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Cervical metastasis of maxillary squamous cell carcinoma

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Abstract. A retrospective study of maxillary squamous cell carcinoma (SCC) patients attending a department of oral and maxillofacial surgery was performed for the period 2000–2010. The clinical information of 100 cases treated during this period was acquired and analyzed. Patient survival was calculated using the Kaplan–Meier method. For these 100 cases, the total metastatic rate was 34.0% and occult metastatic rate was 27.5%. Positive lymph nodes were mostly detected at levels I–III. There was no significant difference in metastatic rate between the primary sites of maxillary gingiva and hard palate. Tumours involving the gingival–buccal sulcus presented a significantly higher risk of metastasis. Advanced stage (T3/4) was significantly correlated with a higher metastasis rate. The pathological grade also showed a significant relationship with metastasis. Twenty-four patients presented regional recurrence. Elective neck dissection could significantly reduce the recurrence rate. The overall 3-year and 5-year survival rates were 66.3% and 56.7%, respectively. Both the T and the N stages had a significant impact on survival rates. Selective neck dissection from level I to III is recommended for T3/4 stage cN0 patients, especially those with gingival–buccal sulcus involvement.

Keywords: squamous cell carcinoma; maxillary gingiva; hard palate; cervical metastasis; elective neck dissection.

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Squamous cell carcinoma (SCC) is the most common malignant tumour of the oral cavity, accounting for more than 80% of all oral cancers. Cervical metastasis is one of the well-known behaviours of oral SCC, and it may have a distinct influence on the prognosis and clinical outcome for the patient. It is well documented that oral SCCs of the tongue, floor of the mouth, and mandibular gingiva have a strong tendency for cervical metastasis. Elective neck dissection (END) is already well accepted in these patients.[1,2] However, the management of the cN0 neck patient with hard palate, maxillary alveolar, or gingival SCC remains on a 'watch and wait' basis due to the low metastatic rate. Only recently have studies focused on the cervical metastasis of maxillary SCC.[3–9] However, prospective and evidence-based studies are still lacking and the treatment of the clinical negative neck remains controversial.

The aim of this retrospective study was to determine the incidence of cervical metastasis of SCC of the maxilla and to define the risk factors and outcome of cervical metastasis. We also sought to propose recommendations in relation to the treatment strategy for the clinically negative neck.

Patients and methods

A series of cases of SCC originating from the hard palate and maxillary alveolus or gingiva, treated in the department of oral and maxillofacial surgery of the university hospital between 2000 and 2010, were reviewed. Clinical information including the primary site of the tumours, TNM staging, pathological staging, and type of neck dissections, as well as other demographic and clinical data, were retrieved from the electronic medical record system (EMRS) of the hospital. A total of 137 patients fulfilled the inclusion criteria, which were the following:

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(1) pathologically confirmed primary SCC of the hard palate and maxillary alveolus or gingiva; (2) primary treatment comprising surgery only. Exclusion criteria were the following: (1) SCC originating from the nasal cavity or paranasal sinus; (2) primary tumour invading the soft palate, oropharynx, or retromolar area; (3) adjunctive radiotherapy given after surgery.

All patients were staged according to the Union for International Cancer Control (UICC) TNM classification based on a complete clinical examination of the head and neck as well as computed tomography (CT) or magnetic resonance imaging (MRI) scan. In all cases, the primary tumour sites were treated with radical resection aimed at 1.5-cm margins. The margins were confirmed intraoperatively by frozen section. For patients with clinically positive lymph nodes (cN+), a radical or modified radical neck dissection was performed at the same time. However, there was no standard protocol for the negative neck (cN0). In most of the early cases, a 'watch and wait' approach was applied. END was carried out in some of the more recent cases. Patients were followed up every 3 months in the first 2 years, then every 6 months until the fifth year, and then annually after 5 years. Local recurrence and regional failure were determined by clinical as well as radiographic examinations, and histopathology if necessary. Salvage surgery was performed if delayed metastasis or regional failure was confirmed. Radiotherapy was recommended to patients with a pN+ neck after neck dissection.

The data collection and statistical analysis were performed using SPSS version 17.0 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. Multivariate analysis by logistic regression was also performed. A Kaplan–Meier plot was used to determine the overall survival rate, and a log-rank test was performed to evaluate any statistical significance ($P < 0.05$).

