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Risk factors for lymph node metastasis in mucosal gastric cancer and re-evaluation of endoscopic submucosal dissection

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Purpose: The selection of the appropriate treatment strategy for patients with mucosal gastric cancer (MGC) remains controversial. In the present study, we aimed to determine the risk factors for lymph node (LN) metastasis in MGC and reassess the role of endoscopic submucosal dissection (ESD).
Methods: We examined 1,191 MGC patients who underwent curative gastrectomy between January 2005 and December 2014. We determined the clinicopathologic risk factors for LN metastasis among the MGC patients.
Results: Among 1,191 patients with MGC, 42 patients (3.5%) had LN metastasis. Univariate analysis indicated that age ≤ 50 years (P = 0.045), tumor invasion to the muscularis mucosa (P < 0.001), tumor size > 2 cm (P = 0.014), presence of ulceration (P = 0.01), diffuse type as per Lauren classification (P = 0.005), and undifferentiated-type histology (P = 0.001) were associated with LN metastasis. Moreover, multivariate analysis indicated that tumor invasion to the muscularis mucosa (P = 0.001; odds ratio [OR], 4.909), presence of ulceration (P = 0.036; OR, 1.982), and undifferentiated-type histology (P = 0.025; OR, 4.233) were independent risk factors for LN metastasis. In particular, LN metastasis was observed in some MGC cases with indications for ESD, including absolute indications (1 of 179, 0.6%) and expanded indications (9 of 493, 1.8%).
Conclusion: Although MGC patients can be treated via ESD, we recommend that they undergo a more aggressive treatment strategy if they have tumor invasion to the muscularis mucosa, ulceration, or undifferentiated-type histology in the final pathology report.
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Key Words: Lymph nodes, Neoplasm metastasis, Stomach neoplasms, Risk factors

INTRODUCTION

The increased interest in cancer screening—represented by the national cancer screening program in Korea that includes biannual upper endoscopy for all individuals aged >40 years—and the development of endoscopic equipment and techniques have facilitated the early detection of gastric cancer. Early gastric cancer (EGC) is defined as a cancer confined to the mucosal or submucosal layers of the stomach, regardless of the presence of lymph node (LN) metastasis [1].

The prognosis of patients with EGC has improved with surgical treatment. In fact, the 5-year survival rate after curative

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resection is >90% in cases of EGC [2,3]. However, in cases with mucosal gastric cancer (MGC), minimally invasive treatments such as endoscopic submucosal dissection (ESD) have been actively substituted for conventional radical gastrectomy with LN dissection, particularly among those with advanced age and comorbidities, and those wishing to maintain their quality of life after treatment, in countries with a high prevalence rate of gastric cancer [4-6].

Despite the development of novel diagnostic and treatment methods, we often treat the patients diagnosed preoperatively as MGC without LN metastasis, but they are pathologically confirmed as having LN metastasis after the surgery (Fig. 1). The prognostic factors for EGC include depth of tumor invasion, LN metastasis, grade of histologic differentiation, and curative surgery, and many studies have reported that LN metastasis is the most important risk factor for MGC recurrence [7-9].

Endoscopic ultrasonography (EUS), computerized tomography, and positron emission tomography are used to predict LN metastasis before surgery, or frozen sections may be used to evaluate LN metastasis intraoperatively. However, the diagnostic accuracy is a limitation of these methods, and hence, the minimally invasive trend in treatment for MGC such as ESD could consequently lead to an increased risk of early recurrence in MGC. Accordingly, the prediction of LN metastasis would be useful for selecting the appropriate therapeutic strategy in MGC.

In the present study, we examined surgically resected cases of MGC, wherein tumor invasion was confined to the mucosa, in terms of their clinicopathological outcomes, as well as the frequency and risk factors of LN metastasis. Moreover, we evaluated the indications for ESD that were recently established, and re-assessed their role in the treatment of MGC.

METHODS

We enrolled a total of 1,191 patients with MGC who underwent curative gastrectomy between January 2005 and December 2014. They were diagnosed with MGC without LN metastasis preoperatively based on the findings of imaging studies such as esophagogastroduodenoscopy, CT, or EUS. Among these patients, 42 (3.5%) were pathologically confirmed as having LN metastasis after resection.

