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Predictors of lymph node metastasis in patients with non-curative endoscopic resection of early gastric cancer

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Abstract

Background Although surgery is recommend for non-curative endoscopic resection of early gastric cancer (EGC), only a part of patients are found to have lymph node (LN) metastasis. This study aimed to identify the predictors of LN metastasis in patients with non-curative endoscopic resection.

Methods Between April 2005 and July 2013, consecutive patients who received non-curative endoscopic resection and then underwent gastrectomy with lymphadenectomy or followed at least 1 year with abdominal computed tomography were retrospectively enrolled at a single tertiary hospital. Non-curative resection was defined as a resection beyond the expanded criteria in pathologic mapping. The predictors for LN metastasis were identified by fitting a multivariate logistic regression model.

Results Among the 1783 consecutive patients who received endoscopic resection of EGC, non-curative resection was performed in 323 (18.1 %) patients. Of these patients, a total of 267 patients were enrolled, and the rate of LN metastasis was 6.7 % (18/267). In multivariate analysis, venous invasion [odds ratio (OR), 7.83; 95 % confidence interval (CI) 2.20–27.86; $p = 0.001$], sm2 invasion (tumor invasion ≥500 μm into submucosa; OR 4.98; 95 % CI 1.34–18.47; $p = 0.016$), or antral tumor location (OR 12.65; 95 % CI 1.57–102.00; $p = 0.017$) were independent predictors for LN metastasis. The rates of LN metastasis were 1.1 % (95 % CI 0–2.7) for patients with one or no predictor and 17.8 % (95 % CI 9.7–25.8) for those with two or more predictors.

Conclusions Additional gastrectomy with lymphadenectomy after non-curative endoscopic resection of EGC is recommended for the patients with two or more identified predictors. However, close follow-up without immediate surgery might be considered cautiously for those with only one or no predictor.

Keywords Early gastric cancer · Non-curative endoscopic resection · Lymph node metastasis · Predictor

Gastric cancer is the fourth most common cancer in the world and the second most common cause of cancer-related mortality [1]. Although the incidence is decreasing worldwide, Eastern Asia remains the area with a high incidence of gastric cancer, where half of the cases occur. In Korea, as well as Japan, with increased endoscopic screening for gastric cancer, the proportion of patients who are diagnosed with early gastric cancer (EGC) is increasing [2, 3]. Accordingly, endoscopic resection has been widely performed for the treatment of EGC with minimal risk of lymph node (LN) metastasis [4, 5]. Endoscopic resection of EGC has been reported to offer excellent long-term survival, while avoiding the need for surgery [6].

Endoscopic resection can be considered as curative only when the resected specimen reveals no risk factors for LN metastasis, as well as tumor-free resection margins. The risk factors for LN metastasis reported from a large-scale review of surgically resected EGCs included lymphovascular invasion (LVI), depth of invasion ≥500 μm into

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submucosa, large tumor size, and undifferentiated histology [7], and based on the data, the expanded criteria have been suggested and largely accepted [8, 9]. Accordingly, the patients with those risk factors, i.e., non-curative resection, are recommended to receive additional surgery [8]. However, the LN metastasis is found in only about 5–10 % of the patients who underwent surgery [10–14]. Therefore, further risk stratification for LN metastasis in the patients with non-curative resection is needed.

Although several studies have addressed the surgical outcome after non-curative or incomplete endoscopic resection [10–16], there is little available clinical information on the predictive factors of LN metastasis after non-curative resection, and the results from several studies are inconsistent [10–13].

Therefore, in this study, we aimed to identify the predictors of LN metastasis and, based on the results, tried to stratify the risk of LN metastasis in patients with non-curative endoscopic resection of EGC.

Materials and methods

Patients

In this retrospective cohort study, we screened consecutive patients who underwent endoscopic resection of EGC by two experienced endoscopists from April 2005 to July 2013 at Seoul National University Hospital, Seoul, Korea. From these patients, those who received non-curative endoscopic resection were included in the study. Non-curative resection was defined as a resection beyond the expanded criteria in pathologic mapping [8, 9]. Expanded criteria were defined as tumor-free resection margin, no evidence of LVI, and any of the followings: (1) any size of differentiated mucosal cancer without ulcer, (2) differentiated mucosal cancer ≤3 cm with ulcer, (3) differentiated sm1 (depth of invasion <500 μm from the muscularis mucosa) cancer ≤3 cm, or (4) undifferentiated mucosal cancer ≤2 cm without ulcer [8, 9]. Exclusion criteria were as follows: patients with piecemeal resection where complete reconstitution of the lesion was impossible; and patients who refused to receive additional surgery for non-curative endoscopic resection and did not complete 1 year follow-up assessment including abdominal computed tomography (CT), which was considered as a minimum requirement for the judgment on the presence or absence of LN metastasis. The medical records of the patients were reviewed with regard to demographics, endoscopic tumor findings, histological findings in the endoscopically resected specimens, and specimens from additional surgical treatment.