Results

One hundred and thirty-seven patients were included in this study; 59 were male and 78 were female. The median age of patients at the time of diagnosis was 70.1 years (range 44–99 years). Detailed clinical information was available for only 100 of these 137 patients. The follow-up rate was 73.0%. We were unable to make contact with the remaining 37 patients after the primary surgery and were therefore not able to define the exact N stage or the survival rate of these cases; thus they were excluded from the study. The follow-up period ranged from 2 to 140 months and the mean was 45.8 ± 34.2 months.

Of the 100 patients included, nine were diagnosed as cN+ and this was confirmed by histopathological examination after radical neck dissection. The other 91 patients were considered as cN0 cases based on the clinical or radiographic examinations. END was not performed routinely for these cN0 cases and only 34 underwent a selective neck dissection from level I to III. Positive lymph nodes were detected in seven cases. The other 57 patients underwent routine observation and 18 presented with delayed metastasis. There were palpable lymph nodes in the necks of these 18 patients, and lymph nodes larger than 10 mm with suspected liquefaction were examined with CT/MRI scans. Metastasis was confirmed histopathologically, and salvage neck dissections were performed in all of these cases. Hence the overall rate of metastasis was 34.0% (34/100), while the rate of occult metastasis was 27.5% (25/91) (Fig. 1).

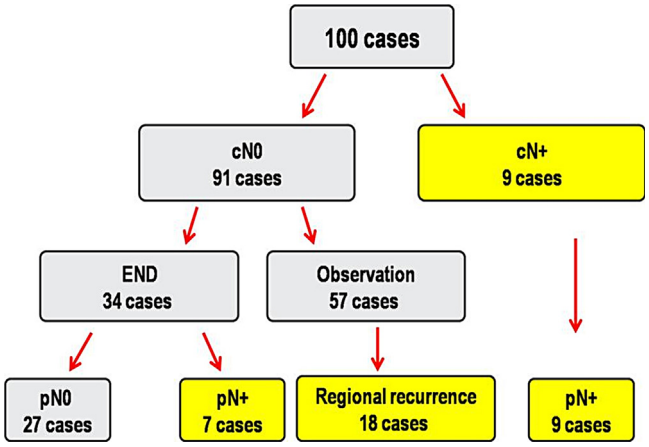

Fig. 1. Flowchart of the case series for cervical metastasis and occult metastasis. The flowchart presents the treatment strategy and outcome for the series of 100 patients and indicates the cervical metastasis and occult metastasis rates of maxillary SCC.

Table 1. Primary site, T stage, N stage, and pathological characteristics of maxillary squamous cell carcinoma patients.

	Total	N stage				N+%	*P*-value
		N0	N1	N2	N3		
T stage							
T1/2	51	44	3	4	0	13.7	0.002
T3/4	49	29	9	11	0	40.8	
Primary site							
Palate	30	22	5	3	0	26.7	0.454
Gingiva	70	46	8	16	0	34.3	
Gingival–buccal sulcus							
Involved	20	6	4	10	0	70.0	<0.01
Not involved	80	62	9	9	0	22.5	
Pathological grade							
I	55	47	4	4	0	14.5	<0.01
II	38	19	6	13	0	50.0	
III	7	2	3	2	0	71.4	

A summary of the details of these 100 cases is presented in Table 1. There was no significant difference in the rate of metastasis according to the primary site ($P = 0.454$), although SCC of the maxillary gingiva showed a higher risk (34.3%) when compared to that of the hard palate (26.7%). Of note, when the tumour involved the gingival–buccal sulcus, the cervical metastasis rate increased to 70.0%, which was significantly different from those without sulcus involvement ($P < 0.01$). Histopathologically, positive lymph nodes were mostly detected at level I (70.5%), followed by levels II (56.8%) and III (13.6%); only 4.5% were found at level IV and none at level V. The rate of metastasis of advanced stage

Table 2. Multivariate analysis of factors related to cervical metastasis of maxillary squamous cell carcinoma by logistic regression.

