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Survival of young and elderly adults with oral squamous cell carcinoma in a population in northeastern Brazil

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Aim: To compare the profile and overall survival of young adults and elderly people diagnosed with SCC. **Methods:** A retrospective study was carried out at a High Complexity Oncology Unit, between 2010 and 2016. A descriptive analysis, a bivariate analysis using the chi-square and Fisher's exact test and the Kaplan-Meier estimator were performed. The predictor variables were tested using the log-rank test and those with statistical significance and the literature were maintained for the Cox regression model. **Results:** 282 cases of SCC were recorded, with only 12.4% diagnosed in young adults. The profile was similar between groups, with the majority of cases of the disease occurring in males, smokers and alcohol consumers. The lesions predominantly located on the tongue and were diagnosed in an advanced stage of the disease, resulting in 35.7% of deaths. The median survival time was 30 months in the elderly and 31 months in young people. In the multivariate analysis, age was not statistically significant, only staging and treatment were predictors of reduced overall survival. **Conclusion:** Tumor staging, and treatment were prognostic factors for the disease.

Keywords: Carcinoma, squamous cell. Survival analysis. Young adults. Prognosis.

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Introduction

The oral cavity is one of the most common sites for head and neck malignancies. Oral squamous cell carcinoma (SCC) is the most common oral malignancy, occurring mainly in individuals aged 60 years or over[1,2]. The traditional risk factors include smoking and alcohol consumption[2].

The occurrence of SCC is considered rare among young adults, with a prevalence ranging from 4 to 6% in relation to all oral cancers in this group[2,3]. The studies are controversial regarding its clinical course, prognosis and survival. Some studies have stated that young patients showed better results in the clinical course of the SCC when compared to the elderly[4]. Others showed a worse prognosis and lower survival in young people[5,6], while other authors showed a similar prognosis between these groups[7,8].

There is no consensus in the literature on prognosis and survival in relation to SCC in different age groups. Thus, this study aims to compare the profile and overall survival of young and elderly adults diagnosed with SCC in a High Complexity Oncology Unit in Brazil.

Material and Methods

This is an observational study, developed from a retrospective hospital-based cohort, where all cases of SCC registered in the High Complexity Oncology Unit of Feira de Santana, Bahia, Brazil, were retrospectively analyzed. The Research Ethics Committees of the institution reviewed and approved this study (protocol number: 2,399,237).

All individuals with histopathological diagnosis of SCC during the period of 2010 and 2016, according to the classification of the World Health Organization[9], were included.

Data collection was performed from the analysis of clinical records. The variables analyzed were: Age (elderly or young, using 45 as the cut-off age), sex, tobacco use, alcohol use, primary tumor location, tumor differentiation, staging and type of treatment.

The tumors were classified into categories C00 to C09 of the International Classification of Diseases for Oncology, third edition (ICD-10). Individuals with any other type of cancer, potentially malignant lesions or disorders, metastatic disease to the oral cavity or tumors of questionable malignant potential were excluded. Clinical records lacking the information "date of death" or "date of last consultation" were also excluded.

The survival time, in months, was defined as the period between the individual's entry into the study (date of diagnosis) until the occurrence of the event of interest (death) - failure or the last consultation - censorship.

A descriptive analysis and bivariate analysis were performed using chi-square test and variables with values lower than 5 in the 2x2 table evaluated using Fisher's exact test. The variables that were evaluated by the chi-square test were: tobacco use, alcohol use, and tumor differentiation. The variables that were evaluated by Fisher's exact test were: sex, primary location, staging, and treatment. To estimate the probabilities of survival at each time, the Kaplan-Meier estimator was used. The predictor variables

were tested using the log-rank test, given the proportionality of the risks. The variables that were statistically significant, considering p> 0.05 and the literature, were maintained for the final regression model. In order to estimate the effects of each covariate on the survival of individuals, the Cox proportional hazards model was adjusted for each one of them and based on the significance of the relative risks at each time (defined by the exponential of the parameters). The variables that remained in the final model were those that proved to be statistically and epidemiologically significant, after controlling for the others in the multivariable Cox model. The proportionality assumption necessary for the Cox model was tested with the graphical method and with the time-dependent covariate test. All were performed using the SPSS software version 22.0, and the STATA® version 14 (StataCorp LLC).

