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Oral Squamous Cell Carcinoma: Clinicopathological Features in Patients with and without Recurrence

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Key Words
Squamous cell carcinoma · Recurrence · Survival · Oral cancer

Abstract
Aim: To compare the clinicopathological profile of oral squamous cell carcinoma (OSCC) in groups with and without recurrence. ***Methods:*** Records of all patients who underwent surgery for primary OSCC at a single institution during 1999 were identified. Patient demographics, lesion site, clinical and pathologic stage, pathologic grading, pattern of invasion, lymphocytic infiltrate, perineural invasion, and treatment and survival data were collected. Descriptive statistics were calculated for each variable and survival was calculated using Kaplan-Meier and Cox models. Patients were divided into 2 groups: with (n = 25) and without (n = 28) recurrence. ***Results:*** Tongue (p = 0.02) and poorly differentiated (p = 0.04) tumors were associated with recurrence. Kaplan-Meier and Cox models revealed tobacco use and the absence of lymphocytic infiltrate to be associated with the poorest survival in recurrent OSCC. ***Conclusion:*** The tumor site, tobacco use, and pathological features were involved in the recurrence of OSCC and should be taken into account for OSCC treatment and follow-up.

Introduction

Squamous cell carcinoma is the most common malignant neoplasm of the oral cavity. Oral squamous cell carcinoma (OSCC) is a significant public health threat worldwide [1]. Management of OSCC varies considerably; small cancers of the oral cavity are usually managed by surgery alone, whereas advanced oral cancers are usually treated with primary radical surgery followed by radiation or chemoradiation. Neck treatment is offered to patients who have a greater than 20% chance of having lymph node metastasis or who have neck involvement at the time of presentation [2].

Up to 47% of patients with OSCC develop local recurrence, second primary tumors, and regional or distant metastases [3]. A high risk of local recurrence and new

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mucosal malignancies of the upper aerodigestive tract is seen in patients treated for oral cancer. The prognosis is unclear for these patients. A typical failure may be located at the site of the first tumor, i.e. a local recurrence, or separately as a second primary tumor. The similarities in survival and the pattern of presentation among patients with local recurrence versus second primary tumors suggest that these 2 entities may be biologically analogous [4]. Overall, there is a lack of independence between relapse at the primary, secondary, and distant sites [5].

Several clinicopathological parameters have been implicated in prognosis, recurrence, and survival following OSCC, including differentiation, perineural invasion, lymphatic invasion, bone invasion, location, invasion depth, and margin distances. The presence of multiple significant factors correlates with disease recurrence [6].

The aim of this study was to analyze OSCC patients who were surgically treated with neck dissection and free margins, relating clinical and histopathological features to the presence or absence of regional recurrence, second primary tumors, and distant recurrence.

Patients and Methods

Fifty-three cases from a total of 320 consecutive patients with OSCC diagnosed between January 1999 and December 1999 at the National Institute of Cancer (INCA), Rio de Janeiro, Brazil, were included in this study. Patients were screened using the following criteria: (1) patients had undergone surgery as the primary treatment for a first primary OSCC, (2) patients were subjected to neck dissections, and (3) clear margins were verified in intraoperative frozen sections. Patients with distant metastasis or fewer than 12 months of follow-up or who were not deceased due to the disease before 12 months were excluded.

Clinicopathological Features

Clinicopathological features were obtained from medical records and tumor registries and included age, gender, alcohol and tobacco use, tumor location, treatment, clinical and pathologic stage, presence or absence of tumoral recurrence, and patient survival. Slides from all cases were retrieved from the filing section of the Department of Pathology of the INCA (DIPAT) to confirm the diagnosis. Whenever there were slides available from salvage surgery they were also analyzed. The grade of differentiation was categorized according to WHO guidelines (2005). Lymphocytic infiltrate at the tumor-host interface, pattern of invasion, and perineural invasion were evaluated as described by Brandwein-Gensler et al. [3].

For purposes of comparison, patients were divided into 2 groups: with recurrence (R) (n = 25) and without recurrence (NR) (n = 28). The sites of the first relapse were identified as local, second primary, neck, or distant.

Relapse was confirmed histologically in patients who had curative salvage treatment and assumed in patients with clinical disease progression who had no further curative treatment. Within-site second primaries were also considered recurrences. The outcomes of interest were the date of diagnosis of first relapse and the date of death. All other events were censored. The date of treatment completion was used as time 0 for relapse. The mean follow-up period was 52.2 months (range 3.03–86.73). At the end of this period, 27 patients (50.9%) had died (21 of them due to the cancer), 18 cases (33.9%) were alive and free of recurrence, and 8 cases (15%) were recurrence free up to their last visit but were then lost to follow-up (ranging 16.3–65.7 months after the tumor treatment).