Factors	B	Wald	Sig. (*P*-value)	OR	95% CI of OR	
					Lower	Upper
Primary site (gingiva/palate)	0.298	0.248	0.619	1.347	0.417	4.358
Sulcus involvement (involved/not involved)	1.667	5.615	0.018	5.298	1.334	21.043
T stage (T3–4/T1–2)	0.306	1.295	0.255	1.357	0.802	2.298
Pathological grade		12.556	0.002			
I/III	−3.090	6.197	0.013	0.046	0.004	0.520
II/III	−1.295	1.554	0.277	0.274	0.027	2.828

OR, odds ratio; CI, confidence interval.

tumours (T3/4) was 40.8%, which was higher than that of early stage tumours (T1/2) (13.7%). This result showed the T stage to be significantly correlated with cervical metastasis in maxillary SCC patients ($P = 0.002$). Concerning the histological grading, the prevalence of nodal disease differed significantly in relation to the differentiation of the primary tumours. Poorly differentiated tumours tended to have a much higher risk than the moderately or well-differentiated tumours ($P < 0.01$).

The results of the multivariate analysis are shown in Table 2. The risk of cervical metastasis of maxillary SCC was highly correlated with the pathological grade and the involvement of the gingival–buccal sulcus. The primary site and clinical stage were not significant in this context.

The mean follow-up time for these 100 patients was 45.8 ± 34.2 months, ranging from 2 to 140 months. During follow-up, 15 patients presented with local recurrence and 24 presented with regional recurrence; two of them had both local and regional recurrence. Ninety-one of the 100 patients were diagnosed with a cN0 neck and 34 of them underwent END together with primary tumour resection. The remaining 57 patients were managed by observation only. Four patients in the END group presented with regional recurrence and only one of them survived after the salvage surgery within the follow-up period. In the observation group, 18 patients presented with regional recurrence and seven had a salvage neck dissection and survived. The results indicated that END can significantly reduce the risk of regional recurrence ($P = 0.033$). In the nine cN+ patients, a modified radical neck dissection was performed and recurrence occurred in two patients. Both of them died within 6 months (Table 3).

The overall 3-year and 5-year survival rates were 66.3% and 56.7%, respectively (Fig. 2). The 3-year and 5-year survival rates were 80.7% and 72.3%, respectively, in the N0 group, while the survival rates were 30.8% and 20.5%, respectively, in the pN+ group ($P < 0.01$). With regard to the T stage, advanced T stage tumours had a higher cervical metastatic rate than early T stage tumours. The 5-year survival rates were 93.3%, 73.2%, 32.7%, and 25.4% for T1 to T4 stage tumours, respectively ($P < 0.01$). The survival rates according to the T and N stages are shown in Table 4. Kaplan–Meier survival curves for the various T and N stages are shown in Figs 3 and 4.

Cox regression was performed for multivariate analysis of the survival outcome of maxillary SCC patients (Table 5). The results showed that the N stage had a greater impact on the survival outcome than the T stage, indicating that the N stage is a more important factor with regard to the survival outcome of maxillary SCC patients, after adjusting for T stage.

Discussion

SCC is the most common malignant tumour of the oral cavity, and cervical metastasis is one of the most common features and can affect the prognosis significantly. Many studies have proven that SCC at oral sub-sites such as the tongue, floor of the mouth, buccal mucosa, and mandibular gingiva, presents a particularly high risk of cervical metastasis, and END is required in such patients.[1,2] However, cervical metastasis of SCC from the maxillary gingiva and hard palate has been considered to be lower than from the other primary sites; the management of cN0 patients has been to 'watch and wait'. More recently, several retrospective studies[3–9] have reported cervical metastasis of maxillary SCC ranging from 21.5% to 66.7%. This is much higher than expected and

Table 3. Correlation between regional failure and primary neck treatment in the follow-up of maxillary squamous cell carcinoma patients.

Present status	Treatment of primary neck disease	Total	Regional recurrence	Treatment of regional failure	Salvage rate, %	*P*-value for recurrence
cN0	END	34	4 (11.8%)	Surgery	25% (1/4)	0.033
	Observation	57	18 (31.6%)	Surgery	38.9% (7/18)	
cN+	MRND + RT	9	2 (22.2%)	RT + chemotherapy	0% (0/2)	
Total		100	24 (24%)		33.3%	

Table 4. Survival outcome according to T/N stage for maxillary squamous cell carcinoma patients.

