Original Article

Development and validation of a nomogram to predict occult cervical metastasis in early oral squamous cell carcinoma

Teng Xu[1,2,3#^], Zhihong Chen[1,2,3#], Zhonghao Yin[4], Yiren Chen[1,2,3], Yao He[1,2,3], Zaiou Zhu[1], Xu Ding[1], Hongchuang Zhang[5], Gang Li[6], Junbo Zhou[7], Wei Zhang[2,3], Xiaomeng Song[1,2,3], Yunong Wu[1,2,3^]

[1]Department of Oral and Maxillofacial Surgery, Affiliated Hospital of Stomatology, Nanjing Medical University, Nanjing, China; [2]Jiangsu Key Laboratory of Oral Diseases, Nanjing Medical University, Nanjing, China; [3]Jiangsu Province Engineering Research Center of Stomatological Translational Medicine, Nanjing Medical University, Nanjing, China; [4]Department of Stomatology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [5]Department of Stomatology, Xuzhou No. 1 People's Hospital, Xuzhou, China; [6]Department of Stomatology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; [7]Department of Stomatology, Nanjing Integrated Traditional Chinese and Western Medicine Hospital, Nanjing, China

Contributions: (I) Conception and design: T Xu, Z Chen; (II) Administrative support: W Zhang, X Song, Y Wu; (III) Provision of study materials or patients: Z Zhu, X Ding; (IV) Collection and assembly of data: Z Yin, Y Chen, Y He; (V) Data analysis and interpretation: H Zhang, G Li, J Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yunong Wu. Affiliated Hospital of Stomatology, Nanjing Medical University, No. 140, Hanzhong Road, Nanjing, China. Email: yunongwu@njmu.edu.cn.

Background: Lack of adequate objectivity and universality, available models are still difficult to be applied to clinical practice in predicting occult cervical metastasis of early oral squamous cell carcinoma (OSCC). Taking abnormal metabolic state into consideration, the current model is helpful to distinguish those patients with or without occult cervical metastasis.

Methods: This study retrospectively analyzed 330 OSCC patients initially diagnosed cT1-2N0M0 stage and received neck dissection from January 2020 to July 2022. The occult cervical metastasis was identified by pathological examination.. After screening independent risk factors using logistic regression, patients were divided into training and validation cohorts at the ratio of 2:1 randomly, and a novel diagnostic model was constructed. Performances of this model were evaluated by the area under the curve (AUC), calibrating curve, decision curve analysis (DCA) and clinical impact curve (CIC).

Results: Of the 330 included patients {age mean [standard deviation (SD)], 61.24 (12.99) years; 202 (61.2%) males}, 49 (14.8%) had occult nodal metastasis. Five variables, including body mass index (BMI) [high odds ratio (OR): 1.132; 95% confidence interval (CI): 1.019–1.258, P=0.021], primary tumor site (tongue & floor of mouth (TF) OR: 3.756; 95% CI: 1.295–10.898, P=0.015), depth of invasion (DOI) (5–10 mm OR: 2.973; 95% CI: 1.266–6.981; P=0.012), pathological differentiation (Poor differentiation OR: 2.65; 95% CI: 1.341–5.239; P=0.005), and diabetes (OR: 3.123; 95% CI: 1.23–7.929; P=0.017) were screened to establish the predictive model. In training cohort (n=220), this model achieved an AUC of 0.814 and had a sensitivity of 78.1% and specificity of 70.2%. Calibration plots showed favorable consistency between the prediction of the model and actual observations (Hosmer-Lemeshow value >0.05). Decision curve analysis (DCA) and clinical impact curve (CIC) showed the model was clinically useful and had better discriminative ability under the threshold probability of 0.5. Above evaluations were verified in the validation cohort (n=110). Compared to previous reported models, the concordance index (C-index), net reclassification index (NRI), and integrated discrimination improvement (IDI) values were superior in both training and validation cohorts (P<0.05).

Conclusions: This constructed model might have reference value for clinicians in making neck management decisions of early OSCC patients.

^ ORCID: Teng Xu, 0000-0002-6209-5928; Yunong Wu, 0000-0003-3256-4890.

