

Clinicopathological Features and Statistical Associations in Squamous Cell Carcinoma of the Lip

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ABSTRACT: Background: Lip squamous cell carcinoma (SCC) is frequently associated with chronic ultraviolet exposure and actinic cheilitis. Although prognosis is generally favorable, clinicopathological parameters may correlate with tumor characteristics and risk-related patterns. Materials and Methods: A retrospective study was conducted on 21 cases of lip SCC diagnosed at the County Clinical Emergency Hospital of Craiova between January 2021 and June 2025. Epidemiological and clinical variables (age, sex, area of residence, tumor site and size, macroscopic appearance) and histopathological parameters (subtype, grade, tumor extension, resection margin status, depth of invasion, perineural and vascular invasion) were evaluated. Associations were tested using the Chi-square (χ^2) tests in IBM SPSS software. Results: The mean age was 74.2 ± 10.88 years, with male predominance (71.4%) and rural residence 71.4% of patients. Most tumors were located on the lower lip (90.4%). Keratinizing SCC was the most frequent histological subtype (61.9%), and well to moderately differentiated tumors (G1-G2) predominated. Muscular invasion was identified in 71.4% of cases, and pT3 was the most frequent (71.4%). Actinic cheilitis was present in all cases. Statistically significant associations were observed between gender and histological grade, tumor site and differentiation, and between histological subtype and degree of differentiation ($p < 0.05$). Conclusions: Lip SCC predominantly affects elderly male patients and most frequently involves the lower lip. Tumor localization, depth of invasion, and histological grade showed relevant associations with the aggressiveness of lip SCC.

KEYWORDS: Lip squamous cell carcinoma, actinic cheilitis, clinicopathological features, histopathological grading, depth of invasion.

Introduction

Actinic cheilitis (AC) is regarded as a potentially malignant disorder with the ability to progress to invasive SCC of the lip.

However, the clinical and morphological assessment of AC lesions is inherently subjective and lacks sufficient reliability in predicting which cases will subsequently undergo malignant transformation [1].

Squamous cell carcinoma (SCC) of the lip is a malignant epithelial tumor characterized by infiltrative and destructive growth, with the capacity for both lymphatic and hematogenous metastasis.

The reported incidence of lip cancer is approximately 13.5 per 100,000 inhabitants in Oceania, 12 per 100,000 in Europe, and 12.7 per 100,000 in North America [3].

The majority of lip SCC cases involve the lower lip, which accounts for nearly 90% of presentations.

The disease predominantly affects males, a pattern commonly attributed to increased

cumulative ultraviolet exposure related to occupational activities, as well as a higher prevalence of tobacco use and alcohol consumption [3].

Epidemiological distinctions observed between cancers of the upper and lower lips support the hypothesis that these neoplasms may arise from distinct oncogenic pathways [1,2].

The prognosis of lip SCC is generally favorable, with reported five-year survival rates approaching 90% in several published studies.

In contrast, patients diagnosed with advanced primary tumors (T3 or T4) or with regional lymph node involvement exhibit poorer outcomes.

Following treatment, long-term surveillance is recommended for a minimum of five years to allow early detection of local recurrence or regional disease progression.

Notably, approximately 75% of metastatic events occur within the first year after surgical management, underscoring the need for meticulous follow-up during this interval [3].

Lip SCC is generally regarded as a neoplasm with relatively low biological aggressiveness and a favorable prognosis, largely attributable to its typically slow rate of progression.

In more advanced stages, patients may develop pain in association with ulceration and surface changes such as exudation, scaling, and crust formation.

Clinical examination often reveals indurated margins and an infiltrated, non-healing base.

The tumor may manifest as a friable or bleeding lesion and can adopt verrucous or exophytic growth patterns [1,3].

Conventional oral squamous cell carcinoma (OSCC) constitutes a distinct clinicopathological subset within the spectrum of squamous cell carcinomas and, while sharing histopathological features with lip SCC, differs in epidemiology and clinical behavior.

It has been reported to account for approximately 10-15% of SCC cases, depending on anatomical location and study population [4].

According to the latest World Health Organization (WHO) criteria, several histopathological variants of OSCC are recognized, including basaloid, acantholytic, adenosquamous, spindle cell (sarcomatoid), papillary, and lymphoepithelial carcinomas [4].