To determine the possible relationship between LN metastasis and MGC, we analyzed the demographic and clinicopathological characteristics of all the patients. These data included sex, age, tumor location, macroscopic type, depth of tumor invasion, tumor size, presence of ulceration, Lauren classification, histologic type (differentiated or undiffer-

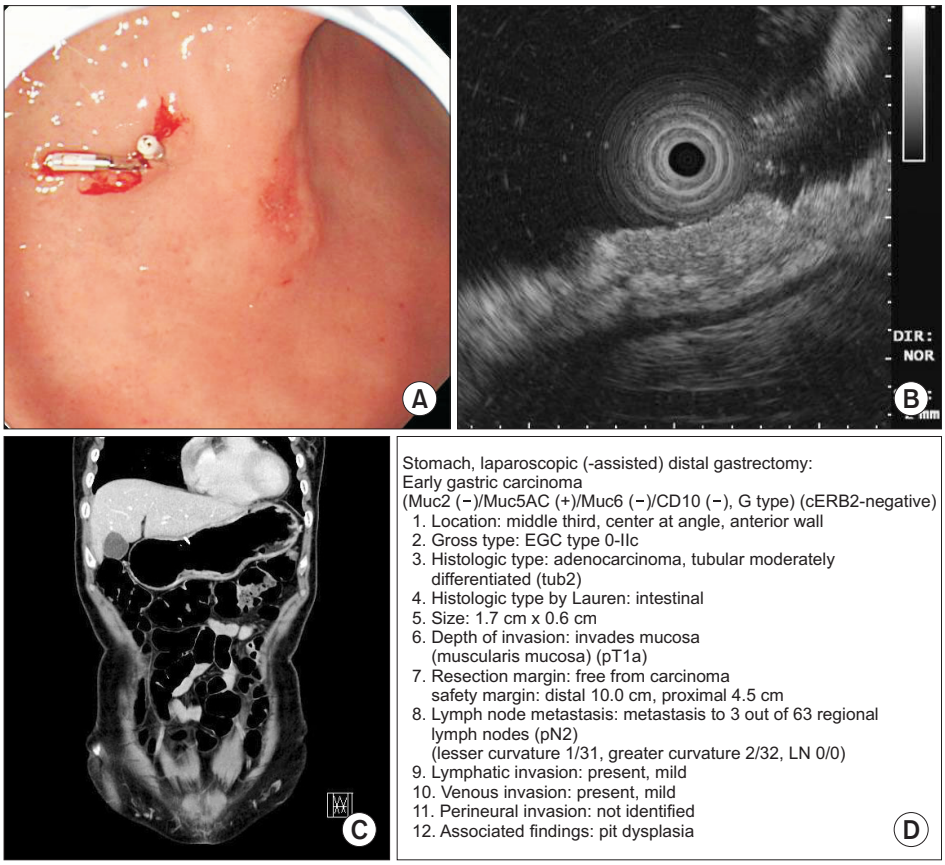

Fig. 1. A 51-year-old woman with a preoperative clinical diagnosis of mucosal gastric cancer without lymph node (LN) metastasis, who was eventually pathologically confirmed as having LN metastasis after surgery. (A) Endoscopic image: early gastric cancer (EGC) gross type IIc with irregular margin at the lesser curvature of the lower body. (B) Endoscopic ultrasound image: a hypoechoic disruption of the superficial and deep mucosal layers is noted. The third (submucosal) layer is intact. (C) Abdominal computed tomography image: no evidence of focal wall thickening or a mass in the stomach is observed. (D) Final histological report.

