

ORIGINAL ARTICLE

Comparative clinicopathological study of the main anatomic locations of oral squamous cell carcinoma

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Abstract

Objective: To analyze the clinicopathological and evolutionary profile of the main locations of oral squamous cell carcinoma (OSCC).

Materials and Methods: This is a retrospective study on 133 patients treated for OSCC. The group was composed of 48 women and 85 men, with a mean age 63.9 ± 12.73 years. Most cases involved the lingual border of tongue (63), followed by the gingiva (36) and the floor of mouth (34). A comparative analysis was performed using multinomial regression.

Results: There were significant differences regarding age, sex, tobacco and alcohol consumption, liver pathology, oral potentially malignant disorders, and bone and perineural invasion. In multivariate regression, tobacco consumption, and bone invasion remained significant. There were no significant differences in relation to prognosis.

Conclusion: The location of OSCC is an important factor in the clinicopathological assessment of this neoplasm. The main locations of OSCC show differential etiopathogenic and clinicopathological aspects. Tobacco consumption has a great relevance in the floor of mouth; nonetheless, it is less important in the tongue border and the gum, which suggests other pathogenic factors. It is necessary to consider the anatomical location of OSCC in preventive protocols, with the aim of reducing its high mortality.

KEYWORDS

anatomic location, cancer, floor of mouth, gingiva, lateral tongue, oral, oral squamous cell carcinoma

1 | INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most frequent and important oral malignant neoplasm in our environment and still has a poor prognosis (Amézaga-Fernández et al., 2024). The high mortality rate, which has not improved in recent decades, makes it necessary to review the preventive, diagnostic and therapeutic protocols for this malignant neoplasm. Moreover, there are no markers that allow to prevent it, improve its early diagnosis and plan a more successful therapy (Zanoni et al., 2019).

An important aspect is the clinicopathological, pathogenic, and evolutionary characteristics of OSCC in relation to its different primary sites (Farhood et al., 2019; Lin et al., 2021). The classical carcinogenic factors, tobacco and alcohol, have been found to be implicated diversely (Pentenero et al., 2011; Radoi et al., 2013; Yan et al., 2023). Differences have also been reported in relation to gender, as well as different age ranges (DeAngelis et al., 2018; Lin et al., 2021; Oh et al., 2021; Xu et al., 2019). In addition, some clinicopathological data have been related to the location of this neoplasm (de Araújo et al., 2008; Liu et al., 2017). Finally, although results have been reported in relation to survival, these have been disparate, some having shown no differences (Bell et al., 2007; Ong et al., 2017) and others (Farhood et al., 2019; Lin et al., 2021), on the contrary, observing prognostic relationships in some oral locations. However, very few studies (Lin et al., 2021; Liu et al., 2017) and none in the Spanish population have compared the complete clinicopathological and evolutionary profiles of OSCC in relation to the different oral anatomical areas where it developed.

The initial assumption of this study is that OSCC is not a single malignancy, but rather a "group of malignant neoplasms", which share a similar morphotype ("squamous cell carcinoma"), but whose biological evolution is variable and dependent on different factors, including anatomical location. In order to try to demonstrate this hypothesis, a clinicopathological and evolutionary study was planned in a cohort of patients diagnosed and treated for OSCC in a single hospital institution in Spain, grouping them according to the main intraoral locations. The final objective was to find data that would facilitate prevention and early diagnosis and improve the prognosis of this malignant pathology.

2 | MATERIALS AND METHODS

A retrospective observational study was conducted of all patients diagnosed and treated for OSCC in the main intraoral locations (lateral border of the tongue, gingiva, and floor of the mouth) at the University Hospital Complex of Santiago de Compostela (Galicia, Spain) between 2010 and 2015. All patients were histopathologically diagnosed of oral squamous cell carcinoma. Inclusion of cases required a minimum of 5 years of follow-up after the initial diagnosis of OSCC. Data was reported following the STROBE guidelines. This study was approved by the Santiago-Lugo Research Ethics Committee (Reference 2020/247).

A total of 133 patients diagnosed and treated for OSCC were included, of which 63 (47.3%) were on the lateral border of the

tongue (TSCC), 36 (27.1%) on the gingiva (GSCC) and 34 (25.5%) on the floor of the mouth (FOMSCC). These neoplasms were present in 48 females (36.1%) and 85 males (63.9%), with a mean age of 66.6 ± 12.73 years (range 20–93 years) at the time of histopathological diagnosis. In cases where more than one contiguous site was affected (gingiva and floor of mouth or lateral tongue and floor of mouth), the location with the greatest involvement was recorded. Cases with multiple synchronous SCCs affecting separate locations were not included.

