Original Research
Oral Pathology

Clinical outcomes and prognostic factors of head and neck squamous cell carcinoma: a ten-year follow-up study

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Abstract: Traditional guidelines for determining the prognosis of patients with head and neck squamous cell carcinoma (HNSCC) are used to make therapeutic decisions. However, only 50% of the patients had lived for more than five years. The present study aimed to analyze the correlation of traditional prognostic factors such as tumor size, histological grading, regional metastases, and treatment with the survival of patients with HNSCC. A total of 78 patients diagnosed with HNSCC were followed up for 10 years after diagnosis and treatment. The health status of the patients was tracked at four time points, and according to the evolution of the patients and their final clinical status, we performed a prognostic analysis based on the clinical outcomes observed during the follow-up period. The final study cohort comprised 50 patients. Most patients had tumors < 4 cm in size (64%) and no regional metastases (64%); no patients had distant metastases at the time of diagnosis. Most individuals had tumors with good (48%) and moderate (46%) degrees of malignancy. At the end of the follow-up period, only 14% of the patients were discharged, 42% died of the tumor, and 44% remained under observation owing to the presence of a potentially malignant disorder, relapse, or metastases. This analysis showed that traditional prognostic factors were not accurate in detecting subclinical changes or predicting the clinical evolution of patients.

Keywords: Disease-Free Survival; Head and Neck Neoplasms; Prognosis.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 18th most prevalent cancer worldwide. However, its incidence and mortality rates are high in certain regions with low human development indices, and in men.[1] This disease is related to risk factors such as smoking, alcohol consumption, human papillomavirus (HPV) infection, oropharyngeal and laryngeal tumors, sun exposure, and eating habits.[2]

Currently, the guidelines for determining prognosis include tumor size measurement, histological grading, local and/or distant lymph node involvement, and tumor staging, which are carefully used in the therapeutic decision-making and follow-up of patients with HNSCC.[3] These guidelines have been discussed because only 50% of patients live for more than

5 years,[4] with even lower mean survival rates in cases of metastases and recurrence (rarely exceeding 1 year).[5] Therefore, other clinical and pathological factors associated with survival, such as treatment, age, and tumor location, are increasingly being considered in the prognosis analysis.[6] Additionally, research on the development of biomarkers for precision medicine is increasingly being undertaken.[5]

Thus, the present study aimed to analyze the correlation between prognostic factors such as tumor size, histological grading, regional metastases, and treatment, and the survival of patients with HNSCC over a 10-year follow-up period.

Methodology

Study cohort and clinical parameters

The convenience cohort comprised patients diagnosed with primary HNSCC who were treated at the Head and Neck Surgery Outpatient Clinic of the Otorhinolaryngology Department of Hospital de Clínicas de Porto Alegre (HCPA) between October 2009 and October 2010.

During the diagnostic process, the participants were interviewed to obtain information regarding sex, age, ethnic group, and tobacco and/or alcohol consumption. Data on the characteristics of the tumors and follow-ups were obtained from hospital records after the treatment of the patients, a procedure that did not affect adequate therapy for each case. These patients were followed up for 10 years, and those without complete records were excluded.

Treatment

Patients received the treatment indicated in the hospital's HNSCC care protocol for each case, which included: surgery alone, surgery plus radiotherapy, surgery plus radiotherapy and chemotherapy, chemotherapy alone, or chemotherapy plus radiotherapy. Patients who had undergone radiotherapy or chemotherapy before surgery were excluded from the study.

Clinical staging and histological grading

Tumors were classified according to the TNM system of the American Joint Committee on Cancer.[7] Histological grading (HG) was performed according to the standardization of Bryne et al.[8] by blinded pathologists to identify the specimens. Reproducibility was confirmed over the study period by selecting one out of every 20 slides for reassessment after a 7-day interval (kappa > 0.7). HG was performed on the surgical specimens in all patients except one, who was considered inoperable (HG performed on incisional biopsy tissue).

Survival analysis

Follow-up

Data were collected at four time points: F1, 2.5 years; F2, 5 years; F3, 7.5 years; and F4, 10 years. At different follow-up time points, the cohort was categorized into the following groups of patients: without recurrence; with recurrence; with metastases; and who died due to the tumor. Therefore, this categorization varied depending on the condition of the patient at the time of data collection.

Prognosis

Prognosis was determined according to the progression of the patient during the follow-up period, and categorized as follows: good prognosis - absence of clinical signs, recurrence, metastasis, or progression to death; reserved prognosis - potentially malignant disorders (PMD), recurrence or metastasis; and poor prognosis - death due to the tumor.

Final clinical status

At the end of the 10-year follow-up period, patients were reclassified according to their final clinical status: discharged; without recurrence; with PMD; with recurrence, metastasis, or death from the tumor.

Statistical analysis

The Statistical analysis was performed using the Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, USA). Age is presented as mean and standard deviation. Data such as sex, ethnic group, smoking habits, alcohol consumption, type of treatment, evaluation of tumor samples, prognosis, current status, and cause of death are

expressed as percentages. The distribution of patient status according to follow-up time was analyzed using the Kruskal–Wallis test. The association of prognosis, current events, and cause of death with tumor grade, TNM, and smoking or alcohol habits was assessed using the Pearson's chi-square test. Survival analysis was performed using the Kaplan–Meier test, and the association between variables was assessed using the log-rank test. Statistical significance was set at 5% ($p \leq 0.05$).