Objective

This study aims to analyze epidemiological characteristics associated with lip tumors in a cohort from the Oltenia region.

The analysis includes variables such as sex, age, area of residence, tumor localization, macroscopic appearance, and histopathological aspects.

The study is based on cases diagnosed at the County Clinical Emergency Hospital of Craiova.

Methods

The study included 21 cases of lip squamous cell carcinoma diagnosed at the Anatomical Pathology Laboratory of the County Clinical Emergency Hospital of Craiova between January 2021 and June 2025.

Tissue samples were processed using standard histopathological techniques, involving paraffin embedding and hematoxylin-eosin staining following fixation in 10% buffered formalin.

Lesions were classified according to WHO criteria.

An epidemiological assessment (age, sex, tumor location, tumor size) and a histopathological evaluation (histological subtype, grade, pathological tumor stage, resection margin status, depth of invasion, perineural invasion, and vascular invasion) were performed. Statistical analyses were conducted using the chi-square (χ^2) test with SPSS software.

Results

The epidemiological analysis of the 21 cases of lip squamous cell carcinoma showed that patient age ranged from 44 to 89 years, with a mean age of 74.2 ± 10.88 years. Most patients (71.5%) lived in rural areas.

Age-group analysis demonstrated that the highest proportion of cases occurred in the 70-79-year age group, comprising 7 cases (33.3%), followed by patients aged 80-89 years (5 cases, 23.8%), 50-59 years (5 cases, 23.8%), 60-69 years (3 cases, 14.3%), and those younger than 50 years (1 case, 4.8%) (Table 1).

Sex distribution revealed a predominance of male patients, accounting for 15 cases (71.4%).

Regarding anatomical localization, the lower lip was the most frequently affected site, observed in 19 cases (90.4%) (Table 1, Figure 1).

Table 1. Epidemiological characteristics of lip SCC.

GRADE	No. cases	gender		age					residence	
		Male	Female	<50	≥ 50 & <60	≥ 60 & <70	≥ 70 & <80	≥ 80 & <89	Rural	Urban
G1	10	6	4	1	3	2	3	1	8	2
G2	10	8	2	0	2	1	4	3	6	4
G3	1	1	0	0	0	0	0	1	1	0
p value		P<0.05				p>0.05			p>0.05	



Figure 1. Clinical aspects of actinic cheilitis and lip squamous cell carcinoma.
(A, B) Actinic cheilitis of the lower lip; (C) Ulcerated squamous cell carcinoma of the lower lip;
(D) Vegetative squamous cell carcinoma of the lower lip.

Tumor size ranged from 0.7 to 5.4cm, with a mean diameter of 2.38cm.

Based on lesion size, most tumors (66.7%) measured ≤ 2 cm, while 19% were between >2 and ≤ 4 cm, and 14.3% exceeded 4cm in diameter.

The ulcerated lesions of lip SCC represented the most common presentation, accounting for 66.7% of cases (Table 2, Figure 1).

All examined cases were histologically associated with actinic cheilitis.

The histopathological analysis evaluated tumor grade, histological subtype, resection margin status, depth of invasion, perineural invasion, and vascular invasion.

Tumor differentiation assessment showed that 10 cases (47.6%) were classified as well-differentiated (G1), 10 cases (47.6%) as moderately differentiated (G2), and 1 case (4.8%) as poorly differentiated (G3).

Resection margins were free of tumor involvement in 61.9% of cases (Table 3) (Figure 2).

Based on pathological tumor stage, most tumors were classified as pT3 (15 cases, 71.5%), followed by pT1 (4 cases, 19%) and pT2 (2 cases, 9.5%).

No pT4 tumors were identified (Table 3).

Evaluation of invasion depth demonstrated extension into the underlying striated muscle in 15 cases (71.5%), invasion limited to the chorion in 5 cases (23.8%), and involvement of the underlying adipose tissue in 1 case (4.7%) (Table 3, Figure 3).

Perineural invasion was present in 5 cases (23.8%) (Figure 4), while vascular invasion was identified in 1 case (4.7%).

