

Original Article



Extragastric Metastasis of Early Gastric Cancer After Endoscopic Submucosal Dissection With Lymphovascular Invasion and Negative Resected Margins

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ABSTRACT

Purpose: Lymphovascular invasion is a criterion for non-curative resection in patients who have undergone endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). We aimed to determine the rate of extragastric metastasis (EGM) and identify the predictors of EGM in patients with negative resection margins (R0 resection) and lymphovascular invasion in post-ESD pathology.

Materials and Methods: A total of 2,983 patients underwent ESD for EGC. Among them, 110 had a pathology of R0 resection and positive lymphovascular invasion. Patients underwent additional gastrectomy (n=63) or further follow-up without gastrectomy (n=47).

Results: The 110 patients were assigned to one of the 3 groups according to ESD indications based on post-ESD pathology. The first group satisfied the absolute indication for ESD (n=18), the second group satisfied the expanded indications for ESD (n=34), and the last group satisfied the beyond indication (n=58). The number of occurrences of EGM in each group was 1 (5.6%), 3 (8.8%), and 3 (5.2%), respectively. The logistic regression analysis adjusted for age, sex, tumor size, and indication for ESD, showed that larger tumor size was associated with EGM (odds ratio, 1.76; 95% confidence interval, 1.00–3.10; P=0.048). In contrast, ESD indication criteria did not affect EGM (P=0.349).

Conclusions: Tumor size was the only predictive indicator for EGM in patients who underwent R0 resection and lymphovascular invasion on post-ESD pathology. Even patients with pathology corresponding to the absolute indication criteria of ESD had lymphovascular invasion, which means that they require additional gastrectomy due to the risk of EGM.

Keywords: Stomach neoplasms; Lymphatic metastasis; Neoplasm metastasis; Endoscopic submucosal dissection

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Conflict of Interest

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

Author Contributions:

Conceptualization: L.H.M., C.S.J.; Data curation: L.H.M.; Formal analysis: L.H.M.; Investigation: L.H.M.; Methodology: K. Y., K.S.G., C.H., C.S.J.; Resources: K.Y., K.S.G., C.H., C.S.J.; Supervision: C.S.J.; Validation: L.H.M., C.S.J.; Visualization: L.H.M., C.S.J.; Writing - original draft: L.H.M.; Writing - review & editing: L.H.M., C.S.J.

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a standard treatment for patients with early gastric cancer (EGC) who have a negligible risk of lymph node metastasis [1-3]. Additional surgery may be required after ESD in cases of non-curative resection, such as deeper submucosal invasion than predicted, positive lymphovascular invasion, or worse histologic differentiation [4-6]. Lymphovascular invasion is one of the criteria for non-curative resection in patients who undergo ESD for EGC [7,8]. However, none of the patients who were treated with non-curative ESD with negative resection margins (R0 resection) had lymph node metastasis. Thus, identifying patients with a high risk of lymph node metastasis is important to determine whether additional gastrectomy is required. Liu et al. [9] reported that patients with lymphovascular invasion had a significantly lower 5-year survival rate than patients with lymphovascular invasion [9]. In contrast, Pyo et al. [10] reported that additional surgery after endoscopic resection might be unnecessary in patients with lymphovascular invasion who meet the absolute criteria for endoscopic resection. Here, we aimed to determine the rate of extragastric metastasis (EGM) and identify the predictors of EGM in EGC patients with R0 resection and lymphovascular invasion in post-ESD pathology.

MATERIALS AND METHODS

Study population and data collection

This single-center retrospective study was performed at Seoul National University Hospital, Korea. From January 2005 to July 2020, 2,983 consecutive patients underwent ESD for EGC at the Seoul National University Hospital with at least 12 months of follow-up. ESD was performed for well-differentiated or moderately differentiated tubular adenocarcinoma no larger than 3 cm on diagnostic endoscopic examination, which is expected to be confined to the mucosa [3,11]. Patients without an obvious medication history, past medical history, or pathologic reports were excluded. Basic demographic data, comorbidities, medications, laboratory data, endoscopic findings, and pathological findings of the ESD specimens were reviewed retrospectively. The Charlson comorbidity index was used for evaluation as described previously [12].

