A Retrospective Cohort Study of Factors Influencing Lymph Node Metastasis in Patients With Early Gastric Papillary Adenocarcinoma

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INTRODUCTION: **High risk of lymph node metastasis (LNM) in gastric papillary adenocarcinoma causes endoscopists to worry about the suitability of endoscopic resection for early gastric papillary adenocarcinoma (EPAC). We compared risk factors and attempted to establish a scoring system to stratify LNM risk in patients with EPAC.**

METHODS: **A retrospective analysis was performed on 2,513 patients with early gastric carcinoma (EGC) who underwent radical resection in 4 tertiary hospitals in China. Univariate and multivariate analyses were performed to compare the invasiveness in EPAC and other types of EGC and to evaluate potential factors in predicting LNM risk in EPAC groups.**

RESULTS: **Three hundred thirty-five patients with EPAC were enrolled in our study, of which 62 patients were found to have LNM. After comparing clinicopathological characteristics of EPAC with and without LNM, the following factors were included in the risk scoring system: 1 point each for lower stomach location and tumor size >2.0 cm, 3 points for lymphovascular invasion, and 4 points for submucosal invasion; the risk scoring system was validated in a small internal validation set with an area under the curve of 0.844.**

DISCUSSION: **Our results suggested that EPAC was highly invasive compared with other EGCs, especially differentiated EGC types, and need to be treated more rigorously. This proposed risk scoring system could stratify LNM risk in patients with EPAC, and endoscopic resection may only be performed safely on the groups with a low LNM rate.**

INTRODUCTION

Gastric carcinoma (GC) remains one of the most common cancers and the leading cause of cancer deaths worldwide (1–3). According to the *World Health Organization (WHO) Classification of Tumours*, 5th edition, GC can be classified into 5 main types including tubular, papillary, mucinous, poorly cohesive, and mixed. In the 5 types, papillary adenocarcinoma (PAC) is characterized by finger-like epithelial proliferation with neoplastic columnar cells surrounding a fibrovascular core, which is known to be differentiated histologic type approximately accounting for 6%–11% of all gastric cancers (4–6).

Early detection and resection of early gastric carcinoma (EGC) can improve the survival of patients with GC effectively. EGC is defined as GC confined to the mucosa or submucosa, regardless of lymph node metastasis (LNM) (7). The latest version of Japanese Gastric Cancer Association guidelines recommends that endoscopic resection is relatively effective compared with surgical treatment of

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differentiated, ulcer-free, smaller than 2 cm EGC; reduces trauma; and improves quality of life (8,9). Early gastric papillary adenocarcinoma (EPAC) is classified as differentiated-type EGC, together with well or moderately differentiated tubular adenocarcinoma in the Japanese classification and as intestinal-type cancer in the Lauren classification (10). Because EPAC is classified as differentiated adenocarcinoma (4–6), EPAC smaller than 2 cm is theoretically at little risk of LNM.

However, many studies on EGC in Japan and Korea have reported a high invasive potential of EPAC (11–14). EPAC accounts for 1%–18% of EGC from previous reports (4–6). In our most recent study on EGC in Chinese patients, we also found that the patients with EPAC had worse prognosis than tubular EGC, and LNM was present in half of the EPAC cases with a micropapillary component (15). Aforementioned previous findings raised serious concerns on the suitability of endoscopic therapy on EPAC. Therefore, it is vital and valuable to predict the LNM rate in patients with EPAC accurately. In this study, we aimed to confirm that EPAC had a higher LNM rate than other histological types of EGCs, especially other differentiated EGC types and further reassessed the relationship between LNM and other clinicopathological features in patients with EPAC, trying to clarify the risk factors of LNM in patients with EPAC by a large-scale, retrospective, multicenter, cohort study.