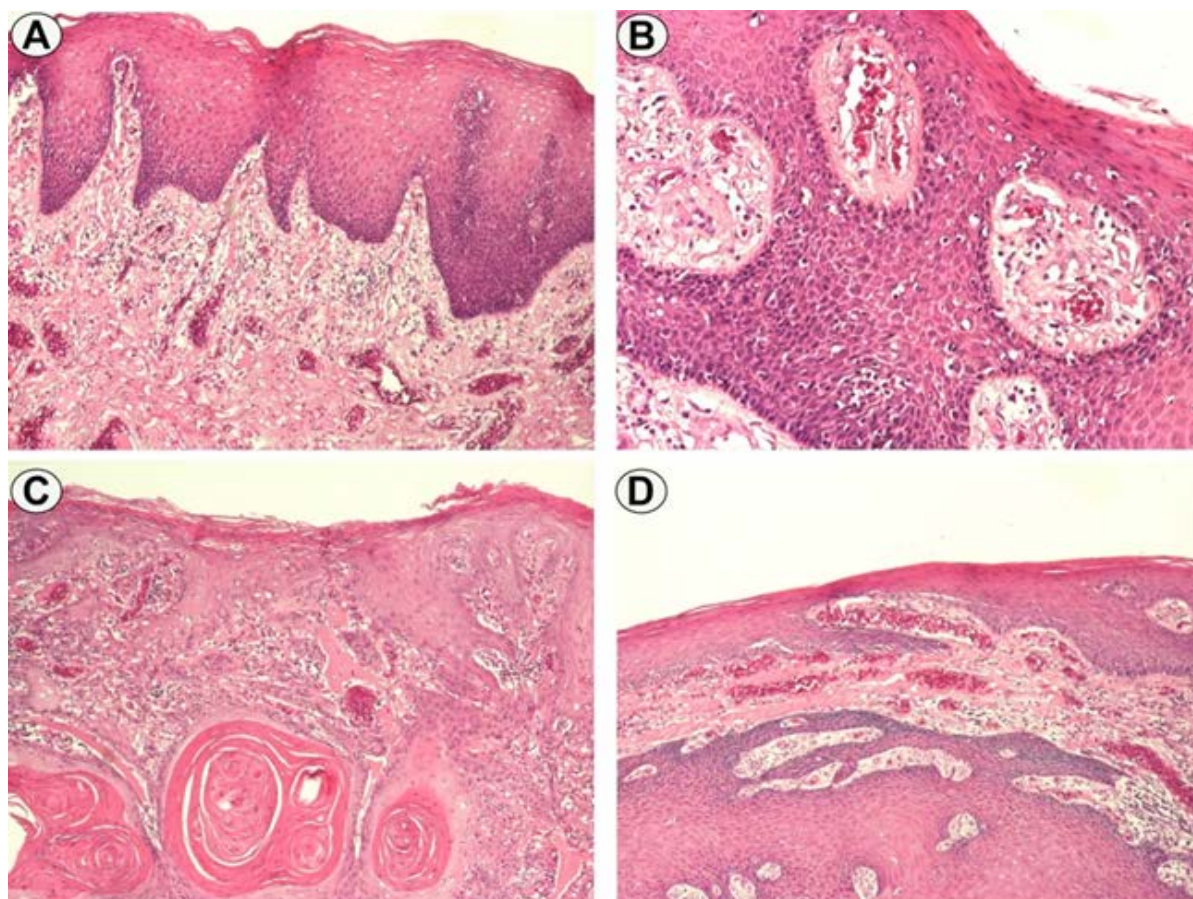
The keratinizing histological subtype was the most frequent (61.9%), followed by acantholytic and verrucous variants (19% each), and basosquamous carcinoma (4.7%) (Table 3, Figure 4).

Table 2. Clinical characteristics of lip SCC.

GRADE	No. cases	size (cm)			macroscopy			localization		
		<2	≥2&≤4	>4	Ulcerated	Vegetative	Ulcerovegetative	Lower lip	Upper lip	Commissure
G1	10	7	3	0	8	1	1	9	1	0
G2	10	7	1	2	5	3	2	9	0	1
G3	1	0	0	1	1	0	0	1	0	0
p value		p>0.05			p>0.05			p>0.05		

Table 3. Histopathological characteristics of lip SCC according to tumor grade.