T/N stage	Mean survival time	3-year overall survival rate	5-year overall survival rate	*P*-value
T stage				
T1	118.4 ± 6.4	100.0%	93.3%	<0.01
T2	95.3 ± 9.5	82.3%	73.2%	
T3	56.1 ± 14.7	32.7%	32.7%	
T4	53.8 ± 9.9	46.2%	25.4%	
N stage				
N0	107.7 ± 7.3	80.7%	72.3%	<0.01
N+	41.6 ± 8.3	30.8%	20.5%	

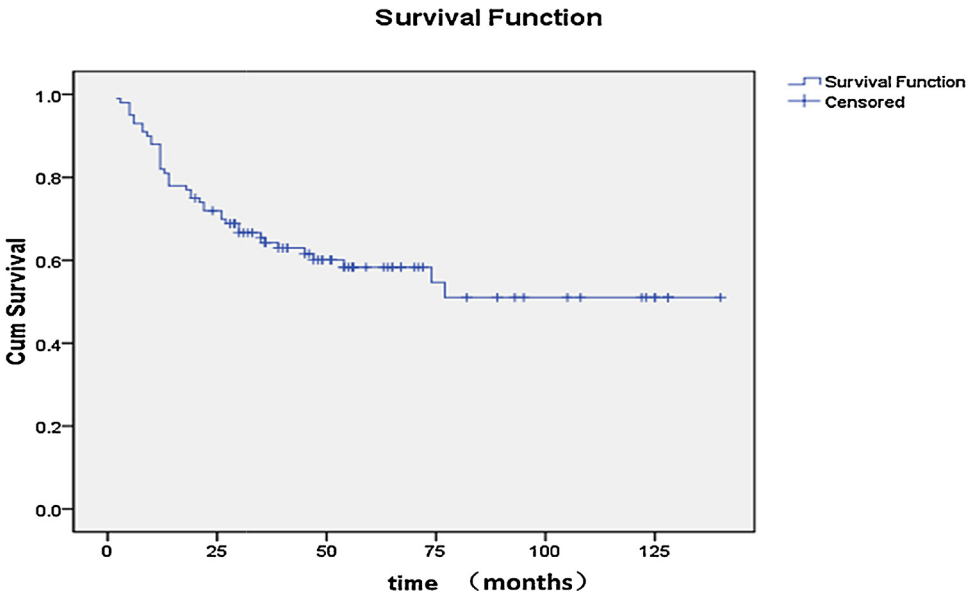

Fig. 2. Kaplan–Meier overall survival curve for maxillary SCC patients. The analysis indicated overall survival rates at 3 and 5 years of 66.3% and 56.7%, respectively.

Table 5. Cox regression analysis with related factors for the survival rate of maxillary squamous cell carcinoma patients.

Factor	B	Wald	Sig. (*P*-value)	OR	95% CI of OR	
					Lower	Upper
T	0.419	8.443	0.004	1.634	1.173	2.276
N	1.454	17.570	<0.001	4.281	2.169	8.451

OR, odds ratio; CI, confidence interval.

Table 6. Cervical metastasis rate of maxillary squamous cell carcinoma in recent studies.

Author (year) [Ref.]	Number of patients	Age, years, mean	F/M ratio	Primary site	Overall metastatic rate, %
Montes and Schmidt (2008)[3]	14	77.6	0.56	Hard palate and maxillary gingiva	42.9
Simental et al. (2006)[4]	26	–	–	Hard palate and maxillary gingiva	34.6
Ogura et al. (2003)[5]	21	64.5	0.91	Maxillary gingiva	66.7
Kruse and Gratz (2009)[6]	30	73.1	1.37	Hard palate and maxillary gingiva	36.7
Morris et al. (2010)[7]	139	–	0.69	Hard palate and maxillary gingiva	31.6
Mourouzis et al. (2011)[8]	17	68.0	1.83	Hard palate and maxillary gingiva	35.3
Beltramini et al. (2012)[9]	65	68.5	0.91	Hard palate and maxillary gingiva	21.5

F, female; M, male.

comparable to rates for other primary oral sites (Table 6).

