Lip Cancer: A Clinicopathological Study and Treatment Outcomes in a 25-Year Experience

Éder Ricardo Biasoli, DDS, MS, PhD, * Vitor Bonetti Valente, DDS,†
Bruna Mantovan, DDS,‡ Francisco Urbano Collado, MD,§
Sebastião Conrado Neto, MD, MS,‖ Maria Lúcia Marçal Mazza Sundefeld, MS, PhD,¶
Glauco Issamu Miyahara, DDS, MS, PhD,#
and Daniel Galera Bernabé, DDS, MS, PhD**

Purpose: There are few clinical studies focusing on treatment outcomes of lip cancer. This study investigated the clinicopathologic variables of a large sample of patients with lip squamous cell carcinoma (LSCC) treated in a reference head and neck cancer center for the past 25 years and analyzed the influence of these variables on treatment outcomes.

Materials and Methods: This retrospective cohort study reviewed the clinical records of patients with LSCC. Epidemiologic data were age, gender, ethnicity, type of occupation, tobacco smoking, alcohol consumption, comorbid conditions, and family cancer history. Clinicopathologic features included the lip location of the tumor, TNM classification, clinical staging, histopathologic grade, surgical margin analysis, and treatment modality. Local recurrence, second primary tumor, and survival were the outcome variables. Statistical analysis was performed by χ^2 test, Fisher exact test, and binary logistic regression analysis. Survival analysis was assessed through the Kaplan-Meier curve. Level of statistical significance was set at a P value less than .05 for all tests.

Results: In total, 144 patients with LSCC were studied. There were 117 men (81.25%) and 27 women (18.75%) with a mean age of 60.21 years. One hundred thirty-four patients (93.05%) were considered of white ethnicity, and in 57 cases (39.58%), the patients reported an occupation that was related to long-term solar exposure. Most cancers had initial clinical staging of 1 or 2 (84.02%). Microscopically, lesions were predominantly well (43.05%) and moderately (40.96%) differentiated tumors. Clinical staging was related to a specific higher survival rate (P = .0049). One hundred twelve cases (77.78%) underwent surgical treatment and only 6 patients (4.80%) had local recurrence, which was directly associated with compromised surgical margins (P = .0320).

Conclusion: A high success rate in LSCC treatment was observed in this study. Compromised surgical margin was associated with tumor recurrence and is a critical event in lip cancer treatment.
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Received from the Oral Oncology Center, Araçatuba Dental School, Univ Estadual Paulista (UNESP), Araçatuba, SP, Brazil.

*Adjunct Professor.

†MS Student in Stomatology.

‡Dental Surgeon.

§Oncologist.

‖Head and Neck Surgeon.

¶Adjunct Professor.

#Adjunct Professor.

**Assistant Professor.

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Lip cancer is a type of oral cancer that develops at the junction of the oral cavity and the skin.[1,2] It is the most frequent tumor of the oral and maxillofacial region, comprising 25 to 30% of all oral cancers.[2] Squamous cell carcinomas (SCCs) constitute most lip cancers; in most cases, these tumors arise on the vermilion border.[3,4] SCCs occur more frequently in elderly white men (male-to-female ratio, 28.5:4.3), has a peak incidence in the sixth and seventh decades, and is more common in the lower lip (>95% of cases).[2-5] The main risk factors are long-term sunlight exposure (carcinogenic action causing DNA damage induced by ultraviolet [UV] radiation, eg, C-T transition mutations in the p53 gene), which affects people with fair complexion (deficiency of melanin pigment) living in rural and agricultural residences or having outdoor occupations, and long-term tobacco consumption, particularly pipe smoking.[2,3,6,7] In addition, low sociodemographic conditions, genetic susceptibility, and immunosuppression are other risk factors for lip SCC (LSCC).[6,8] Initial clinical signs of lip cancer can include crusting or asymptomatic ulceration; in advanced stages, extensive ulcerative or infiltrative lesions are usually observed.[2] In general, regional lymph node metastases represent late occurrences of the disease (10 to 15% of cases) because of the slow overall growth rate of the tumor.[9] The accessible site of the lesions favors full-thickness resection of the neoplasm (with wide excision of skin, muscle, and underlying mucosa allowing a safe surgical margin), which is considered curative treatment for most lip tumors.[10] LSCC typically presents a high rate of cure in the early stages and a low local recurrence compared with other head and neck tumors (mortality rate, 10 to 15%).[11] In well-differentiated lip cancers, a 5-year survival rate of 80 to 90% has been observed, thus showing a better prognosis compared with other oral cancers.[12,13]