Results

Study cohort and clinical parameters

The initial cohort comprised 78 patients, twenty-eight of them were excluded. The patients were aged between 37 and 77 years, and the majority were men (84%). Most individuals had used tobacco (98%) and alcohol (94%) at some point before diagnosis, and the mouth (oral 50% and lip 20%) was the predominant tumor site. Data related to alcohol and tobacco consumption were analyzed, including the type of substance and amount consumed per day, and habit duration. However, no statistically significant results were found in relation to prognosis. Considering comorbidities, 46% of the patients had systemic diseases (diabetes, heart disease, or hypertension). The characteristics of the patients, clinical staging, HG, and the type of treatment performed in the final sample (50 patients) are summarized in Table 1.

Treatment

In particular, 68% of the patients underwent surgery alone, and 30% received some form of adjuvant treatment. One patient (2%) had an inoperable tumor and received radiotherapy plus chemotherapy.

Clinical staging and histological grading

Most patients in the cohort had tumors < 4 cm (64%) in size, no regional metastasis (64%), or distant metastases at the time of diagnosis. Most individuals (94%) had tumors with good or moderate histological grades.

Survival analysis

The overall analysis showed that events related to patient survival occurred from the first month

Table 1. Clinical parameters, type of treatment, and specimen evaluation.

Variable		
Age	Mean 58,2	SD 9,953 (%)
	n	%
Gender		
Male	42	84
Female	8	16
Skin		
Caucasian	40	80
Non-Caucasian	5	20
Tobacco		
Current	21	42
Former	28	56
Never	1	2
Alcohol		
Current	25	50
Former	22	44
Never	3	6
Location		
Oral	35	70
Tongue	11	22
Floor	5	10
Palate	6	12
Cheek mucosa	3	6
Neck	15	30
Oropharynx	3	6
Hypopharynx	5	8
Larynx	7	16
Lip	10	20
Size		
T1/T2	32	64
T3/T4	18	36
Regional metastases		
N0	32	64
N1/N2/N3	18	36
Treatment		
Surgery	34	68
Surgery/ radiotherapy	13	26
Surgery/radiotherapy/ chemotherapy	2	4
Radiotherapy/chemotherapy	1	2
Histological grading		
Good	24	48
Moderate	23	46
Poor	3	6
Total	50	100

up to nine years and nine months of follow-up (Figure 1A). The proportion of surviving patients gradually decreased up to 7.5 years (F1, 48/50 = 96%; F2, 37/50 = 74%; F3, 30/50 = 60%; F4, 29/50 = 58%). During the first 2.5 years of follow-up, there was no significant change in the clinical status of the patients (p = 0.070) (data not shown); however, there was a significant increase in the number of deaths after 2.5 years (p = 0.028) and 5 years (p < 0.0001) of follow-up. The number of patients without recurrence increased (p < 0.0001) between 7.5 and 10 years (Figure 1B). Smoking cessation (p = 0.622) and alcohol consumption (p = 0.204) did not affect patient prognosis. Systemic comorbidities were not associated with patient prognoses.

HG did not influence patient survival for up to 5 years of follow-up (F1, p = 0.955; F2, p = 0.699). However, after 5 years of follow-up, patients with tumors with a good degree of malignancy had a higher survival rate (F3, p = 0.001; F4, p = 0.033) (Figure 2).