entiated), lymphatic invasion, vascular invasion, and perineural invasion. The stomach was anatomically divided into 3 portions—the upper, middle body (MB), and lower parts—using lines connecting the trisected points on the lesser and greater curvatures. Tumor location was described based on the parts involved. The primary lesions were macroscopically classified according to the Japanese Classification [10] as follows: type 0-I (protruded type), type 0-IIa (superficial elevated type), type 0-IIb (flat type), type 0-IIc (superficial depressed type), and type 0-III (excavated type). In the present study, the primary lesions were classified as follows: elevated type (protruded or elevated: I, IIa, IIa + IIb, and IIa + IIc), flat type (IIb, IIb + IIa, and IIb + IIc), and depressed type (depressed or excavated: IIc, IIc + IIb, IIc + III, IIc + IIa, and III). The depth of tumor invasion of MGC was classified as either invasion of the lamina propria or invasion of the muscularis mucosae without penetration (Fig. 2). The degree of differentiation was classified into 2 groups: differentiated type, which included papillary, well-differentiated or moderately differentiated type; and undifferentiated type, which included poorly differentiated or signet ring cell carcinoma and mucinous carcinoma. The indications for ESD were reassessed according to the Japanese gastric cancer treatment guidelines 2010 (ver. 3) outlined by the Japanese Gastric Cancer Association [11].

All statistical analyses were conducted using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). The chi-square test or Fisher exact test was used to compare differences in categorical variables, whereas Student t-test was used to compare differences in continuous variables. The independent risk factors associated with LN metastasis in MGC were analyzed using logistic regression analysis. Accordingly, the odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A P-value of <0.05 was considered significant for all statistical analyses.