This study was reviewed and approved by the institutional ethics committee.

Statistical Analysis

All data were tabulated and statistical analyses were carried out with the Statistical Program for Social Sciences (SPSS) for Windows version 10.0 (SPSS Inc., Chicago, Ill., USA). All relapse sites were combined for failure analysis because of the lack of independence between relapse at the primary, secondary, and distant sites [5]. Relationships between clinicopathological factors were assessed using the χ^2 test. Factors with significant statistical differences in χ^2 and univariate analysis (Kaplan-Meier method) were included in a multivariate analysis using Cox proportional hazards regression. $p \leq 0.05$ was considered statistically significant.

Results

Clinicopathological Results and Bivariate Analysis

Patients

The results of the 53 patients as a whole were previously described [7]. Recurrence was identified in 25 cases (47.1%) – local recurrence and regional recurrence occurred in 9 cases each (36%). Local recurrence occurred in the tongue (n = 3), floor of the mouth (n = 2), buccal mucosa (n = 2), soft palate, and tongue and floor of the mouth simultaneously. Out of these, locoregional recurrence was present in 2 cases at the same time. Distant metastasis occurred in 3 cases (12%; lungs and brain) and second primaries in 4 cases (16%; uvula, esophagus, and oropharinx). In 6 cases (24%) a second episode of recurrence was detected (second primaries and local recurrence in 2 cases each and a regional and distant metastasis in 1 case each). Only 2 patients experienced a third recurrence (both at the base of the tongue). The recurrence interval ranged from 2.3 to 73.9 months with an average of 26.1 months (median 19.7). Fifteen patients (60%) developed recurrence within 2 years. Sex, age, alcohol and tobacco consumption, clinical stage, and initial treatment were similar between the R and NR groups. Only tumors located in the tongue presented a higher number of recurrences (p = 0.02) (table 1).

After the first episode of recurrence, the majority of patients (n = 12, 48%) received supportive care only.

Table 1. Clinicopathologic features comparing the R and NR groups using Fisher's exact test and univariate analysis of survival for the R group according to Kaplan-Meier and log-rank tests

Variable/ category	NR cases (n = 28)		R cases (n = 28)		p value	Overall survival (R group)		Cancer-specific survival (R group)	
	n	%	n	%		95% CI	p value	95% CI	p value
Gender									
Male	25	89.3	18	72	0.16	27.02–51.74	0.48	28.82–71.75	0.56
Female	3	10.7	7	28		28.82–71.75		28.27–53.85	
Age									
<60 years	13	46.4	11	44	1	19.61–51.86	0.43	20.97–55.50	0.59
≥60 years	15	53.6	14	56		33.65–62.41		33.65–62.41	
Alcohol									
Yes	20	71.4	18	72	1	27.18–50.34	0.23	27.18–50.39	0.11
No	8	28.6	7	28		28.05–75.35		35.93–83.07	
Tobacco									
Yes	24	85.7	5	20	0.71	25.19–46.90	0.03	26.23–48.71	0.03
No	4	14.3	20	80		46.28–89.22		46.28–89.22	
Tumor site[a]									
Tongue	9	32.1	16	64	0.02	29.79–57.43	0.93	31.77–60.21	0.78
Other	19	67.9	9	36		22.83–56.82		22.83–56.82	
Floor of the mouth	14	53.6	11	44	0.58	26.49–58.04	0.99	28.56–61.57	0.81
Other	11	46.4	15	56		27.50–57.46		27.50–57.46	
Retromolar gingiva	5	82.1	2	8	0.42	16.03–56.21	0.58	16.03–56.21	0.49
Other	23	17.9	5	92		31.29–54.99		32.60–56.85	
Upper alveolar ridge	1	3.6	0	0	1	X	X	X	X
Other	27	96.4	1	100		X		X	
Lower alveolar ridge	3	10.7	1	4	0.61	X	0.19	[c]	0.83
Other	25	89.3	3	96		X		[c]	
Hard palate	0	0	0	0	X	X	X	X	X
Other	28	100	25	100				X	
Buccal mucosa	0	0	0	0	X	X	X	X	X
Other	28	100	25	10		X		X	
Clinical stage									
I + II	13	46.4	17	68	0.16	32.64–57.55	0.75	34.39–59.86	0.64
III + IV	15	53.6	8	32		15.83–57.87		15.83–57.87	
Treatment									
Surgery	8	28.6	11	44	0.72	36.85–69.64	0.13	36.85–69.64	0.19
Surgery + RXT	20	71.4	14	56		21.03–46.17		22.13–48.78	
Pathologic stage									
I + II	15	53.6	11	44	0.58	37.36–71.40	0.06	37.36–71.40	0.09
III + IV	13	46.4	14	56		21.02–45.18		22.11–47.66	
Grading									
W + M	27	96.4	19	76	0.04	25.61–48.31	0.07	26.72–50.21	0.09
P	1	3.6	6	24		36.78–82.02		36.78–82.02	
Lymphocytic infiltrate									
Type 1 + 2	26	92.9	22	88	0.65	35.04–57.98	0.004	56.96–73.67	0.005
Type 3	2	7.1	3	12		1.37–26.16		10.71–27.26	
Pattern of invasion									
1 + 2 + 3[b]	6	21.4	0	0	0.02	X	X	X	X
4 + 5	22	78.6	25	100		X		X	
Perineural invasion									
None	18	64.3	11	44	0.17	27.12–50.76	0.47	56.96–73.67	0.34
Present	10	35.7	14	56		28.13–61.88		10.71–27.26	

