were included in a Cox regression model by the stepwise forward method. Kaplan-Meier analyses were also performed.
Results: Three hundred and one medical records were included, and most participants were male (84.1%) with a mean age of 63.62 years (±12.19). Eighty-three patients died (27.6%) and 56 (18.6%) developed metastases. A significant association (p=0.046) was found between alcoholism/smoking and death. The presence of metastasis (p=0.039) and advanced staging (p=0.021) also showed an association, increasing the risk of death by over two-fold.
Conclusion: A high prevalence of metastasis was found in the patients evaluated, which was a risk factor for death. Other variables also influenced the survival rate of the participating individuals.

Keywords: head and neck cancer; retrospective study; metastasis; death; radiotherapy.

RESUMO

Objetivo: avaliar a prevalência de metástase e taxa de sobrevivência de pacientes diagnosticados e tratados com câncer de cabeça e pescoço e associá-los a possíveis fatores de risco.
Métodos: Prontuários de pacientes com diagnóstico de tumores de cabeça e pescoço tratados no setor de radioterapia de um hospital público foram avaliados retrospectivamente. Trezentos e cinquenta e um pacientes foram selecionados e dados sobre o paciente, doença e tratamento foram coletados e analisados descritivamente. A associação entre as variáveis independentes e os desfechos foram determinadas por análise univariada, utilizando modelos de odds brutas. Variáveis com valor de p < 0,20 na análise univariada foram

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incluídas em um modelo de regressão de cox pelo método stepwise forward. Análises de kaplan-meier também foram realizadas.
Resultados: Foram incluídos trezentos e um prontuários, sendo a maioria dos participantes do sexo masculino (84,1%) com idade média de 63,62 anos (±12,19). Oitenta e três pacientes morreram (27,6%) e 56 (18,6%) desenvolveram metástases. Foi encontrada associação significativa (p=0,046) entre alcoolismo/tabagismo e óbito. A presença de metástase (p=0,039) e o estadiamento avançado (p=0,021) também mostraram associação, aumentando o risco de morte em mais de 2 vezes.
Conclusão: Foi encontrada alta prevalência de metástase nos pacientes avaliados, o que foi um fator de risco para morte. Outras variáveis também influenciaram a taxa de sobrevivência dos indivíduos participantes.

Palavras-chave: *Câncer de cabeça e pescoço; estudo retrospectivo; metástase; morte; radioterapia.*

INTRODUCTION

Head and neck cancer, encompassing the oropharynx, hypopharynx, and larynx, is one of the most prevalent types of neoplasms. Tumors most frequently manifest in the upper aerodigestive tract (Salvajoli 2013). Notably, alcohol consumption and smoking are the primary risk factors for cancer in these regions, accounting for a significant portion, roughly three-quarters, of cases in developed countries. The quantity of alcohol consumed and the duration of tobacco use play critical roles in cancer risk. Furthermore, the combined exposure to alcohol and tobacco exhibits a multiplicative effect on carcinogenesis (Pelucchi 2008).

In Brazil, estimates suggest 11,200 new cases of oral cavity cancer in men and 3,500 in women for each year within the 2018-2019 biennium, although these figures remain unconfirmed. These estimates translate to an approximate risk of 10.86 new cases per 100,000 men, ranking it as the 5th most frequent cancer, and 3.28 per 100,000 women, ranking it as the 12th most frequent among all cancers. In southern Brazil, this type of cancer is the 6th most common among men (15.40/100,000) and the 15th most common among women (3.59/100,000) (Instituto Nacional de Câncer 2018). The diagnosis relies on a comprehensive approach, including a physical examination, biopsy, imaging studies, dental evaluations, and treatment planning. Thus, the prevalence and prognosis of head and neck tumors hinge on multiple factors, including risk factor exposure, tumor molecular characteristics, clinical staging, comorbidities, and treatment received (Carvalho 2005).

The optimal treatment for head and neck tumors involves a multidisciplinary approach with teams from surgery, radiotherapy, clinical oncology, as well as support from nutritionists, speech therapists, psychologists, and dental evaluations. Radiotherapy plays a pivotal role in treating patients diagnosed with localized and locally advanced head and neck cancer. In some cases, combining it with surgery yields superior results. For more advanced lesions, radiotherapy serves as a postoperative adjuvant therapy to reduce the risk of local recurrence or is used in conjunction with chemotherapy for definitive treatment (Salvajoli 2013; Katz 2017).