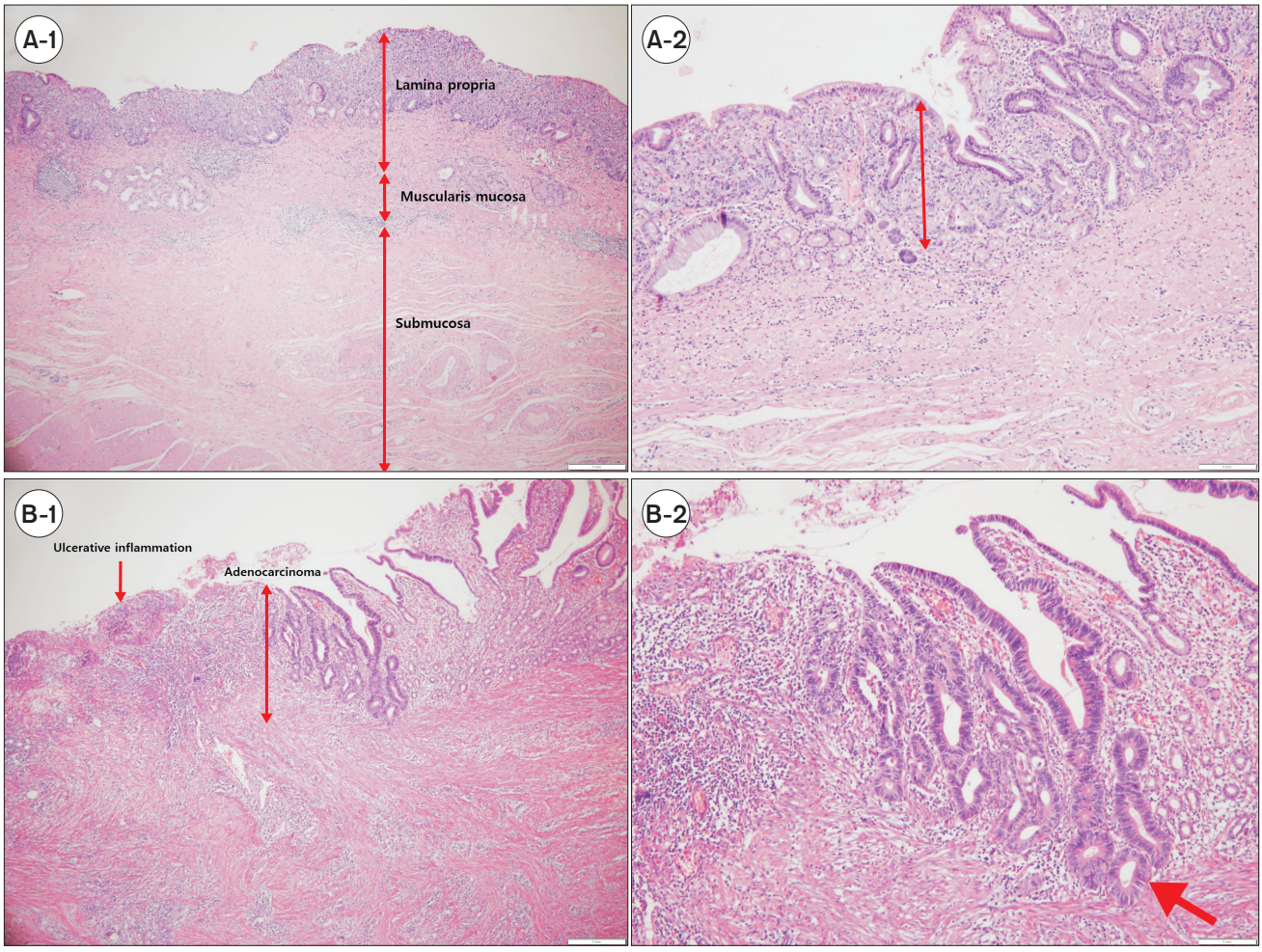

Fig. 2. Mucosal gastric cancer within the lamina propria. (A-1) Well-differentiated adenocarcinoma only invading the lamina propria (H&E, ×40). (A-2) Cancer only invading the lamina propria (H&E, ×100) and mucosal gastric cancer with muscularis mucosa invasion. (B-1, -2). mucosal gastric cancer with muscularis mucosa invasion; (B-1) Well-differentiated adenocarcinoma invading the lamina propria and muscularis mucosa, in the background of ulcerative inflammation (H&E, ×40). (B-2). Tumor invading the muscularis mucosa, in the background of ulcerative inflammation (H&E, ×100) (arrow).

RESULTS

Comparisons between the LN metastasis-positive group and LN metastasis-negative group

The clinicopathological features of the 2 groups are presented in Table 1. Significant differences were observed between the LN metastasis-positive group and LN metastasis-negative group. In particular, the LN metastasis-positive group had younger age (P = 0.019), deeper invasion depth (muscularis mucosa invasion, P < 0.001), larger tumor size (P = 0.002), more frequent ulceration on preoperative endoscopy (P = 0.01), more diffuse type as per Lauren classification (P = 0.005), and more undifferentiated type (P = 0.001); however, the other features did not significantly differ between the groups.

Univariate and multivariate analyses of risk factors for LN metastasis in MGC

Patients from both the groups we further classified based on age (≤50 years or >50 years) and tumor size (≤2 cm or >2 cm). Univariate analysis of the clinicopathological features of MGC indicated that age ≤50 years (P = 0.045), tumor invasion to the muscularis mucosa (P < 0.001), tumor size >2 cm (P = 0.014), presence of ulceration (P = 0.01), diffuse type as per Lauren classification (P = 0.005), and undifferentiated-type histology (P = 0.001) were associated with LN metastasis in MGC. These 6 factors were entered into the multivariate analysis, which indicated that tumor invasion to the muscularis mucosa (P = 0.001; OR, 4.909), presence of ulceration (P = 0.036; OR, 1.982), and undifferentiated-type histology (P = 0.025; OR, 4.233) were independent risk factors for LN metastasis in MGC (Table 2).

Frequency of LN metastasis according to differentiation, ulceration, and tumor size based on the indications for ESD

The patients with MGC were divided into 2 groups based on tumor invasion depth: invasion of the lamina propria and invasion of the muscularis mucosae without penetration. Moreover, the frequency of LN metastasis in each group was assessed according to differentiation, ulceration, and tumor size, based on the indications for ESD (Fig. 3). Among the cases of MGC invading the lamina propria, 5 of 444 (1.1%) exhibited LN metastasis, whereas only 1 of 186 (0.5%) had extended indications for ESD (Fig. 3, Table 3). Furthermore, among the cases of MGC invading the muscularis mucosae without penetration, 37 of 747 (5.0%) exhibited LN metastasis, whereas only 1 of 107 (0.9%) had absolute indications and 8 of 307 (2.6%) had expanded indication for ESD (Fig. 3).