X = Statistics could not be calculated because all values were censored; W + M = well and moderately differentiated; P = poorly differentiated; RXT = radiation treatment.

[a] There are more locations than the total number of tumors because 1 tumor could be at multiple sites. [b] Bland pattern of invasion. [c] Statistics could not be calculated because all values were censored.

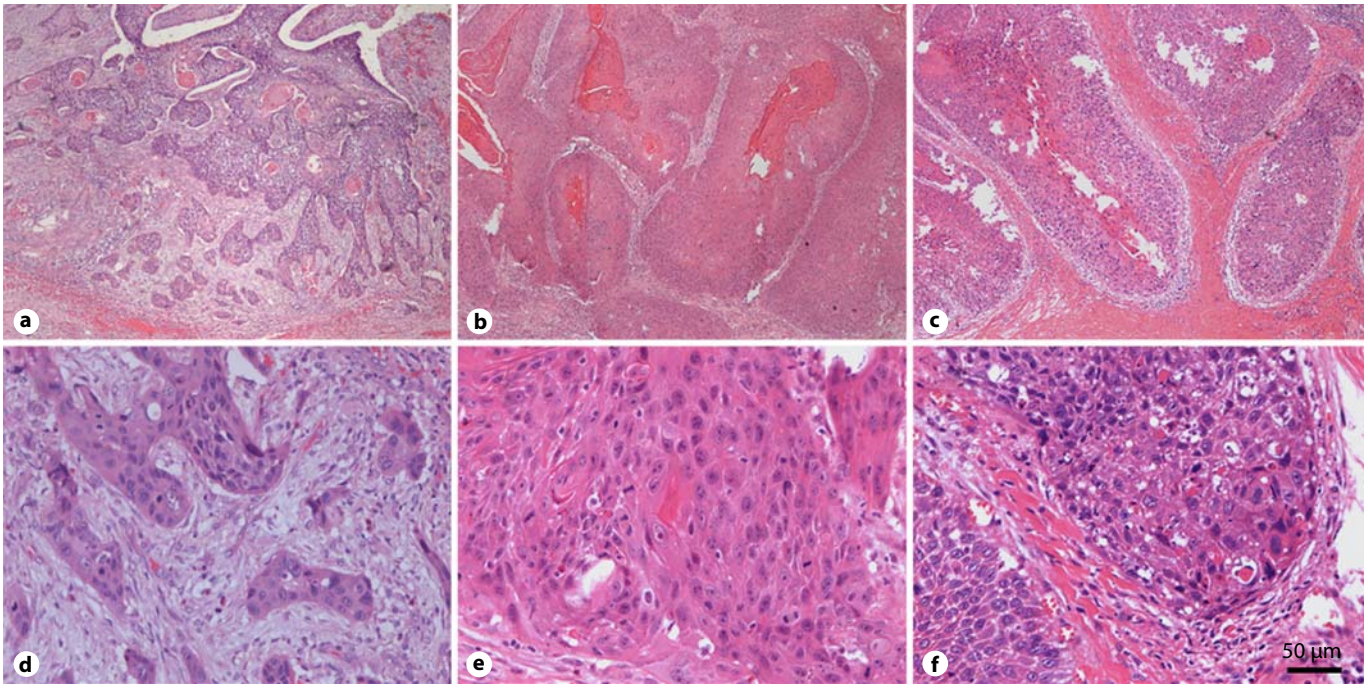

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Fig. 1. Histopathologic aspects of a single patient with OSCC in 3 distinct periods: surgery of the primary tongue cancer (**a**, **d**), surgery of a first recurrence in the soft palate (**b**, **e**), and surgery of a second recurrence in the oropharynx (**c**, **f**). Note small islands featuring pattern of invasion 4 (**a**) with numerous cellular pleomorphisms and scarce lymphocytic infiltrate (**d**). First recurrence presented a blander pattern of invasion (pattern of invasion 2) (**b**) but with evident mitoses and pleomorphism (**e**). In the second recurrence there was a strong desmoplastic reaction (**c**, **f**).

Other therapeutic modalities included salvage surgery in 6 patients (24%) and radiation treatments in 7 patients (28%), with concomitant chemotherapy in one and brachytherapy in another.

The histopathologic results presented in table 1 refer to the primary tumor. Statistically significant differences were observed for poorly differentiated tumors mostly present in the R group ($p = 0.04$) and tumors with a bland pattern of invasion present only in the NR group ($p = 0.02$). Histopathologic analysis of recurrent samples (fig. 1) subjected to salvage surgery ($n = 6$) revealed that the tumors were mostly moderately differentiated ($n = 4$, 66%) without perineural invasion, showing lymphocytic infiltrate and a bland pattern of invasion (type 2 or 3 in all but 1 case). Three of these patients died from their disease and 3 were alive and well.