ESD was performed using an electrosurgical IT knife (KD-610L, KD-611L; Olympus, Tokyo, Japan), dual knife (KD-650Q; Olympus), or both. Among the 2,983 consecutive patients, 350 did not meet the expanded curability criteria. The curability of ESD was based on the Korean Practice Guidelines for Gastric Cancer [3]. Criteria for curative resection by absolute indication include the following: 1) lesion resection *en bloc*; 2) lesions <2 cm in diameter, predominantly differentiated type, pathologically intramucosal carcinoma (pT1a), without ulcerative findings (UL[-]); 3) not associated with lymphovascular invasion (ly0, v0); and 4) negative resected margins (R0 resection). The criteria for curative resection by expanded indications include the following: 1) lesion resection *en bloc*; 2) either of 4 possibilities including: i) lesion \geq 2 cm in diameter, predominantly differentiated type, pT1a, and UL(-), ii) lesion <3 cm, predominantly differentiated type, pT1a, and UL(+), or iii) lesion <2 cm, predominantly undifferentiated type, pT1a, and UL(-), or iv) lesion <3 cm, predominantly differentiated type, pathologically minute submucosal (SM) cancer less than 500 mm (pT1b/SM1); 3) no lymphovascular invasion; and 4) negative resected margins (R0 resection).

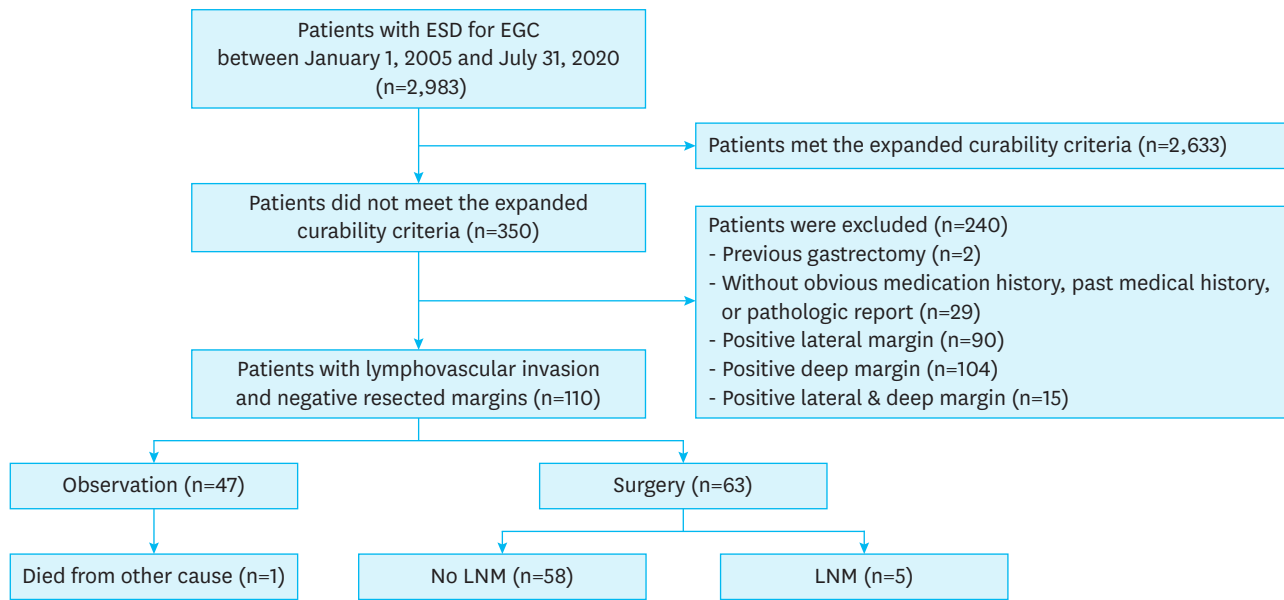


Fig. 1. Flowchart and clinical outcomes of patients enrolled in this study. EGC = early gastric cancer; ESD = endoscopic submucosal dissection; LNM = lymph node metastasis.

