Original Research
Stomatology

Prognostic factors from squamous cell carcinoma of the hard palate, gingiva and upper alveolar ridge

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Abstract: The purpose of this study was to evaluate the clinicodemographic characteristics and treatment protocol as prognostic factors in patients with oral squamous cell carcinoma (OSCC) of the hard palate, upper gingiva, and alveolar ridge (HPUGAR). This retrospective cohort study collected data of patients treated in two head and neck surgery departments in southern Brazil between 1999 and 2021. Information on clinicodemographic data, habits, site, size, clinical aspect, clinical staging, cervical metastasis, treatment, and survival was collected. Associations between independent variables and outcomes were assessed using Pearson's chi-square test and binary regression. Kaplan–Meier test was employed to compare the survival between the neck approaches. Forty-one patients were included; most were male (61%), with a mean age of 68.8 (± 13.9) years. The consumption of tobacco ($p = 0.003$) and alcohol ($p = 0.02$) was significantly higher in male than in female patients. The main clinical features observed in the study sample were lesions larger than 2 cm (48.7%), no cervical (90.2%), or distant metastasis (90.2%). Surgery alone was the main treatment approach (48.8%). The watch-and-wait strategy was adopted in 34 cases (83.0%), while elective neck dissection was applied in five (12.2%). Only two patients with cN0 disease (4.9%) presented with cervical metastasis at follow-up. Eight patients (12.2%) died of the disease. Clinicodemographic variables, habits, surgical margins, and histological subtype were not significantly associated with cervical metastasis or survival. Cervical metastasis ($p = 0.004$) was associated with poor survival. No difference was detected in survival between different neck approaches ($p = 0.28$). Cervical metastasis and local recurrence are negative prognostic factors for HPUGAR OSCC.

Keywords: Carcinoma, Squamous Cell; Head and Neck Neoplasms; Alveolar Process; Palate, Hard.

Introduction

Oral cancer represents 2% of all cancers, and in 2018, 354,864 new cases were diagnosed worldwide.[1] In Brazil, approximately 15,000 new cases are expected every year.[2] Among the malignancies affecting the oral cavity, oral squamous cell carcinoma (OSCC) is the most prevalent.[1] A higher incidence of OSCC is observed in Southeast Asia, especially India. This

may be explained by the increased consumption of tobacco and its derivatives, together with high alcohol consumption, two of the leading causes of oral cancer.[1]

The occurrence of OSCC in the hard palate, upper gingiva, and alveolar ridge (HPUGAR) is uncommon, accounting for approximately 9% of all cases.[3] Because of its lower prevalence, few case series have been reported, resulting in scarce literature regarding its clinical and demographic characteristics, prognostic factors in survival, and treatment protocol.[4-6] Generally, the treatment of OSCCs in the HPUGAR depends on the tumor size, anatomical location, disease staging, tumor thickness, patient age, degree of differentiation, nodal metastasis, and extracapsular spread.[7] Surgery is the treatment of choice for cervical lymph node removal. Adjuvant radiotherapy with or without chemotherapy is occasionally performed.[7,8] In terms of management, there is a critical dilemma regarding the necessity of elective neck dissection (END). At diagnosis, approximately 69.7% of these tumors are detected without cervical metastasis (cN0), and cervical dissection is usually not indicated or performed.[9,10] However, recent studies have shown that there may be hidden metastases in 21% to 42.9% of cases. Additionally, 64% of these metastases may occur in the first year after treatment.[6,9,10] In light of these data, currently, two treatment strategies are followed: "watch-and-wait" and END.[9,11,12]

The "watch-and-wait" approach in the cN0 neck consists of performing surgical treatment to control the tumor locally, followed by a rigorous follow-up and careful observation of the primary tumor location and the neck.[9,10] Advocates of this strategy claim that END is a treatment approach that may cause postsurgical comorbidities. The "watch-and-wait" strategy is usually followed by radiotherapy. Furthermore, tumor recurrence rates in the neck may vary considerably. In terms of scientific evidence on this topic, few case series are available.[13-15]

However, advocates of END claim that cervical metastasis rates are high after the "watch-and-wait" approach, ranging from 21% to 42.9%.[5,12,16,17] According to the available literature, neck dissection should be performed in tumors with cervical metastasis rates higher than 20%.[5,18] Recent studies have reported a higher survival rate in patients who underwent END than in those who did not.[12,19] Additionally, a more significant number of cervical metastases have been reported in T2 and T3 OSCCs of the HPUGAR and cases of perineural and perivascular invasion.[5,20] Considering this controversial scientific evidence, this retrospective cohort study aimed to analyze the clinicopathological characteristics and treatment protocols as prognostic factors of OSCC in the HPUGAR in a southern Brazilian population. Based on previous reports, cervical metastasis seems to be an important prognostic factor for OSCC in the HPUGAR. Persistence of local disease may also play an important role in survival.

