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HEAD & NECK

Predictive factors for late cervical metastasis in stage I and II squamous cell carcinoma of the lip

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Abstract

Purpose Many authors have described clinicopathologic parameters as factors related to cervical lymph node metastasis development in $_{C}$N0 stage lip cancer. However, predictive factors for occult lymph node metastasis and criteria for elective neck dissection, especially for early tumour, remain undefined.

Methods A multi-institutional study with 193 consecutive patients with early lip SCC treated from January 1990 to March 2006 was carried out retrospectively to determine factors predicting occult metastasis.

Results The overall late LNM rate was 13% (25/193). In the multivariate logistic regression study, tumour size and pattern of tumour invasion were factors related to the occurrence of late LNM with rates of sensitivity, specifity and accuracy for occult LNM prediction of 50%, 89.5% and 87%, respectively.

Conclusion Our results indicate that patients with stage I and II SCC of the lip with tumour size greater than 18 mm and more aggressive pattern of invasion must be considered a high-risk group for LNM and an END should be performed.

Keywords Lip neoplasms · Squamous cell carcinoma · Sentinel lymph node biopsy · Neck dissection · Neoplasm micrometastasis

Introduction

The prognosis of squamous cell carcinoma (SCC) of the lip is good if early diagnosis and adequate treatment is established, with a mean survival rate at 5 years of 90% [1], and the most important prognostic factor of survival for these patients is the occurrence of cervical lymph node metastasis (LNM). The frequency of LNM in lip SCC ranges from 6 to 37% [2–6] and only 25%–50% of these patients are still alive after 5 years [4, 7, 8]. Therefore, it is important to detect patients with high risk of occult LNM to prevent an unfavorable clinical evolution.

Many authors have described prognostic factors for LNM in lip SCC such as tumour size; grading of differentiation; vascular invasion, depth of invasion; perineural invasion; mitotic activity, mode of tumour invasion and positive surgical margins [2, 9–14]. However, the criteria for elective neck dissection (END) according to predictive factors are still controversial. There are studies indicating END in almost all cN0 patients [15, 16] whereas others suggest a "wait and see" management and neck dissection only when the neck

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relapses [17–20] or, even, authors propose the sentinel node biopsy (SNB) to detect an occult disease [21, 22].

This study was a retrospective analysis of the clinicopatologic factors related to late lymph node metastasis (LLNM) occurrence and to identify patients at risk, to improve neck management and prognostic outcomes in stage I and II SCC of the lip.

Patients and methods

The medical records of consecutive patients treated for SCC of the lip at four tertiary referral hospitals in the County of São Paulo between January 1990 and March 2006 were retrieved and retrospectively reviewed. The protocol of the study was approved by all four Institution's Ethic Committee (protocols 228/03, 774/04, 605/04 and 291/04).

The elegibility criteria included previously untreated patients with early SCC (T_{1-2}) of the lower lip and commissure treated in those institutions by surgical resection with clinically negative neck metastasis or those with suspected lymph node enlargement who underwent neck dissection (ND) but no lymph node metastasis were found in the histopathologic study (pN0).

The exclusion criteria were patients with nonsquamous cell carcinoma, previous treatment with radiotherapy, patients with a second primary tumour and tumours arising from skin of the lip.

The patients were divided into two groups: late lymph node metastasis (LLNM) and non-LNM groups, and the clinical variables evaluated were gender; age, TNM stage according to American Joint Committee on Cancer TNM 7th edition [23]; subsite of the primary tumour; local recurrence and development of LLNM. The histologic specimens from all primary tumours and elective neck dissections were reviewed by a single pathologist (DNC) and the variables analyzed (Table 1) were tumour size, tumour depth [24], perineural invasion, microvascular invasion, grade of tumour differentiation, nuclear polymorphism, number of mitoses, surgical margins and the status of the lymph nodes in the surgical specimens from END. Additionally, the pattern of invasion at the deepest point of tumour invasion based on Anneroth et al. [25] criteria was evaluated and tumours were classified from pattern type 1–4 [pattern type 1 = pushing, well-delineated infiltrating borders; pattern type 2 = infiltrating, solid cords, bands and/or strands; pattern type 3 = small groups or cords of infiltrating cell ($n > 15$); pattern type 4 = marked and widespread cellular dissociation in small groups of cells ($n < 15$) and/or in single cells].

