BJO
Brazilian Journal of Oncology

ORIGINAL ARTICLES RADIOTHERAPY

Cross-sectional study of 1-to-5- year head and neck cancer survivors

Estudo transversal de sobreviventes de 1 a 5 anos de câncer de cabeça e pescoço

Pedro Bastos Cruvinel[1], Raony Molim de Sousa Pereira[1], André Luiz de Macedo Fressatti[1], Bianka Jurca Gonçalves-da Motta[1], Ana Carolina Fragoso Motta[2], Harley Francisco de Oliveira[3], Hilton Marcos Alves Ricz[4], Leandro Dorigan de Macedo[5], Camila Tirapelli[1]

ABSTRACT

Objectives: This study aimed to determine the demographic and clinical profile of 1-to-5-year head and neck cancer (HNC) survivors, and they oral features that could affect QoL. **Material and Methods:** In this cross-sectional study, medical records of 184 were reviewed concerning demographic, clinical and tumour characteristics. 40 of them underwent a quality of life (QoL) questionnaire and assessment of xerostomia (XA), using the oral health impact profile -14 (OHIP-14) and the xerostomia inventory (XI). Salivary flow was determined by measurement of stimulated whole salivary flow rate (SWSFR) and the number of teeth (NT) by determining the number of extracted and/or lost teeth. One-sample t-test, absolute and relative frequencies and Spearman's correlation test was used for statistical analysis of data. **Results:** Most HNC patients were male, aged between 50 and 60 years, alcohol and tobacco users, with low educational attainment, several comorbidities, and pharyngeal tumours. The high scores in the OHIP-14 (23.82±14.0) and XI (39.2±7.6) indicated that most patients had their QoL adversely affected and had xerostomia. Mean SWSFR was 0.2mL/min, and 15% (n=28) of patients were edentulous. The Spearman test showed a significant correlation between QoL and xerostomia, and salivary flow and QoL. **Conclusion:** This study evaluated characteristics of head and neck cancers (HNC) concerning demographic, clinical and tumour characteristics, quality of life (QoL), xerostomia, salivary flow, and number of teeth (NT) through an observational and cross-sectional study.

Headings: Oral health; Xerostomia; Head and neck neoplasms.

1. Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Materiais Dentários e Prótese - Ribeirão Preto - São Paulo - Brazil.
2. Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Departamento de Estomatologia, Saúde Pública e Odontologia Legal - Ribeirão Preto - São Paulo - Brazil.
3. Faculdade de Odontologia de Ribeirão Preto, Universidade de São Paulo, Departamento de Clínica Infantil - Ribeirão Preto - São Paulo - Brazil. Centro de Tratamento em Radio-Oncologia (CTR) - Ribeirão Preto - São Paulo - Brazil. Hospital Márcio Cunha (HMC/FSFX) - Departamento de Radioterapia - Ipatinga - Minas Gerais- Brazil.
4. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Departamento de Clínica Médica - Ribeirão Preto - São Paulo - Brazil.
5. Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Serviço de Odontologia e Estomatologia - Ribeirão Preto - São Paulo - Brazil.

Funding: This research was financed by the funds FAPESP (#13/03351-9) and CAPES (#001).
Conflicts of interest: The authors declare that there are no competing interests that could be perceived as prejudicing to the impartiality of the research reported. They also have full control of all primary data and agree to allow the journal to review their data if requested. The research described was supported by grants from São Paulo Research Foundation (FAPESP) (#13/03351-9) and from the coordination for the improvement of higher education (CAPES) (grant #001) and there are no potential competing interests for these funds.
Regulatory statement: This study was approved by the institutional review board of the institutions (CAAE 27765714.0.000.5419).
Author's Contribution: Conception and design, Data analysis and interpretation, Final approval of manuscript, Manuscript writing, Provision of study materials or patient
Correspondence author: Camila Tirapelli.
E-mail: catirapelli@forp.usp.br / Alternative E-mail: pedrobcruvinel@gmail.com

Received on: Nov 8, 2021 | **Accepted on:** Dec 17, 2021 | **Published on:** Feb 18, 2022
DOI: https://doi.org/10.5935/2526-8732.20220316