Results

In this study, 282 cases of SCC were diagnosed. Of this, 87.6% occurred in elderly individuals and 12.4% in young adults. The mean age of the participants was 59.9 (± 13.1) years, 39.9 (± 6) years in the young group and 62.7 (± 11.2) years in the elderly. In both groups, most cases occurred in males (78,1% - elderly; 88,6% - young adults) (Table 1).

Table 1. Distribution of individuals with squamous cell carcinoma in the oral cavity, according to age groups.

	Young Adult N= 35	Elderly N= 247	P value
Sex			
Male	31 (88.6%)	193(78.1%)	0.18*
Female	4 (11.4%)	54 (21.9%)	
Tobacco			
Yes	22 (73.3)	202 (91.8%)	**0.00****
No	8 (26.7%)	18(8.2%)	
Alcoholic beverages			
Yes	18 (62.1%)	192 (88.1%)	**0.00****
No	11(37.9%)	26 (11.9%)	
Primary location			
Lip	3 (8.6%)	26 (10.5)	0.64*
Tongue	18 (51.5%)	89 (36.1%)	
Gum (gingiva)	1 (2.9%)	6 (2.4%)	
Floor	4 (11.4%)	36 (14.6%)	
Palate	3 (8.6%)	25 (10.1%)	
Other parts	6 (17.1)	65(26.3%)	
Tumor differentiation			
Well differentiated	12 (41.4%)	69 (34.5 %)	0.19**
Moderately differentiated	10 (34.5%)	102(51.0%)	
Poorly differentiated	7 (24.1%)	29 (14.5%)	

Continue

Continuation		
Staging		
I e II	2 (6.2%)	0.18*
III e IV	30 (93.8%)	
Treatment		
Surgery	4 (12.1%)	0,66*
Radiotherapy	0 (0%)	
Chemotherapy	2 (6.1%)	
Surgery, Radiotherapy and Chemotherapy	11(33.3%)	
Surgery and Chemotherapy	1 (3.0%)	
Chemotherapy and Radiotherapy	10 (30.3%)	0,66*
Refusal of treatment	5 (15.2%)	

*Fisher's exact test; **Test χ^2
The record sums for each variable differ due to missing data.

Use of tobacco was reported by 91.8% and 73.3% of participants (elderly and young adults, respectively). Alcohol consumption was descripted by 88.1% and 62.1% of individuals (elderly and young adults, respectively), with a statistically significant difference between groups (p = 0.008 and p = 0.00, respectively) (Table 2).

Table 2. Overall survival according to sex, lifestyle, clinical, histopathological characteristics, and treatment among young and elderly adults with oral squamous cell carcinoma.

Variable	Young		Elderly	
	%	P value	%	P value
Sex				
Male	88.6	0.97	78.1	0.25
Female	11.4		21.9	
Tobacco				
Yes	73.3	0.53	91.8	0.08
No	26.7		8.2	
Alcoholic beverages				
Yes	62.1	0.74	88.1	0.13
No	37.9		11.9	
Primary location				
Lips	8.6	**0.003**	10.5	**0.03**
Tongue	51.5		36.1	
Gum (Gingiva)	2.9		2.4	
Floor	11.4		14.6	
Palate	8.6		10.1	
Other parts	17.1		26.3	

Continue

Continuation					
Tumor differentiation					
Well differentiated	41.4	0.71	34.5	0.39	
Moderately differentiated	34.5		51.0		
Poorly differentiated	24.1		14.5		
Staging					
I e II	6.2	0.41	16.6	**0.00**	
III e IV	93.8		83.4		
Treatment					
Surgery	12.1	**0.00**	15.0	**0.00**	
Radiotherapy	0		6.5		
Chemotherapy	6.1		11.3		
Combination therapy	66.7		51.0		
Refusal of treatment	15.2		16.2		

*log rank test
The record sums for each variable differ due to missing data.

