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The strategy on managing cervical lymph nodes of patients with maxillary gingival squamous cell carcinoma

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ABSTRACT

Purpose: We aimed to determine the risk of occult cervical metastasis of maxillary gingival squamous cell carcinoma (SCC), the predisposing factors for occult cervical metastasis and the therapeutic value of elective neck dissection (END) in survival of clinically negative neck node (cN0) patients.
Methods: A retrospective study of patients with maxillary gingival SCC was conducted in our hospital. Clinical information including age, gender, TNM staging, pathological staging, as well as other demographic and clinical data was acquired and analyzed. The Kaplan–Meier method was used to evaluate overall survival rate. Descriptive and bivariate statistics were computed.
Results: The sample was composed of 107 patients (43 men, 64 women). The overall lymph node metastasis (LNM) rate was 28%. The LNM rates were 7.1%, 15%, 41.7% and 44.8% for T1 to T4 stage tumors, and were 9.3%, 46.8%, and 50% for pathological grades I to III. The tumor stage and pathological grade showed a significant relationship with cervical metastasis ($P < 0.01$). The 5-year survival rate was higher in those who had an END (76%) when compared to those who did not receive an END (46.4%; $P < 0.05$). With regard to the nodal status, pN0 group had a higher survival rate than pN + group ($P < 0.01$).
Conclusion: The results of this study suggest that the risk of LNM for SCC originating from the maxillary gingiva is higher than expected and comparable to that for other oral sites. We recommend END for T3 and T4 stage cN0 patients, especially for moderately and poorly-differentiated tumors.

1. Introduction

SCC constitutes more than 90% of all oral cavity cancer, 25% of which occur in the gingiva (Warnakulasuriya, 2009; Fitzpatrick et al., 2012). Maxillary gingival SCC is more rare than SCC located in the mandibular gingiva. Metastasis of cervical lymph nodes is a well-known biological behavior of oral SCC and has a distinct influence on clinical outcome and prognosis (Cheng & Schmidt, 2008; Paleri et al., 2016). It has been well-documented that SCC in the tongue, mouth floor, and mandibular gingiva has a strong tendency for cervical metastasis, and so END is a well accepted treatment in these patients with cN0 (Tao et al., 2006; Hori et al., 2017). Because of its lower occurrence compared to other carcinomas in the head and neck region, maxillary gingival SCC is a less-studied tumor in regards to its need for END for cases with cN0. Therefore, there are no binding treatment recommendations or guidelines involving the management of the neck in patients with maxillary gingival SCC. Some recent studies indicate that the metastatic risk in maxillary gingival SCC is much higher than expected, and suggest that END should be recommended in patients with cN0 (Mourouzis et al., 2010; Dalal & McLennan, 2013; Eskander et al., 2013; Yang et al., 2014; Tang & Leung 2016). This retrospective, single-centre study aimed to address the question of whether END should be performed in maxillary gingival SCC with a cN0 through assessing the clinical results of SCC primarily located in the maxillary gingiva and evaluating the predictive factors of metastasis. Through increasing our understanding of different neck management options, we hope to contribute to the adoption of a more strategic treatment policy in the future.

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2. Materials and methods

Following the approval of the Human Research Ethics Committee of Capital Medical University, a series of cases of SCC originating from the maxillary gingiva, treated in the department of Oral and Maxillofacial-Head and Neck Oncology from 2005 to 2012 were reviewed. In addition to TNM status, tumor grade, the patients' age and gender, tumor location as well as other demographic and clinical data were retrieved from the electronic medical record system (EMRS) of the hospital. A total of 107 patients fulfilled the inclusion criteria, which were the following: (1) pathologically confirmed primary SCC of the maxillary gingiva; (2) primary treatment comprising surgery only; (3) no metastasis of lymph nodes in the clinical examination. Exclusion criteria were the following: (1) SCC originating from the hard palate, nasal cavity and paranasal sinus invading gingiva; (2) primary tumor invading the oropharynx, or retromolar area; (3) distant metastases; (4) other malignant tumors.