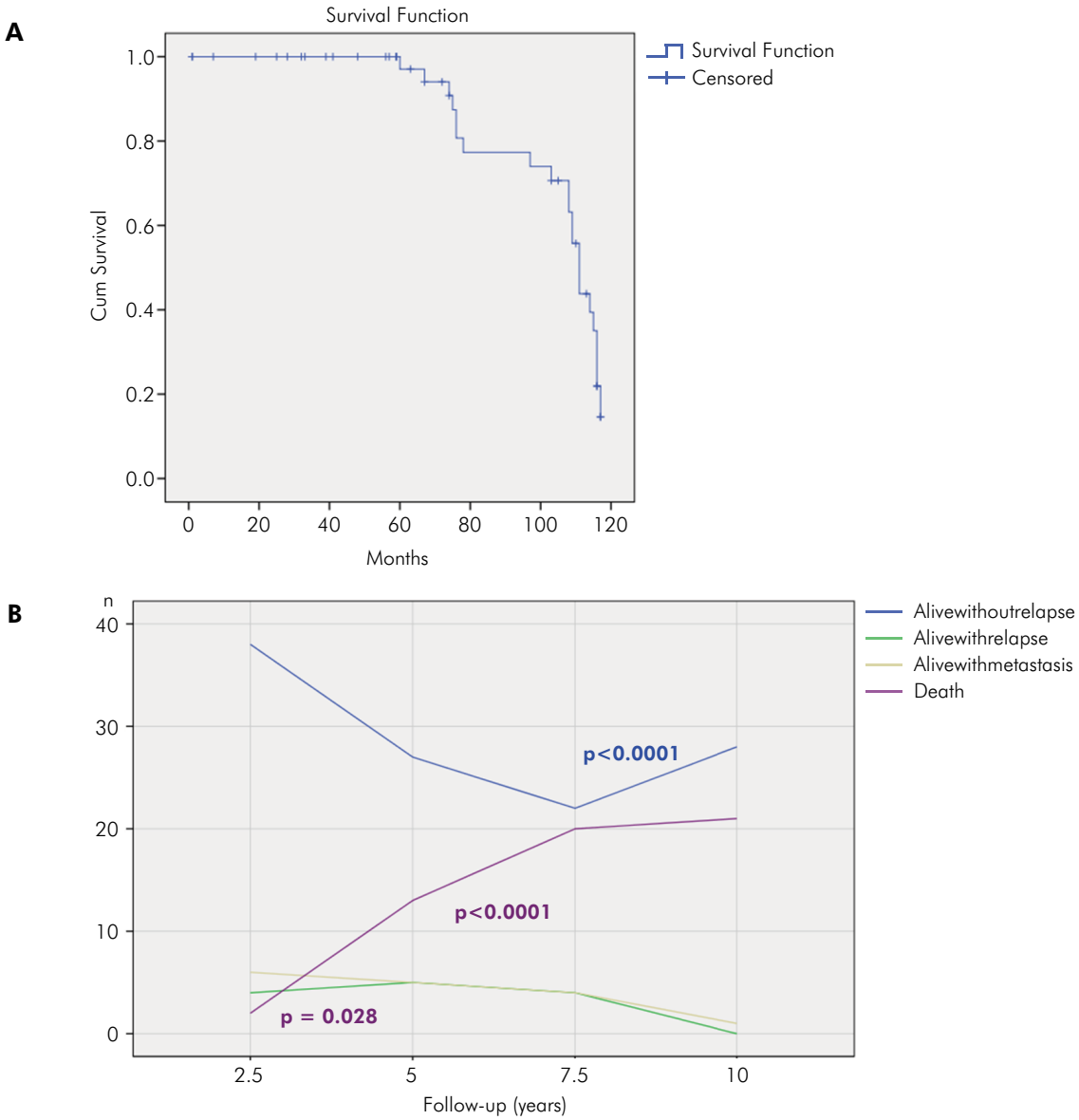

Figure 1. (a) Kaplan–Meier of global survival. *p* values from Kruskal-Wallis test, p ≤ 0.05; (b) Kaplan–Meier analysis showing evaluation of patients at the four time points of data collection. p values from Kruskal–Wallis test, p ≤ 0.05.

At 5 years, there was an association between tumor size < 4 cm (T1/T2) and a higher patient survival rate (F2, p=0.010). This association was not observed at other follow-up time points (F1, p = 0.217; F3, p = 0.514; F4, p = 0.439) (Figure 3).

Regional metastases were associated with higher patient survival in the follow-up period of up to 2.5 years (F1, p = 0.046). This relationship was not observed at other follow-up time points (F2, p = 0.378; F3, p = 0.084; F4, p = 0.311) (Figure 4).

The proportions of patients with good and poor prognoses were similar (44% and 42 %, respectively). At the end of the study, only 14% of the patients were discharged, whereas 44% remained under follow-up because of the presence of a potentially malignant disorder (PMD) at the primary tumor site, treatment for another tumor, and the presence of metastases (Table 1).

An association was observed between good prognosis and treatment with surgery alone (p = 0.022), tumor size < 4 cm (p = 0.005), absence of regional

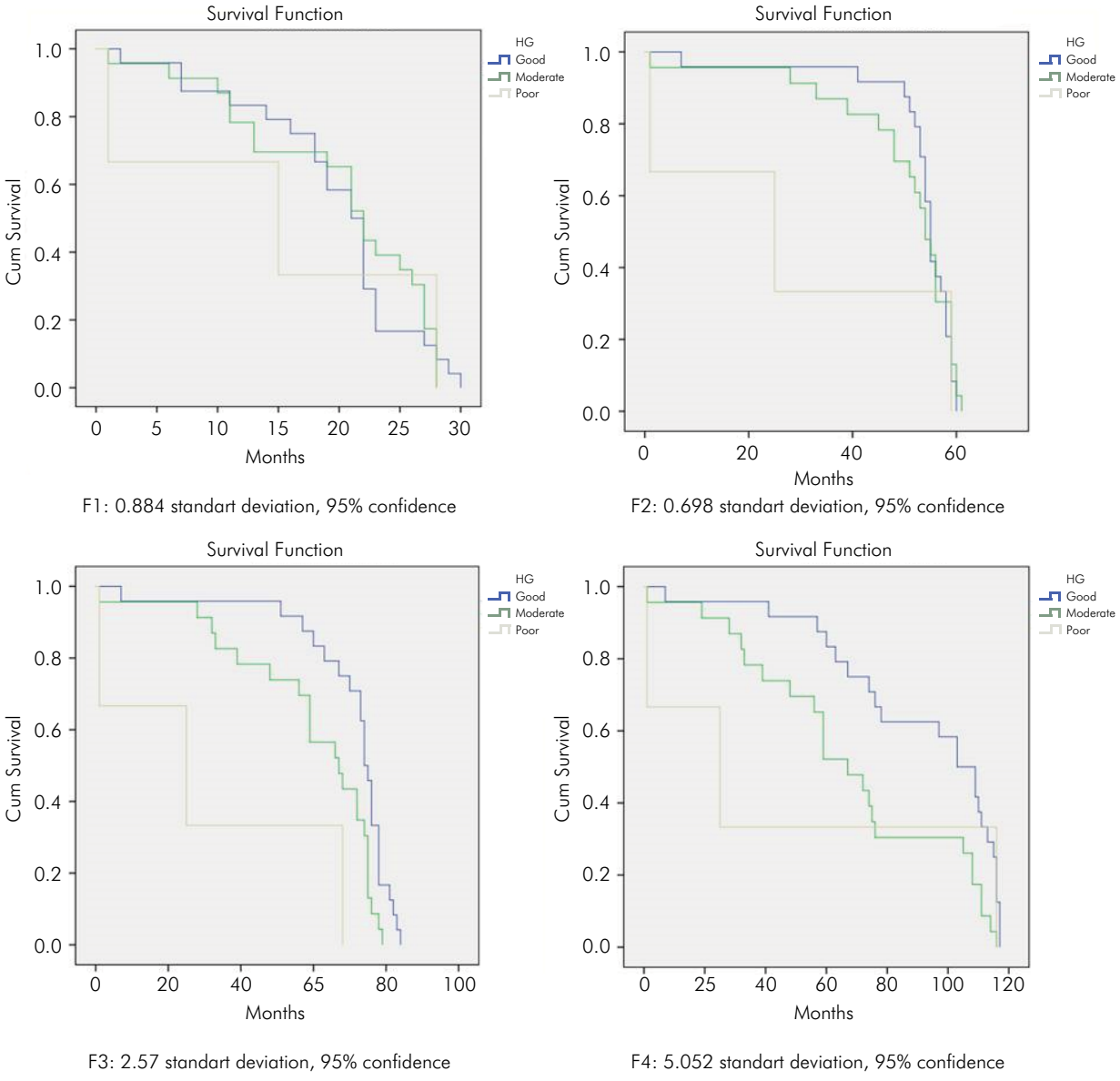

Figure 2. Kaplan–Meier survival curves at different follow-up time points according to the histopathological grade (HG).