RESUMO

Objetivos: Este estudo teve como objetivo determinar o perfil demográfico e clínico de sobreviventes de 1 a 5 anos de câncer de cabeça e pescoço (CCP) e as características bucais que podem afetar a QV. **Material e Métodos:** Neste estudo transversal, foram revisados prontuários de 184 prontuários quanto às características demográficas, clínicas e tumorais. 40 deles foram submetidos a um questionário de qualidade de vida (QV) e avaliação de xerostomia (XA), usando o perfil de impacto na saúde bucal -14 (OHIP-14) e o inventário de xerostomia (XI). O fluxo salivar foi determinado pela medição da taxa de fluxo salivar total estimulado (MTFSTE) e o número de dentes (NT) pela determinação do número de dentes extraídos e/ou perdidos. O teste-t para uma amostra, frequências absolutas e relativas e o teste de correlação de Spearman foram utilizados para análise estatística dos dados. **Resultados:** A maioria dos pacientes com CCP era do sexo masculino, com idade entre 50 e 60 anos, usuários de álcool e tabaco, com baixa escolaridade, várias comorbidades e tumores de faringe. Os altos escores no OHIP-14 (23,82±14,0) e XI (39,2±7,6) indicaram que a maioria dos pacientes teve sua QV prejudicada e apresentou xerostomia. A média do SWSFR foi de 0,2mL/min e 15% (n=28) dos pacientes eram desdentados. O teste de Spearman mostrou correlação significativa entre QV e xerostomia, e fluxo salivar e QV. **Conclusão:** Este estudo avaliou características dos cânceres de cabeça e pescoço (CCP) quanto às características demográficas, clínicas e tumorais, qualidade de vida (QV), xerostomia, fluxo salivar e número de dentes (NT) por meio de um estudo observacional e transversal.

Descritores: Saúde bucal; Xerostomia; Neoplasias de cabeça e pescoço.

INTRODUCTION

Head and neck cancer (HNC) accounted estimated 41,000 cases in Brazil in 2020, corresponding to 7.9% of all neoplasms, except for non-melanoma skin cancer.[1] The treatment of HNC is largely based on tumour site and disease stage, and mostly involves surgical resection associated with radiotherapy (RT) and/or chemotherapy.[2] Despite the radiotherapy technology advances, the toxic effects of anticancer treatment remain challenging, potentially leading to early and late side effects, such as mucositis, oral opportunistic infections, dysgeusia, ageusia, trismus, dysphagia, odynophagia, chronic pain, xerostomia (XA), dental hypersensitivity, radiation-induced tooth decay, and osteoradionecrosis.[3,4] Patients usually report a worsening of quality of life (QoL) due to these side effects.

The overall survival of HNC patients has improved over the last decades, but still depends on tumor location.[5] Recent data from South America show three-year survival rates of 56.0% for larynx cancer, 54.7% for oral cavity cancer, 48.0% for oropharynx cancer, and 37.8% for hypopharynx cancer.[6] In Brazil, survival comparison between two time periods (2001-2006 and 2007-2012) showed stable results for oral squamous cell carcinoma (SCC) but a significant increase for oropharyngeal SCC.[7] Consequently, a large cohort of HNC survivors with complex needs is identified, highlighting the importance of studies on this population, focusing on QoL issues,[8] and on the development of cancer survivorship initiatives. Although the theme of the HNC profile has already been addressed previously, the inclusion of a complete oral examination is usually lacking.[9] Thus, the present study aimed to determine the demographic and clinical profile of HNC survivors, and oral features that could affect QoL.

MATERIAL AND METHODS

Patients (adults ≥ 18 years old) of both sexes, with complete remission of HNC after 1-5 years of antineoplastic therapy including RT were included in this study.

This was an observational, cross-sectional study of 184 HNC patients treated with RT through a medical records review. Demographic and clinical data included gender, race, marital status, place of origin, level of education, smoking history, alcohol consumption, comorbidities, topographic location of the tumour, time from first medical evaluation to diagnosis, and the therapy combined with RT. All patients were contacted and invited to attend the cancer outpatient of a university medical service, for an interview on QoL and clinical examination for the number of healthy teeth, XA, and salivary flow, but only 40 patients agreed to participate. This study was approved by the institutional review board of the institutions (CAAE 27765714.0.000.5419).

