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Original Article

Scoring Model Based on Nodal Metastasis Prediction Suggesting an Alternative Treatment to Total Gastrectomy in Proximal Early Gastric Cancer

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ABSTRACT

Purpose: Total gastrectomy (TG) with lymph node (LN) dissection is recommended for early gastric cancer (EGC) but is not indicated for endoscopic resection (ER). We aimed to identify patients who could avoid TG by establishing a scoring system for predicting lymph node metastasis (LNM) in proximal EGCs.
Materials and Methods: Between January 2003 and December 2017, a total of 1,025 proximal EGC patients who underwent TG with LN dissection were enrolled. Patients who met the absolute ER criteria based on pathological examination were excluded. The pathological risk factors for LNM were determined using univariate and multivariate logistic regression analyses. A scoring system for predicting LNM was developed and applied to the validation group.
Results: Of the 1,025 cases, 100 (9.8%) showed positive LNM. Multivariate analysis confirmed the following independent risk factors for LNM: tumor size >2 cm, submucosal invasion, lymphovascular invasion (LVI), and perineural invasion (PNI). A scoring system was created using the four aforementioned variables, and the areas under the receiver operating characteristic curves in both the training (0.85) and validation (0.84) groups indicated excellent discrimination. The probability of LNM in mucosal cancers without LVI or PNI, regardless of size, was <2.9%.
Conclusions: Our scoring system involving four variables can predict the probability of LNM in proximal EGC and might be helpful in determining additional treatment plans after ER, functioning as a good indicator of the adequacy of treatments other than TG in high surgical risk patients.

Keywords: Stomach neoplasms; Gastrectomy; Lymph node metastasis; Endoscopic submucosal dissection

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No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Endoscopic resection (ER), including endoscopic mucosal resection or endoscopic submucosal dissection (ESD), has recently been performed in select patients with early gastric cancer (EGC), resulting in a relatively low local recurrence rate and a high resection rate [1-4]. However, gastrectomy with lymph node dissection (LND) remains the standard treatment modality for EGC beyond the ER criteria.

Total gastrectomy (TG) with LND remains the standard surgical treatment for EGC as per the Japanese Gastric Cancer treatment guidelines [5]. However, patients who underwent TG developed more symptomatic and functional problems associated with quality of life (QOL), with several studies reporting major complication rates between 4.0%–18.3% [6-10]. To minimize the sequelae of TG, proximal gastrectomy [6,11], segmental gastrectomy [12,13], and local resection have been proposed [14-16]. However, these surgeries included LND to a lesser extent than that in TG and were also associated with a risk of metachronous cancers in the residual stomach.

Likewise, other minimally invasive treatments, such as ER with sentinel node navigation and hybrid natural orifice transluminal endoscopic surgery (NOTES), have been attempted [5,17,18]. However, studies investigating potential candidate groups with proximal EGCs for these limited treatments are insufficient, and the optimal treatment for these tumors has not been established.

Thus, we aimed to determine the features of proximal EGCs that do not satisfy the absolute ER criteria by reviewing the data of patients who underwent TG with LND and identify groups that could avoid TG by developing a scoring system for predicting lymph node metastasis (LNM).

MATERIALS AND METHODS

Study design and population

Between January 2003 and December 2017, a total of 1,255 patients with EGCs in the upper third of the stomach (non-junctional) underwent curative TG with extended LND, including D1+ or D2, at Asan Medical Center, Seoul, Korea. We excluded 107 patients, among whom had undergone previous treatment for gastric cancer (n=45), received neoadjuvant chemotherapy (n=17), and had other malignant tumors (n=45). Of the remaining 1,148 patients, 46 who met the pathological criteria for ER and 77 who had other epithelial tumors [19], such as clear cell carcinoma, neuroendocrine carcinoma, and carcinoma with lymphoid stroma, were excluded. Finally, 1,025 patients were included, and we retrospectively analyzed and compared the pathological outcomes of LNM-negative and LNM-positive tumors (**Fig. 1**). This study was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2018-0722).