Methodology

This retrospective cohort study was approved by the Ethics Committee on Human Research of Complexo Hospitalar Santa Casa de Misericordia de Porto Alegre and Ana Nery Hospital Ethics Committee (CAAE:76804117.7.0000.5335), (CAAE: 44857021.7.0000.5343).

Study population

This was a convenience sample with a total of 44 patients with clinical and histopathological diagnoses of primary OSCC (International Classification of Disease for Oncology code 8070/3) of the HPUGAR, who attended the head and neck department of Santa Casa de Misericordia de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil, between January 1999 and January 2019, and the same department in Ana Nery Hospital, Santa Cruz do Sul, Rio Grande do Sul, Brazil, between 2011 and 2021. Of these, 41 were included in the present study owing to their complete and available medical records. The following information was manually collected with the help of a standardized data collection form: patient profile (age, sex, occupation, skin color, and housing), medical history, habits (smoking, alcoholism), clinical information (date of diagnosis, clinical aspect, pain, size, regional metastasis, and distant metastasis), histopathological aspects (histologically differentiated grade and histological subtype), staging (American Joint Committee on

Cancer, TNM 8th edition), primary tumor treatment, neck dissection, recurrence (yes or no), treatment of relapse, and clinical outcome. Follow-up information was collected using medical records for consultations and phone calls. The data were collected by L.N.S.K, F.M.G, and V. G. Z. At the end of data collection, all three collectors evaluated the data and established a consensus about the data register.

Inclusion criteria

All patients treated at the head and neck surgery department of the Irmandade Santa Casa de Misericordia de Porto Alegre and Ana Nery Hospital diagnosed with OSCC of the HPUGAR, who had the data required for this research available in their medical records, were included.

Exclusion criteria

Patients diagnosed with OSCC at sites other than those of interest to the present study. Cases in which disease progression led the lesion to reach the HPUGAR locations. Patients whose clinical information regarding staging, habits, treatment, and prognosis was not available in the medical records.

Statistical analysis

A descriptive analysis of all collected variables was performed. Associations between the outcomes and independent variables were assessed using binary regression and Pearson's chi-square test, with a 5% significance level. Univariate survival analysis was performed using the Kaplan–Meier method. SPSS software (version 15.0, SPSS Inc., Chicago, USA) was used for all statistical analyses.

Results

Overall characteristics

Forty-one eligible patients were included in the study. The patients' overall characteristics and information regarding their disease and treatment are described in Table 1. Men represented 61.0% of the sample, while women represented 39.0%. The mean age was 68.8 ± 13.9 (ranging from 45 to 95) years at the time of diagnosis. Regarding potential etiological factors, tobacco use was mentioned by 46.3% of the patients and alcohol consumption by 34.1%. Table 2 illustrates the associations between the patient's sex and tobacco and alcohol consumption. The consumption of tobacco ($p = 0.003$) and alcohol ($p = 0.02$) was significantly higher in male than in female patients.

In general, patients exhibited ulcerative lesions (36.6%) larger than 2 cm (48.7%), without regional (cN0) (90.4%) or distant metastasis (90.2%) and were classified as stage III or IV tumors (51.2%).

Treatment and neck management

For local control, surgery was the only treatment in 20 cases (48.8%) and was associated with radiotherapy in 13 patients (31.7%). END was employed in five (12.2%) of the 37 cN0 cases for neck management. The "watch-and-wait" strategy was adopted in 83% of cN0 cases. Neck dissection was performed in one case because of clinical confirmation of neck metastasis, and one patient received radiotherapy (Table 1).

Histological differentiated grade and surgical margins

Well-differentiated SCC was the most prevalent histological profile (59.0%), followed by moderately differentiated SCC (30.8%). Most cases (61%) had free margins (Table 1).

Follow-up, local recurrence, cervical metastasis, and survival predictors

The median follow-up time was 42 months (range, 2–97 months). During the follow-up period, eight patients (19.5%) experienced local recurrence. The statistical analysis did not show an association, but a trend was observed between poor survival and local recurrence ($p = 0.051$). Only two patients (4.9%) with cN0 presented with cervical metastasis at follow-up, and one patient with cN2b developed a new cervical metastasis. For neck metastasis treatment, one patient underwent neck dissection followed by radiotherapy, one underwent neck dissection only, and one underwent neck dissection along with radiotherapy followed by chemotherapy. Eight (19.5%) patients died of the disease.

