A prediction model for lymph node metastasis in T1 esophageal squamous cell carcinoma

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ABSTRACT

Background: Endoscopic resection is widely used for the treatment of T1 esophageal cancer, but it cannot be used to treat lymph node metastasis (LNM). This study aimed to develop a prediction model for LNM in patients with T1 esophageal squamous cell carcinoma.

Methods: A prospectively maintained database of all patients who underwent surgery for esophageal cancer between January 2002 and June 2010 was retrospectively reviewed, and patients with T1 squamous cell carcinoma were included in this study. Correlations between LNM and clinicopathological variables were evaluated using univariable and multivariable logistic regression analyses. The penalized maximum likelihood method was used to estimate regression coefficients. A prediction model was developed and internally validated using a bootstrap resampling method. Model performance was evaluated in terms of calibration, discrimination, and clinical usefulness.

Results: A total of 240 patients (197 male, 43 female) with a mean age of 57.9 years (standard deviation $\pm$ 8.3 years) were included in the analysis. The incidence of LNM was 16.3%. The prediction model consisted of four variables: grade, T1 stage, tumor location and tumor length. The model showed good calibration and good discrimination with a C-index of 0.787 (95% confidence interval [CI], 0.711-0.863). After internal validation, the optimism-corrected C-index was 0.762 (95% CI, 0.686-0.838). Decision curve analysis demonstrated that the prediction model was clinically useful.

Conclusions: Our prediction model can facilitate individualized prediction of LNM in patients with T1 esophageal squamous cell carcinoma. This model can aid surgical decision making in patients who have undergone endoscopic resection. (J Thorac Cardiovasc Surg 2018;155:1902-8)

Decision curve analysis for the prediction model to predict lymph node metastasis.

Central Message

Clinically available tumor-specific variables can be used to predict lymph node metastasis in patients with T1 esophageal squamous cell carcinoma with good discriminatory accuracy.

Perspective

We have developed and internally validated a prediction model for lymph node metastasis in patients with T1 esophageal squamous cell carcinoma. This model can be used to facilitate individualized prediction of lymph node metastasis in patients with T1 esophageal squamous cell carcinoma, and can aid surgical decision making in patients who have undergone endoscopic resection.

See Editorial Commentary page 1909.

Endoscopic therapy has recently become an alternative to surgery for the treatment of T1 esophageal cancer.¹⁻³ Compared with traditional surgical resection of the esophagus, endoscopic resection is less invasive and has a lower morbidity rate.² Furthermore, highly specialized centers have achieved excellent long-term results with endoscopic resection for T1a (mucosal) esophageal cancer.^{1,2}

Despite these advances, however, endoscopic resection cannot be used to treat lymph node metastasis (LNM).

The use of endoscopic resection for the treatment of T1 esophageal cancer is based on 2 assumptions. First, it is assumed that the risk of LNM is relatively low in early-stage disease, but the actual risk is not zero. Second, it is assumed that LNM is predictable, and thus that endoscopic resection can be performed selectively in patients who are unlikely to develop LNM. However,

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Abbreviations and Acronyms

C- index	= concordance index
FP	= false-positive
LNM	= lymph node metastasis
NB	= net benefit
PML	= penalized maximum likelihood
P_t	= threshold probability
TP	= true-positive

current diagnostic procedures including endoscopic ultrasonography and positron emission tomography-computed tomography, are inadequate for predicting LNM in patients with T1 esophageal cancer.⁴⁻⁶ Thus, tools for predicting the risk of LNM in patients with T1 esophageal cancer are needed to identify the patients most likely to benefit from endoscopic resection.

Previous reports have identified several clinicopathological factors associated with the risk of LNM in patients with T1 esophageal cancer.^{1,3,7-12} The majority of those reports involved adenocarcinoma^{3,9,10} or a mixture of adenocarcinoma and squamous cell carcinoma.^{1,7,8,12} A recent study combined risk factors into a model-based scoring system to predict the risk of LNM in T1 esophageal adenocarcinoma,¹³ but currently no individualized prediction model aimed at predicting the risk of LNM in patients with T1 esophageal squamous cell carcinoma is available. Thus, the aim of this study was to develop a prediction model for LNM in patients with T1 esophageal squamous cell carcinoma.