Invariably, metastasis can occur, a highly complex process where cancer cells spread to other parts of the body and organs, thus forming secondary tumors (Bacac 2008). This colonization to other organs can be a significant contributor to death as most patients are already weakened by the primary disease and still require a new therapy to treat metastases. The prognosis is grim, and it is estimated that most patients with metastases have a 5-year survival rate because, with existing treatments, there is no possibility of cure, only relief and comfort measures with slight improvements (Steeg 2016).

Given this context, conducting a study to assess tumor prevalence in the head and neck region and the development of metastasis, along with their association with potential independent variables, is crucial for better understanding the manifestations of this cancer. This study aims to concentrate on specific strategies for risk and protection factors and contribute to disease prevention programs by evaluating the survival rate and the prevalence of metastases in patients diagnosed with head and neck cancer and undergoing treatment in the radiotherapy department of a public hospital in southern Brazil.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and was carried out according to Resolution 466/2012 (BRAZIL, 2012) and approved by the Research Ethics Committee of Franciscan University (CAAE number: 26490019.2.0000.5306) and the Research Committee of the Research and Technological Innovation Sector of the Teaching and Research Management of Federal University of Santa Maria (SIEWeb UFSM no. 052584).

STUDY TYPE

This is a cross-sectional retrospective study carried out at the University Hospital of Santa Maria, RS, Brazil, at the radiotherapy department.

LOCAL, PARTICIPANTS AND PERIOD

The survival rates of patients diagnosed with head and neck cancer and the prevalence of lesions during metastasis were retrospectively evaluated for a six-year and ten-month period. The information was acquired through the patients' medical records (June 2013 to April 2020) and correlated with a database of the hospital radiotherapy department.

Medical records that did not comply with the data to be extracted were excluded and included a lack of information on dates of diagnostic tests, biopsies, and care protocols necessary for completing the data collection form or loss of some medical records. Medical records of patients who treated

the head and neck regions due to brain metastases from other body areas, including breast and prostate tumors, were also excluded.

DATA COLLECTION METHODS

Data were acquired using a radiation dose delivery system (MOSAIQ version 2.41.01F8; Elekta Linear Accelerator, Precise model) associated with the radiotherapy treatment planning system (XIO - Release 5.00.02, Linux), in which all patients who treated exclusively head and neck tumors in the study period (June 2013 to April 2020) were selected, totaling 351 patients. Therefore, information collection contained in the physical records was performed by filling out a data collection form that included information such as sociodemographic profile, diagnosis, confirmation of pathology, staging, exams performed in the treatment period, clinical and surgical data, chemotherapy, radiotherapy, development of metastases, and recurrences.

DATA ORGANIZATION

All the characteristics of the patients were obtained from the medical records filled out by health professionals during outpatient care. The researcher manually analyzed the medical records by filling out the data collection form, from which the characteristics were divided for a better understanding and analysis of the information. Because there were numerous possibilities, occupations were classified into two groups: individuals who worked in sun-exposed environments versus non-exposed ones. Dental procedures requiring surgical or outpatient procedures were classified as invasive and non-invasive, the intention of treatment according to the protocol established by the medical team were categorized as adjuvant, palliative, radical, and neoadjuvant, and the staging of the disease was labeled as early or advanced. Other variables were also organized and are described in the results.

DATA ANALYSIS

The collected data were analyzed using SPSS 24 for MAC (SPSS Inc, Chicago, IL), and a descriptive analysis was used to describe the patients included in the study. The association between independent variables and outcomes was determined by univariate analysis using crude odds ratios (OR) assuming 95% confidence intervals (95% CI). Variables with a p-value <0.20 in the univariate analysis were included in a Cox regression model by the stepwise forward method. Kaplan-Meier analysis was also used to determine the survival curves for the sample and according to some variables.

RESULTS

Three hundred and fifty-one medical records were selected, and 49 were from patients who had treated head and neck metastases from tumors in other regions of the body and were therefore excluded. Only one medical record was from a pediatric patient with Teebi hypertelorism syndrome, which was also excluded. Hence, three hundred and one records of patients diagnosed with head and neck tumors were analyzed, and from these, 83 died. The mean age of the patients was 63.62 years (±12.19), ranging from 23 to 93 years; most of them were male, self-reported white, with a predominance of low education (less than eight years of schooling) (Table 1).

