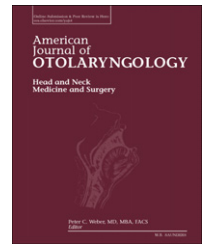


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Management of neck metastases in T2N0 lip squamous cell carcinoma

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ARTICLE INFO

Article history:

Received 1 August 2012

ABSTRACT

Background: Prophylactic neck dissection (PND) is indicated when the chance of occult lymph node metastases from head and neck tumors is significant. There is no consensus regarding which tumor size PND would be indicated in cases of lip cancer.

Methods: A total of 139 patients with surgically treated lip cancer were selected. The size of the lesion (T) and the presence of lymph node metastases (N) were assessed by examining the medical records. For analysis purposes, the T2 group was divided into T2a (2 to 3 cm) and T2b (3 to 4 cm).

Results: The following distribution of incidence of neck metastases was observed in the study groups: 11.7% in T1, 9% in T2a, 43.7% in T2b, and 52.2% in T3+T4. Statistical comparison of the groups (p) revealed the following results: T2a X T2b=0.03; T2a X T3+T4=0.001.

Conclusion: PND is indicated for tumors larger than 3 cm.

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1. Introduction

Cancer of the lip is the most frequent malignant neoplasm of the mouth. The main risk factor for this type of cancer is exposure to ultraviolet radiation, with the lower lip being mainly affected in white men. Squamous cell carcinoma (SCC) is the most prevalent histopathological type of lip cancer [1–4]. The most important prognostic factor for SCC of the lip is the presence of neck or distant metastases, which directly influences mortality and disease-free time [2,5–7]. However,

other factors such as tumor size, thickness, location, degree of differentiation, invasion of neighboring structures, perineural and/or vascular infiltration may also affect patient survival [4,5,8,9].

Although surgical excision of the lesion is the gold standard treatment for most SCCs of the lips, inoperable or unresectable cases could receive radiotherapy in combination or not with chemotherapy [1,10–12].

As well as other SCC of head and neck region, lip SCCs tend to exhibit cervical lymph nodes metastases during their

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progression. Thus, neck dissection has been adopted in combination with lip lesion resection in situations where these metastases have a significant incidence [1,2,5,6,11,12].

Studies have shown that the pattern of lymphatic drainage of the lips with the production of ganglion metastases occurs for levels I, II and III established by the Sloan Kettering Cancer Center. For this reason, these are the neck levels commonly dissected when there is an indication of prophylactic neck dissection (PND) [1,2,5,6,11,12].

However, doubts exist about what tumor size the risk of micrometastases is sufficiently high to indicate neck dissection. Despite the large number of studies regarding PND [1,2,5,6,11,12], there is no consensus in the literature about when to dissect prophylactically the neck of patients with cancer of the lips.

The purpose of this study was to determine the incidence of neck metastases in cancer of the lip considering the initial size of the tumor and the long-term follow-up of the patients in order to establish an initial tumor size that could justify the indication of PND.

2. Materials and methods

The research protocol was approved by the Research Ethics Committee of the University Hospital and School of Medicine of Ribeirão Preto-USP, protocol 1084/2011. A retrospective study was conducted on 250 medical records of patients with lip cancer who attended the University Hospital of the School of Medicine of Ribeirão Preto-USP, from 1986 to 2011. Only previously untreated SCC cases were selected. Exclusion criteria were: patients previously submitted to surgical or non-surgical treatment, patients with other types of tumors, cases of recurrence of the primary tumor, impossibility of surgical treatment, or patients who were not followed up for at least one year. The 139 patients selected were submitted to a biopsy of the primary lesion, to preoperative laboratory tests and to surgical treatment with tumor exeresis and neck dissection when they presented neck metastases or with PND in more advanced tumors. Data regarding the clinical and pathological TNM classification of the American Joint Committee on Cancer (AJCC), the location of the lesion (lower lip, upper lip or lip commissure) and follow-up time were extracted from the medical records.

For analysis, the patients were assigned to the following groups according to the classification of the American Joint Committee on Cancer (AJCC) regarding tumor (T) size: T1, lesions of up to 2 cm; T2, lesions ranging from more than 2 cm to 4 cm; T3, lesions of more than 4 cm, and T4, lesions that invaded structures adjacent to the primary site. Group T2 was subdivided into T2a, lesions ranging from more than 2 cm to 3 cm, and T2b, lesions ranging from more than 3 cm to 4 cm. The presence of cervical metastases was classified as N+ and their absence as N-. The patients were evaluated regarding the presence or absence of metastases after long-term follow-up. The information was organized on Excel® spreadsheets and analyzed statistically by the two-tailed chi-square or two-tailed Fisher exact test. The Openepi* software for epidemiologic statistics was used for statistical analysis.