METHODS
Study design
The clinicopathological data of 2,513 patients with EGC who underwent radical gastrectomy were retrospectively enrolled consecutively from 4 participating tertiary medical centers (Drum Tower Hospital, Jiangsu Provincial Hospital of Traditional Chinese Medicine, Changzhou Second Hospital, and Soochow University First Hospital) from 2005 to 2016. Eighteen patients with EPAC were retrospectively enrolled consecutively from 2017 to 2021 and included as an internal validation set. The study design was performed in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Nanjing University Medical Affiliated Drum Tower Hospital. Written consent was waived by the Medical Ethics Committee of Nanjing University Medical Affiliated Drum Tower Hospital because anonymous data were collected retrospectively in each hospital's medical database. The relevant clinicopathological data were made into a table, including the patient's age, sex, tumor location (upper stomach including cardia, body, and fundus; lower stomach including angle, antrum, and pylorus), and presence of ulceration (Table 1).

Pathology investigation
Each pathology report was carefully reviewed to determine the final diagnosis and described in accordance with the WHO definition (4). There were 5 types of tumor micropapillary morphology: (i) wide base protruding, (iia) slightly taller rough, (iib) flat, (iic) sunken surface, and (iii) ulcer (15). All histological sections of each EGC tumor were re-examined by a designated senior pathologist, and any problems were discussed and resolved in strict accordance with procedures (16). Personal information of all patients was deleted from the data set, and each case was coded with a login number to protect the privacy of patients.

Under the guidance of WHO diagnostic criteria, PAC was divided into 2 main morphological development modes: (i) traditional pattern: papillary epithelial with thin fibrous cores (12,13);

(ii) micropapillary type: small pseudopapillary tumor clusters without fibrous cores and surrounded by cavities (15). We defined PGC as a tumor in which more than 50% of the tumor area contained papillary structures. Tumor differentiation was divided into 2 groups: Well-differentiated/medium-differentiated was defined as well-shaped tumor glands in more than 50% of tumors and poorly differentiated tumor glands in less than 50% (15). The depth of invasion was determined semiquantitatively on the best-oriented tumor slices, and the depth of invasion was divided into 3 subgroups: M subgroup: confined to the mucosa; SM1 subgroup: <500 μm from the muscularis mucosae; and SM2 subgroup: confined to the submucosa and >500 μm from the muscularis mucosae (15). The micropapillary morphology was characterized by morula-like clusters of small cells, without a fibrous blood vessel core, and a clear space around it (4). The presence of tubular adenocarcinoma, serrated adenoma, or poorly cohesive carcinoma was classified according to our previous article (16). Absolute indication of EGC was defined as differentiated mucosal adenocarcinoma smaller than 2 cm without ulceration. Expanded indications covered one of the following circumstances: (i) differentiated mucosal adenocarcinoma larger than 2 cm without ulceration or lymphovascular invasion (LVI); (ii) differentiated ulcer-positive mucosal adenocarcinoma smaller than 3 cm without LVI; (iii) poorly differentiated or undifferentiated ulcer-negative mucosal adenocarcinoma less than 2 cm without LVI; and (iv) differentiated ulcer-negative cancer with submucosal invasion less than 500 μm in depth smaller than 3 cm without LVI. Relative indication was a standard therapy of surgical resection for tumors that do not fulfill the absolute or expanded indications (17).

Statistical analysis
All statistical analyses were performed using SPSS 13 (IBM, Armonk, NY). The differences in categorical variables such as age, sex, tumor location, size, gross pattern, depth of invasion, differentiation, micropapillary adenocarcinoma, LVI, LNM, and perineural invasion were calculated between the groups using the χ^2, Fisher exact test, or Kruskal-Wallis H test. In multivariate analysis, the odds ratio (OR) with the confidence interval (CI) at the 95% level was calculated, and P value <0.05 was defined as the critical value of the evaluation factor included in the final risk model. The assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by the lowest β value and rounded to the nearest integer (18). The scoring points of the patients were added and divided into 3 LNM risk categories: low risk (<3%), intermediate risk (3%–19.6%), and high risk (>19.6%) (18). The classification models were compared based on the area under the receiver operating characteristic curve (AUC-ROC). The value of this metric ranges from 0 to 1, and a higher score is preferred.