Patient TNM status was determined according to the clinical and pathological classifications set by the International Union Against Cancer based on a complete clinical examination of the head and neck as well as computed tomography (CT) and/or magnetic resonance imaging (MRI) scan. In all cases, the primary tumor sites were treated with radical surgical resection aimed at 1.5-cm margins. After surgery, patients were followed up every 3–6 months until the fifth year. A telephone interview for survivors was also completed every 12 months if necessary. For patients who survived over 5 years, we still followed up annually, but relevant data are not shown in this article. Local recurrence and regional failure were determined by clinical as well as radiographic examinations, and histopathology if necessary.

The data collection and statistical analysis were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). The χ^2 test or Fisher's exact test was used to determine the incidence of metastasis and correlated factors. Survival curves were generated using the Kaplan–Meier method and differences between survival curves were compared by the log-rank test. Statistics were considered significant if $P < 0.05$.

3. Results

One hundred and seven patients (43 men, 64 women) were included in the study. The male-to-female ratio was 1:1.5, with an average age of 64.4 ± 11.8 years (range, 25–89 yr). The follow-up period ranged from 1 to 60 months and the mean was 36.2 ± 20.6 months. Of these 107 patients, T1 stage was present in 14 patients, T2 in 40 patients, T3 in 24 patients, and T4 in 29 patients. Well-differentiated tumors were found in 54 of the cancers, 47 were moderately differentiated, and 6 cases were poorly differentiated cancers. All patients had undergone resection of primary SCC, while 25 patients underwent END. These 25 patients were in T3 or T4 stages. A summary of patients' clinicopathologic characteristics is presented in Table 1.

All of the 107 patients were considered as cN0 cases based on the clinical and radiographic examinations. Twenty five of them received END from level I to III and 6 were found to have pathologic node involvement. A submandibular combined with mental incision was used for the above patients. Primary tumor resection, END and reconstruction of maxilla defect with forearm free flap were performed at the same time. Of the 82 patients who underwent routine observation, 24 patients were diagnosed with pathologic node involvement during the follow-up period from 1 to 51 months after first operation. Metastasis was confirmed histopathologically, and salvage neck dissections were performed in all of these cases. Thus, the overall rate of cervical lymph node metastasis was 28% (30/107).

Table 1
Patient demographics and tumor characteristics at presentation.

	n	%
Total patients	107	100
Gender		
Male	43	40.2
Female	64	59.8
Tumor location		
Anterior region	34	31.8
Posterior region	73	68.2
Clinical T stage		
T1	14	13.1
T2	40	37.4
T3	24	22.4
T4	29	27.1
Pathological grade		
I	54	50.5
II	47	43.9
III	6	5.6
Nodal status		
pN0	77	72
pN+	30	28
Neck dissection		
END	25	23.4
None	82	76.6

Table 2 shows cervical lymph node metastasis rates by Age, Gender, T stage, Pathological grade and Tumor location. T3 and T4 tumors had higher cervical metastasis rates than T1 and T2 tumors ($P = 0.005$). Of note, the metastasis rates were 7.1%, 15%, 41.7% and 44.8% for T1 to T4 stage tumors, respectively. This result showed the T stage to be significantly correlated with cervical metastasis in maxillary gingival SCC. Concerning the histological grading, the prevalence of nodal disease differed significantly in relation to the differentiation of the primary tumors. Poorly and moderately differentiated tumors tended to have a much higher risk than well-differentiated tumors ($P = 0.0001$). The metastatic rates were 9.3%, 46.8%, and 50% for grades I to III, respectively.

Tumor location was classified according to the central position of the primary tumor. There was no statistically significant difference in lymph node metastatic rate between the anterior and posterior regions of the maxilla ($P = 0.805$). Furthermore, the patients' age had no influence on cervical LNM ($P = 0.345$). Incidentally, it should be noted that gender had no significant statistical influence on cervical metastatic risk ($P = 0.679$), although there is a tendency for increased incidence of LNM in male patients (30.2%).