Cancer epidemiology should consider the lip a distinct cancer site, which should not be included with others forms of oral cancer.[12] The incidence of lip cancer shows a large worldwide variation, with the highest rates being reported in Australia and in some regions of Canada, Spain, and Eastern Europe.[2,14,15] However, lip cancer also has a high incidence in South American countries, especially in the tropical regions, where there is a high solar radiation level and many people working long periods while exposed to UV radiation.[16] This study investigated the following clinical question: Which clinicopathologic variables affect the prognosis of LSCC? The study's hypothesis was that clinicopathologic variables could affect treatment outcomes in patients with LSCC. The specific aims of the study were to investigate the clinicopathologic variables of a large sample of patients with LSCC treated in a reference head and neck cancer center during the past 25 years and to analyze the influence of these variables on treatment outcomes, such as local recurrence, second primary tumor, and survival rates.

Materials and Methods

STUDY DESIGN AND SAMPLE

To address the research purpose, the authors designed and implemented a retrospective cohort study (approved by the human studies committee, protocol number 2011-01314). This study followed the guidelines of the Declaration of Helsinki. The study population was comprised of all patients presenting for evaluation and treatment of LSCC from January 1989 through December 2013 at the Oral Oncology Center, Araçatuba Dental School, São Paulo State University (UNESP), Brazil.

Patients were included in the study sample if they had tumors located in the lip and a histopathologic diagnosis of SCC. Patients were excluded as study subjects if they had other histopathologic variants or less than 24 months of clinical follow-up.

STUDY VARIABLES

The primary predictor variables were demographic, medical, anatomic, and treatment group. The demographic data were age range (<53, 53 to 65, 66 to 75, and >75 years), gender (men or women), ethnicity (white or nonwhite), and type of occupation (related or unrelated to long-term sunlight exposure). Medical variables included tobacco smoking, alcohol consumption, comorbid conditions, family cancer history, TNM classification, clinical staging, histopathologic grade, and surgical margins. Lip location of the tumor was an anatomic variable. The treatment modality performed for each case (surgery and radiotherapy) also was evaluated. Post-treatment local recurrence of the primary tumor, second primary tumor, and survival were considered the outcome variables of this study. Local recurrence was defined as the reappearance of tumor at the initial site of the primary tumor.

STATISTICAL ANALYSIS

Data were obtained from the clinical records of patients with LSCC. Data management was performed by the statistics service of the cancer center. All data were stored in Excel 2013 (Microsoft, Redmond, WA), and statistical analysis was performed using Epi Info 7 (Centers for Disease Control and Prevention, Atlanta, GA). Statistical evaluation included epidemiologic and clinicopathologic data of the LSCC by χ^2 and Fisher exact tests, and those statistically meaningful variables were subjected to binary logistic regression multivariate analysis while adjusting for potential confounders. Global and specific survival was assessed through the Kaplan-Meier time-to-event

method at 2-year follow-up. All tests were analyzed with a 95% confidence interval and the level of statistical significance was set at a P value less than .05.