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1309-077-521) and was exempted from the requirement to obtain informed consent.

Endoscopic resection

Endoscopic resection was indicated, when the lesion was a differentiated adenocarcinoma, ≤2 cm in size by endoscopic measurement, and without evidence of submucosal invasion or LN metastasis on endoscopic ultrasonography (EUS) and/or abdominal CT using stomach protocol [17]. Positron emission tomography (PET) or PET CT was not performed. There was no anatomical limitation including cardiac region.

For conscious sedation, intravenous midazolam (0.06 mg/kg) was used with cardiorespiratory monitoring throughout the procedure. There were two methods of endoscopic resection procedures the patients received: endoscopic mucosal resection (EMR) was used in selected cases considering the technical feasibility of En-bloc resection, and in most cases, endoscopic submucosal dissection (ESD) was selected. EMR was performed using cap (D-206-05; Olympus Optical Co., Tokyo, Japan) and snare (SD-221L-25; Olympus Optical Co., Tokyo, Japan), and ESD was conducted using an insulation-tipped (IT)-knife (Helmet Snare; Kachu Technology Co., Seoul, South Korea) through single-channel endoscope (Olympus H260; Olympus Optical Co., Tokyo, Japan), as previously described [16, 18]. For both of the procedures, an overtube was not used. All patients were admitted to the hospital on the day of the procedure for at least 2 days.

Evaluation of pathologic specimens

The specimens from endoscopic resection were evaluated as previously reported [16, 18]. In brief, after being fixed in 10 % formalin, specimens were sectioned serially at 2-mm intervals, and the tumor size, depth of invasion, degree of differentiation, and lymphatic and vascular invasion were examined by one pathologist (WHK) with more than 30 years of experience, blinded to clinical data, according to the recommendations in the third edition of Japanese classification of gastric carcinoma [19]. Different histological subtypes were categorized into differentiated type (well- or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma) or undifferentiated type (poorly differentiated tubular adenocarcinoma, mucinous adenocarcinoma, or poorly cohesive carcinoma including signet ring cell carcinoma) [20]. The depth of submucosal invasion was subclassified as sm1 (tumor invasion into submucosa <500 μm from the muscularis mucosa) and sm2 (tumor invasion into submucosa ≥500 μm from the muscularis mucosa) [19]. Immunohistochemical staining using antibodies of podoplanin (D2-40), a specific

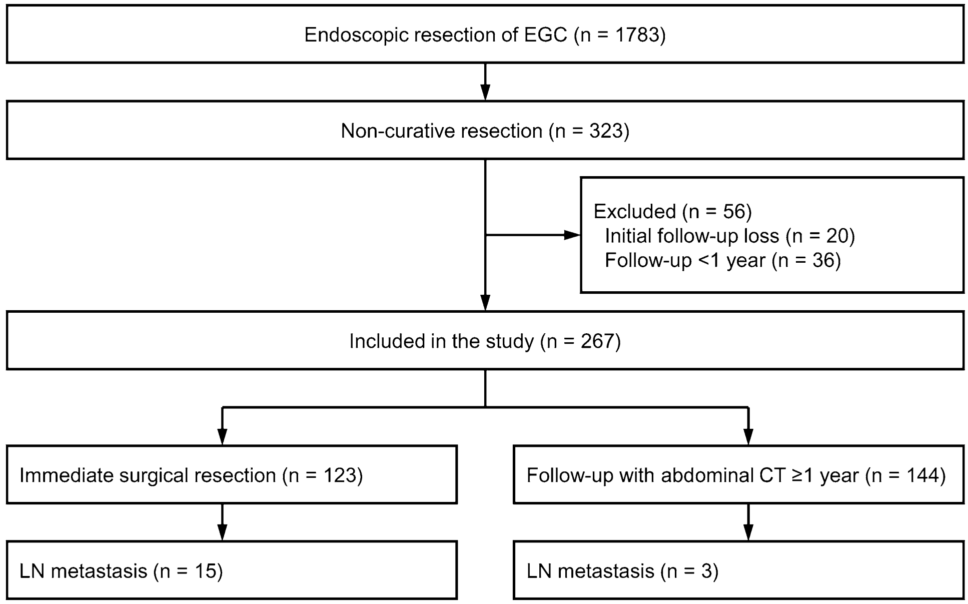

Fig. 1 The study profile of the patients with non-curative endoscopic resection of EGC. *EGC* early gastric cancer, *CT* computed tomography, and *LN* lymph node

biomarker for lymphatic endothelium, was performed to detect lymphatic tumor invasion and to distinguish between small blood vessels and lymphatic capillaries [21].