The Kaplan–Meier graphs show the survival of the study patients. The 5-year overall survival rate was 70.8%, for all 107 patients with maxillary gingival SCC. With regard to the pathological grade, well differentiated tumors had a higher survival rate than moderately and poorly differentiated tumors ($P < 0.01$). The 5-year survival rate was 85.1% for well differentiated tumors, compared with 62.8% and 16.7% for moderately and poorly differentiated tumors, respectively (Fig. 1). With regard to the T stage, early T stage (T1/T2) tumors had higher survival rates than advanced T stage (T3/T4) tumors ($P = 0.013$; Fig. 2). The 5-year survival rates were 91.7%, 81.1%, 54.2%, and 65.5% for T1 to T4 stage tumors, respectively. For patients with advanced T stage tumors, the 5-year survival rate was higher in those who had an END (76%) when compared to those who did not receive an END (46.4 %) ($P = 0.037$) (Fig. 3). In addition, nodal status was an important factor that affected overall survival. Patients with negative cervical node metastasis had better overall survival compared with those who had metastatic lymph nodes ($P = 0.002$) (Fig. 4). Location of the tumor in the anterior region or posterior region of the maxilla was not related to survival rate ($P > 0.05$) (Fig. 5).

Table 2
Neck metastasis of patients with cN0.

	n	Patients with cervical metastases(n)	Metastasis rate (%)	P-value[b]
Age [a]				0.345
≤66	60	19	31.7	
>67	47	11	23.4	
Sex				0.679
Male	43	13	30.2	
Female	64	17	26.6	
Tumor stage classification				0.005*
T1	14	1	7.1	
T2	40	6	15	
T3	24	10	41.7	
T4	29	13	44.8	
Pathological grade				0.0001**
I	54	5	9.3	
II	47	22	46.8	
III	6	3	50	
Tumor location				0.805
Anterior region	34	9	26.5	
Posterior region	73	21	28.8	

*$P < 0.01$, **$P < 0.001$, and ***$P < 0.0001$.
[a] 66 years is the median age of the subjects.
[b] Fisher's exact test, two-sided.

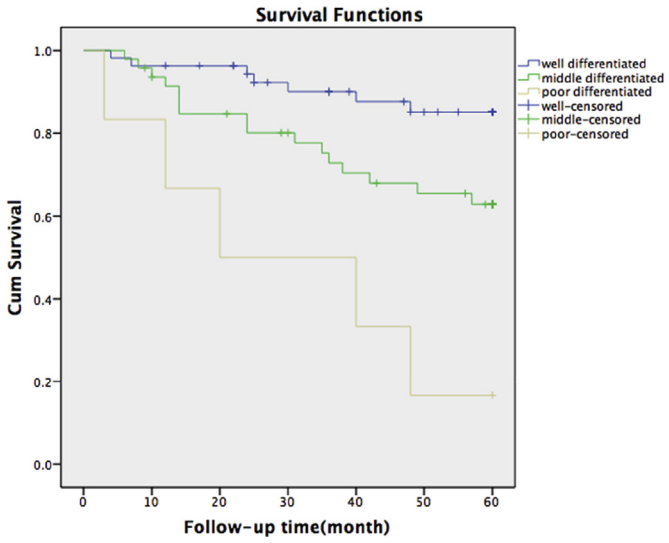

Fig. 1. Kaplan–Meier overall survival curve for tumor grades of squamous cell carcinoma of the maxillary gingiva ($P = 0.00068$).