QoL was assessed using the oral health impact profile (OHIP-14) questionnaire, which had been validated and translated into Portuguese language.[10] The OHIP-14 measures the impact of oral health on QoL; it is composed of 14 questions covering seven domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and disability of oral health condition.[11,12]

The maximum score of OHIP-14 is 70, which would indicate a low QoL. XA was assessed using the xerostomia inventory (XI), previously translated into Portuguese and validated by Da Matta et al. (2012).[10] The instrument is an 11-item rating scale that covers both experiential and behavioural aspects of XA. The total score can range from 11 to 55 and a high score indicates extremely dry mouth.[10,13-15] Salivary flow was assessed by determining the stimulated whole salivary flow rate (SWSFR). Subjects were asked to chew a small piece of silicone for five minutes, and then spit the saliva produced into a test tube. The volume was measured in millimeter, and flow rates <0.70mL/min were considered hyposalivation.[4,14,16] Number of healthy teeth (NT) was determined in relation to lost/extracted teeth.

Demographic and clinical characteristics were statistically analysed using the one-sample t-test ($p<0.05$). Data from the OHIP-14, XI, NT and SWSFR were analyzed by descriptive statistics. Interactions between the clinical variables were assessed by the Spearman's correlation test, considering r values as 0.00-.19 "very weak", 0.20-.39 "weak", 0.40-.59 "moderate", 0.60-.79 "strong", and 0.80-1.0 "very strong". The confidence level for all tests was 95%. Statistical analyses were performed using the GraphPad Prism® software, version 6.0.

RESULTS

From the 184 patients retrospectively evaluated, 145 (78.8%) were male, mostly in the age group of 51 to 60 years (n=71; 38.6%), with a median age of 57.7 (range 14-96) years; 146 (79.3%) were white, and 70 (38.0%) were married. Most of the patients (n=77; 41.8%) were from cities with populations over 100 thousand inhabitants, and 116 (63.0%) had (completed or some) primary education (Table 1).

Table 1. Distribution of patients according to gender, race, marital status, origin and level of education.

Variables	Categories	N*	%	*p*-values
Gender	Male	**145 A**	**78,8**	*p*=0.003
	Female	39 a	21,2	
Race	White	**146 B**	**79,3**	*p*=0.0001
*Uninformed 1 b (0,5%)	Black	22 b	12,0	
	Mulato	15 b	8,2	
Marry status	Single	48 c	26,1	*p*=0.001
*Uninformed 6 c (3,3%)	Married	**70 C**	**38,0**	
	Divorcied	28 c	15,2	
	Separated	14 c	7,6	
	Widower	18 c	9,8	
Origin	< 10.000/hab	14 d	7,6	*p*=0.004
Population size	10-50.000/hab	64 d	34,8	
*Uninformed 2 d (1,1%)	50-100.000/hab	27 d	14,7	
	>100.000/hab	**77 D**	**41,8**	
Level of education	Illiterate	17 e	9,2	*p*=0.0001
*Uninformed 25 e (13,6%)	Fundamental	**116 E**	**63,0**	
	High-school	18 e	9,8	
	Undergraduate	8 e	4,3	
Smoking	Never	25 a	13,6	*p*=0.0001
Duration of use	Until 15 years	9 a	4,9	
*Uninformed 29 a (15,8%)	16-30 years	13 a	7,1	
	>30 years	**108 A**	**58,7**	
Number per day (frequency)	Never	25 b	13,6	*p*=0.004
*Uninformed 27 b (14,7%)	Until 10 units	32 b	17,4	
	11-30 units	**69 B**	**37,5**	
	>30 units	31 b	16,8	
Alcohol consumption	Never	29 c	15,8	*p*=0.001
Duration of use	Until 15 years	7 c	3,8	
*Uninformed 54 c (29,3%)	16-30 years	31 c	16,8	
	>30 years	**63 C**	**34,2**	
Type	Never	29 d	15,8	*p*=0.004
*Uninformed 44 d (23,9%)	Distilled	**46 D**	**25,0**	
	Fermented	25 d	13,6	
	Both	40 d	21,7	

N = Number; *Capital letters indicate statistically significant differences ($p<0.05$) relative to the lower case for each variable according to the *one-sample t-test*.

More than half of the individuals had smoked for more than 30 years (58.7%), in contrast to 13.6% (n=25) who had never smoked (13.6%). Most smokers (37.5% of the HNC patients) consumed from 11 to 30 cigarettes per day, followed by 17.4% who consumed less than 10 cigarettes per day and 16.8% who consumed more than 30 cigarettes per day. The number of individuals who consumed alcohol (n=63, 34.2%) for more than 30 years was significantly higher than the number of non-consumers (n=29, 15.8%) and individuals who consumed for 16-30 years (n=31, 16.8%). Regarding the type of alcoholic beverage, most consumers reported their preference for distilled beverages (n=46, 25%), followed by both distilled and fermented beverages (n=40, 21.7%) and fermented beverages (n=25, 13.6%) (Table 1).

