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Survival rates of patients with cancer of the lip, mouth and pharynx: a cohort study of 10 years

Sobrevida de pacientes com câncer de lábio, boca e faringe: um estudo de coorte de 10 anos

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ABSTRACT: ***Introduction:*** Cancer of the lip, mouth and pharynx is a serious health problem. High incidence rates are found worldwide. In Brazil, the Southern and Southeastern regions have the highest incidences in the country. ***Objective:*** To describe 5 and 10-year survival rates in patients with cancer of the lip, mouth and pharynx at a referral center in Florianopolis, Santa Catarina, Brazil. ***Methods:*** Retrospective cohort study using data from patients diagnosed between January 1st and December 31st, 2001, with follow-up until December 31st, 2011. Descriptive analysis was performed and survival was estimated by Kaplan-Meier method. Cox semi-parametric model was used to estimate death risk. ***Results:*** Survival rates at 5 and 10 years were 33.3 and 26.9%, respectively. Advanced clinical stage in the diagnosis increased death risk by 2.88 and 2.51, respectively. Sex, ethnicity, level of education, previous diagnosis and treatment, as well as age, did not show significant association. ***Conclusion:*** Survival rate at 5 years was 33.3% and, at 10 years, was 26.9%. Advanced stage was an independent risk factor for death due to cancer of the lip, mouth and pharynx in both periods analyzed.

***Keywords*:** Mouth neoplasia. Oropharyngeal neoplasms. Lip neoplasms. Survival analysis. Epidemiology. Longitudinal studies.

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RESUMO: ***Introdução:*** O câncer de lábio, boca e faringe é um sério problema de saúde. Altas taxas de incidência são encontradas no mundo. No Brasil, as regiões Sul e Sudeste são as que apresentam maiores taxas de incidência. ***Objetivo:*** Descrever a taxa de sobrevida em cinco e dez anos em portadores de câncer de lábio, boca e faringe atendidos em um centro de referência de Florianópolis, SC. ***Métodos:*** Estudo de coorte histórica, realizado com dados de pacientes que tiveram diagnóstico entre 1º de janeiro e 31 de dezembro de 2001 e acompanhados até 31 de dezembro de 2011. Foi realizada análise descritiva e estimada a sobrevida pelo método de Kaplan-Meier. O modelo semiparamétrico de Cox foi utilizado para estimar o risco de óbito. ***Resultados:*** As taxas de sobrevida ao final de 5 e 10 anos foram de 33,3 e 26,9%, respectivamente. O estadio clínico avançado ao momento do diagnóstico aumentou em 2,88 e 2,51 o risco de óbito, respectivamente. Sexo, etnia, nível de escolaridade, diagnóstico e tratamento prévios, bem como idade, não se mostraram significativamente associados. ***Conclusão:*** As taxas de sobrevida aos 5 anos foi de 33,3% e, aos 10 anos, foi de 26,9%. O estadio avançado mostrou-se como fator de risco independente para o óbito por câncer de lábio, boca e faringe nos dois períodos analisados.

***Palavras-chave*:** Neoplasias bucais. Neoplasias orofaríngeas. Neoplasias labiais. Análise de sobrevida. Epidemiologia. Estudos longitudinais.

INTRODUCTION

Cancer of lip, mouth and pharynx is a serious and increasing public health problem in many parts of the globe. The latest global estimates indicated that about 300 thousand new cases and 145.000 deaths occurred in 2012[1]. High incidence rates are found in South and Central Asia, Western Europe, and Oceania[1]. The male population carries the highest risk of developing this type of cancer; in Brazil, for each one new case in female population there are three cases in male population[2]. The Southern and Southeastern Brazilian regions have the highest incidences in the country[2].

The main factors associated with cancer of the lip, mouth and pharynx are the use of tobacco and alcohol and exposure to UVA radiation (lip cancer)[3]. The frequent and combined use of tobacco and alcohol causes a synergistic effect, increasing the risk of developing the disease[2,3]. Furthermore, heavy intake of alcoholic beverages is associated with nutrient deficiency. Occupational risk factors have also been cited in literature, such as exposure to toxic agents or solar radiation during the labor. Dietary patterns may be associated with reduced the risk of cancer. Evidence shows that high intake of fiber, fruits and vegetables reduce the risk of head and neck cancer, as well as the poor intake of red meat[4].