Results

EPIDEMIOLOGIC FEATURES

Clinical reports of 144 patients with LSCC were studied. There were 117 men (81.25%) and 27 women (18.75%) whose age ranged from 19 to 98 years (mean, 60.21 yr). The age intervals of younger than 53 years (32.00%), 53 to 65 years (29.80%), 66 to 75 years (17.36%), and older than 75 years (20.84%) were considered for this study, according to age range lip cancer criteria defined by Czerninski et al.[5] Analysis of gender with age range showed no statistical differences (P = .0967). One hundred thirty-four patients (93.05%) were considered of white ethnicity. In 57 cases (39.58%), the patients had an occupation that was related to long-term solar exposure, 70 patients (48.61%) had no sunlight exposure during working periods, and in 17 cases (11.81%) this information could not be obtained from the clinical reports. A significant association between occupations with UV radiation exposure and severe alcohol intake also was observed (P = .0418). Tobacco smoking history was positive in 87 cases (60.41%), with 19 ex-smokers (13.18%), 8 light smokers (5.55%), 28 moderate smokers (19.45%), and 32 severe smokers (22.23%). A history of alcohol consumption was observed in 55 cases (38.19%), with 9 former drinkers (6.25%), 23 light drinkers (15.97%), 15 moderate drinkers (10.42%), and 8 severe drinkers (5.55%). The variable alcohol consumption was significantly higher in men with lip cancer compared with women (P = .0384). Comorbidities of patients with LSCC were hypertension (15.97%), diabetes (4.16%), gastritis (2.77%), pulmonary emphysema (2.08%), hepatitis (0.70%), and hypothyroidism (0.70%). Thirty-five patients had at least 1 family member with cancer and only 8 patients had previous cancerous diseases (bladder, 1 patient; skin, 6 patients; breast, 1 patient). Study variables and primary outcome variables are listed in Table 1.

CLINICOPATHOLOGIC CHARACTERISTICS

The lower lip was affected in 123 patients (85.41%), followed by the upper lip in 11 cases (7.64%) and the lip corners in 10 cases (6.95%; Fig 1). According to anatomic lip subsite criteria defined by Luna-Ortiz et al,[4] lesions were present in 1 subsite in 135 cases (93.75%). In 9 cases of lower lip tumors (6.25%), the disease exhibited multiple sites (Fig 1). Upper lip tumors were more frequent in women than in men (54.54%; P = .1255), whereas lower lip lesions predominated in men (84.56%; P < .0001). Furthermore,

most tumors of the lip corner affected men (72.72%; P < .0001).

Tumor classification of lip cancer showed 98 cases of T1 (68.05%), 28 cases of T2 (19.44%), 7 cases of T3 (4.86%), and only 1 case of T4 (0.70%). Five patients (3.47%) had lymphatic cervical metastases and no patient presented with distant metastases. In 10 cases (6.95%), TNM information could not be evaluated. Ninety-seven patients had clinical stage (CS) 1 (67.37%), 24 had CS2 (16.65%), 9 had CS3 (6.26%), 2 had CS4 (1.38%), and 12 cases (8.34%) could not be staged. Only 6 cases (4.80%) had local recurrence of disease. Univariate analysis of the association between recurrence and clinical staging (P = .9163), gender (P = .2541), age range (P = .3267), and alcohol consumption (P = .6144) was not statistically significant. Patients with LSCC who have had disease recurrence smoked more cigarettes compared with patients who did not have recurrence, but there was no statistical significance (P = .0742). Histopathologic analysis showed 62 cases of well-differentiated (43.05%), 59 cases of moderately differentiated (40.96%), and only 3 cases of poorly differentiated (2.07%) tumors. In 20 cases (13.92%), there was no information about this feature. Most well-differentiated and moderately differentiated tumors were classified as in the initial clinical stages (CS1 and CS2; P < .0001). Analysis of histopathologic grade with local recurrence of disease did not show a significant association (P = .2898). There were only 8 cases (5.56%) of a second primary tumor; 5 occurred in the facial skin, 1 in the buccal mucosa, 1 in the tongue, and 1 in the vocal cords. This variable was associated with the presence of poorly differentiated lip tumors (P = .0330).

Patients with LSCC predominantly underwent surgical treatment. Thus, in 112 cases (77.78%), only a surgical approach was needed, and in 8 cases (5.56%), tumor resection was followed by radiotherapy. Data for the remaining patients could not be obtained. There were no statistical differences between the treatment modality received and the presence of local recurrence (P = .7249), but patients treated with only surgery had a lower frequency of second primary tumors (P = .0466). Kaplan-Meier analysis showed that clinical staging was the only variable related to a higher specific survival rate (P = .0049; Fig 2). The only variable that remained statistically significant in the regression model was surgical margins for local recurrence (P = .0320). According to multivariate analysis, compromised surgical margins found at histopathologic examination increased the risk of having recurrences in approximately 3.30%. There were no statistically associated variables for occurrence of second primary tumor in logistic regression analysis.

