Using the National Cancer Database to create a scoring system that identifies patients with early-stage esophageal cancer at risk for nodal metastases

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ABSTRACT

Objectives: Endoscopic resection is gaining popularity as a treatment for early-stage esophageal adenocarcinoma, particularly for T1a tumors. The goal of this study was to create a scoring system to reflect the risk of nodal metastases in early-stage esophageal adenocarcinoma to be used after endoscopic resection to better individualize treatment.

Methods: The National Cancer Database was queried for patients with T1a or T1b esophageal adenocarcinoma who underwent esophagectomy. We identified variables affecting nodal metastases using multivariable logistic regression, which we then used to create a scoring system. We stratified the model for T1a or T1b tumors, tested model discrimination, and validated the models by refitting in 1000 bootstrap samples. C-statistics greater than 0.7 were considered relevant.

Results: We identified 1283 patients with T1a or T1b tumors; 146 had nodal metastases (11.4%). Tumor category (pT1a vs pT1b), grade, and size and the presence of angiolymphatic invasion significantly affected the risk of nodal metastases. We assigned points to each variable and added them to get a risk score. In patients with T1a tumors, less than 3% of patients with a risk score of 3 or less had nodal metastases, whereas 16.1% of patients with a risk score of 5 or greater had nodal metastases. In patients with T1b tumors, less than 5% of patients with a risk score of 2 or less had nodal metastases, whereas 41% of patients with a score of 6 or greater had nodal metastases (c-statistic = 0.805).

Conclusions: The proposed scoring system seems to be useful in discriminating risk of nodal metastases in patients with T1a or T1b esophageal adenocarcinoma and may be useful in directing patients who received endoscopic resection to esophagectomy or careful follow-up. (*J Thorac Cardiovasc Surg* 2017;154:1787-93)

Risk of nodal metastases in patients with T1a EAC.

Central Message

A scoring system was generated to quantitate the risk of nodal metastasis in T1 esophageal tumors that may be useful in guiding patients to esophagectomy or follow-up after endoscopic resection based on this risk score.

Perspective

Although endoscopic resection is rapidly becoming the standard of care for early-stage esophageal cancer, patients with a high risk of nodal metastasis may be better treated with esophagectomy. We created a scoring system that reflects the risk of nodal metastases and may be useful in appropriately directing patients with T1 tumors to esophagectomy or follow-up after endoscopic resection.

See Editorial Commentary page 1794.

See Editorial page 1785.

The incidence of nodal metastases in patients with esophageal tumors that superficially invade the esophagus (T

category pT1a and pT1b) varies from 10% to 15%.^{1,2} The risk of nodal metastases in patients with T1 esophageal adenocarcinoma (EAC) increases with depth of invasion, poorly differentiated tumors, increasing size, and angiolymphatic invasion.³⁻⁷ Nodal metastases are the most important determinant of long-term survival in patients with superficially invasive EAC.^{5,8}

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Abbreviations and Acronyms

CI	= confidence interval
EAC	= esophageal adenocarcinoma
LVI	= lymphovascular invasion
NCDB	= National Cancer Database
OR	= odds ratio

EACs limited to the mucosa (T1a) are increasingly being treated with endoscopic resection, and survival after endoscopic resection of T1a tumors compares favorably with survival after esophagectomy.⁹ Some practitioners have extended the indications of endoscopic resection to patients with T1b tumors with superficial invasion of the submucosa (sm1), with encouraging results.¹⁰ Clinical staging of T1 EAC is difficult, and endoscopic ultrasound shows a concordance of only 65% in T1 esophageal carcinoma.¹¹ Many authors have recommended endoscopic resection as a staging tool for patients with clinical T1 EAC.^{12,13} For patients with an established diagnosis of T1a or T1b adenocarcinoma after endoscopic resection, multiple authors have devised a scoring system or risk stratification for nodal metastases based on known risk factors.^{6,14,15} These studies were based on a relatively small number of patients, and the largest cohort had 258 patients.