A specific study protocol was designed to address the epidemiological, clinicopathological and prognostic data for each case. The main variables obtained were: age, sex, tobacco, and alcohol consumption, presence of comorbidities, location, clinical appearance, presence of an oral potentially malignant disorder (OPMD) and its type (obtained from the patient's medical history), complete TNM staging, treatment modality, histological subtype of squamous cell carcinoma (SCC), degree of differentiation, presence of invasion (perineural, bone, and vascular), surgical margin involvement, presentation and type of recurrence, presentation of second primaries, death and its cause. SCC type and degree of tumor differentiation were analyzed based on World Health Organization (WHO) recommendations (El-Naggar et al., 2017). TNM staging was performed according to the seventh edition of the Cancer Staging Manual (Edge et al., 2010) which was the consensus at the time of diagnosis. Second primary oral SCCs were addressed following the diagnostic criteria by Warren and Gates (1932). Calculation of overall and specific survival were based on the dates of diagnosis and death.

For the statistical analysis, the IBM SPSS Statistics software (version 23.0) was used. Initially, a descriptive analysis of the groups was carried out, calculating frequencies and percentages for qualitative variables and the mean, standard deviation, minimum, and maximum for quantitative variables. The Chi2 test or ANOVA was used to compare the groups, depending on the nature of the variables. Survival was calculated using the Kaplan–Meier method, comparing the groups with the log rank test. Univariate multinomial regression models were constructed for the variables that had been significant with the Chi2 analysis, taking the FOMSCC group as reference category; subsequently, a multivariate model was constructed. Statistical significance was established at p -values ≤ 0.05 .

3 | RESULTS

The main epidemiological, clinicopathological and evolutionary characteristics of the cohort are shown in Table 1, for the whole group as for each anatomical site.

3.1 | Univariate analysis

The age at diagnosis was significantly lower in patients in the FOMSCC group (60.13 years), than in those in the TSCC (67.37 years)



TABLE 1 Descriptive and comparative analysis of the main clinicopathological variables of the total cohort and subgroups.