Cancer of the lip, mouth and pharynx may cause important functional and esthetic changes, which requires a multidisciplinary approach for treatment[5]. The clinical background may include persistent pain, dyspnea, dysphagia, odynophagia, xerostomia, voice changes, weight loss, rigidity of tissues and decrease or loss of work capacity.

The functions often compromised are related to the anatomo-physiology of the head and neck[6]. Speech, swallowing, phonation and appearance are adversely affected by both the disease and its treatment; some treatment options are associated with relevant dysphonia, dysphagia and facial disfiguring, with loss of function and a considerable impact on social relationships[6].

Approximately a third of the patients develop malnutrition, which is not exclusively caused by tumor growth, but also by associated factors such as the aerodigestive tract location of the tumor and the sequelae of surgical treatment[7]. Malnutrition is associated to higher rates of post-operative complications, poor response to treatment and higher risk of disease recurrence[8].

Cancer originates mostly in the mucosa, where squamous cell carcinoma is the commonest and usually developed from premalignant lesions as leukoplakia and erythroleukoplakia[3]. Periodic examinations by health professionals are recommended, thus there is possibility to referral for diagnostic investigation of premalignant suspected lesions, and not present major difficulties for trained professionals since the groups at highest risks are known and the site is easy to access for clinical examination and biopsy[9]. Careful visual examination of the oral mucosa by a dentist with adequate illumination may result in early detection of the disease. In addition, palpation of the adjacent structures, such as the neck, submandibular regions and jaw bones is of paramount importance. The diagnosis of small early lesions is fundamental for good prognosis[10], which is dictated by tumor site, size, lymph node involvement and age of the patient[11].

Survival studies are the method used in epidemiological research to analyze prognosis. Furthermore, survival data is useful to assess the general impact of disease on public health programs, since they estimate the effectiveness of health systems which depend upon the quality and availability of healthcare. Survival knowledge is essential for planning and managing disease in each region as well as to help monitoring and controlling prognostic factors in the population[12].

In most countries, the 5-year survival rate for cancer of the tongue, mouth and oropharynx is approximately 50%, where cancer of the lip carries the best prognosis, which is higher than 90%[12,13]. Disease stage at diagnosis affects survival rates; for mouth, the survival rate at stage I is 70%, whereas for stage IV, it drops to 30%[13].

One study reported that the 5-year survival rate in patients with cancer of the head and neck, mouth, oropharynx, hypopharynx and larynx was 24.1, 25.91, 19.2, 13.4 and 38%, respectively. This reality highlights the need for early diagnosis to increase treatment effectiveness in order to improve outcome[12].

There are only a few cancer survival studies in Brazil. The knowledge of cancer survival rates may contribute towards monitoring treatment outcome in order to increase population survival as well as to identify prognostic factors. Therefore, the aim of this study was to describe the survival rates at 5 and 10-year follow-up periods for patients with cancer of the lip, mouth and pharynx, who were treated at a referral center in Florianópolis, capital of the State of Santa Catarina, Southern region of Brazil.

METHODS

This was a retrospective cohort study[14] performed with data from patients with cancer of the lip, mouth and pharynx (ICD-O C00 to C06, C09 to C10 and C12 to C14), who were diagnosed between January 1st and December 31st, 2001, treated at the Center for Oncologic Research (CEPON) of Florianópolis and registered at the Hospital Cancer Registry System[15] of this institution. The cancer cases of parothid gland C07 (n = 5) and nasopharynx C11 (n = 17) were excluded from the sample. The only reported cancer case of other lip, mouth and pharynx sites C14 (n = 1) were maintained in the sample.

These registries are systematic sources of information on malignant neoplasia diagnosed and treated at the hospital they were managed, following criteria established by the Brazilian National Institute of Cancer (INCA). CEPON is the core institute for cancer care in the State of Santa Catarina.

Data regarding death, such as date and cause, were gathered from the Mortality Information System of the Brazilian Ministry of Health, based on death certificates. This database was made available by the Health Secretariat of Santa Catarina and analyzed between 2001 and 2011. The final follow-up date was December 31st, 2011.