Histological examination of resected specimens

The resected specimens were stretched, pinned to a polystyrene plate, and completely immersed in 10% neutral-buffered formalin. They were then analyzed to confirm the lesions and closest resection margins. Surgical specimens were sliced into 4-mm-thick pieces, and each sectioned specimen was embedded in paraffin, after which 5-μm sections were cut and stained with hematoxylin and eosin, as previously described [20]. The lymph nodes

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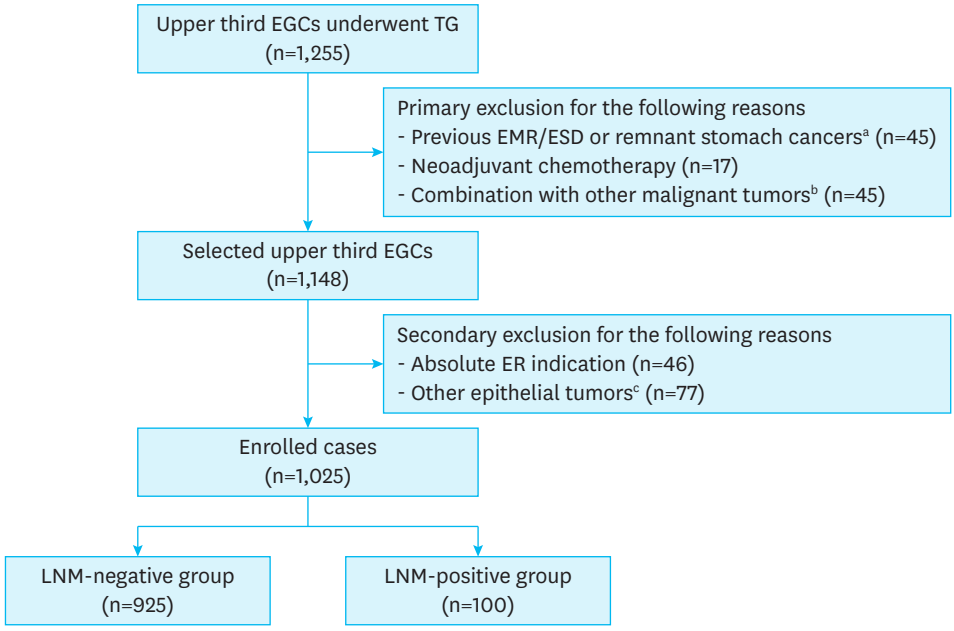

Fig. 1. Flow chart of patient inclusion.
EGC early gastric cancer; TG = total gastrectomy; EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; ER = endoscopic resection; LNM = lymph node metastasis.
[a]Patients who had previously received EMR, ESD, or surgery for stomach cancer; [b]Upon total gastrectomy, other malignant tumors of the gastrointestinal tract were simultaneously identified; [c]The histological types of these tumors included clear cell carcinoma, carcinoma with lymphoid stroma, and neuroendocrine carcinoma.

(LNs) were cut into two pieces, and the cut surfaces were analyzed to confirm the status of the nodes. Lymphovascular invasion (LVI) and perineural invasion (PNI) were defined as observable spread of tumor cells via lymphatic vessels and tumor cell infiltration in, around, and through the nerves, respectively.

Description of tumor

The resected tumors were described according to the Japanese Gastric Cancer Association classification [19]. The locations were classified as the upper, middle, or lower thirds of the stomach. The tumors were then classified as well-differentiated (WD), moderately differentiated (MD), or undifferentiated adenocarcinoma, which included poorly differentiated (PD), signet ring cell (SRC), and combined PD and SRC adenocarcinomas [21]. The depth of tumor was determined according to the deepest invasion based on the classification by the World Health Organization (lamina propria, muscularis mucosa, and submucosa) [21]. Submucosal invasion was divided into SM1 (invasion of the upper third of SM), SM2 (invasion of the middle third of SM), and SM3 (invasion of the lower third of SM). The tumor size, presence of ulceration, LVI, PNI, and tumor involvement in the proximal and distal margins were assessed.

Pathologic definition

Absolute indication for ER

The absolute indication for ER is undifferentiated adenocarcinoma without ulcer, with a depth of invasion (DOI) confined to the mucosa and a diameter of ≤2 cm [1,5].

