



**MINISTÉRIO DA DEFESA
EXÉRCITO BRASILEIRO
HOSPITAL CENTRAL DO EXÉRCITO
(Hospital Real Militar e Ultramar-1769)**

ANA CAROLINA DA SILVA SOUTO

**UM PANORAMA EPIDEMIOLÓGICO DO CÂNCER DE LÍNGUA EM PACIENTES JOVENS NO
INSTITUTO NACIONAL DE CÂNCER**

Rio de Janeiro

2023

ANA CAROLINA DA SILVA SOUTO

**UM PANORAMA EPIDEMIOLÓGICO DO CÂNCER DE LÍNGUA EM PACIENTES JOVENS NO
INSTITUTO NACIONAL DE CÂNCER**

Trabalho de Conclusão de Residência apresentado ao Hospital Central do Exército como requisito parcial para a conclusão do Programa de Residência Multiprofissional em Oncologia.

Orientador: Major Otávio Augusto Brioschi Soares

Coorientador: Dr. Daniel Cohen Goldemberg

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**ATA DE DEFESA DO TRABALHO DE CONCLUSÃO DE RESIDÊNCIA DO PROGRAMA DE
RESIDENCIA MULTIPROFISSIONAL DE ONCOLOGIA DO HOSPITAL CENTRAL DO EXÉRCITO**

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Aos 14 dias do mês de dezembro de 2023 reuniu-se a banca examinadora do Trabalho de Conclusão de Residência de ANA CAROLINA DA SILVA SOUTO, apresentado como requisito parcial de conclusão do Programa de Residência Multiprofissional em Oncologia do Hospital Central do Exército, intitulado "UM PANORAMA EPIDEMIOLÓGICO DO CÂNCER DE LÍNGUA EM PACIENTES JOVENS NO INSTITUTO NACIONAL DO CANCER". Compuseram a banca examinadora os professores MAJOR VET OTÁVIO AUGUSTO BRIOSCHI SOARES (orientador), DANIEL COHEN GOLDEMBERG (avaliador 1) e MARILUCIA ALVES DA VENDA (avaliador 2). Após a exposição oral, a discente foi arguida pelos componentes da banca que, em seguida, reuniram-se reservadamente e decidiram por:

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Otávio E.B. S-Mej

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Avaliador 2:

Residente: *Ana Carolina da Silva Souto*

DEDICATÓRIA

À minha amada família, cujo apoio inabalável foi essencial nessa trajetória. Obrigada por serem a fonte constante de amor, inspiração e coragem que me impulsionam.

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**" O sofrimento humano só é intolerável
quando ninguém cuida"**

Cicely Saunders.

RESUMO

SOUTO, ACS. **An Epidemiological Landscape Of Tongue Cancer In Young Patients At The Brazilian National Cancer Institute**. 2023. Total de 36 folhas. Publicação Científica. (Especialização em Oncologia) – Hospital Central do Exército. Rio de Janeiro, 2023.

Objetivo: Comparar o perfil epidemiológico de pacientes em duas faixas etárias, abaixo de 40 anos e de 41 a 50 anos, diagnosticados com câncer de língua no Instituto Nacional do Câncer. **Métodos:** Foi realizado um estudo descritivo retrospectivo, abrangendo dados de prontuários médicos entre 2000 e 2012. Os pacientes foram categorizados em duas faixas etárias (≤ 40 anos; 41-50 anos). Foram avaliadas as características sociodemográficas e clinicopatológicas. Todas as análises foram realizadas com o IBM SPSS Statistics. **Resultados:** Foram elegíveis para o estudo 108 pacientes, a maioria com idade entre 41-50 anos (72,5%). O consumo de álcool foi mais frequente (65,7%) do que o tabagismo (43,3%), sendo que 56,7% dos pacientes com idade ≤ 40 anos nunca consumiram tabaco. Independentemente da idade, a topografia mais afetada foi a borda lateral da língua (57,4%) e o estadiamento predominante foi III e IV (67,3%). A cirurgia foi feita em 44% dos pacientes, sendo mais frequente no grupo ≤ 40 anos (60,0%). A sobrevida global foi influenciada pelo estadiamento clínico e pela cirurgia. Não se observou diferença significativa na sobrevida em relação à idade. **Conclusões:** Com base na nossa metodologia, os pacientes jovens com carcinoma espinocelular não estão associados a fatores tradicionais como o tabagismo. Além disso, estes pacientes também são frequentemente submetidos a cirurgia e, na sua maioria, têm margens livres de doença. No entanto, a sobrevivência global não revelou disparidades significativas entre os diferentes grupos etários. A natureza intrínseca desta neoplasia, independentemente do grupo etário, realça a importância de políticas externas de diagnóstico precoce, abrangendo não só os grupos de risco.

