

Prognostic factors in mandibular gingival squamous cell carcinoma: A 10-year retrospective study

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Abstract. The mandibular gingiva is the second most common site of oral cavity squamous cell carcinoma. This retrospective study was designed to determine the clinicopathological features of squamous cell carcinoma of the mandibular gingiva (MGSCC) and to establish a new risk model to predict overall survival. The study included 207 patients with primary MGSCC from January 2000 to September 2009. The medical charts were reviewed and data related to clinical characteristics, treatment provided, histopathological analysis, and follow-up were recorded. All patients underwent surgery as the first-line therapy; follow-up ranged from 1 to 171 months (median 63 months). Clinical characteristics and pathological outcomes were analyzed with respect to the 5-year overall survival rate. A survival risk model was established, and patients were classified into low-, moderate-, and high-risk groups based on the prognostic index designed in this study. The 5-year overall survival rates for the low-, moderate-, and high-risk groups were 92.3%, 76.9%, and 34.2%, respectively. Pathological node metastasis, perineural invasion, and extracapsular spread were the most significant predictive factors for 5-year overall survival. MGSCC is not aggressive, and the survival outcomes of MGSCC are better than those of squamous cell carcinoma (SCC) at other sites. It is suggested that patients with T2–T4 tumours undergo elective neck dissection and those with T1 tumours be followed up without addressing the neck.

Keywords: gingival mucosa; squamous cell carcinoma; prognostic factors; perineural invasion; ECS; vascular emboli.

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In the population of northern China, the mandibular gingival mucosa is the second most common site of oral cancer, followed by the buccal mucosa (BSCC) and the floor of the mouth; the tongue is the most

commonly affected site.^{1,2} The mandibular gingival mucosa is also the second most common site in the Japanese population,³ following tongue and floor of the mouth, and the third most common site in

the USA.^{4–7} In South Africa, the mandibular gingiva is the most common site, followed by tongue and floor of the mouth. Thus there are geographical differences in the tumour locations.^{8,9} The clinical and

pathological characteristics may differ in different regions of the world.

Squamous cell carcinoma of the mandibular gingival mucosa (MGSCC) is more common in elderly patients, and mandibular bone is more likely to be involved. It may be misdiagnosed as peri-apical or periodontal disease.^{10,11} Patients usually present with complaints of pain, swelling, tooth loosening, numbness of the lower lip, etc. The mandibular gingival mucosa site is thought to be rare, and the outcomes of treatment have been deemed to be poor.^{12,13} However, in the present authors' experience, the survival outcomes of patients with MGSCC are better than those of patients with squamous cell carcinoma (SCC) at other sites of the oral cavity. Many institutions worldwide have investigated prognostic factors in MGSCC patients, but this research has been limited by the numbers of patients and prognostic factors investigated.

The hospital at which the present study was performed is one of the major medical institutions in the north of China, which has a population of more than 600 million. The aims of this hospital-based retrospective study were (1) to investigate the clinicopathological features and patterns of neck nodal metastasis of MGSCC in the population of northern China; (2) to compare the oncologic behaviour of MGSCC in this homogeneous population with that found in studies performed in other areas, such as America, Europe, and South Africa; and (3) to establish a new risk model to predict the survival of MGSCC patients.

Materials and methods

Patients

This research project was approved by the institutional review board of the study hospital in Beijing, China. Two hundred and seven patients with primary MGSCC treated in the department of oral and maxillofacial surgery of this hospital were identified from January 2000 to September 2009 and were included in the study. All 207 patients had primary cancer and had not undergone previous treatment. Patients who had not received previous treatment and who had pathologically proven SCC were included in the study; those with tumours arising primarily in the mandibular bone or retromolar trigone were excluded.