GRADE	PT				Resection margins		invasion			HISTOLOGIC TYPE			
	pT 1	pT 2	pT 3	pT 4	Invaded	Noninvaded	Chorion	Adipose tissue	Muscle	Keratizing	Verrucous	Acantholytic	Basosquamous
G1	4	0	6	0	1	9	3	1	6	5	3	2	0
G2	0	2	8	0	6	4	2	0	8	8	1	1	1
G3	0	0	1	0	1	0	0	0	1	0	0	1	0
p value	p>0.05				p>0.05		p>0.05			P<0.05			

**Figure 2. Histopathological features of actinic cheilitis and lip squamous cell carcinoma.**

(A) Actinic cheilitis, HE, x100; (B) Actinic cheilitis, HE, x200;

(C) Squamous cell carcinoma G1, HE, x100; (D) Squamous cell carcinoma G2, HE, x100.

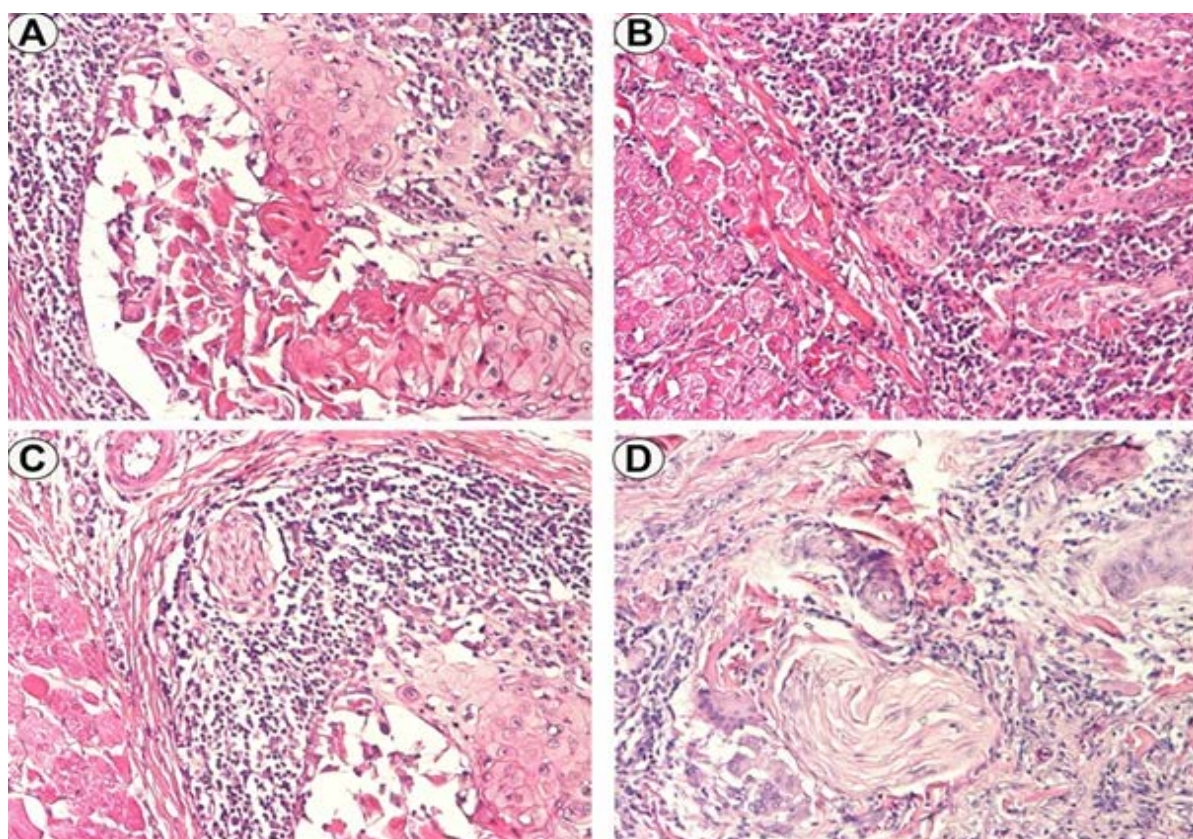


Figure 3. Invasion patterns in lip squamous cell carcinoma.
(A) Squamous cell carcinoma-acantholytic, HE, x200; **(B)** Squamous cell carcinoma G3-invasive in striated muscle, HE, x200; **(C)** squamous cell carcinoma G2-perineural invasion, HE, x100; **(D)** Squamous cell carcinoma G3-perineural invasion, HE, x200.