Keywords: Oral squamous cell carcinoma (OSCC); occult metastasis; body mass index (BMI); diabetes; nomogram

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Introduction

Elective neck dissection (END) is regarded as standard practice in the treatment of oral squamous cell carcinoma (OSCC), which is characterized by a high incidence and mortality worldwide (1). However, it is still hard to determine for early OSCC patients, as some studies showed END improved the survival rate of patients, other studies showed the difference was not significant (2-4). According to previous assessment, occult cervical metastasis ratio of cT1-2N0M0 OSCC is about 20% (5). To obtain a balance between clinical benefit and overtreatment in clinical node negative OSCC patients, several predictive models for occult cervical metastasis diagnosis were constructed. For example, Mermod *et al.* (6) reported a model based on the CD31, PROX1 examination and relevant histological parameters, which achieved an area under the curve (AUC) of 0.89 and accuracy of 0.88. But the immunohistochemical score of indicated markers was relative subjectivity. Sinha *et al.* (7) performed similar work using acoustic radiation force impulse imaging, which also achieved exciting results with an AUC of 0.88 and accuracy of 0.93. However, this model might be excessively dependent on the special examination. More objective and convenient markers based model might be more suitable for clinical application.

Existing evidences show disorders of glucose and lipids metabolism, such as diabetes and obesity, are critical promoters of tumor metastasis (8-10). Diabetes patients are always accompanied by excessive reactive oxygen species formation, chronic inflammation, and healing barrier, which contribute to its carcinogenicity (11-13). Interestingly, some anti-diabetic drugs possess anti-tumor effects, which implies hyperglycemia can accelerate tumor progression (14,15). In obese patients, excess free fatty acids and intrinsic immunosuppression status are considered to promote the possibility of tumor metastasis (16-18). Based on the basic research, under hyperglycemic conditions, MYC upregulates glucose-regulated protein 75 in megakaryocytes and increases platelet activation via the Ca^{2+}-PKCα pathway, which promote cancer metastasis (19). Furthermore, CD36 mediates the lipid-enriched vesicles from tumor cells are preferentially entered into macrophages, which fuel macrophages to create a highly immunosuppressive microenvironment and promote tumor metastasis (20). In this way, we believe that model incorporating above two factors might have potentially high predictive accuracy.

In this study, we constructed a novel model and validated it for predicting the probability of cervical occult metastasis in early OSCC based on demographic parameters, pathological characteristics, and metabolic disorders [assessed by body mass index (BMI) and diabetes]. Compared to previous studies (21,22), our model exhibits superior discrimination and calibration capabilities. This model might have certain reference value when clinicians make neck management decisions for the clinical neck negative early OSCC patients. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5859/rc).

Highlight box

Key findings

- We identified five clinical factors and constructed a nomogram to predict occult cervical metastasis in early OSCC.

What is known and what is new?

- The regional cervical metastasis ratio of cT1-2N0M0 OSCC is about 20%. But accurately predicting occult cervical metastasis is difficult.
- This study constructs the model can effectively help surgeons make better individualized decisions for the management of early OSCC patients.

What is the implication, and what should change now?

- This study identified obesity and diabetes patients have more risk of occult cervical metastasis with early OSCC. For low-risk patients, the neck management can be relatively conservation, such as wait and see.

Methods

Patient selection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics and Research Committee of Nanjing Medical University (No. 2020-230). Informed consent was taken from all the patients. We retrospectively analyzed patients initially diagnosed as T1-2N0M0 stage OSCC at the Department of Oral and Maxillofacial Surgery, Affiliated Hospital of Stomatology, Nanjing Medical University from January 2020 to July 2022. After acquiring complete information, following inclusion criteria were further convinced: (I) primary T1 or T2 status according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification; (II) negative cervical lymph node metastasis by clinical or imaging examination (MRI and/or CT and/or PET). Patients with (I) history of radiation or chemotherapy; (II) without neck dissection; (III) detection of distant metastasis; and (IV) unknown or multiple primary cancer, were excluded. All patients received tumor extended tumor resection and END. The outcome indicator was positive occult cervical metastasis, which was ascertained via pathological examination by two pathologists independently.

Variables incorporation

Predictors included gender, age, history of smoking and alcohol, primary tumor site, tumor size, pathological differentiated degree, and depth of invasion (DOI) were incorporated. The primary tumor site comprised lip and buccal (LP), tongue and floor of mouth (TF), gingiva and hard palate (GP), and oropharynx (OP). Tumor size was defined as the maximum diameter measured by vernier caliper. The pathological differentiated degree and DOI were confirmed by two pathologists independently, according to instructions from the 8th edition of the AJCC. The BMI and diabetes history of patients were also obtained. The formula for calculating BMI is weight (kilograms)/height (meters)^2.