Most tumors were primarily located on the tongue, both in the elderly and young individuals (36.1% and 51.5%, respectively). Tumors were classified mainly as moderately differentiated in the elderly (51%) and well differentiated in young adults (41.4%). As for tumor staging, in both groups, individuals were diagnosed in advanced stages of the disease (Stage III and IV). Among the elderly individuals, 34.8% were treated with chemotherapy and radiotherapy, and the young individuals (33.3%) were treated by combined surgery, chemotherapy, and radiotherapy. In addition, 16.2% and 15.2% of participants refused treatment (elderly and young adults, respectively). There was no statistically significant difference between groups (Table 1).

Table 3 shows the bivariate analysis for risk factors and death. In the elderly group, statistically significant differences were found for alcohol consumption (p = 0.03), primary location (p = 0.001), staging (p = 0.0) and treatment (p = 0.0). In young individuals, no variable showed statistically significant differences.

Table 3. Distribution of death according to sex, lifestyle, clinical, histopathological characteristics, and treatment among young and elderly adults with squamous cell carcinoma in the oral cavity.

Variable	Death					
	Young Adult			Elderly		
	Yes	No	P value	Yes	No	P value
Sex						
Male	7	24	1.0*	74	117	0.18**
Female	1	3		15	37	
Tobacco						
Yes	5	17	0.41*	79	119	0.07*
No	3	5		3	15	

Continue

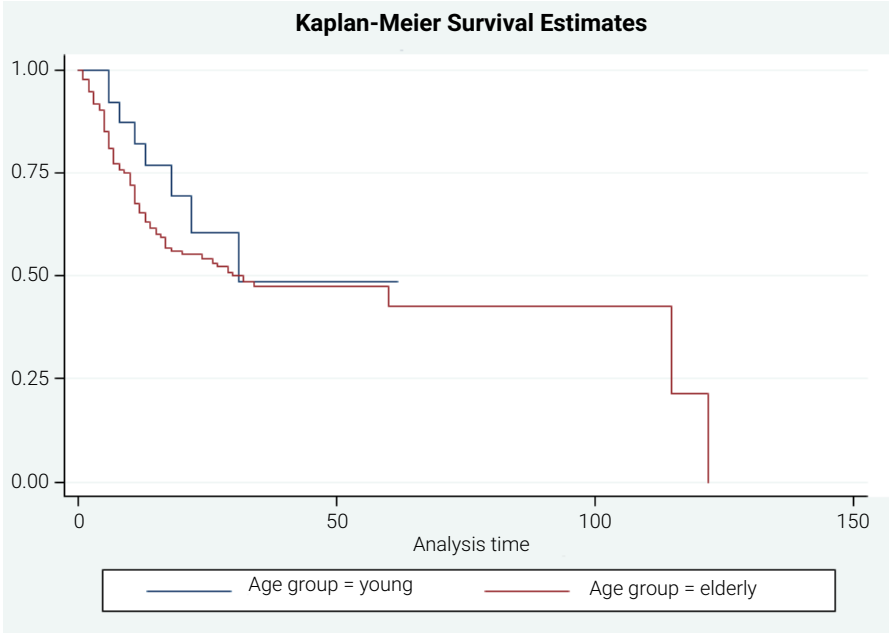
Continuation

Alcoholic beverages						
Yes	4	14	0.43*	77	111	**0.03****
No	4	7		5	21	
Primary location						
Lips	0	3	0.17*	1	25	**0.001***
Tongue	6	12		39	49	
Gum (Gingiva)	1	0		0	6	
Floor	0	4		16	19	
Palate	1	2		11	13	
Other parts	0	6		22	42	
Tumor differentiation						
Well-differentiated	3	9	1.0*	21	46	0.47**
Moderately differentiated	2	8		41	60	
Poorly differentiated	1	6		11	18	
Staging						
I e II	0	2	1.0*	2	35	**0.0***
III e IV	8	22		83	106	
Treatment						
Surgery	0	4	0.80*	2	35	**0.0***
Radiotherapy	0	0		11	4	
Chemotherapy	0	2		17	10	
Combination therapy	7	15		49	76	
Refusal of treatment	1	3		10	29	

*Fisher's exact test/ **Test χ^2
The record sums for each variable differ due to missing data.

According to the survival status, 35.7% of the individuals died; 10.1% were without evidence of the disease; 9.4% with partial remission of the disease; 11.6 % with stable disease; 31% with progressing disease, and 2.2% out of therapeutic possibilities. In addition, 11.3% of deaths were related to patients who refused treatment.

