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Development and validation of a nomogram to predict the risk of occult cervical lymph node metastases in cN0 squamous cell carcinoma of the tongue

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Abstract

We have explored the relations between clinicopathological features and cervical lymph node metastases (LNM) in patients with cN0 squamous cell carcinoma (SCC) of the tongue, and developed and validated a nomogram for predicting the risk of their development. Clinical data on 230 patients with cN0 SCC of the tongue who had had primary extended excision and lymph node dissection of the neck were collected retrospectively. They were divided into a development cohort and a validation cohort in a 4:1 ratio. Logistic regression analysis was used to assess the risk factors of cervical LNM in patients in the development cohort, and a nomogram was established to predict the risk of such nodes. In the validation cohort, the predictive performance and compliance of the model were evaluated using the consistency index (C-index) and calibration curve, and the clinical value was evaluated by decision curve analysis. Of the 230 patients, 60 had cervical LNM, of which 60 were invaded (26%). Analysis of the development cohort showed that the site of the primary lesion, depth of invasion, size of the tumour, and histopathological grade were included in the prediction model, which was validated in the validation cohort. Consistency was high (C-index = 0.846), calibration good, and it was clinically valuable. The nomogram could be used to predict the probability of occult cervical LNM before operation in patients with stage cN0 SCC of the tongue. It could also be used as a reference tool for dissection of cervical nodes and a communication tool between the doctor and the patient.

Keywords: cN0 tongue squamous cell carcinoma; cervical lymph node metastasis; nomogram; prediction model; diagnosis

Introduction

Statistical analysis has shown that in 2018 the number of new cases and deaths worldwide from oral cancer ranked 20th and 15th among all malignant tumours.[1] Squamous cell carcinoma (SCC) of the tongue is the most common type of oral cancer, and lymph node metastases (LNM) are an important factor in the prognosis of affected patients, the reported incidence being 40%-80%, [2] with the probability of occult LNM being 20%-30%.[3] Although there is no objection to therapeutic dissection of lymph nodes for patients with SCC of the tongue and LNM, there is no consensus about whether selective cervical LN dissection should be done for patients with cN0 SCC of the tongue.[4]

We have used logistic regression analysis to screen high risk factors for cervical LNM in these patients, and estab-

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lished a nomogram-based, predictive model to help clinicians to analyse the possible incidence of cervical LNM, and make decisions about whether concurrent cervical LN dissection is necessary. We hope that this model can be used as an intuitive and easy-to-understand tool for communication between doctors and patients about the selection of surgical treatment and management of the prognosis.

Methods

Study design and settings

We collected clinical data from 265 patients with histologically confirmed stage cN0 SCC of the tongue who had had extended excision and lymphadenectomy between May 2008 and October 2016. Of these, 230 patients were enrolled; from them 46 were randomly selected as the validation cohort, and the remaining 184 acted as the development cohort (Fig. 1).

Variables included for analysis

Variables collected included age, sex, duration of the disease, site of the primary lesion, size of the tumour, depth of invasion (DOI), pathological grade of the primary lesion, histopathological results, and site of cervical LN.

To measure the DOI, a horizontal line was established at the basement membrane of the squamous epithelium of the normal oral mucosa adjacent to the tumour in the pathological specimen of the primary lesion. The vertical distance from the horizontal line to the deepest point of infiltration of the tumour was taken as the DOI.[5]

Statistical analysis

Univariate and multivariate logistic regression analyses were used to analyse the high risk factors for LNM in patients with stage cN0 SCC of the tongue. We used IBM SPSS software for Windows (version 22.0, IBM Corp) to calculate the odds ratio (OR), 95% CI, and consistency index (C-index). After the SPSS operation we put the data file into R software (R Foundation for Statistical Computing), and then ran "regplot", "rms", "foreign" packages to draw the nomogram. R software was also used to calculate and draw the calibration curve, and the decision curve analysis (DCA) curve. Probabilities of < 0.05 were accepted as significant.

Results

Baseline characteristics

LNM were found in 47 of the 184 patients in the development cohort, and in 13 of the 46 patients in the validation cohort (Table 1).

Table 1
Characteristics of the two cohorts.