The association between cervical metastasis during follow-up and survival was statistically significant

Table 1. Overall profile of patients diagnosed with squamous cell carcinomas in the hard palate, superior gingiva, and alveolar ridge (n = 41).

Variable	
Sex	n (%)
Male	25 (61.0)
Female	16 (39.0)
Age, in years	Mean ± SD
	68.8 ± 13.9
Range	45–95
Residence	n (%)
Urban	18 (43.9)
Rural	3 (7.3)
Not informed	20 (48.8)
Smoking status	n (%)
Yes/former user	19 (46.3)
No	10 (24.4)
Not informed	12 (29.3)
Alcohol status	n (%)
Yes/former user	14 (34.1)
No	15 (36.6)
Not informed	12 (29.3)
Site	n (%)
Hard palate	21 (51.2)
Upper alveolar ridge	8 (19.5)
Gingiva	12 (29.3)
Clinical aspect	n (%)
Ulcer	15 (36.6)
Nodule	5 (12.2)
Patch	2 (4.9)
Not informed	19 (46.3)
Pain	n (%)
Yes	17 (41.5)
No	3 (7.3)
Not informed	21 (51.2)
Tumor size	n (%)
T1	8 (19.5)
T2	11 (26.8)
T3	6 (14.6)
T4	14 (34.1)
Tis	1 (2,4)
Not informed	1(2.4)
Node	n (%)
N0	37 (90.4)
N 2b	1 (2.4)
N 3b	1 (2.4)
X	1 (2.4)
Not informed	1 (2.4)
Distant metastasis	n (%)
Yes	1 (2.4)
No	37 (90.2)
Not informed	3 (7.3)
Clinical Stage (TNM)	n (%)
Stage Tis, I and II	19 (46.3)
Stage III/IV	21 (51.2)
Not informed	1 (2.5)
Cellular differentiation, n = 39	n (%)
Well-differentiated	23 (59.0)
Moderately differentiated	12 (30.8)
Poorly differentiated	4 (10.2)
Treatment	
Surgery	20 (48.8)
Surgery + RT	13 (31.7)
Surgery + RT + CH	6 (14.6)
RT + CH	2 (4.9)
Surgical margins status	n (%)
Free	25 (61.0)
Narrow	2 (4.9)
Compromised	10 (24.3)
Not informed	4 (9.8)
Neck management	n (%)
Elective neck dissection	5 (12.2)
Watch and wait	34 (83.0)
Neck dissection	1 (2.4)
Radiotherapy	1 (2.4)
Cervical metastasis	n (%)
No	29 (70.7)
Yes	3 (7.3)
Not Informed	9 (22.0)
Local recurrence	n (%)
Yes	8 (19.5)
No	18 (43.9)
Not informed	15 (36.6)
Survival	n (%)
Alive	29 (70.7)
Died from the disease	8 (19.5)
Lost to follow-up	4 (9.8)

Continue

Table 2. Association between sex and use of tobacco and alcohol.

Variable	Tobacco - n(%)	No tobacco - n(%)	p-value	95%CI*	Alcohol - n(%)	No alcohol - n(%)	p-value	95%CI*
Male	17 (89.5%)	3 (30.0%)		1	13 (92.9%)	7 (46.7%)		1
Female	2 (10.5%)	7 (70.0%)	0.003	0.050 0.07–0.370	1 (7.1%)	8(53.3%)	0.02	0.067 (0.007–0.65)

*Binary logistic regression; CI: confidence interval.