Table 1. STUDY VARIABLES VERSUS PRIMARY OUTCOME VARIABLES LOCAL RECURRENCE AND SECOND PRIMARY TUMOR

Variables	Recurrence			SPT		
	Present	Absent	P Value	Present	Absent	P Value
Age range (yr), n (%)						
<53	1 (2.2)	45 (97.8)	.3267	2 (4.4)	44 (95.6)	.9282
53-65	3 (7.0)	40 (93.0)		2 (4.7)	41 (95.3)	
66-75	2 (8.0)	23 (92.0)		2 (8.0)	23 (92.0)	
>75	0 (0.0)	30 (100)		2 (6.7)	28 (93.3)	
Gender, n (%)						
Men	6 (5.2)	111 (94.8)	.2541	6 (5.2)	111 (94.8)	.4390
Women	0 (0.0)	27 (100)		2 (17.5)	25 (92.5)	
Ethnicity, n (%)						
White	5 (3.8)	129 (96.2)	.2975	7 (5.3)	127 (94.7)	.3855
Nonwhite	1 (10.0)	9 (90.0)		1 (10.0)	9 (90.0)	
Chronic solar exposure, n (%)						
Present	3 (5.3)	54 (94.7)	.5514	5 (8.8)	52 (91.2)	.3480
Absent	3 (4.3)	67 (95.7)		3 (4.3)	67 (95.7)	
Tobacco smoking, n (%)						
Nonsmokers	1 (1.8)	56 (98.2)	.0742	3 (5.3)	54 (94.7)	.7299
Ex-smokers*	0 (0.0)	19 (100)		0 (0.0)	19 (100)	
Light†	0 (0.0)	8 (100)		2 (25.0)	6 (75.0)	
Moderate‡	1 (3.6)	27 (96.4)		1 (3.6)	27 (96.4)	
Severe§	4 (12.5)	28 (87.5)		2 (6.3)	30 (93.7)	
Alcohol consumption, n (%)						
Nondrinkers	3 (4.3)	68 (95.7)	.6144	6 (8.5)	65 (91.5)	.6426
Former drinkers‖	0 (0.0)	9 (100)		0 (0.0)	9 (100)	
Light¶	0 (0.0)	23 (100)		0 (0.0)	23 (100)	
Moderate#	2 (13.4)	13 (86.6)		2 (13.4)	13 (86.6)	
Severe**	1 (12.5)	7 (87.5)		0 (0.0)	8 (100)	
Comorbid conditions, n (%)						
Present	3 (7.9)	35 (92.1)	.4350	5 (13.2)	33 (86.8)	.1641
Absent	3 (4.7)	62 (95.3)		3 (4.7)	62 (95.3)	
Family cancer history, n (%)						
Present	1 (2.9)	34 (97.1)	.5841	8 (22.9)	27 (77.1)	.0803
Absent	5 (4.6)	104 (95.4)		0 (0.0)	109 (100)	
Tumor classification, n (%)						
T1 or T2	5 (4.1)	121 (95.9)	.9025	7 (5.0)	119 (95.0)	.3367
T3 or T4	1 (12.5)	7 (87.5)		1 (12.5)	7 (87.5)	
Clinical staging, n (%)						
1 or 2	5 (4.2)	116 (95.8)	.9163	6 (5.0)	115 (95.0)	.3977
3 or 4	1 (10.0)	10 (90.0)		2 (18.2)	9 (81.8)	
Histopathologic grade, n (%)						
Well differentiated	5 (8.1)	57 (91.9)	.2898	3 (4.9)	59 (95.1)	.0330††
Differentiated	1 (1.7)	58 (98.3)		3 (5.1)	56 (94.9)	
Poorly differentiated	0 (0.0)	3 (100)		2 (66.7)	1 (33.3)	
Surgical margins, n (%)						
Compromised	4 (36.4)	7 (63.6)	.0436††	0 (0.0)	11 (100)	.5626
Uncompromised	2 (1.9)	107 (98.1)		8 (7.4)	101 (92.6)	

Table 1. Cont'd

Variables	Recurrence			SPT		
	Present	Absent	*P* Value	Present	Absent	*P* Value
Treatment, n (%)						
Surgery	5 (4.5)	107 (95.5)	.7249	6 (5.4)	106 (94.6)	.0466[††]
Surgery + RT	1 (12.5)	7 (87.5)		2 (25.0)	6 (75.0)	

Abbreviations: RT, radiotherapy; SPT, second primary tumor.