	Development cohort (n = 184)	Validation cohort (n = 46)
Age (years):		
≤56	98	25
>56	86	21
Duration of disease (months):		
≤12	97	22
>12	87	24
Sex:		
Male	87	23
Female	97	23
Site:		
Anterior/middle	125	26
Back	59	20
Tumour size (cm):		
≤1	36	10
1-2	44	12
2-4	93	21
>4	11	3
Differentiation:		
Well	73	20
Moderate/low	111	26
Depth of invasion (mm):		
≤5	76	18
5-10	85	19
>10	23	9
Cervical lymph node metastasis	47	13
Distribution of involved cervical lymph nodes:		
I	12	4
II	25	10
III	18	7
IV	2	0

Model training

Univariate and multivariate logistic regression analyses were made on the development cohort, and the results showed that the location of the primary lesion, size of the tumour, DOI, and the degree of pathological differentiation were independent influencing factors of cervical LNM in patients with cN0 SCC of the tongue (Table 2). A predictive model was established using the four variables stated above (Fig. 2).

Validation of the model in a separate dataset

In the validation cohort, the model showed good discrimination (C-index = 0.837) in differentiating cervical LNM, and the actual probability of cervical LNM was consistent with the probability predicted by the model (Fig. 3). In the study of clinical efficacy, the model showed a high net benefit, good clinical effects, and was safe, compared with the extreme curves in the threshold probability of 0%-78%. (Fig. 4).

Discussion

For patients with stage cN0 SCC of the tongue, the 2018 National Comprehensive Cancer Network (NCCN) clinical

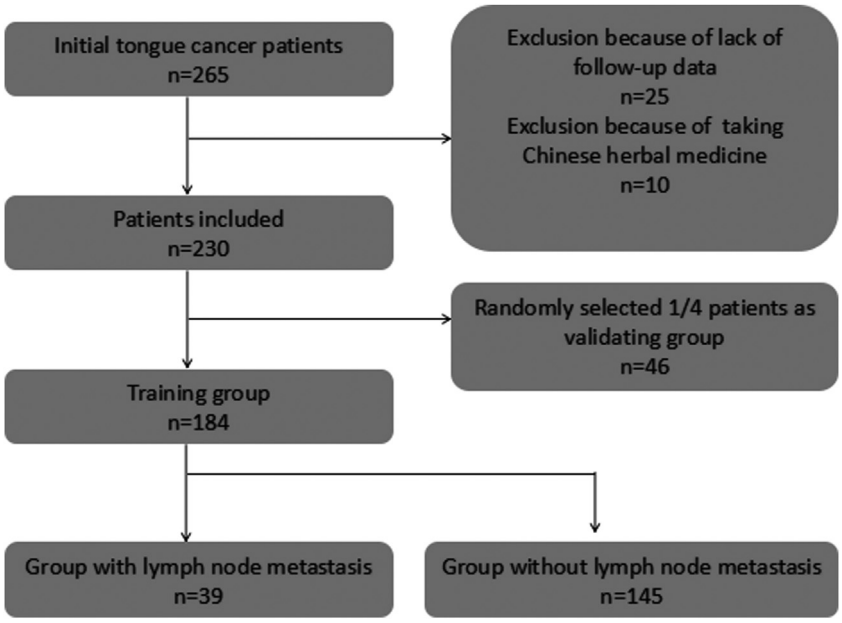

Fig. 1. Flow chart for the selection of patients.

Table 2
Univariate and multivariate logistic regression analyses in the development cohort.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (years):		0.305		
≤56	Reference		–	
>56	0.706 (0.363 to 1.373)	0.305	–	
Duration of disease (months):		0.108		
≤12	Reference		–	
>12	1.732 (0.887 to 3.384)	0.108	–	
Sex:		0.348		
Male	Reference		–	
Female	0.727 (0.374 to 1.414)	0.348	–	
Site:		0.013		0.016
Anterior/middle	Reference		Reference	
Back	2.378 (1.198 to 4.723)	0.013	2.652 (1.200 to 5.859)	0.016
Tumour size (cm):		0.014		0.041
≤1	Reference		Reference	
1-2	5.667 (1.166 to 27.537)	0.032	6.814 (1.301 to 35.683)	0.023
2-4	7.323 (1.645 to 32.601)	0.009	8.634 (1.832 to 40.683)	0.006
>4	20.400 (3.191 to 130.434)	0.001	13.301 (1.673 to 105.777)	0.014
Differentiation:		0.000		0.003
Well	Reference		Reference	
Moderate/low	4.401 (1.916 to 10.107)	0.000	3.971(1.600 to 9.855)	0.003
Depth of invasion (mm):		0.002		0.006
≤5	Reference		Reference	
5-10	2.325 (1.050 to 5.146)	0.037	2.522 (1.066 to 5.967)	0.035
>10	6.446 (2.283 to 18.203)	0.000	6.801 (2.020 to 22.898)	0.002

