

Management of and risk factors for regional recurrence in upper lip squamous cell carcinoma

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Abstract

Our goal was to evaluate the risk factors for regional recurrence in upper lip squamous cell carcinoma (SCC).

A total of 109 patients with upper lip SCC were retrospectively enrolled. Clinical and pathologic information was collected and analyzed.

Fifteen (13.8%) patients had a regional metastasis, 2 patients had parotid node metastasis, and no local or distant metastasis was noted. There was neck level I node metastasis in 15 (100%) patients. In multivariate analysis, invasion depth and degree of differentiation were significantly associated with regional metastasis. The 5- and 10-year disease-specific survival rate was 95.4% and 80.1%, respectively.

Invasion depth and degree of differentiation have reliable value for predicting regional metastasis.

Abbreviation: SCC = squamous cell carcinoma.

Keywords: head neck, prognosis analysis, squamous cell carcinoma, upper lip cancer

1. Introduction

Cancer of the lip is relatively uncommon and accounts for approximately 10% of all carcinomas of the head and neck.^[1] The minority of these are located at the upper lip, and squamous cell carcinoma (SCC) is one of the most frequent pathological types.

Although upper lip SCC usually has a good prognosis, consistent disease-related death is observed.^[2–8] A number of variables, including tumor stage, perineural invasion, tumor subsite, and differentiation extent, have been described as being associated with the chance of mortality in head and neck SCC.^[9,10] It is widely accepted that lymphatic metastasis is the most important factor in determining prognosis, and the survival rate can be reduced by 50% if there are cervical positive pathological nodes found at diagnosis. Although both Luna-Ortiz et al^[5] and Zitsch et al^[8] reported the apparent association between lymph node metastases and clinical-pathologic variables such as tumor stage and tumor differentiation, the detailed prognostic factors for lymphatic metastasis still remain unclear in upper lip cancer. Therefore, we aimed to evaluate the risk factors for regional recurrence systemically and sought to identify which

patients had a sufficient risk of occult lymph node metastases to justify elective regional treatment.

2. Patients and methods

The Zhengzhou University institutional research committee approved our study and all participants signed an informed consent agreement.

Medical records of patients diagnosed with upper lip SCC in the Department of Stomatology, the First Affiliated Hospital of Zhengzhou University, from January 1995 to December 2016, were reviewed. A total of 119 (50 men and 69 women) patients were enrolled. All patients had undergone preoperative ultrasound, computed tomography, or magnetic resonance imaging examination, and 10 patients were excluded due to clinical positive nodes. The mean age was 68.8 (range: 42–92) years old.

Detailed information about the histologic specimens is presented in Table 1. Fifty-two cases were staged as T1 according to union for international cancer control 2010 classification, 30 cases as T2, 15 cases as T3, and 12 cases as T4. The pathology reports indicated poorly differentiated SCC in 13 patients, moderately differentiated SCC in 37 patients, and well differentiated SCC in 59 patients. Tumor-free resection margins were achieved in all patients, but 37 patients had a close margin (<5 mm). The mean invasion depth was 2.5 (range: 1–4) mm. Perineural invasion and lymphovascular invasion were found in 11 and 17 patients, respectively.

To evaluate the potential risk factors of histologic and clinical parameters for the relation to the likelihood of regional metastasis, Chi-squared test was used for univariate analysis and the logistic regression model for multivariate analysis. All statistic analysis was performed by SPSS13.0 (IBM, Chicago). Statistical significance was set at the 0.05 level.

3. Results

The mean follow-up time was 98.4 (range: 18–165) months. Fifteen (13.8%) patients had a regional metastasis (Fig. 1), and no local or distant metastasis was noted. All disease recurrence

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Table 1**Detailed information of the histologic specimens.**

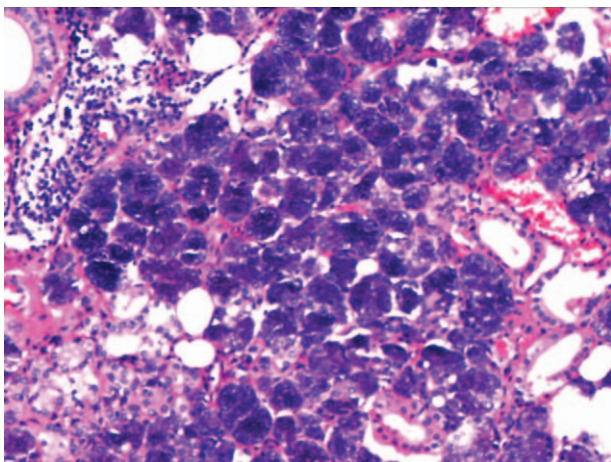
Variable	N (%)
Tumor stage	
T1	52 (47.7%)
T2	30 (27.5%)
T3	15 (13.8%)
T4	12 (11.0%)
Differentiation degree	
Well	59 (54.1)
Moderately	37 (33.9%)
Poorly	13 (11.9%)
Resection margin	
≥5 mm	72 (66.1%)
<5 mm	37 (33.9%)
Invasion depth	
≥3 mm	19 (17.4%)
<3 mm	90 (82.6%)
Perineural invasion	11 (10.1%)
Lymphovascular invasion	17 (15.6%)

occurred within 24 months after operating. In the patients with recurrent disease, parotid node metastasis was noted in 2 (13.3%) patients, neck level I node metastasis in 15 (100%) patients, neck level II node metastasis in 5 (33.3%) patients, neck level III node metastasis in 2 (13.3%) patients, and no lymphatic metastasis was found at the IV and V levels.