In order to carry out patient follow-up, the probabilistic relationship method of registration was used[16], relating the Hospital Cancer Registry System database with Mortality Information System. The RecLink III software was used (http://www.iesc.ufrj.br/reclink/RecLink_arquivos /RecLinkdl.html). The association rules were determined between the two databases, using variables from each of them. The Mortality Information System variables were death certificate number, patient name, date of birth, date of death, cause of death and town of residence. The Hospital Cancer Registry variables were patient record number, patient name, date of birth and town of residence. A single database was then created containing all the information pertinent to this study.

The independent variables were sex, age at diagnosis (years), ethnicity (white/black and mixed), level of education (higher education and high school, complete primary school, incomplete primary school or illiterate), previous diagnosis and treatment (with diagnosis/with treatment, with diagnosis/no treatment or no diagnosis/no treatment), clinical stage at diagnosis (stages I and II: early; stages III and IV: advanced).

Survival was calculated as the interval between date of diagnosis (biopsy or surgery) from the Hospitalar Cancer Registry database and date of death or last date of follow-up. The maximum follow-up was ten years — patients not found on Mortality Information System or who did not have a date of death on Hospitalar Cancer Registry were censored at the last follow-up date.

The survival curves were estimated using Kaplan-Meier, with or without stratification. The probability of survival up to the specified date was estimated, considering that survival up to each studied time was independent from the survival up to other times. In order to compare the stratified survival curves, log-rank test was used, which compared values observed and the expected values for each stratum, considering the null hypothesis that the risk was the same for all strata[17].

The estimation of the effect of the independent variables was performed based on the semi-parametric model of proportional risks, Cox model, which estimates proportionalities of risks along the period of observation[17]. The variables included in the model were those that presented a p-value < 0.20. All analyses were carried out for 5 and 10 years of follow-up using the Stata SE 9.0 software.

The research project was approved by the Ethics Committee in Research of the CEPON.

RESULTS

In the period studied, 141 people had a diagnosis of cancer of the lip, mouth and other pharynx. Tumors of the tongue (17.7%) and oropharynx (15.6%) were the most incident. The data on death incidence as well as on 5 and 10-year survival rates by specific sites are described in Table 1. Amongst the patients analyzed, 81.6% were male, with a mean age of 57.1 years (standard deviation – SD = 12.0). In terms of ethnicity, the vast majority was white (93.6%); 60.7% did not complete primary education and only 8.9% completed high school or higher education. Most tumors were diagnosed at stage III (47.9%) or IV (44.3%); 64.1% of the patients presented to the service with a diagnosis, however without previous treatment (Table 2).

The survival rates and factors were analyzed together: lip, mouth and other pharynx, because the groups were very small, and they did not differ statistically among them. In 5 years, 94 subjects were deceased (66.7%) (Table 1). From the total of followed men and women, 70.4% (n = 81) and 50.0% (n = 13) had died, respectively (Table 2). At 10-year follow-up, 103 subjects were deceased (73.0%) (Table 1); 77.4% (n = 89) of all men and 53.9% (n = 14) of all women were died (Table 3). All causes of death were due or related with cancer.

The overall 5-year survival was 33.3% (95%CI 25.7 – 41.1) (Table 1). Female patients showed a better survival rate, 50.0% (95%CI 26.6 – 63.6), against 29.5% (95%CI 21.5 – 38.0) of males; however, such difference did not reach significance (p = 0.102). "This also occurred with ethnicity (p = 0.083), level of education (p = 0.276) as well as diagnosis and previous treatment (p = 0.856). Cancer stage was a significant variable on bivariate analysis, i.e., those at stages I and II had a likely survival of 63.6% (95%CI 22.8 – 78.0), whilst those at stages III and IV, 30.8% (95%CI 23.7 – 38.8), thus making clinical stage an independent variable, increasing the chance of death by 2.88 (95%CI 1.04 – 7.92) (Table 2).