Expanded indication for ER

(a) Tumor size >2 cm, differentiated mucosal invasion, and absence of ulcers.
(b) Tumor size ≤3 cm, differentiated mucosal invasion, and presence of ulcers.

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(c) Tumor size ≤2 cm, undifferentiated mucosal invasion, and absence of ulcers.
(d) Tumor size ≤3 cm, differentiated, submucosal invasion 1 (SM1, <500 μm from the muscularis mucosae) [1,5].

Statistical analysis

The demographic and pathological characteristics between the LNM-negative and LNM-positive groups were compared using independent t-tests and chi-square tests. Univariate and multivariate logistic regression models were used to identify the prognostic or risk factors for LNM. In the latter, regression coefficients were estimated using the maximum likelihood method along with the application of stepwise variable selection. The estimated regression coefficients (β) in the multivariate model were used to create a risk score equation for predicting LNM, which was used to draw the corresponding graph.

To evaluate the LNM scoring validation internally, two-thirds and one-third of the dataset were randomly assigned to the training and validation groups, respectively. A receiver operating characteristic (ROC) curve was used to evaluate the discrimination ability of the prediction model and its scoring system. The predictive performance of the score was evaluated by calculating the area under the curve (AUC), with AUCs of 0.5 and 1 indicating no and perfect discrimination, respectively. Statistical analyses were performed using SAS (version 9.4).

RESULTS

Demographic and pathologic characteristics

The demographic and pathological characteristics of the 1025 included patients are shown in **Table 1**. Among them, 622 (60.7%) were male, 100 (9.8%) had positive LNMs, and the mean age and BMI were 56.0 years and 23.6 kg/m^2, respectively. There were no significant differences in family history of gastric cancer between the LNM-negative and LNM-positive groups (15.5% vs. 18.0%, P=0.507).

Table 1 shows that the LNM-positive group not only had larger and deeper tumors but also had more frequent LVI and PNI than that of the LNM-negative group. The histologic type and composition was significantly different between the two groups. Moreover, the LNM-negative group had more WD- and SRC-type tumors than the LNM-positive group (P=0.001).

Among the patients, 112 (10.9%) had a differentiated tumor satisfying the expanded ER indications, of which one had LNM. Pathological evaluation of this patient revealed an MD-type mucosal cancer measuring 4.9 cm in size, which was confined to the muscularis mucosa, and one of the 34 dissected LNs revealed tumor cell invasion.

In contrast, 127 (12.4%) patients had an undifferentiated tumor that met the expanded indications for ER, of which none had LNM.

Risk factors related to LNM and establishment of its scoring equation

Table 2 and **Supplementary Table 1** show the analysis of the potential risk factors associated with LNM in proximal EGCs. Multivariate analysis confirmed the following significant independent risk factors: tumor size >2 cm (odds ratio [OR], 2.348; β=0.854; P=0.0460), SM2 or SM3 (OR, 3.105; β=1.133; P=0.0017), LVI (OR, 9.814; β=2.284; P<0.0001), and PNI (OR, 3.266; β=1.184; P=0.0182). Based on these results, we established an equation for an

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Table 1. Demographic and pathologic characteristics in the LNM-negative and LNM-positive groups