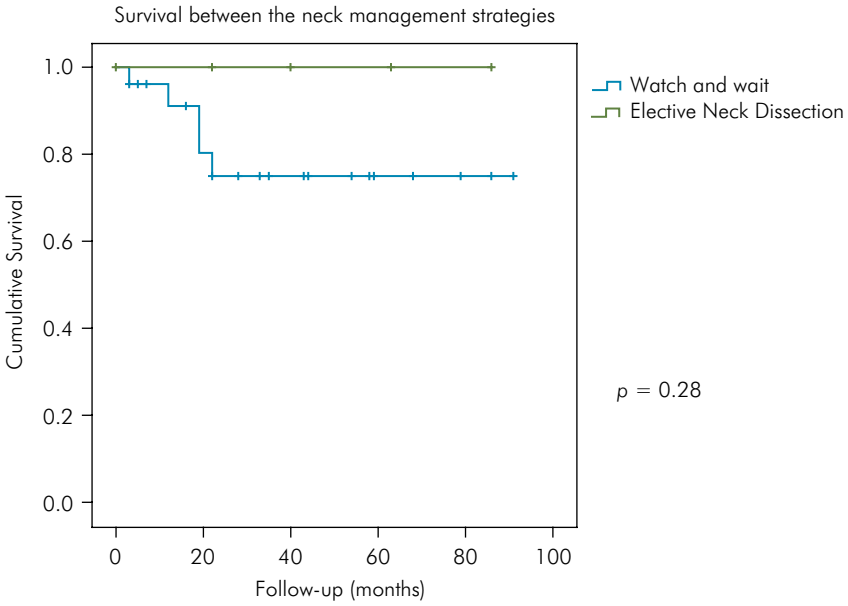

Figure 1. Survival in each neck management strategy.

(p=0.004). Clinicodemographic variables, habits, surgical margins, and histological subtype did not reveal a significant association with survival. Cervical metastasis was not associated with clinicopathological variables, habits, margins, or histological subtype. Kaplan–Meier analysis did not show significantly different survival rates between the "watch-and-wait" and END strategies (p = 0.28) (Figure).

Discussion

OSCCs of the HPUGAR are unusual, representing only 9% of oral cavity carcinomas.[3] The objectives of this study were to evaluate the main prognostic clinical factors for OSCC in this location and to compare the survival between the two neck management strategies. Unlike other sites of OSCC, such as the tongue and floor of the mouth, HPUGAR tumors usually present cN0 at diagnosis and have a favorable prognosis.[21,22] Based on this, the neck treatment approach usually involves the "watch-and-wait" strategy.[23] However, recent studies have questioned this option and suggested END.[6,9,12,15] The present cohort study evaluated 41 new cases of OSCC of the HPUGAR from two centers in south Brazil to elucidate the main clinicopathological aspects, treatment characteristics, and some prognostic factors, including the neck approach. The tumors were diagnosed in an advanced clinical stage, but only eight patients died of the disease. Clinicodemographic variables, habits, surgical margins, and histological subtype were not significantly associated with poor survival. Regarding neck management, "watch-and-wait" was the most adopted strategy. In the survival analysis, the two neck management strategies, "watch-and-wait" and END, did not indicate significant differences.

During follow-up, neck metastasis was significantly associated with poor survival, following the tendency of other head and neck sites.[21,24,25] Local recurrence was also significantly associated with poor survival; this association was previously reported in OSCCs of the HPUGAR.[23]

The clinical profile was characterized by mostly men (61%), with a mean age of 68.8 years and a smoking habit (46.3%). Surprisingly, the proportion of non-alcoholics was 36.6%. However, it is also crucial to consider that this variable was uninformed for several patients (29.3%). According to the literature, the clinical profile observed in this study follows the recognized characterization of patients with oral cancer: usually men, between the fifth and sixth decade of life, with smoking habits.[26-28] These well-established characteristics may be explained by the higher susceptibility of men to consume cancer promoting products, such as tobacco and alcohol. According to the current scientific evidence, the correlation of oral cancer with alcohol and tobacco consumption is unrestricted to the tumors of the HPUGAR.[7,12,27,29]

Late diagnosis of oral cancer integrates the current health scenario in Brazil. Diagnosis is usually performed when the lesions are in the T3 or T4 stage.[30] Similarly, the present study observed the frequencies of 14.6% and 34.1% for T3 and T4 tumors, respectively. However, late diagnosis seems to be a reality in most countries worldwide. Regarding tumors located in the HPUGAR, studies in the USA, Canada, and France have reported incidence rates of 57.1%, 56%, and 65.3%, respectively.[16,31,32] Tumors with an advanced T stage make the surgical treatment much more aggressive, even though surgery alone remains the gold standard.

Furthermore, surgery (48.8%) is the most commonly performed treatment in the two centers that provided data to this cohort study.[4,13,20,23] In this study, surgery with adjuvant radiotherapy was the second most frequently performed treatment for local disease control (31.7%). No association was identified between the local treatment strategies and survival. In contrast, Alonso et al.[8] reported favorable predictors of overall survival and disease-specific survival ($p < 0.05$) in patients who underwent surgery with or without radiotherapy in the primary location.[8] In the present study, 90.4% of patients presented with cN0 at the time of diagnosis, following the tendency of these tumors reported in other studies.[6,9,16,33]