Two patients with parotid node metastasis underwent total parotidectomy, and the rest of the patients underwent therapeutic level I to IV neck dissection. The mean number of resected pathological positive nodes was 1.6 (range: 1–4).

The univariate analysis showed that tumor stage, differentiation degree, invasion depth, and perineural invasion were significantly associated with lymphatic node recurrence. In further multivariate analysis, invasion depth and differentiation degree had reliable value for predicting regional metastasis (Table 2).

The 15 patients had all received postoperative radiotherapy, and in our follow-up, 4 patients died of the disease. The 5- and 10-year disease-specific survival rate was 95.4% and 80.1%, respectively.

**Figure 1.** Hematoxylin and eosin stain of lymphatic metastasis.**Table 2****Univariate and multivariate analysis of risk factors.**

Factors	Univariate	Multivariate
Age (<65 vs ≥65)	0.756	
Sex	0.677	
Tumor stage	0.031	0.256
Differentiation degree	0.017	0.023
Resection margin	0.384	
Invasion depth	<0.001	0.003
Perineural invasion	0.021	0.417
Lymphovascular invasion	0.459	

4. Discussion

Due to the rare incidence of upper lip SCC, the existing literature was usually descriptive. Calabrese et al^[2] only reported high frequency of early relapses and the importance of regular and careful follow-up without an evaluation of the risk factors affecting regional recurrence. Another study^[4] focused on the demographic data, clinicopathologic features and therapeutic outcome of a series of upper lip malignancies, and the authors concluded that there were some differences regarding the etiology of pathologic type and in survival with respect to those found in the lower lip. A similar finding was also noted in research reported by Czerninski et al.^[3] Therefore, lip SCC might have different biologic behavior associated with the tumor site and the risk factors for regional recurrence, which were widely accepted in lower lip SCC. Further research regarding upper lip SCC is necessary.

The regional metastasis rate was 13.8%, and this finding was consistent with previous reports.^[5,8] There was no skip metastasis. Gooris et al^[11] found that all recurrent neck disease developed within levels I to III. These findings supported other research that found that level I lymph nodes were the first group of lymphatic involved in lip carcinomas, and skip metastasis to level II to IV was extremely rare.^[12] Moreover, Gooris et al^[11] concluded that a therapeutic elective neck dissection (END) could be an oncologically effective and sound procedure for managing SCC of the lip. Recently, Guney and Yigitbasi^[12] compared clinical results in patients undergoing classical suprahyoid neck dissection (without preserving the submandibular gland) or functional suprahyoid neck dissection (with preserving the submandibular gland); the authors reported that the average number of dissected lymph nodes was similar for both functional- and classical-type operations, and there was no recurrence. Therefore, the authors concluded that functional neck dissection was a reliable diagnostic method in cN0 neck management. All the abovementioned studies consisted of upper and lower lip SCC, and there was a general belief that cancer of the upper lip had a worse prognosis than cancer of the lower lip, owing to the more extensive lymph node metastasis pathway, and parotid node metastasis was noted in 2 patients. However, in the current study, all recurrent neck disease was treated with functional level I to IV neck dissection, and the 5-year disease-specific survival rate was 95.4%. Our favorable outcome could be partially explained by the fact that the mean number of resected positive nodes was just 1.6, and Sinha et al^[13] found metastatic node number (≥5), not extracapsular spread or high N-classification, was independently prognostic for recurrence in SCC of the head and neck. Additionally, tumor-free resection margins were achieved in all patients by various reconstructive procedures.^[14,15]

Risk factors for regional recurrence in head and neck SCC have been widely evaluated. Fang et al^[16] reported that the differentiation degree significantly affected the locoregional control in buccal SCC, and Ozkul et al^[9] described tumor thickness as being positively correlated with recurrence; perineural invasion and invasion depth were also predictors for regional metastasis.^[10,17] However, few authors have described the possible factors affecting regional metastasis in upper lip SCC. We were the first to report that invasion depth and differentiation degree had reliable value for predicting regional metastasis, and a similar finding was noted in SCC of other subsites.^[16,18] A recent study^[18] reported that in 286 patients with a diagnosis of oral squamous cell carcinoma, with a depth of invasion of ≤ 1 mm, there were no patients with a positive node. From 1.1 mm to 2 mm of depth of invasion, there was just 1 of 11 patients (9%) who had at least 1 positive node. At 2.1 mm to 3 mm, 5 of 25 patients (20%) had at least 1 positive node. Therefore, depth of invasion was an important variable to consider when making treatment recommendations to patients with clinical N0 disease.