Table 1. Relationship between clinicopathologic factors and lymph node metastasis in 1,191 cases of mucosal gastric cancer

Variable	Lymph node metastasis		P-value
	Positive (n = 42)	Negative (n = 1,149)	
Sex			
Male:female	23:19 (54.8:45.2)	714:435 (62.1:37.9)	0.333
Age (yr)	53.1 ± 12.0	57.2 ± 11.3	0.020
Location			
UB:MB:LB	3:12:27 (7.1:28.6:64.3)	80:334:735 (7.0:29.1:64.0)	0.997
Macroscopic type			
Elevated:flat:depressed	6:4:32 (14.3:9.5:76.2)	188:262:699 (16.4:22.8:60.8)	0.088
Depth of invasion			
Lamina propria:muscularis mucosa	5:37 (11.9:88.1)	439:710 (38.2:61.8)	<0.001
Tumor size (cm)	3.78 ± 2.06	2.79 ± 2.07	0.002
Ulcer			
Positive:negative	18:24 (42.9:57.1)	290:859 (25.2:74.8)	0.010
Lauren classification			
Intestinal:diffuse	12:30 (28.6:71.4)	584:565 (50.8:49.2)	0.005
Differentiation			
Differentiated:undifferentiated	9:33 (21.4:78.6)	554:595 (48.2:51.8)	0.001
Lymphatic invasion			
Positive:negative	1:41 (2.4:97.6)	8:1141 (0.7:99.3)	0.277
Vascular invasion			
Positive:negative	1:41 (2.4:97.6)	3:1146 (0.3:99.7)	0.134
Perineural invasion			
Positive:negative	0:42 (0:100)	1:1148 (0.1:99.9)	0.965

Values are presented as number (%) or mean ± standard deviation.
UB, upper body; MB, middle body; LB, lower body.

Table 2. Univariate and multivariate analyses of risk factors for mucosal gastric cancer (logistic regression analysis; P < 0.10)

Pathologic factor	Univariate analysis			Multivariate analysis		
	P-value	95% CI	Odds ratio	P-value	95% CI	Odds ratio
Age, <50 yr *vs*. ≥50 yr	0.045	1.005–3.595	1.901	0.175		
Lamina propria *vs*. muscularis mucosa	0.001	1.785–11.73	4.575	0.001	1.877–12.833	4.909
Tumor size, ≤2 cm *vs*. >2 cm	0.014	1.175–5.583	2.561	0.215		
Ulcer *vs*. no ulcer	0.010	1.189–4.152	2.222	0.036	1.046–3.756	1.982
Intestinal *vs*. diffuse	0.005	1.310–5.097	2.584	0.723		
Differentiated *vs*. undifferentiated	0.001	1.619–7.199	3.414	0.025	1.196–14.987	4.233

CI, confidence interval.

Review of LN metastasis-positive cases with indications for ESD

A total of 10 patients (10 of 672, 1.5%) with indications for ESD, including 1 with absolute indications (1 of 179, 0.6%) and 9 with expanded indications (9 of 493, 1.8%), also had LN metastasis. The clinicopathological outcomes of these 10 patients are described in Table 4. Of these 10 patients, nine had tumor invasion of the muscularis mucosae without penetration and four had undifferentiated histologic features without any ulceration but with tumor size >2 cm. Moreover, 2 patients exhibited ulceration, although they exhibited differentiated-type histology and tumor size <3 cm.

DISCUSSION

The treatment guidelines were recently modified to indicate that therapeutic strategies such as ESD can be applied in patients with MGC who exhibit a low possibility of LN metastasis during preoperative diagnosis. This preference is associated with the increased interest in maintaining the quality of life and the potential complications after conventional standard gastrectomy [4-6].

Although LN metastasis is rare in MGC, it should nevertheless be considered when selecting the ideal treatment modality; hence, it is important to clarify the clinicopathologic characteristics of MGC patients with LN metastasis. In fact, LN metastasis is often encountered in the clinical setting, with an incidence of approximately 2.6%–4.6% [12,13]. The incidence of LN metastasis in MGC patients was 3.5% (42 of 1,191) in the present study, consistent with that reported previously.