The National Cancer Database (NCDB) collects data from more than 1500 facilities and includes 70% of all new cancer diagnosis in the United States.¹⁶ The NCDB has data points for all factors previously associated with a high risk of nodal metastases in patients with EAC. The aim of this study was to create a simple scoring system that can assess the risk of nodal metastases in patients with T1 EAC using this large national database.

MATERIALS AND METHODS

The NCDB was queried for all patients from 2010 to 2013 who underwent esophagectomy with pathologically confirmed T1a or T1b EAC. Patients were excluded if they received preoperative chemotherapy or radiation therapy, if they had metastases at diagnosis, and if data on T status or N status were incomplete. From the participant user files provided by the NCDB, we extracted basic patient demographics, pathologic information, including tumor category, tumor grade, presence of angiolymphatic invasion, number of lymph nodes examined, number of lymph nodes positive for metastases, and any neoadjuvant therapy received by the patient. The NCDB categorizes tumor grade as well as differentiated, moderately differentiated, poorly differentiated, and anaplastic. We combined poorly differentiated and anaplastic into 1 category of poorly differentiated tumors. The NCDB data are completely deidentified; therefore, this study was deemed exempt from approval and informed consent by the Institutional Review Board of the University of Tennessee Health Science Center.

Statistical Analysis

Data are represented as mean $\pm$ standard deviation or median and interquartile range for continuous variables and as n (%) for categorical variables. Unadjusted differences between positive and negative nodes were tested with Student *t* test and chi-square analysis, where appropriate. Missing

data for candidate variables were substituted using multiple imputation methods with sequential regression using IVware software.¹⁷ The association between tumor size and positive node status also was evaluated as a continuous variable by means of spline regression, using methods as described by Desquilbet and Mariotti.¹⁸ For this analysis, restricted cubic spline functions were used in the adjusted logistic regression model relating positive node status to natural tumor size to identify the shape of the curve and to test the hypothesis of nonlinearity of this relationship. Using this functional relationship and the Youden index,¹⁹ we created 3 categories for tumor size: less than 15 mm, 15 to 25 mm, and greater than 25 mm.

To identify independent predictors of positive nodes, we developed a multivariable logistic regression model with the preidentified variables: age, sex, T status, tumor differentiation, tumor size, Charlson comorbidity score, academic institution, and lymphovascular invasion (LVI). Model discrimination was tested with the c-statistic.

Next, we created a point-scoring system using the most prognostic variables for positive nodal status as determined by the beta weights of the variables.²⁰ We intentionally did not give a weight to tumor status (T1a/T1b) because we used this variable for stratification. We then graphically assessed the ability of the point system to discriminate between positive and negative nodal status, and computed the c-statistic using only the point system.

Finally, after fitting the model in the entire dataset, we conducted internal validation by refitting the model in 1000 bootstrap samples with replacement. This method of model validation has been found to have lower variability and lower bias potential compared with traditional split-sample validation and k-fold cross-validation.²¹ All measures of model performance were corrected for optimism and a calculated “shrinkage” factor derived from the calibration slope. This analysis led to minimal adjustments to the full model (data not shown).

RESULTS

We identified 1283 patients with T1a or T1b tumors; 146 had nodal metastases (11.4%). There were 572 patients with T1a tumors (44.6%) and 711 patients with T1b tumors (55.4%) (Table 1). The most frequently missing variables in the dataset were tumor size (missing in 18%), tumor grade (missing in 13%), and angio-LVI (missing in 16%). Patients with T1a tumors (18/572) had a 3.1% incidence of nodal metastases, and patients with T1b tumors (128/711) had an 18% incidence of nodal metastases. The median age for the full cohort was 65 (interquartile range, 59-71), and 1095 were male (85.3%). In multivariable analysis, tumor category (pT1a vs pT1b; odds ratio [OR], 3.45; 95% confidence interval [CI], 2.47-4.81; *P* < .001), tumor differentiation (moderately differentiated vs well differentiated; OR, 4.39; 95% CI, 1.55-12.42; *P* = .006; poorly differentiated vs well differentiated; OR, 6.69; 95% CI, 2.33-19.18; *P* < .001), tumor size (15-25 mm vs < 15 mm; OR, 2.07; 95% CI, 1.21-3.53; *P* = .008; >25 mm vs <15 mm; OR, 2.98; 95% CI, 1.82-4.90; *P* < .001), and the presence of LVI (*P* < .001) were identified as significantly affecting the risk of nodal metastases (Figure 1). On the basis of our multivariable analysis, we assigned points to each variable to create a scoring system (Table 2) and then added the points to get the patients’ risk scores (Figures 2 and 3).