Regarding comorbidities, 46.7% of the patients did not have any type of comorbidities, 30.4% reported arterial hypertension, 8.7% diabetes mellitus, 4.9% dyslipidemia, 3.8% chronic obstructive pulmonary disease, 4.9% heart disease, 3.8% kidney disease, 6% hypothyroidism, and 19.6% other comorbidities.

Considering the tumour site, most (59.2%) of HNC patients had pharyngeal neoplasms, 40.8% of them in the oropharynx, 8.7% in the nasopharynx and 8.1% in the hypopharynx (Table 2). Oral cavity neoplasms represented 22.8% of total neoplasms; 7.6% were located in the floor of the mouth, 1.1% in the hard palate, 1.1% on the lateral tongue, 7.6% in other (non-specified) areas of the tongue with, and 2.7% in the retromolar area; 1.1% of total neoplasms were in the lower lip. Of salivary gland neoplasms, 6.0% were located in the parotid gland, and 0.54% in the submandibular gland; 9.24% of total neoplasms were in facial sinuses (Table 2).

Table 2. Distribution of patients according to the head and neck cancer (HNC) characteristics: anatomical location, duration to diagnosis, year of diagnosis, antineoplastic treatment used in combination with RT, and systemic comorbidities.

Variables	Categories		n	%
Anatomical location	Pharynx[A]	Hypopharynx	15	8,15
p=0.001		Nasopharyngeal	16	8,70
		Oropharynx	75	40,76
		Not informed	3	1,63
		Total	**109**	**59,24**
	Oral cavity[a]	Floor of mouth	14	7,61
		Hard palate	2	1,09
		Lateral tongue	2	1,09
		Not informed (tongue)	14	7,61
		Retromolar area	5	2,72
		Other areas	5	2,72
		Total	**42**	**22,83**
	Lip[a]	Lower lip	2	1,09
		Total	**2**	**1,09**
	Salivary gland[a]	Parotid	11	5,98
		Submandibular	1	0,54
		Not informed	2	1,09
		Total	**14**	**7,61**
	Other regions[a]	Facial sinuses	17	9,24
First evaluation to diagnosis	Until 6 months		106 B	57,61
p=0.001	7-12 months		39 b	21,20
	>12 months		27 b	14,67
	Not informed		12 b	6,52
Year of diagnosis	2010		21 a	11,41
p=0.001	2011		31 a	16,85
	2012		35 a	19,02
	2013		64 A	34,78
	2014		33 a	17,93
Treatment combined	Chemotherapy		74 B	40,22
with radiotherapy	Surgery		31 b	16,85
p=0.04	Surgery and chemotherapy		65 b	35,33
	None		14 b	7,61

*Capital letters indicate statistically significant differences ($p<0.05$) relative to the lower case for each variable according to the *one- sample t-test*.

Analysis of the time between patient's first evaluation at this medical service and the diagnosis revealed that 57.6% of the individuals were diagnosed within six months, 21.2% were diagnosed in 7-12 months, and 14.7% in more than 12 months. Only 7.6% of patients were treated with RT alone; most patients were treated with RT combined with chemotherapy (40.22%), followed by chemotherapy and surgery (35.3%), and surgery (16.8%) (Table 2).

Table 3 shows the survival rate profile of the patients in this study, with the largest distribution of individuals being between 0 and 1 and between 1 and 2 in sequence, representing 36% and 30% respectively. For the other years, the distribution was 15% for those between 2 and 3 years, 11% between 3 and 4 years, and finally 8% between 4 and 5 years. The average survival time of these patients was 1.8 years.