METHODS

Study Population

Between January 2002 and June 2010, 1886 patients underwent esophagectomy for the treatment of esophageal cancer at our institution. We retrospectively reviewed demographic, clinical, and pathological data for these patients from a prospectively collected database, and identified patients whose final surgical pathology reports indicated T1 squamous cell carcinoma. Patients with high-grade dysplasia were excluded from the study. None of the patients underwent neoadjuvant therapy. The preoperative workup included physical examination, laboratory tests, endoscopy with biopsy, barium swallow examination, computed tomography studies of the chest and abdomen, and ultrasonography of the neck. Pulmonary and cardiac function tests were performed to assess the patients' operability. Endoscopic ultrasonography was not routinely used. Histopathological diagnosis was confirmed for each patient before surgery. This study was reviewed and approved by the Institutional Review Board of Zhejiang Cancer Hospital. Because of the retrospective character of this study, the requirement for individual patient consent was waived.

Esophagectomy Procedures

Three types of esophagectomy were used depending on the tumor location: the McKeown procedure for upper tumors, the Ivor Lewis procedure for middle tumors, and the Sweet procedure for lower tumors. The choice of procedure also depended on surgeon preference. Both the McKeown and Ivor Lewis procedures were performed via a right

VIDEO 1. Lymphadenectomy along the right recurrent laryngeal nerve in minimally invasive esophagectomy. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)32484-4/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)32484-4/fulltext).

thoracotomy and laparotomy. For the McKeown procedure, a left cervical approach was added. The Sweet procedure was performed via a left thoracotomy. Two-field (mediastinal and upper abdominal) lymphadenectomy was performed in all patients (Video 1). The extent of mediastinal lymphadenectomy was defined according to a consensus conference of the International Society for Diseases of the Esophagus.¹⁴ Total mediastinal lymphadenectomy was performed in the patients undergoing the McKeown and Ivor Lewis procedures, and standard mediastinal lymphadenectomy was performed in those undergoing the Sweet procedure. Upper abdominal lymphadenectomy included the paracardial, lesser curvature, left gastric, common hepatic, celiac, and splenic nodes. Gastrointestinal reconstruction was accomplished using a gastric tube for all patients. Esophagogastric anastomoses were constructed at the subaortic arch in the Sweet procedure, right apex of the chest in the Ivor Lewis procedure, and left neck in the McKeown procedure.

Pathological Evaluation

Pathological staging was performed according to the criteria set forth in the 7th edition of the American Joint Committee on Cancer classification.¹⁵ T1 tumors were subclassified as T1a or T1b. T1a was defined as tumor invading the lamina propria or muscularis mucosae but not involving the submucosa. T1b was defined as tumor invading the submucosa but not involving the muscularis propria. All pathological data, including tumor grade, tumor length, lymph node status, lymphovascular invasion, number of resected lymph nodes, and proximal and distal surgical resection margins, were obtained from the final surgical pathology reports in the prospectively maintained database. Radial surgical resection margins were not reported. Complete resection was defined as R0 resection; incomplete resection with microscopic or macroscopic residual disease was defined as R1 or R2 resection, respectively.

Statistical Analysis

Normally distributed continuous variables are reported as mean $\pm$ standard deviation; non-normally distributed continuous variables, as median and interquartile range. Categorical variables are expressed as count or proportion. A univariable logistic regression model was used to assess the associations between LNM and clinicopathological variables. Variables identified as statistically significant on univariable analyses were entered into a multivariable logistic regression analysis. This multivariable logistic regression model formed the basis of the LNM prediction model. The linearity assumption of continuous variables

in the prediction model was examined using restricted cubic splines. To limit the overfitting of the prediction model and to improve predictions for subjects outside the sample, the penalized maximum likelihood (PML) method was adopted for the estimation of regression coefficients.¹⁶ PML estimation is a generalization of the ridge regression method that uses a penalty factor to estimate regression coefficients. The penalty factor was chosen by maximizing a modified Akaike information criterion. With this penalty factor, the final penalized (PML-based) model was produced.¹⁶ On the basis of the final penalized model, a nomogram predicting the probability of LNM was constructed.