Data		Total	Floor of mouth (n = 34)	Gingiva (n = 36)	Lateral tongue (n = 63)	p value
Mean age (SD)		66.60 (±12.73)	59.79 (±12.00)	72.31 (±9.76)	67.02 (±12.99)	<0.001
Sex	Female	48 (36.1%)	5 (14.7%)	17 (47.2%)	26 (41.3%)	0.009
	Male	85 (63.9%)	29 (85.3%)	19 (52.8%)	37 (58.7%)	
Tobacco consumption (n = 118)	No	58 (49.2%)	7 (20.6%)	23 (79.3%)	28 (50.9%)	<0.001
	Yes	47 (39.8%)	22 (64.7%)	4 (13.8%)	21 (38.2%)	
	Former	13 (11%)	5 (14.7%)	2 (6.9%)	6 (10.9%)	
Alcohol consumption (n = 115)	No	35 (30.4%)	5 (15.2%)	15 (53.6%)	15 (27.8%)	0.001
	Yes	70 (60.9%)	21 (63.6%)	13 (46.4%)	36 (66.7%)	
	Former	10 (8.7%)	7 (21.2%)	0 (0%)	3 (5.6%)	
Comorbidities	Yes	99 (74.4%)	24 (70.6%)	27 (75%)	48 (76.2%)	0.830
Cardiovascular	Yes	65 (49.2%)	14 (41.2%)	16 (24.6%)	35 (55.8%)	0.356
Dyslipidemia	Yes	51 (38.6%)	12 (35.3%)	12 (34.3%)	27 (42.9%)	0.633
Diabetes Mellitus	Yes	18 (13.6%)	4 (11.8%)	6 (17.1%)	8 (12.7%)	0.774
Thyroid	Yes	14 (10.6%)	3 (8.8%)	5 (14.3%)	6 (9.5%)	0.708
Gastrointestinal	Yes	22 (16.7%)	6 (17.6%)	4 (11.4%)	12 (19.0%)	0.615
Hepatic	Yes	23 (17.4%)	9 (26.5%)	1 (2.9%)	13 (20.6%)	0.023
Immunologic	Yes	4 (3%)	1 (2.9%)	2 (5.7%)	1 (1.6%)	0.521
Psychiatric	Yes	15 (11.4%)	6 (17.6%)	1 (2.9%)	8 (12.7%)	0.138
Neurologic	Yes	4 (3%)	2 (5.9%)	1 (2.9%)	1 (1.6%)	0.499
Other cancers	Yes	41 (31.1%)	12 (35.3%)	12 (34.3%)	17 (27%)	0.624
Clinical appearance	Ulcer	55 (41.4%)	17 (50%)	12 (33.3%)	26 (41.3%)	0.416
	Ulcerated tumor	45 (33.8%)	10 (29.4%)	13 (36.1%)	22 (34.9%)	
	Non-ulcerated tumor	17 (12.8%)	4 (11.8%)	7 (19.4%)	6 (9.5%)	
	Leukoplakia	12 (9.1%)	1 (2.9%)	3 (8.4%)	8 (12.7%)	
	Erythroleukoplakia	4 (3%)	2 (5.9%)	1 (2.8%)	1 (1.6%)	
Previous OPMD	Yes	28 (21.1%)	5 (14.7%)	7 (19.4%)	16 (25.4%)	0.560
Type of previous OPMD	Leukoplakia	17 (60.7%)	5 (100)	2 (28.6)	10 (62.5)	0.042
	Erythroleukoplakia	2 (7.1%)	0 (0)	0 (0)	2 (12.5)	
	Lichen	4 (14.3%)	0 (0)	1 (14.3)	3 (18.8)	
	PVML	5 (17.9%)	0 (0)	4 (57.1)	1 (6.3)	
T stage	Tx	1 (0.8%)	0 (0%)	0 (0%)	1 (1.6%)	0.745
	T1	45 (33.8%)	9 (26.5%)	12 (33.3%)	24 (38.1%)	
	T2	49 (36.8%)	13 (38.2%)	12 (33.3%)	24 (38.1%)	
	T3	5 (3.8%)	1 (2.9%)	1 (2.8%)	3 (4.8%)	
	T4	33 (24.8%)	11 (32.4%)	11 (30.6%)	11 (17.5%)	
N stage	Nx	2 (1.5%)	0 (0%)	1 (2.8%)	1 (1.6%)	0.671
	N0	88 (66.2%)	21 (61.8%)	27 (75%)	41 (66.1%)	
	N1	15 (11.3%)	3 (8.8%)	4 (11.1%)	8 (12.9%)	
	N2	27 (20.3%)	9 (26.5%)	5 (3.9%)	13 (21%)	
	3	1 (0.8%)	1 (2.9%)	0 (0%)	0 (0%)	
M stage	M0	130 (97.7%)	34 (100%)	35 (97.2%)	61 (96.8%)	0.586
	M1	3 (2.3%)	0 (0%)	1 (2.8%)	2 (3.2%)	

(Continues)

TABLE 1 (Continued)