Table 4 shows descriptive statistics of the OHIP-14, XI, SWSF and NT results. The mean OHIP-14 score was 24±14, and the most frequent domains that negatively impacted on QoL were functional limitations, physical limitations and pain, which are related to eating problems. The mean XI score was 39±7, and patients had high scores on seven of the 11 items of the questionnaire, which contributed to the high degree of XA. The objective evaluation of saliva flow showed a SWSFR rate of 0.2mL/min ± 0.25 (ranging from 0.0 to 0.9mL/min), with 37.5% (n=15) of patients showing a saliva flow of 0.0mL/min. Clinical and radiographic (panoramic when necessary) examination of the teeth showed a mean of 28.5 extracted or lost teeth, and 28 patients were edentulous. The Spearman test showed a moderate, significant positive, correlation between QoL and XA (p=0.0001, r=0.59) and a very weak, significant, negative correlation between SF and QoL (p=0.029, r=-0.35). The correlation between the other variables analysed was not statistically significant (Table 5).

DISCUSSION

This study described demographic and clinical characteristics of HNC survivors in a university medical service, and showed that most of these patients were men, older than 50 years, with low education level. This is in agreement with results of previous studies conducted in different regions of the world.[17-21] The most common tumour locations were the oropharynx (40.8%), followed by nasopharynx (8.7%) and hypopharynx (8.2%). Additionally, we performed clinical examination of 40 patients from this cohort and found that the majority had a mild impact on QoL despite a high level of XA, low SWSFR and high prevalence of edentulism.

The high prevalence of HNC in male patients is reported worldwide, and this type of cancer represents 7.6% of all cancers in Brazil.[1] The increased risk of HNC in male patients can be explained by the abuse of substances such as alcohol and tobacco,[22-24]

Table 3. Survival rate profile of the HNC patient in this study.

	0 to 1	1 to 2	2 to 3	3 to 4	4 to 5
Number	67	55	27	20	15
Total percentile (of 184)	36%	30%	15%	11%	8%

Table 4. Descriptive statistics for OHIP-14, XI, SWSF, and NT.

	OHIP	XI	SWSF	NT
Minimum	4	26	0,0	15
25% percentile	11	32	0,0	26
Median	24	40	0,1	32
75% percentile	37	46	0,3	32
Maximum	56	51	0,9	32
Mean	24	39	0,2	29
Std. deviation	14	8	0,3	5
Std. error of mean	2	1	0,04	0,8
Lower 95% CI of mean	19	37	0,1	27
Upper 95% CI of mean	28	42	0,3	30

Table 5. Correlation values between variables assessed.

Variables	r	*p*
OHIP vs XI	0.59	0.0001
OHIP vs SWSF	-0.35	0.029
OHIP vs NT	-0.22	0.177
XI vs SWSF	-.018	0.260

which is more common among men than women, in our cohort, 70.6% of the patients had a history of smoking and 71.7% of alcohol consumption. In addition, the most prevalent comorbidity in these patients was arterial hypertension (30.4%), as observed in previous studies,[25,26] and can be explained by the fact that alcohol and tobacco consumption are risk factors for this condition.

The XI is a useful tool to determine the severity of XA through scores assigned to issues related to daily activities.[27] In the current study, we found an average score of 40 (out of a maximum of 55) resulted from high scores (ranging from 3.6 to 4.7) in seven of the 11 questions 5. It indicates severe XA, which may have been caused by RT. Measurement of the SWSFR was used to evaluate salivary gland function and showed that all patients had hyposalivation (0.2mL/min). Although there is no consensus on SWSFR classification, values of 0.5-0.9mL/min for SWSFR, and below 0.1mL/min for unstimulated whole salivary flow are considered hyposalivation.[14] Our findings were similar to other studies,[16,28-31] and reinforce the effects of RT on salivary gland function.

A negative impact of RT on oral health related QoL of survivors of HNC patients has been previously reported.[31] In our study, QoL was assessed using the OHIP-14, with an average score of 24 (out of a maximum of 70). However, we found a moderate positive correlation (r=0.59) between OHIP-14 and XI scores, and a weak inverse correlation (r=-0.35) between OHIP-14 and SWSFR. Of note, despite the high score in the XI, low SWSFR and the high number of edentulous patients, we observed a low OHIP-14 score, suggesting a mild impact on QoL. Considering the 1-to-5-year period, patients experienced hyposalivation, it seems reasonable to suggest that a process of adaptation might have occurred. Soldera et al. (2020)[31] evaluated the QoL of HNC patients three months after RT and identified that hyposalivation had a high impact on QoL. Then, XA can become mild over time even with low SF.[16]