RESULTS
Baseline data of all EGC population
Among 2,513 patients with EGC, 773 (30.8%) were women. The patient age ranged from 18 to 83 years (mean 61 ± 11 years). In total, 335 cases (13.3%) were diagnosed as EPAC, in which 62 cases (18.5%) had LNM (Figure 1). We then compared the clinicopathological characteristics of patients with EGC stratified by indication types according to the *Japanese Gastric Cancer Treatment Guidelines 2018* (5th edition) (19). Many clinicopathological characteristics showed significant differences among

Table 1. Univariate analyses in clinicopathological characteristics of EGC meeting different indications

	Absolute indication (N = 421)	Expanded indication (N = 746)	Relative indication (N = 1,346)	P—univariate analysis
PAC	51 (12.4%)	89 (11.8%)	195 (14.5%)	0.179
Sex, N (%)				<0.001
Male	318 (77.2%)	533 (70.6%)	889 (66.0%)	
Female	94 (22.8%)	222 (29.4%)	457 (34.0%)	
Age, N (%)				<0.001
<60 yr	116 (28.2%)	313 (41.5%)	544 (40.4%)	
≥60 yr	296 (71.8%)	442 (58.5%)	802 (59.6%)	
Tumor location, N (%)				0.598
Upper stomach	180 (43.7%)	307 (40.7%)	566 (42.1%)	
Lower stomach	232 (56.3%)	448 (59.3%)	780 (57.9%)	
Tumor size, cm, N (%)				<0.001
≤2.0	412 (100.0%)	522 (69.1%)	649 (48.2%)	
>2.0	0 (0.0%)	233 (30.9%)	697 (51.8%)	
Ulceration, N (%)	0 (0.0%)	147 (19.5%)	362 (26.9%)	<0.001
Differentiation, N (%)				<0.001
Well/moderate	412 (100.0%)	496 (65.7%)	519 (38.6%)	
Poor	0 (0.0%)	259 (34.3%)	827 (61.4%)	
Gross pattern, N (%)				<0.001
0–I + IIa	68 (16.5%)	124 (16.4%)	232 (17.2%)	
0–IIb	175 (42.5%)	239 (31.7%)	271 (20.1%)	
0–IIc + III	169 (41.0%)	392 (51.9%)	843 (62.6%)	
Invasion depth, N (%)				<0.001
M	412 (100.0%)	519 (68.7%)	232 (17.2%)	
SM1	0 (0.0%)	236 (31.3%)	260 (19.3%)	
SM2	0 (0.0%)	0 (0.0%)	854 (63.4%)	
Necrosis, N (%)	116 (28.2%)	235 (31.1%)	472 (35.1%)	0.017
Micropapillary adenocarcinoma, N (%)	0 (0.0%)	2 (0.3%)	28 (2.1%)	<0.001
LVI, N (%)	0 (0.0%)	1 (0.1%)	345 (25.6%)	<0.001
Perineural invasion, N (%)	1 (0.2%)	3 (0.4%)	113 (8.4%)	<0.001
LNM, N (%)	4 (1.0%)	49 (6.5%)	311 (23.1%)	<0.001

Upper stomach: cardia, body, and fundus; lower stomach: angle, antrum, and pylorus.
EGC, early gastric carcinoma; LNM, lymph node metastasis; LVI, lymphovascular invasion; M, confined to mucosa; PAC, papillary adenocarcinoma; SM1, <500 μm from the muscularis mucosae; SM2, confined to the submucosa and >500 μm from the muscularis mucosae.

different indications, including sex, age, tumor size, ulceration, differentiation, gross pattern, invasion depth, necrosis, and micropapillary adenocarcinoma ($P < 0.05$), whereas no difference was observed in EPAC and tumor location ($P = 0.179$ and 0.598, respectively). We also compared the clinicopathological characteristics of patients with EGC, EPAC, non-PAC differentiated EGC, and poorly differentiated EGC (see Supplementary Table 1, Supplementary Digital Content, http://links.lww.com/CTG/A860). The prevalence of LVI was higher in the EPAC group than the other groups (21.5% vs 8.3% vs 16.8% with $P < 0.001$, respectively). The perineural invasion and LNM rates of EPAC were more frequent than non-PAC differentiated carcinoma, although less frequent than poorly differentiated

carcinoma (5.1% vs 2.0% vs 7.1% with $P = 0.003$, 18.5% vs 6.5% vs 21.2% with $P < 0.001$, respectively).