We defined curative ESD as cases that met either absolute or expanded indications and non-curative ESD as cases that did not satisfy any of these criteria. We excluded patients with a history of gastrectomy for gastric cancer (n=2), patients without an obvious medication history, past medical history, or pathologic report (n=29), and patients with positive resection margins (n=209). Finally, 110 patients were enrolled in this study (Fig. 1). The enrolled patients were treated with non-curative ESD with R0 resection and lymphovascular invasion in post-ESD pathology. The Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB number 2106-114-1227) and waived the need for informed consent. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Categorical data were analyzed using Pearson's χ^2 test or Fisher's exact test and are presented as numbers with percentages. Continuous data were compared using Student's t-test and were presented as mean \pm standard deviation or median with interquartile range. Survival curves were plotted using the Kaplan-Meier method, and differences in survival among the groups were tested using log-rank tests.

Overall survival was measured from the date of ESD to the date of death from any cause or to the censoring date of 31 August 2021. Disease-free survival was measured from the date of ESD to the date of recurrence with lymph node metastasis or to the censoring date of 31 August 2021. The association between potential risk factors and the presence of EGM was tested using logistic regression analysis. In the multivariate analysis, we adjusted for possible confounding factors, including the patient's age and sex, tumor size, histology, depth of invasion, and ESD indication. A Cox proportional hazard model was used to estimate the hazard ratio (HR) and 2-sided 95% confidence intervals (CI). Statistical significance was set at P-value <0.05. All statistical analyses were performed using SPSS version 22 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics and clinicopathologic characteristics

A total of 110 patients were treated with ESD, with pathology showing R0 resection and lymphovascular invasion: 98 (89.1%) had only lymphatic invasion, 9 (8.2%) had only venous invasion, and 3 (2.7%) had both lymphatic and vascular invasion. Patients underwent either additional gastrectomy (n=63, surgery group) or follow-up without gastrectomy (n=47, observation group). All patients were followed for a median period of 53 months (range, 12–171 months). The patient baseline characteristics are summarized in **Table 1**. Patients in the observation group tended to be older (70.2±9.8 vs. 63.6±8.5 years, P<0.001), had higher (≥5) Charlson comorbidity index (70.2% vs. 39.7%, P=0.002), and had less submucosal invasion (51.1% vs. 87.3%, P<0.001) than those in the surgery group. No significant differences were observed between the groups with respect to sex, tumor location, macroscopic appearance of the tumor, tumor size, presence of ulceration, and tumor histology.

Comparison of EGM in the observation and surgery groups

Five patients (7.9%) in the surgery group had lymph node metastases in their gastrectomy specimens. One patient (1.6%) in the surgery group who had SM1 invasion with lymphatic invasion on the initial ESD specimen did not have lymph node metastasis in postgastrectomy pathology, but had recurrence with lymph node metastasis 25 months after gastrectomy. The patient did not have pathological lymph node metastasis in the postsurgical specimen. The patient underwent distal gastrectomy with D1+ lymph node dissection, and EGM occurred in

Table 1. Comparison of clinicopathologic features between patients followed up without gastrectomy and patients who received additional gastrectomy