The main strength of this work was the characterization of both demographic and clinical profile of HNC survivors with complete remission after antineoplastic treatment. However, there are some limitations, including the lack of information in the medical records, and the subjectivity of the OHIP-14 to assess QoL, which may be affected by individual and cultural issues. Another point to be discussed is the absence of data regarding the quality of life of these same patients prior to HNC and treatment, preventing this baseline from being compared to the patient's current condition. This missing baseline also makes it difficult to compare the impact of surgery on the patient's salivation because salivary flow was not measured before treatment, making it difficult to identify its impact on hyposalivation or xerostomia. Another important fact is the lack of knowledge of the technique and radiation dose that the patients received during the radiotherapy, making it difficult to identify its influence on each patient. Another limitation of this study was the small number of patients subjected to clinical oral examination (40/184; 21.7%), which limited more robust statistical analyses to better explore the correlations. The fact that most patients were older than 60 years, had a low income, were users of the public health care, and lived outside the region of the study may have affected the willingness of patients to participate in the study.

CONCLUSION

It was possible to observe that the demographic and clinical profile of our group of HNC survivors with a 1-to-5-year of complete remission was similar to those reported worldwide: predominantly white males, 51 to 60 years old, consumers of alcohol and/or tobacco, and who have some comorbidity. Most of the neoplasms were pharyngeal, taking up to 6 months to be identified. When they were diagnosed, most patients were treated with a combination of radiotherapy and chemotherapy, which had the effect of XA in 37.5% of the individuals. It could also be seen that low SWSFR had a negative impact on QoL when XA was present.

ACKNOWLEDGMENTS

Our thanks to all the patients who participated in the study, as well as the institutions and professionals involved. We are also grateful for the financial support provided by FAPESP and CAPES.

REFERENCES

1. Instituto Nacional de Câncer José de Alencar Gomes da Silva (INCA). Estimativa 2020 - Apresentação | INCA - Instituto Nacional de Câncer n.d. https://www.inca.gov.br/estimativa. [acess in october, 01, 2021].
2. Cohen EEW, LaMonte SJ, Erb NL, Beckman KL, Sadeghi N, Hutcheson KA, et al. American Cancer Society Head and Neck Cancer survivorship care guideline. CA Cancer J Clin. 2016 May;66(3):203-39.
3. Chaukar DA, Walvekar RR, Das AK, Deshpande MS, Pai PS, Chaturvedi P, et al. Quality of life in head and neck cancer survivors: a cross-sectional survey. Am J Otolaryngol. 2009 May/Jun;30(3):176-80.
4. Han P, Suarez-Durall P, Mulligan R. Dry mouth: a critical topic for older adult patients. J Prosthodont Res. 2015 Jan;59(1):6-19.
5. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist. 2010;15(9):994-1001.
6. Abrahão R, Perdomo S, Pinto LFR, Carvalho FN, Dias FL, Podestá JRV, et al. Predictors of survival after head and neck squamous cell carcinoma in South America: the InterCHANGE study. JCO Glob Oncol. 2020 Mar;6:486-99.
7. Kowalski LP, Oliveira MM, Lopez RVM, Silva DRM, Ikeda MK, Curado MP. Survival trends of patients with oral and oropharyngeal cancer treated at a cancer center in Sao Paulo, Brazil. Clinics. 2020;75:1-8.
8. Mehanna HM, Morton RP. Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. Clin Otolaryngol. 2006 May;31(3):204-11.
9. Oliveira LR, Ribeiro-Silva A, Zucoloto S. Perfil da incidência e da sobrevida de pacientes com carcinoma epidermóide oral em uma população brasileira. J Bras Patol Med Lab. 2006 Oct;42(5):385-92.

10. Mata A, Marques DS, Freitas F, Amaral JAR, Trindade R, Barcelos F, et al. Translation, validation, and construct reliability of a Portuguese version of the xerostomia inventory. Oral Dis. 2012 Apr;18(3):293-8.

11. Almeida A, Loureiro C, Araújo V. Um estudo transcultural de valores de saúde bucal utilizando o instrumento OHIP-14 (Oral Health Impact Profile) na Forma Simplificada. Parte I: adaptação cultural e lingüística. UFES Rev Odontol. 2004;6(1):6-15.

12. Alvarenga F, Henriques C, Takatsui F, Montandon A, Telarolli Júnior R, Monteiro A, et al. Oral health impact profile in the quality of life of patients over 50 years old of two public institutions of Araraquara city, SP, Brazil. Rev Odontol UNESP. 2011;40(3):118-24.