Table 1 - General characteristics of the patients (n=301).

Variables	Death		Total (%)*
	No (%)	Yes (%)	
Sex			
Female	40 (18.3)	8 (9.6)	48 (15.9)
Male	178 (81.7)	75 (90.4)	253 (84.1)
Race			
White	183 (84.3)	69 (84.1)	252 (84.3)
Black	34 (15.7)	13 (15.9)	47 (15.7)
Education			
≤ 8 years of study	178 (84.4)	68 (82.9)	246 (84.0)
> 8 years of study	21 (9.9)	8 (9.8)	29 (9.9)
Illiterate	12 (5.7)	6 (7.3)	18 (6.1)
Marital status			
Married	113 (53.0)	39 (47.6)	152 (51.5)
Single	47 (22.1)	27 (32.9)	74 (25.1)
Separated/widowed	53 (24.9)	16 (19.5)	69 (23.4)
Profession			
Sun exposure	92 (57.9)	28 (45.2)	120 (54.3)
No sun exposure	67 (42.1)	34 (54.8)	101 (45.7)
Alcoholism			
Yes	114 (56.4)	54 (73.0)	168 (60.9)
No	88 (43.6)	20 (27.0)	108 (39.1)
Smoker			
Yes	167 (81.1)	69 (92.0)	236 (84.0)
No	39 (18.9)	6 (8.0)	45 (16.0)
Smoker and alcoholism			
Yes	111 (54.7)	54 (73.0)	165 (54.8)
No	92 (45.3)	20 (27.0)	112 (40.4)
Family history (cancer)			
Yes	82 (37.6)	33 (39.8)	115 (38.2)
No	136 (62.4)	50 (60.2)	186 (61.8)
Chronic disease			
Yes	140 (64.2)	51 (61.4)	191 (63.5)
No	78 (35.8)	32 (38.6)	110 (36.5)

*When the total are less than 301, the data was missing.

Alcoholism and smoking were highly expressive in the sample, being alcoholism (60.9%), smoking (84.0%), and both habits (54.8%). These habits were predominant in patients who died. Regarding the family history of cancer, 61.8% had no relatives with the disease and over 63% of the sample had chronic diseases, being the most reported hypertension, diabetes, heart disease, and lung disease (Table 1).

The characteristics of the pathologies analyzed in patients with head and neck tumors are listed in Table 2. The location varied widely, with the larynx and oropharynx being the most prevalent. Pathological data included tumor stage in the TNM classification, where T1 and T2 are initial staging indices corresponding to 32.1%, and T3 and T4 are locally advanced indices of the disease and correspond to 67.9% of the total number of cases. As for metastasis development, this occurred in 18.6% of patients in various regions, including the liver, lungs, and bones. The same proportion was found for patients who presented tumor relapses.

Table 2 - Head and neck tumor sites found in the patients (n=301).

Variable	Death		Total (%)
	No (%)	Yes (%)	
Tumor site			
Larynx	61 (28.0)	22 (26.5)	83 (27.6)
Oral cavity	40 (18.3)	20 (24.1)	60 (19.9)
Oropharynx	44 (20.2)	16 (19.3)	60 (19.9)
Hypopharynx	16 (7.3)	7 (8.4)	23 (7.7)
Salivary gland	14 (6.4)	3 (3.6)	17 (5.7)
Non-hodgkin lymphoma	3 (1.4)	1 (1.2)	4 (1.3)
Nasopharynx	3 (1.4)	1 (1.2)	4 (1.3)
Other	37 (17.0)	13 (15.7)	50 (16.6)
Local staging			
Home	51 (35.2)	11 (22.9)	62 (32.1)
Advanced	94 (64.8)	37 (77.1)	131 (67.9)
Chemotherapy			
Yes	151 (80.3)	66 (91.7)	217 (83.5)
No	37 (19.7)	6 (8.3)	43 (16.5)
Chemo + radiotherapy			
Yes	128 (65.0)	50 (67.6)	178 (65.7)
No	69 (35.0)	24 (32.4)	93 (34.3)
Treatment intention			
Adjuvant	110 (57.9)	34 (49.3)	144 (55.6)
Palliative	54 (28.4)	29 (42.0)	83 (32.0)
Radical	24 (12.6)	5 (7.2)	29 (11.2)
Neoadjuvant	2 (1.1)	1 (1.5)	3 (1.2)
Tracheostomy			
Yes	69 (32.2)	37 (44.6)	106 (35.7)
No	145 (67.8)	46 (55.4)	191 (64.3)