Data		Total	Floor of mouth (n = 34)	Gingiva (n = 36)	Lateral tongue (n = 63)	<i>p</i> value
Overall stage	I	38 (28.6%)	7 (20.6%)	10 (27.8%)	21 (33.3%)	0.546
	II	38 (28.6%)	11 (32.4%)	10 (27.8%)	17 (27.0%)	
	III	12 (9%)	2 (5.9%)	2 (5.6%)	8 (12.7%)	
	IV	45 (33.8%)	14 (41.2%)	14 (38.9%)	17 (27%)	
Treatment type	Surgery alone	65 (48.9%)	12 (35.3%)	19 (52.8%)	34 (54%)	0.460
	Surgery+adjuvant RT	33 (24.8%)	13 (38.2%)	9 (25%)	11 (17.5%)	
	Surgery+adjuvant CRT	18 (13.5%)	6 (17.6%)	5 (13.9%)	7 (11.1%)	
	Radical RT	3 (2.3%)	1 (2.9%)	0 (0%)	2 (3.2%)	
	Radical CRT	6 (4.5%)	1 (2.9%)	1 (2.8%)	4 (6.3%)	
	Palliative	4 (3%)	1 (2.9%)	0 (0%)	3 (4.8%)	
	No treatment	4 (3%)	0 (0%)	2 (5.6%)	2 (3.2%)	
Neck dissection	Yes	65 (48.9%)	20 (58.8%)	17 (47.2%)	28 (44.4%)	0.390
Histologic type	Conventional	128 (96.2%)	33 (97.1%)	32 (88.9%)	63 (100%)	0.117
	Verrucous	1 (0.8%)	0 (0%)	1 (2.8%)	0 (0%)	
	Basaloid	2 (1.5%)	1 (2.9%)	1 (2.8%)	0 (0%)	
	Papillary	2 (1.5%)	0 (0%)	2 (5.6%)	0 (0%)	
Grade of differentiation	Well differentiated	54 (43.9%)	9 (29%)	17 (54.8%)	28 (45.9%)	0.133
	Moderately differentiated	62 (50.4%)	18 (58.1%)	13 (41.9%)	31 (50.8%)	
	Poorly differentiated	7 (5.7%)	4 (12.9%)	1 (3.2%)	2 (3.3%)	
Perineural invasion	Yes	29 (21.8%)	8 (23.5%)	3 (8.3%)	18 (28.6%)	0.061
Bone invasion	Yes	24 (18%)	7 (20.6%)	16 (44.4%)	1 (1.6%)	<0.001
Lymphovascular invasion	Yes	13 (9.8%)	2 (5.9%)	4 (11.1%)	7 (11.1%)	0.676
Affected surgical margins	Yes	32 (27.6%)	11 (36.7%)	13 (40.6%)	8 (14.8%)	0.015
Recurrence	No	83 (62.4%)	23 (67.6%)	20 (55.6%)	40 (63.5%)	0.910
	Local	19 (14.3%)	4 (11.8%)	8 (22.2%)	7 (11.1%)	
	Regional	12 (9%)	2 (5.9%)	3 (8.3%)	7 (11.1%)	
	Locoregional	11 (8.3%)	3 (8.5%)	3 (8.3%)	5 (7.9%)	
	Distance	8 (6%)	2 (5.9%)	2 (5.6%)	4 (6.3%)	
Second primary OSCC	Yes	4 (3%)	1 (2.9%)	2 (5.6%)	1 (1.6%)	0.539
Death	No	46 (43.6%)	11 (32.4%)	13 (36.1%)	22 (34.9%)	0.867
	Yes (tumour and related causes)	57 (42.9%)	13 (38.2%)	16 (44.4%)	28 (44.4%)	
	Yes (other causes)	30 (22.6%)	10 (29.4%)	7 (19.4%)	13 (20.6%)	
5-year OS		54 (40.6%)	13 (38.2%)	19 (47.2%)	24 (38.1%)	0.638
5-year DSS		48 (46.6%)	11 (45.8%)	15 (51.7%)	22 (44%)	0.800

Note: All *p*-values are shown in italics. Boldface is used to show the significance when $p < 0.05$.

Abbreviations: CRT, chemoradiotherapy; DSS, disease-specific survival; OPMD, oral premalignant disorder; OS, overall survival; PVML, proliferative verrucous/multifocal leukoplakia; RT, radiotherapy; SCC, squamous cell carcinoma; SD, standard deviation.

and in the GSCC (72.50 years) ($p < 0.001$). This result was significant in the multinomial regression analysis (Table 2), resulting in an increased risk of SCC in the tongue (OR=1.05; 95% CI=1.01–1.09) and gingiva (OR=1.09; 95% CI=1.04–1.14) with each year of age, taking the FOMSCC group as a reference.

The percentage of women was significantly higher in the GSCC group (47.2%) than in the other locations (TSCC: 41.3%; FOMSCC:

14.7%) ($p=0.009$). In the regression analysis, women showed a higher risk than men of developing SCC at the gingiva (OR=5.19; 95% CI=1.64–16.44) and at the lateral tongue (OR=4.08; 95% CI=1.39–11.92).

There was a significantly higher number of tobacco and/or alcohol users in the FOMSCC group, followed by the TSCC and the GSCC ($p < 0.001$ and $p=0.001$). Non-smoking patients had

TABLE 2 Multinomial regression of the variables associated with anatomical location. The floor-of-mouth group is taken as reference category.

