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ORIGINAL ARTICLE

Oral cavity squamous cell carcinoma: factors related to occult lymph node metastasis☆,☆☆

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KEYWORDS
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Abstract
Introduction: Elective neck dissection is recommended in cases of oral cavity squamous cell carcinoma without lymph node metastasis because of the risk of occult metastasis.
Objective: The present study aimed to evaluate predictive factors for occult lymph node metastasis in patients with oral cavity squamous cell carcinoma treated with elective neck dissection and their impact on overall and disease-free survival.
Methods: Forty surgically treated patients were retrospectively included.
Results: Ten cases (25%) had lymphatic metastasis. Of the studied variables, perineural and angiolymphatic invasion in addition to tumor thickness were statistically associated with lymph node metastasis. Only angiolymphatic invasion was identified as an independent risk factor for occult metastasis in the logistic regression (OR = 39.3; $p = 0.002$). There was no association between overall and disease-free survival with the presence of occult lymph node metastasis.
Conclusion: Metastatic disease rate was similar to that found in the literature. Perineural and angiolymphatic invasion and tumor thickness were associated with occult metastasis, but only angiolymphatic invasion showed to be an independent risk factor

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PALAVRAS-CHAVE
Carcinoma;
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Boca;
Metástase linfática;
Prognóstico

Carcinoma espinocelular da cavidade oral: fatores relacionados à presença de metástases linfonodais ocultas

Resumo
Introdução: O esvaziamento cervical eletivo é realizado de maneira sistemática nos casos de carcinoma espinocelular da cavidade oral sem linfonodos clinicamente comprometidos devido à alta incidência de metástases ocultas.
Objetivo: Avaliar pacientes com carcinoma espinocelular de cavidade oral tratados com esvaziamento cervical eletivo quanto a fatores preditivos para ocorrência de metástases ocultas e o impacto das mesmas na sobrevivência global e livre de progressão destes pacientes.
Método: Quarenta pacientes cirurgicamente tratados foram avaliados em estudo retrospectivo.
Resultados: Dez casos (25%) apresentaram metástases ocultas. Das variáveis analisadas, invasão perineural e angiolinfática e também a espessura tumoral foram estatisticamente significantes à análise univariada. Apenas a invasão angiolinfática foi fator independente de risco de metástases ocultas pela regressão logística (OR = 39,3; $p = 0,002$). A presença de metástase oculta não apresentou diferença estatisticamente significante em relação às taxas de sobrevivência global e livre de progressão.
Conclusão: A incidência de metástase oculta foi semelhante à literatura. A invasão perineural, angiolinfática e a espessura tumoral foram fatores associados à presença de metástase oculta, porém apenas a invasão angiolinfática apresentou-se como um fator de risco independente para ocorrência do fenômeno.

Introduction

Squamous cell carcinoma is the most common histological type of cancer of the oral cavity, and has an important and well-established pattern of dissemination to cervical lymph nodes.[1] Even in patients clinically without evidence of metastatic lymph nodes (N0), elective neck dissection in conjunction with resection of the primary tumor, is part of the standard treatment of the disease because the risk of occult metastasis is greater than 20%.[1–6]

Several studies have tried to assess factors that would predict occult metastases and their influence on survival rates, such as tumor thickness, perineural invasion and angiolymphatic invasion.[1,7–10] In attempts to reduce surgical morbidity, some have proposed alternatives to elective neck dissection, such as sentinel lymph node mapping[11,12] and even avoiding any surgical approach to the neck in selected cases;[13,14] the latter has the poorest survival results.[5,15,16] Thus, elective neck dissection currently remains the most widely used treatment.

The present study aimed to evaluate the risk of the presence of occult lymph node metastases in patients with squamous cell carcinoma of the oral cavity submitted to resection and elective neck dissection, in order to identify factors related to the development of nodal metastases, and to identify its impact on overall and disease-free survival.