All of the patients underwent radiographic examinations, including panoramic radiography, computed tomography, magnetic resonance imaging, and ultraso-

nography. A baseline chest X-ray, complete blood count, and blood chemistries were also obtained. Clinical staging was based on the clinical and imaging findings according to the 2010 Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC), staging criteria, 7th edition. T4 tumours were defined as those invading the cortical bone. The mandibular gingiva refers to the mucosa overlying the alveolar process of the mandible. This lies between the line of attachment of the mucosa at the lower gingivobuccal sulcus and the line of free mucosa of the floor of the mouth, and extends posteriorly to the ascending ramus of the mandible. Clinical information, including tumour location, sex, age, clinical stage, smoking history, alcohol use, and treatment characteristics, were collected from the medical records.

Treatment

All patients underwent surgery as the first-line therapy. Local excision of the primary tumour was performed with a margin of at least 15 mm. Frozen biopsies of the margins were obtained and if they were positive, additional tissue was resected and cryosectioned to ensure that the revised margin was free of tumour. Patients were treated with neck dissections if the nodes contained suspected metastatic lesions. A flow chart outlining the treatment of the 207 patients is presented in Fig. 1. Marginal or segmental mandibulectomies were performed according to the extent of the bone invasion. Reconstruction plates with forearm flaps or vascularized fibula grafts were used to restore the defects. Postoperative radiotherapy was advised for patients with positive lymph nodes, pT4 tumours, or close margins (<4 mm).

Follow-up

As routinely practiced in the study hospital, patients were advised to return regularly at

1-month intervals for the first year, at 2-month intervals for the second year, 3-month intervals for the third year, and at intervals of 3–6 months for the fourth and fifth years.

Histological outcomes

Tumours were graded into well-differentiated, moderately differentiated, or poorly differentiated SCC. Perineural invasion was defined as carcinoma specifically tracking along or within a nerve.¹⁴ The detection of minor degrees of extracapsular spread (ECS) is aided by harvesting lymph nodes with their immediate pericapsular adipose tissue in position.¹⁵ Histological differentiation of regional lymph node metastases was obtained retrospectively from the pathology reports. One experienced pathologist (JYZ), who was blinded to the patient outcomes, reviewed all the available slices and recorded perineural invasion, vascular emboli, diffuse infiltration, and ECS features.

Data analysis

The clinical and pathological characteristics were analyzed using the Kaplan–Meier method, and factors significantly influencing the outcome were determined with the log-rank test. Univariate and multivariate analysis using a Cox proportional hazards model was applied to determine the covariates that best predicted survival rates. Statistical calculations were performed using commercially available software (IBM SPSS Statistics for Mac, version 20.0; IBM Corp., Armonk, NY, USA).

Results

Clinical characteristics

Two hundred and seven patients satisfying the inclusion criteria were included in the study. Of these 207 patients, 121 (58.5%) were male and 86 (41.5%) were female.

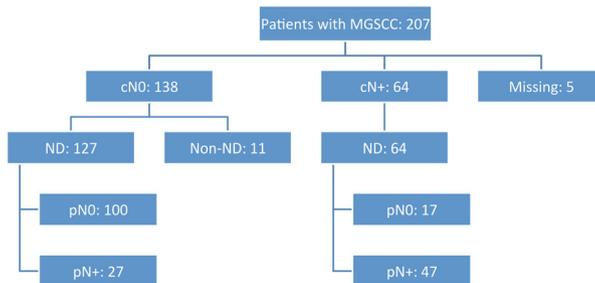


Fig. 1. Flow chart showing the treatment of the 207 patients with mandibular gingival squamous cell carcinoma (MGSCC).

Table 1. Clinical characteristics of the 207 patients with mandibular gingival carcinoma enrolled in the study.

Characteristics	No. of patients (%)
Age, years	
Median (range)	64 (15–86)
<60	76 (36.7)
≥60	130 (62.8)
Missing	1 (0.5)
Sex	
Male	121 (58.5)
Female	86 (41.5)
T stage	
T1	37 (17.9)
T2	81 (39.1)
T3	22 (10.6)
T4	62 (30.0)
Missing	5 (2.4)
Clinical N stage	
N0	138 (66.7)
N1	42 (20.3)
N2	22 (10.6)
Missing	5 (2.4)
Growth pattern	
Exophytic	104 (50.2)
Ulcerative	60 (29.0)
Infiltrative	35 (16.9)
Missing	8 (3.9)
Smoking history	
Smoker	80 (38.6)
Non-smoker	124 (59.9)
Missing	3 (1.4)
Alcohol history	
Drinker	49 (23.7)
Non-drinker	155 (74.9)
Missing	3 (1.4)