  * One year without cigarette use.

  † From 1 to 10 cigarettes per day.

  ‡ From 11 to 19 cigarettes per day.

  § At least 20 cigarettes per day.

  ‖ One year without alcohol use.

  ¶ One bottle of beer or 1 dose of distilled drink or 1 glass of wine per day.

  # Two bottles of beer or 2 doses of distilled drink or 2 glasses of wine per day.

  ** At least 3 bottles of beer, distilled drink, or glasses of wine per day.

  †† Values considered statistically significant at $P < .05$ by χ^2 and Fisher exact tests; univariate analysis.

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Discussion

The purpose of this study was to investigate the clinicopathologic profile and treatment outcomes of patients with LSCC treated in a single institution for the past 25 years. Based on the literature and the authors' clinical experience, the study's main hypothesis predicted that clinicopathologic variables would affect treatment outcomes in patients with LSCC. In this retrospective cohort study, most patients with LSCC were men (81.25%), had white ethnicity (93.05%), had the tumor located in the lower lip (85.41%), had the disease in the initial clinical stage (84.02%), and underwent only surgical treatment (77.78%). Regarding treatment outcomes, multivariate analysis showed an important association between compromised surgical margins and local recurrence.

Frequencies of recurrence and second primary tumor in the LSCC sample were 4.80 and 5.56%, respectively. The variable second primary tumor was
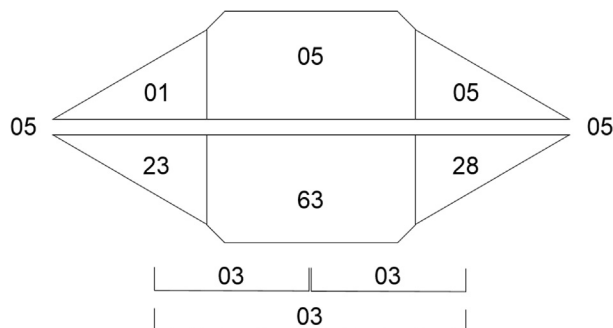

FIGURE 1. Subsite localization of lip tumors and number of patients with these tumors.

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associated with the presence of poorly differentiated lip tumors, but this association lost importance after logistic regression testing. Based on the results of this study, compromised surgical margins were associated with an increased risk of local recurrences in approximately 3.30%. Although the number of patients who had local recurrences in this study was small (only 6 cases), the results indicate that involvement of surgical margins by tumor can determine an important clinical impact in the treatment of lip cancer. The literature has shown no meaningful correlations between second primary tumor occurrences and lip[17] or oral[18] cancer treatment modalities. In the present study, although univariate analysis indicated a higher occurrence of second primary tumors in patients undergoing radiotherapy, this association was not found after multivariate analysis. Moreover, as expected, Kaplan-Meier survival analysis showed that tumors at the initial clinical stages were associated with a higher survival rate.