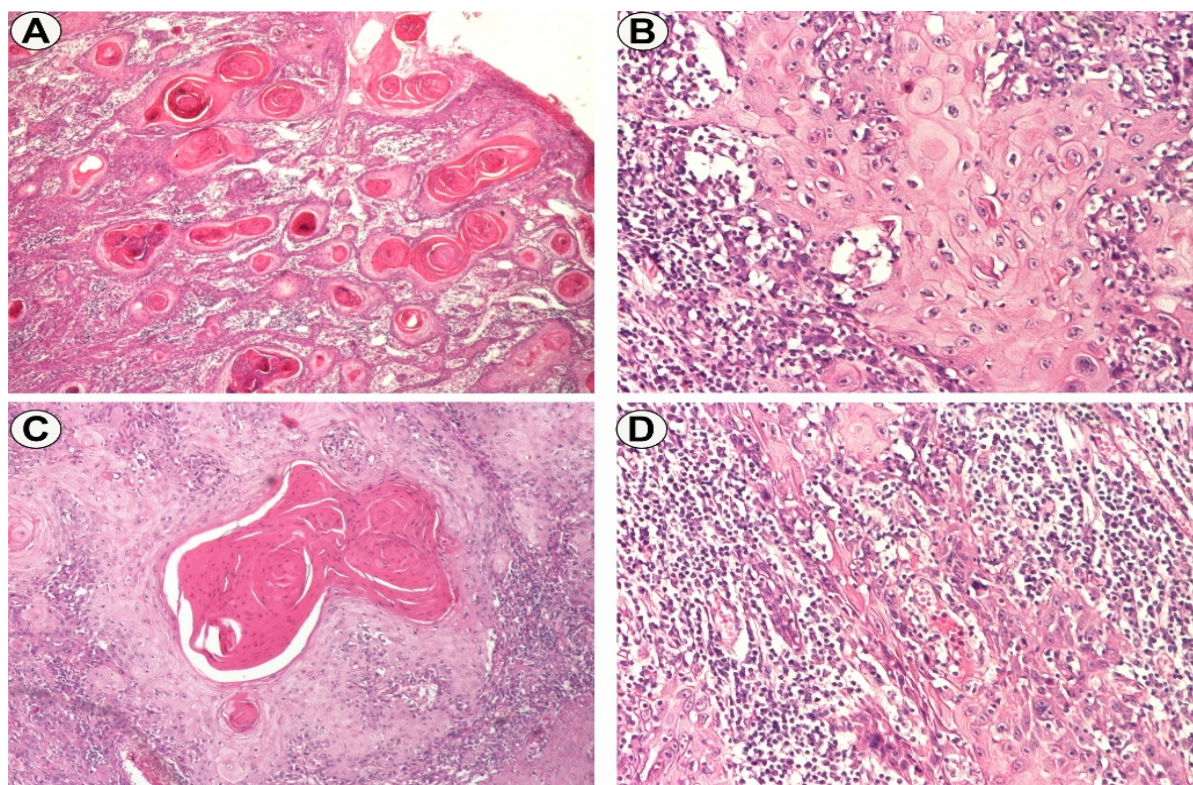


Figure 4. Histopathological grading of lip squamous cell carcinoma.
(A) Squamous cell carcinoma G1-ulcerated, HE, x100; **(B)** Squamous cell carcinoma G2, HE, x200; **(C)** Squamous cell carcinoma G1-keratin pearl, HE, x200; **(D)** Squamous cell carcinoma G3, HE, x200.

Statistical Associations

Statistical analysis identified significant associations between patient sex and histological grade, as well as between tumor localization and histological differentiation.

A statistically significant association was also observed between histological subtype and degree of differentiation (Table 1, Table 2, Table 3, Figure 5).

Although larger tumor sizes were more frequently observed in patients aged 70-90 years, this trend did not reach statistical significance ($p>0.05$).

Lower lip tumors and moderately to poorly differentiated carcinomas (G2-G3) occurred significantly more often in male patients ($p<0.05$).

The acantholytic histological subtype also showed a statistically significant association with these variables ($p<0.05$) (Figure 5).