Initial management strategy, follow-up, and definition

On an initial follow-up visit after endoscopic resection, the patients with non-curative resection were recommended to undergo additional surgery. For those who refused surgery due to their advanced age, concomitant illness, or individual preferences, close follow-up was recommended alternatively. However, follow-up without surgery was not recommended just because the risk of LN metastasis was expected to be low despite non-curative resection. They were followed with endoscopy at month 3 and with endoscopy, chest radiography, and abdominal CT at months 6 and 12, and then annually. They did not receive any adjuvant therapy including chemotherapy.

In patients who underwent immediate surgical resection, LN metastasis was diagnosed pathologically in surgical specimens. In patients with close follow-up, LN metastasis was diagnosed radiologically in abdominal CT, and then confirmed pathologically in surgical or excisional biopsy specimen or clinically in follow-up abdominal CT.

Statistical analysis

Continuous variables were compared using the Student's *t* test or Mann–Whitney *U* test, and categorical variables were compared using the Pearson's Chi squared or Fisher's exact test as appropriate. To identify independent predictive factors of LN metastasis, a multiple logistic regression model was fitted. The clinically or statistically significant variables in univariate analysis ($p < 0.1$) were included in multivariate analysis. Then, the number of identified predictors was evaluated in terms of the association with the rate of LN metastasis using linear-by-linear association and in terms of the predictive accuracy by measuring the area under the receiver-operating characteristic curve (AUROC). The cumulative probability of disease-specific survival was estimated by means of the Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed with SPSS (version 21.0; SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered significant.

Results

Study population

The study profile is shown in Fig. 1. Between April 2005 and July 2013, a total of 1783 patients had received endoscopic resection of EGC. Non-curative resection was performed in 323 (18.1 %) patients, for whom additional surgery was recommended. Among these patients, 56 were excluded: 20 were initially lost to follow-up, and 36 followed less than 1 year. Consequently, the remaining 267 (82.7 %) patients who underwent additional surgical resection immediately ($n = 123$) or were followed more than 1 year ($n = 144$) were included in the study.

The baseline characteristics are summarized in Table 1. The median age was 63.8 (range = 35.7–91.0), and 73.4 % (196/267) were male. The tumors were >3 cm in 30.3 % (81/267), showed undifferentiated histology in 22.5 % (60/267), invaded more than sm2 in 49.8 % (133/267) and had

Table 1 Baseline characteristics of patients with non-curative endoscopic resection of EGC

	Overall ($n = 267$) [No. (%)]	Immediate surgery ($n = 123$) [No. (%)]	Follow-up ($n = 144$) [No. (%)]	p value[a]
Age (years)[b]	63.8 (35.7–91.0)	61.3 (35.7–82.5)	65.1 (38.1–91.0)	0.008
Sex				0.080
Female	71 (26.6)	39 (31.7)	32 (22.2)	
Male	196 (73.4)	84 (68.3)	112 (77.8)	
Type of endoscopic resection				0.054
EMR	17 (6.4)	4 (3.3)	13 (9.0)	
ESD	250 (93.6)	119 (96.7)	131 (91.0)	
Location of tumor				1.000
Body and fundus	89 (33.3)	41 (33.3)	48 (33.3)	
Antrum	178 (66.7)	82 (66.7)	96 (66.7)	
Gross type				0.058
Elevated	74 (27.7)	41 (33.3)	33 (22.9)	
Flat or depressed	193 (72.3)	82 (66.7)	111 (77.1)	
Ulcer finding				0.028
No	236 (88.4)	103 (83.7)	133 (92.4)	
Yes	31 (11.6)	20 (16.3)	11 (7.6)	
Tumor size				0.249
≤3 cm	186 (69.7)	90 (73.2)	96 (66.7)	
>3 cm	81 (30.3)	33 (26.8)	48 (33.3)	
Differentiation				0.030
Differentiated	207 (77.5)	88 (71.5)	119 (82.6)	
Undifferentiated	60 (22.5)	35 (28.5)	25 (17.4)	
Lauren's classification				0.194
Intestinal	203 (76.0)	89 (72.4)	114 (79.2)	
Diffuse	64 (24.0)	34 (27.6)	30 (20.8)	
Depth of invasion[c]				<0.001
Mucosa or sm1	134 (50.2)	30 (24.4)	104 (72.2)	
Sm2 or more	133 (49.8)	93 (75.6)	40 (27.8)	
Lateral resection margin				<0.001
Free	190 (71.2)	101 (82.1)	89 (61.8)	
Involve	77 (28.8)	22 (17.9)	55 (38.2)	
Deep resection margin				<0.001
Free	185 (69.3)	61 (49.6)	124 (86.1)	
Involve	82 (30.7)	62 (50.4)	20 (13.9)	
Lymphatic invasion				<0.001
No	147 (55.1)	46 (37.4)	101 (70.1)	
Yes	120 (44.9)	77 (62.6)	43 (29.9)	
Venous invasion				<0.001
No	248 (92.9)	105 (85.4)	143 (99.3)	
Yes	19 (7.1)	18 (14.6)	1 (0.7)	
Perineural invasion				0.337
No	263 (98.5)	120 (97.6)	143 (99.3)	
Yes	4 (1.5)	3 (2.4)	1 (0.7)	