Palavras-chaves: Câncer oral; Carcinoma de células escamosas; Câncer da língua; Adulto jovem

ABSTRACT

Objective: This study aimed to compare the epidemiological profile of patients in two age groups, under 40 years old and 41 to 50 years, and diagnosed with tongue cancer at the Brazilian National Cancer Institute. **Methods:** A retrospective descriptive study was conducted, covering data from medical records between 2000 and 2012. Patients were categorised into two age groups (≤ 40 years; 41-50 years). Sociodemographic and clinicopathological characteristics were evaluated. All analyses were performed using IBM SPSS Statistics. **Results:** A total of 108 patients were eligible for the study, the majority of whom were 41-50 years old (72.5%). Alcohol consumption was more frequent (65.7%) than smoking (43.3%), with 56.7% of patients aged ≤ 40 years having never consumed tobacco. Regardless of age, the most affected topography was the lateral border of the tongue (57.4%) and the predominant staging was III and IV (67.3%). Surgery was performed in 44% of patients, being more frequent in the group ≤ 40 years old (60.0%). Overall survival was influenced by clinical staging and surgery. No significant difference in survival was observed with regard to age. **Conclusion:** Based on our methodology, young patients with squamous cell carcinoma are not associated with traditional factors such as smoking. Furthermore, these patients also frequently undergo surgery and, for the most part, have disease-free margins. However, overall survival did not reveal significant disparities between different age groups. The intrinsic nature of this neoplasm, regardless of age group, highlights the importance of external policies for early diagnosis, covering not only risk groups.

Keywords: Oral cancer; Oral squamous cell carcinoma; Tongue cancer; Young patients.

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LISTA DE ABREVIATURAS E SIGLAS

AJCC - *do inglês, American Joint Committee on Cancer*

CAAE - Certificado de Apresentação para Apreciação Ética

HR - *do inglês, Hazard Ratio*

HPV - Human Papillomavirus

IBGE - Instituto Brasileiro de Geografia e Estatística

ICD-O-3 - Classificação Internacional de Doenças para Oncologia, 3ª edição

INCA - Instituto Nacional de Câncer

SCC - Carcinoma de Células Escamosas

SPSS - *Statistical Package for the Social Sciences*

TMN – Classificação de Tumores Malignos

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1 CONSIDERAÇÕES INICIAIS

O câncer de cabeça e pescoço, correspondente à sétima neoplasia mais recorrente globalmente e registra anualmente aproximadamente 930 mil novos casos (SUNG et al., 2021). No Brasil, as projeções do Instituto Nacional de Câncer (INCA) para o triênio 2023-2025 apontam para a ocorrência de 704 mil novos casos de câncer, excluindo os casos de câncer de pele não melanoma, sendo o câncer de cavidade oral responsável por 15.100 novos casos, predominantemente entre o sexo masculino (10.900). A distribuição heterogênea dos novos casos de câncer oral no país destaca o Sudeste como a região mais afetada (INCA, 2022).

O carcinoma de células escamosas (CEC) é a principal neoplasia maligna que acomete a cavidade oral, tendo como localização preferencial a língua, seguida pela orofaringe. O mesmo demonstra maior incidência em adultos de meia idade, predominantemente do sexo masculino, sendo associado ao tabagismo e etilismo (LIU et al., 2023). No entanto, é equivocado perpetuar a concepção de que essa patologia se restringe exclusivamente a esse segmento populacional. Tota e colaboradores (2017) evidenciaram em seu estudo um aumento progressivo da doença nos Estados Unidos no período de 1973 a 2012, em especial em pacientes mais jovens e sem predileção por gênero (TOTA et al., 2017). No contexto brasileiro, o predomínio de CEC ainda é em homens com idade superior a 50 anos e comumente diagnosticados em estágios avançados da doença. No entanto, observa-se uma notável ocorrência de casos de CEC em pacientes jovens nos últimos anos, com idade inferior a 45 anos, e sem associação aos fatores de risco tradicionais (COHEN GOLDEMBERG et al., 2018). O desafio principal na atualidade reside em compreender as causas que têm levado as mudanças do perfil epidemiológico dos pacientes com CEC em cavidade oral.

Nessa perspectiva, o presente estudo é importante para proporcionar um panorama e contribuir na compreensão dos padrões epidemiológicos em pacientes afetados pelo CEC, utilizando dados do Instituto Nacional do Câncer no contexto brasileiro.

2 OBJETIVOS

2.1 OBJETIVO GERAL

Analisar o perfil epidemiológico do CEC de língua oral em pacientes jovens atendidos e tratados no Instituto Nacional do Câncer (INCA).

2.2 OBJETIVOS ESPECÍFICOS

- Descrever o perfil epidemiológico do carcinoma epidermoide em língua nos pacientes com faixa etária de 22 a 50 anos atendidos e tratados no Instituto Nacional do Câncer (INCA) em um intervalo de doze anos (2000-2012);
- Efetuar uma categorização entre indivíduos com idades iguais ou inferiores a 40 anos e aqueles situados na faixa etária de 41 a 50 anos, a fim de realizar uma comparação detalhada das características clínicas e epidemiológicas associadas aos fatores de risco;
- Identificar e comparar a taxa de sobrevida global, livre de doença nos subgrupos ≤ 40 anos e 41-50 anos.