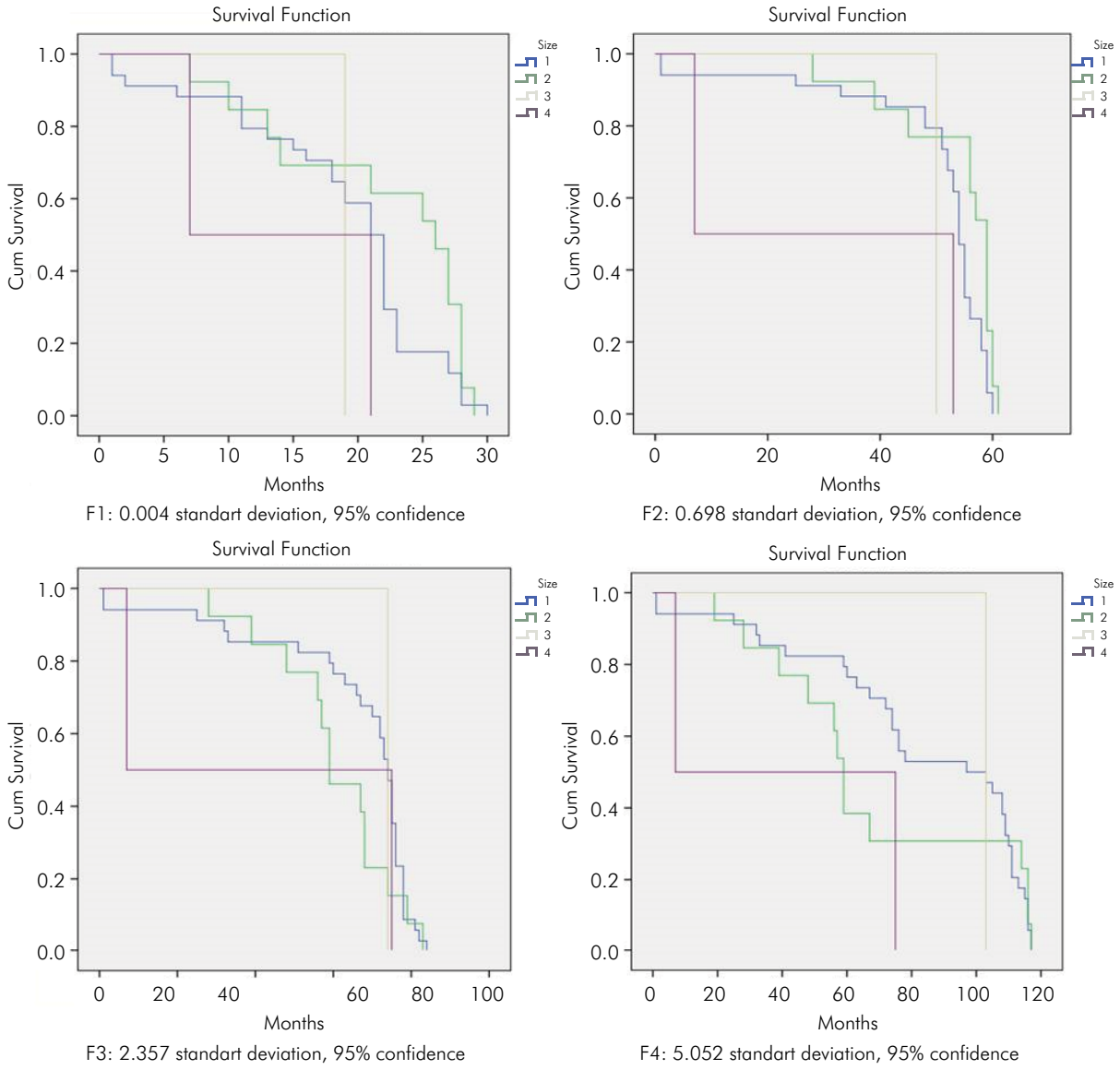

Figure 3. Kaplan–Meier survival curves at different follow-up time points according to the size of the primary tumor.

metastases (p=0.026), and tumors with a low degree of malignancy (p = 0.016). We observed an association trend between poor prognosis and T3 and T4 lesions in the mouth (p = 0.052). In cases of lip lesions, patients who underwent surgery alone showed a good prognosis (p = 0.035) and patients with N0 at the time of diagnosis had a good outcome (p = 0.035) (Table 2).

According to the tumor location, the patients had reserved and poor prognoses after 7.5 years of follow-up. The prognosis of patients with tumors located in the hypopharynx, buccal mucosa, palate, and floor of the mouth worsened after F3 (p = 0.045). At F4, the prognosis of patients with lip tumors also worsened (p = 0.002). Tumor location had no influence on prognosis for up to 7.5 years of follow-up (F1, p = 0.105; F2, p = 0.100) (Figure 5).