Nasoenteral tube			
Yes	85 (39.7)	39 (47.0)	124 (41.8)
No	129 (60.3)	44 (53.0)	173 (58.2)
Metastasis			
Yes	32 (14.7)	24 (28.9)	56 (18.6)
No	186 (85.3)	59 (71.1)	245 (81.4)
Tumor recurrence			
Yes	38 (17.4)	18 (21.7)	56 (18.6)
No	180 (82.6)	65 (78.3)	245 (81.4)

The Cox regression to associate the variables with the outcomes of death is described in Tables 3 and 4. Given the notable influence of the alcoholism/smoking variable, two models were created, with one disregarding this variable. The final models were created after other models were tested, where only those variables that previously showed significant association remained in the final models. The information in Table 3 shows a significant association (p=0.046) between alcoholism/smoking and death, and patients with these habits have an over two-fold increased risk of death. Nonetheless, patients with metastasis had a 2.09 higher risk of death (p=0.042) than patients without metastasis. Without the influence of the variable alcoholism/smoking, there were some distinct variables in the final model (Table 4). Metastasis remained a variable that increased the risk of death, albeit advanced staging (p=0.021) and working in an occupation with sun exposure (p=0.008) had a 2.58 and 2.45 higher risk of death than initial staging working in environments without sun exposure, respectively.

Table 3 - Cox regression results for variables associated with death in patients with head and neck tumors considering the variable alcoholism/smoking.

Variable	p-value	Risk	95% Confidence interval	
			Lower	Higher
Step one				
Gender	0.417	0.596	0.171	2.081
Race	0.444	0.704	0.287	1.730
Education	0.485	1.405	0.541	3.647
Staging	0.109	1.838	0.872	3.873
Metastasis	0.085	1.897	0.915	3.932
Recurrence	0.625	1.190	0.592	2.393
Chronic diseases	0.283	0.703	0.370	1.337
Alcoholism/smoking	0.043	2.154	1.025	4.530
Last step				
Staging	0.090	1.855	0.908	3.787
Metastasis	0.042	2.095	1.027	4.275
Alcoholism/smoking	0.046	2.089	1.012	4.313

Table 4 - Cox regression results for variables associated with death in patients with head and neck tumors, disregarding the variable alcoholism/smoking.

Variable	p-value	Risk	95% Confidence interval	
			Lower	Higher
Step one				
Gender	0.732	0.802	0.227	2.830
Race	0.616	1.245	0.530	2.925
Marital status	0.347	0.827	0.556	1.229
Profession	0.011	2.511	1.232	5.120
Education	0.510	1.394	0.519	3.745
Staging	0.025	2.662	1.134	6.253
Metastasis	0.046	2.303	1.015	5.226
Recurrence	0.993	1.003	0.470	2.142
Chronic diseases	0.800	0.916	0.462	1.813
Last step				
Profession	0.008	2.459	1.266	4.777
Staging	0.021	2.580	1.152	5.778
Metastasis	0.039	2.261	1.041	4.912

The survival curves related to the sample analyzed are illustrated in Figures 1, 2, and 3, accordingly to patient's age (A) and follow-up time (B). The Kaplan-Meier graph presents the survival curve of the 301 patients included in the study (Figure 1A and B). It is possible to note the beginning of the curve's decline after 50 years of age (A) (i.e., a high morbidity rate after this period). The Kaplan-Meier plots were constructed considering the variables metastasis and alcoholism/smoking, respectively (Figures 2 and 3 – A and B). The log-rank test was applied in both, being the presence of metastasis associated with death (0=0.004) and concomitant alcoholism and smoking habits also being associated with patients evolving to death (p<0.001).

Figure 1 - Kaplan-Meier plot of deaths in patients with head and neck tumors. It can be seen that most deaths occur after the age of 50.