In patients with T1a tumors, the majority (448/572, 78.3%) had a risk score of 3 or less and had a risk of nodal metastases less than 3%. There were 93 patients (93/572,

TABLE 1. Patient characteristics

	Full cohort (n = 1283)	T1a (n = 572)	T1b (n = 711)	P value
Age, y, median (IQR)	65 (59-71)	64 (58-70)	66 (60-72)	<.001
Male sex, n (%)	1095 (85.3)	477 (83.4)	618 (86.9)	.075
White race, n (%)	1233 (97.1)	551 (97.2)	682 (97.0)	.757
Academic institution, n (%)	820 (64.5)	383 (67.5)	437 (62.0)	.039
Charlson comorbidity score, n (%)				.089
0	812 (63.3)	367 (64.2)	445 (62.6)	
1	359 (28.0)	166 (29.0)	193 (27.1)	
>1	112 (8.7)	39 (6.8)	73 (10.3)	
Tumor grade				<.001
Well differentiated	281 (21.9%)	180 (31.5%)	101 (14.2%)	
Moderately differentiated	635 (49.5%)	291 (50.9%)	344 (48.4%)	
Poorly differentiated	367 (28.6%)	101 (17.6%)	266 (37.4%)	
Angiolymphatic invasion, n (%)	203 (15.8)	42 (7.3)	161 (22.6)	<.001
Tumor size, mm $\pm$ SD	16.5 $\pm$ 14.6	12.2 $\pm$ 13.0	19.9 $\pm$ 14.9	<.001
Tumor size, n (%)				<.001
<15 mm	691 (53.9)	399 (69.8)	292 (41.1)	
15-25 mm	286 (22.3)	94 (16.4)	192 (27.0)	
>25 mm	306 (23.9)	79 (13.8)	227 (31.9)	
Nodal metastases, n (%)	146 (11.4)	18 (3.1)	128 (18.0)	<.001
Lymph nodes sampled, median (IQR)	14 (9-21)	14 (8-21)	15 (9-22)	.003
Incomplete resection (R1/2), n (%)	16 (1.2)	1 (0.2)	15 (2.1)	.001
Mortality, n (%)*				
30-d	28 (2.8)	11 (2.5)	17 (3.1)	.570
90-d	46 (4.6)	15 (3.4)	31 (5.6)	.095

IQR, Interquartile range; SD, standard deviation. *Mortality only available for cases between 2010 and 2012.

16.3%) with a score greater than 4, and those patients had a 6.5% risk of nodal metastases. In patients with T1a tumors with a score greater than 5 (31/572, 5.4%), the risk of nodal metastases was greater than 15%. A minority of patients with T1b tumors had a risk score of 1 or less (72/711, 10.1%) and a risk of nodal metastases of less than 5%. Patients with T1b tumors and scores 2 or greater had an increasing risk of nodal metastases, ranging from 5.7% in patients with a score of 2 to greater than 40% in patients with scores greater than 5. The model c-statistic was 0.805. The c-statistic was 0.830 for the T1a point system and 0.775 for the T1b point system. A bootstrap validation cohort did not demonstrate a significant change in the fitness of the model (c-statistic = 0.800) or the strength of the predictor variable.