Statistical analysis

Statistical analysis was performed using R studio (Version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). For continuous variables comparisons, Student's *t*-test was used when variables were normally distributed, and when not, Mann-Whitney *U* test was used. For categorical variables comparisons, difference analysis was calculated using the Pearson's chi-square test. A logistic regression algorithm was applied for variables screening to construct the predictive model. Considering the occult cervical metastasis incidence rate is approximate 20% in early OSCC, and five predictive variables were selected by multivariable logistic analysis, we estimate the sample size according to the formula developed by Riley *et al.* (23). After setting the shrinkage factor of 0.9, the Cox-Snell R^2 of 0.2, we obtain the required sample size of 199 patients and 8.0 events per variable. Therefore, we divided the cohort into training and validation groups at the ratio of 2:1 randomly. The performance of this model was evaluated by AUC, which was equivalent to concordance index (C-index) in binary regression model. The sensitivity was calculated as true positive/(true positive + false negative) and specificity was calculated as true negative/(true negative + false positive). Discrimination, calibration, and actual clinical utility value were assessed by calibration curves, decision curve analysis (DCA) curves, and clinical impact curves (CICs). Comparisons between models were evaluated by C-index, Akaike index criterion (AIC), net reclassification index (NRI), and integrated discrimination improvement (IDI). Two-side P values <0.05 were considered statistically significant.

Results

Patient characteristics

The study was conducted as shown in the flow chart (*Figure 1*). A total of 330 eligible patients [age mean (SD), 61.24 (12.99) years; 202 (61.2%) males], were enrolled finally, of which 49 (14.8%) were ascertained occult cervical metastasis by pathological examination. Patients with occult nodal metastasis had higher BMI (26.11±3.15 *vs.* 24.47±3.1; P=0.001), higher frequency of diabetes (20.4% *vs.* 7.1%; P=0.003) and TF location (63.3% *vs.* 35.9%; P<0.001) compared with those without pathological lymph node metastasis. In addition, patients with *vs.* those without occult nodal metastasis had a higher frequency of poor pathological differentiation (44.9% *vs.* 21.7%; P=0.001) and greater DOI (83.7% *vs.* 61.9%; P=0.003) (*Table 1*).

Logistic regression analyses and model construction

Based on univariate and multivariable logistic regression analysis, five variables, including BMI [high odds ratio (OR):