13. Enoki K, Matsuda KI, Ikebe K, Murai S, Yoshida M, Maeda Y, et al. Influence of xerostomia on oral health-related quality of life in the elderly: a 5-year longitudinal study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014 Jun;117(6):716-21.

14. Hahnel S, Schwarz S, Zeman F, Schäfer L, Behr M. Prevalence of xerostomia and hyposalivation and their association with quality of life in elderly patients in dependence on dental status and prosthetic rehabilitation: a pilot study. J Dent. 2014 Jun;42(6):664-70.

15. Thomson WM. Measuring change in dry-mouth symptoms over time using the xerostomia inventory. Gerodontology. 2007 Mar;24(1):30-5.

16. Likhterov I, Ru M, Ganz C, Urken ML, Chai R, Okay D, et al. Objective and subjective hyposalivation after treatment for head and neck cancer: long-term outcomes. Laryngoscope. 2018 Dec;128(12):2732-9.

17. Melo NB, Bernardino ÍM, Melo DP, Gomes DQC, Bento PM. Head and neck cancer, quality of life, and determinant factors: a novel approach using decision tree analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 Dec;126(6):486-93.

18. Melo NB, Sousa VM, Bernardino ÍDM, Melo DP, Gomes DQC, Bento PM. Oral health related quality of life and determinant factors in patients with head and neck cancer. Med Oral Patol Oral Cir Bucal. 2019 May;24(3):e281-e9.

19. Palmieri M, Sarmento DJS, Falcão AP, Martins VAO, Brandão TB, Morais-Faria K, et al. Frequency and evolution of acute oral complications in patients undergoing radiochemotherapy treatment for head and neck squamous cell carcinoma. Ear Nose Throat J. 2021 Sep;100(5 Suppl):449S-55S.

20. Roick J, Danker H, Dietz A, Papsdorf K, Singer S. Predictors of changes in quality of life in head and neck cancer patients: a prospective study over a 6-month period. Eur Arch Otorhinolaryngology. 2020 Feb;277(2):559-67.

21. Visacri MB, Ferrari GB, Pimentel R, Ambrósio RDFL, Lima CSP, Mazzola PG, et al. Evaluation of the quality of life of patients before treatment of squamous cell carcinoma of the head and neck by means of chemoradiotherapy. Contemp Oncol (Pozn). 2015;19(2):148-53.

22. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. Surg Oncol Clin N Am. 2015 Jul;24(3):379-96.

23. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: Differences by country, sex and anatomic site. Oral Oncol. 2014 May;50(5):387-403.

24. Thun M, Peto R, Boreham J, Lopez AD. Stages of the cigarette epidemic on entering its second century. Tob Control. 2012 Mar;21(2):96-101.

25. Chu CN, Chen SW, Bai LY, Mou CH, Hsu CY, Sung FC. Increase in stroke risk in patients with head and neck cancer: a retrospective cohort study. Br J Cancer. 2011 Oct;105(9):1419-23.

26. Amberbir A, Lin SH, Berman J, Muula A, Jacoby D, Wroe E, et al. Systematic review of hypertension and diabetes burden, risk factors, and interventions for prevention and control in Malawi: the NCD BRITE Consortium. Glob Heart. 2019 Jun;14(2):109-18.

27. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. Int J Oral Maxillofac Surg. 2011 Mar;40(3):229-43.

28. Palma LF, Gonnelli FAS, Marcucci M, Dias RS, Giordani AJ, Segreto RA, et al. Impact of low-level laser therapy on hyposalivation, salivary pH, and quality of life in head and neck cancer patients post-radiotherapy. Lasers Med Sci. 2017 May;32(4):827-32.

29. Randall K, Stevens J, Yepes JF, Randall ME, Kudrimoti M, Feddock J, et al. Analysis of factors influencing the development of xerostomia during intensity-modulated radiotherapy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Jun;115(6):772-9.

30. Silveira MH, Dedivitis RA, Queija DS, Nascimento PC. Quality of life in swallowing disorders after nonsurgical treatment for head and neck cancer. Int Arch Otorhinolaryngol. 2015 Jan;19(1):46-54.

31. Soldera EB, Ortigara GB, Bonzanini LIL, Schulz RE, Danesi CC, Antoniazzi RP, et al. Clinical and sociodemographic factors associated with oral health-related quality of life in survivors of head and neck cancer. Head Neck. 2020 Jan;42(5):886-97.