3 PUBLICAÇÃO CIENTÍFICA

UM PANORAMA EPIDEMIOLÓGICO DO CÂNCER DE LÍNGUA EM PACIENTES JOVENS NO INSTITUTO NACIONAL DE CÂNCER

AN EPIDEMIOLOGICAL LANDSCAPE OF TONGUE CANCER IN YOUNG PATIENTS AT THE BRAZILIAN NATIONAL CANCER INSTITUTE

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INTRODUCTION

Around 90% of neoplasms located in the head and neck region are identified as squamous cell carcinoma (SCC), with the tongue being the most frequent primary tumour site and generally associated with an unfavourable prognosis (Engholm *et al.* 2010; Vigneswaran and Williams 2014; Matsuo *et al.* 2022; Liu *et al.* 2023). Historically, SCC of the tongue mainly affects adult men and is strongly linked to tobacco and alcohol consumption. The combination of these two habits substantially increases the chances of developing SCC, compared to non-smokers or non-alcohol consumers (Mello *et al.*, 2019). Although anti-smoking and awareness campaigns have contributed to the reduction in cases of oral SCC, the incidence of tongue SCC is increasing in groups not traditionally associated with risk factors, such as female gender, and young people, with no apparent relationship with harmful habits (Joseph and D'Souza 2012; Patel *et al.* 2011; Al-Dabbagh *et al.* 2022). Schantz and Yu (2002), in a comprehensive study covering the period from 1985 to 1997 and focussing on young North American patients, showed a significant increase in this neoplasm, with the tongue identified as the main site of incidence (Schantz and Yu 2002). This finding is in line with other studies that indicate a notable increase in cases of SCC of the tongue among young individuals aged between 18 and 44, especially those who self-identify as white females. Notably, this trend is observed mainly among non-users of tobacco or alcohol, differing from the conventional risk factors associated with this neoplasm (Brown *et al.*, 2012; Tota *et al.*, 2017). However, it remains unclear whether this pattern of increased incidence also applies to young, white men (Joseph *et al.*, 2015).

The complexity of this scenario reinforces the need for additional investigations to understand the causes underlying this change in the profile of head and neck cancer, especially in the context of demographic groups previously considered at low risk for this disease. Therefore, the present study aims to analyse the epidemiological profile of SCC of the oral tongue in young patients seen and treated at the Brazilian National Cancer Institute (INCA).

MATERIALS AND METHODS

Study Design

A retrospective cohort study comprising patients with SCC of the oral tongue diagnosed between 2000 and 2012 enrolled and treated at INCA, in Rio de Janeiro, Brazil was performed. In order to include young patients, this current study selected an age group up to 50 years old with SCC diagnosis according to the 3rd edition of the International Classification of Diseases for Oncology - ICD-O-3 - (C01, C02, C02.0, C02.1, C02.2, C02.3, C02.8, C02.9). Sociodemographic and clinicopathological data were obtained from medical records. The following variables were collected: age, sex, race/ethnicity (according to the Brazilian Institute of Geography and Statistics - IBGE, classified in white, black, yellow, brown or indigenous) as well as alcohol and tobacco consumption. Tumour-related characteristics

such as tumour topography, clinical staging (according to the *American Joint Committee on Cancer* - AJCC - TNM), morphology and histological differentiation (well; moderately or poorly - differentiated), treatment (surgery, neck dissection, margins, radiotherapy and/or chemotherapy) and survival outcomes were collected. To investigate the frequency of tongue cancer according to age, the patients were categorised into two age groups: ≤ 40 years or 41-50 years old.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, New York).

Descriptive analysis was performed using measures of central tendency and dispersion for continuous variables, and absolute and relative frequency for categorical variables.

The Pearson chi-square test was used to compare the distribution of categorical variables between two age groups: ≤ 40 versus 41-50 years old. The normality of the distribution of the age variable was assessed using the Kolmogorov-Smirnov test. Considering its non-parametric distribution, the variable was described using the median accompanied by interquartile values (interquartile range (IQR)).

The exploratory assessment of survival was conducted at 5 and 10-year intervals following the commencement of treatment, employing the Kaplan-Meier methodology. The comparison between strata was performed using the log-rank test, assuming a statistical significance level of 5%. To identify independent variables associated with the risk of recurrence and death, the Cox regression model was used. The calculations for the statistical analyses were only carried out with valid data, and missing information was disregarded.

Ethical Statements

The Ethics in Human Research Committee of the Brazilian National Cancer Institute approved this study in Rio de Janeiro, Brazil under the registration number 0104.0.007.000-11 (CAAE).