To determine the optimal cutoff for tumour size and depth of invasion to predict LLNM occurrence, the distribution of these variables in both groups were analyzed using the receiver operating characteristics (ROC) curve and the optimal cutoff value was determined by calculating the Youden's index.

To analyse the differences between the groups, Pearson's chi-squared test was applied for categorical variables, and for continuous ones the Mann–Whitney U test was applied as a non-parametric test in non-normally distributed data, and the independent t test was performed for normally distributed variables. Overall survival (OS) and disease-specific survival (DSS) rates were calculated according to Kaplan–Meier and differences were calculated using the log-rank and Breslow tests. Multivariate logistic regression analysis was used to model the predictive factors associated with LLNM occurrence.

All statistical analyses were calculated using the Statistical Package for Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA) and the results were considered significant when the p value was < 0.05.

Results

A total of 193 patients were included in the study. Twenty-five (13%) in the LLNM group and 168 (87%) in the non-LNM group. The period of LLNM occurrence ranged from 3 to 23 months (median 9.5 months) and all relapses occurred at level I. There were 155 (80%) men and 38 (20%) women and mean age was 59 years (range 14–97 year). All patients underwent full-thickness resection of the tumour as the primary form of treatment and there were no positive surgical margins at the intraoperative frozen section analysis. One hundred and forty (72.5%) tumours were categorized as T_1 and 53 (27.5%) as T_2.

Twenty-one patients (10.9%) with clinically palpable cervical lymph nodes at level I (7 tumours $T1$ and 14 tumours $T2$) were submitted to a neck dissection at the time of primary tumour resection but none of them had lymph node metastasis at the histopathological study and were included in the non-LNM group. Twenty of these patients underwent selective neck dissection of levels I–III and only one a modified radical neck dissection.

The follow-up period was at least 16 months (mean 72.7 months, range 16–181 months) and at the end of the follow-up, 141 (73%) patients were alive with no evidence of disease, 6 (3.1%) died from disease, 2 (1.1%) were alive with disease and 44 (22.8%) patients had died of other causes than cancer.

Analysing the TNM stage, there were 9.3% (13/140) of T_1 tumours and 22.6% (12/53) of T_2 tumours that developed LLNM. Only 13 (6.7%) patients developed local recurrence and were treated by surgical re-resection, and of these patients with local recurrence, 4 (30.7%) were in the LLNM group but no statistical correlation was observed ($p = 0.069$).

Table 1 Occurrence of late cervical lymph node metastasis

Factors	No. of cases	No. of nodal metastasis (%)	*p* Value
Age			
≤ mean 59	88	11 (12.5)	> 0.999
> mean 59	105	14 (13.3)	
Gender			
Male	155	22 (14.2)	0.421
Female	38	3 (7.9)	
Tumour stage			
T_1	140	13 (9.3)	0.028
T_2	53	12 (22.6)	
Local recurrence			
No	180	21 (11.7)	0.069
Yes	13	4 (30.7)	
Subsite of the tumour			
Lower lip	185	24 (13.0)	0.830
Lower lip + commissure	6	1 (16.7)	
Commissure	2	0	
Tumour size (ROC)			
≤ 18 mm	119	8 (6.8)	0.001
> 18 mm	74	17 (23.0)	
Tumour depth (ROC)			
≤ 5 mm	129	11 (8,5)	0.012
> 5 mm	64	14 (21,9)	
Perineural invasion			
Absent	159	17 (10.7)	0.052
Present	34	8 (23.5)	
Microvascular invasion			
Absent	170	20 (11.7)	0.189
Present	23	5 (21.7)	
Grade of tumour differentiation			
G_1/G_2	166	18 (10.8)	0.056
G_3/G_4	27	7 (25.9)	
Nuclear polymorphism			
Little/moderately abundant	161	16 (9.9)	0.009
Abundant/extreme	32	9 (28.1)	
Number of mitoses/HPF*			
0–1; 2–3	176	19 (10.8)	0.011
4–5; > 5	17	6 (35.5)	
Pattern of invasion			
Pushing, well delineated borders (pattern type 1)	80	4 (5.0)	< 0.001
Infiltrating, solid cords, bands and/or strands (pattern type 2)	54	6 (11.1)	
Small groups or cords of infiltrating cell ($n > 15$) (pattern type 3)	40	6 (15.0)	
Marked and widespread cellular dissociation in small groups of cells ($n < 15$) and/or in single cells (pattern type 4)	19	9 (47.4)	

*High power field

No one developed distant metastasis during the follow-up period.