Discussion

We present the clinical evolution of 50 patients diagnosed with HNSCC in a 10-year follow-up study to determine how traditional prognostic factors correlate with patient survival at four distinct time

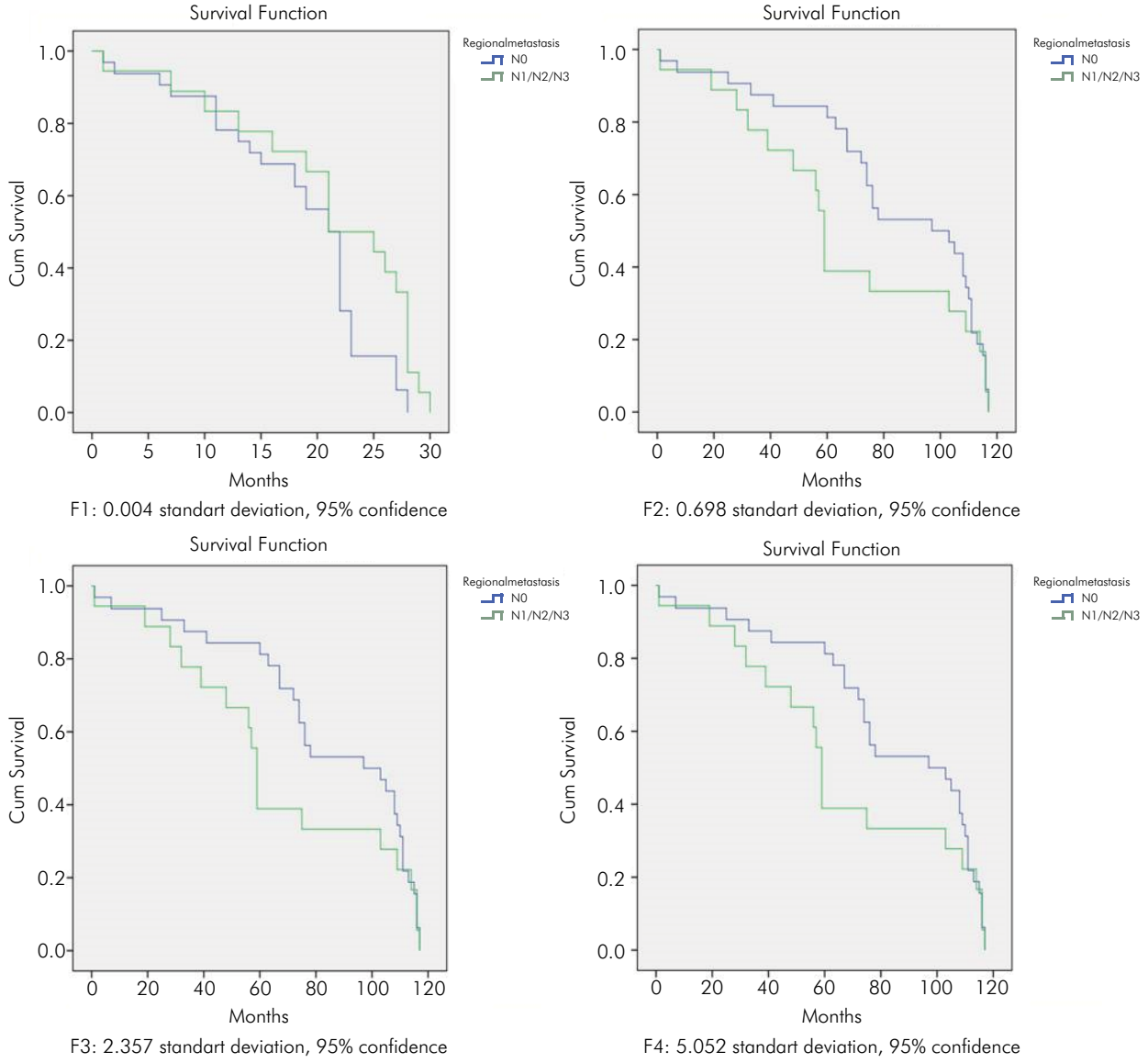

Figure 4. Kaplan–Meier survival curve showing the influence of a positive lymph node on the final clinical status of patients after a 10-year follow-up period.

points. The study contribute to the understanding of a disease with a heterogeneous clinical course.

An association between good prognosis and treatment with surgery alone, tumor size < 4 cm, absence of regional metastases, and a low degree of malignancy was observed in patients with a less advanced clinical stage of the primary tumor when treated with a single therapeutic modality (surgical removal of the tumor), and the patients did not develop secondary tumors. This finding indicates that better patient prognosis is a consequence of early diagnosis rather than surgical treatment. Patients with tumors in the neck area have been treated exclusively with radiotherapy, with good results in terms of quality of life, because avoiding mutilating surgery is a positive factor.[1,9]. An important aspect of therapy choice is bias in sample selection because studies on adjuvant therapies include patients who cannot be treated surgically (at advanced stages of the disease), which does not allow a comparison between modalities.[9]

In this study, 56% and 44% of the individuals were ex-smokers and former alcohol users, respectively.

Table 2. Association between patient prognosis over the 10-year follow-up period and clinical parameters, treatment modalities, and tumor histological grading.