In our series, the cervical metastasis of SCC of the maxilla was 34.0%, which is similar or even higher than rates reported in previous studies. 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. With regard to the 34 patients who underwent END, seven were found to have a positive neck after pathological examination, while 18 patients presented delayed metastasis during the 'watch and wait' period. We found a 27.5% occult metastatic rate for maxillary SCC. Montes and Schmidt[3] stated that for cN0 maxillary SCC patients, occult metastasis was responsible for the early regional recurrence. Simental et al.[4] and Ogura et al.[5] reported regional failure rates of 29% and 38.8%, which are similar to our metastasis rate. The occult metastasis rate for other oral sites has been reported to be around 20–30%.[10,11] However, our results suggest that the metastatic rate, especially the occult metastasis rate of SCC in the maxillary gingiva and hard palate, is much higher than expected and comparable to those for other oral sites.

There are two pathways for maxillary SCC metastasis to the neck. Lymph from the maxillary gingiva drains into the submandibular lymph nodes through the buccal lymphatic system, including the gingival–buccal complex. On the other hand, the lymphatics from the hard palate drain directly into the deep cervical lymph nodes through the parapharyngeal or retropharyngeal lymphatic system.[12] In our study, most of the positive lymph nodes were detected at levels I–III. Morris et al.[7] also suggested that most of the lymph nodes affected by maxillary SCC metastasis were limited to levels I–III; metastasis to levels IV and V was found to be rather low in these patients. The lymphatic drainage pathway can also explain the relationship of the primary sites and cervical metastasis. The results of our study

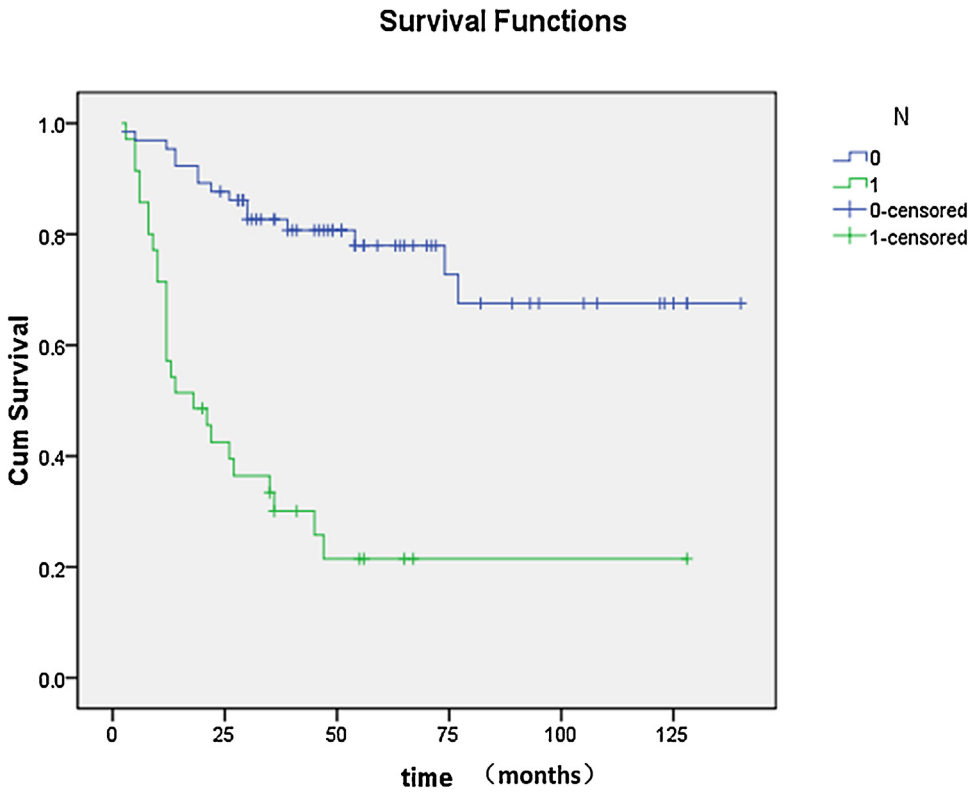

Fig. 3. Kaplan–Meier overall survival curves based on the N stage. The analysis indicated that N0 patients had a better survival rate compared with N+ patients.