The quality of the prediction model was determined using several model performance measures, including calibration, discrimination, and clinical usefulness.¹⁷ Calibration refers to the agreement between observed outcomes and predictions and was summarized in a calibration plot. The Brier score was calculated as the mean squared distance between the observed outcomes and the predictions. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate the model's fit. Discrimination describes how well a prediction model can distinguish those with the outcome from those without the outcome. The concordance index (C-index) was used to indicate the model's discriminative ability. The C-index is identical to the area under the receiver operating characteristic curve and ranges from 0.5 to 1.0. A prediction model is considered clinically useful if better decisions are made with the model than without it.

Decision curve analysis was performed to quantify the clinical usefulness of the prediction model.¹⁸ In decision curve analysis, a single threshold probability, P_t , can be used both to categorize cases as positive or negative and to weight false-positive (FP) and false-negative classifications. The odds of the P_t , $P_t/(1-P_t)$, is the relative weight for FP versus true-positives (TP), which equals the harm-to-benefit ratio. The performance of a prediction model can be summarized as a net benefit (NB): $NB = (TP - wFP)/N$, where TP is the number of TP classifications, FP is the number of FP classifications, N is the number of subjects, and w a weight equal to the odds of P_t , $P_t/(1-P_t)$. We compared the NB of the prediction model with that of default policies of “assuming all patients have the disease” (treat all) and “assuming no patients have the disease” (treat none). If the NB of the decision curve for a prediction model is higher than that for both treating none and treating all within a range of threshold probabilities, the model is clinically useful.^{17,18}

To correct overfitting and quantify optimism, the prediction model was internally validated using a bootstrap resampling method. We drew 1000 resamples with replacements from the original sample, each with a sample size of 240 cases.

All statistical analyses were performed in PASW Statistics for Windows version 17.0 (SPSS, Chicago, Ill) and R version 3.1.3 (www.r-project.org), with a 2-sided significance level set at $P < .05$.

RESULTS

Patient Characteristics

The study cohort comprised 240 patients (197 males and 43 females) with esophageal squamous cell carcinoma who underwent surgical resection during the study period were included. The mean age was 57.9 ± 8.3 years. All patients underwent R0 resection. The McKeown, Ivor Lewis, and Sweet procedures were performed in 53, 173, and 14 patients, respectively. Upper, middle, and lower esophageal tumors were present in 9, 139, and 92 patients, respectively. For comparison with the Sweet procedure (left thoracotomy), we combined the McKeown and Ivor Lewis procedures into a right thoracotomy group. Similarly, we combined upper and middle esophageal tumors into a single group for comparison with lower esophageal tumors. The incidence

of LNM was 16.3% (39 of 240). LNM was present in 3 of the 68 patients with T1a disease (4.4%), compared with 39 of 172 patients with T1b disease (20.9%) ($P < .001$). All 3 patients with T1a disease and LNM had tumors in the muscularis mucosae. Univariable analyses identified 4 variables—grade, location, T1 stage, and tumor length—as significantly associated with LNM (Table 1).

Model Development and Presentation

Before these 4 variables were entered into a multivariable analysis, tumor length was tested for linearity using restricted cubic splines. The linearity assumption was proven ($\chi^2 = 1.500$; $P = .220$); thus these 4 variables were included in an initial model to predict LNM (Table 2). To improve the model's performance, the PML method was used to shrink the regression coefficients. The final penalized model was the prediction model for LNM (Table 2). An individual's predicted probability of LNM was computed as follows: $\text{Pr (LNM)} = 1/(1 + \exp(-(\text{linear predictor})))$, in which linear predictor = $-2.384 - 0.259 \times \text{well grade (or } + 0.533 \times \text{poor grade)} + 1.692 \times \text{location} - 1.654 \times \text{T1 stage} + 0.05 \times \text{length (cm)}$. If the tumor grade was moderately differentiated, then the grade term in the equation was 0. The location term was 0 if the tumor was located in the upper or middle segment, and 1 if the tumor was located in the lower segment. The T1 stage term was 0 if the tumor was stage T1b, and 1 if the tumor was stage T1a. Based on the results of the prediction model, we developed a nomogram for predicting the probability of LNM (Figure 1).