In the authors' experience, surgery was the most frequent treatment modality for patients with LSCC. Other studies have reported a higher recurrence incidence,[19-21] reaching 20.00% for surgery with or without radiotherapy treatment. The present data showed a meaningful association between compromised surgical margins (with the presence of tumor remains) and tumor recurrence. Interestingly, there is no consensus about what constitutes an adequate or safe surgical margin,[22] and this aspect would be directly related to the development of local recurrences of disease, as clearly observed in this study. In accord with previous studies,[4,23] the authors suggest that the surgical approach is probably best indicated for early and small lesions; ample resections for large tumors can severely affect the functional prognosis.
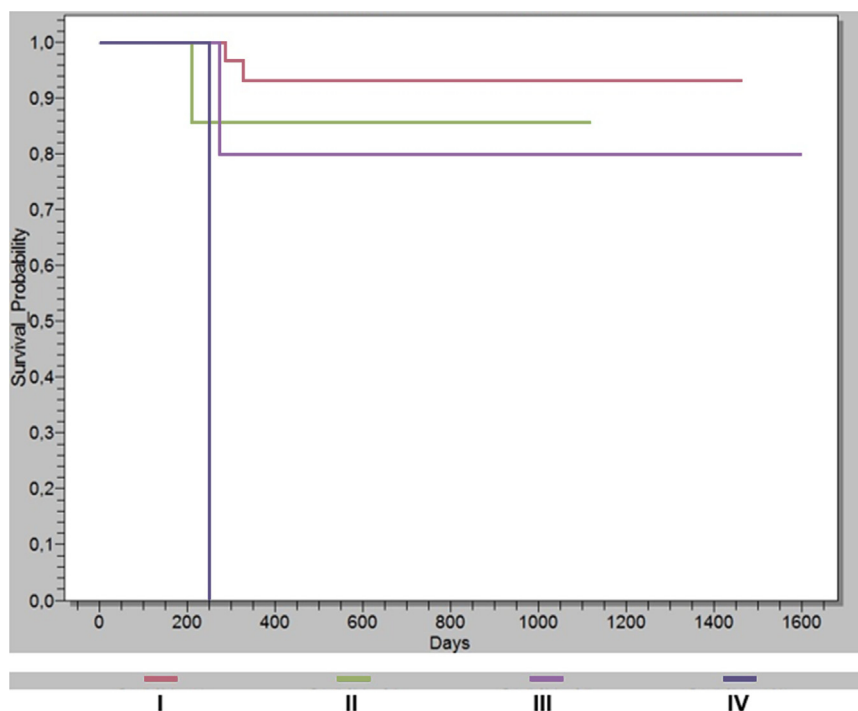
FIGURE 2. Clinical staging was directly related to a higher specific survival rate (*P* = .0049).

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This study showed a larger proportion of lip cancer cases in men, with a low incidence of the disease in women. LSCCs have been commonly found in men, because they usually dedicate more time working under prolonged solar exposure.[4,5] In contrast, Géraud et al[24] reported a balanced ratio of men (50.30%) to women (49.70%); they suggested that this increasing similarity of lip tumor frequency is related to a changing risk profile, with increasing prevalence of sunlight exposure and tobacco use in women during the past 30 years, as Abreu et al[14] similarly suggested. The present data showed that patients who worked in occupations with UV radiation exposure had higher alcohol intake, which might have an important carcinogenic impact. In several studies[14,16,25] alcohol consumption has been associated with lip tumor development. In general, the vast majority of lip cancer cases occur on the lower lip from greater UV radiation exposure.[4,5,14] Moreover, this lip site is more exposed to the harmful effects of tobacco (cigarette, cigar, or pipe placement) and alcohol.[5,25] The presence of malignant neoplasms on the upper lip has been estimated at 2.00 to 12.00%[19]; those investigators observed a low incidence of upper lip tumors (7.64%) and more than half (54.54%) occurred in women. Luna-Ortiz et al[4] noted a larger proportion of upper lip tumors (33.70%) after they included histologic types of lip cancer other than SCC. In another study, Luna-Ortiz et al[23] found a similar number of upper lip malignancies in men and women, and most patients affected by LSCC had histories of long-term sunlight exposure and tobacco consumption.

Compared with the study by Czerninski et al,[5] the authors found an increase in lip cancer incidence in patients younger than 53 years (32.00%) and in patients 53 to 65 years old (29.80%). The age range profile considered in this study was proposed by Czerninski et al[5] who estimated the lip cancer incidence in a very large population. Géraud et al[24] noted older mean ages in women (73.50 yr) and men (68.70 yr); they mentioned that lip cancer occurs preferentially in elderly patients and could be a result of an accumulation of molecular changes and DNA damage from long-term exposure to lip carcinogenic risk factors or as part of the biological aging process. The authors observed an important change in the age group profile, with a higher incidence of young and middle-aged patients with LSCC compared with the data reported by Czerninski et al[5] who found a similar distribution of lip cancer according to age range. Thus, the authors believe these patients probably were exposed to risk factors, such as sunlight exposure during routine leisure activities (eg, fishing), tobacco smoking, and drinking intake, at increasingly younger ages. Similar to Souza et al,[16] the present study did not show an association between family cancer history and clinical parameters of patients with LSCC.