showed no significant difference for cervical metastasis between the maxillary gingiva and hard palate, although the metastatic rate for the maxillary gingiva was relatively higher (Table 1). This is similar to the results of the study by Lin and Bhattacharyya.[13] Moreover, we found that tumours involving the gingival–buccal sulcus had a significantly higher potential for regional metastasis than those not involving the sulcus (Table 1). There are rich lymphatic networks in the buccal

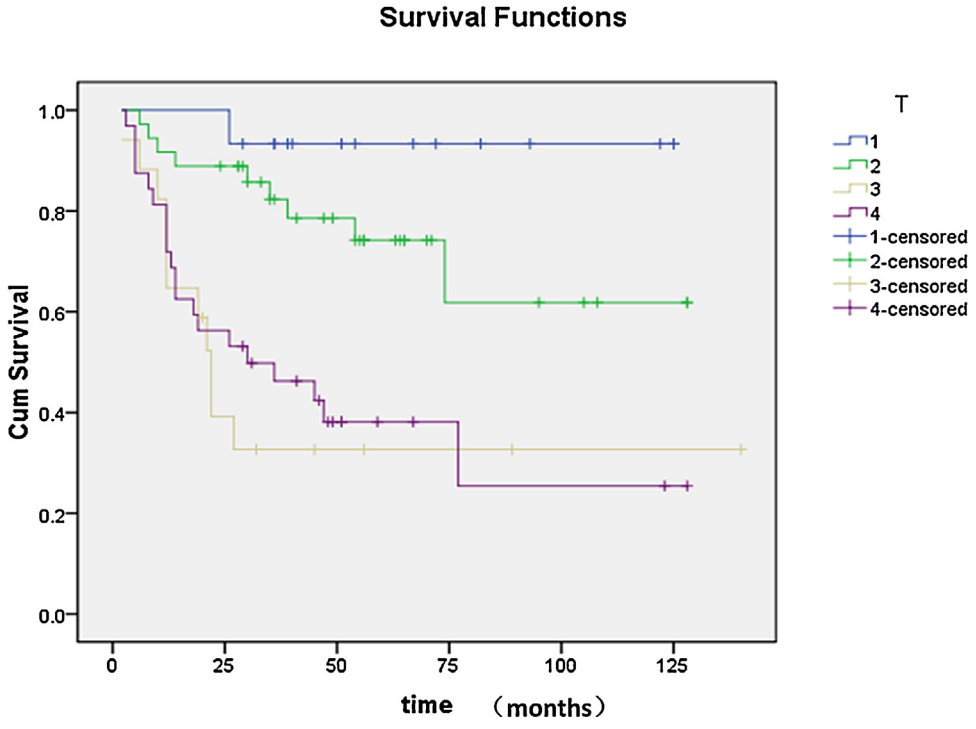

Fig. 4. Kaplan–Meier overall survival curves based on the T stage. The analysis indicated a much lower survival rate at advanced T stages (T3/4).

mucosa and thus metastasis may be more likely if the mucosa of the sulcus is involved. We conclude that the clinical behaviours of SCC of the maxillary gingiva and hard palate are similar if the gingival–buccal sulcus is not involved. However, the risk of metastasis increases with the involvement of the gingival–buccal sulcus.

The T stage is related to tumour size, depth of invasion, and the close proximity to the surrounding structures. Lin and Bhattacharyya[13] reported that the N stage was significantly correlated with the T stage–patients with advanced T stage tumours always presented with advanced N stage disease. The study of Ogura et al.[5] reported that the risk of regional metastasis had a significant relationship with bone invasion by the maxillary SCC. In our research, advanced T stage tumours (T3/4) had a significantly higher metastatic risk than early T stage tumours (T1/2) (Table 1). These results confirm the findings of some previous studies that have recommended END for advanced T stage tumours (T3/4), especially T4 cases with bone invasion. Further, it is noteworthy that all cases in which the gingival–buccal sulcus was involved were at least T3 stage. As a result of these study findings, we strongly recommend selective neck dissection from level I to III for T3/4 stage maxillary SCC, especially for those involving the gingival–buccal sulcus.