practice guidelines in oncology, head and neck [4] points out that patients with T1-2 and cN0 SCC of the tongue are recommended to have the primary lesion resected with or without ipsilateral neck dissection (based on the thickness of the tumour) or bilateral neck dissection (based on the site of the primary lesion), but there is no clear explanation about the relation between thickness of the tumour and the selection of LN dissection of the neck.

Sagheb et al[6] found that the probability of cervical LNM when the SCC of the tongue was located in the posterior lingual region was significantly higher than when it was located elsewhere. Wu et al[7] studied 171 patients with early SCC of the tongue and found that the incidence of LNM

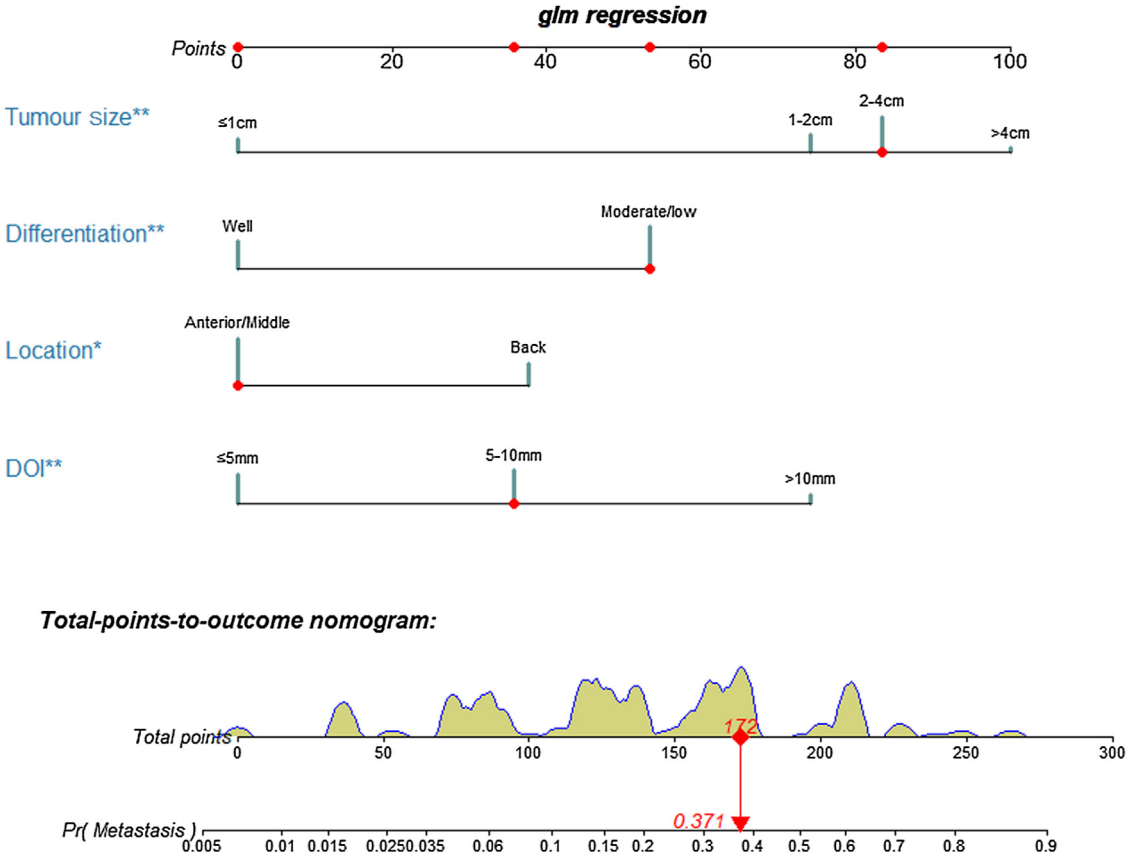

Fig. 2. The nomogram for the prediction of cervical lymph node metastases.
(DOI = depth of invasion; and metastasis = cervical lymph node metastasis). A representative patient is shown to illustrate how to use the nomogram - there is a red dot at each scale that indicates the value of each of the four predictors for the patient. Given the values of the four predictors, the patient can be mapped on to the nomogram. The patient's total number of points was 172, which corresponds to a probability of 0.371 for cervical lymph node metastasis.