Survival Analysis – Univariate and Multivariate Cox Regression Analysis

Based on the Kaplan-Meier survival analysis, the 5-year cancer-specific survival rate was 92% in the NR group and 30% in the R group ($p < 0.0001$, log-rank test) (fig. 2a). Overall survival also showed statistically significant differences between groups (mean survival 76.8 months in the NR group and 42.5 months in the R group; $p < 0.0001$, log-rank test). Further survival analysis of the R group revealed that patients who presented recurrence before 26.1 months (average time for the first recurrence) showed the lowest cancer-specific survival ($p = 0.042$, log-rank test) (fig. 2b). Moreover, smokers ($p = 0.03$, log-rank test) and patients whose tumors presented scarce or absent lymphocytic infiltrate ($p = 0.005$, log-rank test) showed the worst cancer-specific and overall survival rates (table 1).

Multivariate Cox regression analyses of the R group showed scarce or absent lymphocytic infiltrate to be a significant independent prognostic factor for both overall survival and cancer-specific survival. Furthermore, pathologic stage was an independent prognostic factor for overall survival, and pattern of invasion was an independent prognostic factor for cancer-specific survival (table 2).

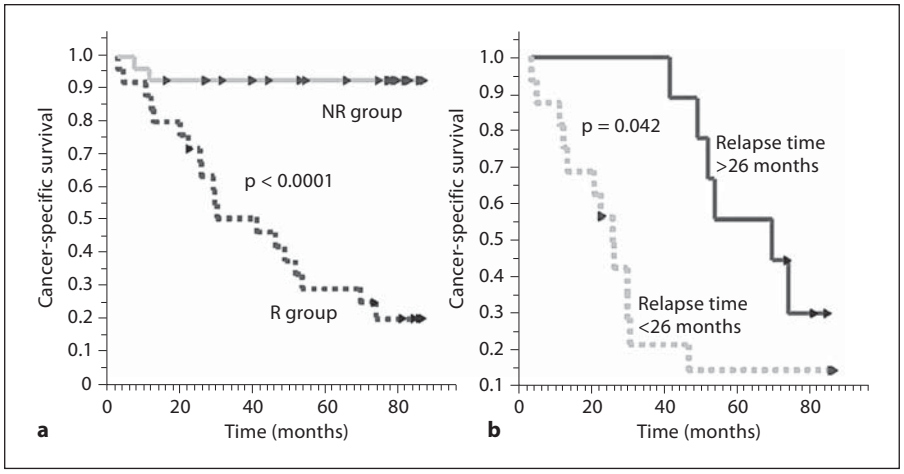

Fig. 2. Based on the Kaplan-Meier survival analysis, the 5-year cancer-specific survival rate was 92% in the NR group and 30% in the R group (**a**). Further survival analysis of the R group revealed that patients who presented recurrence before 26.1 months (average time for first recurrence) showed the worst cancer-specific survival (**b**).