RESULTS

Patients Data

A total of 108 patients aged 22-50 years old with tongue SCC were eligible for the study. The average age was 45 years old (IQR 39-48), with 30 (27.8%) patients aged less than or equal to 40 years. Among all patients included, 60% were men and 63.3% identified as white. There was no statistically significant difference between the sexes of patients ≤ 40 and 41-50 years old.

Regarding habits, alcohol consumption was highly frequent, regardless of age (65.7%). Data on smoking revealed that 67.6% of patients were current or former smokers, with 43.3% aged ≤ 40 years and 76.9% 41-50 years ($p=0.001$). Furthermore, 56.7% of patients aged ≤ 40 years reported never having smoked, compared to 23.1% in the group of patients aged 41-50 years ($p=0.001$) (Table 1).

Clinical Profile

The most affected topography was the lateral border of the tongue (57.4%), in both age groups evaluated (≤ 40 years, 66.7%; 41-50 years, 53.8%, $p = 0.178$). In addition, 67.3% of patients were diagnosed in advanced staging (III or IV) having the highest predominance in 41-50 years old (73.1%) than ≤ 40 years old (51.7%) ($p=0.036$). As for the degree of differentiation, 67.4% were moderately differentiated, with no significant difference between ages (Table 1).

With regard to the characteristics associated with the treatment, only 44.0% of the total cohort of patients underwent surgery either alone or in combination with other therapeutic modalities (≤ 40 years, 60%; 41-50 years, 38.0%). Within this subgroup of surgically treated patients, 37.0% underwent neck dissection and 44.4% had disease-free surgical margins. Although the differences were not statistically significant, there was a greater number of patients under the age of 40 who were eligible for neck dissection, reaching a rate of 46.7%, compared to the group of patients over 40 years of age (33.3%). Interestingly, patients ≤ 40 years old had a 60% higher prevalence of disease-free surgical margins compared to patients over 40 years of age (Table 1).

Survival Analysis

When looking at the determinants of overall survival across the entire sample (Table 2), the factors that had a significant impact on survival were advanced clinical staging ($p < 0.001$), no neck dissection ($p < 0.001$), no free margin of disease ($p < 0.001$) and no surgery in the therapeutic proposal ($p < 0.001$).

Patients under 40 years old had an overall survival of 32.1% in five and ten years while patients 41-50 years had lower rates (28.0% and 17.1% respectively) ($p= 0.204$) (Table 2). In relation to topography, patients with cancer of the lateral border of the tongue had worse overall survival, both at 5 and 10 years. It is interesting to note that among the group of patients with the base of the tongue affected, 93.8% died, compared to 64.5% of the patients with an affected lateral border of the tongue (Table 2).

Kaplan-Meier curves revealed that patients with tongue SCC had a worse 10-year overall survival (Fig. 1A). In more detail, it can be seen that patients diagnosed at an advanced stage had a worse survival (Fig. 1B). However, those eligible for surgery, radiotherapy, disease-free margins and neck dissection have a better survival (Fig. 1C-F).

Univariate analysis revealed that advanced clinical stage (HR= 4.3; 95%CI 2.3-7.8), not undergoing surgery (HR= 6.1; 95%CI 3.5-10.6), and lacking neck dissection (HR= 4.1; 95%CI 2.3-7.1) were significantly associated with increased risk of death associated with tongue cancer. Conversely, achieving disease-free margins was a protective factor, associated with a lower risk of death (HR= 0.2; 95%CI 0.09-0.3). However, upon analysing adjusted hazard ratios (HRs), only advanced clinical staging with HR=2.6; 95%CI 1.4-5.0 ($p=0.004$) and patients not undergoing surgery with HR= 4.6; 95%CI=2.5-8.2 ($p<0.001$) emerged as significant risk factors. Alcohol and tobacco consumption, cancer topography, age and gender, among others, were not indicated as risk factors for death in this study (Table 3)

Table 1. Characteristics of tongue cancer patients (N=108)

Variables	Total n*(%)	≤ 40 years n*(%)	41-50 years n*(%)	p value
Sex				0.237
Male	74(68.5)	18(60.0)	56(71.8)	
Female	34(31.5)	12(40.0)	22(28.2)	
Race/ethnicity				0.085
White	62(57.4)	19(63.3)	43(55.1)	
Black	10(9.3)	5(16.7)	5(6.4)	
Brown	36(33.3)	6(20.0)	30(38.5)	
Alcohol consumption				0.092
Never	37(34.3)	14(46.7)	23(29.5)	
Current and former	71(65.7)	16(53.3)	55(70.5)	
Smoking status				0.001
Never	35(32.4)	17(56.7)	18(23.1)	
Current and former	73(67.6)	13(43.3)	60(76.9)	
Topography				0.178
Base of the tongue	16(14.8)	3(10.0)	13(16.7)	
Lateral border of the tongue	62(57.4)	20(66.7)	42(53.8)	
Not specified	18(16.7)	2(6.7)	16(20.5)	
Overlapping	12(11.1)	5(16.7)	7(9.0)	
Clinical staging**				0.036
III-IV	72(67.3)	15(51.7)	57(73.1)	
I-II	35(32.7)	14(48.3)	21(26.9)	
Neck dissection				0.199
No/NA	68(63.0)	16(53.3)	52(66.7)	
Yes	40(37.0)	14(46.7)	26(33.3)	
Free margin				0.044
No/NA	60(55.6)	12(40.0)	48(61.5)	
Yes	48(44.4)	18(60.0)	30(38.5)	
Differentiation				0.109
Well differentiated	14(13.0)	6(20.0)	8(10.3)	