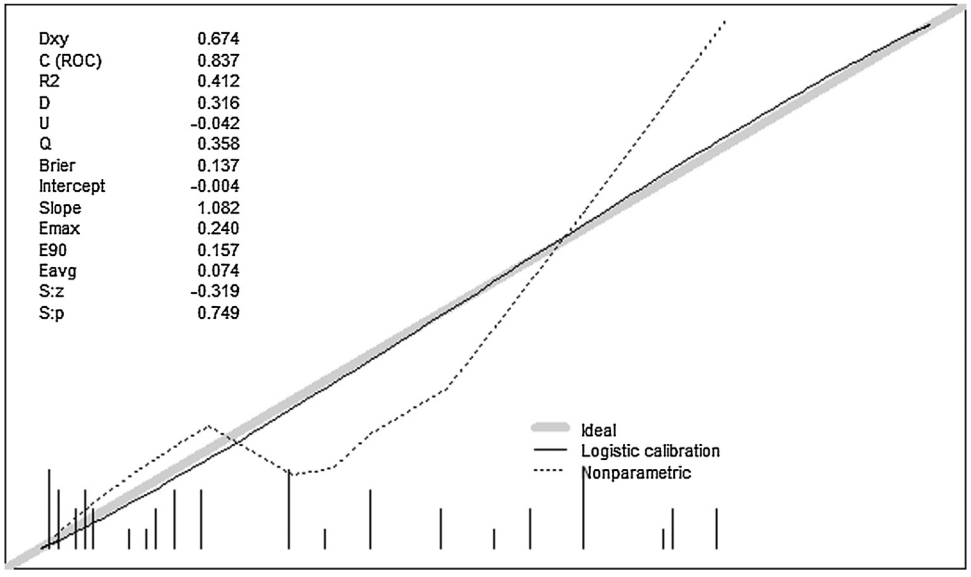

Fig. 3. Calibration and discrimination of the model. The range of the C-index is 0.5-1. The higher the value, the stronger the ability to distinguish lymph node metastases in cN0 patients with squamous cell carcinoma of the tongue. The logistic calibration curve was close to the ideal, and there was no significant difference in the population indicated by the two curves (p = 0.749).

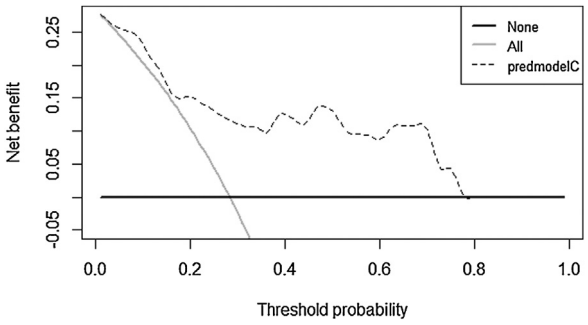

Fig. 4. Analysis of the decision curve for the prediction model. The curve labelled "all" assumes that all patients had dissection of the lymph nodes in the neck. The curve labelled "none" assumes that no patient had dissection of the lymph nodes in the neck.

when tumours were located in the anterior third or middle tongue was 30/131 compared with 10/40 in the posterior tongue, with no significant difference between the groups. Our rate of metastases in the posterior third was 22/59 and that in the anterior two- thirds was 25/125. The difference was significant and could be used as an independent factor for the incidence of cervical LNM in patients with SCC of the tongue. We thought that this was related to the relatively abundant lymphatic drainage in the posterior third of the tongue, and the difficulty of finding the posterior third of the tongue during the early stage.