LNM rates were higher in patients with EPAC than in patients with non-PAC differentiated EGC
To further determine the effect of PAC on LNM in patients with EGC, we conducted univariate and multivariate analyses of the clinicopathological characteristics of 2,513 EGC patients with and without LNM (see Supplementary Table 2, Supplementary Digital Content, http://links.lww.com/CTG/A860). After adjusting for confounding factors, we determined that EPAC was an independent risk factor of LNM (OR = 1.8, 95% CI 1.2–2.7, $P = 0.004$) in patients with EGC.
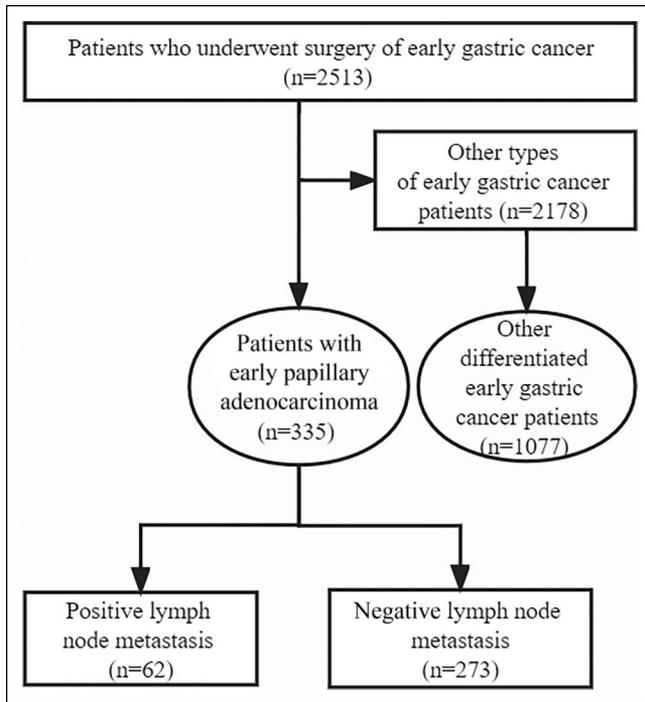
Figure 1. Clinicopathological features of the 2,513 patients with early gastric carcinoma.

The subgroup analysis of the difference in LNM rates among patients with EPAC, non-PAC differentiated carcinoma, and poorly differentiated carcinoma is presented in Table 2. When grouped by tumor size, depth of invasion, or ulceration, the EPAC group showed higher percentages of LNM than non-PAC differentiated EGC in the subgroups of M, SM1, and SM2. When grouped by indications, the EPAC group showed a higher percentage of LNM than both non-PAC differentiated EGC and poorly differentiated EGC groups in the subgroups of expanded indication and relative indication (10.1% vs 3.2% vs 9.7%, $P = 0.001$ in expanded indication and 26.7% vs 16.2% vs 25.1%, $P = 0.002$ in relative indication, respectively).

To further explore the biological reasons for the higher risk of LNM in patients with PAC, we conducted difference analysis and pathway enrichment between papillary and tubular carcinomas based on GSE66229 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE66229) (20). As shown in Supplementary Figure 1, Supplementary Digital Content, http://links.lww.com/CTG/A860, some immune-related pathways in tubular carcinoma were upregulated when compared with papillary carcinoma, which may partly explain the worse prognosis of patients with PAC.

Univariate analyses of clinicopathological characteristics of EPAC with and without LNM

In view of the high incidence of the LNM rate in patients with EPAC, we explored the risk factors of LNM in patients with EPAC. LNM was found in 62 of 335 patients with EPAC (18.5%). Table 3 summarizes clinicopathological characteristics of EPAC patients with (LNM group) and without (non-LNM group) LNM. Sex, ulceration, differentiation, gross pattern, and necrosis were not associated with LNM in patients with EPAC ($P = 0.070$, 0.593, 0.241, 0.713, and 0.125, respectively). Nevertheless, EPAC patients with LNM were 60 years and younger (28.4% vs 16.0% in >60 years, $P = 0.020$) and exhibited lower stomach location (23.8% vs 13.5% in upper stomach location, $P = 0.015$), larger size >2.0 cm (25.8% vs 12.5% in size ≤2.0 cm, $P = 0.002$), and submucosal invasion (SM2 vs SM1 vs M: 29.6% vs 14.3% vs 3.1%, $P < 0.001$). In addition, we divided EPAC patients into two groups based on the presence or absence of LNM, and univariate analysis were performed, finding that occurrence of LNM in EPAC was associated with the presence of micropapillary adenocarcinoma, LVI, and perineural invasion ($P = 0.002$, $P < 0.001$, $P < 0.001$, respectively). Factors with a P value of <0.05 in univariate analysis were included into multivariate analysis. Multivariate analysis demonstrated that LNM in EPAC was independently associated with lower stomach location (OR = 1.9,