Variables	Observation	Surgery	P-value
Total	47 (42.7)	63 (57.3)	
Age (yr)	70.2±9.8	63.6±8.5	<0.001
Charlson comorbidity index			0.002
≤4	14 (29.8)	38 (60.3)	
≥5	33 (70.2)	25 (39.7)	
Sex			0.270
Male	33 (70.2)	50 (79.4)	
Female	14 (29.8)	13 (20.6)	
Tumor location			0.475
Upper third	1 (2.1)	5 (7.9)	
Middle third	13 (27.7)	15 (23.8)	
Lower third	33 (70.2)	43 (68.3)	
Macroscopic appearance			0.803
Elevated	10 (21.3)	16 (25.4)	
Flat	11 (23.4)	12 (19.0)	
Depressed	26 (55.3)	35 (55.6)	
Tumor size (mm)	2.2±1.3	2.1±1.1	0.425
Ulceration			>0.999
(-)	44 (93.6)	60 (95.2)	
(+)	3 (6.4)	3 (4.8)	
Depth of invasion			<0.001
Lamina propria	3 (6.4)	1 (1.6)	
Muscularis mucosa	20 (42.6)	7 (11.1)	
Submucosa, SM1	14 (29.8)	20 (31.7)	
Submucosa, SM2	10 (21.3)	35 (55.6)	
Histology			0.121
Differentiated	43 (91.5)	51 (81.0)	
Undifferentiated	4 (8.5)	12 (19.0)	
Follow-up duration (mon)	57 (12–171, 53)	51 (14–157, 77)	0.356

Values are presented as number (%), mean ± standard deviation, or median (range, interquartile range).

Table 2. Clinical features of all patients who had extragastric metastasis

Case No.	Age/ Sex	CCI	Gross type	Ulcer	Loca- tion	CLO	ESD indication	Size (cm)	Pathol- ogy	Depth	Lymphatic invasion	Venous invasion	Surgery	LN dissection	Surgery LN_n	LN_ location	Recur- rence	Recurrence time
1	69/M	5	Depressed	(-)	Lower	(+)	Expanded	1.8	Adeno MD	SM1	(+)	(-)	STG-BI	D1	0	(-)	LNM, #17	26
2	62/M	4	Flat	(-)	Lower	(+)	Expanded	5.5	Adeno MD	MM	(+)	(-)	(-)	(-)	(-)	(-)	LNM, #6	60
3	66/M	4	Elevated	(-)	Lower	(-)	Absolute	1.5	Adeno WD	MM	(+)	(-)	STG-BI	D1+beta	1	#5	(-)	
4	55/M	4	Elevated	(-)	Lower	(+)	Expanded	3	Adeno MD	MM	(+)	(-)	STG-BI	D2	1	#3	(-)	
5	69/M	4	Depressed	(-)	Mid	(-)	Beyond	5.4	PCC	SM1	(+)	(+)	STG-BI	D2	1	#3	(-)	
6	68/M	4	Flat	(-)	Lower	(-)	Beyond	1.3	Adeno MD	SM2	(-)	(+)	STG-BI	D1+	1	#6	(-)	
7	65/M	4	Depressed	(-)	Lower	(-)	Beyond	1.9	Adeno MD	SM2	(+)	(-)	STG-BI	D1+	1	#6	(-)	

CCI = Charlson comorbidity index; CLO = rapid urase test; ESD = endoscopic submucosal dissection; LN = number of lymph node metastases identified in surgical specimen; MD = moderately differentiated; WD = well differentiated; PCC = poorly cohesive carcinoma; SM = submucosa; MM = muscularis mucosa; STG-BI = subtotal gastrectomy with Billroth-I anastomosis; D1 = D1 lymphadenectomy; D2 = D2 lymphadenectomy; LNM = lymph node metastasis.

the suprapancreatic node. This may be due to skip metastases or inadequate node dissection during surgery [13-15].

The clinical features of the patients with EGM are shown in **Table 2**. One patient (2.1%) in the observation group had recurrence of lymph node metastasis 60 months after ESD. The Kaplan-Meier curve for overall survival and disease-free survival of the surgery and observation groups did not show significant differences between the groups (P=0.280 and P=0.804, respectively, log-rank test) (**Figs. 2 and 3**).