Method

This was a longitudinal historical cohort study that, after approval by the Ethics Committee of Institutional Research under No. 507/11, retrospectively assessed electronic medical records of consecutive patients submitted to primary tumor resection with intent to cure combined with elective neck dissection in patients with oral cavity squamous cell carcinoma (including the lip). Forty patients were selected from April of 2009 (beginning of the Head and Neck Surgery Service) until December of 2012.

Inclusion criteria consisted of cases of squamous cell carcinoma of the oral cavity, whose initial treatment was a surgical procedure with primary lesion resection and elective unilateral or bilateral neck dissection, depending on the lesion location, with all patients being considered N0 at clinical examination and preoperative imaging tests. Neoplasms in other sites than the oral cavity were excluded, as well as other histological types, patients who had suspected lymph node detected intraoperatively, leading to conduct change into radical dissection, and patients submitted to previous surgical treatment or chemotherapy and/or radiotherapy, even for neoplasms located at another site in the head and neck.

Patients were assessed regarding:

1. Demographic data: gender and age;
2. Clinical data: primary tumor location (for this variable, major oral cavity subsites were divided into tongue, floor of the mouth, retromolar area, lip, buccal mucosa, and alveolar border). Patients were only included with squamous cell carcinoma of the lip when it extended to the buccal mucosa, justifying elective neck dissection according to the institutional protocol;
3. Anatomopathological data: pT stage (analyzed in independent subgroups and also in pT1 and pT2 *vs.* pT3

and pT4a and pT1–pT3 *vs.* pT4a stratification), primary tumor thickness (in mm), presence or absence of perineural and angiolymphatic invasion, surgical margins, pN stage, number of lymph nodes in pN+ cases, presence or absence of capsular leakage in metastatic lymph nodes, and anatomopathological stage per groups (I–IV) according to the classification of American joint Committee on Cancer/Union for International Cancer Control, UICC/AJCC (7th edition, 2010);
4. Surgical data: related to the performed neck dissection;
5. Adjuvant treatments performed: radiotherapy and/or chemotherapy;
6. Development of locoregional recurrence, distant metastasis, and second primary tumor, as well as time of occurrence of these events;
7. Follow-up time in months, requiring a minimum of 12 months for patients who did not die during this period;
8. Most recent oncological status (alive and disease-free, alive with the disease, asymptomatic dead, and dead due to cancer).

Statistical analysis was performed as described below. The values obtained by the study of each continuous variable were organized and expressed as mean and standard deviation, whereas qualitative variables were expressed as absolute and relative frequencies. Sample distribution was defined as parametric using the Kolmogorov–Smirnov test. Comparisons of the frequency of a phenomenon between groups of qualitative variables were performed using Fisher's exact test or the chi-squared test. The comparison between the means of a continuous variable with parametric distribution between two groups was performed using Student's *t*-test. The logistic regression model was used in the multivariate analysis, establishing values of odds ratio (OR) and 95% confidence interval (95% CI).

The Kaplan–Meier method was used for survival analysis and comparison of groups was performed using the log-rank test. All analyses were performed using Statistical Package for the Social Sciences, (SPSS statistical software), version 17.0 (SPSS Inc – Illinois, USA), with a significance level of 5% ($p < 0.05$).

Results

Of the 40 patients, 35 (87.5%) were males and mean age was 60 years (minimum 40 and maximum of 89 years, standard deviation of 12.9 years).

The most often affected subsites were the tongue and the floor of the mouth (65%) and there was a predominance of advanced stages (stages III and IV = 52.5%). As for the histological characteristics of primary tumors, mean tumor thickness was 1.4 ± 1.2 cm; in five cases (12.5%) the final surgical margins were considered involved; 24 tumors (60%) had perineural invasion and nine (22.5%) showed angiolymphatic invasion. Mean follow-up was 18 months and nine cases of disease progression were identified (five exclusively locoregional recurrences, one case of pulmonary metastasis with controlled primary site and neck, and three patients with both) and more than half of the patients (52.5%) required adjuvant treatment. The descriptive data of the entire series are shown in Table 1.