The mean tumour size was 17 mm (range 3–40 mm) and mean depth of invasion was 5 mm (range 1–16 mm). The ROC curve and Youden's index were applied to determine the optimal cutoff point associated with LLNM for those variables showing values of 18 mm for tumour size and 5 mm for depth of invasion, and the sensitivity and specificity related to LLNM occurrence were 68% and 65.5%

Table 2 Logistic regression predicting likelihood of late lymph node metastasis (LLNM) based on tumour size and pattern of tumour invasion

	B	SE	Wald	*df*	*p*	Odds ratio	95% Cl for OR	
							Lower	Upper
Pattern invasion			14.38	3	0.002			
Pattern invasion (type 2)	0.85	0.68	1.54	1	0.215	2.32	0.61	8.81
Pattern invasion (type 3)	1.00	0.69	2.10	1	0.147	2.72	0.70	10.53
Pattern invasion (type 4)	2.58	0.71	13.33	1	0.000	13.16	3.30	52.53
Tumour size (ROC)	1.16	0.49	5.63	1	0.018	3.18	1.22	8.24
Constant	− 3.43	0.58	34.80	1	0.000	0.03		

B estimated logit coefficient, *SE* standard error, *Wald* Wald test, *df* degrees of freedom, *p* significance level, *CI* confidence interval, *OR* odds ratio

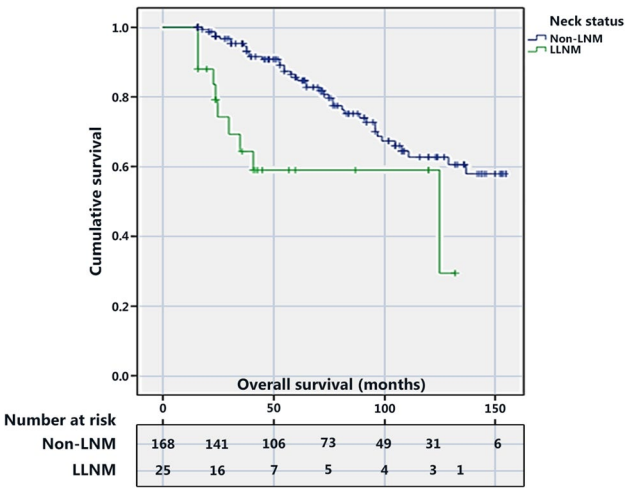

Fig. 1 Overall survival curves for LLNM and non-LNM groups

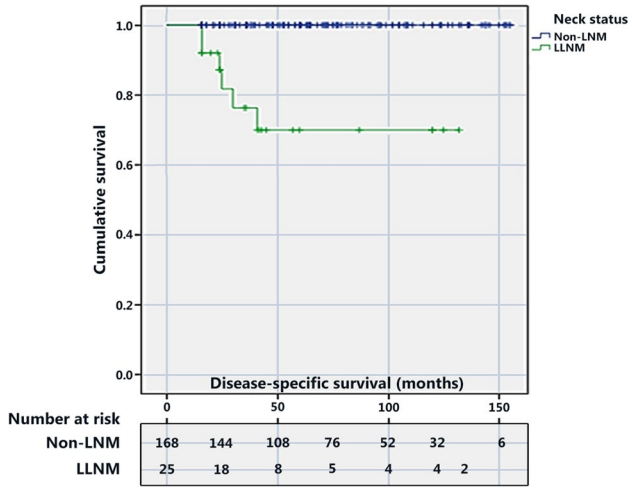

Fig. 2 Disease-specific survival curves for LLNM and non-LNM groups

for tumour size and 56% and 70.2% for depth of invasion, respectively.