Clinical outcomes according to ESD indications

The 110 patients were assigned to 3 groups according to ESD indications based on post-ESD pathology (absolute indication, n=18; expanded indication, n=34; and beyond indication, n=58). Criteria for absolute indication included the following: lesions <2 cm in diameter, predominantly differentiated type, pathologically intramucosal carcinoma (pT1a), and without ulcerative findings (UL[-]). Criteria for expanded indications included either of 4 possibilities: i) lesion ≥2 cm in diameter, predominantly differentiated type, pT1a, and UL(-),

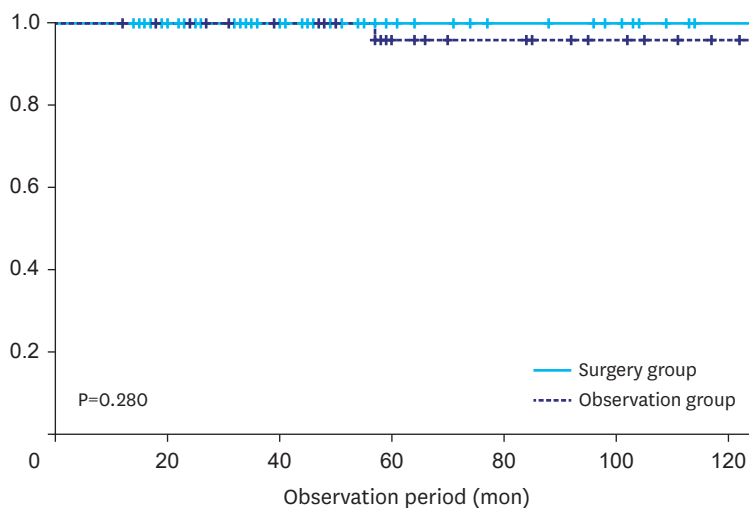


Fig. 2. Overall survival curves for patients in observation group and surgery group.

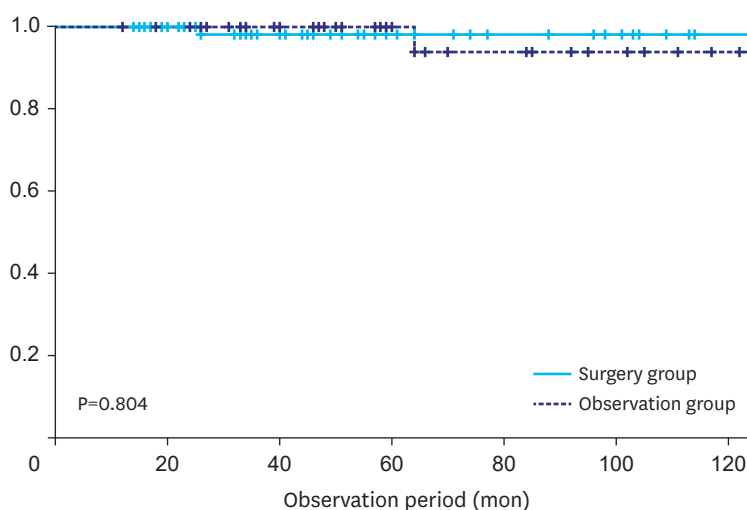


Fig. 3. Disease-free survival curves for patients in observation group and surgery group.