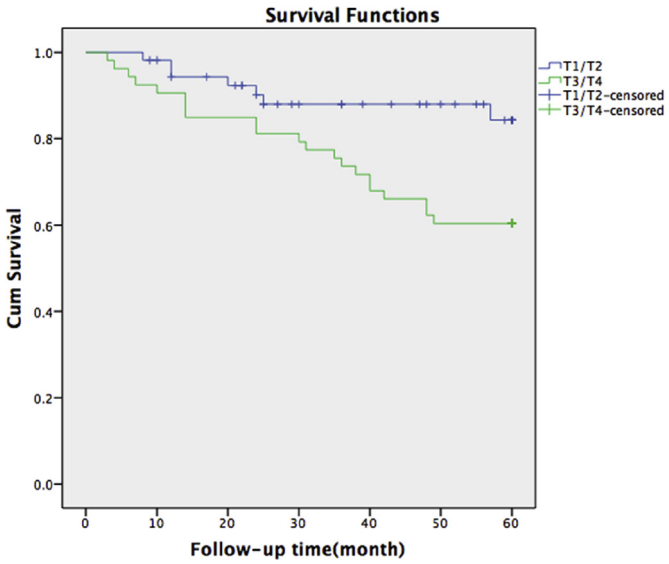

Fig. 2. Kaplan–Meier survival curves of overall survival for T stage of squamous cell carcinoma of the maxillary gingiva ($P = 0.013$).

4. Discussion

There are abundant data to support the requirement of END for treating patients with SCC at oral sub-sites such as the tongue, floor of the mouth, buccal mucosa, and mandibular gingiva, as the risk of cervical metastasis is particularly high. However, there are currently no explicit treatment recommendations for neck dissection in patients with maxillary gingival SCC, because data for the risk of cervical LNM in these patients are sparse (Philip & James, 2014). The recent literature finds the risk of LNM in patients with maxillary gingival SCC higher than expected and similar to SCC of the tongue or the floor of mouth (Promish, 1998; Kruse & Grätz, 2009; Morris et al., 2011; Sagheb et al., 2014). In the series of 34 patients reported by Zwetyenga et al. (2006), the overall incidence of invaded lymph nodes was 28%, and although these patients had a significantly worse prognosis the authors concluded that END in those with N0 necks was debatable. Simental et al. (Simental et al., 2006) reviewed 26 patients with carcinoma of the maxillary gingiva and found an incidence of 27% of occult nodal metastasis. They recommended END for all patients with carcinoma of the maxillary alveolus and hard palate. Tang and Leung conducted a systematic review and concluded that END is recommended in patients with cN0 maxillary SCC, especially in stage T3 or T4 cases (Tang & Leung, 2016).

The incidence of occult node in the present study including 107 cases of cN0 maxillary SCC was 28% which is similar to other reports (Simental et al., 2006). Since the present study includes more cases than previous studies, we have reason to believe that this metastasis rate is credible. Moreover, incidence of occult metastasis of T3 and T4 stage were 41.7% and 44.8% which were higher than the 20% threshold for END. The management of the cN0 neck has been the subject of debate in our department, especially in early cases. Either END or observation was applied for the cN0 patients. All patients who received END are only in T3 or T4 stage. With regard to the 25 patients who underwent END, six were found to

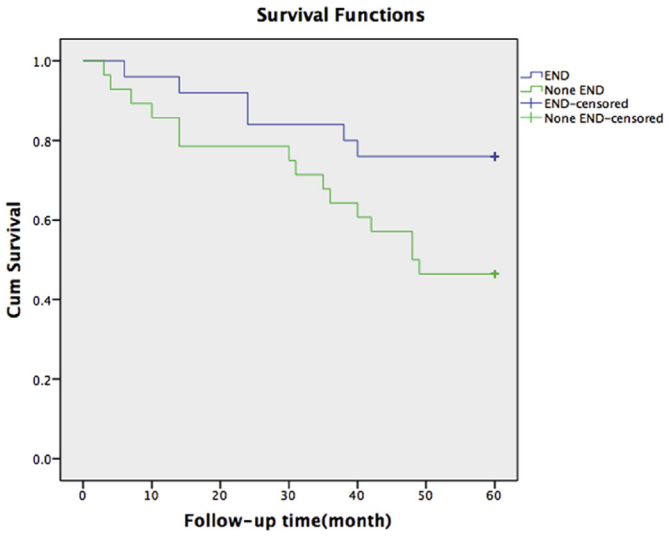

Fig. 3. Kaplan–Meier survival curves of overall survival for neck dissection of squamous cell carcinoma of the maxillary gingiva ($P = 0.013$).