SCC is the most frequent histologic type of lip malignant tumor, corresponding to more than 95% of all cases[20]; for this reason, in the present study, only LSCC was included as a histologic type. Histopathologic grade analysis showed a large number of cases classified as well (43.05%) and moderately (40.96%) differentiated tumors; higher rates of well-differentiated tumors were noted by Casal et al[26] (70.80%) and higher rates of moderately differentiated tumors were observed by Géraud et al[24] (54.70%). In the present study, most well and moderately differentiated tumors were classified as in the initial clinical stages (CS1 and CS2).

A strong correlation between clinical staging and tumor size has been found.[26] In the tumor classification of this report, it was notable that most tumors (T1 and T2; 87.49%) were relatively thinner. Géraud et al[24] observed that almost all cases of LSCC (95.00%) had a tumor thickness less than 6.00 mm. The presence of advanced-tumor stage lip tumors considerably increases the possibilities of metastatic lymphadenopathies, making a search in the ganglionic chains necessary.[4,24] Lymphatic cervical metastases were found in only 5 patients (3.47%) in the entire LSCC sample, in accord with several studies that reported an incidence of 2.00 to 12.00%.[27,28]

The highest survival rates in patients with LSCC are frequently observed when compared with rates in patients with SCC of intraoral sites.[5] According to Czerninski et al[5] and Abreu et al,[14] this could be the result of the easier recognition by patients or health care providers, leading to an early diagnosis. Czerninski et al[5] reported on a national Israeli skin cancer prevention campaign conducted for 15 years, which could have contributed directly to the early detection of the lip lesions beyond actions for population awareness taken by the public system and health care services; according to them, considerable changes in occupational risk factors (eg, less sun exposure) and a decrease in Israelis working outdoors were noted. Likewise, the decrease of UV exposure, through the practice of preventive precautions, and the decrease of smoking tobacco can contribute to a decrease in lip cancer incidences.[24]

One weakness of the present study was a natural absence of some data ("no information"), because it was a retrospective cohort study. Moreover, some important demographic variables were not available for analysis, such as socioeconomic conditions, and a 2-year follow-up is a short period for survival analysis. Nonetheless, this study investigated a large sample of 144 patients with LSCC treated at a single institution whose epidemiologic and outcomes data were subjected to univariate and multivariate analyses. It is worth noting that the vast majority of patients treated in the authors' institution are from a Brazilian region characterized by a high solar radiation level. Therefore, in conjunction with the treatment protocols, the development of programs that could improve lip cancer prevention is essential.

This study showed a high success rate in the treatment of patients with LSCC in a 25-year period. There was a low incidence of local recurrences and second primary tumors and an excellent survival rate. Compromised surgical margins directly influenced tumor recurrence. Thus, future research involving LSCC must be focused on defining a safe surgical margin during surgical treatment and the development of programs for disease prevention.