Moreover, studies have indicated that tumor size, depth of tumor invasion, lymphatic invasion, and undifferentiated histology are risk factors for LN metastasis in EGC. However, the definite indications for ESD or the standard treatment of MGC are varied and inconsistent among those studies [7-9]. In the present study, we observed that tumor invasion to the muscularis mucosa, presence of ulceration, and undifferentiated-type histology were independent risk factors for LN metastasis. The number of lymphatic vessels in the mucosal layer is lower than that in the submucosal layer. Hence, the presence of tumor invasion to the muscularis mucosa and presence of ulceration indicate the destruction of the muscularis mucosa, which usually acts as a barrier against lymphatic vessel invasion (Fig. 2). Hence, these findings can be explained by the breakdown of the muscularis mucosa due to histological ulceration that resulted in interchange between lymph flow in the mucosa and submucosa, and consequently led to an increase in the risk of regional LN metastasis [3].

In fact, MGC patients with the above-mentioned risk factors had a significantly higher incidence of LN metastasis in the present study. In particular, LN metastasis was detected in 16 of 216 cases (7.4%) of MGC with invasion to the muscularis mucosa and the presence of ulceration, and in 11 of 105 cases (10.5%) of MGC with all three risk factors (tumor invasion to the muscularis mucosa, presence of ulceration, and undifferentiated-type histology; Fig. 3). Although the mean tumor size was larger in the LN metastasis group, it did not serve as an independent risk factor for LN metastasis in MGC when applied as 2 cm based on the conventional ESD indication (Table 3). In addition, there may be discrepancies in tumor size between surgically resected specimens and endoscopically resected specimens. In the case of surgical resection, the tumor size is measured after fixation with formalin, which could cause shrinkage. In contrast, in endoscopic resection, the specimen is creased and fixed with a pin, which could cause exaggeration of the size. Thus, endoscopically resected cases would be more likely to have expanded indications for tumor size, as compared to surgically resected cases [14]. Hence, this discrepancy in tumor size should be carefully considered when applying the indications for ESD.

Furthermore, lymphatic invasion in cases with MGC is very rare. In the present study, only 9 of 1,149 MGC patients (0.8%) showed lymphatic invasion, and this feature did not have any significant effect on LN metastasis.

In addition, the conventional indications of endoscopic resection for EGC (which are based on the established treatment guidelines for gastric cancer in Japan) are described in Table 3 [11]. However, these indications are primarily based on data