The overall 10-year survival rate was 26.9% (95%CI 19.9 – 34.4) (Table 1). Females had a better survival, 46.1% (95%CI 26.6 – 63.6), against 22.6% (95%CI 15.5 – 30.6) in males, however, the difference only just reached significance (p = 0.051). Non-significant difference was also observed for ethnicity (p = 0.098), level of education (p = 0.441) as well as for previous diagnosis and treatment (p = 0.905). The variable age showed an increase of death risk of 2% every year from diagnosis, however statistical significance was missed in the adjusted analysis. The variable stage was significant on bivariate analysis, i.e., those at stage I and II had a survival rate of 54.5% (95%CI 22.8 – 78.0), against 24.6% (95%CI 17.6 – 32.3), making it an independent variable increasing death risk by 2.51 (95%CI 1.01 – 6.23) (Table 3). Figure 1 shows the overall survival curves for each variable studied.

Table 1. Death incidence and chance of survival at 5 and 10 years, 2001–2011.

CID-10		n (%)	5 years		10 years	
			Death (%)	% of survival (95%CI)	Death (%)	% of survival (95%CI)
C00	Lip	3 (2.1)	1 (33.3)	66.7 (5.4-94.5)	2 (66.7)	33.3 (0.9-77.4)
C01	Ventral tongue	16 (11.3)	15 (93.7)	6.2 (0.4-24.7)	15 (93.8)	6.2 (0.4-24.7)
C02	Tongue - not otherwise specified	25 (17.7)	14 (56.0)	44.0 (21.3-58.1)	17 (68.0)	32.0 (15.2-50.2)
C04	Floor of the mouth	14 (9.9)	13 (92.9)	7.1 (0.4-27.5)	13 (92.9)	7.1 (0.4-27.5)
C05	Palate	17 (12.1)	7 (41.2)	58.8 (32.5-77.8)	11 (64.7)	35.3 (14.5-57.0)
C06	Mouth - not otherwise specified	17 (12.1)	11 (64.7)	35.3 (14.5-57.0)	11 (64.7)	35.3 (14.5-57.0)
C09	Tonsils	7 (5.0)	4 (57.1)	42.9 (9.8-73.4)	4 (57.1)	42.9 (9.8-73.4)
C10	Oropharynx	22 (15.6)	16 (72.7)	27.3 (11.1-46.4)	16 (72.7)	27.3 (11.1-46.4)
C12	Piriform recess	2 (1.4)	-	100.0	-	100.0
C13	Hypopharynx	17 (12.1)	12 (70.6)	29.4 (10.7-51.1)	13 (76.5)	23.5 (7.3-44.9)
C14	Other lip, oral cavity and pharynx sites	1 (0.7)	1 (100.0)	0.0	1 (100.0)	0.0
Total		141 (100.0)	94 (66.7)	33.3 (25.7-41.1)	103 (73.0)	26.9 (19.9-34.4)

95%CI: confidence interval of 95%.

DISCUSSION

This study aimed at estimating survival rates at five and ten years from a diagnosis of cancer of the lip, mouth and pharynx. The high incidence, prevalence and mortality rates observed as well as the low survival[18] reported in some studies warranted the importance of the present study. This type of cancer can be curable at the time of diagnosis; however, it is associated with a low survival rate due to the conditions presented by the patient, which are related to an unhealthy lifestyle, which involves smoking and alcohol consumption[19,20].

Table 2. Deaths, chance of survival in 5 years and crude and adjusted death risk, 2001–2006.