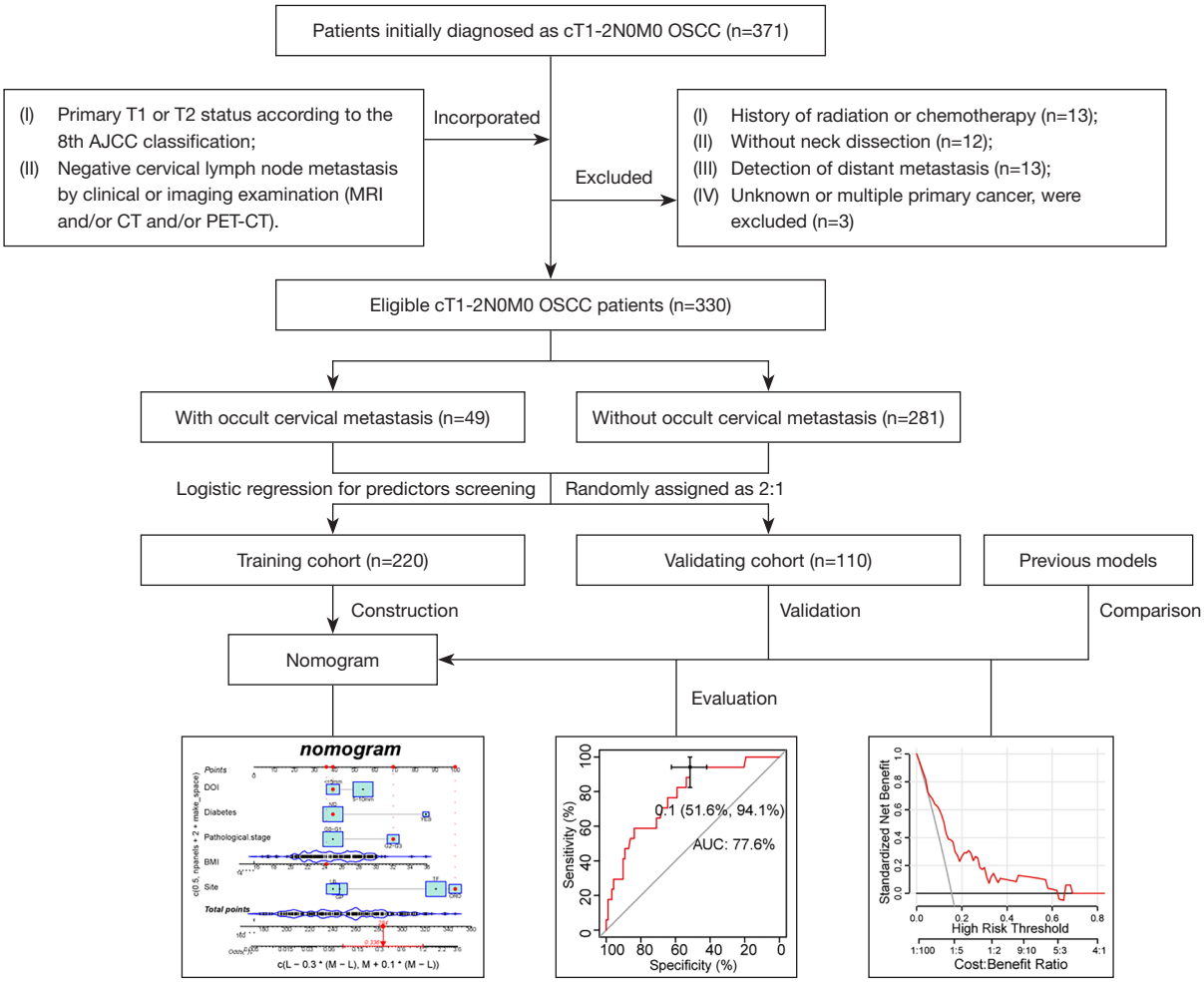

Figure 1 Flow chart for the nomogram construction and evaluation. Data are presented as cut-off value (sensitivity, specificity) in the middle figure. OSCC, oral squamous cell carcinoma; AJCC, American Joint Committee on Cancer; MRI, magnetic resonance imaging; CT, computerized tomography; PET-CT, positron emission tomography-computed tomography.

1.132; 95% confidence interval (CI): 1.019–1.258, P=0.021], primary tumor site [TF OR: 3.756; 95% CI: 1.295–10.898, P=0.015], DOI (5–10 mm OR: 2.973; 95% CI: 1.266–6.981; P=0.012), pathological differentiation (poor differentiation OR: 2.65; 95% CI: 1.341–5.239; P=0.005), and diabetes (OR: 3.123; 95% CI: 1.23–7.929; P=0.017) were identified as independent predictors for occult cervical metastasis (*Figure 2A*,*2B*). Utilizing the training group, a novel model was established and visualized as a nomogram. *Figure 3* showed an example of using this to predict the probability of occult cervical metastasis. The total score was determined based on the individual score calculated using the nomogram and most patients had total risk points ranging from 200 to 300.

Validation and evaluation of the model

The nomogram achieved the AUC of 0.814 and 0.776 in training and validation group respectively, meanwhile, the optimal cut-off value of prediction probability was verified as 0.1 (*Figure 4A*,*4B*). In training group, the sensitivity and specificity were 78.1% and 70.2%, while in validation group, those were 94.1% and 51.6%. The calibration curve indicated the nomogram was well calibrated between the predicted probability and observed probability (Hosmer-Lemeshow test P=0.814 in the training cohort and P=0.715 in the validation cohort) (*Figure 4C*,*4D*). According to the DCA analysis, patients could gain net benefits from neck dissection when the prediction probability was greater

Table 1 Demographic and clinical characteristics of OSCC patients

Characteristics	Whole cohort (n=330)	Without occult cervical metastasis (n=281)	With occult cervical metastasis (n=49)	P value
Age (year)	61.24±12.99	61.44±12.89	60.12±13.69	0.514
Tumor size (mm)	20.86±10.83	20.7±10.61	21.76±12.11	0.53
BMI (kg/m^2)	24.71±3.16	24.47±3.1	26.11±3.15	0.001*
Gender				0.524
Male	202 (61.2)	170 (60.5)	32 (65.3)	
Female	128 (38.8)	111 (39.5)	17 (34.7)	
Marital status				0.39
Unmarried	23 (7.0)	21 (7.5)	2 (4.1)	
Married	307 (93.0)	260 (92.5)	47 (95.9)	
Smoking				0.756
None	209 (63.3)	177 (63.0)	32 (65.3)	
Yes	121 (36.7)	104 (37.0)	17 (34.7)	
Alcohol				0.593
None	296 (89.7)	199 (90.5)	97 (88.2)	
Yes	34 (10.3)	21 (9.5)	13 (11.8)	
Diabetes				0.003*
No	300 (90.9)	261 (92.9)	39 (79.6)	
Yes	30 (9.1)	20 (7.1)	10 (20.4)	
Primary site				0.003*
LB	64 (19.4)	59 (21.0)	5 (10.2)	
TF	132 (40.0)	101 (35.9)	31 (63.3)	
GP	83 (25.2)	77 (27.4)	6 (12.2)	
OP	51 (15.5)	44 (15.7)	7 (14.3)	
Pathological differentiation				0.001*
Well + moderate	247 (74.8)	220 (78.3)	27 (55.1)	
Poor	83 (25.2)	61 (21.7)	22 (44.9)	
DOI				0.003*
≤5 mm	115 (34.8)	107 (38.1)	8 (16.3)	
5–10 mm	215 (65.2)	174 (61.9)	41 (83.7)	