3. Results

Of the 139 patients selected, 126 (91%) had SCC of the lower lip, seven (5%) had SCC of the upper lip, and six (4%) had SCC on the lip commissure. Mean follow-up time was 36.1 months. The T size and the presence of lymph node metastases (N) of the patients were as presented in Table 1, which shows that there was a steady increase in the incidence of metastases with increasing tumor size and T2 already had a high rate of metastases that would justify neck dissection. However, when T2 was divided into T2a and T2b (Table 2), we observe that most metastases occurred in tumors larger than 3 cm (T2b).

Cross-analysis of the neck metastasis factor in the T2, T2a, T2b and T3+T4 groups by the chi-square or Fisher exact test revealed the results presented in Table 3.

4. Discussion

There is still no consensus in the literature regarding when the neck of patients with lip cancer should be prophylactically dissected, and what levels should be considered. This debate has generated various studies with quite diverse results. Some authors suggest to perform neck dissection in all cases regardless of other prognostic factors [6,13], while others suggest to stratify the risk of cervical metastases in order to justify PND, based on factors directly related to the metastatic process such as lesion size, degree of differentiation, location, and thickness, among others [5,9,14]. Other authors still suggest to base dissection on the search for the sentinel lymph node [7,12].

Although most investigators indicate suprahyoid cervical dissection for elective neck treatment in N0 cases [1,2,15], some authors indicate dissection only for level I, approaching levels II and III only if level I is involved and levels IV or V if there are metastases beyond level I [2,3]. The literature about neck dissection commonly indicates prophylactic lymphadenectomy when the risk of occult metastases of this level is 20% or more [4,5].

In 1996, in a study of 45 cases of lip SCC, Mello-Filho et al. [16] reported that tumors measuring more than 3.0 cm have a large number of metastases that are not always detected clinically, while tumors measuring less than 3.0 cm have a significantly lower rate of metastases. Other studies, although not intending to show similarities or differences between these groups, have reported rates of metastases per group similar to those described by Mello-Filho et al. [3,9,17]. In 1999, Zitsch et al. [17] published a study of 1001 cases of lip SCC in which they aimed to identify the incidence of late metastases

Table 1 – Incidence of neck metastases.

T	N+	N–	Total
T1	9 (11.7%)	68 (88.3%)	77
T2	9 (23%)	30 (77%)	39
T3+T4	12 (52.2%)	11 (47.8%)	23
Total	30 (21.6%)	109 (78.4%)	139

T: Tumor, N+: Metastases, N–: No metastases.

Table 2 – Incidence of neck metastases in T2 tumors subdivided into T2a and T2b.

T	N+	N-	Total
T2	9 (23%)	30 (77%)	39
T2a	2 (9%)	21 (91%)	23
T2b	7 (43.7%)	9 (56.3%)	16

T: Tumor, N+: Metastases, N-: No metastases.

after treatment. They observed that tumors measuring less than 3 cm presented a rate of late metastases of less than 5%, while tumors of more than 3 cm presented a rate of more than 8%, with a statistically significant difference between groups (P=0.034). Amar et al. [3] reported similar results regarding the risk of occult metastases, i.e., T1: 5%, T2a: 13%, T2b: 25% and T3+T4: 45% of a total of 70 cases, and concluded that for tumors of less than 3 cm there is no need for PND [3].

Zitsch et al. [9] assessed the factors related to survival in a study of 1047 patients with SCC of the lips and observed that patients with tumors larger than 3 cm had a significantly shorter survival than patients with smaller tumors (64% X 92%, P=0.001) [9]. Some studies support the use of PND in patients in stage T2 and even in stage T1 [6,13]. However, these studies have some limitations because they do not distinguish between tumors of 2 to 3 cm and tumors of 3 to 4 cm [6,8,13,14,18] and some of them report on very small samples [8,13,18] or do not even distinguish between groups in terms of clinical T [5].

The present study detected an expressive statistical difference between T2 and T3+T4 regarding the ability to produce metastases. However, when the T2 classification of AJCC was subdivided into T2a and T2b, an important statistical difference was detected between T2a and T2b. Cross-analysis of groups by tests of statistical significance showed great similarity between groups T1 and T2a and between the groups T2b and T3+T4.

Considering the size of the lesion as a separate factor, there is a statistically identified cut-off point that divides these tumors into two groups with different biological behaviors, with the group of tumors larger than 3 cm being the one more likely to present neck metastases, with a consequent worse prognosis. Based exclusively on the long-term incidence of neck metastases in T1 (11.7%), T2a (9%), T2b (43.75%) and T3+T4 (52.17%), PND would be justified for the last two groups, which involve tumors of more than 3 cm, since they present an incidence of neck metastases of more than 20%. Similarly, if we compare group T2a X T3+T4 and group T2b X T3+T4 and if we consider that the latter includes all the criteria that

Table 3 – Probability of similarity of T groups expressed as P-value.