Variable	Good	Reserved	Bad	Total	p-value	Full sample
Size						
Oral						
T1/T2	6	4	5	15		
T3/T4	2	0	8	10	0,052	
Neck						
T1/T2	5	1	3	9		Total: 50
T3/T4	1	0	5	6	0,156	p = 0,005
Lip						
T1/T2	7	1	0	8		
T3/T4	1	1	0	2	0,236	
Regional metastasis						
Oral						
N0	6	3	5	14		
N1/N2/N3	2	1	8	11	0,184	
Neck						
N0	4	1	4	9		Total: 50
N1/N2/N3	2	0	4	6	0,574	p = 0,026
Lip						
N0	8	1	0	9		
N1/N2/N3	0	1	0	1	*0,035	
Treatment						
Oral						
Surgery alone	7	4	5	16		
Other treatment	1	0	8	9	0,095	
Neck						
Surgery alone	4	1	4	9		Total: 50
Other treatment	2	0	4	6	0,486	p = 0,022
Lip						
Surgery alone	8	1	0	9		
Other treatment	0	1	0	1	*0,035	
Histopathological grading						
Oral						
Low	6	3	3	12		
Moderate	2	1	7	10		
Hight	0	0	3	3	0,109	
Neck						
Low	1	1	2	4		
Moderate	5	0	6	11		Total: 50
Hight	0	0	0	0	0,216	p = 0,016
Lip						
Low	6	2	0	8		
Moderate	2	0	0	2		
Hight	0	0	0	0	0,429	

*Pearson's chi-square test, $p \leq 0.05$.

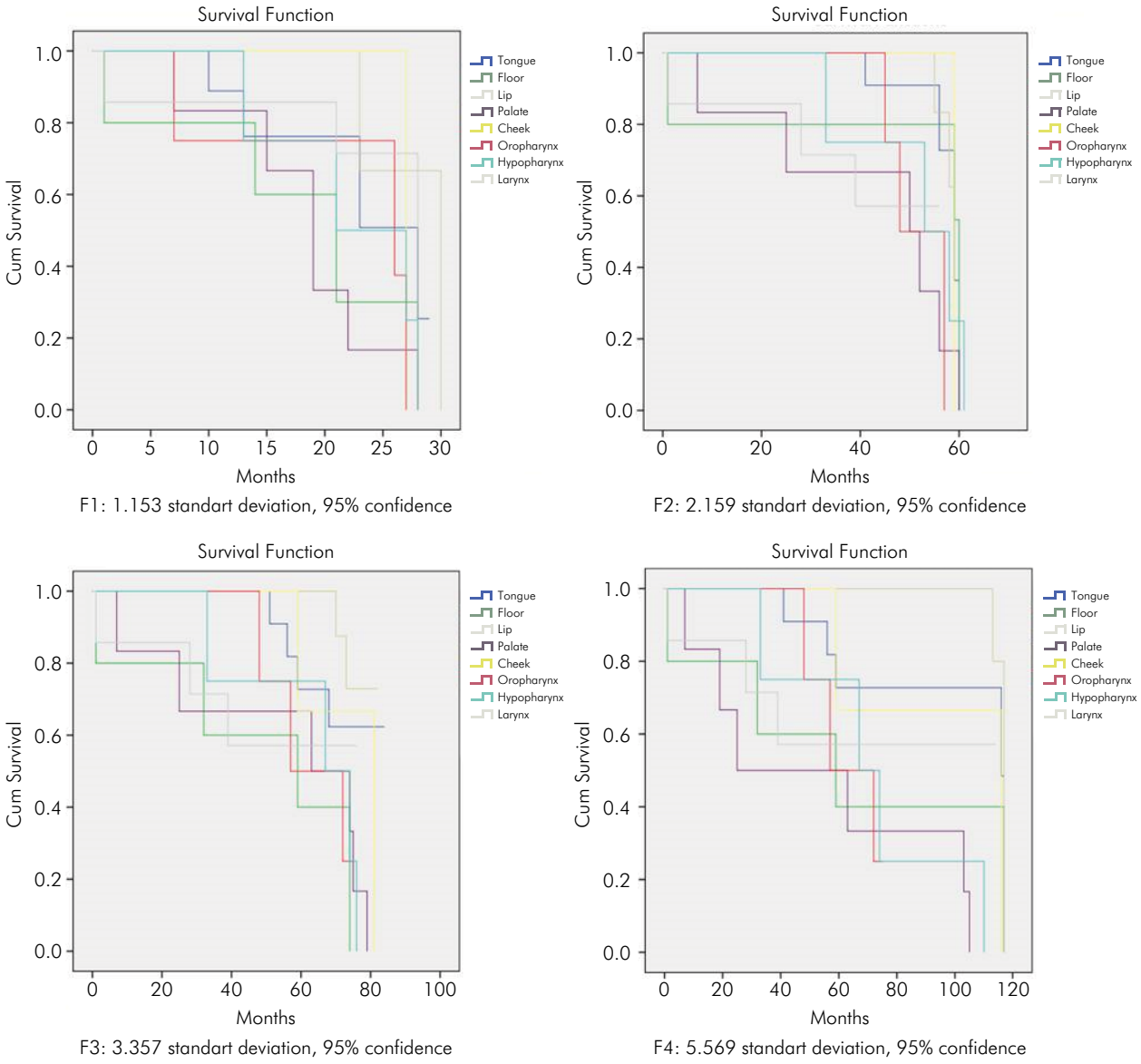

Figure 5. Kaplan–Meier survival curve showing the influence of tumor location on patient prognosis in the 10-year follow-up period.

However, an interesting finding was that cessation of these habits did not affect patient survival, probably because of the cumulative damage caused by these substances.[10] We found a worse prognosis after 7.5 years of follow-up for tumors that were strongly associated with smoking (hypopharynx and mouth).

The literature discusses the issue of the ideal follow-up time, as 45% of patients experience some type of secondary event after primary curative treatment. The traditional 5-year follow-up period is based on a consensus on guideline standardization and not on scientific evidence.[11,12] In line with this, we observed changes in the clinical status of patients up to nine years and nine months after the initial treatment.