Data	Location (ref: FOM)	Category	Univariate multinomial regression		Multivariate multinomial regression	
			OR (CI 95%)	<i>p</i> value	OR (CI 95%)	<i>p</i> value
Age	Tongue		1.05 (1.01–1.09)	0.009	—	>0.05
	Gingiva		1.09 (1.04–1.14)	<0.001		
Gender (ref: male)	Tongue	Female	4.08 (1.39–11.92)	0.010	—	>0.05
	Gingiva	Female	5.19 (1.64–16.44)	0.005		
Risk factors (ref: tobacco + alcohol)	Tongue	No	2.8 (0.81–9.74)	0.106	—	>0.05
		Alcohol	2.8 (0.91–8.61)	0.720		
		Tobacco	0.7 (0.19–2.53)	0.586		
	Gingiva	No	14 (2.81–69.76)	0.001		
		Alcohol	6.67 (1.38–32.28)	0.018		
		Tobacco	0.58 (0.05–6.59)	0.663		
Tobacco consumption (ref: yes)	Tongue	No	4 (1.49–10.71)	0.006	3.81 (1.34–10.44)	0.009
	Gingiva	No	14.79 (4.35–50.29)	<0.001	16.46 (4.30–62.97)	<0.001
Alcohol consumption (ref: yes)	Tongue	No	2.15 (0.7–6.62)	0.180	—	>0.05
	Gingiva	No	6.46 (1.93–21.61)	0.002		
Liver disease (ref: yes)	Tongue	No	1.39 (0.52–3.68)	0.513	—	>0.05
	Gingiva	No	12.6 (1.5–105.9)	0.020		
Degree of differentiation (ref: PD)	Tongue	WD	6.22 (0.97–39.81)	0.054	—	>0.05
		MD	3.44 (0.57–20.71)	0.177		
	Gingiva	WD	7.56 (0.73–78.09)	0.090		
		MD	2.89 (0.23–28.94)	0.367		
Perineural invasion (ref: yes)	Tongue	No	0.77 (0.29–2.01)	0.593	—	>0.05
	Gingiva	No	3.39 (0.19–14.04)	0.093		
Bone invasion (ref: yes)	Tongue	No	16.07 (1.89–137.1)	0.011	0.08 (0.01–0.68)	0.021
	Gingiva	No	0.32 (0.11–0.94)	0.037	5.63 (1.42–22.35)	0.014
Affected surgical margins (ref: yes)	Tongue	No	3.33 (1.16–9.57)	0.026	—	>0.05
	Gingiva	No	0.85 (0.3–2.36)	0.846		

Note: All *p*-values are shown in italics. Boldface is used to show the significance when *p* < 0.05.

Abbreviations: CI, confidence interval; FOM, floor of mouth; MD, moderately differentiated; OR, odds ratio; PD, poorly differentiated; ref, reference; WD, well differentiated.

a higher risk of GSCC (OR = 14.79; 95% CI = 4.35–50.29) compared to mouth floor, as did non-alcohol users (OR = 6.46; 95% CI = 1.93–21.61). In addition, non-smoking and non-drinking patients showed an increased risk of developing a GSCC (OR = 14; 95% CI = 2.81–69.76).

As for the presence of comorbidities, differences on liver pathologies were observed, which were more frequent in the FOMSCC (26.5%) and TSCC (20.6%) groups and much less frequent in the GSCC (2.8%) (*p* = 0.020). This was also significant in the univariate regression. Although a total of 41 cases developed other malignancies, there were no differences between the three groups studied (Table 1).

The clinical appearance of OSCC as an “ulceration” was predominant in all three groups studied. Regarding the previous presence of OPMDs, they were more frequent in the TSCC group (25.4%), with no significant differences. With respect to the type of OPMD,

leukoplakia was predominant in the TSCC and FOMSCC groups, while in the GSCC group, proliferative verrucous/multifocal leukoplakia (PVML) was the most frequent (*p* = 0.042).

Regarding tumor staging, only slight differences were observed between the groups, with a higher number of T4 cases in the FOMSCC (32.4%) and in the GSCC (30.6%). Nodal involvement was lower in the GSCC group (25.7%) than in TSCC (33.9%) and FOMSCC (38.2%). More than half of the cases analyzed in all locations were diagnosed at an early stage (I and II), with no significant differences between the groups (Table 1).

There were no significant differences in relation to the treatment implemented and the location of the OSCC, including cervical lymph node dissection (Table 1).

Referring to the histopathological aspect, most of the SCCs analyzed were conventional, comprising the 100% of the TSCC group.