Table 1 Demographic, clinical, and anatomopathological data ($n = 40$).

Variable	Absolute frequency	Relative frequency (%)
Gender		
Male	35	87.5
Female	5	12.5
Subsite		
Tongue	15	37.5
Floor of the mouth	11	27.5
Retromolar area	7	17.5
Buccal mucosa or lip with buccal extension	6	15.0
Alveolar border	1	2.5
Anatomopathological	24	60.0
Perineural invasion	9	22.5
Angiolymphatic invasion	24	63.2
Tumor thickness >7 mm ($n = 38$)[a]	35	87.5
Free margins	13	32.5
pT	9	22.5
pT1	4	10.0
pT2	14	35.0
pT3	30	75.0
pT4a	4	10.0
pN	6	15.0
pN0	3	30.0
pN1	12	30.0
pN2b	7	17.5
Extracapsular leakage ($n = 10$)	5	12.5
Stage	16	40.0
I		
II		
III		
IVa		
Follow-up	2	5.0
Second primary tumor	21	52.5
Adjuvant treatment	14	35.0
Isolated radiotherapy	7	17.5
Chemoradiation	9	22.5
Recidivism	8	20.0
Locoregional	4	10.0
Distant metastasis	9	22.5
Death		

[a] Thickness: mean ± standard deviation = 1.4 ± 1.2 cm.

Regarding the analysis of neck dissection, 14 patients underwent bilateral surgery, as the primary tumor surpassed the anatomical midline, totaling 54 dissections. The mean number of dissected lymph nodes was 27.2 ± 11.4. Most cases (87.5%) underwent dissection at levels I, II, and III, but five patients were submitted to level IV dissection due to intraoperative decision of the attending surgeon, and there were no occult metastases to lymph nodes at that level in any of these cases. Ten patients (25.0%) had occult lymph node metastases in the anatomopathological

Table 2 Univariate analysis of factors related to the presence of occult lymph node metastasis.

Comparison	Lymph node metastasis/total (%)	*p*
Gender		**1.000**[a]
Male	9/35 (25.7)	
Female	1/5 (20.0)	
Age[b]		**0.240**[b]
Absence of lymph node metastasis	61.5 ± 12.5	
Presence of lymph node metastasis	58.2 ± 14.4	
Subsite		0.544[c]
Tongue	2/15 (13.3)	
Floor of the mouth	4/11 (36.4)	
Retromolar area	3/7 (42.9)	
Lip	1/4 (25.0)	
Buccal mucosa	0/2 (0.0)	
Alveolar border	0/1 (0.0)	
Perineural invasion		0.032[a]
No	1/16 (6.3)	
Yes	9/24 (37.5)	
Angiolymphatic invasion		<0.0001[a]
No	3/31 (9.7)	
Yes	7/9 (77.8)	
Tumor thickness >7 mm		0.043[a]
No	1/14 (7.1)	
Yes	9/24 (37.5)	
pT[d] *Stage*		0.230[c]
pT1	1/13 (7.7)	
pT2	2/9 (22.2)	
pT3	2/4 (50.0)	
pT4a	5/14 (35.7)	

[a] Fisher's exact test.
[b] Comparison between means of age – Student's *t*-test.
[c] Chi-squared test.
[d] Note: no statistically significant difference was observed between the stratified pT stage and the presence of occult lymph node metastasis ($p = 0.274$ and $p = 0.278$, respectively for pT1 and pT2 *vs.* pT3 and pT4a, and pT1–pT3 *vs.* pT4a).

assessment (Table 1), and none of the patients undergoing bilateral neck dissection had N2c stage.

The variable tumor thickness was submitted to ROC curve analysis, and it was determined that the best cutoff for risk stratification of occult lymph node metastases was >7 mm (area under the ROC curve of 68.2%; 95% CI: 50.3%–86.1%). The univariate analysis, detailed in Table 2, showed that the presence of perineural invasion ($p = 0.032$; Fisher's exact test), angiolymphatic invasion ($p < 0.0001$; Fisher's exact test), and tumor thickness >7 mm ($p = 0.043$; Fisher's exact test) were factors related to the presence of occult lymph node metastases.