Moderately differentiated	86(79.6)	20(66.7)	66(84.6)	
Poorly differentiated	8(7.4)	4(13.3)	4(5.1)	
Treatment				0.054
RXT	12(11.0)	0(0.0)	12(15.2)	
CIR	15(13.8)	5(16.7)	10(12.7)	
CIR+RXT	23(21.1)	7(23.3)	16(20.3)	
CIR+RXT+QT	10(9.2)	6(20.0)	4(5.1)	
QT + RXT	42(38.5)	11(36.7)	31(39.2)	
No treatment	7(6.4)	1(3.3)	6(7.6)	
Surgery				0.039
Yes	48(44.0)	18(60.0)	30(38.0)	
No	61(56.0)	12(40.0)	49(62.0)	
Radiotherapy				0.133
Yes	77(70.6)	18(60.0)	59(74.7)	
No	32(29.4)	12(40.0)	20(25.3)	
Final status				0.186
Alive	33(30.6)	12(40.0)	21(26.9)	
Death	75(69.4)	18(60.0)	57(73.1)	
Total	108(100.0)	30(27.5)	79(72.5)	

NA= Not applicable; RXT= radiotherapy; CIR= surgery; QT= chemotherapy

* Valid data only

** Missing: 2 cases.

Statistically significant results are in bold

Table 2. Assessment of overall survival for tongue cancer patients (N=108)

Variables	Death		5 yr. OS	10 yr. OS	Median yr.	p value (log rank)
	n*	%	% (SD)	% (SD)	(95%CI)	
Age						.204
≤ 40 years	18	60.0	32.1(9.2)	32.1(9.2)	1.4(1.2-1.6)	
> 40 years	57	73.1	28.0(5.3)	17.1(6.4)	1.1(0.9-1.3)	
Sex						.528
Male	55	74.3	27.0(5.3)	16.2(6.2)	1.2(1.0-1.4)	
Female	20	58.8	34.4(8.7)	34.4(8.7)	1.2(0.9-1.5)	
Race/ethnicity						.139
White	39	62.9	31.9(6.2)	31.9(6.2)	1.2(.9-1.5)	
Black	6	60.0	57.1(16.4)	0(0)	6.9(0-17.9)	
Brown	30	83.3	17.2(6.5)	0(0)	1.0(0.7-1.3)	
Alcohol consumption						.196
Never	22	59.5	40.7(8.4)	32.6(9.9)	1.3(0.9-1.7)	
Current and former	53	74.6	23.4(5.3)	13.6(6.6)	1.2(0.9-1.5)	
Smoking status						.327
Never	20	57.1	36.9(8.8)	36.9(8.8)	1.2(1.0-1.4)	
Current and former	55	75.3	26.2(5.3)	13.6(6.6)	1.2(0.9-1.5)	
Topography						.082
Base of the tongue	15	93.8	18.8(9.8)	6.3(6.1)	1.0(0.8-1.2)	
Lateral border of the tongue	40	64.5	31.4(6.2)	27.9(6.5)	1.3(1.1-1.5)	
Not specified	14	77.8	20.0(9.9)	20.0(9.9)	0.6(0.4-0.8)	
overlapping	6	50.0	46.3(15.0)	46.3(15.0)	1.6(**)	
Clinical staging						< .001
III-IV	60	84.5	15.6(4.5)	0 (0)	1.0(0.9-1.1)	
I-II	13	37.1	59.1(8.8)	59.1(8.8)	NR	
Surgery						< .001
No	57	95.0	5.1(2.9)	2.6(2.3)	0.9(0.7-1.1)	
Yes	18	37.5	62.1(7.5)	43.0(13.9)	9.0(5.0-13.0)	
Neck dissection						< .001
No/NA	58	85.3	12.6(4.2)	8.4(4.4)	0.9(0.7-1.1)	
Yes	17	42.5	58.3(8.3)	35.3(15.6)	9.0(3.5-14.5)	
Free margin						< .001
No/NA	57	95.0	5.1(2.9)	2.6(2.3)	0.9(0.7-1.1)	
Yes	18	37.5	62.1(7.5)	43.0(13.9)	9.0(5.0-13.0)	
Differentiation						.392
Well differentiated	12	85.7	8.6(8.1)	8.6(8.1)	1.0(0.5-1.6)	
Moderately differentiated	58	67.4	33.4(5.3)	21.2(7.4)	1.2(0.9-1.5)	
Poorly differentiated	5	62.5	16.7(15.2)	16.7(15.2)	1.3(0-2.9)	
Treatment						<.001
RXT	12	100.0	0(0)	0(0)	0.5(0.05-1.0)	
CIR	2	13.3	82.1(11.7)	82.1(11.7)	NR	
CIR+RXT	11	47.8	56.5(10.3)	48.4(11.6)	6.9 (**)	
CIR+RXT+QT	5	50.0	51.9(17.6)	0(0)	9.0 (**)	
QT + RXT	38	92.7	7.5(4.2)	3.8(3.4)	1.0(.9-1.1)	
No treatment	7	100.0	0(0)	0(0)	0.4(0.3-0.5)	
Total	75	69.4	29.2(4.6)	20.0(5.9)	NA	NA