Previous studies[8] have postulated that the lower the differentiation of oral SCC, the worse the prognosis of patients. Kademani et al[9] confirmed that the lower the degree of differentiation, the greater the possibility of local recurrence and distant metastases. However, some other studies[10,11] reported that the degree of differentiation of oral SCC did not correlate significantly with the prognosis of patients and the probability of cervical LNM. In that study, the rate of cervical LNM in patients with well differentiated SCC of the tongue was 8/73, compared with 39/111 in patients with intermediate and poorly differentiated SCC. The difference was significant, and could be used as an independent influential factor for cervical LNM of patients with cancer of the tongue. We think that, although there are still some controversies, it has been widely accepted that the degree of differentiation of tumours is closely related to the malignancy, invasion, and possibility of cervical lymph node metastases.

T-staging of tumours has long been considered to be associated with cervical LNM in SCC of the tongue. Ramirez-Amador et al[12] investigated 170 such patients and found a significant association between size of the tumour and lymph node involvement. In the study by Wu et al,[7] the rate of cervical LNM in patients with early SCC of the tongue (stages T1 and T2) was 12/65 and 28/106, respectively. In previous studies, the criterion of T staging was the diameter of the tumour alone, giving only a 2-dimensional picture of the tumour, but the 3-dimensional depth of invasion also had an important impact on the occult metastases. In the eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual,[13] DOI and diameter of tumours were used as indicators for T staging. Haksever et al[14] studied 50 cases of oral SCC and showed that the depth of invasion was closely related to the risk of cervical LNM. Angadi et al[15] studied 75 patients with oral SCC and found that DOI was an independent predictor of cervical LNM, showing that the greater the DOI the greater the risk of LNM. Our results showed that size of tumour and DOI could be used as independent predictors of cervical LNM. The risk of cervical LNM in patients with SCC of the tongue, the maximum diameter of which was > 4 cm, was 13.301-fold as high as that in patients with SCC who had tumours the maximum diameter of which was < 1 cm. The risk of cervical LNM in patients whose DOI was > 10 mm was 6.801-fold as high as that in patients whose DOI was < 5 mm.

In the nomogram, we can see that the probability of cervical LNM is higher than 0 for all patients. Although the cervical LNM specimens were examined by immunohistochemistry, and the patients were followed up for at least two years, we were unable to guarantee the absence of micrometastases from cervical LN. We think, therefore, that for cN0 oral cancer, particularly patients with SCC of the tongue, supraomohyoid neck dissection is reliable and safe, and coincides with the selection of the surgical treatment in clinical practice.[16] For some patients who are subjectively expecting conservative treatment or in whom physical conditions do not allow, communication and discussion between doctors and patients based on the predicted results of the nomogram are practical.

A total of 230 patients from two research centres were enrolled in this study, and because the number of cases was insufficient, the representation and reliability of the established model are not high enough. The research centres are two hospitals at the same level in the same region, which also affects the scope of the application of the prediction model. Although we used a validation cohort that was independent of the model cohort to validate the model and to avoid overfitting errors, the results would have been more convincing if we had used a large number of external (other centre) data as the validation cohort. Because of the limitation in the sample size, and to reduce statistical errors, we analysed only seven clinicopathological indicators. To make the prediction model suitable for most hospitals, we have not made in-depth pathological studies to find innovative predictive indicators. These are our current shortcomings. In future work we will collect data from different regions and levels of multiple medical centres to optimise and validate the model.

Conclusion

Because of their simplicity, intuition, and ease of understanding, nomograms have become one of the most popular clinical decision-making aids. The occult metastases of cervical LN in patients with cN0 SCC of tongue is a problem that oral and maxillofacial surgeons often encounter and pay close

attention to in clinical practice. Through the establishment and validation of the prediction model and combining it with the nomogram form, we hope to provide an efficient clinical decision-making tool to aid continuous improvement and validation in the future.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Ethics approval not required. We obtained the patients' permission.

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