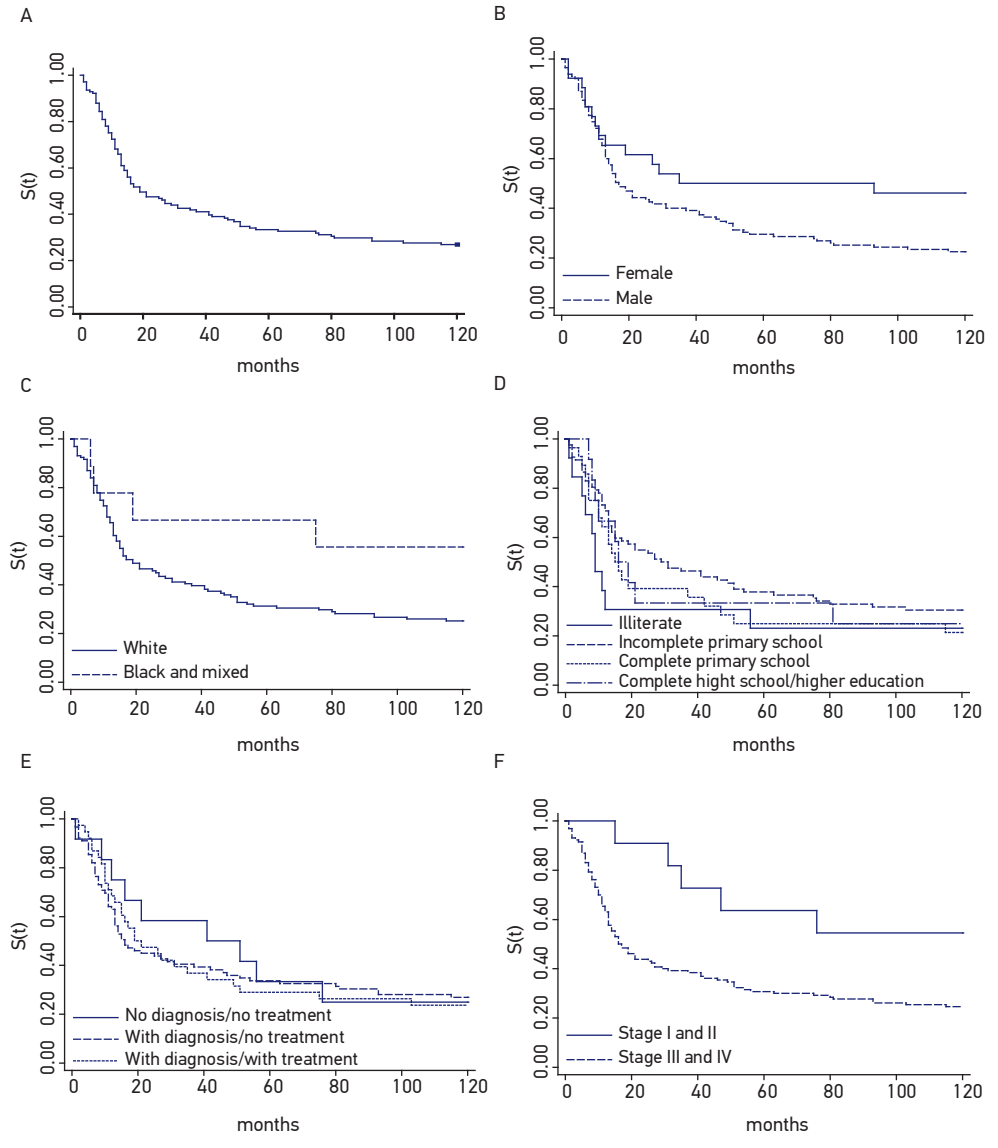
Variable	n (%)	Deaths (%)	Chance of survival after 5 years (95%CI)	p-value (log-rank)	Crude Hazard-ratio (95%CI)	Adjusted Hazard-ratio (95%CI)
Sex (n = 141)				0.102		
Male	115 (81.6)	81 (70.4)	29.5 (21.5 – 38.0)		1.61 (0.89 – 2.90)	1.39 (0.77 – 2.53)
Female	26 (18.4)	13 (50.0)	50.0 (26.6 – 63.6)		1.00	1.00
Ethnicity (n = 140)				0.083		
White	131 (93.6)	101 (66.5)	31.3 (23.5 – 39.3)		0.38 (0.12 – 1.20)	1.00
Black and mixed	9 (6.4)	3 (33.3)	66.6 (28.2 – 87.8)		1.00	0.41 (0.12 – 1.33)
Level of education (n = 135)				0.276		
Illiterate	13 (9.6)	10 (76.9)	23.1 (05.5 – 47.4)		0.55 (0.28 – 1.09)	
Incomplete primary school	82 (60.7)	51 (62.2)	37.8 (27.4 – 48.1)		0.78 (0.35 – 1.61)	
Complete primary school	28 (20.7)	21 (75.0)	25.0 (11.1 – 41.8)		0.63 (0.24 – 1.60)	
Complete high school/higher education	12 (8.9)	8 (66.7)	33.3 (10.3 – 58.8)		1.00	
Previous diagnosis and treatment (n = 139)				0.856		
No diagnosis/ no treatment	12 (8.6)	8 (66.7)	33.3 (10.3 – 58.8)		1.00	
With diagnosis/ no treatment	89 (64.1)	59 (66.3)	33.7 (24.1 – 43.5)		1.22 (0.58 – 2.56)	
With diagnosis/ with treatment	38 (27.3)	27 (71.1)	26.3 (13.7 – 40.8)		1.22 (0.55 – 2.70)	
Stage (n = 141)				0.026		
I and II	11 (7.8)	4 (36.4)	63.6 (22.8 – 78.0)		1.00	1.00
III and IV	130 (92.2)	90 (69.2)	30.8 (23.7 – 38.8)		2.92 (1.07 – 7.95)	2.88 (1.04 – 7.92)
Age (n = 141)						
					1.01 (0.99 – 1.03)	1.01 (0.99 – 1.03)