In the univariate analysis (Table 1), the association between clinicopathologic factors and the LLNM was found to be *T* stage ($p=0.028$), tumour size ($p=0.001$), depth of invasion ($p=0.012$), nuclear polymorphism ($p=0.009$), number of mitoses/HPF ($p=0.011$), and pattern of tumour invasion ($p<0.001$).

The multivariate logistic regression analysis showed a correlation between tumour size > 18 mm and the most infiltrative pattern of invasion type 4 with LLNM with 50%, 89.5% and 87% of sensitivity, specificity and accuracy, respectively (Table 2).

The 5-year overall survival rates were 55% and 42% ($p=0.001$) for non-LNM and LLNM groups (Fig. 1), and the 5-year disease-specific survival rates were 100% and 68% ($p<0.0001$), respectively (Fig. 2).

Discussion

The status of regional lymph nodes has long been considered the most important factor for predicting survival in head and neck SCC and survival rates may decrease 25–50% [7, 26] when it occurs, this was also observed in our study with a decrease of 24% in the 5-year overall survival rate in the LLNM group ($p=0.001$). A similar result was found in 5-year disease-specific survival rate with a decrease of 32% in the LLNM group ($p=0.0001$). Therefore, early detection of occult lymph node metastasis is important to improve survival.

However, the management of the clinical $_{C}$N0 neck in SCC of the lip is controversial with some authors suggesting END in almost all cases [15, 16], whereas others indicate a wait-and-see management [17–20]. More recently, some authors have proposed a sentinel node biopsy (SNB) in lip SCC, reporting a high rate of sentinel lymph node (SLN) localization (range 90%–93%), and rates from 7.1 to 16.6% of micrometastasis [21, 22].

Although many methods have been used to detect occult lymph node metastases, END is the most accurate one but unnecessary in the majority of patients, particularly in stage I and II lip SCC. The sentinel node biopsy (SNB) is a minimally invasive technique that could be used to detect lymph node micrometastasis, but the procedure involves a lot of technical procedures [22] which are not available in the majority of the public hospitals in our country. Furthermore, the SNB technique requires training and experience for an appropriate outcome.

On the other hand, the wait-and-see management can delay the treatment and worsen the prognosis if careful follow-up is not carried out [22].

Regarding lymphatic spread pattern from lip SCC, several studies [8, 27] demonstrated that the submental (sublevel IA) and submandibular (sublevel IB) lymph nodes are the most frequently involved when LNM occurs. However, a clinically enlarged lymph node does not necessarily imply tumour metastasis as reported by Larson et al. [28] who found 38.5% of false-positive results in a series of 79 patients. Bilkay et al. [8] in a series of 118 patients performed prophylatic suprahyoid neck dissection in 15 cases but only 20% (3/15) were positive at pathological analysis. In our study, 21 patients with clinically enlarged lymph nodes had a ND which did not demonstrate lymph node metastases histopathologically. On the other hand, 25 patients with no clinically palpable lymph nodes developed LNM during the follow-up. Our results confirm the low accuracy of clinical evaluation.

Subsequent development of cervical LNM following successful treatment of the SCC of the lip was reported by many authors and ranged from 5 to 15% [4, 7]. In our series, a LLNM overall rate of 13% was found which was 9.3% for *T*1 and 22.6% for *T*2, $p = 0.028$, showing the high risk of occult LNM in the last group. Thus, the percentage of LNM varies according to tumour size and its occurrence has been described ranging from 0 to 15% in T_1, 11%–35% in T_2 and 17%–100% in T_3/T_4 stages [9]. Zitsch et al. [20] similarly reported tumour size as a factor associated with the presence of occult LNM and the rates of occult LNM increased with increasing primary tumour size. However, the overall LLNM rate was only 4%.

Nevertheless, analysis of the tumour size at our series demonstrated that tumour greater than 18 mm was the best predictor of LLNM in univariate ($p = 0.001$) and multivariate logistic regression analyses ($p = 0.018$). Therefore, based on our findings, the concept that early lip SCC has a low risk of occult LNM should be reconsidered, mainly tumours classified as T_2 and the studies must consider population characteristics, environmental and molecular biology influences to explain the significant frequency of LLNM found in our study and in others [2–6, 16].