Data are presented as mean ± standard deviation or n (%). *, statistical significance (P<0.05). OSCC, oral squamous cell carcinoma; BMI, body mass index; LB, lip & buccal; TF, tongue & floor of mouth; GP, gingiva & palate; OP, oropharynx; DOI, depth of invasion.

than the threshold probability (the maximum threshold probability was 0.5 in the training cohort and 0.63 in the validation cohort) (*Figure 4E*,*4F*). Moreover, the CIC showed the number of patients with early OSCC, who had true occult cervical metastasis (blue), and who had a predicted high-risk of occult cervical metastasis (red), and these were classified according to the nomogram of each threshold probability (*Figure 4G*,*4H*).

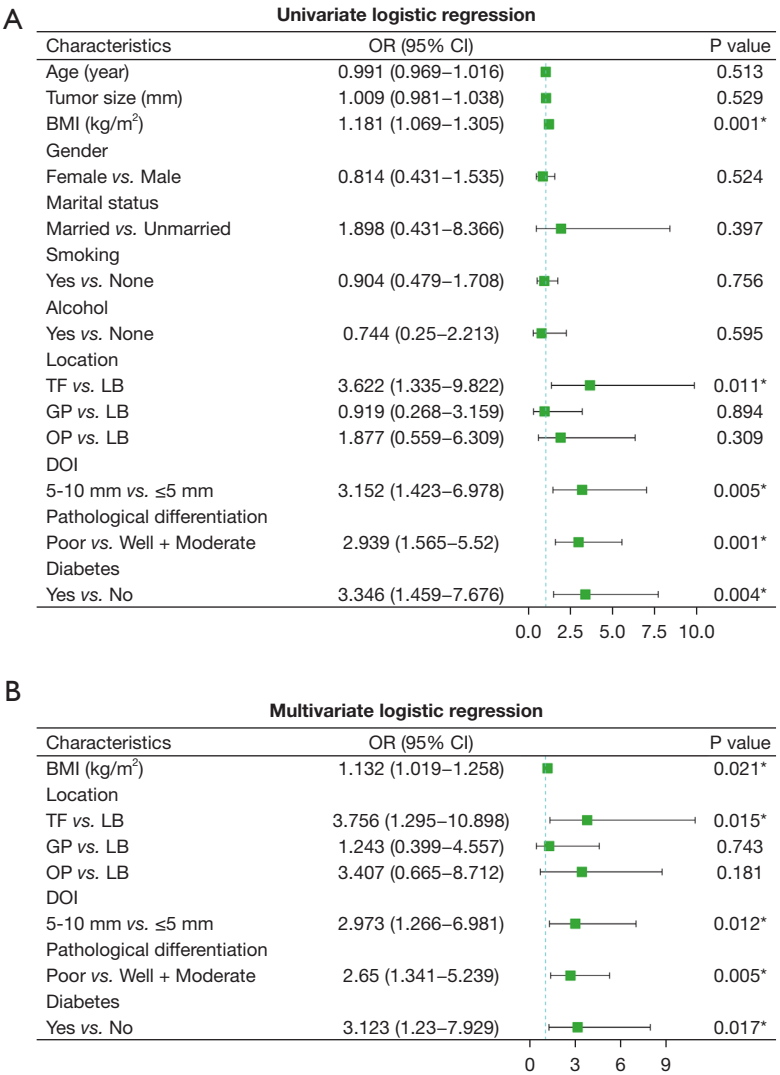

Figure 2 Forest plot for univariate and multivariate logistic regression in training cohort. *, statistical significance (P<0.05). BMI, body mass index; LB, lip & buccal; TF, tongue & floor of mouth; GP, gingiva & palate; OP, oropharynx; DOI, depth of invasion; OR, odds ratio; CI, confidence interval.

Comparison with previous models

To examine the advantages of this model, we calculated the C-index, AIC, NRI, and IDI compared to previously reported versions (21,22). The results showed our model had advantages on the overall trend, although some changes were not significant. The discrimination ability (C-index in our model improved 0.129 compared to that of Yuan *et al.*, P=0.044) and the calibration ability (AIC decreased 18.6 compared to the Yuan *et al.* model and 8.62 compared to the Jiang *et al.* model) were significantly improved. Compared to the model of Yuan *et al.*, the NRI value was 0.327 (95% CI: 0.013–0.639, P=0.049) in the training cohort, and the IDI values were 0.116 (95% CI: 0.057–0.175, P<0.001) and 0.120 (95% CI: 0.036–0.204, P=0.005) in the training cohort and the validation cohort, respectively. Relative to the model of Jiang *et al.*, the IDI value was 0.072 (95% CI: 0.001–0.142, P=0.047) in the validation cohort (*Table 2*).