Table 2. Comparison of LNM prevalence in different subgroups of patients with EPAC, non-EPAC differentiated EGC, and poorly differentiated EGC

	EPAC (N = 335)	Non-EPAC differentiated EGC (N = 1,077)	Poorly differentiated EGC (N = 1,101)	P—univariate analysis
≤2.0 cm	23 (12.5%)	31 (4.3%)	117 (17.2%)	<0.001
>2.0 cm, ≤3.0 cm	18 (20.5%)	22 (9.5%)	64 (24.8%)	<0.001
>3.0 cm	21 (33.3%)	17 (13.4%)	51 (31.5%)	0.001
M	3 (3.1%)	8 (1.4%)	60 (12.4%)	<0.001
SM1	11 (14.3%)	13 (5.8%)	47 (24.2%)	<0.001
SM2	48 (29.6%)	49 (18.1%)	125 (29.6%)	0.002
No ulceration	51 (18.0%)	47 (5.4%)	162 (18.9%)	<0.001
Ulceration	11 (21.2%)	23 (10.9%)	70 (28.5%)	<0.001
Absolute indication	1 (2.0%)	3 (0.8%)	—	0.412
Expanded indication	9 (10.1%)	12 (3.2%)	28 (9.7%)	0.001
Relative indication	52 (26.7%)	55 (16.2%)	204 (25.1%)	0.002

EGC, early gastric carcinoma; EPAC, early gastric papillary adenocarcinoma; LNM, lymph node metastasis; M, confined to mucosa; SM1, <500 μm from the muscularis mucosae; SM2, confined to the submucosa and >500 μm from the muscularis mucosae.

Table 3. Univariate analyses and multivariate analyses in clinicopathological characteristics of EPAC with and without LNM

	LNM (N = 62)	Non-LNM (N = 273)	P—univariate analysis	Odds ratio (95% CI)	P—multivariate analysis	β regression coefficient	Risk points[a]
Sex, N (%)			0.07				
Male	37 (15.9%)	195 (84.1%)					
Female	25 (24.3%)	78 (75.7%)					
Age, N (%)			0.02				
<60 yr	19 (28.4%)	48 (71.6%)		1 (reference)			
≥60 yr	43 (16.0%)	225 (84.0%)		0.7 (0.3–1.5)	0.342	−0.36	—
Tumor location, N (%)			0.015				
Upper stomach	23 (13.5%)	148 (86.5%)		1 (reference)			
Lower stomach	39 (23.8%)	125 (76.2%)		1.9 (1.0–3.7)	0.047	0.66	1
Tumor size, N (%)			0.002				
≤2.0 cm	23 (12.5%)	161 (87.5%)		1 (reference)			
>2.0 cm	39 (25.8%)	112 (74.2%)		1.6 (1.1–3.3)	0.023	0.45	1
Ulceration, N (%)	11 (21.2%)	41 (78.8%)	0.593				
Differentiation, N (%)			0.241				
Well/moderate	57 (17.8%)	263 (82.2%)					
Poor	5 (33.3%)	10 (66.67%)					
Gross pattern, N (%)			0.713				
0–I + IIa	26 (25.2%)	77 (74.8%)					
0–IIb	3 (3.8%)	76 (96.2%)					
0–IIc + III	33 (21.6%)	120 (78.4%)					
Invasion depth, N (%)			<0.001				
M	3 (3.1%)	93 (96.9%)		1 (reference)			
SM1	11 (14.3%)	66 (85.7%)		5.1 (1.3–19.6)	0.018	1.626	4
SM2	48 (29.6%)	114 (70.4%)		6.4 (1.8–22.7)	0.004	1.858	4
Necrosis, N (%)	33 (22.1%)	116 (77.9%)	0.125				
Micropapillary adenocarcinoma, N (%)	10 (45.5%)	12 (54.5%)	0.002	2.2 (0.7–6.5)	0.157	0.78	—
LVI, N (%)	34 (47.2%)	38 (52.8%)	<0.001	3.6 (1.8–7.3)	< 0.001	1.29	3
Perineural invasion, N (%)	11 (64.7%)	6 (35.3%)	<0.001	3.0 (0.9–10.3)	0.077	1.11	—