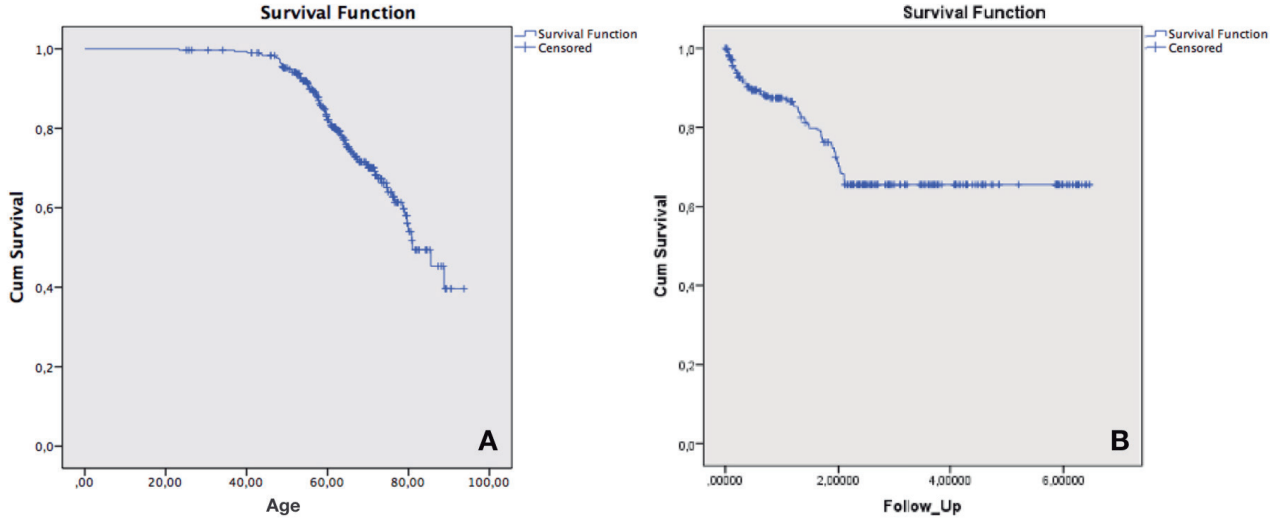


Figure 2 - Kaplan-Meier plot for the presence or absence of metastasis in patients with head and neck tumors (log-rank test; p=0.004 (A) and p<0.001(B)).