The GSCC group had the highest percentage of histological variants (11.1%) and the highest frequency of well-differentiated SCCs (Table 1). SCCs from the lingual border and the floor of the mouth showed the highest percentage of perineural invasion (28.6% and 23.5%, respectively) ($p=0.061$). On the other hand, as expected, bone invasion was much more common in the GSCC group (44.4%; $p<0.001$); this was also significant in multinomial regression. The presence of affected surgical margins was also significantly more frequent in gingival carcinomas ($p=0.015$; Table 1).

In relation to prognosis, there were no significant differences between the groups with regard to the development of tumor recurrences, occurrence of second primaries and survival, neither overall (OS) nor disease-specific (DSS; Figure 1). However, in the GSCC group a higher percentage of local recurrences was observed (22.2%), in addition to higher OS (47.2%) and DSS (51.7%) (Table 1).

3.2 | Multivariate regression

In the multivariate regression model, only two variables remained significant in relation to the location of OSCC: tobacco consumption and the presence of bone invasion (Table 2). Non-smokers had a higher risk of SCC on the lingual border (OR=3.81; 95% CI=1.34–10.44) or gingiva (OR=16.46; 95% CI=4.30–62.97) than those on the floor of the mouth (Table 2). As noted above, the risk of bone invasion was significantly higher in SCC located in the gingiva (OR=5.63; 95% CI=1.42–22.35).

4 | DISCUSSION

After performing a global analysis of OSCC cases diagnosed, treated and monitored for at least 5 years in a single center in Galicia (Spain) (Amézaga-Fernández et al., 2024), we planned to describe and compare the clinicopathological and evolutionary profiles of the main

locations of OSCC, with the aim of finding particular data that would facilitate prevention, early diagnosis, and improve the poor prognosis of this pathology. The results obtained indicate that OSCC shows some particularities in epidemiological and clinicopathological data depending on its location.

In the present study, SCC located on the floor of the mouth mostly affected men, with an average age over 60 years, most of whom were smokers and alcohol consumers. These results are consistent with those obtained in other studies (Pires et al., 2013; Radoi et al., 2013; Xu et al., 2019), which indicate that OSCC is mainly associated with smoking and alcohol consumption, and more common in men aged between 50 and 60 years. Histologically, these SCCs were almost entirely of the conventional type, with a greater percentage of poorly differentiated carcinomas, and frequent perineural and vascular invasion. It was also observed a higher percentage of cases with lymph node involvement and advanced stages (III and IV) in this group, although the differences were not significant. Some studies (Kim et al., 2019; Liu et al., 2017; Saggi et al., 2018) have obtained similar results, suggesting that FOMSCC would have a higher biological aggressiveness than that of other locations. This could be due to the anatomical and histological particularities of the mucosa in the floor of the mouth, with a thin epithelium and high permeability. This particularity would make it very susceptible to the carcinogenic effect of tobacco and alcohol, and would facilitate tumor invasion.

GSCC was more frequent in people over 70 years of age, affecting women and men equally. This was the location least associated with tobacco and alcohol consumption, data also reported by other authors (Lee et al., 2019; Oh et al., 2021; Xu et al., 2019). The low alcohol consumption observed in this group could explain the low rate of liver pathology of these patients, compared to the other groups. This location has the highest percentage of histopathological variants of SCC, as well as the highest differentiation. A distinctive aspect was the high percentage of tumors with bone invasion and