The data obtained in this study showed a disparity between the percentage of patients diagnosed in the early stages of the disease (T1/T2 = 64%, N0 = 64%) and those discharged during hospital follow-up (14%) in the final period. With more than half of the patients diagnosed in the early stages, we expected a higher percentage of cures. Instead, 86% of patients had

potentially malignant disorders, relapsed, metastasis, or died.

The presence of regional metastases at the time of initial diagnosis was associated with higher patient survival at 2.5 years of follow-up with the use of a more aggressive therapeutic approach at this clinical stage to avoid the occurrence of secondary events. The authors believe that the development of undetectable regional metastases increased the number of deaths between 2.5 and five years.

In the present study, there was a relationship between tumor size < 4 cm and prolonged patient survival in the 5-year follow-up period, which is in line with the literature. However, due to the heterogeneous clinical behavior of HNSCC, the major cause of death was the development of regional metastases within 10 years.[1,11]

Additionally, important changes in the health status of patients were observed after five years, with a gradual increase in the number of deaths up to 7.5 years of monitoring and an increase in the number of living patients without recurrence after this time point, indicating that the disease may be controlled in cases of reserved prognosis. In such cases, the success of the oncological treatment strategy depends on the age of the patient and the presence of associated comorbidities.[13] However, in the present study, data on the presence of systemic diseases were not related to patient prognosis.

The mean age of the patients in the cohort was slightly lower than the overall mean age for HNSCC,[14] which may have contributed to disease control (even if a worsening prognosis was detected at specific time points). Given this fact, a follow-up longer than 5 years is also recommended as a result of the longer life expectancy, as the risk of secondary events related to the tumor increases with time.[6]

Many researchers have considered using a single follow-up routine for the entire head and neck. However, although there are common etiological factors for the entire anatomical structure, those that differ between sites affect both the course and prognosis of the disease.[11,15] In line with this, in the present study involving a heterogeneous sample of mouth and neck SCC, patient prognosis changed from good to poor after 7.5 years of follow-up in cases of hypopharynx, cheek mucosa, palate, mouth floor, and lip SCCs.

According to the literature, HG has a high prognostic value, with prognosis worsening with the rate of tumor undifferentiation.[8] We only observed an association between well-differentiated tumors and a good prognosis after 5 years of survival; we did not find an association between undifferentiated tumors and a worse prognosis. Thus, even if HG is relevant for the prediction of good long-term prognosis, its predictive ability in patients with poor HG requires improvement. This difficulty was encountered in the present study because only 14% of the patients were discharged after 10 years of follow-up.

HPV status is an important factor in guiding therapeutic decision-making with respect to patient monitoring and predicting patient survival. Although the literature refers to HNSCC as a single disease, HPV-positive tumors of the oropharynx have distinct microscopic and molecular characteristics and a definite clinical course.[16] This study had a bias. HPV infection was not evaluated in the initial data collection because it was only in 2017 that the new TNM classification, considering its important role in patient staging, was published.[17]

The 8th TNM edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system introduced the tumor depth of invasion (DOI) at the T stage and the incorporation of extracapsular spread (ECS) at the N stage to improve its prognostic value.[18,19] Because the present study was retrospective, data referring to pretreatment imaging examinations and access to histological slides were no longer possible, and we were unable to reclassify the samples using the 8th TNM edition. Despite this limitation, we believe that the follow-up period of the patients was longer than that in previous studies.[19,20]

Therefore, the cohort was classified according to the 7th edition, which does not consider pathological findings, such as the DOI of the primary tumor or tumor ECS in cervical lymph node metastasis. Although previous studies failed to find a direct relationship between the DOI and prognosis, they found a strong correlation between the DOI and the risk of nodal metastasis, especially in early stage

tumors.[19,20] In the present study, several patients progressed from less advanced to more advanced cancer stages during the follow-up period and had similar or better survival rates. Patients with higher N1 stage had improved 5-year survival rates, probably because of the association between surgery and neck dissection, radiotherapy, and/or chemotherapy during the second treatment. This change in treatment planning is an advantage of the new 8th edition classification over the previous one; upstaging T1 to T2 is decisive, as T1 patients could be at risk of developing occult metastatic lymph nodes and locoregional recurrences [20]. Tumor staging is essential as it provides guidelines for the treatment and management of patients. In the present study, analysis of the 10-year follow-up showed that traditional prognostic factors were not accurate in detecting subclinical changes or predicting patient prognosis.[6]