They ranged in age from 15 to 86 years (median 64 years). Eighty patients (38.6%) had a history of smoking and 49 (23.7%) consumed alcohol. An exophytic lesion was the most common presentation, seen in 104 patients (50.2%), followed by ulcerative in 60 patients (29.0%) and infiltrative in 35 patients (16.9%). The clinical TNM staging was recorded for each patient and is presented in Table 1.

Pathological characteristics

The pathological nodal status, degree of differentiation, perineural invasion, vascular emboli, diffuse infiltration, and ECS were recorded. The actual numbers of these pathological outcomes are presented in Table 2.

Of the cN0 patients, 32.6% (45/138) had moderate-to-poor differentiation of the tumour, whereas 64.1% (41/64) of cN+ patients had moderate-to-poor differentiation. In the cN0 patients, perineural invasion, vascular emboli, ECS, and diffuse infiltration occurred in 6.0%, 10.5%, 4.2%, and 69.7%, respectively. Of the cN+ patients, perineural invasion, vascular

emboli, ECS, and diffuse infiltration occurred in 22.6%, 32.3%, 24.6%, and 90.3% of the patients, respectively (see details in Table 3).

Occult metastasis in cN0 patients

Overall, 138 patients were diagnosed as having a clinically negative neck. The distribution according to tumour size and the nodal status are presented in Table 3.

Of the 127 cN0 patients who had a neck dissection, 27 had positive neck metastasis. Of these, 13 patients were pathologically N1, 11 were N2b, and three were N2c. The percentage of total occult neck metastasis was 21.3%. The rates of occult neck metastasis were 11.1%, 24.5%, 28.6%, and 21.2% for T1, T2, T3, and T4, respectively.

Treatment outcomes

Among the total 207 patients, 196 (94.7%) had a neck dissection. Of these, 93.9% (184/196) had an ipsilateral neck dissection, while 6.1% (12/196) had a bilateral neck dissection. Of the 184 patients who had an ipsilateral neck dissection, 93 had an elective I–III neck dissection, 15 had an elective I–IV neck dissection, 21 had an elective I–V neck dissection, and 55 had a therapeutic neck dissection. Of the 12 patients who had a bilateral neck dissection, nine had a contralateral elective I–III neck dissection, one had a contralateral elective I–IV neck dissection, one had a contralateral elective I–V neck dissection, and one had a contralateral therapeutic I–V neck dissection.

Furthermore, 37.2% (77/207) of the patients received a marginal mandibulectomy and 62.8% (130/207) received a segmental mandibulectomy. Reconstruction required 107 free flaps and two pedicled flaps, including 87 fibular flaps, 17 forearm flaps, two iliac flaps, one rectus muscle flap, and two pectoralis major myocutaneous flaps. Eighteen patients underwent reconstruction with titanium plates and 58 patients had primary closure.

Follow-up results

The follow-up period ranged from 1 to 171 months (median 63 months). A recurrence or metastasis occurred in 49.3% (102/207) of patients. Table 4 describes the types of recurrence, treatment provided, and the true survival rates after salvage treatment. Four patients who were free of recurrence or metastasis died of other causes. One had paralysis after radiation therapy, another

Table 2. Pathological outcomes of patients according to the T stage (n = 202).