Variables with $p < 0.20$ in the univariate analysis were submitted to a logistic regression model, shown in Table 3. It was verified that angiolymphatic invasion was the only independent risk factor for the presence of occult lymph node metastasis (OR = 39.3; 95% CI: 3.7–420.9; $p = 0.002$). As this was a retrospective study, the calculation of power for this estimate was conducted during the analysis, using the method for cohort studies. Considering the OR of 39.3 and the proportion of 25% of occult lymph node metastases in this group, the inclusion of 40 patients determined that this estimate demonstrated power >90%.

Table 3 Multivariate analysis of risk factors for the presence of occult lymph node metastasis.

Factor	OR	95% IC	*p*[a]
Presence of angiolymphatic invasion	39.3	3.7–420.9	0.002
Presence of perineural invasion	1.5	0.1–23.7	0.766
Tumor thickness >7 mm	11.6	0.7–204.3	0.093

[a] Logistic regression.

Survival analysis showed that disease-free survival and overall cumulative survival (Figure 1) were 68.2% and 64.1%, respectively. Even though there was no statistically significant difference, patients with occult lymph node metastases showed a lower disease-free survival rate, a lower overall survival, and a median survival of 28 months in the final analysis, compared to patients without this factor (Table 4; Figure 2).

Discussion

The presence of occult metastases in squamous cell carcinoma of the oral cavity is very prevalent due to its aggressiveness[1] and neck treatment is mandatory, even in cases without clinical signs of involvement. Surgical treatment has an advantage over radiotherapy, since it establishes the patient's complete pathological staging, preventing unnecessary use of radiotherapy in some cases.[17]

This sample showed a prevalence of male patients, with most tumors located in the tongue and floor of the mouth, consistent with the literature.[3,7,16] The presence of occult metastases in 25% of cases was in agreement with other studies.[1,3,4,18] With regard to all cases with positive neck involvement, it is noteworthy that three cases had metastasis in more than one cervical level, and in three cases the metastases were stages II and/or III, with level I disease-free. No patient had level IV involvement. This shows that although some cases of skip metastases occurred, dissection at levels I–III would have been sufficient treatment for all patients in this series.

However, some authors have reported 3–28% of affected lymph nodes at level IV, especially in tongue and floor-of-the-mouth tumors, but studies have disagreed about elective dissection extension to level IV in the oral cavity tumors, with most of them favoring the non-extension.[19–22] It is noteworthy that the present study included 40 consecutive patients, which at first may be considered a small sample and a limitation of the study; however, the calculation of power of the main estimate performed (angiolymphatic invasion as an independent risk factor for the presence of occult lymph node metastasis) was >90%, which demonstrates the statistical significance of the findings.