Over the last three decades, the panorama of HNSCC etiopathogenesis has changed. Early exposure to risk factors has made the disease more common among young adults,[21] and the differences in prognosis between analyses of anatomical areas[15,22,23] and advances in knowledge of tumor molecular biology[24] support the idea that the disease should be studied and analyzed on an individual basis. Because the outcome of HNSCC is difficult to predict [3], the knowledge of factors that reflect the biological profile of the disease and changes in its behavior over time are important for improving patient survival.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 May;71(3):209-49. https://doi.org/10.3322/caac.21660
2. Bezerra NV, Leite KL, Medeiros MM, Martins ML, Cardoso AM, Alves PM, et al. Impact of the anatomical location, alcoholism and smoking on the prevalence of advanced oral cancer in Brazil. Med Oral Patol Oral Cir Bucal. 2018 May;23(3):e295-301. https://doi.org/10.4317/medoral.22318
3. Duffy MJ, Crown J. Precision treatment for cancer: role of prognostic and predictive markers. Crit Rev Clin Lab Sci. 2014 Feb;51(1):30-45. https://doi.org/10.3109/10408363.2013.865700
4. Gaździcka J, Gołąbek K, Strzelczyk JK, Ostrowska Z. Epigenetic Modifications in Head and Neck Cancer. Biochem Genet. 2020 Apr;58(2):213-44. https://doi.org/10.1007/s10528-019-09941-1
5. Saada-Bouzid E, Peyrade F, Guigay J. Molecular genetics of head and neck squamous cell carcinoma. Curr Opin Oncol. 2019 May;31(3):131-7. https://doi.org/10.1097/CCO.0000000000000536
6. Li Y, Ju J, Liu X, Gao T, Wang Z, Ni Q, et al. Nomograms for predicting long-term overall survival and cancer-specific survival in patients with major salivary gland cancer: a population-based study. Oncotarget. 2017 Apr;8(15):24469-82. https://doi.org/10.18632/oncotarget.14905
7. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology 2010; 17: 1471-1474. https://doi.org/10.1245/s10434-010-0985-4
8. Bryne M, Koppang HS, Lilleng R, Kjaerheim A. Malignancy grading of the deep invasive margins of oral squamous cell carcinomas has high prognostic value. J Pathol. 1992 Apr;166(4):375-81. https://doi.org/10.1002/path.1711660409
9. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head Neck. 2014 Jan;36(1):144-51. https://doi.org/10.1002/hed.23227
10. Rogers SN, Swain A, Carroll C, Lowe D. Incidence, timing, presentation, treatment, and outcomes of second primary head and neck squamous cell carcinoma after oral cancer. Br J Oral Maxillofac Surg. 2019 Dec;57(10):1074-80. https://doi.org/10.1016/j.bjoms.2019.09.018
11. Brands MT, Brennan PA, Verbeek ALM, et al. Follow-up after curative treatment for oral squamous cell carcinoma: a critical appraisal of the guidelines and a review of the literature. Eur J Surg Oncol. 2018 May;44(5):559-65. https://doi.org/10.1016/j.ejso.2018.01.004

12. Brands MT, Smeekens EA, Takes RP, Kaanders JH, Verbeek AL, Merkx MA, et al. Time patterns of recurrence and second primary tumors in a large cohort of patients treated for oral cavity cancer. Cancer Med. 2019 Sep;8(12):5810-9. https://doi.org/10.1002/cam4.2124
13. Bossi P, Alfieri S, Strojan P, Takes RP, López F, Mäkitie A, et al. Prognostic and predictive factors in recurrent and/or metastatic head and neck squamous cell carcinoma: A review of the literature. Crit Rev Oncol Hematol. 2019 May;137:84-91. https://doi.org/10.1016/j.critrevonc.2019.01.018
14. Peres MA, Daly B, Guarnizo-Herreño CC, Benzian H, Watt RG. Oral diseases: a global public health challenge - Authors' reply. Lancet. 2020 Jan;395(10219):186-7. https://doi.org/10.1016/S0140-6736(19)32997-6
15. Almangush A, Mäkitie AA, Triantafyllou A, de Bree R, Strojan P, Rinaldo A, et al. Staging and grading of oral squamous cell carcinoma: an update. Oral Oncol. 2020 Aug;107:104799. https://doi.org/10.1016/j.oraloncology.2020.104799
16. Huang SH, O'Sullivan B. Overview of the 8th Edition TNM Classification for Head and Neck Cancer. Curr Treat Options Oncol. 2017;18: 40. https://doi.org/10.1007/s11864-017-0484-y
17. Doescher J, Veit JA, Hoffmann TK. [The 8th edition of the AJCC Cancer Staging Manual : updates in otorhinolaryngology, head and neck surgery]. HNO. 2017 Dec;65(12):956-61. German. https://doi.org/10.1007/s00106-017-0391-3
18. Tagliabue M, De Berardinis R, Belloni P, et al. Oral tongue carcinoma: prognostic changes according to the updated 2020 version of the AJCC/UICC TNM staging system. Acta otorhinolar Italica. 2022;42:140-9. https://doi.org/10.14639/0392-100X-N2055
19. Matos LL, Dedivitis RA, Kulcsar MA, Mello ES, Alves VAF, Cernea CR. External validation of the AJCC Cancer Staging Manual, 8th edition, in an independent cohort of oral cancer patients. Oral oncology 2017; 71: 47-53. https://doi.org/10.1016/j.oraloncology.2017.05.020
20. Ghantous Y, Nashef A, Sidransky D, Abdelraziq M, Alkeesh K, Araidy S, et al. Clinical and prognostic significance of the eighth edition oral cancer staging system. Cancers 2022; 14. https://doi.org/10.3390/cancers14194632
21. Challapalli SD, Simpson MC, Adjei Boakye E, Pannu JS, Costa DJ, Osazuwa-Peters N. Head and neck squamous cell carcinoma in adolescents and young adults: survivorship patterns and disparities. J Adolesc Young Adult Oncol. 2018 Aug;7(4):472-9. https://doi.org/10.1089/jayao.2018.0001
22. Panarese I, Aquino G, Ronchi A, Longo F, Montella M, Cozzolino I, et al. Oral and oropharyngeal squamous cell carcinoma: prognostic and predictive parameters in the etiopathogenetic route. Expert Rev Anticancer Ther. 2019 Feb;19(2):105-19. https://doi.org/10.1080/14737140.2019.1561288
23. Silveira EJ, Godoy GP, Lins RD, Arruda ML, Ramos CC, Freitas RA, et al. Correlation of clinical, histological, and cytokeratin profiles of squamous cell carcinoma of the oral tongue with prognosis. Int J Surg Pathol. 2007 Oct;15(4):376-83. https://doi.org/10.1177/1066896907304992
24. Ragin CC, Langevin SM, Marzouk M, Grandis J, Taioli E. Determinants of head and neck cancer survival by race. Head Neck. 2011 Aug;33(8):1092-8. https://doi.org/10.1002/hed.21584