Upper stomach: cardia, body, and fundus; lower stomach: angle, antrum, and pylorus.
EPAC, early gastric papillary adenocarcinoma; LNM, lymph node metastasis; LVI, lymphovascular invasion; M, confined to mucosa; SM1, <500 μm from the muscularis mucosae; SM2, confined to the submucosa and >500 μm from the muscularis mucosae.
[a]The coefficient of each variable was divided by 0.45 (the lowest β value, corresponding to tumor size) and rounded to the nearest integer.

95% CI 1.0–3.7, P = 0.047), tumor size >2.0 cm (OR = 1.6, 95% CI 1.1–3.3, P = 0.023), submucosal invasion (SM1: OR = 5.1, 95% CI 1.3–19.6, P = 0.018, SM2: OR = 6.4, 95% CI 1.8–22.7, P = 0.004), and LVI (OR = 3.6, 95% CI 1.8–7.3, P < 0.001).

Risk factors and stratification for LNM in EPAC
According to multivariate regression analysis, lower stomach location, tumor size >2.0 cm, submucosal invasion, and LVI were associated with LNM in patients with EPAC. After weighing points proportional to β regression coefficient values, we gave 1 point each for lower stomach location and tumor size >2.0 cm, 3 points for LVI, and 4 points for SM1/SM2 (Table 3). A total risk score, which ranged from 0 to 9 points, was calculated for each patient in the EPAC cohort by adding together the

points. Subsequently, according to the definition, this risk score was categorized as low (0–2 point), intermediate (3–6 points), and high (7–9 points) risk for LNM (18). As a result, the rates of LNM for each risk category were 3.2%, 14.5%, and 49.3%, respectively (Table 4), with a significantly increasing trend of risk from low-risk to high-risk groups (P < 0.001, linear-by-linear association).

Then, the risk scoring system was validated in a small internal validation set, and the details of patients with EPAC are given in Supplementary Table 3, Supplementary Digital Content, http://links.lww.com/CTG/A860. Of the 18 patients with EPAC, 8 patients developed LNM, with risk scores of 4, 8, or 9 and risk categories of intermediate or high risk. The efficiency and sensitivity were evaluated based on AUC-ROC, and AUCs

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Table 4. Distribution of risk scores and risk classification for LNM in the cohort

Total points	Total patients (N = 335)	LNM (N = 62)	Rate of LNM, %	95% CI, %
0	25	0	0.0	0.0–13.3
1	46	1	2.2	0.1–11.3
2	22	2	9.1	1.6–27.8
3	1	0	0.0	0.0–94.9
4	61	5	8.2	3.6–17.8
5	77	12	15.6	9.2–25.3
6	34	8	23.5	12.4–40.0
7	13	5	38.5	17.7–64.5
8	34	13	38.2	23.9–55.0
9	22	16	72.7	51.9–86.9

Risk category	Total points	Total patients (N = 335)	LNM (N = 62)	Rate of LNM, %	95% CI, %
Low	0 to 2	93	3	3.2	−0.4 to 6.9
Intermediate	3 to 6	172	25	14.5	9.2 to 19.9
High	7 to 9	69	34	49.3	37.8 to 60.8

LNM, lymph node metastasis.

were both 0.844 in the 9-point scoring system and 3-risk classification system (Figure 2).

DISCUSSION

This retrospective multicenter study aimed to identify the high risk of LNM in patients with EPAC and attempted to explore the biological reasons for the higher risk of LNM in patients with EPAC. Through exploring the relationship between LNM with other features in the EPAC group, we established a novel clinicopathological scoring system to predict LNM rates in patients with EPAC and validated the system in a small internal validation set.