Table 3. Total extragastric metastasis in 110 patients who had R0 resection and lymphovascular invasion in their post-ESD pathology

Depth	Ulcer	Differentiated		Undifferentiated	
M	(-)	≤2 cm	>2 cm	≤2 cm	>2 cm
		1/16	2/10	0/2	0/1
	(+)	≤3 cm	>3 cm	≤2 cm	>2 cm
		0/2	0	0	0
SM1		≤3 cm	>3 cm		1/7
		1/20	0/7		
SM2		2/36	0/3		0/6

R0 resection = negative resected margins; ESD = endoscopic submucosal dissection; M = mucosa; SM1 = submucosal SM1; SM2 = submucosal SM2.

ii) lesion <3 cm, predominantly differentiated type, pT1a, and UL(+), or iii) lesion <2 cm, predominantly undifferentiated type, pT1a, and UL(-), or iv) lesion <3 cm, predominantly differentiated type, pathologically minute SM cancer less than 500 mm (pT1b/ SM1). Criteria for beyond indication included cases that did not satisfy any of those criteria [3]. We determined the number of occurrences of EGM in each group as 1 (5.6%), 3 (8.8%), and 3 (5.2%), respectively (Table 3).

Risk factors for EGM

Multivariate logistic regression analysis adjusted for age, sex, tumor size, and indication for ESD (Table 4) showed that a larger tumor size was associated with EGM (odds ratio [OR], 1.76; 95% CI, 1.00–3.10; P=0.048). However, the ESD indication criteria did not affect EGM (OR for expanded indication referent to absolute indication, 0.398; 95% CI, 0.03–5.49; P=0.492; OR for beyond indication referent to absolute indication, 0.157; 95% CI, 0.01–2.38; P=0.182; overall P=0.349). Additional models adjusted for age, sex, tumor size, indication for ESD, undifferentiated tumor histology, and submucosal invasion showed no significant results. However, larger tumor sizes tended to have more EGM (OR, 1.714; 95% CI, 0.954–3.079; P=0.071). This seems to be because the larger the tumor size, the deeper is the tumor depth, and it is thought that there is an interaction between the 2 variables.

Table 4. Multivariate logistic analysis of factors associated with extragastric metastasis in patients with lympho-vascular invasion and negative resected margins for gastric cancer

Variables	Model 1			Model 2			Model 3		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age	0.985	0.910–1.065	0.702	0.980	0.899–1.068	0.638	0.980	0.900–1.068	0.647
Sex	N/A	N/A	0.998	N/A	N/A	0.998	N/A	N/A	0.998
Size	1.583	0.951–2.636	0.077	1.763	1.004–3.095	0.048	1.714	0.954–3.079	0.071
ESD indication			0.778			0.349			0.796
Absolute	1			1			1		
Expanded	1.548	0.149–16.110	0.714	0.398	0.029–5.485	0.492	0.487	0.026–9.097	0.630
Beyond	0.857	0.803–8.813	0.857	0.157	0.010–2.375	0.182	0.241	0.004–15.252	0.502
Histology (undifferentiated)	0.978	0.110–8.707	0.984				1.140	0.102–12.706	0.915
SM invasion	0.498	0.105–2.366	0.380				0.665	0.044–9.967	0.768

Model 1: Non-adjusted, Model 2: Adjusted by age, sex, tumor size and indication for ESD, and Model 3: Adjusted by age, sex, tumor size, indication for ESD, histology, and SM invasion.

HR = hazard ratio; CI = cumulative index; N/A = not applicable; ESD = endoscopic submucosal dissection; SM = submucosa.

DISCUSSION

This study evaluated the risk factors for EGM in patients who underwent R0 resection and lymphovascular invasion in post-ESD pathology. The data indicated that patients with larger tumors tended to have a higher risk of EGM. No other predictive indicators for EGM were identified. To the best of our knowledge, this is a rare study to identify a predictive indicator and determine the risk of EGM in patients who underwent R0 resection and lymphovascular invasion on post-ESD pathology. Toya et al. [16] reported no local recurrence in any patient with EGC treated with non-curative ESD with R0 resection during long-term follow-up. In contrast, we observed 7 cases (6.4%) of EGM in our retrospective study of 110 patients; 5 were detected as lymph node metastasis in the surgery group, and 2 were recurrences at 25 months after surgery and 60 months after ESD during follow-up. These findings suggest that additional surgery may be required in patients with lymphovascular invasion even though they underwent R0 resection.