Model Performance and Internal Validation

The prediction model's C-index was 0.787 (95% confidence interval [CI], 0.711–0.863). The calibration plot showed good agreement between the observed and predicted probabilities in all quartiles (Figure 2). The model's Brier score was 0.113. Results of the Hosmer–Lemeshow goodness-of-fit test were not significant ($P = .680$).

To assess the model's clinical usefulness, we performed decision curve analysis (Figure 3). At a P_t of 15%, for example, the odds of P_t or the harm-to-benefit ratio was $0.15/(1-0.15)$. The model's NB was $(TP - wFP)/N = (26 - [15/85] \times 47)/240 = 0.074$. The numbers of TP and FP classifications for the default policy of treating all were the numbers of patients with and without LNM, respectively. This default policy had a NB of $(39 - 15/85 \times 201)/240 = 0.014$. The NB of the defaulted policy was lower than the NB of 0.074 from the model (Table 3). The numbers of TP and FP classifications for the default policy of treating none were both 0, so the default policy had a NB of 0. Thus, at a P_t of 15%, the NB of the prediction model was higher than that of both default policies, treating all and treating none.

TABLE 1. Univariable analyses of factors predicting lymph node metastasis in 240 patients with T1 esophageal squamous cell carcinoma

Variable	All (n = 240)	Node-negative (n = 201)	Node-positive (n = 39)	P value
Age, y, mean ± SD	57.9 ± 8.3	58.0 ± 8.4	57.5 ± 8.2	.694
Sex, n (%)				
Male	197 (82.1)	167 (69.6)	30 (12.5)	.361
Female	43 (17.9)	34 (14.2)	9 (3.8)	
BMI, kg/m ² , mean ± SD	21.7 ± 2.3	21.7 ± 2.3	21.7 ± 2.4	.959
Cigarette abuse, n (%)				.392
No	82 (34.2)	71 (29.6)	11 (4.6)	
Yes	158 (65.8)	130 (54.2)	28 (11.7)	
Alcohol abuse, n (%)				.786
No	97 (40.4)	82 (34.2)	15 (6.3)	
Yes	143 (59.6)	119 (49.6)	24 (10.0)	
Surgical approach, n (%)				.590
Left thoracotomy	14 (5.8)	11 (4.6)	3 (1.3)	
Right thoracotomy	226 (94.2)	190 (79.2)	36 (15.0)	
Differentiation, n (%)				.029
Well	49 (20.4)	45 (18.8)	4 (1.7)	
Moderate	152 (63.3)	127 (52.9)	25 (10.4)	
Poor	39 (16.3)	29 (12.1)	10 (4.2)	
Location, n (%)				<.001
Upper and middle	148 (61.7)	137 (57.1)	11 (4.6)	
Lower	92 (38.3)	64 (26.7)	28 (11.7)	
Vascular invasion, n (%)				.125
No	199 (82.9)	170 (70.8)	29 (12.1)	
Yes	41 (17.1)	31 (12.9)	10 (4.2)	
T1 stage, n (%)				.005
T1a	68 (28.3)	65 (27.1)	3 (1.3)	
T1b	172 (71.7)	136 (56.7)	36 (15.0)	
Length, cm, median (IQR)	2.0 (2.2)	2.0 (1.8)	3.0 (2.2)	.042
Number of resected lymph nodes, median (IQR)	19 (10.8)	19 (11.0)	19 (8.0)	.965

SD, Standard deviation; BMI, body mass index; IQR, interquartile range.