The 5-year survival rate of patients with EGC after complete gastrectomy of lymph nodes is more than 90% (21,22). LNM is an important indicator of the prognosis of EGC, and EGC with a low LNM rate is suitable for endoscopic resection (3,23,24). Some studies have revealed a significant correlation between the presence of a papillary component with high LNM rates (12,25–27). This was especially true for submucosal EPAC, which had the
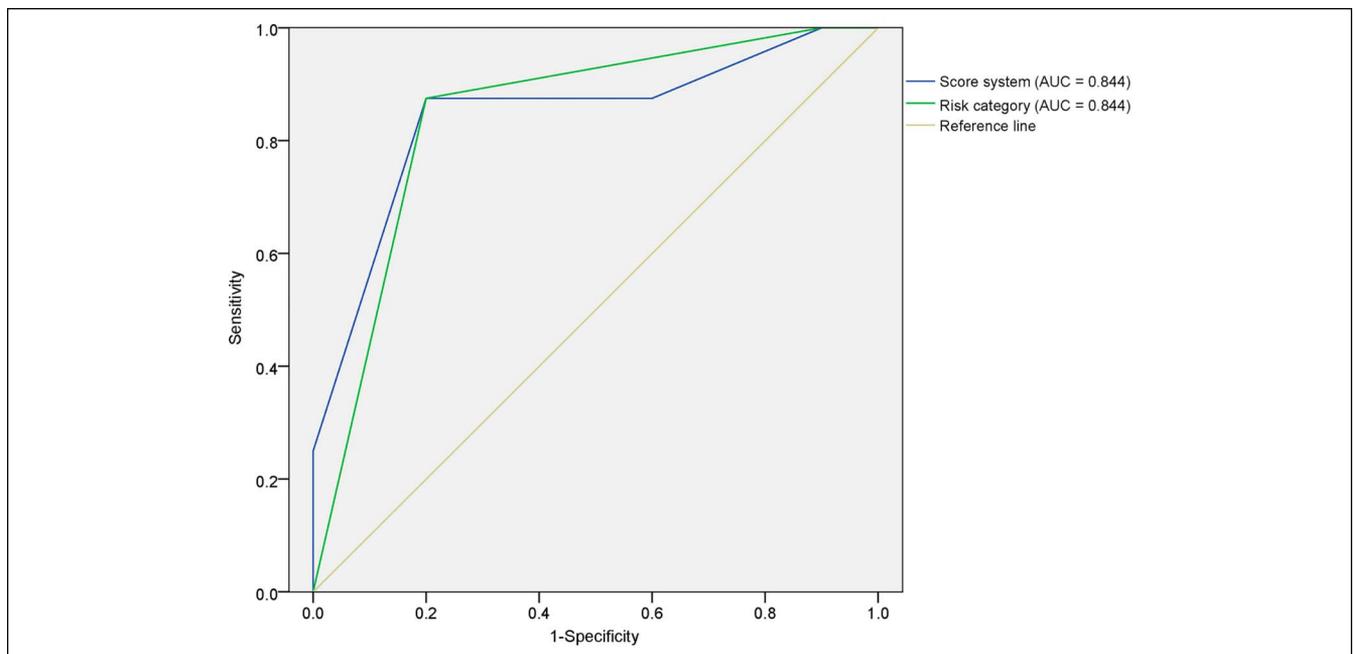

Figure 2. Receiver operating characteristic curves of the scoring system (blue line), risk category (green line), and reference line (yellow line). AUC, area under the receiver operating characteristic curve.

highest LNM rate of 27.5% (28). In our cohort, the overall incidence of LNM in 335 patients with EPAC was 18.5% (N = 62) while the incidence of LNM was 6.5% for other differentiated EGC patients ($P < 0.001$), similar to previous studies (9,14,29,30). This difference persisted when subgroup analysis was performed for tumor size, depth of invasion, ulceration, and indication. Furthermore, we conducted univariate and multivariate analyses of clinicopathological characteristics of 2,513 EGC patients with and without LNM and determined that PAC was an independent risk factor of LNM (OR = 1.8, 95% CI 1.2–2.7, P = 0.004) in patients with EGC. These results suggested that EPAC was highly invasive and may not be suitable for endoscopic resection (14,28).