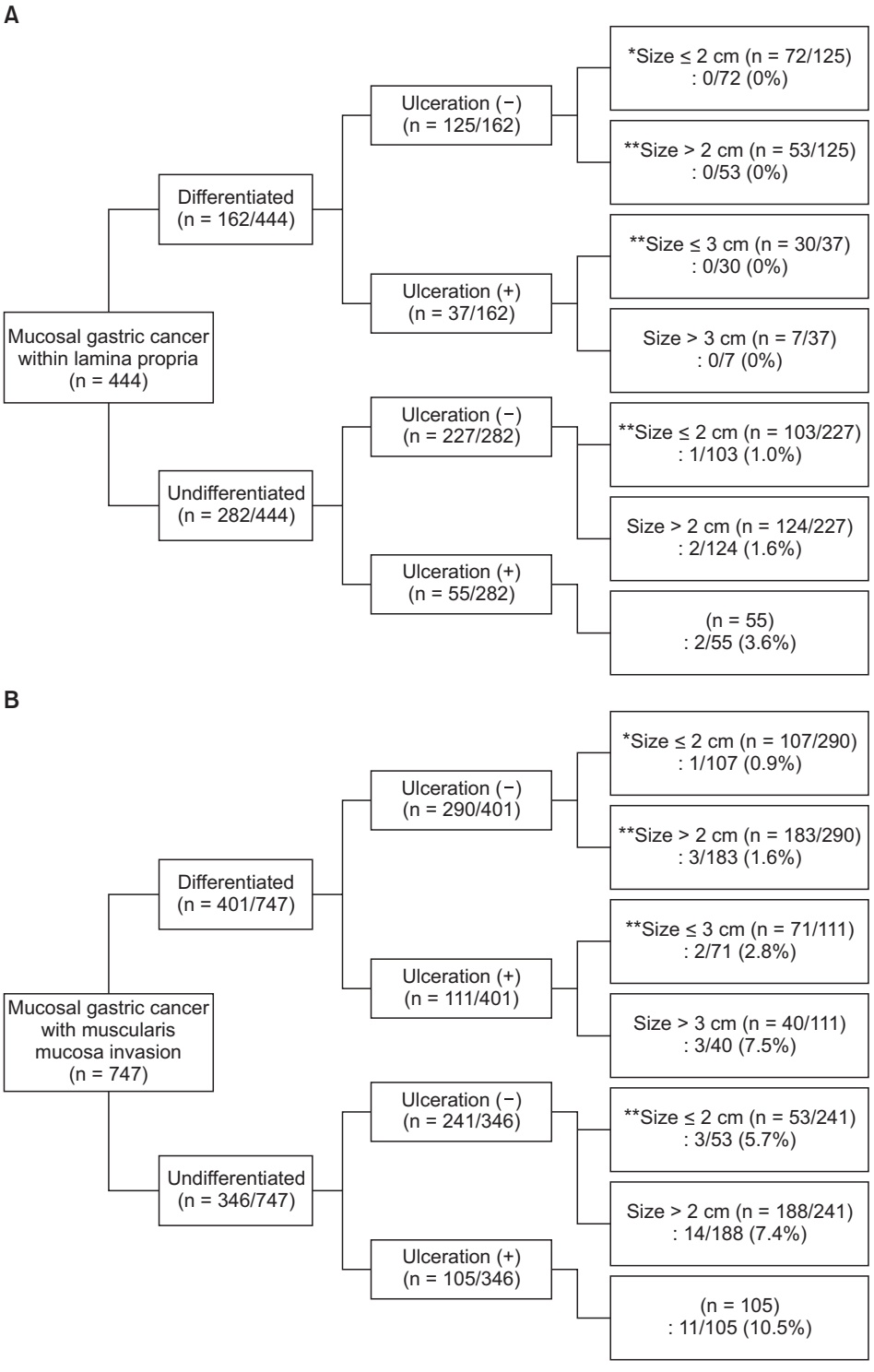

Fig. 3. (A) The frequency of lymph node metastasis according to differentiation, ulceration, and size, based on the indications of endoscopic submucosal dissection (ESD) in mucosal gastric cancer within lamina propria. (B) The frequency of lymph node metastasis according to differentiation, ulceration, and size, based on the indications of ESD in with muscularis mucosa invasion. *Absolute indications according to the new Japanese classification and treatment guidelines for gastric cancer. **Expanded indications according to the new Japanese classifications and treatment guidelines for gastric cancer.

from Japanese patients, and hence may not be completely applicable in Korea or other countries. In the present study, 672 MGC patients had indications for ESD, including 1 of 179 (0.6%) with absolute indications and 9 of 493 (1.8%) with expanded indications; of these, 10 patients (10 of 672, 1.5%) had LN metastasis. The incidence of LN metastasis among these cases of MGC with indications for ESD exceeds the risk of mortality of standard surgery for gastric cancer in Korea (0.6%) [15]. Hence, to ensure that the prognosis is better than that of surgical resection, LN metastasis should be thoroughly ruled out before switching conventional radical gastrectomy with ESD. However, as noted in Table 4 in the present study, there are certain limitations to the prediction of LN metastasis in MGC even when considering the indications for ESD or the current risk

Table 3. Incidence of lymph node metastasis in mucosal gastric cancer: the present and reassessment of the criteria for endoscopic submucosal dissection

Criteria	Incidence
Present	
Absolute indication	
A differentiated-type adenocarcinoma without ulcerative findings (UL (–)), wherein the depth of invasion is clinically diagnosed as T1a and the tumor diameter is ≤2 cm.	1/179 (0.6%)
Expanded indication	
Tumors clinically diagnosed as T1a and:	
(a) differentiated-type, UL (–), but >2 cm in diameter	3/236 (1.1%)
(b) differentiated-type, UL (+), and ≤3 cm in diameter	2/101 (2.0%)
(c) undifferentiated-type, UL (–), and ≤2 cm in diameter	4/156 (2.6%)
Reassessment	
Absolute indication	
A differentiated-type adenocarcinoma without ulcerative findings (UL (–)), wherein the depth of invasion is clinically diagnosed as T1a(within the lamina propria) and the tumor diameter is ≤2 cm.	0/72 (0%)
Expanded indication	
Tumors clinically diagnosed as T1a (within the lamina propria) and:	
(a) differentiated-type, UL (–), but >2 cm in diameter	0/53 (0%)
(b) differentiated-type, UL (+), and ≤3 cm in diameter	0/30 (0%)
(c) undifferentiated-type, UL (–), and ≤2 cm in diameter	1/103 (1.0%)

UL, ulcer.