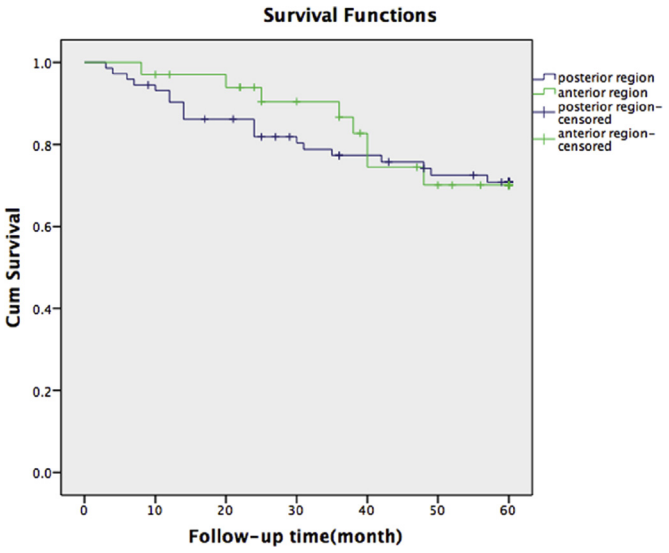

Fig. 5. Kaplan–Meier survival curves of overall survival for tumor location of squamous cell carcinoma of the maxillary gingiva ($P = 0.798$).

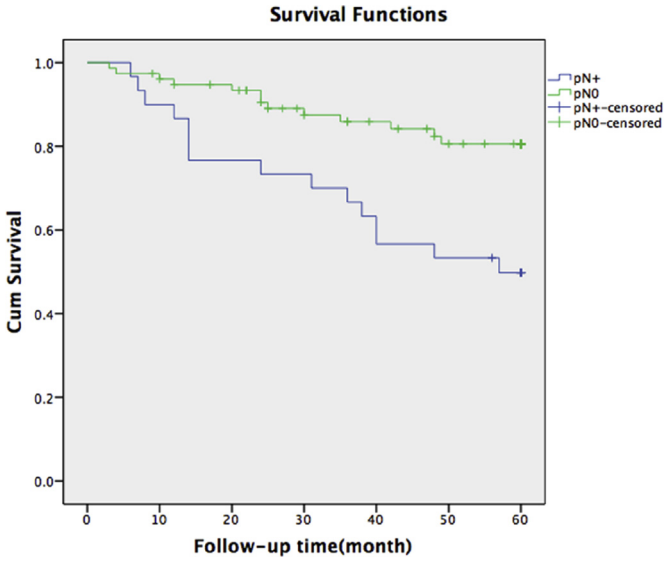

Fig. 4. Kaplan–Meier survival curves of overall survival for nodal status of squamous cell carcinoma of the maxillary gingiva ($P = 0.002$).

have a positive neck after pathological examination, while 19 patients presented delayed metastasis during the 'wait-and-see' period. The occult metastasis rate for other oral sites has been reported to be around 20–30% (Pimenta Amaral et al., 2004; Sparano et al., 2004). Therefore, our results suggest that the metastasis rate, especially the occult metastasis rate of SCC in the maxillary gingiva, is much higher than expected and comparable to those for other oral sites. Several well-known cancer researchers have recommended that surgeons perform an END for patients with oral SCC when the risk of occult metastasis is more than 15–20% (Pitman, 2000; Haddadin et al., 1999). The 5-year survival rate for the group of patients who had an END was higher than that of the patients who did not have an END (76% vs. 46.4%). Therefore, we hold that END can improve the survival outcome of maxillary gingival SCC patients of T3 and T4 stage.