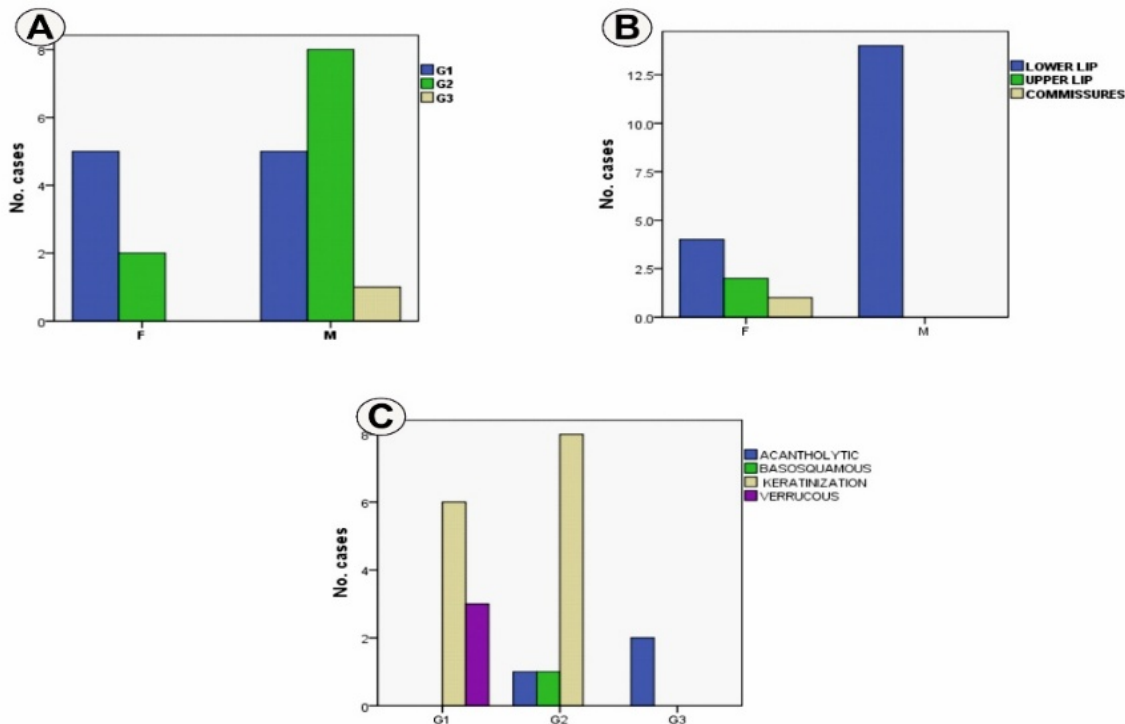


Figure 5. Statistical distribution of clinicopathological parameters. (A) Gender and degree of differentiation; (B) Gender and anatomical site; (C) Degree of differentiation and histological subtype.

Discussion

Actinic cheilitis is a precancerous condition most commonly affecting the lower lip and is regarded as the counterpart of cutaneous actinic keratosis, resulting primarily from chronic ultraviolet radiation exposure.

The disease typically follows a chronic course and represents a recognized precursor lesion for lip SCC.

The reported risk of malignant transformation ranges between 6% and 10%, with some studies documenting rates of up to 16.92% [5,6].

Furthermore, it has been estimated that approximately 95% of lip SCCs arise in association with pre-existing actinic cheilitis, underscoring the importance of early diagnosis

and appropriate management of this condition in the prevention of lip SCC.

In agreement with previously published data and with our own findings, actinic cheilitis was identified in all cases included in the present analysis.

In the present study, lip SCC predominantly affected male patients, who accounted for 71% of cases, and most tumors were located on the lower lip (90%).

These findings are consistent with previously published data indicating that lip SCC represents approximately 15-30% of all head and neck squamous cell carcinomas and nearly one-fifth of malignancies arising in the upper aerodigestive tract, with an overall reported prevalence of 1-2% [7].

A marked male predominance in lip SCC incidence has been widely reported and is commonly attributed to higher rates of tobacco and alcohol consumption, as well as increased cumulative ultraviolet exposure related to outdoor occupational activities and insufficient photoprotection [8].

In contrast, several studies have described a relatively higher incidence of upper lip SCC among female patients, suggesting potential differences in etiological factors and exposure patterns between sexes [9].

Lip SCC most frequently occurs in individuals with light skin phototypes and is particularly prevalent among male smokers, with most cases diagnosed in the sixth decade of life or later [10].

Although the mean age in our cohort was higher than that reported in some series, this discrepancy may reflect regional demographic characteristics and patterns of healthcare access.

A study conducted by Perea-Milla López E et al. reported that lip cancer occurred predominantly in older men, particularly among individuals residing in rural areas, with a clear predilection for the lower lip [11].