Therefore, the recognition of the high-risk patients to occult LNM could be used to select patients who would benefit from prophylactic surgical treatment of the neck. With this purpose, many authors have reported studies trying to predict high-risk patients to occult LNM in $_{C}$N0 oral and lip SCC to improve neck management and prognostic outcomes [9, 11, 13]. Factors such as tumour size, *T* stage, depth of invasion, location in the commissure subsite, histologic degree of differentiation, perineural and or vascular invasion, positive surgical margins, local recurrence, more aggressive pattern of tumour invasion and mitotic activity were described [2, 6, 9, 12–14, 20].

Analyzing the histopathological factors, the depth of invasion has been recognized as an important factor in predicting LNM and many authors reported that tumours invading less than 2 mm do not metastatize [19, 29], whereas those greater than 5 mm have a high risk of developing LNM [2, 6, 13, 30]. Our results were similar and a tumour depth of invasion cutoff > 5 mm was identified as the best value associated with LLNM ($p = 0.012$).

The grade of tumour differentiation was another factor correlated with the risk of LLNM in Zitsch et al.'s [20] study and rates of LLNM were 2% (14/705) for grade 1, 4% (7/171) for grade 2, 8% (2/24) for grade 3 and 20% (9/45) for grade 4 ($p < 0.0001$). Based on these findings, the authors suggested that poorly differentiated tumours would be the most likely group to benefit from elective treatment of the neck. Many other studies have reported the same findings [2, 4, 14, 30]. However, in this series, a statistically significant association between G3/4 tumours and LLNM ($p = 0.056$) was not found.

Byers et al. [31] reported a rate of 2% (25/1308) of perineural invasion in SCC of lower lip associated with 80% of LNM (16/20 cases) and concluded that the neck should be treated regardless of clinical status of the lymph nodes if perineural invasion is present. In Frierson et al.'s [2] study, it was reported a rate of 16% of perineural invasion with 60% of LNM in these patients versus 10% of LNM in its absence ($p < 0.0001$). In our series, a total of 21% of perineural invasion was found and was associated with 23.5% of LLNM. When perineural invasion was absent, only 10.7% developed LLNM but it did not reach statistical significance ($p = 0.052$).

One important histopathologic factor described in the literature is the appearance of the tumour/host interface at the deepest point of invasion as proposed by Anneroth et al. [25] and although the pattern of tumour invasion has not been evaluated in lip tumours but only in oral cavity SCC [32], we found an association between more infiltrative pattern of invasion (pattern type 4) and LLNM development in univariate ($p < 0.001$) and multivariate logistic regression analyses ($p < 0.0001$) suggesting the importance of this histopathological variable in lip SCC.

Baker and Krause [7] in a series of 291 patients with lip cancer reported 39 cases (13.4%) of local recurrence related to large tumours and subsequent cervical LNM in 10 cases (25.6%). Similar report has been described by other authors [13, 20]. In our study, thirteen patients (6.7%) developed local recurrence but no statistical correlation was found ($p = 0.069$). This result might be explained because our series was only composed of early tumours and the routine use of intraoperative frozen section, despite its limitations, ensures an adequate surgical margin in the majority of the cases.

The most frequent subsite for SCC of the lip is the lower lip on the exposed vermilion border [7], and commissure lesions are reported to show a greater propensity for regional metastases as compared with other lip regions [8], but in our study, there was no correlation of lip subsites and LLNM ($p = 0.83$), similar to the findings of Zitsch et al. [20].

SCC of the lower lip appears to have a worse prognosis in younger patients [8], but in our study, this variable was not related to LLNM, as reported by other authors [13, 20].

Conclusion

In our study, SCC of the lip measuring > 18 mm with more infiltrative pattern of tumour invasion (pattern type 4), which is easily evaluated in histologic studies, might be used to identify high-risk patients after resection for stage I and II lip SCC. The decision as to whether to do an END prophylactically, or not, can then be made.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by all four Ethics Committees of the participating institutions (protocols 228/03, 774/04, 605/04 and 291/04) and all procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent A formal consent was released by all four Ethics Committees due to the retrospective nature of the study.

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