Table 1 continued

	Overall ($n = 267$) [No. (%)]	Immediate surgery ($n = 123$) [No. (%)]	Follow-up ($n = 144$) [No. (%)]	p value[a]
Number of risk factors[b, d]	2 (0–5)	2 (1–5)	1 (0–4)	<0.001

EGC early gastric cancer, *EMR* endoscopic mucosal resection, and *ESD* endoscopic submucosal dissection

[a] Comparison between the patients with immediate surgery and those with follow-up

[b] Value expressed as median (range)

[c] *Sm1* submucosal invasion <500 μm from the muscularis mucosa; *sm2* submucosal invasion ≥500 μm from the muscularis mucosa

[d] Risk factors include tumor size >3 cm, undifferentiated histology, sm2 invasion, tumor-involved deep resection margin, and lymphovascular invasion

LVI in 47.2 % (126/267). When the patients who received immediate surgery were compared to those who did not, there were significant differences in demographic and tumor-related characteristics: they were significantly younger in age ($p = 0.012$) and more likely to have ulcer ($p = 0.028$), undifferentiated histology ($p = 0.030$), sm2 invasion ($p < 0.001$), tumor-free lateral resection margin ($p < 0.001$), tumor-involved deep resection margin ($p < 0.001$), and lymphatic ($p < 0.001$) and vascular ($p < 0.001$) invasion. Consequently, the patients with immediate surgery had significantly higher number of known risk factors compared to those with close follow-up ($p < 0.001$). Endoscopic resection-related adverse event developed in 12.7 % (34/267) patients: there were 27 (10.1 %) patients who experienced bleeding requiring endoscopic or radiologic intervention, transfusion, or a drop of hemoglobin >2 g/dL, five (1.9 %) with microperforation documented by the presence of free air on an abdominal radiograph, one (0.4 %) with pneumonia, and one (0.4 %) with pyloric stricture.

Surgery

Surgery was conducted median 1.4 months (range = 0.3–3.3) after the endoscopic resection. The most commonly performed procedure was distal gastrectomy ($n = 96$, 78.0 %), which was followed by proximal gastrectomy ($n = 12$, 9.8 %), pylorus-preserving gastrectomy ($n = 12$, 9.8 %), and total gastrectomy ($n = 3$, 2.4 %). The mean number of harvested LNs ± standard deviation was 35.2 ± 14.2. During the operation, there were gross LN metastases in four (3.3 %) patients, but only two of them were proved to have LN metastasis in pathologic examination.

Lymph node metastasis in the patients with non-curative endoscopic resection of EGC

Of a total 267 patients, 18 patients (6.7 %) were diagnosed to have LN metastasis. First, among the 123 patients who received immediate gastrectomy with lymphadenetomy, 15 patients revealed LN metastasis in pathological examination. Second, among the 144 patients who did not undergo immediate surgical resection and were followed with abdominal CT for a median of 24.4 months (range = 12.0–89.7), three patients developed LN metastasis at 6.5, 7.9, and 15.0 months of follow-up, respectively. One patient underwent radical gastrectomy with lymphadenectomy, and the surgical specimen revealed 4 metastatic LNs among 42 harvested nodes. Another patient was conducted surgical excisional biopsy which confirmed nodal metastasis and was treated with systemic chemotherapy instead of surgical treatment due to concomitant illness. The other patient received supportive care only owing to old age, and follow-up CT showed progression of LN metastasis and new metastasis to liver.

Predictors of lymph node metastasis

The univariate analysis revealed that the venous invasion ($p = 0.001$), sm2 invasion ($p = 0.003$), and antral location of tumor ($p = 0.010$) were significantly associated with LN metastasis (Table 2). In the multivariate logistic regression model, the presence of venous invasion (odds ratio [OR], 7.83; 95 % confidence interval [CI], 2.20–27.86; $p = 0.001$), sm2 invasion (OR, 4.98; 95 % CI, 1.34–18.47; $p = 0.016$), and antral location of tumor (OR, 12.65; 95 % CI, 1.57–102.00; $p = 0.017$) was still independent predictors associated with LN metastasis (Table 3).