Similarly, an epidemiological analysis of lip and oral cavity carcinomas performed by Cracana A et al. in North-East Romania demonstrated a marked male predominance, with men accounting for 83.3% of cases and women for 16.7% among patients hospitalized between 2011 and 2015 [12].

These observations are in line with the demographic and clinical patterns identified in the present cohort.

Regarding the macroscopic appearance of lip tumors, most cases in the present study manifested as ulcerative or ulcero-vegetative forms of lip carcinoma.

Comparable findings were reported by Salan et al., who observed that the ulcerative pattern was the most frequent presentation, accounting for 18.29% of lesions located on the upper lip and 36.82% of those affecting the lower lip [13].

These observations further support the predominance of ulcerative morphology in lip SCC.

Owing to the high visibility of the lips, which facilitates early clinical detection, lip cancers are generally associated with a favorable prognosis.

Reported cure rates exceed 90%, and the risk of metastatic spread remains low, at less than 4% in most series [14].

Nevertheless, tumor localization appears to influence metastatic potential, as lesions arising on the lip-particularly those involving the lower

lip-have been associated with an increased risk of cervical lymph node metastasis [15].

In the present study, the majority of cases were classified as advanced pathological tumor stage, with pT3 tumors accounting for 71% of the cohort, and the keratinizing histological subtype representing the most frequent variant.

In contrast, Pătraşcu V et al. reported a predominance of early-stage disease, with most patients presenting with T1 (190 cases) and T2 tumors (106 cases), while only 26 patients (8.07%) were diagnosed with advanced tumors (17 T3 and 9 T4 cases) [16].

Regarding prognostic correlations, Santos et al. found no statistically significant association between histopathological grade of malignancy and tumor size or extent ($p=0.110$), regional lymph node metastasis ($p=0.925$), or clinical stage ($p=0.829$) [17].

Conversely, Quaedvlieg PJ et al., in a study of 63 lip SCCs, demonstrated that histopathological grade-categorized as well, moderately, or poorly differentiated-was a significant predictor of metastatic development [18].

Regarding depth of invasion, the majority of tumors in the present study demonstrated extension into the underlying muscular tissue, a finding that is consistent with previously published data.

Other studies have indicated that tumors located on the tongue and lips exhibit muscular invasion more frequently compared to tumors arising at other sites, with high statistical significance [19].

Several studies have reported a higher incidence of lip cancer among men older than 60 years, with a male-to-female ratio ranging between approximately 2.5:1 and 3:1.

In a large multicenter retrospective study conducted in Western Australia that included 2,152 cases, Abreu et al. reported that 88% of female patients and 80% of male patients were older than 40 years at diagnosis [6].

In addition, other investigations have demonstrated no statistically significant association between patient sex and tumor site for most oral locations, with the notable exception of the lips, where the occurrence of SCC is significantly higher in males [20].

In a study conducted by Ilie et al., well-differentiated conventional lip SCC was identified exclusively in male patients, comprising four cases aged between 72 and 86 years, all originating from rural areas.

These patients shared common risk factors, including tobacco use, prolonged ultraviolet radiation exposure, and poor oral hygiene [19].

In the same study, the verrucous variant of OSCC was diagnosed in three male patients aged between 52 and 67 years, with all lesions localized to the lips.

Conclusions

This study highlights a clear predominance of lip SCC among male patients, with most cases diagnosed in older individuals and preferentially involving the lower lip.

Histopathologically, keratinizing SCC was the most frequent subtype, with well and moderately differentiated tumors (G1-G2) predominating, and muscular invasion observed in the majority of cases.

These findings support the relevance of tumor localization, depth of invasion, and histological grade as key factors influencing the biological behavior and prognosis of lip SCC.

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None to declare.

Author Contributions

Conceptualization, ICV, BCA and RNC; Methodology, AMV, LES; Histopathological evaluation, MMF, AMB, OIC; Data analysis, ICV, IAM, BCA; Manuscript writing and initial draft preparation, ICV, BCA; Manuscript review and editing, RNC; Supervision, RNC, CM.

All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki; the study and the protocols utilized therein were approved by local Ethics Committee of the University of Medicine and Pharmacy of Craiova (No. 246/04.09.2024).

Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability

Data are available from the corresponding author upon reasonable request.

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