Table 2. Multiple regression analysis of survival in patients who presented at least 1 recurrence

Variable	Category	Overall survival		Cancer-specific survival	
		HR (95% CI)	p value	HR (95% CI)	p value
Pathologic stage	I + II/III + IV	4.50 (1.54–13.15)	0.006	a	a
Pattern of invasion	1 + 2 + 3/4 + 5	a	a	2.59 (1.01–6.68)	0.048
Lymphocytic infiltrate	type 1 + 2/type 3	10.37 (2.15–49.96)	0.004	14.06 (2.94–67.22)	0.001

a = Variable not included in the analysis.

Discussion

OSCC outcomes are often determined by clinical factors; therefore, clinicopathological parameters can be valuable to understand discrepancies among apparently similar tumors [8]. The present study demonstrated that, among all features studied, poorly differentiated tumors located in the tongue and showing a pattern of invasion in small or isolated islands are associated with OSCC recurrence. Tobacco use and scarce or absent lymphocytic infiltrate were related to lower rates of survival in these patients.

The tongue is the most common site for oral cancer development worldwide, except in countries where use of smokeless tobacco is a cultural habit and buccal mucosa tumors outnumber tongue tumors [1]. Moreover, there are significant differences in tumor behavior between anatomic sites within the oral cavity that affect the treatment outcome [9], which may explain the association found between tongue tumors and recurrence. In fact, studies that analyzed samples from the same institution where the present work was conducted have recommended elective neck dissection in clinical stage I and II tongue and floor-of-the-mouth squamous cell carcinomas. This procedure has been adopted due to the higher likelihood of occult neck metastasis and consequent aggressiveness in such tumors [10, 11].

It has been customary to grade OSCC according to WHO guidelines, which take into account mainly cellular differentiation. The WHO grading system alone shows a poor correlation with outcome and response to treatment in an individual patient [12, 13]. However, in the present study a positive correlation between recurrence and poorly differentiated tumors was found; this association was previously reported to influence disease-specific survival [6, 14, 15]. This feature may reflect the aggressive behavior of these tumors when compared to moderately and well-differentiated tumors. It must be emphasized that all of the tumors we examined were reclassified according to the worst area present, as recommended by the WHO [13, 16].

Lymphocytic infiltrate presence was able to independently predict better overall and cancer-specific survival. Also, the pattern of invasion was associated with recurrence and cancer-specific survival, corroborating the importance of these features in OSCC prognosis prediction, as proposed by Brandwein-Gensler et al. [3, 17]. In the oral cavity the presence of lymphocytic infiltrate seems to be related to a protective response, rather than a destructive one [18], as occurs in colorectal cancers [19]. The pattern of invasion correlates with several in vitro markers of malignancy such as loss of contact inhibition, tumor-cell mobility, and secretion of proteolytic enzymes, and its observation in routine histological preparations provides a simple measure of tumor behavior [12]. Unfortunately, infiltrate and pattern of invasion analysis, as proposed, cannot be applied to biopsy samples [3], which impairs its use as a primary treatment selection tool though it remains a good aid for adjuvant therapy indication.

The prognostic importance of general patient features has been shown to be weak compared with the pathological extent and characteristics of the tumor, but survival is reportedly associated with gender, age, and the absence of usual risk factors, among other things [12]. This was the case with tobacco use, which was significantly associated with overall survival and cancer-specific survival in this study. de Aguiar et al. [8] evaluated early recurrence in a pair-matched study with similar smoking habits for both groups, and tobacco use had a negative impact on overall survival. The smoking status at diagnosis did not seem to affect the probability of experiencing tumor recurrence (table 1) [8].

Based on the Kaplan-Meier survival analysis, the cancer-specific survival rate was 92% in the NR group and 30% in the R group, which is similar to the results of other studies [14, 20]. The impact of the recurrence interval on survival has been a matter of debate, with no agreement as to what is the ideal cutoff which varies from 10 to 18 months after the initial treatment [20–22]. However, it seems there is a consensus that tumors recurring within a shorter interval present worse survival, as was shown in the present study with a 26.1-month interval for cancer-specific survival (fig. 2b).

Conclusions

Clinicopathological features such as location in the tongue, tobacco use, tumor grading, lymphocytic infiltrate, and pattern of invasion were all factors related to recurrence in OSCC and should be taken into account for OSCC treatment and follow-up.

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Disclosure Statement

The authors have no conflict of interest to declare.

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