Many studies reported a correlation between advanced maxillary SCC T stage and LNM (Warnakulasuriya, 2009; Yang et al., 2014; Hori et al., 2017). Lin & Bhattacharyya (2009) reported that the N stage was significantly correlated with the T stage: patients with advanced T stage tumors always presented with advanced N stage disease. In the present study, the cervical metastasis rates were 7.1% and 15% among patients who were diagnosed with T1 and T2, early-stage SCC, compared with 41.7% and 44.8% among patients who were diagnosed with the advanced disease (T3/T4) ($P = 0.005$). Moreover, we found that the prevalence of nodal disease differed significantly in relation to the differentiation of the primary tumors. Poorly and moderately differentiated tumors tended to have a much higher risk than the well-differentiated tumors. Location of the primary tumor, patients' age and gender were not significant predisposing factors for occult cervical metastasis.

As a result of these study findings, we strongly recommend END for T3 and T4 stage patients, especially for moderately and poorly-differentiated tumors. As far as radical maxillectomy is concerned for patients with maxillary SCC, the classical Weber Ferguson incision has been routinely used since last century and still is being used widely due to its advantages of excellent exposure and minimal scarring as the incision follows the natural skin crease (Chen et al., 2008; Bhavana et al., 2012). In our hospital, for the patients with maxillary gingival SCC and requiring END, we chose a submandibular combined with mental incision which simultaneously meets the criteria of the good operation visual field, elective radical neck dissection, maxillary bone defect repair, good oral cavity function and aesthetics for the above patients.

Finally, the overall survival rate of maxillary gingival SCC patients in our series was 70.8%, which is similar to figures reported by other institutions (Mourouzis et al., 2010; Dalal & McLennan, 2013; Eskander et al., 2013). There are very few published studies on factors correlating with survival rate for maxillary gingival SCC patients. Zhang et al. (Zhang et al., 2015) showed that the 5-year survival rates were 93.3%, 73.2%, 32.7%, and 25.4% for T1 to T4, respectively. Both the 3-year and 5-year survival rates in patients with nodal disease (pN+) were significantly lower than those of patients without nodal disease (pN0). Yang et al. (2015) reported that overall survival was associated with tumor differentiation grade, T classification, marginal status, cervical lymphatics, and local recurrence.

In our study, the 5-year survival rate in the cN0 maxillary gingival SCC case with T1, T2, T3, and T4 was 91.7%, 81.1%, 54.2%,

and 65.5%, respectively. T1/T2 had a higher 5-year survival rate than T3/T4. Depending on the pathological grade, patients had a different prognosis. For example, the patients with well-differentiated tumors had a better prognosis, as the 5-year survival rates were 85.1%. According to the results we suggest that grade II and III patients need to receive additional therapy, such as radiotherapy or chemotherapy. As expected and demonstrated in other oncological centres, LNM has a negative influence on the patients' survival (Morris et al., 2011; Sagheb et al., 2014; Zhang et al., 2015). The 5-year survival rates in patients with nodal disease were lower than those of patients without nodal disease in our studies. All these outcomes above also support our recommendation of END.

This study has the limitations of small sample size and surgeon bias for selection of END, such as the predilection toward END for advanced T stages. Moreover, there is insufficient information about the likelihood of metastasis at the different neck levels in relation to the T staging to comment on the type of neck dissection required. There is a sustained need for prospective randomised, controlled, multicentre studies in order to achieve strong evidence-based data and to investigate an overall accepted treatment recommendation for SCC of the maxillary gingiva.

5. Conclusion

Based on the outcomes of our study and a review of the literature, we conclude that the risk of LNM for SCC originating from the maxillary gingiva is higher than expected and comparable to that for other oral sites. The metastatic rate is strongly correlated with the T stage and pathological staging. Advanced T stage, grade II and III tumors show a significantly higher metastatic risk. END for the cN0 neck can reduce the regional recurrence rate significantly. T stage, N stage and END significantly affect the survival of patients with maxillary gingival SCC. We recommend END for T3 and T4 stage cN0 patients with maxillary gingival SCC, especially for moderately and poorly differentiated tumors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2018.12.008.

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