DISCUSSION

By using the NCDB, we created a simple scoring system that predicts the risk of nodal metastases in patients with T1a or T1b EAC. Our scoring system identified a small population of patients with T1a tumors (5.4% of all T1a patients) with a high risk of nodal metastases (>15% in patient with scores >5) and a small population of patients with T1b tumors (10.1% of T1b patients) with a very low

risk of nodal metastases (<5%). This system may assist practitioners in selecting patients with high-risk T1a tumors for treatment with esophagectomy and patients with low-risk T1b tumors for follow-up only, after endoscopic resection of T1 EAC. There was also a group of patients with T1b tumors (score >5) with a very high risk of nodal metastases (>40%), and these are potentially patients grouped in stage IIB or IIIA. Consideration should be given to neoadjuvant therapy for these patients.

Endoscopic resection has become the standard of care for patients with T1a EACs,²² and some authors have been suggesting treatment with endoscopic resection for patients with T1b tumors and superficial invasion of the submucosa (sm1).¹⁰ It is interesting that although some authors found that superficial invasion into the submucosa was not a risk factor for nodal metastases,^{3,5} others have not been able to demonstrate that superficial invasion into the submucosa conveys little-to-no risk for nodal metastases and recommend esophagectomy for all patients with T1b tumors.^{23,24} Our study suggests that there are additional risk predictors that should be considered to determine the best treatment course for patients with T1b tumors.

Tumor category (pT1a or pT1b) is likely the most important factor associated with nodal metastases.^{1,4,6} The

FIGURE 1. Forest plot of predictors for positive lymph nodes. OR, Odds ratio; CI, confidence interval.

incidence of nodal metastases in T1a EAC is low, only 0% to 7% in several series.^{1,4,6,14} The incidence of nodal metastases in T1a patients in our series was comparable with those results at 3.1%. A previous NCDB study by Merkow and colleagues²⁵ found a 5% incidence of nodal metastases in patients with T1a tumors, a rate slightly higher than ours. It is largely agreed that T1b tumors have a significantly higher incidence of nodal metastases than T1a tumors, ranging from 16% to 27.5%.^{5,6,14,15} The previous NCDB study reported an incidence of 16.6%,²⁵ similar to the incidence of nodal metastases of 18% in patients with T1b tumors in our study. The differences in the NCDB study of Merkow and colleagues²⁵ and ours may

be because our study only included patients who underwent esophagectomy, whereas Merkow and colleagues included all patients. There is also the possibility of understaging of the T category and classification of some patients with T1b tumors as T1a and or vice versa.²⁶ Previous retrospective studies that re-reviewed the pathology in patients with T1 esophageal cancer^{1,4,6} did not provide the number of pathologic diagnosis reversed on reviewed.

To our knowledge, there is 1 other recent attempt to create a scoring system to assess the risk of nodal metastases in patients with T1 EAC. Lee and colleagues¹⁴ analyzed a cohort of patients with T1 esophageal cancer who underwent esophagectomy at 5 different institutions. Variables with a prognostic impact in their study were the same as in ours: T status, tumor differentiation, tumor size, and LVI. The authors assigned scores to each variable, including T1a and T1b tumor categories. The final model fit was similar to ours with a c-statistic of 0.82. The main difference between Lee and colleagues' model and ours is that we stratified the score to T1a and T1b tumors. By applying Lee and colleagues' scoring system in our cohort, the scoring systems were equivalent in predicting nodal metastases in patients with T1a tumors (data not shown). However, in patients with T1b tumors, Lee and colleagues' model was less discriminant in patients with a low risk of nodal metastases.

Davison and colleagues⁶ examined records from 210 patients with T1 EAC who underwent esophagectomy at a single institution. The authors did not create a risk score, but

TABLE 2. Points awarded for predictors of lymph node metastasis to calculate risk score

Variable	Points
Grade	
Well differentiated	0
Moderately differentiated	2
Poorly differentiated	3
Tumor size	
<15 mm	0
15-25 mm	1
>25 mm	2
Angiolymphatic invasion	
No	0
Yes	2

FIGURE 2. Percentage of T1a tumors with nodal metastases, plotted by risk score.