Instead of a single P_t of 15%, P_t can be varied to create a decision curve. We plotted the NB of the prediction model and of both default policies (treating all and treating none) on such a decision curve. The curve

showed that the model was clinically useful for P_t values between 2% and 47%. Internal validation with the bootstrap method was used to quantify the optimism of the prediction model. The optimism was 5.06%, and the

TABLE 2. Multivariable analyses of factors predicting lymph node metastasis in 240 patients with T1 esophageal squamous cell carcinoma

Variable	Initial model			Penalized model		
	Regression coefficient	OR (95% CI)	P value	Regression coefficient	OR (95% CI)	P value
Grade						
Moderate	Reference	Reference		Reference	Reference	
Well	−0.335	0.715 (0.211-2.428)	.591	−0.258	0.773 (0.266-2.453)	.636
Poor	0.635	1.887 (0.746-4.744)	.180	0.533	1.704 (0.715-4.061)	.229
Location						
Upper and middle	Reference	Reference		Reference	Reference	
Lower	1.875	6.518 (2.880-14.754)	<.001	1.692	5.430 (2.536-11.626)	<.001
T1 stage						
T1b	Reference	Reference		Reference	Reference	
T1a	−1.996	0.136 (0.038-0.485)	.002	−1.654	0.192 (0.066-0.553)	.002
Length	0.037	1.037 (0.850-1.265)	.719	0.050	1.051 (0.868-1.274)	.611

OR, Odds ratio; CI, confidence interval.

FIGURE 1. Nomogram for predicting the probability of lymph node metastasis (LNM) in patients with T1 esophageal squamous cell carcinoma. Locate the patient's characteristic on a variable row and draw a vertical line straight up to the points row (*top*) to assign a point value for the variable. Add up the total number of points and drop a vertical line from the total points row to obtain the probability of LNM.

optimism-corrected C-index was 0.762 (95% CI, 0.686-0.838).

DISCUSSION

In this study, we developed and internally validated a prediction model for LNM in patients with T1 esophageal

FIGURE 2. Calibration plot of the prediction model for lymph node metastasis (LNM) in patients with T1 esophageal squamous cell carcinoma. The ideal 45-degree line indicates perfect calibration. Triangles indicate outcomes for quartiles of predictions with 95% confidence intervals. Spikes at the bottom indicate predictions for patients with LNM and patients without LNM.

FIGURE 3. Decision curve analysis for the model to predict lymph node metastasis (LNM). Blue line, prediction model; red line (treat all): assume all patients have LNM; black line (treat none), assume no patients have LNM. The x-axis represents threshold probabilities of LNM; the y-axis, net benefit (NB). For example, at a threshold of 15%, the NB of the prediction model is 7.4%, and the NB of treating all is 1.4%, with a difference of 6%. This means that when using the prediction model, for every 100 patients, 6 additional true-positives will be identified without increasing the false-positive rate. A decision curve analysis shows that the prediction model is clinically useful within a range of threshold probabilities between 2% and 47%.

squamous cell carcinoma. This model displayed good calibration, good discrimination, and reasonable optimism-corrected performance estimates. The 4 variables included in this model are tumor grade,^{1,3,9,10,12,13} tumor location,¹ T1 stage,^{1,3,7-13} and tumor length,^{1,3,10,12,13} each of which has been previously reported to be related to the risk of LNM in patients with early-stage esophageal cancer. At present, endoscopic ultrasonography and positron emission tomography-computed tomography remain unreliable for assessing lymph node status in patients with early-stage esophageal cancer.⁴⁻⁶ Along with its use as a treatment with curative intent, endoscopic resection can be used as a diagnostic modality to identify patients with early-stage disease at high risk of LNM.^{10,11} Data related to the 4 variables included in our prediction model can be obtained directly via endoscopic resection and subsequent pathological examination; thus, this prediction model could be used to facilitate individualized prediction of LNM after endoscopic resection.