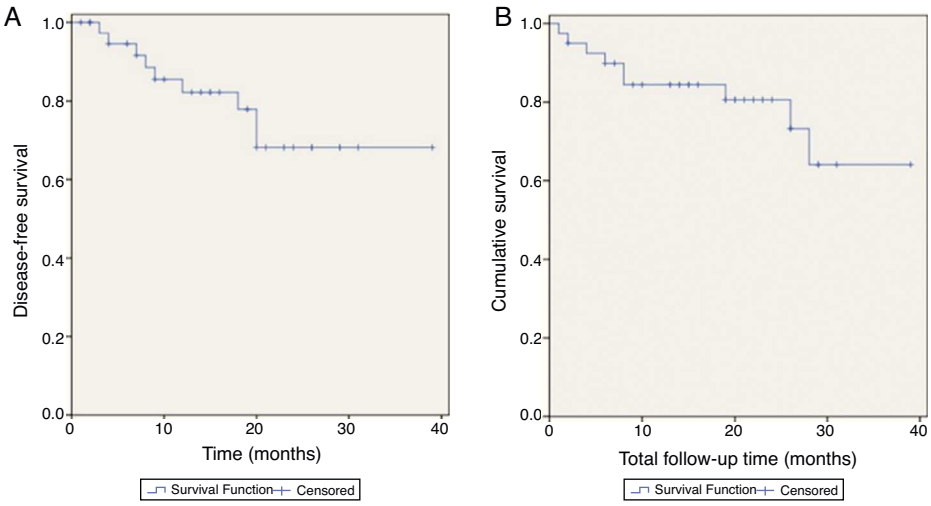

Figure 1 Kaplan–Meier Curves. (A) Cumulative disease-free survival of 68.2%; (B) Cumulative overall survival of 64.1%.

Table 4 Analysis of overall and disease-free survival.

Variable	Events/total	Accumulated survival (%)	p^a
Disease-free survival			0.587
Absence of lymph node metastasis	6/30	71.4	
Presence of lymph node metastasis	3/10	60.0	
Overall survival			0.248
Absence of lymph node metastasis	5/30	80.4	
Presence of lymph node metastasis	4/10	40.0[b]	

[a] Log-rank test.
[b] Median of survival attained at 28 months.

In the many existing studies, the major risk factors for occult metastases are angiolymphatic invasion, perineural invasion, and tumor thickness.[1,2,4,8,9,17,19] This was corroborated by the present study, but only angiolymphatic invasion was shown to be an independent risk factor of occult metastases.

Although studies increasingly focus on these characteristics as predictors of lymphatic dissemination, from a clinical

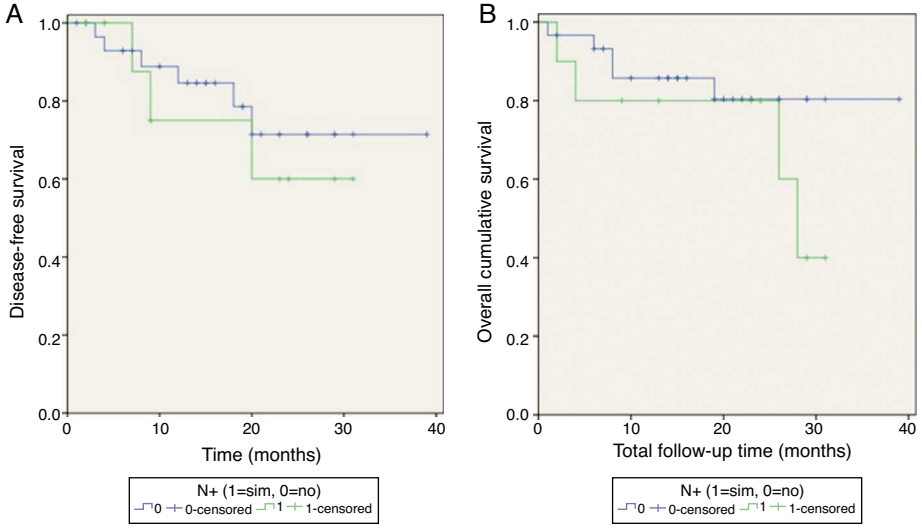

Figure 2 Kaplan–Meier curves comparing the groups with absence and presence of occult lymph node metastasis. (A) Cumulative disease-free survival of 71.4% and 60.0%, respectively, for the absence and presence of occult lymph node metastases ($p = 0.587$ – log-rank test); (B) Cumulative overall survival of 80.4% and 40.0%, respectively, for the absence and presence of occult lymph node metastases ($p = 0.248$ – log-rank test).

point of view, except for thickness, all are factors that are inaccessible until tumor resection and therefore may not be used for decision-making, such as not treating the neck or using less invasive treatments such as sentinel lymph node technique. When positron emission tomography-computed tomography (PET-CT), which has been increasingly used and studied, is negative for the neck, it is considered enough evidence to justify expectant conduct, but the patient samples evaluated were few and follow-up was not long enough to evaluate survival or morbidities when salvage neck dissection is employed.[19,23]