T stage	Differentiation grade			Perineural invasion		Vascular emboli		Diffuse infiltration		ECS	
	Well	Moderately	Poorly	Yes	No	Yes	No	Yes	No	Yes	No
T1 n = 37	25 (67.6%)	11 (29.7%)	1 (2.7%)	1 (2.7%)	36 (97.3%)	4 (10.8%)	33 (89.2%)	23 (63.9%)	13 (36.1%)	3 (9.1%)	30 (90.9%)
T2 n = 81	52 (64.2%)	25 (30.9%)	4 (4.9%)	7 (9.0%)	71 (91.0%)	11 (14.1%)	67 (85.9%)	58 (74.4%)	20 (25.6%)	5 (7.1%)	65 (92.9%)
T3 n = 22	8 (36.4%)	14 (63.6%)	0 (0)	3 (15%)	17 (85%)	4 (20%)	16 (80%)	14 (70%)	6 (30%)	2 (10%)	18 (90%)
T4 n = 62	31 (50%)	25 (40.3%)	6 (9.7%)	11 (18.3%)	49 (81.7%)	15 (25%)	45 (75%)	53 (88.3%)	7 (11.7%)	10 (17.2%)	48 (82.8%)
Total n = 202	116	75	11	22	173	34	161	148	46	20	161

ECS, extracapsular spread.

Table 3. Pathological characteristics for the 138 clinically N0 patients.

	Number of patients	pN+	Vascular emboli	Diffuse infiltration	ECS	Perineural invasion	Differentiation (moderate-poor)
T1	31	3/27 (11.1%)	4/31 (12.9%)	18/30 (60%)	1/27 (3.7%)	0/31 (0)	8/31 (25.8%)
T2	59	13/53 (24.5%)	5/57 (8.8%)	39/57 (68.4%)	1/50 (2%)	2/57 (3.5%)	17/59 (28.8%)
T3	15	4/14 (28.6%)	2/14 (14.3%)	9/14 (64.3%)	1/13 (7.7%)	1/14 (7.1%)	8/15 (53.3%)
T4	33	7/33 (21.2%)	3/31 (9.7%)	26/31 (83.9%)	2/30 (6.7%)	5/31 (16.1%)	12/33 (36.4%)

pN+, pathologically positive neck; ECS, extracapsular spread.

Table 4. Patient status after tumour metastasis or recurrence (n = 102).

Recurrence	Patients	Treatment	Success rate of operative salvage	Death
Local	33	OP (n = 17), OP + RT (n = 3), RT (n = 2), quit (n = 8), missing (n = 3)	21.2%, 7/33	78.8% (26/33)
Regional	17	OP (n = 5), OP + RT (n = 6), quit (n = 6)	11.8%, 2/17	88.2% (15/17)
Local-regional	15	OP (n = 3), OP + RT (n = 1), CCRT (n = 2), quit (n = 9)	20%, 3/15	80% (12/15)
Distant	9	Quit (n = 8), CCRT (n = 1)	–	100% (9/9)
Second primary malignancy	28	OP (n = 18), OP + RT (n = 4), quit (n = 3), CCRT (n = 3)	39.3%, 11/28	60.7% (17/28)

OP, operation; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

died of a stroke at 14 months following surgery, and two patients died of heart disease without disease recurrence after 77 months of follow-up. Eight patients were lost to follow-up.

Survival analysis

The relationship between the overall survival rate and the survival time is shown in Fig. 2. The total 5-year overall survival rate was 71.8%. The actuarial overall survival rates of the patients according to the various clinicopathological factors are shown in Table 5. An advanced T stage was found

to adversely affect the survival rate. There was a significant difference between the T2 and T4 stages (P = 0.020). The 5-year overall survival rates for the different TNM stage groups were 88.1% for stage I, 92.4% for stage II, 61.4% for stage III, and 53.5% for stage IV (stage I vs. stage II, P = 0.846; stage I vs. stage III, P = 0.034; stage I vs. stage IV, P < 0.001; stage II vs. stage III, P = 0.017; stage II vs. stage IV, P < 0.001; stage III vs. stage IV, P = 0.201). The 5-year overall survival rates in cases of perineural invasion, vascular emboli, and ECS were 35.6%, 54.3%, and 15.4%, respectively, but they were

significantly increased in patients with negative pathological characteristics. However, the growth pattern and the patients' smoking history, alcohol consumption, and sex had no effect on the survival rate.