The rate of LN metastasis increased progressively as the number of these factors (venous invasion, sm2 invasion, and antral location) increased, which showed significant linear association ($p < 0.001$ for trend; Table 4). The AUROC of the number of the predictors detecting LN metastasis was 0.817 (95 % CI, 0.707–0.927; Fig. 2A), indicating excellent discrimination [22]. At a cut-off of ≥2 predictors, LN metastasis could be predicted with a sensitivity of 88.9 % and specificity of 70.3 %. When stratified by this cut-off point, the rates of LN metastasis were

Table 2 Univariate analysis of predictors for lymph node metastasis in non-curative resection of EGC

	No LN metastasis (n = 249, 93.3 %) [No. (%)]	LN metastasis (n = 18, 6.7 %) [No. (%)]	*p* value
Age (years)[a]	62.8 ± 10.2	62.3 ± 8.8	0.814
Sex			1.000
Female	66 (26.5)	5 (27.8)	
Male	183 (73.5)	13 (72.2)	
Type of endoscopic resection			1.000
EMR	16 (6.4)	1 (5.6)	
ESD	233 (93.6)	17 (94.4)	
Location of tumor			0.010
Body and fundus	88 (35.3)	1 (5.6)	
Antrum	161 (64.7)	17 (94.4)	
Gross type			1.000
Elevated	69 (27.7)	5 (27.8)	
Flat or depressed	180 (72.3)	13 (72.2)	
Ulcer finding			0.141
No	222 (89.2)	14 (77.8)	
Yes	27 (10.8)	4 (22.2)	
Tumor size			0.414
≤3 cm	175 (70.3)	11 (61.1)	
>3 cm	74 (29.7)	7 (38.9)	
Differentiation			0.564
Differentiated	194 (77.9)	13 (72.2)	
Undifferentiated	55 (22.1)	5 (27.8)	
Lauren's classification			0.775
Intestinal	190 (76.3)	13 (72.2)	
Diffuse	59 (23.7)	5 (27.8)	
Depth of invasion[b]			0.003
Mucosa or sm1	131 (52.6)	3 (16.7)	
Sm2 or more	118 (47.4)	15 (83.3)	
Lateral resection margin			0.086
Free	174 (69.9)	16 (88.9)	
Involve	75 (30.1)	2 (11.1)	
Deep resection margin			0.066
Free	176 (70.7)	9 (50.0)	
Involve	73 (29.3)	9 (50.0)	
Lymphatic invasion			0.153
No	140 (56.2)	7 (38.9)	
Yes	109 (43.8)	11 (61.1)	
Venous invasion			0.001
No	236 (94.8)	12 (66.7)	
Yes	13 (5.2)	6 (33.3)	
Perineural invasion			1.000
No	245 (98.4)	18 (100.0)	
Yes	4 (1.6)	0 (0.0)	

EGC early gastric cancer, *LN* lymph node, *EMR* endoscopic mucosal resection, and *ESD* endoscopic submucosal dissection

[a] Value expressed as mean ± standard deviation

[b] *Sm1* submucosal invasion <500 μm from the muscularis mucosa; *sm2* submucosal invasion ≥500 μm from the muscularis mucosa

1.1 % (95 % CI, 0–2.7) for the patients with one or no predictor and 17.8 % (95 % CI, 9.7–25.8) for those with two or more predictors.

Predictors of lymph node metastasis in patients who received immediate surgery

Since the pathologic evaluation of the dissected LNs is the most accurate method to determine the presence or absence of LN metastasis, we further analyzed the subgroup of 123 patients who received immediate surgery after non-curative resection to elucidate whether the identified risk factors would also be able to predict LN metastasis in these patients.

In multivariate analysis, venous invasion (OR, 4.55; 95 % CI, 1.23–16.80; $p = 0.023$) and antral location (OR, 9.72; 95 % CI, 1.19–79.8; $p = 0.034$) were independently associated with LN metastasis, while sm2 invasion was not (Table 3). However, the number of the predictors maintained the significant linear relationship with the rate of LN metastasis ($p = 0.004$ for trend; Table 4) and the acceptable predictability of LN metastasis with AUROC of 0.714 (95 % CI, 0.568–0.860; Fig. 2B) [22]. Consequently, LN metastasis was demonstrated in 3.6 % (95 % CI, 0–8.7) of the patients with one or no predictor and 19.1 % (95 % CI, 9.5–28.7) of those with two or more predictors (Table 4).

Survival according to the surgery and risk stratification

During a median 40.7 (range = 7.6–102.9) months of follow-up for survival, two patients (0.7 %) developed metastatic disease and three patients (1.1 %) died of gastric cancer. The 5-year disease-specific survival was 98.1 % for the overall patients, 98.7 % for those who received immediate surgery, and 97.4 % for those who did not. The survival between those with immediate surgery and those without were not different ($p = 0.539$).