OS= Overall survival; SD= Standard deviation; CI = Confidence interval; NA= Not applicable; NR= Median not reached

* Valid data only

** Incalculable Statistically significant results are in bold

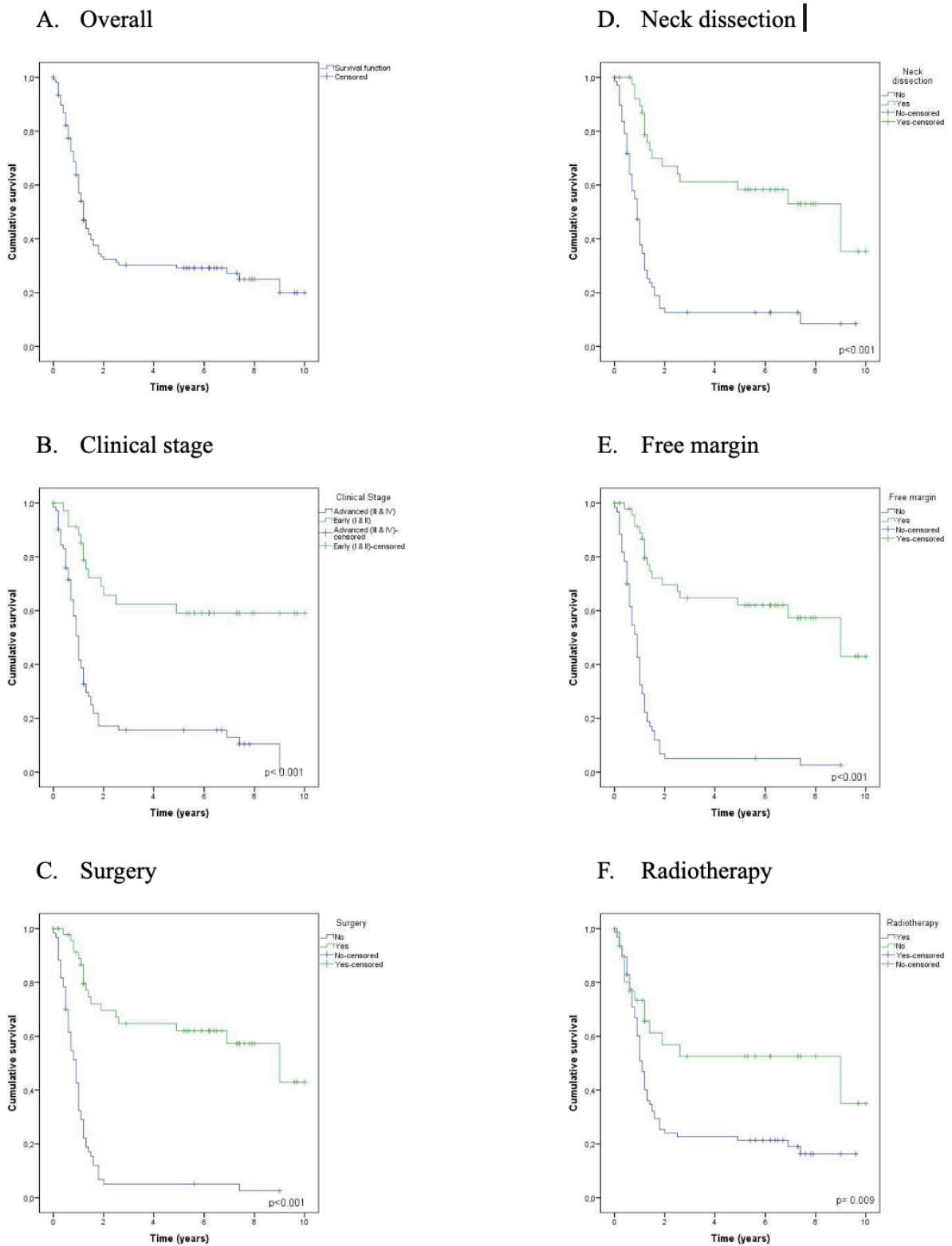


Figure 1. Overall survival for tongue cancer patients.