Discussion

Whether patients with cT1-2N0M0 OSCC can benefit from neck dissection remains controversial. Although

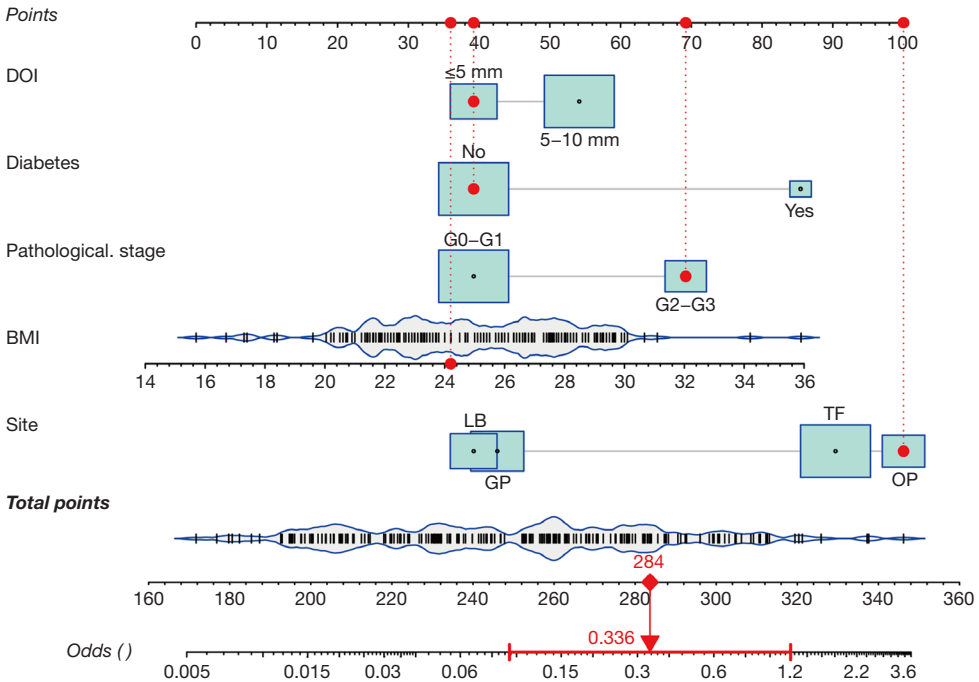

Figure 3 The constructed nomogram for neck occult metastasis prediction of a patient with early-stage oral squamous cell carcinoma. A representative patient is shown to illustrate how to use the nomogram. Red dots at each scale indicate the value of the five predictors. According to the total points of five values of the five predictors, the corresponding probability is 0.336 for neck occult metastasis. DOI, depth of invasion; BMI, body mass index; LB, lip & buccal; TF, tongue & floor of mouth; GP, gingiva & palate; OP, oropharynx.

a variety of advanced auxiliary examinations have been applied, the presence and likelihood of occult metastasis remains uncertain. Synthetically considering the driving factors of metastasis and tumor intrinsic characteristics would facilitate reliable prediction results, and in this study, we incorporated obesity and diabetes, common metabolic diseases recently identified as tumor metastasis promoters, to construct a model to predict early OSCC metastasis events. As validation and comparison to previous studies (21,22), this constructed model has reference value for clinicians in making neck management decisions of early OSCC patients.

The 8th AJCC staging manual redefined the T staging of tumors originating from the lip and oral mucosa by taking DOI into consideration. DOI was originally defined as the distance from the theoretical reconstructed normal mucosal surface line to the deepest extent of tumor invasion. While an increase in DOI is significantly related to cervical metastasis and adverse tumor factors (24,25), the cut-off value for the decision to perform END is still inconclusive. van Lanschot *et al.* (26) confirmed a DOI ≥4 mm as the accurate cut-off value for END through a retrospective analysis of 300 early OSCC patients. Larson *et al.* (27) reported the rate of occult cervical metastases was very low when DOI was ≤4 mm in small (≤2 cm) tongue cancer, despite the existence of unfavorable perineural invasion and lymphovascular invasion. Other researchers (28-30), including the authors of this study, still use 5 mm as the category criterion, and obtain favorable hazard discrimination and prediction capabilities. Such phenomenon may result from the different cohort sources and incorporated factors, and more evidence-based research is required.