Univariate and multivariate analysis of MGSCC patients

Univariate Cox proportional hazards regression analysis indicated that T stage, pathological node metastasis, pathological grade, vascular emboli, perineural invasion, and ECS predicted the 5-year overall survival rate (Table 6). Multivariate analysis showed that pathological node metastasis, perineural invasion, and ECS were predictive factors for 5-year overall survival.

Risk factors model

Patients were classified into three groups (low-, moderate-, and high-risk) according to the prognostic index calculated for each patient by studying the Cox proportional hazards regression and the partial regression coefficient. The prognostic index (PI) can be calculated with the following equation: $PI = \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_6 X_6$ (where $\beta_1, \beta_2, \dots, \beta_6$ are the partial regression coefficients and X_1, X_2, \dots, X_6 are the six prognostic factors) (Table 7).

The prognostic index was calculated for all patients and they were then ranked accordingly from the lowest score to the highest. The patients were then divided into three equal groups: the low-risk group ($5.1 \leq PI < 8.3$), moderate-risk group ($8.3 < PI \leq 12.2$), and high-risk group

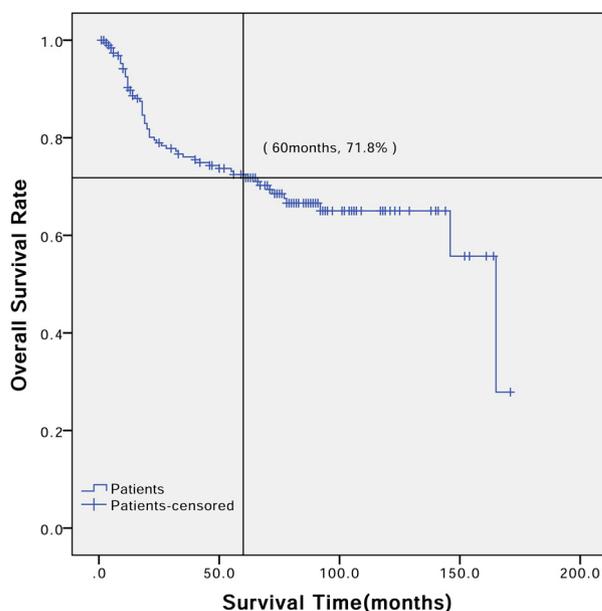


Fig. 2. The 5-year overall survival rate of the 207 patients with mandibular gingival squamous cell carcinoma was 71.8%.

Table 5. Five-year overall survival rates of patients in the different groups.

	5-Year overall survival rate	Log rank <i>P</i> -value
T stage		
T1	77.6%	T1 vs. T2, <i>P</i> = 0.017
T2	76.7%	T2 vs. T4, <i>P</i> = 0.020
T3	72.4%	
T4	58.0%	
N stage ^a		
N0	85.6%	N0 vs. N1, <i>P</i> = 0.002
N1	58.6%	N0 vs. N2, <i>P</i> < 0.001
N2	37.0%	
Differentiation grade		
Well	81.8%	Well vs. moderately, <i>P</i> = 0.001
Moderately	56.7%	Well vs. poorly, <i>P</i> = 0.006
Poorly	42.9%	
Neural invasion		<i>P</i> < 0.001
Yes	35.6%	
No	75.6%	
Vascular emboli		<i>P</i> = 0.012
Yes	54.3%	
No	74.5%	
ECS		<i>P</i> < 0.001
Yes	15.4%	
No	78.0%	

ECS, extracapsular spread.

^aN stage: pathological neck stage.

(12.2 ≤ PI < 29.3). The equal number of patients in each group ensures comparability.

The overall survival rate curves are shown in Fig. 3. The 5-year overall sur-

vival rates were 92.3%, 76.9%, and 34.2% for the low-, moderate-, and high-risk groups, respectively. There was a significant difference in 5-year overall survival rate among the three groups.

Table 6. Univariate and multivariate analysis of the 5-year overall survival rate.