Variables	Overall (n=1,025)	LNM-negative (n=925)	LNM-positive (n=100)	P-value
Sex				0.563
Male	622 (60.7)	564 (61.0)	58 (58.0)	
Female	403 (39.3)	361 (39.0)	42 (42.0)	
Age (yr)	56.0±11.3	55.9±11.3	56.4±11.6	0.727
BMI (kg/m^2)	23.6±3.1	23.6±3.1	23.4±3.1	0.525
ASA score				0.439
1	266 (26.0)	237 (25.6)	29 (29.0)	
2	733 (71.5)	666 (72.0)	67 (67.0)	
3	26 (2.5)	22 (2.4)	4 (4.0)	
Family history of gastric cancer	161 (15.7)	143 (15.5)	18 (18.0)	0.507
Presence of ulceration	14 (1.4)	14 (1.5)	0 (0.0)	0.384
Size (cm)	3.6±2.1	3.4±2.0	5.1±2.9	<0.001
Size (cm)				<0.001
≤2.0	254 (24.8)	244 (26.4)	10 (10.0)	
>2.0	771 (75.2)	681 (73.6)	90 (90.0)	
Depth of invasion				<0.001
Mucosa	442 (43.1)	433 (46.8)	9 (9.0)	
Submucosa	583 (56.9)	492 (53.2)	91 (91.0)	
Subdivision of depth				<0.001
Lamina propria	246 (24.0)	244 (26.4)	2 (2.0)	
Muscularis mucosa	196 (19.1)	189 (20.4)	7 (7.0)	
Submucosa 1	126 (12.3)	116 (12.5)	10 (10.0)	
Submucosa 2	164 (16.0)	141 (15.2)	23 (23.0)	
Submucosa 3	293 (28.6)	235 (25.4)	58 (58.0)	
Histology				0.001
WD	88 (8.6)	85 (9.2)	3 (3.0)	
MD	236 (23.0)	202 (21.8)	34 (34.0)	
PD	233 (22.7)	210 (22.7)	23 (23.0)	
SRC	209 (20.4)	200 (21.6)	9 (9.0)	
PD, SRC	259 (25.3)	228 (24.6)	31 (31.0)	
Lauren type				0.053
Intestinal	372 (36.3)	334 (36.1)	38 (38.0)	
Diffuse	472 (46.0)	436 (47.1)	36 (36.0)	
Mixed	176 (17.2)	150 (16.2)	26 (26.0)	
Indeterminate	5 (0.5)	5 (0.5)	0 (0.0)	
LVI				<0.001
No	903 (88.1)	861 (93.1)	42 (42.0)	
Yes	122 (11.9)	64 (6.9)	58 (58.0)	
PNI				<0.001
No	982 (95.8)	894 (96.6)	88 (88.0)	
Yes	43 (4.2)	31 (3.4)	12 (12.0)	

Data are presented as number (%) or mean±SD.
LNM = lymph node metastasis; =BMI = body mass index; ASA = American Society of Anesthesiologists; WD = well-differentiated adenocarcinoma; MD = moderately differentiated adenocarcinoma; PD = poorly differentiated adenocarcinoma; SRC = signet ring cell carcinoma; PD, SRC = poorly differentiated adenocarcinoma with signet ring cell components; LVI = lymphovascular invasion; PNI = perineural invasion.

LNM risk score calculated using tumor size, DOI, LVI, and PNI. The LVI and tumor size had the highest and lowest scores, respectively. The equation used is as follows:

LNM Risk Score=0.85×Size (≤2 cm=0 or >2 cm=1)+1.13×DOI (Mucosa, SM1=0 or SM2, SM3=1)+2.29×LVI (No=0 or Yes=1)+1.18×PNI (No=0 or Yes=1)

Estimation of LNM probability according to the risk score

Fig. 2 shows the relationship between the risk score and LNM probability and indicates that the probability of LNM increases with an increase in the risk score. **Table 3** shows that LNM probability corresponds with the risk score in the variable pathological results of proximal EGCs.

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Table 2. Univariate and multivariate analyses of risk factors related to lymph node metastasis

Variables	Univariate analysis		Multivariate analysis		
	OR (95% CI)	P-value	OR (95% CI)	β	P-value
Size (cm)					
≤2.0	1		1		
>2.0	2.647 (1.238–5.600)	0.0120	2.348 (1.015–5.429)	0.854	0.0460
Depth of invasion					
Mucosa, SM1	1		1		
SM2, SM3	10.370 (4.113–26.149)	<0.0001	3.105 (1.531–6.299)	1.133	0.0017
Histology					
WD	1				
MD	3.873 (0.879–17.066)	0.0156			
PD	2.685 (0.596–12.085)	0.3470			
SRC	0.954 (0.179–5.078)	0.0539			
PD, SRC	3.793 (0.861–16.709)	0.0193			
Lauren type					
Intestinal	1				
Diffuse	0.620 (0.340–1.131)	0.9733			
Mixed	1.822 (0.970–3.422)	0.9592			
Indeterminate	N/A	N/A			
LVI					
No	1		1		
Yes	15.189 (8.637–26.713)	<0.0001	9.814 (5.386–17.883)	2.284	<0.0001
PNI					
No	1		1		
Yes	5.838 (2.573–13.247)	<0.0001	3.266 (1.223–8.721)	1.184	0.0182