classified patients into different risk categories based on the following factors: T1a or T1b, low or high tumor grade, presence of LVI, and tumor size 2 cm or greater. They identified 6 risk categories that stratified the risk of nodal metastases: (1) T1a tumor with no other risk factors (3.5% of nodal metastases); (2) T1a with 1 or more risk factor (6.7% incidence of nodal metastases); (3) T1b with no other risk factors (7.4% incidence of nodal metastases); (4) T1b

tumors greater than 2 cm with no other risk factors (15.8% incidence of nodal metastases); (5) T1b tumors with high-grade differentiation and no other risk factors (23% incidence of nodal metastases); and (6) T1b tumors with 2 or more risk factors (45% incidence of nodal metastases). Likewise, Barbour and colleagues¹⁵ retrospectively analyzed the records of 85 patients with T1 EAC and identified depth of tumor invasion, LVI, and poor differentiation

FIGURE 3. Percentage of T1b tumors with nodal metastases, plotted by risk score.

Using the National Cancer Database to Create a Scoring System that Identifies Patients with Early-Stage Esophageal Cancer at Risk for Nodal Metastases

VIDEO 1. Significance and application of the present study. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)31578-7/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)31578-7/fulltext).

as predictors of nodal metastases. They then stratified the patients into 4 risk groups: group I, T1a tumors (0% incidence of nodal metastases); group II, T1b tumors, well/moderate differentiation, no LVI (4% incidence of nodal metastases); group III, T1b tumors, poor differentiation, no LVI (22% incidence of nodal metastases); group IV, any T1b tumor with LVI (46% incidence of nodal metastases). These findings are consistent with the ability of our point-scoring system to predict the risk of nodal metastasis in patients with pT1a or pT1b EAC (Video 1).

Study Limitations

There are inherent limitations in the data from the NCDB. This is a retrospective study, and the data points cannot be verified. The tumor pathology cannot be reviewed for accuracy, and it is possible that some tumors may have been misclassified. In a relatively small study of 25 patients undergoing endoscopic resection of early esophageal cancer, there was a high rate of discordance (48%) among pathologists in interpreting the depth of invasion.²⁶ Most commonly, patients with T1a tumors were classified as T1b, and this comprised 83% of all discordant cases. Another important shortcoming is the number of nodes harvested in the NCDB. In previous studies, the median number of lymph nodes harvested in the NCDB was only 10,²⁵ whereas current guidelines recommend that at least 15 nodes be harvested during surgery.²⁷ Our study included

only patients who underwent esophagectomy, which may introduce a selection bias, because during the study period endoscopic therapy was already being performed. This may have selected patients at a higher risk for nodal metastases than the general population of patients with T1 EAC. Finally, one of the most important factors predicting nodal metastases, LVI, was incorporated in the NCDB in 2010, and data on this factor are available for only 4 years. Although the variables we used to create the scoring system have been repeatedly shown to predict nodal metastases, our scoring system needs validation in other datasets, preferentially in prospective studies.

CONCLUSIONS

By using NCDB data, we constructed a simple scoring system that strongly predicts the risk of nodal metastases in patients with EAC. With this system, we identified a small group of patients with T1a tumors with a relatively high risk of nodal metastases and another small group of patients with T1b tumors with a low risk of nodal metastases. As in other scoring and risk stratification models, we identified a group of patients with T1b tumors with a very high risk of nodal metastases. We believe our scoring system can be incorporated into daily practice and will assist surgeons, gastroenterologists, and multidisciplinary tumor boards in deciding which patients should undergo esophagectomy and who could be observed after endoscopic resection. Of note, consideration should be given to preoperative neoadjuvant therapy to patients with T1b tumors with a very high risk of nodal metastases. We suggest a management algorithm for patients with suspected early esophageal carcinoma based on our score for risk stratification for nodal metastases (Figure 4).

Conflict of Interest Statement

B.W. is a proctor for Intuitive Surgery, consultant for Bard, and on the scientific advisory board for BioSix. All other authors have nothing to disclose with regard to commercial support.

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FIGURE 4. Suggested management algorithm for the management of patients with suspected early EAC. EAC, Esophageal adenocarcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

- submucosal esophageal adenocarcinomas? A Multi-Center Study. *J Gastrointest Surg*. 2016;20:6-12.
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