References

1. World Health Organization. International Statistical Classification of Diseases, Injuries and Causes of Death (Rev 9). Geneva, Switzerland, World Health Organization, 1975
2. Moore SR, Johnson NW, Pierce AM, et al: The epidemiology of lip cancer: A review of global incidence and aetiology. Oral Dis 5: 185, 1999
3. de Visscher JG, Schaapveld M, Otter R, et al: Epidemiology of cancer of the lip in the Netherlands. Oral Oncol 34:421, 1998
4. Luna-Ortiz K, Güemes-Meza A, Villavicencio-Valencia V, et al: Lip cancer experience in Mexico. An 11-year retrospective study. Oral Oncol 40:992, 2004
5. Czerninski R, Zini A, Sgan-Cohen HD: Lip cancer: incidence, trends, histology and survival: 1970-2006. Br J Dermatol 162: 1103, 2010
6. Perea-Milla Lopez E, Minarro-Del Moral RM, Martinez-Garcia C, et al: Lifestyles, environmental and phenotypic factors associated with lip cancer: A case-control study in southern Spain. Br J Cancer 88:1702, 2003
7. Ostwald C, Gogacz P, Hillmann T, et al: P53 mutational spectra are different between squamous-cell carcinomas of the lip and the oral cavity. Int J Cancer 88:82, 2000
8. van Leeuwen MT, Grulich AE, McDonald SP, et al: Immunosuppression and other risk factors for lip cancer after kidney transplantation. Cancer Epidemiol Biomarkers Prev 18:561, 2009
9. Rowe DE, Carroll RJ, Day CL: Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol 26:976, 1992
10. Faulhaber J, Geraud C, Goerdt S, et al: Functional and aesthetic reconstruction of full-thickness defects of the lower lip after tumor resection: Analysis of 59 cases and discussion of a surgical approach. Dermatol Surg 36:859, 2010
11. Babington S, Veness MJ, Cakir B, et al: Squamous cell carcinoma of the lip: Is there a role for adjuvant radiotherapy in improving local control following incomplete or inadequate excision. ANZ J Surg 73:621, 2003
12. Jovanovic A, Schulten EA, Kostense PJ, et al: Squamous cell carcinoma of the lip and oral cavity in the Netherlands; an epidemiological study of 740 patients. J Craniomaxillofac Surg 21:149, 1993
13. Antoniades DZ, Styanidis K, Papanayotou P, et al: Squamous cell carcinoma of the lips in a northern Greek population. Evaluation of prognostic factors on 5-year survival rate—I. Eur J Cancer B Oral Oncol 31B:333, 1995
14. Abreu L, Kruger E, Tennant M: Lip cancer in Western Australia, 1982-2006: A 25-year retrospective epidemiological study. Aust Dent J 54:130, 2009
15. Warnakulasuriya S: Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 17:309, 2008
16. Souza RL, Fonseca-Fonseca T, Oliveira-Santos CC, et al: Lip squamous cell carcinoma in a Brazilian population: Epidemiological

study and clinicopathological associations. Med Oral Patol Oral Cir Bucal 16:e757, 2011

17. van der Tol IG, de Visscher JG, Jovanovic A, et al: Risk of second primary cancer following treatment of squamous cell carcinoma of the lower lip. Oral Oncol 35:571, 1999

18. Farhadieh RD, Otahal P, Rees CG, et al: Radiotherapy is not associated with an increased rate of second primary tumours in oral squamous carcinoma: A study of 370 patients. Oral Oncol 45: 941, 2009

19. Baker SR, Krause CJ: Carcinoma of the lip. Laryngoscope 90:19, 1980

20. Zitsch RP, Park CW, Renner GJ, et al: Outcome analysis for lip carcinoma. Otolaryngol Head Neck Surg 113:589, 1995

21. Cruse CW, Radocha RF: Squamous cell carcinoma of the lip. Plast Reconstr Surg 80:787, 1987

22. Chidzonga MM: Lip cancer in Zimbabwe. Report of 14 cases. Int J Oral Maxillofac Surg 34:149, 2005

23. Luna-Ortiz K, Güemes-Meza A, Villavicencio-Valencia V, et al: Upper lip malignant neoplasms. A study of 59 cases. Med Oral Patol Oral Cir Bucal 17:e371, 2012

24. Géraud C, Koenen W, Neumayr L, et al: Lip cancer: Retrospective analysis of 181 cases. J Dtsch Dermatol Ges 10: 121, 2012

25. Maruccia M, Onesti MG, Parisi P, et al: Lip cancer: A 10-year retrospective epidemiological study. Anticancer Res 32:1543, 2012

26. Casal D, Carmo L, Melancia T, et al: Lip cancer: A 5-year review in a tertiary referral center. J Plast Reconstr Aesthet Surg 63:2040, 2010

27. Zitsch RP, Lee BW, Smith RB: Cervical lymph node metastases and squamous cell carcinoma of the lip. Head Neck 21:447, 1999

28. McGregor GJ, Davis NL, Hay JH: Impact of cervical lymph node metastases from squamous cell cancer of the lip. Am J Surg 163: 469, 1992