95%CI: confidence interval of 95%.

Table 3. Deaths and chance of survival after 10 years and crude and adjusted risk of death, 2001–2011.

Variable	n (%)	Deaths (%)	Chance of survival after 10 years (95%CI)	p-value (log-rank)	Crude hazard-ratio (95%CI)	Adjusted hazard-ratio (95%CI)
Sex (n = 141)				0.051		
Male	115 (81.6)	89 (77.4)	22.6 (15.5 – 30.6)		1.72 (0.98 – 3.04)	1.54 (0.86 – 2.74)
Female	26 (18.4)	14 (53.9)	46.1 (26.6 – 63.6)		1.00	1.00
Ethnicity (n = 140)				0.098		
White	131 (93.8)	98 (74.8)	25.1 (18.1 – 32.9)		1.00	1.00
Black and mixed	9 (6.4)	4 (44.4)	55.6 (20.4 – 80.5)		0.44 (0.16 – 1.20)	0.51 (0.18 – 1.42)
Level of education (n = 135)				0.441		
Illiterate	13 (9.6)	10 (76.9)	23.8 (05.6 – 47.5)		1.00	
Incomplete primary school	82 (60.7)	57 (69.5)	30.4 (20.9 – 40.6)		0.61 (0.31 – 1.21)	
Complete primary school	28 (20.8)	22 (78.8)	21.4 (08.7 – 37.8)		0.80 (0.38 – 1.70)	
Complete high school/higher education	12 (8.9)	9 (75.0)	25.0 (06.0 – 50.5)		0.71 (0.29 – 1.76)	
Previous diagnosis and treatment (n = 139)				0.905		
No diagnosis/ no treatment	12 (8.6)	9 (75.0)	25.0 (06.0 – 50.5)		1.00	
With diagnosis/ no treatment	89 (64.0)	65 (73.0)	27.0 (18.2 – 36.4)		1.16 (0.58 – 2.34)	
With diagnosis/ with treatment	38 (27.4)	29 (76.3)	23.7 (11.7 – 37.9)		1.16 (0.55 – 2.45)	
Stage (n = 141)				0.027		
I and II	11 (7.8)	5 (45.5)	54.5 (22.8 – 78.0)		1.00	1.00
III and IV	130 (92.2)	98 (75.4)	24.6 (17.6 – 32.3)		2.61 (1.06 – 6.42)	2.51 (1.01 – 6.23)
Age (n = 141)						
					1.02 (1.00 – 1.03)	1.01 (0.99 – 1.03)

95%CI: confidence interval of 95%.



(A) general survival; (B) survival stratified by sex; (C) survival stratified by ethnicity; (D) survival stratified by level of education; (E) survival stratified by previous diagnosis and treatment; (F) survival stratified by clinical stage.

Figure 1. General and stratified survival curves.

The synergistic effect between tobacco and alcohol results in a 30-fold increase in the risk of developing the disease[18].

Tobacco smoking is the main risk factor for cancer of the lip, mouth and pharynx, especially regarding long-term heavy smoking (20 or more cigarettes a day) or users of black tobacco with a high tar content[21]. A study performed by Rodriguez and Adelstein[19] reported a negative

impact on survival with the continued use of tobacco after treatment, thus suggesting that smoking cessation may improve survival. According to Galbiatti et al.[22], there is a significant reduction in the risk of developing the disease when the patient quits smoking.