We also found a correlation between cervical metastasis and pathological grading. The metastatic rate was 14.5%, 50.0%, and 71.4% for grades I to III, respectively ($P < 0.01$). This is in agreement with the results of the study by Sparano et al.[11] for tongue cancer; their study also indicated that the higher the grading, the higher the risk of metastasis. There has been no other study on the correlation between pathological grading and cervical metastasis except that of Kruse and Gratz.[6] However, the results were limited by the small sample size of 30 cases only.

Several studies have discussed the risk factors of cervical metastasis of maxillary SCC, but to our knowledge no multivariate analysis has yet been done. Therefore, we established a model for cervical metastatic risk in maxillary SCC using logistic regression (Table 2). The results indicated that, among all the related factors, pathological grading was the most important factor, followed by involvement of the gingival–buccal sulcus; the T stage should also be considered. Although there was a difference between the metastatic rates of the maxillary gingiva and hard palate, the primary site was of less importance.

We observed that a number of patients returned due to delayed metastasis or regional recurrence following the primary tumour resection. For most of the recurrence cases (22/24), the regional failure occurred with no local recurrence, which suggests that regional recurrence or delayed metastasis is strongly related to occult metastasis, as we have mentioned above. The most common management for tumour recurrence was salvage surgery accompanied by adjuvant therapy. However, the success rate for salvage surgery was much lower than expected; it was 33.3% in our study and 34.3% in the study by Morris et al.[7] (Table 3). Morris et al.[7] also reported a 2-year survival rate for the salvaged patients of less than 50%. The low success rate and low survival rate of salvage surgery indicate the importance of neck management of patients with maxillary SCC, especially for cN0 cases.

It has been reported that when the occult metastasis rate is over 20%, END should be performed on cN0 patients with oral cancer. Further, it has been well accepted that END should be performed routinely for SCC of the tongue, floor of the mouth, mandibular gingiva, and other sub-sites.[14]

Nevertheless, controversy remains regarding the treatment of the cN0 neck in maxillary SCC patients. The traditional management has been observation; however some studies have proposed that END for cN0 patients at the time of primary tumour resection is beneficial. In our study, 34 cN0 patients underwent a selective neck dissection at levels I–III. During follow-up, only four patients presented with regional recurrence. Meanwhile, the other 57 cN0 patients were observed for recurrence throughout the follow-up period and regional failure occurred in 18 of them. There was a significant difference in the recurrence rate between the END group and the observation group ($P = 0.033$), as shown in Table 3. Poeschl et al.[15] divided 74 cN0 cases into two groups, an END (+) group and an END (−) group. They found that there was no significant difference in regional recurrence rate between the two groups, but all of the recurrence cases were T4 stage. In contrast, we found that simultaneous END with primary tumour resection can reduce the rate of regional recurrence significantly. However, with the limited number of 34 END cases followed up, we are unable to draw any conclusions on the relationship between END and the survival outcome. Of note, Feng et al.[16] showed that patients with T2 to T4 stages who underwent END had improved survival compared to those in the observation group. Hence, we suggest that END can reduce the recurrence rate and improve the survival outcome of maxillary SCC patients. Prospective, evidence-based studies with larger sample sizes are required to clarify this matter.

Finally, the overall survival rate of maxillary SCC patients in our series was 66.3% at 3 years and 56.7% at 5 years. There are very few published studies on factors correlating with the survival rate for maxillary SCC patients. We found that both the T stage and N stage significantly affect the survival duration and survival rate of patients with maxillary SCC and that the N stage is the more important factor (Tables 4 and 5; Figs 3 and 4). 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). These results are consistent with those of the study by Lin and Bhattacharyya.[13] The low survival rate of T3/4 stage tumour and pN+ cases also supports our recommendation of END.

In conclusion, based on the results of our study and a review of the literature, we conclude that the risk of cervical metastasis for SCC originating from the maxillary gingiva and hard palate 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 and higher grade tumours present a significantly higher metastatic risk. Elective neck dissection for the cN0 neck can reduce the regional recurrence rate significantly. Both the T stage and N stage significantly affect the outcome of patients with maxillary SCC. We recommend a selective neck dissection at levels I–III for T3/4 stage cN0 patients, especially for cases involving the gingival–buccal sulcus.

Competing interests

None declared.

Ethical approval

Not required.

Patient consent

Not required.

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