The head and neck region contains diverse lymphatic drainage cascades. A high lymph vessel density (LVD) within the tumor microenvironment is thought to promote susceptibility to cervical metastasis. Mermod *et al.* (31) utilized the pan-vascular endothelial antibody CD31 as a marker of occult LNM, indicting the stimulatory effect of LVD on tumor metastasis, and another study confirmed this relationship by using lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) as a marker (32). However, no significant value estimating LVD was found to predict occult LNM by Faustino *et al.* (33). In all patients with occult

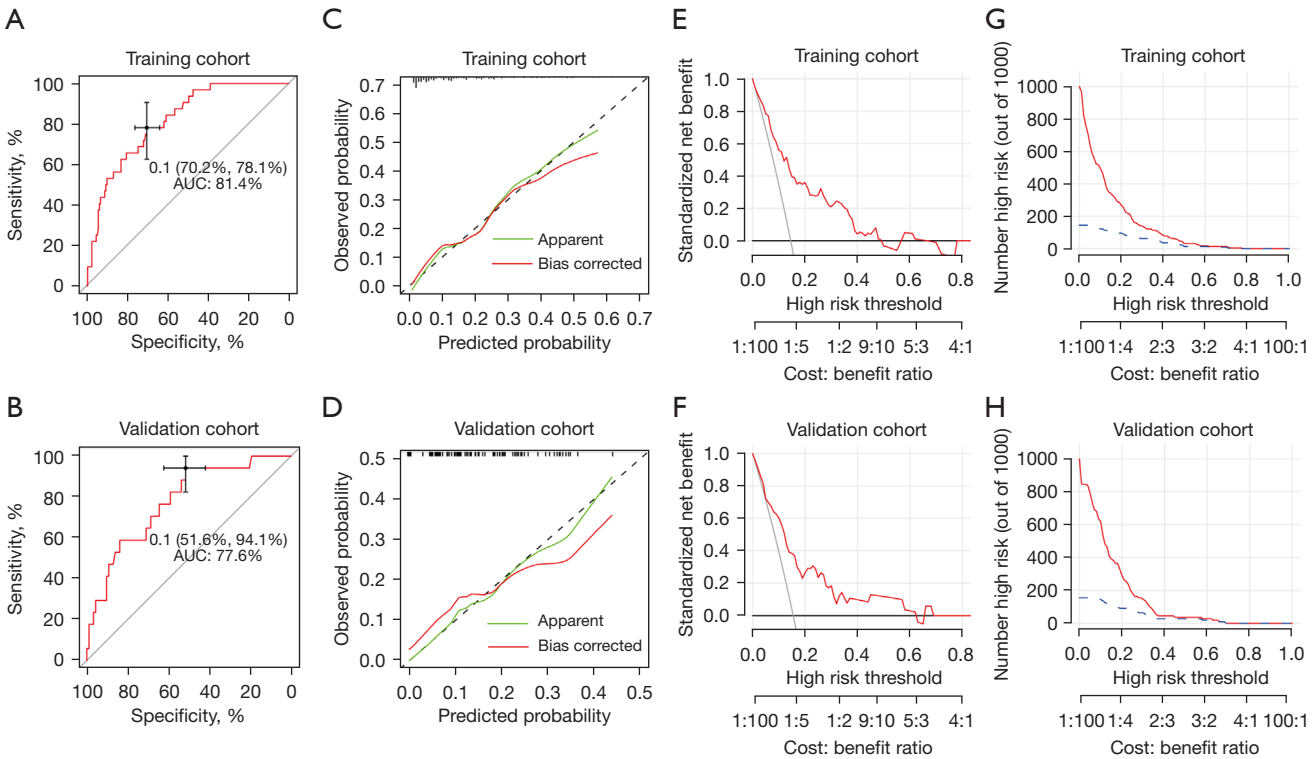

Figure 4 Internal and external validation of the nomogram. (A,B) The AUCs are 0.814 and 0.776 in the training and validation cohorts respectively. (C,D) The calibration plots indicate good agreement between the predicted probabilities and the actual results in both cohorts. (E,F) DCA curves indicate the net benefit of the model in both cohorts. The grey lines represent the net benefit of all patients underwent elective neck dissections. The red lines represent the net benefit of patients underwent elective neck dissections if the occult cervical metastasis is high risk. (G,H) CIC curves indicate the predictive value of the model in both cohorts. The blue lines represent under different probability thresholds, the number of people who are judged by the model as high risk and the occult cervical metastasis actually occur. The red lines represent under different probability thresholds, the number of people judged as high risk by the model. Data are presented as cut-off value (sensitivity, specificity) in *Figure 4A* and *Figure 4B*. AUC, area under the curve; DCA, decision curve analysis; CIC, clinical impact curve.

metastasis in the present study, tongue cancer accounted for the highest percentage of LVD at 63.3% (31/49), followed by oropharynx cancer [14.3% (7/49)]. This is consistent with previous studies (34,35), and suggests greater caution must be taken when dealing with these tumor subtypes.