Table 3. Factors associated to risk of death in tongue cancer patients (N=108)

Variables	Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age				
> 40 years	Ref.			
≤ 40 years	0.7(0.4-1.2)	0.218		
Sex				
Male	Ref.			
Female	0.9(0.5-1.4)	0.538		
Race/ethnicity				
White	Ref.			
Black	0.8(0.3-1.9)	0.626		
Brown	1.5(0.9-2.4)	0.091		
Alcohol consumption				
Never	Ref.			
Current and former	1.4(0.8-2.3)	0.209		
Smoking status				
Never	Ref.			
Current and former	1.3(0.8-2.1)	0.340		
Topography				
Base of the tongue	Ref.			
Lateral border of the tongue	0.6(0.3-1.1)	0.096		
Not specified	1.1(0.5-2.2)	0.837		
Overlapping	0.5(0.2-1.2)	0.115		
Clinical staging				
I-II	Ref.			
III-IV	4.3(2.3-7.8)	<0.001	2.6(1.4-5.0)	0.004
Neck dissection				
Yes	Ref.			
No/NA	4.1(2.3-7.1)	<0.001		
Free margin				

No/NA	Ref.			
Yes	0.2(0.09-0.3)	<0.001		
Differentiation				
Well differentiated	Ref.			
Moderately differentiated	0.7(0.4-1.2)	0.186		
Poorly differentiated	0.7(0.3-2.0)	0.533		
Treatment				
No treatment	Ref.			
RXT	0.6(0.3-1.7)	0.359		
CIR	0.02(0.004-0.1)	<0.001		
CIR+RXT	0.07(0.02-0.2)	<0.001		
CIR+RXT+QT	0.08(0.02-0.3)	<0.001		
QT + RXT	0.3(0.1-0.6)	0.002		
Surgery				
Yes	Ref.		Ref.	
No	6.1(3.5-10.6)	<0.001	4.6(2.5-8.2)	<0.001
Radiotherapy				
No	Ref.		Ref.	
Yes	2.1(1.2-3.8)	0.013		

HR= Hazard ratio; CI = Confidence interval; NA= Not applicable; RXT= radiotherapy; CIR= surgery; QT= chemotherapy
 Statistically significant results are in bold

DISCUSSION

Historically, SCC of the tongue has been more prevalent in male patients, middle-aged, smokers and alcohol drinkers (Hashibe *et al.*, 2007; Ferreira E Costa *et al.*, 2022). However, scientific literature shows an increase in the number of SCC cases among specific groups, including young people aged between 18 and 44 years old, females, and among patients who do not use tobacco or alcohol (Brown *et al.*, 2012; Tota *et al.*, 2017). Park *et al.* (2010) observed that, in a group of 85 patients diagnosed with SCC of the tongue, 27.1% were under 40 years of age (Park *et al.*, 2010), while Liao *et al.* reported that, among 296, patients with SCC of the tongue, 76 (25.8%) were ≤ 40 years-old (Liao *et al.*, 2006), corroborating the present study, where it was found that 27.7% of patients were younger than 40 years old. Although there is no agreement between tongue SCC studies regarding the definition of the age range for classifying young individuals, some studies establish young patients as up to 40 years of age (Garavello *et al.*, 2007; Rusthoven *et al.*, 2008).

Studies that have highlighted this increasing frequency of young patients affected by SCC of the tongue have also demonstrated that they are not associated with traditional risk factors (Carniol and Fried, 1982; McGregor *et al.*, 1983; Tsukuda *et al.*, 1993; Deneuve *et al.*, 2022). Santos-Silva *et al.*, observed that 48.6% of patients in the younger subgroup declared themselves as non-smokers, compared to 10.7% in the subgroup of older patients who did not smoke (Santos-Silva *et al.*, 2011). These results corroborate the findings of our study, in which it was found that 56.7% of patients aged ≤ 40 years reported never having smoked, in contrast to the group of patients aged >40 years, in which this percentage was 23.1%. Similarly to what was observed by Santos-Silva and co-workers, the present study did not demonstrate significant differences in alcohol consumption between ages, with both groups showing high percentages of consumption. Although retrospective analyses have not identified other potential risk factors related to SCC of the tongue in the young population, some investigations suggest the involvement of Human Papillomavirus (HPV) (Bachar *et al.*, 2011; Majchrzak *et al.*, 2014; Ng *et al.*, 2017), mainly in cases where the base of the tongue is the affected subsite, which may be correlated with HPV-related oropharyngeal carcinoma (Slootweg and El-Naggar 2018). Additionally, Heller *et al.*, 2023, in a systematic review and meta-analysis on patients with oral cancer and non-smokers suggested the association of these patients with other factors such as alcohol consumption, diet, oral health and medical comorbidities (Heller *et al.* 2023). These studies reinforce the need for further investigation into the factors associated with young patients with oral cancer.