Alcohol intake also increases the risk of developing this type of cancer — a heavy drinker (a weekly intake of more than 300 mL) has a risk 10 times higher than non-drinkers or those who drink sporadically. This risk factor seems to be related to exposure to an intermediate metabolite of ethanol, acetaldehyde, which is a known carcinogen[20].

When analyzing the socio-demographic profile of the patients included in this study, a higher prevalence of cancer diagnoses and deaths was observed amongst males, which was also reported in other studies[23-25]. There is evidence that exposure to tobacco is higher in men than in women[26], and that women notice the symptoms of the disease more easily than men, which may lead them to seek medical assistance earlier[23], thus resulting in earlier diagnosis and improved survival. However, in this study, no significant difference was observed either at five or ten years of follow-up.

The information reported in this study regarding age at diagnosis does not corroborate the findings of another study[27], which reported a decrease in survival with an age increase. The authors pointed out that older patients at the time of diagnosis may die as a result of complications of treatment, as they may be unable to tolerate the aggressiveness of the therapeutic approach[27].

Regarding ethnicity, both diagnosis and death rates were higher in white individuals, although this did not reach statistical significance. The results of this study are therefore inconclusive and one must take into account the data in the literature, which shows death rates higher in individuals of mixed ethnic background[23]. Regarding level of education, no significant difference was found at five or ten years of follow-up. The literature reports that death rates are higher in less educated individuals[23].

Regarding previous diagnosis and treatment, the death rates found were similar in the three categories. Although this study has been carried out in a referral center, it is worth to highlight that nearly 10% of the subjects arrived with no previous diagnosis and consequently with no treatment. The literature shows that the most frequently performed treatment for cancer of the lip, mouth and pharynx is radiotherapy; however, for patients with loco-regional disease, the use of radiotherapy did not alter survival[27].

On the other hand, the clinical stage at diagnosis was an independent factor associated with survival, both at five and ten years of follow-up. This finding corroborates that of a different study, which described a higher prevalence of stage IV disease associated with a decrease in survival for all sites[13]. Furthermore, another study has reported poorer survival rates in metastatic disease, in which survival decreased from 41.5 to 32.5% during the follow-up period[27].

The most effective way to improve the prognosis of patients with cancer of the lip, mouth and pharynx is the prevention of risk factors and early diagnosis, since early treatment results in a high percentage of resolution. The main causes of delayed diagnosis are lack of information and symptom neglect by the patients, as well as health professional failure at routinely screening patients[22]. The reason for a low rate of early diagnosis is related to a low level of preparation of dentists, as other health professionals, to actively screen and recognize potentially malignant oral lesions, which could be diagnosed and treated before malignant

transformation[10]. Such lack of preparation makes health professionals underprepared to establish an earlier diagnosis. This limitation, in turn, affects patient referral to the appropriate services, which further complicates treatment and reduces the chances of a cure[10].

Health professionals have the obligation to be prepared to recognize suspicious lesions and carry out a diagnostic biopsy or, at least, refer the patient. Therefore, periodic visits to the dentist are paramount to increase detection of early lesions and to monitor changes. Furthermore, the dental professional must instruct their patients to examine their own mouth, aiming at detecting lesions as early as possible[10]. Hopefully, higher levels of awareness to the problem and appropriately trained health professionals, especially dentists, both at the undergraduate and the following professional development levels, may cause an impact on the rates of early diagnosis and, consequently, on higher survival rates[9].

The strong points of this study were the reports of data from official sources, as established by INCA, as well as the inclusion of the follow-up time of ten years, which permitted an insight into survival rates over a long period of time and is not commonly encountered in Brazilian studies. However, the limitations must be taken into consideration when interpreting the results; one of them was the dependence on information stored on the database system used, which did not provide some important data, such as the presence of other relevant risk factors. Furthermore, the database used for this study generated a considerably high number of cases, for which no information on smoking or alcohol intake was available, which led to the exclusion of those variables. Another aspect to be considered is the difficulty imposed by the need of including cancer cases with different topographies in this survival study, in order to compose a minimum sample for analysis.

CONCLUSION

Survival rate at 5 years was 33.3% and, at 10 years, 26.9%. Advanced stage at diagnosis was an independent risk factor of death due to cancer of the lip, mouth and pharynx in both periods analyzed.

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