Eight patients (19.5%) presented with a local recurrence. Of these eight, three died of the disease. This cohort showed a trend between local recurrence and poor survival ($p = 0.051$). It is necessary to note the small sample size of the study population; this limitation prevents the establishment of a causal relationship. However, is important to mention that local control is usually considered a crucial factor for a favorable prognosis. As observed in the study by Park et al.,[26] the authors demonstrated a positive correlation between death and unsuccessful local recurrence control, with only a 33.3% success rate.[23]

Cervical metastasis is a significant prognostic factor for OSCC.[24,34] During follow-up (40.1 months), only three patients presented with cervical metastasis; two patients with cN0 (4.9%) at the time of diagnosis and one with cN2b at the time of diagnosis developed a new cervical metastasis at follow-up. Eight patients (19.5%) died of the disease, and a significant correlation was detected between poor survival and cervical metastasis at follow-up ($p = 0.004$). All three patients with cervical metastasis died of the disease. Considering this, it is reasonable to affirm that cervical metastasis is an unfavorable prognostic factor for OSCC, which also applies to the HPUGAR locations.[12,24,35]

Literature has been compelling at recommending END for tumors with a cervical metastasis rate equal to or higher than 20%.[21,34] The "watch-and-wait" strategy for neck management was the most adopted strategy in this cohort (83.0%). Reported rates of cervical metastasis in HPUGAR until 2011 were less than 20% since the "watch-and-wait" strategy was consistently adopted.[5] In the present cohort, END was performed in five patients because of clinical suspicion of cervical metastasis. Considering the 20% criteria, the data presented here do not recommend END for HPUGAR tumors since the cervical metastasis rate was only 4.9% in our cohort.

To date, several studies have reported HPUGAR cervical metastasis rates higher than 20%, including studies by Montes et al.,[6] 42.9%; Kruse et al.,[17] 36.7%; Cariati et al.,[9] 34.4%; and Beltrami et al.,[5] 21%. These high rates motivated us to conduct the present

research. In these studies, END was recommended for all of these tumors, even those that were in the early T stages.[5,6,9,17] However, other authors have recommended END only in advanced-stage tumors. Moreno-Sánchez et al.[36] reported a rate of 45% for cervical metastases in T3/T4 tumors. Similarly, Yang et al.[11] observed a rate of 20% to 40% and recommended END for tumor stage ≥T2.[20,36-38] In the present cohort analysis, there was no significant correlation between the T stage and cervical metastasis.

Regarding the neck management strategy, Givi et al.[33] reported significantly higher survival rates in patients who underwent END ($p = 0.026$). In this study, Kaplan–Meier analysis showed no significant difference in survival between the two neck management strategies ($p = 0.28$). The findings of several previous studies support the "watch-and-wait" strategy. Hakim et al.[13] reported a 5-year overall survival rate of 88.9% in patients managed with this approach, and 72.4%. for treated with END. Likewise, Park et al.[23] did not recommend END because of the cervical metastasis rate of 14.9% in their study. The authors also highlighted the struggle of locally controlling the disease and the relevance of early diagnosis of cervical metastasis [23]. The importance of early diagnosis and periodic follow-up was also emphasized by van Os et al.[14] In their study, 26 patients presented with cervical metastasis during follow-up, 22 were successfully operated, one case was inoperable, and the remaining were treated with radiotherapy.[14] Nevertheless, neck metastasis was the main unfavorable prognostic factor for patients included in the present study. Early diagnosis could change this scenario, as indicated by Park et al.,[26] who attributed the success of this strategy to neck metastasis control and also proposed periodical surveillance with ultrasound examinations.[23]

Cellular differentiation and margin status, respectively, were not associated with survival and cervical metastasis, but previous studies have reported otherwise. A significant overall survival rate was detected in patients who had surgical free margin was demonstrated by Yang et al.[37] A compromised surgical margin is a negative prognostic factor, as revealed by Hakim et al.[13] Poorly differentiated tumors seem to be a negative prognostic factor, similar to lymphatic infiltration.[16,39]

This study has some clear limitations, such as the small sample size, attributed to low disease prevalence. This may have limited the statistical tests, preventing statistical differences in clinical variables and survival from being detected.

Conclusion

No significant difference in survival was observed between the two neck management strategies, that is, "watch-and-wait", which includes treating the primary tumor and clinically monitoring the neck and END. However, neck metastasis continues to be an unfavorable prognostic factor. Rigorous follow-up might be an appropriate strategy for early identification and treatment of neck metastasis and local recurrence. Campaigns that advocate early diagnosis and limiting alcohol and tobacco consumption are necessary to decrease oral cancer incidence and increase survival rates.

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