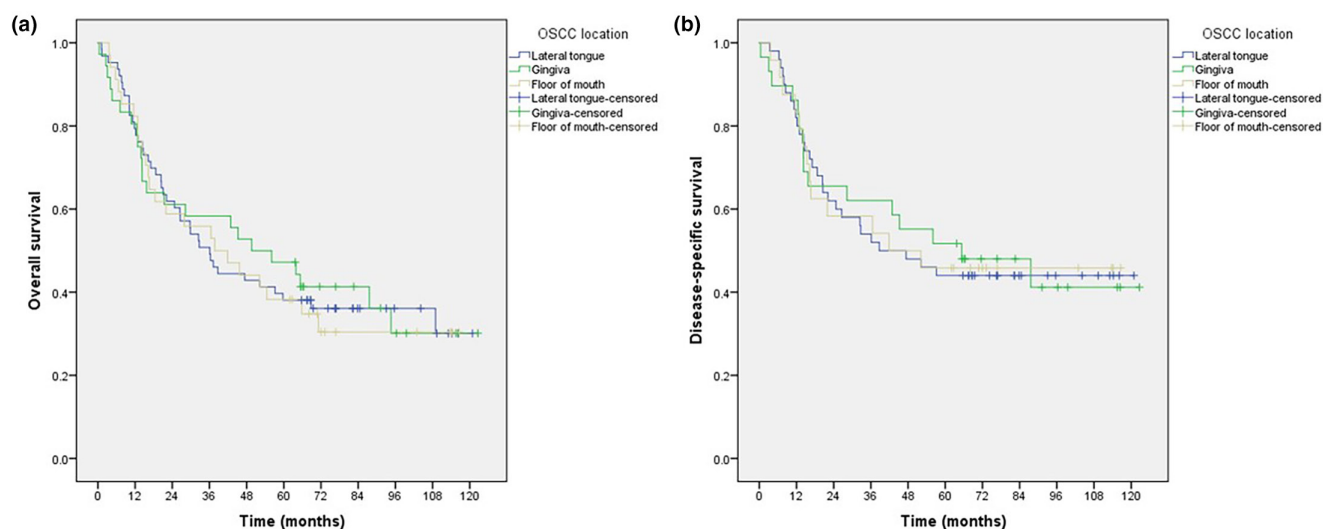


FIGURE 1 Kaplan-Meier survival curves stratified by anatomic location. (a) Overall survival; (b) disease-specific survival.

affected surgical margins, which could indicate a greater difficulty in performing adequate surgical excision of gingival tumors.

An interesting result of this study was that PVML was the most frequent OPMD associated with gingival SCC (57.1%). This premalignant disorder presents with multifocal, homogeneous and non-homogeneous, proliferative leukoplakias, which are frequently located in the gingiva (Lafuente-Ibáñez de Mendoza et al., 2022; Warnakulasuriya et al., 2021). The relevance of PVML resides in its high risk of malignant development, often located in the gum (Arduino et al., 2021; Bagán et al., 2003; Lafuente-Ibáñez de Mendoza et al., 2022). In addition, many of these patients are not associated with well-known carcinogenic elements (tobacco-alcohol) and have a better prognosis of developed SCCs, which would suggest particular biological aspects (Akrish et al., 2019; González-Moles et al., 2021). However, in the current study there were no significant differences in relation to survival (50% in PVML and 40.3% in the rest), which could be related to the small number of patients in this subgroup with OSCC and PVML.

The lingual border is undoubtedly the most paradigmatic intraoral location for OSCC, both in terms of frequency and clinico-pathological and prognostic characteristics. The average age of the patients with TSCC was intermediate compared to that of the other sites, around 67 years. On the other hand, the gender distribution was more balanced in this group than in the FOMSCC group, possibly due to lower tobacco consumption. However, tobacco and alcohol consumption clearly have an important carcinogenic role in this location (Pentenero et al., 2011; Radoi et al., 2013). Inside the TSCC group, two defined subgroups of patients could be observed: one of tobacco consumers, composed mainly of men (92.6%) under 65 years of age (71.7%), and another of non-smokers, with a higher percentage of women (67.9%) over 70 years of age (63.8%). These results are suggestive of a strong relationship between smoking, alcohol drinking, sex, age, and this anatomical location, and most likely, other carcinogenic factors. Given the anatomical, histological and physiological particularities of the lingual margin, it is reasonable to consider the existence of other carcinogenic elements at this site, including chronic irritation associated with the friction of this mucosa with teeth, prostheses, food, etc., (Piemonte et al., 2022).

In the multivariate analysis, tobacco consumption was the only variable that remained significant in relation to the main OSCC groups according to their location, with the rest of the associated variables being dependent on this carcinogenic habit. This result supports the fact that tobacco remains the most important oral carcinogenic agent in our environment. However, its effect is different according to the oral anatomical location, with the floor of the mouth being the most related area, followed by the lingual margin and the gingiva, which is consistent with other studies (Pentenero et al., 2011; Radoi et al., 2013). In addition, non-smoking patients with OSCC tend to be older than smokers, suggesting a more prolonged carcinogenic process over time and involving other factors (DeAngelis et al., 2018; Pentenero et al., 2011; Xu et al., 2019; Yan et al., 2023). Considering that men still consume more tobacco than women (DeAngelis et al., 2018; Oh et al., 2021), it would explain why

SCC of the floor of the mouth appears mostly in men and somewhat younger. In contrast, gingival SCC, which would be the least related to tobacco and alcohol use, would affect women and men equally, and would take longer to develop, as already suggested (DeAngelis et al., 2018; Lee et al., 2019; Pentenero et al., 2011; Xu et al., 2019).