Table 3 Multivariate analysis of predictors for lymph node metastasis in patients with non-curative resection and in those with immediate surgery after non-curative resection

	Overall			Immediate surgery		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
Location of tumor			0.017			0.034
Body and fundus	1			1		
Antrum	12.65	1.57–102.00		9.72	1.19–79.8	
Depth of invasion[a]			0.016	NA		
Mucosa or sm1	1					
Sm2 or more	4.98	1.34–18.47				
Venous invasion			0.001			0.023
No	1			1		
Yes	7.87	2.20–27.86		4.55	1.23–16.80	

CI confidence interval, *NA* not available

[a] *Sm1* submucosal invasion <500 µm from the muscularis mucosa; *sm2* submucosal invasion ≥500 µm from the muscularis mucosa

Table 4 The observed and estimated rate of lymph node metastasis according to the number of identified predictors in patients with non-curative resection and in those with immediate surgery after non-curative resection

	Overall		Immediate surgery	
	Observed rate (%)	95 % CI (%)	Observed rate (%)	95 % CI (%)
Number of predictors[a]				
0	1/37 (2.7)	0–8.2	1/7 (14.3)	0–49.2
1	1/140 (0.7)	0–2.1	1/48 (2.1)	0–6.3
2	11/80 (13.8)	6.0–21.5	9/59 (15.3)	5.8–24.7
3	5/10 (50.0)	12.3–87.7	4/9 (44.4)	3.9–85.0
p-trend	<0.001		0.004	
Number of predictors[a]				
<2	2/177 (1.1)	0–2.7	2/55 (3.6)	0–8.7
≥2	16/90 (17.8)	9.7–25.8	13/68 (19.1)	9.5–28.7
p value	<0.001		0.009	

CI confidence interval

[a] Predictors include venous invasion, sm2 invasion, and antral tumor location

For the patients with one or no predictor, there were one metastatic disease and one death from gastric cancer. The disease-specific survival was not significantly different between those who received immediate surgery and those who did not (5-year survival rate, 97.1 % versus 100.0 %; $p = 0.128$; Fig. 3A). For the patients with two or more predictors, there were one metastatic disease and two deaths from gastric cancer. The disease-specific survival was significantly higher in those who received immediate surgery than in those who did not (5-year survival rate, 100.0 % versus 81.1 %; $p = 0.004$; Fig. 3B).

Discussion

In the current study, we evaluated the predictive factors of LN metastasis in patients with non-curative endoscopic resection of EGC. The results showed that the risk of LN metastasis was significantly increased, when the tumor had venous invasion or sm2 invasion or was located at antrum. Moreover, we showed that the risk stratification for LN metastasis was feasible based on the identified predictors.

Non-curative endoscopic resection beyond the expanded criteria is an inevitable consequence because the evaluations using endoscopy, EUS, and even diagnostic biopsies before the procedure are not always accurate [23, 24]. Considering favorable long-term survival after surgical treatment of EGC [25], it is intuitive decision to make all the patients with non-curative resection receive surgery. However, low rate of LN metastasis found in surgical specimen led researchers to try to define the patients with low risk of LN metastasis even after non-curative resection so that they can avoid unnecessary operation [10–13]. Oda et al. [11] reported that the patients only with positive lateral resection margins showed no LN metastasis and suggested that they can be treated endoscopically without surgery. However, there was no attempt to identify independent risk factors for LN metastasis from the cohort. Although Son et al. [13] identified tumor size >2 cm as a significant risk factor for LN metastasis, the result is not clinically applicable because many tumors sized between 2 and 3 cm are currently being treated with endoscopic resection if they are differentiated mucosal cancer. In our study, we performed multiple logistic regression analysis with the potential risk factors compatible with the current practice and revealed that venous invasion, sm2 invasion, and antral location were independent predictive factors for LN metastasis. These results are consistent with those of