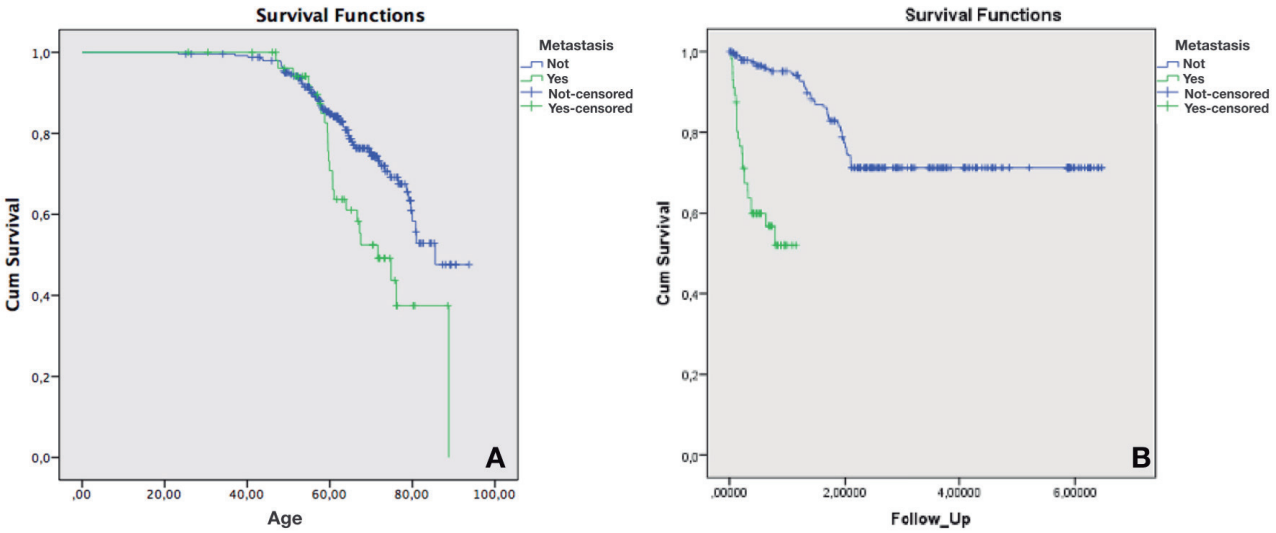
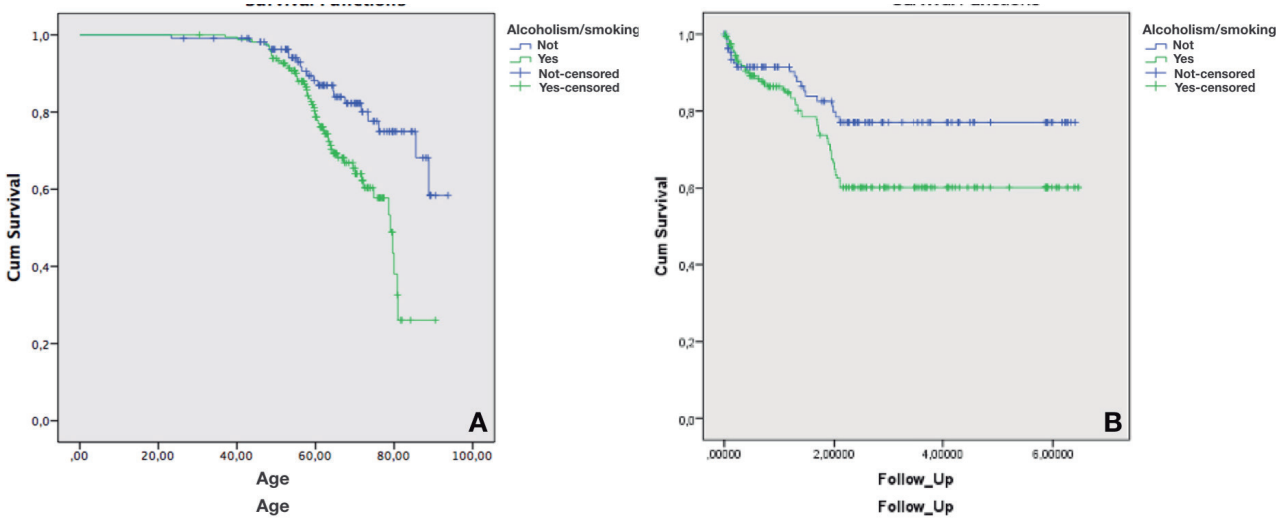


Figure 3 - Kaplan-Meier plot for the concomitant habit of alcoholism and smoking in patients with head and neck tumors (log-rank test; p<0.001 (A) and p=0.021(B)).



DISCUSSION

Roughly one in five patients (18.6%) exhibited metastasis, underscoring a high prevalence. Furthermore, metastasis emerged as a primary risk factor for patient mortality, emphasizing the significance of closely monitoring patients diagnosed with head and neck cancer. This becomes even clearer when considering the studies by Florescu and Thariat (2014), which reported notably low survival rates, estimating that only 10 to 15% of patients survive five years after their initial diagnosis. Pisani (2020) reported a lower prevalence of metastasis, approximately 10% of cases, but with an equally unfavorable prognosis and an overall survival of up to 10 months. The authors attributed this to the rapid progression of these metastases and the uncertainty surrounding the

clinical and therapeutic approach, a pattern also evident in our study, where palliative care remains the most effective measure for patient comfort.

In terms of patient characteristics, there was a higher prevalence of white and male individuals, who also exhibited the highest rates of alcohol use and smoking. This combination diminishes the efficacy of treatment, increases the risk of developing metastasis and relapses (Döbróssy 2005), and exacerbates factors associated with mortality. Other variables, such as lifestyle, behavioral habits, and exposure to carcinogens (e.g., sun exposure and pesticide exposure in the fields), may be linked to cancer development (Döbróssy 2005). These findings align with our own, where patient with more significant external exposure had a higher risk of mortality.

While there was no significant influence on the "death" outcome in the regression model, radiotherapy administered to patients with the intention of adjuvant treatment yielded a survival benefit (57.9% compared to palliative and radical treatments). Furthermore, we observed that patients seeking care at the hospital often did so well after experiencing symptoms, thereby impeding diagnosis and referral to the multidisciplinary team. This type of referral can significantly impact patients' day-to-day lives, as treatments by dentists, nutritionists, and speech therapists provide effective follow-up, yielding better results and alleviating discomforts such as xerostomia, loss of appetite, and difficulty swallowing, thus improving the quality of life during treatment (Minasian 1998).