The median survival time in the elderly was 30 months, and 31 months in the young group, with no statistically significant difference between them (p = 0.18) (Figure 1).



Log rank test p = 0.18

Figure 1. Survival curve of individuals with squamous cell carcinoma in the oral cavity, according to age groups (Kaplan Meier curve).

The variables that showed statistical significance in relation to survival and the predictor variables in the elderly group were **primary location** (p = 0.03), **staging** (p = 0.00) and **treatment** (p = 0.00). In the young group, they were **primary location** (p = 0.003) and **treatment** (p = 0.00) (Table 4).

Table 4. Cox regression model for survival analysis in individuals with squamous cell carcinoma in the oral cavity.

	HR (CI 95%)	P Value
Age (Young group vs Elderly group)	1.51 (0.65 – 3.5)	0.43
Location (Tongue or floor vs others)	0.73 (0.45 – 1.17)	0.19
Tumor differentiation		
Well differentiated	Reference	
Moderately differentiated	1.4 (0.83 – 2.38)	0.20
Poorly differentiated	0.66 (0.31 – 1.38)	0.27
Staging (I e II vs III e IV)	9.8 (2.33 – 41.4)	**0.002**
Treatment		
Isolated therapy	Reference	
Combination therapy	0.36 (0.21 – 0.63)	**0.000**
Refusal of treatment	2.9 (1.31 – 6.58)	**0.009**

*Cox regression model

In the multivariate analysis, using the Cox proportional hazards model, it was revealed that only the **staging** (HR = 9.8, CI 95% = 2.33 – 41.4 and p = 0.002) and the **type of treatment** (HR = 0.36, CI 95% = 0.21 – 0.63 and p = 0.000; HR = 2.9, CI 95% = 1.31 – 6.58, p = 0.009) were statistically significant predictors for reduced overall survival in both groups. In the univariate and multivariate analysis, age was not associated with survival.

Discussion

The data in our study are consistent with the literature, which reports that the highest incidence of cases of SCC occurs in middle-aged and elderly individuals, generally exposed to the main risk factors for the disease[1,2]. In this study, only 12.4% of the cases of SCC occurred in young individuals aged 45 years or less. Park et al.[6], who used the same cut-off age, found a prevalence of this tumor in 27.1% of young patients. Other authors using a cut-off age of 40 years observed that only 8.5% of cases occurred in this group[10]. Some differences found in the studies about the prevalence of SCC in young adults may be related to different inclusion criteria, in addition to the time of follow-up and the different age limits used in the studies[10-12].

In our study, in both groups, the disease was more frequent in males, with results similar to those found by Sun et al.[7]. Gender-related differences are attributed to greater male exposure to risk factors, but this prevalence has decreased over the decades due to women's lifestyle changes, with greater exposure to carcinogenic agents from tobacco and alcohol[2]. For Halboulb et al.[13], the predominance of males found in elderly individuals was not observed in young adults, with an increase in the number of cases in young women.

With regard to life habits, in both groups, the majority of individuals were smokers and chronic alcohol consumers, with statistical significance between the groups (p = 0.008, p = 0.00, respectively). These results corroborate the findings of Ho et al.[4]. The risk for the development of SCC is increased depending on the type, frequency, and duration of these habits[14]. Although some authors claim that these factors may not be as relevant for the development of the disease in young patients since the exposure time may be short for the malignant transformation of the lesions, other authors reveal that exposure to these risk factors can start in adolescence, making the time conducive to the development of SCC[15].

With regard to clinical findings, most tumors were primarily located on the tongue, both in young and elderly adults. These results are in accordance with the findings of Sun et al.[7]. Regarding histopathological data, the results of our study show that most tumors were classified as moderately differentiated in the elderly and well differentiated in young individuals. Different results were found in the studies by Soundry et al.[8] and Fang et al.[11], where in both groups, the tumors were classified as well differentiated. However, for most authors, there are no significant differences in the histological classification of the SCC between the elderly and young adults[11,16].