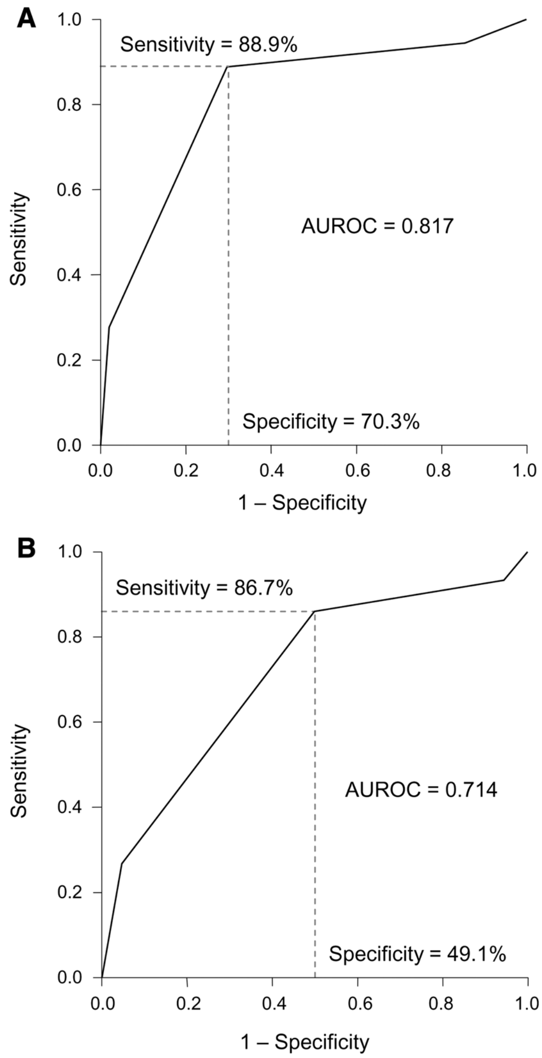

Fig. 2 The receiver-operating characteristic curves of the number of identified risk factors for predicting lymph node metastasis **A** in patients with non-curative resection and **B** in those with immediate surgery after non-curative resection. *AUROC* area under the receiver-operating characteristic curve

small sized studies; one study demonstrated that venous invasion was a risk factor for LN metastasis in a cohort of 41 patients with 4 LN metastases [12], and another study showed that three of four patients with LN metastasis among 43 patients had sm2 cancers [10]. Meanwhile, antral location has never been reported as a risk factor of LN metastasis in the studies involving surgically or endoscopically resected EGCs. The possible explanation for this is that tumors located at antrum might be more eligible for endoscopic resection than those located at body or fundus, even though they were estimated to be more advanced in size or depth. This is supported by the previous report that the antral location of tumor was strongly associated with the shorter procedure time and lower perforation rate compared to the other locations [26]. In practice, the procedure time and risk of potential complication, as well as the absolute or expanded indications, are important considerations in selecting endoscopic resection for treatment modality. It has been also proposed that antral cancer is different compared to corpus or cardiac cancer from the pathophysiologic perspective [27, 28]. From this point of view, however, antral cancer showed lower stage and more favorable outcome than cancers in other locations. Thus, it is suggested that the antral disease as a predictor of LN metastasis might be a technical factor rather than a physiologic one.

When the rate of LN metastasis was assessed with respect to the number of the identified predictive factors, we could suggest risk stratification for LN metastasis. The observed rate of LN metastasis was as high as 17.8 % in the patients with two or more predictors, while the rate was as low as 1.1 % in those with only one or no predictor. Therefore, if the non-curative resection was associated with two or more factors among venous invasion, sm2 invasion, or antral location, additional curative surgery would be highly recommended due to the increased risk of LN metastasis as soon as possible but no later than 3 months from endoscopic resection. Currently, there is no evidence to support delayed surgery after non-curative resection especially when the risk of LN metastasis is high. On the contrary, if no or only one factor was present, the risk of nodal metastasis (1.1 %) can be weighed against the risk of gastrectomy and lymphadenectomy, which was reported to be 0.6 % for mortality and 1.3 % for intraabdominal bleeding in a recent research from Korea [29]. Thus, for those who are vulnerable to post-operative complications, close follow-up with regular abdominal CT scan might be applied cautiously.

In the subgroup analysis, we could exhibit that the risk factors in the patients with immediate surgery where regional LN metastasis was confirmed pathologically were consistent with the abovementioned risk factors, except for sm2 invasion. It seems that sm2 invasion lost its statistical discrimination power, since most of the patients who underwent surgery had sm2 invasion. Nevertheless, the risk stratification based on those factors could present still acceptable performance in predicting LN metastasis in the subgroup. This strengthens our results from the main analysis, implying that the identified predictors and risk stratification might be used reliably.

Last but not least, we explored whether the risk stratification would be able to impact favorably on clinical outcome and patient survival. In the patients with one or no predictor, the disease-specific survival was not influenced by whether or not the patient had received immediate surgery. On the contrary, in the patients with two or more predictors, the disease-specific survival was significantly better when the surgery was conducted immediately than