OR = odds ratio; CI = confidence interval; SM1 = submucosal invasion of the upper third; SM2 = submucosal invasion of middle third; SM3 = submucosal invasion of lower third; WD = well-differentiated adenocarcinoma; MD = moderately differentiated adenocarcinoma; PD = poorly differentiated adenocarcinoma; SRC = signet ring cell carcinoma; PD, SRC = poorly differentiated adenocarcinoma with signet ring cell component; LVI = lymphovascular invasion; PNI = perineural invasion.

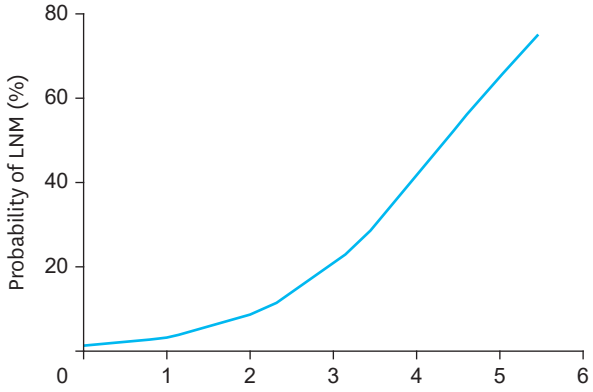

Fig. 2. Probability of LNM according to the risk score.
LNM = lymph node metastasis.

The LNM risk score and probability of mucosal or SM1 tumors (≤2 cm) without LVI and PNI (**Table 3-A**) were zero point and 1.3%, respectively. Mucosal or SM1 tumors (>2 cm) without LVI or PNI (**Table 3-B**) had a 2.9% LNM probability. SM2 or SM3 tumors (≤2 cm) without LVI and PNI (**Table 3-C**) and mucosal or SM1 tumors (≤2 cm) with PNI alone (**Table 3-D**) had 3.8% and 4.0% probability of LNM, respectively.

When the tumors were positive only for LVI (**Table 3-G**), they had an 11.2% probability of LNM. It was higher than that of mucosal or SM1 tumors (measuring >2 cm) with PNI (9.0%, **Table 3-F**). In cases where all four variables were positive, the LNM risk score and probability were 5.45 points and 75.0%, respectively (**Table 3-P**).

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Table 3. The LNM risk score and the probability of LNM in various cases

The pathologic result of EGC	LNM risk score	Probability of LNM (%)
(A) ≤2 cm, Mucosa/SM1 invasion, LVI-, PNI-	0	1.3
(B) >2 cm, Mucosa/SM invasion, LVI-, PNI-	0.85	2.9
(C) ≤2 cm, SM2/SM3 invasion, LVI-, PNI-	1.13	3.8
(D) ≤2 cm, Mucosa/SM1invasion, LVI-, PNI+	1.18	4.0
(E) >2 cm, SM2/SM3 invasion, LVI-, PNI-	1.98	8.6
(F) >2 cm, Mucosa /SM1 invasion, LVI-, PNI+	2.03	9.0
(G) ≤2 cm, Mucosa/SM1 invasion, LVI+, PNI-	2.29	11.2
(H) ≤2 cm, SM2/SM3 invasion, LVI-, PNI+	2.31	11.5
(I) >2 cm, Mucosa/SM1 invasion, LVI+, PNI-	3.14	22.9
(J) >2 cm, SM2/SM3 invasion, LVI-, PNI+	3.16	23.5
(K) ≤2 cm, SM2/SM3 invasion, LVI+, PNI-	3.42	28.2
(L) ≤2 cm, Mucosa/SM1 invasion, LVI+, PNI+	3.47	29.2
(M) >2 cm, SM2/SM3 invasion, LVI+, PNI-	4.27	47.9
(N) >2 cm, Mucosa/SM1 invasion, LVI+, PNI+	4.32	49.2
(O) ≤2 cm, SM2/SM3 invasion, LVI+, PNI+	4.6	56.2
(P) >2 cm, SM2/SM3 invasion, LVI+, PNI+	5.45	75.0

LNM = lymph node metastasis; EGC = early gastric cancer; LVI = lymphovascular invasion; PNI = perineural invasion; SM1 = submucosal invasion of the upper third; SM2 = submucosal invasion of middle third; SM3 = submucosal invasion of lower third.