	T2	T2a	T2b	T3 X T4
T1	0.10	>0.99	0.01	
T2				0.01
T2a			0.03	0.001
T2b				0.60

T: Tumor, P: Level of significance.

indicate PND, this procedure would be justified in group T2b, which shows considerable statistical similarity to group T3+T4.

5. Conclusion

Considering i) the high incidence (more than 20%) of cervical metastases in tumors measuring 3 to 4 cm, and ii) the statistical similarity of the incidence of metastases in these tumors and in those one larger than 4 cm, the results of this study suggest that PND should be indicated in SCCs larger than 3 cm in order to prevent cervical metastases.

REFERENCES

- Morselli P, Masciotra L, Pinto L, et al. Clinical parameters in T1N0M0 lower lip squamous cell carcinoma. *J Craniofac Surg* 2007;18:1079-82.
- Gooris PJJ, Vermey A, Visscher JGAM, et al. Supraomohyoid neck dissection in the management of cervical lymph node metastases of squamous cell carcinoma of the lower lip. *Head Neck* 2002;24:678-83.
- Amar A, Franzi SA, Curioni OA, et al. Esvaziamento cervical no tratamento do carcinoma epidermóide de lábio (Neck dissection in the treatment of epidermoid carcinoma of the lip). *Rev Bras Otorrinolaringol* 2004;70:772-5.
- Önerci M, Yilmaz T, Gedikoğlu G. Tumor thickness as a predictor of cervical lymph node metastases in squamous cell carcinoma of the lower lip. *Otolaryngol Head Neck Surg* 2000;122:139-42.
- Vartanian JG, Carvalho AL, Filho MJA, et al. Predictive factors and distribution of lymph node metastases in lip cancer patients and their implications on the treatment of the neck. *Oral Oncol* 2004;40:223-7.
- Buccur A, Stefanescu L. Management of patients with squamous cell carcinoma of the lower lip and N0-neck. *J Craniomaxillofac Surg* 2004;32:16-8.
- Khalil HH, Elaffandi AH, Afifi A, et al. Sentinel lymph node biopsy (SLNB) in management of N0 stage T1-T2 lip cancer as a "same day" procedure. *Oral Oncol* 2008;44:608-12.
- Abreu MAMM, Pimentel DRN, Silva OMP, et al. Carcinoma espinocelular do lábio: avaliação de fatores prognósticos (Spinocellular carcinoma of the lip: evaluation of prognostic factors). *Rev Bras Otorrinolaringol* 2004;70:765-70.
- Zitsch RP, Park CW, Renner GJ, et al. Outcome analysis for lip carcinoma. *Otolaryngol Head Neck Surg* 1995;113:589-96.
- Hoffman HS, Karnell LH, Funk GF, et al. The National Cancer Data Base Report on cancer of the head and neck. *Arch Otolaryngol Head Neck Surg* 1998;124:951-62.
- McCombe D, MacGill K, Ainslie J, et al. Squamous cell carcinoma of the lip: a retrospective review of the Peter MacGallum Cancer Institute Experience 1979-88. *Aust N Z J* 2000;70:358.
- Altinyollar H, Berberoğlu U, Çelen O. Lymphatic mapping and sentinel lymph node biopsy in squamous cell carcinoma of the lower lip. *EJSO* 2002;28:72-4.
- Yılmaz S, Ercocen AR. Is elective neck dissection in T1-2, N0 patients with lower lip cancer necessary? *Ann Plast Surg* 2009;62:38-43.
- Rodolico V, Barresi E, Lorenzo R, et al. Lymph node metastases in lower lip squamous cell carcinoma in relation to tumor size, histologic variables and p27Kip1 protein expression. *Oral Oncol* 2004;40:92-8.

- [15] Shah J. Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. *Am J Surg* 1990;160:282-6.
- [16] Mello-Filho FV, Mamede RCM, Velludo MASL, et al. Squamous cell carcinoma of the lip: a proposal of a modification for the treatment of type T₂N₀. *Folha Med* 1996;113:5-9.
- [17] Zitsch RP, Lee BW, Smith RB. Cervical lymph node metastases and squamous cell carcinoma of the lip. *Head Neck* 1999;21:447-53.
- [18] Önerci M, Yılmaz T, Gedikoğlu G. Tumor thickness as a predictor of cervical lymph node metastases in squamous cell carcinoma of the lower lip. *Otolaryngol Head Neck Surg* 2000;122:139-42.