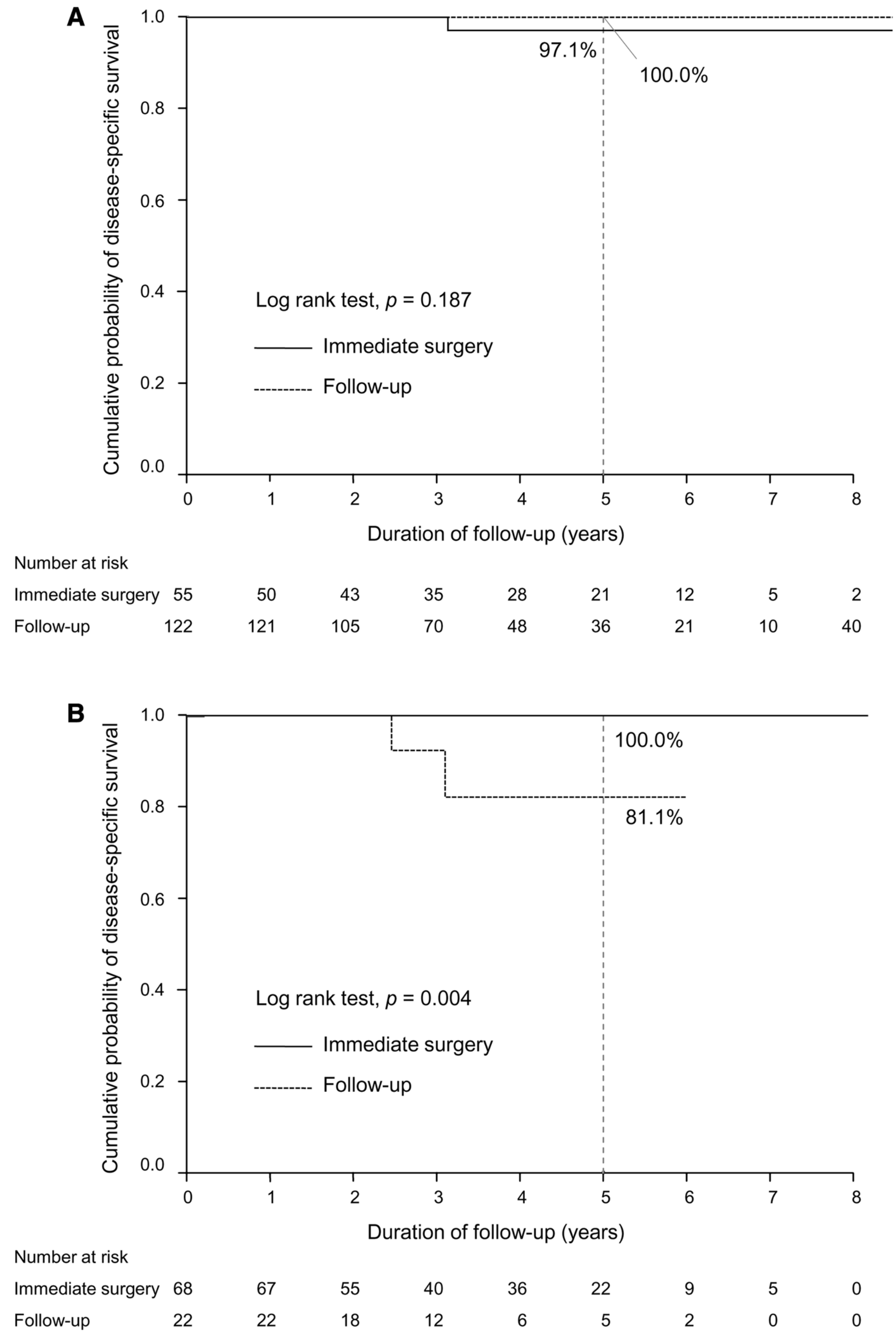

Fig. 3 The cumulative probability of disease-specific survival **A** in the patients with one or no predictor and **B** in the patients with two or more predictors of lymph node metastasis according to the immediate surgery after non-curative resection

when that was not. These contrasting findings imply that the risk stratification for LN metastasis after non-curative resection might reduce surgical resection while maintaining patient survival.

There are several limitations in our study. First, due to the retrospective observational design, the extensive demographic data such as smoking, blood type, or family history of gastric cancer were not available for the analysis. Second, we defined the absence of LN metastasis not only pathologically but also radiologically. However, considering approximately 90 % negative predictability of stomach protocol CT [17], among the patients with normal CT findings at 12 months of follow-up, there is a possibility, although low, that LN metastasis might have existed without being detected. As an alternative, combining EUS, PET, or both may be considered [17, 30]. Third, the predictive model for LN metastasis we fitted lacked external validation and had the risk of overfitting. Although we presented that our risk stratification was feasible also in the subgroup with immediate surgical resection, there was no external validation for this criteria. Considering that our criteria were designed to fit our own cohort optimally and that we included three covariates for 18 events, there might be a risk of overfitting [31]. Fourth, although we showed survival data, the follow-up duration was relatively short, and the events were very rare. Therefore, the generalizability of the current result needs to be confirmed in a larger prospective cohort with longer follow-up.

In conclusion, the patients with two or more predictors among venous invasion, sm2 invasion, and antral location after non-curative resection are recommended for additional gastrectomy and lymphadenectomy due to the increased risk of LN metastasis. Nevertheless, close follow-up without immediate surgery might be considered cautiously for those with only one or no predictor.

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