Variable	HR	95% CI	<i>P</i> -value
Univariate analysis			
T stage	1.387	1.100–1.748	0.006
pN status (N0, N1, N2)	1.768	1.428–2.188	<0.001
Pathological grade (I, II, III)	2.024	1.393–2.943	<0.001
ECS	6.586	3.520–12.321	<0.001
Vascular emboli	2.141	1.166–3.933	0.014
Perineural invasion	3.638	1.909–6.935	<0.001
Diffuse infiltration	1.078	0.816–1.424	0.599
Multivariate analysis			
pN status	1.599	1.215–2.104	0.001
Perineural invasion	2.844	1.415–5.716	0.003
ECS	2.669	1.240–5.745	0.012

HR, hazard ratio; CI, confidence interval; ECS, extracapsular spread.

Table 7. Risk model for mandibular gingival squamous cell carcinoma.

Variable	Point assignment for scoring				
	0	1	2	3	4
T		T1	T2	T3	T4
pN		pN0	pN1	pN2	
Differentiation		Well	Moderately	Poor	
Vascular emboli	No	Yes			
Perineural invasion	No	Yes			
ECS	No	Yes			
Prognostic index		Points		5-Year overall survival rate	
Low risk		5.1–8.3		92.3%	
Moderate risk		8.3–12.2		76.9%	
High risk		12.2–29.3		34.2%	

T, tumour stage; pN, pathological neck status; ECS, extracapsular spread.

Discussion

The mandibular gingiva is considered a rare site of oral SCC,^{16,17} and little attention has been paid to this particular site. However, the mandibular gingiva is the second most common site at the study hospital, and this study is one of the largest studies on this unique site. The characteristics of MGSCC are summarized, the survival outcomes analyzed, and a new risk model to predict the overall survival and outcomes of patients with MGSCC is proposed.

Aggressive or not?

In this study, 118 (52.6%) patients were stage T1/T2 and 84 (46.9%) patients were T3/T4. As the gingival mucosa is very thin, the tumour can easily invade the underlying mandibular bone, thereby upgrading the stage to T4. As suggested by other studies, this bony invasion can significantly increase the chance of nodal metastasis and decrease the overall survival rate,⁷ just by virtue of the proximity to the bone and not because of the aggressiveness of the MGSCC. This study group has previously followed 168 patients with SCC of the buccal mucosa over 3 years.¹⁸ On comparison of MGSCC with BSCC, pN0 (64.3% vs. 56.1%), well-differentiated grade (57.4% vs. 55.3%), the occult metastasis rate (21.3% vs. 28.4%), and 3-year overall survival rate (76% vs. 74.6%) all suggest that MGSCC is not as aggressive as BSCC. In another study at the present study centre, the occult metastasis rate for maxillary gingiva SCC was found to be 24%.¹⁹

Independent studies by Shingaki et al. and Lubek et al. reported overall survival rates for MGSCC of 73% and 69%, respectively, and implied local recurrence and second primary as the most common causes of failure.^{3,7} These findings are similar to those of the present study, in which 52.6% patients were in stage I or II, and the overall survival rate was 71.8%. In the study by Gomez et al., performed in France, an overall survival rate of only 42.7% was reported, probably because 70% of patients in that study were in stage IV; however, the authors reported local recurrence as the main cause of treatment failure.²⁰ The present study also showed that the success rate of salvage treatment was 21.2% for local recurrence and 39.3% for second primary tumour. All of the data presented confirm that MGSCC is not as aggressive as other SCC, and early diagnosis can lead to a better overall survival rate.