As for tumor staging, the two groups showed higher frequencies in advanced stages (Stage III and IV). Similar results were found in studies by Ho et al.[4] who also compared staging in elderly and young patients and observed that in both groups, the

majority of cases were diagnosed in stages III or IV. Also corroborating these findings, Morais et al.[17], through a systematic review, observed that the proportion of young patients diagnosed with stages III and IV was high, similar to studies with groups of elderly patients. For some authors, the reason for the late diagnosis may probably be the lack of awareness of patients, who usually seek treatment only when the tumor is apparent and presents painful symptoms[16].

The results of our study in relation to the type of treatment show that in the elderly group, the treatment of choice was mainly chemotherapy and radiotherapy, and in the young group, it was predominantly the surgical one associated with radiotherapy and chemotherapy. These choices regarding treatment corroborate the findings of other studies[4,17].

Regarding the association between death and predictor variables, it was observed that in the young group no variable presented statistical significance, probably due to the small number of individuals studied. The significant association in the elderly group with the variable related to the consumption of alcoholic beverages reveals this variable as a risk factor for death. Location, which was also significant in this group, is said to be a prognostic factor since tumors present different behaviors depending on their location, and SCCs located on the tongue and floor present a more aggressive behavior and, consequently, a higher risk of death and a worse prognosis[18].

Staging and the type of treatment performed were also considered risk factors for death in the elderly group in the present study. For some authors, patients diagnosed late have their survival reduced, in addition to the need for more aggressive treatments[19].

The high death rate revealed in our study (35.7%) is in agreement with another study carried out in Brazil. Santos et al.[20] described the clinical and epidemiological profile of individuals with oral cancer treated at referral hospitals in the same state as this present study, revealing that 20.55% of individuals died by the end of the study. Udeabor et al.[21] revealed, in a study carried out in Germany, that this also occurred in 34.2% of the individuals.

As for overall survival, our findings show that there was no statistically significant difference between age groups ($p = 0.18$). Similarly, many studies show that age does not seem to have any significance in the prognosis of individuals with SCC. In the study by Fang et al.[11], age did not show any influence on the survival of individuals. Additionally, Sun et al.[7], verified no association of age with disease-free survival and overall survival ($p = 0.296$ and $p = 0.677$, respectively).

The variables found to be statistically significant through the log rank test in our study are in accordance with the literature. The primary location of the tumor is revealed as a prognostic factor and related to survival in the findings of other authors[21]. According to Woolgar and Scott.[22], this association is related to the presence of regional metastasis, showing that some locations, such as the tongue and mouth floor, are more conducive to these metastases and predict lower survival rates. However, in our study, primary tumor location was not significant after multivariate analysis.

In the multivariate analysis, only tumor staging and the type of treatment performed were statistically significant. The study carried out by Soundry et al.[8] revealed, through

Cox reduction, staging as a predictor for reduced survival, with tumor size being a predictor for disease-free survival and tumor size being a predictor of lymph node involvement for overall survival.

Staging is accepted as an important parameter for indicating tumor aggressiveness, predicting the prognosis, and indicating therapeutic conduct. According to some authors, tumor growth may be associated with the risk of disease recurrence, regional metastases, and, consequently, shorter survival[23].

Although many studies show that age may not be an individual prognostic factor, some studies have observed a higher rate of recurrence in young patients when compared to the elderly. This high rate of recurrence can be explained by the lack of adequate treatment or the different biological behavior of tumors in young individuals[7].

The type of treatment performed, which was also found to be statistically significant in the multivariate analysis in the present study, was considered a prognostic factor for survival in the study by Blanchard et al.[24]. These authors revealed that the absence of surgery had an influence on overall survival (HR: 13.5 [2.0, 90.5], p = 0.007).

Although our study may contribute to a better understanding of the profile and factors related to survival in young and elderly adults diagnosed with SCC, it has limitations that are typical of this retrospective method. Thus, it is recommended to carry out further longitudinal studies.

In conclusion, the present study contributes to describing SCC behavior and prognostic factors in young and elderly patients. In the multivariate analysis, age was not an influencing factor in the survival of diagnosed individuals, only tumor staging and the type of treatment performed revealed statistical significance, showing these variables as prognostic factors for the disease.

Conflict of interest

None.

Acknowledgments

None.

Data availability

Datasets related to this article will be available upon request to the corresponding author.

Author Contribution

M.M.A.: Substantial contributions to the acquisition, analysis, interpretation of data for the work; and drafting the work and Final approval of the version to be published; and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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