Table 3 and **Fig. 2** show that the probability of LNM rapidly increased when the LNM risk score was >2.31 points, which corresponds to submucosal tumors (measuring ≤2 cm in size) with PNI (**Table 3-H**).

Evaluation of the LNM prediction model

A prediction scoring system was then applied to evaluate the training and validation groups. **Fig. 3** shows the ROC curves for both the groups. The AUC-ROC values in the validation and training groups were 0.83 and 0.84. The ROC curve showed excellent discrimination in both the groups.

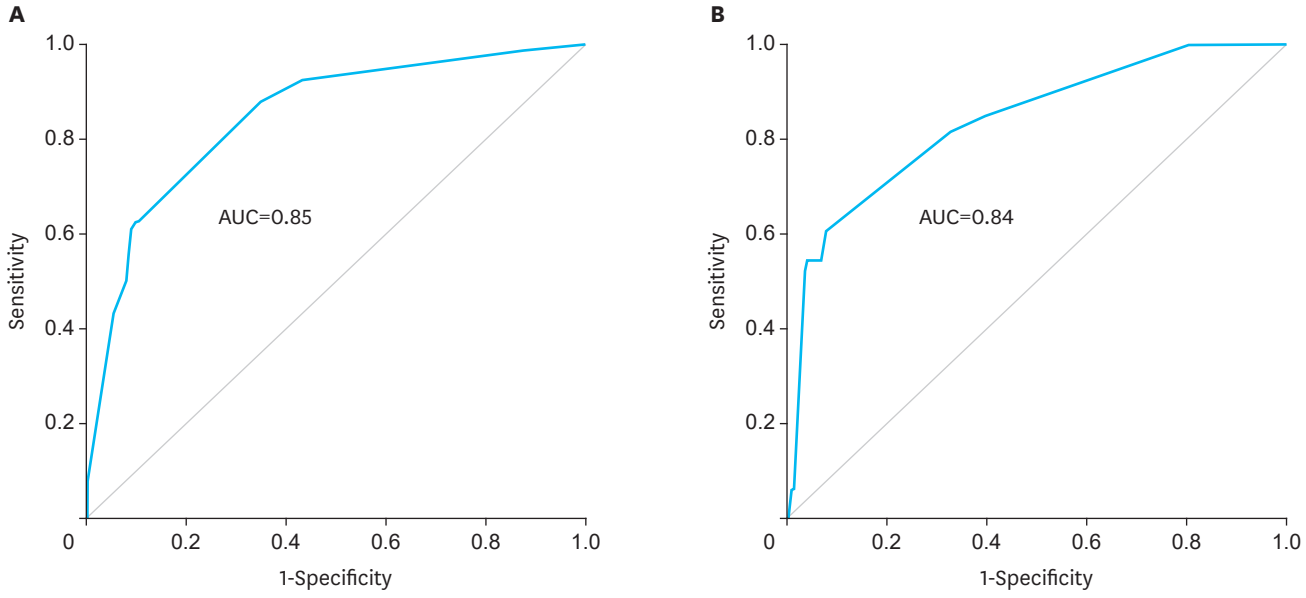

Fig. 3. ROC curves of the risk score predicting lymph node metastasis. (A) ROC curve of the training group. (B) ROC curve of the validation group.
AUC = area under the curve; ROC = receiver operating characteristics.

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DISCUSSION

The incidence of EGC has been steadily increasing as a result of early detection using advanced diagnostic techniques. In deciding the treatment method for EGC, LNM status, tumor depth, and tumor location should be considered, and TG is the treatment of choice for proximal tumors that do not meet the ER criteria. However, TG can result in poorer nutritional status and QOL than subtotal gastrectomy [22-24]. To avoid TG sequelae, several treatment modalities have been investigated to identify their clinical outcomes, efficacy, and safety [6,11-18].