Our study identified a patient in the surgery group who did not have EGM based on the initial surgical specimen but had recurrence with lymph node metastasis 25 months after surgery. The patient had SM1 invasion with lymphatic invasion in the initial ESD specimen and underwent subtotal gastrectomy with D1 lymph node dissection. The surgical specimen did not show any lymph node metastasis. However, the patient had recurrence of lymph node metastasis at the suprapancreatic lymph node 25 months after surgery. Currently, D2 dissection is considered the gold standard for gastric cancer treatment, and D1 dissection is also performed in EGC without the risk of lymph node metastasis in Korea and Japan [1,3]. In gastric cancer surgery, D2 dissection typically consists of standard resection of the perigastric lymph nodes (D1) and resection of suprapancreatic lymph nodes [17]. The case we observed suggests the occurrence of skipped metastasis, which requires surgery with extended lymph node dissection or inadequate dissection of nodes. The prognostic importance of the suprapancreatic node is well documented in gastric cancer [13], and the suprapancreatic node is a target of D2 dissection in patients with gastric cancer. The role of D2 dissection is debated for patients with EGC [18,19], especially for additional surgery following gastric ESD due to the non-curative resection of EGC. However, a rigorous stage-by-stage comparison of D1 and D2 dissection in patients with definite suprapancreatic lymph node positivity is impossible because dissected node information cannot be acquired from retrospective data. Further studies are needed to answer this question regarding the optimal extent of node dissection in additional surgery following gastric ESD due to non-curative resection of EGC.

We aimed to identify a predictive marker for EGM in patients undergoing ESD for EGC, whose pathology showed negative resection margins and positive lymphovascular invasion. A previous study suggested that ESD may be sufficient to treat patients with lymphovascular invasion-positive EGC according to absolute criteria, instead of additional surgery [10]. However, that study included only 28 patients with lymphovascular invasion. Our study included 110 patients who were lymphovascular invasion-positive and resection margin-negative, suggesting that the previous study missed the potential for lymph node metastasis because it included only a small number of patients. The results of our study indicate that regardless of the ESD indication criteria, EGM may occur as node metastasis or recurrence after a few years.

Our study showed that overall survival and disease-free survival did not significantly differ between the surgical and observation groups (**Figs. 2 and 3**). However, patients in the surgery group tended to have more submucosal invasion than those in the observation group (**Table 1**), suggesting that patients in the surgery group might have had more advanced disease stages than those in the observation group. Although the survival rate did not differ between the 2 groups, this does not mean that observation without surgery in EGC patients with R0 resection and lymphovascular invasion in their post-ESD pathology is possible. A previous study by Toya et al. [16] concluded that follow-up without additional gastrectomy may be a feasible strategy for these patients, as there was no recurrence during the follow-up period. However, EGM cases that require careful follow-up were found in our study.

Our study has some limitations. First, it was a small-sample, single-center, retrospective study, which potentially affected selection bias. A multicenter, prospective study with a larger sample size is needed to verify these results. Second, we were unable to follow-up most (61.8%) of the patients after 60 months, which is the standard period of cure. Thus, our results may have been underestimated due to the relatively short follow-up duration. Additional cases of EGM may develop after longer follow-up periods, although previous studies have shown that most EGCs recur within 5 years after curative intent surgery [20,21]. Therefore, our results are unlikely to be substantially different even with longer follow-up periods. The present study only included patients who were uniformly lymphovascular invasion-positive and resection margin-negative in their post-ESD pathology. Further studies are required to determine whether a longer observation period can identify more patients with EGM.

In conclusion, tumor size was the only predictive indicator of EGM in patients who underwent R0 resection and lymphovascular invasion on post-ESD pathology. Even in patients with EGC whose pathology corresponded to the absolute indication criteria of ESD had lymphovascular invasion, additional gastrectomy was required due to the risk of EGM.

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