Unlike previous descriptive studies,^[2,5] we observed no local recurrence or distant metastasis. An important explanation for this is that tumor-free resection margins were achieved in all patients, and various reconstructive procedures were available no matter how great the defect was. Second, primary radiotherapy was not suggested, although surgery and radiotherapy were reported to be equally effective.^[4,19] Residual disease was more common in patients undergoing primary radiotherapy.

Parotid node metastasis occurred in 2 patients, and although the incidence was low, similar to previous findings,^[2,3] it must be considered during the differential diagnosis of parotid tumors. Both of these patients underwent total parotidectomy and postoperative radiotherapy, and neither patient died of the disease in our follow up. The reliability of surgery and postoperative radiotherapy in treating parotid malignancies has been well studied.^[20–22] Shi et al^[21] reported that radiotherapy could decrease local recurrence and increase the survival time in parotid cancers.

In summary, regional recurrence is relatively uncommon in upper lip SCC, nodes in the levels I and II are the most frequently involved, and skip metastasis is rare. Invasion depth and differentiation degree have reliable value for predicting regional metastasis.

References

- Zitsch RP3rd. Carcinoma of the lip. *Otolaryngol Clin North Am* 1993;26:265–77.
- Calabrese L, Ionna F, Tradati N, et al. Squamous-cell carcinoma of the upper lip - analysis of 123 cases. *Int J Oncol* 1993;3:667–9.
- Czerninski R, Zini A, Sgan-Cohen HD. Lip cancer: incidence, trends, histology and survival: 1970–2006. *Br J Dermatol* 2010;162:1103–9.
- 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* 2012;17:e371–6.
- Luna-Ortiz K, Güemes-Meza A, Villavicencio-Valencia V, et al. Lip cancer experience in Mexico. An 11-year retrospective study. *Oral Oncol* 2004;40:992–9.
- Pietersma NS, de Bock GH, de Visscher JG, et al. No evidence for a survival difference between upper and lower lip squamous cell carcinoma. *Int J Oral Maxillofac Surg* 2015;44:549–54.
- McGregor GI, Davis NL, Hay JH. Impact of cervical lymph node metastases from squamous cell cancer of the lip. *Am J Surg* 1992;163:469–71.
- Zitsch RP3rd, Lee BW, Smith RB. Cervical lymph node metastases and squamous cell carcinoma of the lip. *Head Neck* 1999;21:447–53.
- Ozkul Y, Songu M, Imre A, et al. Early stage squamous cell carcinoma of the lower lip: predictive factors for recurrence. *J Laryngol Otol* 2016;130:369–72.
- Pastuszek A, Hanson M, Grigg R. Squamous cell carcinoma of the lip: depth of invasion, local recurrence and regional metastases. Experience of a rural multidisciplinary head and neck unit. *J Laryngol Otol* 2016;130(Suppl):S32–7.
- Gooris PJ, Vermey A, de Visscher JG, 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.
- Guney E, Yigitbasi OG. Functional surgical approach to the level I for staging early carcinoma of the lower lip. *Otolaryngol Head Neck Surg* 2004;131:503–8.
- Sinha P, Kallogjeri D, Gay H, et al. High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol* 2015;51:514–20.
- Fang QG, Shi S, Zhang X, et al. Total lower lip reconstruction with a double mental neurovascular V-Y island advancement flap. *J Oral Maxillofac Surg* 2014;72:834.e1–6.
- Fang QG, Shi S, Li M, et al. Free flap reconstruction versus non-free flap reconstruction in treating elderly patients with advanced oral cancer. *J Oral Maxillofac Surg* 2014;72:1420–4.
- Fang QG, Shi S, Li ZN, et al. Squamous cell carcinoma of the buccal mucosa: Analysis of clinical presentation, outcome and prognostic factors. *Mol Clin Oncol* 2013;1:531–4.
- Harris BN, Bayoumi A, Rao S, et al. Factors associated with recurrence and regional adenopathy for head and neck cutaneous squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2017;156:863–9.
- Brockhoff HC2nd, Kim RY, Braun TM, et al. Correlating the depth of invasion at specific anatomic locations with the risk for regional metastatic disease to lymph nodes in the neck for oral squamous cell carcinoma. *Head Neck* 2017;39:974–9.
- de Visscher JG, Botke G, Schakenraad JA, et al. A comparison of results after radiotherapy and surgery for stage I squamous cell carcinoma of the lower lip. *Head Neck* 1999;21:526–30.
- Rayess HM, Dezube A, Bawab I, et al. Tumor differentiation as a prognostic factor for major salivary gland malignancies. *Otolaryngol Head Neck Surg* 2017;157:454–61.
- Shi S, Fang Q, Liu F, et al. Prognostic factors and survival rates for parotid duct carcinoma patients. *J Craniomaxillofac Surg* 2014;42:1929–31.
- Shi S, Fang QG, Liu FY, et al. Parotid gland metastasis of lung cancer: a case report. *World J Surg Oncol* 2014;12:119.