Diabetes is a risk factor for tumor metastasis, but the underlying mechanism has not been fully determined. Generally, hyperglycemia can induce epithelial-mesenchymal transition (EMT), which is a critical action in the early stage of metastasis (36,37). In malignant pancreatic ductal epithelial cells, hyperglycemia promoted the acquisition of mesenchymal properties by reducing E-cadherin expression and increasing nestin expression in a transforming-growth-factor-beta1 dependent manner (38). Persistent hyperglycemia also results in increased vascular or lymphatic permeability. Several mechanisms, including transcriptional suppression of claudin-5 (39), activating canonical and rapid non-canonical NOTCH1 pathways in endothelial cells (40), and impaired activin receptor-like kinase 1 signaling (41) have been reported to be involved in this process. Furthermore, hyperglycemia was reported to accelerate pancreatic cancer metastasis via aggravating the hypoxia microenvironment by induction of hypoxia inducible factor 1 (42). Our results revealed the positive relationship between diabetes and neck occult metastasis in OSCC, although the exact mechanism needs to be further explored.

Obesity, caused by lipid metabolism disorder, has been showed to be related to tumor metastasis in breast cancer (18), ovarian cancer (43), and gastric cancer (44). Indeed, tumor invasion and metastasis are highly demanding and inefficient processes. Interestingly, the co-culture of

Table 2 Comparison of the models in neck occult metastasis prediction for early-stage OSCC patients

Index	Training cohort			Validation cohort		
	Estimate	95% CI	P value	Estimate	95% CI	P value
C-index						
Our model	0.814	0.743–0.885		0.776	0.662–0.890	
Yuan *et al.* model	0.685	0.581–0.789	0.044*	0.639	0.501–0.776	0.132
Jiang *et al.* model	0.760	0.671–0.849	0.352	0.739	0.633–0.845	0.641
NRI						
Compared to Yuan *et al.* model	0.327	0.013–0.639	0.049*	0.240	–0.143 to 0.756	0.288
Compared to Jiang *et al.* model	0.087	–0.161 to 0.392	0.525	0.246	–0.564 to 1.136	0.275
IDI						
Compared to Yuan *et al.* model	0.116	0.057–0.175	<0.001*	0.120	0.036–0.204	0.005*
Compared to Jiang *et al.* model	0.050	–0.002 to 0.101	0.059	0.072	0.001–0.142	0.047*

*, statistical significance (P<0.05). OSCC, oral squamous cell carcinoma; C-index, concordance index; NRI, net reclassification index; IDI, integrated discrimination improvement.

adipocyte-ovarian cancer cells led to the direct transfer of lipids from adipocytes to ovarian cancer cells, and promoted tumor invasion *in vitro* and *in vivo*, suggesting adipocytes act as an energy source of cancer cells (43). In breast cancer, cancer-associated adipocytes (CAAs) upregulated interleukin (IL)-6, IL-1β, and matrix metalloproteinase-11, leading to a more aggressive behavior of cancer cells (45). Unlike a tumor in the abdominal cavity, OSCC cells have less opportunity to interact with adipocytes, but high BMI still contributes to the probability of cervical metastasis. We supposed the immunosuppressive and proinflammatory effects of obesity as the main reasons of such consequence.

This nomogram was further evaluated compared to previous reports (21,22). Specially for validation cohort, the IDI indicates its superior prediction accuracy, though the difference of NRI is not statistical significance. Considering our outcome event is neck metastasis, which might influence the patients' survival, a certain degree of false positive rate is acceptable. Our study uncovered the phenomenon that the high blood glucose and lipids would promote the metastasis of tumor cells.

This single center study has some limitations. In our cohort, the occult cervical metastasis rate is relatively low, which results in the model sensitivity and specificity are not as good as the AUC shown. Although the validation is conducted, patients were derived from one center of training group. Multi-center external validations are required. In addition, the sample size was limited to 330, a larger cohort would be more representative of the real world. Diabetes has several subtypes with different pathogenesis, and whether these have disparate influences on the results needs further exploration.

Conclusions

In this study, we constructed a novel model to predict occult cervical metastasis of cT1-2N0M0 OSCC. The prediction efficiency was evaluated and comparison with analogous models reported previously (21,22). Our results identified the adverse effects of diabetes and obesity on tumor cell invasion and metastasis in OSCC. We believe this model holds certain reference value in neck management decision-making.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5859/rc

Data Sharing Statement: Available at https://atm.amegroups.

com/article/view/10.21037/atm-22-5859/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5859/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics and Research Committee of Nanjing Medical University (No. 2020-230). Informed consent was taken from all the patients.

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