Although the most frequently affected primary site was the lateral border of the tongue, in agreement with what was observed by da Silva Souto *et al.*, 2021, the data revealed that among the patients who presented SCC at the base of the tongue, 93.8% died, being also one of the sites with the lowest survival rate, with 6.1% overall survival rate in 10 years (da Silva Souto *et al.*, 2023). It is worth emphasising that we cannot exclude the possibility that sites classified as base of the tongue are also related to malignant neoplasms of the oropharynx, along with unspecified sites.

A study by Cohen Goldemberg and co-workers (2018) showed that the majority of patients affected by tongue cancer are diagnosed late in Brazil (65.4%) (Cohen Goldemberg *et al.*, 2018), consistent with the findings of this study, which revealed a percentage of 67.3%, with a high percentage in both age groups, as well as a worse survival rate, 0% in 10 years. In

addition, the analyses in this study show that patients diagnosed with advanced staging have a higher risk of death. These data reflect the need to reinforce public health policies on the importance of early diagnosis of oral cavity cancer (INCA, 2022), in addition to greater attention to the potentially malignant disorders of the oral cavity (Goldemberg 2019). As well as having a direct impact on prognosis, late diagnosis can contribute to the lack of specification of the primary subsite at the time of diagnosis, as observed in some of the cases analysed in this study, and consequently classified as unspecified or overlapping.

Although both age groups were diagnosed at an advanced stage, these data suggest that age was an important factor in the choice of treatment. Young adult patients were mostly eligible for a more invasive treatment, such as surgery (60%) in contrast to 38% of adult patients over the age of 40. In addition, our analyses showed that patients who did not undergo surgery had a higher risk of death, regardless of age.

It is interesting to note that the majority of young patients had disease-free margins (60%) and although the data was not significant, 46.7% of younger patients underwent neck dissection, suggesting a better prognosis. Lee *et al*, in a meta-analysis involving 23,382 patients with oral SCC, showed that although younger patients were eligible for more invasive treatments, there was no significant difference in survival when compared to older adult patients (Lee *et al*, 2021). The same was found in the present study when comparing overall survival in both groups with 32.1% at five years for patients ≤ 40 years and 28.0% for patients >40 years. However, this slight difference suggests that younger patients may have a better survival rate than adult patients over 40, but more research is needed to clarify this relationship.

This study has some limitations that are worth highlighting. The total sample size was 108 patients aged between 22 and 50 diagnosed with tongue cancer. It is important to note that no cases of diagnosis of this neoplasm in patients under the age of 22 were identified. Furthermore, when investigating tongue SCC in patients under the age of 40, it was noted that most of the time they are not associated with traditional risk factors such as smoking and alcohol consumption. However, it is crucial to note that this study did not address other potential risk factors that may be related to the development of this neoplasm. Another relevant limitation is related to late diagnosis, which contributed to the lack of specification of the primary subsite at the time of detection, as observed in some of the cases analyzed in this study. This lack of specificity can result in classifications such as "non-specific" or "overlapping", hindering a more detailed and specific analysis of the patterns of occurrence and risk factors associated with specific areas of the tongue.

CONCLUSION

Most young patients with squamous cell carcinoma were not exposed to traditional risk factors such as smoking. Furthermore, these patients frequently have undergone surgery and, for the most part, had disease-free margins. However, the five- and ten-year survival rates did not show significant differences in relation to the age group. The most affected topography was the lateral border of the tongue, and the predominance of diagnoses in the advanced stage highlights the complexity of this neoplasm regardless of age. Thus, these results highlight the importance of developing public policies aimed at early diagnosis, not only for groups known to be at risk for tongue SCC. Furthermore, it would be extremely important for future studies to investigate other potential risk factors related to this neoplasm.

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4 CONSIDERAÇÕES FINAIS

É essencial reconhecer e abordar as limitações intrínsecas à pesquisa em questão. O enfoque desta investigação esteve primariamente voltado para pacientes jovens diagnosticados com CEC em língua, a maioria dos quais não eram fumantes. No entanto, é de suma importância destacar que, neste estudo, os fatores de risco abordados foram restritos aos convencionalmente reconhecidos, como tabagismo e etilismo. Sugerindo a possibilidade de haver associação com fatores de risco ainda não identificados.

É de suma importância mais estudos sobre outros fatores que podem influenciar o surgimento de CEC nesta população, que não era anteriormente considerada de risco para essa patologia. A análise de elementos suplementares, como comorbidades e estilo de vida, desempenha um papel fundamental na ampliação da compreensão dessa condição.

A compreensão ampliada dos fatores de risco associados ao CEC de língua é crucial para a implementação de estratégias de diagnóstico precoce que beneficiem não apenas os grupos tradicionalmente reconhecidos como de alto risco, mas toda a população em potencial. Assim, reforça-se a necessidade de investimento contínuo em pesquisas que ampliem nossa compreensão e direcionem intervenções mais abrangentes e efetivas no âmbito da saúde pública.

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