To date, no models for predicting LNM in early-stage esophageal squamous cell carcinoma have been reported. Lee and colleagues¹³ developed such a model for early-stage esophageal adenocarcinoma using 4 risk factors: T1 stage, tumor grade, tumor length, and lymphovascular invasion. This model demonstrated

TABLE 3. Classification table for prediction of lymph node metastasis at a threshold probability of 15%

Threshold	Node-positive	Node-negative	Classification characteristics
Threshold ≥15%	26	47	PPV = 36%
Threshold <15%	13	154	NPV = 92%
	39	201	Accuracy = 75%
	Sensitivity = 67%	Specificity = 77%	
	NB _{model} = 0.074	NB _{treat all} = 0.014	Increase in NB = 0.06

PPV, Positive predictive value; NPV, negative predictive value; NB, net benefit.

excellent discrimination (C-index, 0.82; 95% CI, 0.75-0.89) and good calibration. On the basis of that model, the authors developed a 3-level scoring system for LNM risk, consisting of low, moderate, and high categories with risk thresholds of <2%, 3% to 6%, and ≥7%, respectively. The authors suggested follow-up for low-risk patients, esophagectomy and lymphadenectomy for high-risk patients, and management of moderate-risk patients based on preoperative assessment of risk and personal preference.¹³ However, good calibration and discrimination are not sufficient for a prediction model to be clinically useful,¹⁹ and researchers have not conducted further evaluations of the model’s clinical usefulness. In addition, artificially choosing risk thresholds might not be appropriate, given that risk thresholds can differ across physicians and patients.

In contrast, our present model’s clinical usefulness was evaluated with decision curve analysis. For example, with a P_t value of 15%, the relative weight of FP decisions (unnecessary lymphadenectomy) against TP decisions (correct lymphadenectomy) would be 15:85. At this P_t , the NB of this model is 0.074, whereas the NB of treating all is 0.014; that is, this model would be expected to yield 6 more cases of correct lymphadenectomy per 100 patients with the same number of unnecessary lymphadenectomy cases. Further varying P_t for this model, the decision curve shows that within a range of P_t values between 2% and 47%, the NB of the model is higher than that for both treating all and treating none. Clinical application of this result would need to consider the P_t value (ie, the level of risk of LNM) that patients would accept before deciding to undergo lymphadenectomy. A very risk-averse patient might opt for lymphadenectomy even with only a 2% risk of LNM. It seems unlikely that most patients would demand an approximate 50% risk of LNM before undergoing lymphadenectomy, suggesting that using this prediction model to guide decision making about lymphadenectomy will improve patients’ clinical outcomes.

Our analysis indicates that this model can aid surgical decision making in patients who have undergone endoscopic resection. Nonetheless, our study has several limitations. First, pathologists have a different diagnostic focus when analyzing a surgical specimen than when analyzing an endoscopic specimen. For a surgical

specimen, the focus is on the detection of positive lymph nodes, whereas for an endoscopic specimen, it is on the meticulous differentiation of mucosal or submucosal infiltration.²⁰ If a surgical specimen diagnosed with T1a disease is understaged, the risk estimate generated by applying the model after endoscopic resection may be biased. Second, it is possible that a minority of patients may have had a clinical diagnosis of LNM based on the preoperative workup, which would contraindicate endoscopic resection, and thus selection bias may have influenced the results. Third, the sample size may have been too small to enable identification of other commonly reported predictors, such as vascular invasion, which have been found to predict LNM in early-stage esophageal adenocarcinoma.^{9,10,13} However, in a recent report on a large sample of 1225 patients with surgically resected T1 esophageal cancer, vascular invasion was not found to be predictive of LNM.¹² That study found 3 significant predictors of LNM: grade, T1 stage, and tumor size. The main pathologic type in that study was adenocarcinoma, with only 98 cases of squamous cell carcinoma. This evidence suggests that vascular invasion is not predictive of LNM in early-stage esophageal squamous cell carcinoma. In addition, although the PML method is an appropriate method for preventing extreme predictions in a small dataset,^{16,21} such limitations as the retrospective nature of the study, the inhomogeneity of surgical techniques, and interobserver bias among pathologists still could have biased the results. Finally, this prediction model was only internally validated with a bootstrap resampling method; external validation is needed to confirm its generalizability in larger multicenter prospective studies.

CONCLUSIONS

We have developed a prediction model to facilitate individualized prediction of LNM for patients with T1 esophageal squamous cell carcinoma. This model can aid surgical decision making in patients who have undergone endoscopic resection.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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