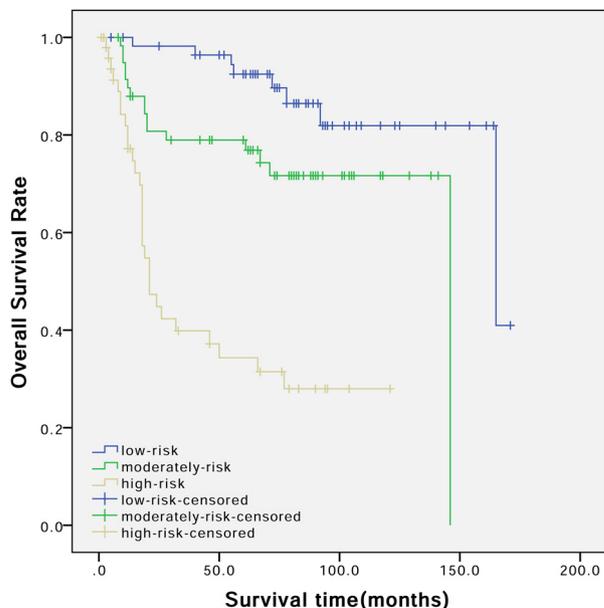


Fig. 3. The 5-year overall survival rate was 92.3% in the low-risk group, 76.9% in the moderate-risk group, and 34.2% in the high-risk group (low-risk vs. moderate-risk, $P = 0.017$; low-risk vs. high-risk, $P < 0.001$; moderate-risk vs. high-risk, $P < 0.001$).

cN0: neck dissection or not?

In 1981, following a 5-year study at M.D. Anderson Hospital, Byers et al. suggested that a prophylactic neck dissection is unwarranted in the initial treatment of cancer of the lower alveolar ridge, unless it is necessary to enter the neck as a surgical technique to expose and resect the primary cancer.²¹ In contrast, another study conducted at the University of Maryland analyzed 72 patients with gingival SCC from 1991 to 2005, and the authors suggested that elective neck dissection should be performed in all patients with MGSCC.⁷

Since then, neck dissection has rarely been discussed for cancers in proximity to the mandibular bone. A common suggestion in relation to patients with primary SCC of the head and neck is to observe the stage N0 neck if the probability of occult cervical metastasis is less than 20%.²² In the present study, the occult metastasis rate for T1 MGSCC tumours was found to be 10.7%. Therefore, neck dissection for T1 staged MGSCC patients is not recommended. However, patients with T2–T4 tumours (which usually have occult metastasis rates higher than 20%) and palpably enlarged lymph nodes should undergo an elective neck dissection. A bilateral neck dissection should be performed if the tumour crosses the midline or if there are apparently enlarged lymph nodes on

both sides. New strategies are recommended to improve the diagnostic accuracy of neck status.

Risk model vs. TNM stage

Over the last three decades, many prognostic models and scoring systems have been developed, most of which have been based on histological characteristics like the depth of invasion, tumour thickness, growth pattern, degree of keratinization, nuclear pleomorphism, lymphocytic response, mitotic rate, pattern of invasion, vascular invasion, and perineural invasion.^{17,23–27} As a number of these studies were based on small patient populations, these models contain few prognostic factors. In this study, a new risk model was established that classifies patients into low-, moderate-, and high-risk groups based on the prognostic index. A statistically significant difference in 5-year overall survival rate was found among the three groups, the values being 92.3%, 76.9%, and 34.2%, respectively. This risk model appears to overcome some of the shortcomings of the TNM staging system. First, the model includes six prognostic factors, both clinical and pathological. Second is the ease of calculation and use of the prognostic index for each patient, which in turn helps the physician to explain the prognosis to the patient. Also, the TNM staging system omits the pathological factors and hence shows no signif-

icant difference in the overall survival rates of stage I vs. stage II, and stage III vs. stage IV. Therefore, this new risk model appears to be more useful than the traditional TNM staging, and it is suggested that this model might be applied in the clinic.

Conclusions

In conclusion, MGSCC has unique clinical and pathological characteristics. MGSCC is not aggressive, and the survival outcomes of MGSCC are better than those of SCC at other sites. It is suggested that patients with T1 tumours are subject to a ‘wait and watch’ policy for the neck, while patients with T2–T4 tumours undergo elective neck dissection. Pathological neck metastasis, perineural invasion, and ECS were the most significant predictive factors of the 5-year overall survival rate. This study establishes a risk model based on six clinical and pathological prognostic factors, which might be of clinical benefit in classifying patients into low-, moderate-, and high-risk groups. It is suggested that these prognostic factors should be regularly shown in pathology reports.

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Competing interests

None.

Ethical approval

This research project was approved by the Institutional Review Board of the Stomatological Hospital of Peking University.

Patient consent

Not required.

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