The sentinel lymph node (SLN) technique for the treatment of N0 patients has been studied since the 1990s. It has similar rates to elective neck dissection for the detection of occult metastases.[24,25] A European multicenter study compared two groups, one using the sentinel lymph node and one with systematic extension to selective neck dissection with a follow-up of five years; it found cervical recurrence in three cases considered negative in the SLN arm but no recurrence in the other group.[24] It also showed difference in disease-free survival, but without statistical significance.[24] Another European study with follow-up of 10 years, in which SLN was carried out without systematic neck dissection in 53 cases from a total of 174, showed method failure rate of 4.8%, with negative predictive value of 95.2%, considered by the author similar to that of elective neck dissection.[25]

Tumor thickness has been widely studied as a predictor of cervical lymph node metastases in patients with squamous cell carcinoma of the upper aerodigestive tract, especially because up to 40% of patients with these tumors exhibit occult metastases.[26] Huang et al.[27] performed a meta-analysis analyzing tumor thickness and the risk of cervical lymph node metastasis. They concluded that a 4-mm cutoff for tumor thickness would be a strong predictor of the presence of occult cervical lymph node metastasis; they found a rate of 16.6% among patients with tumor thickness >4 mm, compared to 4.5% among those with tumor thickness $\leq$4 mm.

Fukano et al.[28] studied 34 patients with tongue carcinoma treated with early surgical resections without preoperative therapy. Mean tumor thickness was 6.4 mm (0–18.2 mm) and 64.7% of patients with tumor thickness >5 mm had lymph node metastases, compared to 5.9% of patients with thickness <5 mm. The present study established a cut-off of 7 mm as a predictor of occult neck metastases, established by the ROC curve analysis. This index, slightly higher than that found in the literature, is probably due to the fact that the present study was performed in a public institution, in which patients present with more advanced neoplasms at the initial diagnosis. The mean tumor thickness was 14 mm and 45% of patients had pT3 and pT4a tumors, which unfortunately is comparable to most Brazilian oncological institutions, and one of the limitations for comparison of results, especially with international case series.

This study also documented a small proportion of occult metastases in patients with pT1 or pT2 stage (17.4%), but this result is similar to that found in the literature. Kelner et al.[29] found rates of 12.5% and 22.4% for the incidence of lymph node metastases in patients with squamous cell carcinoma of the oral cavity that were respectively pT1 and pT2 (20.5% when the stages were added). Thus, Poonacha and Go[30] question whether elective neck dissection should be performed in this population despite the recommendation of the American protocol.

Pathological features are valuable for indication of adjuvant treatment with radiotherapy and/or chemotherapy, as patients with known presence of cervical metastases have lower survival rates, especially disease-free survival, compared to patients without neck involvement. The overall and disease-free survival curves shown in this study demonstrate the effect of the presence of lymph node involvement on disease evolution; even when the involvement is microscopic, the necessary adjuvant therapy is performed. However, these patients have lower overall and disease-free survival rates than patients with tumors confined to the primary site.

The fact that the oncological follow-up period of five years has yet to be completed is a limitation of this study. This occurred because the Institute opened in 2009; however, the authors believe that this fact has little influence on survival analysis. It is well known in the literature that tumor recurrence occurs mainly in the first year of follow-up. Pinto et al. [31] found that 92.8% of locoregional recurrence occurred within the first 12 months of follow-up in patients with squamous cell carcinoma of the oral cavity and oropharynx.

Conclusions

This study demonstrated that the incidence of occult metastases in squamous cell carcinoma of the oral cavity was 25% in a population consisting of 45% pT3 and pT4a patients. Among the factors evaluated, perineural and angiolymphatic invasion and tumor thickness >7 mm were associated with the presence of occult neck metastases, but only angiolymphatic invasion proved to be an isolated risk factor for the occurrence of the event. Disease-free survival and overall survival in the two groups exhibited differences, although they were not statistically significant.

Conflicts of interest

The authors declare no conflicts of interest.

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