However, the reasons for the high metastatic rate of PAC were rarely discussed. Some studies suggested that papillary carcinoma is easily associated with micropapillary adenocarcinoma, which was associated with poorer disease-specific or disease-free survival rates and an increased rate of LVI and liver metastasis (31,32).We found similar results in our study where 22 patients with EPAC (6.6%) were combined with micropapillary adenocarcinoma, and 45.5% of them were found with LNM. However, micropapillary adenocarcinoma was not an independent risk factor of LNM in patients with EPAC (OR = 2.2, 95% CI 0.7–6.5, P = 0.157) in multivariate analyses. In addition, some studies showed that some markers could be used to distinguish different pathological types, such as c-erbB-2 (33) and MUC2 (26). So, we further explored the biological reasons for the higher risk of LNM in patients with PAC based on the data from GSE66229, a sequencing platform with histological classifications. Thousands of differentially expressed genes were found between PAC and tubular adenoma, and pathway enrichment suggested that a poor prognosis of EPAC may be associated with downregulation of immune-related pathways. More studies should be performed to clarify the high metastatic ability of EPAC.

Then, we compared the potential risk factors between the negative-LNM group with the positive-LNM group in EPAC, and size > 2 cm, lower stomach location, submucosal invasion, and LVI were found be independent risk factors of LNM in patients with EPAC. After multivariate analysis, using the eCura system for reference (18), we gave 1 point each for lower stomach location and tumor size >2.0 cm, 3 points for LVI, and 4 points for SM1/SM2 to establish a scoring system for predicting the LNM rate in patients with EPAC after surgery, providing new clues for improving the standard of curative endoscopic resection of EPAC.

As an attempt to complement the eCura system, this risk scoring system had several advantages. First, the potential risk factors we included were important clinicopathological factors in patients with EPAC and were easily ascertainable (18). Meanwhile, we developed the 3 risk categories according to the eCura system (18). The low-risk group showed the lowest rate of LNM (3.2%) in our cohort, despite the lack of prognostic data, making it difficult to verify the 5-year survival. Therefore, we speculated that endoscopic submucosal dissection (ESD) with no additional treatment is an acceptable option for patients with EPAC in the low-risk group, according to previous studies (18,34,35). However, additional radical surgery should be strongly recommended for EPAC patients in the high-risk group with the high LNM rate of 49.3%. No additional treatment after ESD for the intermediate-risk groups (with a LNM rate of 14.5%) of EPAC was seemingly inappropriate, different from the previous criteria. This risk prediction system, which was conducted on LNM, has the potential to become a new guide for making clinical decisions after ESD of patients with EPAC.

Our study did have some limitations. First, lymphatic and venous invasions were recorded together as LVI, limiting the analyzability of our data. Second, this study lacked any follow-up data and external validation cohort, making it difficult to verify our scoring system. Further studies are recommended, especially large sample studies of endoscopically resected specimens, to validate and complement these score systems. Third, the retrospective study design inherits unavoidable selection bias, and the actual number of patients with EPAC and LNM is relatively small for definite conclusions. In the future, we will proactively collect much more EPAC patient data to verify the accuracy of our findings. Finally, although we conducted some research studies on the biological mechanisms underlying the association of papillary components with LNM, more immunohistochemical or genetic experiments are needed to explore the relationships between LNM and EPAC.

In conclusion, given its aggressive pathobiological behavior and high risk of nodal metastases, EPAC needs to be treated more rigorously. Our multicenter study tried to develop a clinically useful risk scoring system based on some easily ascertainable clinicopathological factors for predicting prognosis in patients with EPAC. More studies, especially large-scale prospective trials, are required for verification of this scoring system.

Study Highlights

WHAT IS KNOWN

✓ EPAC has high risk of metastasis.

✓ The early detection and resection of early gastric carcinoma can improve the survival of gastric carcinoma patients effectively.

WHAT IS NEW HERE

✓ A new risk scoring system for EPAC was established.

✓ Given its aggressive pathobiological behavior and high risk of nodal metastases, EPAC need to be treated more rigorously.

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