Despite not yielding significant results, we collected numerous variables, given the importance of understanding the profile of head and neck cancer patients treated in the department. There was a high prevalence of inadequate oral hygiene, often leading to multiple dental extractions before initiating radiotherapy treatment to prevent radionecrosis, consequently causing delays in commencing treatment. We also encountered frequently reported conditions, including xerostomia, fungal mucositis, and dysphagia, as radiotherapy, despite its proven effectiveness, can trigger these side effects, necessitating monitoring by the multidisciplinary team to alleviate symptoms (Jham 2006).

The two primary variables related to mortality were alcoholism/smoking and staging, doubling the risk of death. Many patients reported smoking since adolescence, with prolonged periods of tobacco consumption, potentially contributing to tumor development and complications. However, the duration and frequency of smoking habits were not surveyed. Our study and others (Lewellyn 2004; Dhull 2018; Cho 2020) highlight how these habits increase the incidence of head and neck carcinogenesis and its consequences. The locally advanced stage raised the death rate to 77.1%, with three out of every four deceased patients being in a more advanced stage. This underscores the importance of early diagnosis for improved disease outcomes, particularly given the high prevalence of these tumors in southern Brazil (Casati 2012).

Frequent hospital admissions due to worsening tumors left patients with compromised immune systems, leading to lung infections, cardiovascular disorders, and brain lesions that necessitated specific care in intensive care units. This further diminished patients' well-being and health, potentially increasing the risk of death (Martos-Benítez 2020). However, it is vital to emphasize the challenge of early tumor

diagnosis, which can compromise prognosis and treatment within the Brazilian public health system, potentially explaining the high death rate, especially among patients in advanced stages and with metastasis.

As for tumor prevalence by location, the larynx, oropharynx, and oral cavity exhibited the highest rates. Interestingly, these regions possess mucous membranes sensitive to the combined effects of alcohol and substances present in tobacco, resulting in a high prevalence in the sample studied. When coupled with poor oral hygiene conditions, tooth loss, and localized lesion advancement, this may explain the high mortality rate, as also reported by Wang et al. (2013).

Of the patients who developed distant metastases after the intention to treat was defined, 14.7% died, and the places where metastases predominated were the lungs and liver. Even though the chances of cure for metastases from head and neck tumors are meager, we also found in the records of these patients that they received a follow-up after the end of the intention to treat, new cycles of chemotherapy, hospitalizations, and interventions from multidisciplinary teams. Given this scenario, tumor recurrences have likely occurred and contributed to these patients' higher death rates. It is also not evident that the different types of distant metastasis have the same prognosis, and generally, the location where the metastasis occurs has little influence on the performance of the therapeutic treatment (Wiegand 2015). Also, none case of human papilloma virus was detected in our study, probably due to the characteristics of the sample, with very similar cultural habits, living with their families and most of the patients are from rural areas (Axelsson 2017). Moreover, it is paramount to emphasize that, because this is a public health service, the profile of the population served is particular, which leads us to observe our results with caution given the limited population studied.

The data from this study confirm that the predominant treatment protocol was the adjuvant intention, which can result as an indicator of treatment efficacy. Although it does not have a specific protocol due to the patient's staging and physical conditions, it is the most appropriate intention and has proven to be successful (Vincent 2020). To improve these results, rapid diagnosis and awareness to adapt to this most promising treatment are important.

Upon analyzing some limitations encountered in this study, we noted that the data originated from patient reports and were interpreted by healthcare professionals in their respective medical records. This information occasionally raised doubts about the study's outcomes, leading researchers to exclude certain reports. Ultimately, identifying risk factors associated with the disease is crucial as it enables the implementation of educational programs for prevention and health promotion, increasing awareness and monitoring to reduce the risks of developing head and neck cancer, metastasis, relapses, and mortality.

CONCLUSIONS

A high prevalence of metastasis was found in the patients evaluated and the concomitant habit of alcoholism and smoking being risk factors for death. Cancer staging and the type of profession performed also influenced the survival rate of the participating individuals.

CONFLICT OF INTEREST

The authors declares no conflict of interest.

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