Although these studies revealed fragmentary outcomes and performed comparisons between surgical techniques, an optimal group of EGCs suitable for the application of alternative treatments for TG could not be suggested. Moreover, the indications for alternative treatments to TG have not been established, and little research has been done on LNM of EGC located in the upper third of the stomach. To our knowledge, this is the first study to evaluate nodal status based on a scoring system to suggest another treatment modality for proximal EGC instead of TG.

To determine the optimal group for alternative treatment, we investigated the differences between the LNM-negative and LNM-positive groups and quantified the risk of nodal metastasis by establishing a scoring system using four variables that showed statistical significance in multivariate analysis: tumor size >2 cm, submucosal invasion, LVI, and PNI. Consequently, we estimated the probability of LNM based on the risk scores. However, during surgery, it is not easy to choose the best treatment option based on our scoring system because the abovementioned variables cannot be determined by intraoperative frozen biopsy, but our system may be useful to decide an additional treatment after performing ER of the tumor beyond the ER criteria. In other words, if the pathologic result of the tumor after ER presented a mucosal tumor (regardless of size) without LVI and PNI, which had a <2.9% probability of LNM, careful follow-up could be considered in patients with this tumor. According to the scoring system, if at most one variable, except for LVI, was positive, the tumors had a low LNM probability of <5%. Therefore, considering the major complication rate of TG [6-10], alternative treatments, such as ER with close observation or hybrid NOTES, might be acceptable for patients with high surgical risk who are expected to have a <5% risk of LNM.

Our study showed that all 127 undifferentiated tumors that met the expanded ER indications were LNM negative. This corresponds with the results of recent studies that have attempted to expand the ER criteria for undifferentiated mucosal cancers [4,20,25]. Although ER has been known to be safe in expanded indications [1,2,26], our results showed that one tumor that satisfied the expanded ER indications had invaded a regional LN. This means that even if no LNM is reported for expanded ER indications [1,26], some tumors could spread to the regional LNs in specific situations. Therefore, although a tumor is expected to meet the expanded indications for ER, ESD should be carefully performed.

Recently, several studies have reported the use of scoring systems to predict LNM in EGCs [27-31]. Hatta et al. [31] established the "eCura system" using lymphatic invasion (3 points), tumor size >3 cm (1 point), positive VM (1 point), venous invasion (1 point), and submucosal invasion ≥500 μm (1 point) in patients who underwent radical surgery after non-curative resection of ESD for EGC. Subsequently, the patients were divided into three LNM risk groups: low (0–1 point: 2.5% risk), intermediate (2–4 points: 6.7%), and high (5–7 points: 22.7%). They concluded that ESD without additional treatment may be an acceptable option

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for patients at a low risk of LNM. Moreover, Tran et al. [27] analyzed patients with EGCs who underwent curative-intent surgical resection and revealed that the absence of LNM could be predicted by the absence of several unfavorable factors, including poor differentiation, T stage, LVI, and tumor size >2 cm. However, unlike other studies, we restricted the study patients to those with tumors located in the upper third of the stomach and who received the same surgical procedure to reduce bias arising from surgical diversity, as well as excluded patients with tumors meeting absolute ER indications.

However, this study has several notable limitations. First, our analysis was retrospective and was performed in a single referral center. Second, we did not evaluate the exact nodal stations of the resected specimens. Thus, we could not determine the optimal range of LND for a limited ER. Despite these limitations, this is a promising study that facilitates the estimation of LNM probability in proximal EGCs by establishing a risk-scoring system. In addition, our scoring system provided excellent discrimination between training and validation groups.

In conclusion, our scoring system is useful for evaluating the probability of LNM in proximal EGCs. According to our scoring system, follow-up surveillance without additional curative TG should be carefully considered in selected patients with a very low risk of LNM after ER, particularly in those with high surgical risks.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Multivariate logistic regression analysis of risk factors related to lymph node metastasis

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