These findings suggest the existence of other oral carcinogenic factors in our environment, such as oral dysbiosis, chronic oral inflammatory disorders, diet, etc. In this sense, it may be very interesting to study GSCC, given the high prevalence of non-smoking patients in this group. In this study, the gingiva was the second most frequent intraoral location of OSCC, and in most cases it was not possible to recognize carcinogenic factors, which limits preventive actions for this pathology.

Along with smoking, bone invasion was also significant in the multivariate analysis. As expected, the GSCC group had a much higher percentage of bone involvement than the other groups, mainly due to the proximity of the alveolar bone. However, it has been proposed (Vaassen et al., 2017) that the existence of periodontal inflammation in the environment would facilitate bone invasion, producing areas of hypoxia capable of inhibiting osteoblastic differentiation. This circumstance could also be related to the high percentage of cases in the GSCC group with affected surgical margins, as well as the high rate of local recurrences present. It is important to consider these results in future surgical treatment protocols for SCC of the gingiva.

This study showed a similar prognosis for the three groups of OSCC analyzed in both overall and disease-specific survival, as have other studies (Bell et al., 2007; Ong et al., 2017). However, some differences were observed in TNM staging and survival, although these were not statistically significant. The gingival SCC group was the group with the lowest rate of cervical lymph node involvement, while FOMSCC was the group with the most N+ patients, as well as with advanced stages (III and IV). Survival in the GSCC group was longer than the other two groups, which is consistent with other similar studies (Kim et al., 2016; Ong et al., 2017). The lack of significant differences in these data could be related to the small number of cases in some groups. Other studies (Farhood et al., 2019; Lin et al., 2021) with larger cohorts of patients have found significant prognostic dissimilarities. In the study by Farhood et al. (2019), the tongue had the worst prognosis. Lin et al. (2021) reported worse outcome for hard palate and the alveolar ridge tumors. These contradictory results could be related to the different carcinogenic mechanisms associated with factors specific to each population studied.

This study on the characteristics of OSCC in the main intraoral locations is the largest carried out in Galicia (Spain). The fact that all patients were treated in the same hospital favors the homogeneity of the sample with respect to their geographical origin and the diagnostic and therapeutic protocols applied. The retrospective design of this study has inherent limitations, such as the loss of some data. In addition, given the time period analyzed, the staging of all cases was based on the seventh edition of the AJCC Cancer Staging Manual (Edge et al., 2010). It would be of great interest to conduct comparative studies on larger cohorts, analyzing the etiopathogenic,

clinicopathological, prognostic and molecular aspects of OSCC in relation to its locations. These studies could provide valuable information regarding the genesis, diagnosis, therapy, prognosis and prevention of this malignant neoplastic pathology.

5 | CONCLUSION

The results of this study show that anatomical location is an important factor in the etiopathogenesis of OSCC in Galicia (Spain). SCC of the lateral border of the tongue, gingiva and floor of the mouth show differences that should be taken into account for the prevention of this neoplasm. Tobacco consumption is a very important variable in relation to the SCC of the floor of the mouth. In many patients with SCC of the gingiva and lingual margin there are other carcinogenic factors. There were no significant prognostic differences between the groups. Anatomical location should be a factor to be considered in preventive protocols for this malignant neoplasm.

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AUTHOR CONTRIBUTIONS

Iñaut Amezaga-Fernandez: Conceptualization; data curation; investigation; formal analysis; funding acquisition; writing – original draft; writing – review and editing; resources. **José Manuel Aguirre-Urizar:** Conceptualization; methodology; formal analysis; writing – original draft; writing – review and editing; supervision. **José Manuel Suárez-Peñaranda:** Conceptualization; data curation; writing – review and editing. **Cintia Chamorro-Petronacci:** Investigation; writing – review and editing. **Irene Lafuente-Ibáñez de Mendoza:** Writing – original draft; writing – review and editing. **Xabier Marichalar-Mendia:** Methodology; software; formal analysis; writing – review and editing. **José Manuel Somoza-Martín:** Conceptualization; writing – review and editing. **Andrés Blanco-Carrión:** Conceptualization; writing – review and editing. **José Antúnez-López:** Conceptualization; writing – review and editing. **Abel García-García:** Conceptualization; methodology; formal analysis; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Research data are not publicly available due to privacy or ethical restrictions.

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