Table 4. Lymph node-positive cases with indications for endoscopic submucosal dissection

Patient No.	Age (yr)	Depth	WHO classification	Ulcer	Size (cm)	Ly	Vs	Pn	Lo	LN (P/T)	Lauren classification	Gross type
1	51	Muscularis mucosa	MD	–	1.7	+	+	–	MB	3/63	Intestinal	Depressed
2	33	Muscularis mucosa	MD	–	5	–	–	–	UB	1/97	Diffuse	Depressed
3	58	Muscularis mucosa	MD	–	4.8	–	–	–	LB	1/23	Intestinal	Elevated
4	64	Muscularis mucosa	MD	–	5.8	–	–	–	MB	2/59	Intestinal	Elevated
5	52	Muscularis mucosa	MD	+	2.8	–	–	–	MB	1/30	Intestinal	Depressed
6	72	Muscularis mucosa	MD	+	1.5	–	–	–	MB	1/21	Intestinal	Depressed
7	46	Muscularis mucosa	PD	–	1	–	–	–	LB	1/32	Diffuse	Depressed
8	62	Muscularis mucosa	SRC	–	1.5	–	–	–	LB	5/74	Intestinal	Flat
9	43	Muscularis mucosa	SRC	–	1.7	–	–	–	MB	2/68	Diffuse	Depressed
10	46	Lamina propria	SRC	–	1.5	–	–	–	MB	1/21	Diffuse	Depressed

WHO, World Health Organization; Ly, lymphatic invasion; Vs, vascular invasion; Pn, perineural invasion; Lo, tumor location; LN (P/T), lymph node (positive lymph node/total harvest lymph node); MD, moderately differentiated; MB, middle body of the stomach; UB, upper bodyof the stomach; LB, lower bodyof the stomach; PD, poorly differentiated; SRC, signet ring cell carcinoma.

factors for LN metastasis.

Previous studies have indicated that the recurrence rate of EGC with LN metastasis was relatively higher than that of EGC without LN metastasis due to the pathologic characteristics. Hence, LN metastasis is the most powerful and important prognostic factor; moreover, the long-term follow-up results after ESD remain unclear due to insufficient data, whereas the long-term survival rate has improved to 99%–100% in cases

treated by conventional radical gastrectomy with LN dissection [16-19]. These findings suggest that ESD may represent an incomplete treatment in MGC patients if LN metastasis is present, which would have a negative influence on the recurrence and prognosis of MGC.

Thus, the selection of the ideal treatment option for MGC depends on the accurate diagnosis of tumor invasion to the muscularis mucosa, presence of ulceration, and undifferentiated-type histology. However, these factors cannot be estimated by forceps biopsy during routine endoscopy, EUS, or abdominal CT before surgery. Instead, these features can be identified during the final histological examination of resected specimens. Hence, ESD can yield precise histological information, as the resected ESD specimen (obtained via *en bloc* resection) includes the full thickness of the submucosal layer, and hence facilitates the evaluation of all 3 factors of LN metastasis. However, if MGC patients have specific conditions such as old age or significant comorbidities that could result in postoperative complications, or if the MGC patients are surgically inoperable, ESD should be carefully considered as an alternative treatment option based on their life expectancy, and additional therapy such as conventional radical gastrectomy with LN dissection can be scheduled depending on the final pathologic results after ESD. Thus, in addition to assessing whether MGC should be treated by ESD or conventional radical gastrectomy, this study also considers whether ESD can be utilized not only as a diagnostic modality, but also as a therapeutic strategy in cases without these risk factors.

CONFLICTS OF INTEREST

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

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