



Is Additional Surgery Always Sufficient for Preventing Recurrence After Endoscopic Submucosal Dissection with Curability C-2 for Early Gastric Cancer?

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ABSTRACT

Background. When a lesion does not meet the curative criteria of endoscopic submucosal dissection (ESD) for

early gastric cancer (EGC), referred to as non-curative resection or curability C-2 in the guidelines, an additional surgery is the standard therapy because of the risk of lymph node metastasis (LNM).

Objective. This study aimed to identify high-risk patients for recurrence after additional surgery for curability C-2 ESD of EGC.

Methods. This multicenter retrospective cohort study enrolled 1064 patients who underwent additional surgery after curability C-2 ESD for EGC. We evaluated the recurrence rate and the risk factors for recurrence after additional surgery in these patients.

Results. The 5-year recurrence rate after additional surgery was 1.3%. Multivariate Cox analysis revealed that the

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independent risk factors for recurrence after additional surgery were LNM (hazard ratio [HR] 32.47; $p < 0.001$) and vascular invasion (HR 4.75; $p = 0.014$). Moreover, patients with both LNM and vascular invasion had a high rate of recurrence after additional surgery (24.6% in 5 years), with a high HR (119.32) compared with those with neither LNM nor vascular invasion. Among patients with no vascular invasion, a high rate of recurrence was observed in those with N2/N3 disease according to the American Joint Committee on Cancer TNM staging system (27.3% in 5 years), in contrast with no recurrence in those with N1 disease.

Conclusions. Patients with both LNM (N1–N3) and vascular invasion, as well as those with N2/N3 disease but no vascular invasion, would be candidates for adjuvant chemotherapy after additional surgery for curability C-2 ESD of EGC.

Endoscopic resection is a well-established treatment strategy for early gastric cancer (EGC), with almost no risk for lymph node metastasis (LNM). According to the European and Japanese guidelines,^{1–3} when a lesion does not meet the curative criteria for endoscopic resection of EGC, the lesion is referred to as a ‘non-curative resection’. In the recent update of the Japanese guidelines,⁴ non-curative resection without merely positive for horizontal margin or piecemeal resection is referred to as curability C-2, in which additional gastrectomy with lymph node dissection is the standard therapy. Many studies have attempted to identify high-risk patients for LNM after endoscopic resection with curability C-2 for EGC,^{5–10} however no studies have focused on recurrence after additional surgery in such patients.

We recently conducted a large-scale, multicenter, retrospective cohort study involving endoscopic submucosal dissection (ESD) with curability C-2 for EGC.^{11–14} In this study, we revealed that additional surgery after curability C-2 ESD for EGC reduced cancer-specific mortality to approximately one-third and the 5-year cancer-specific survival in patients who underwent additional surgery was 98.8%.^{11,12} However, we also found that some patients died from gastric cancer even after additional surgery.¹² Although the small number of recurrences has made it challenging to evaluate the risk for recurrence after additional surgery, this large cohort may clarify the risk factors for recurrence. Thus, the present study aimed to identify high-risk patients for recurrence after additional surgery for curability C-2 ESD of EGC.

MATERIALS AND METHODS

Participants

This multicenter, retrospective cohort study included 19 institutions in Japan, all of which were members of the

Establishment of Accommodation of Early Stomach Cancer Treatment (EAST) study group. The present study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Institutional Review Boards of all the institutions before patients were recruited.

The initial inclusion and exclusion criteria have been published elsewhere.¹² Briefly, among the 15,785 consecutive patients who underwent ESD for EGC between January 2000 and August 2011, 1969 patients with curability C-2 ESD for EGC with a follow-up period of ≥ 3 years, except those who died, were initially enrolled. After excluding those without additional treatment, we finally analyzed 1064 patients who underwent additional surgery after curability C-2 ESD for EGC. All patients underwent curative gastrectomy with lymph node dissection, which was performed within 3 months after ESD in most cases.

Data Collection

The clinical and pathological data of the enrolled patients were collected from the medical records of each institution. Based on the Japanese classification of gastric carcinoma,¹⁵ pathological examinations were performed by expert pathologists at each institution.

Surveillance After Additional Surgery

After additional surgery in patients who underwent curability C-2 ESD for EGC, surveillance was usually performed by annual esophagogastroduodenoscopy and computed tomography scan, according to the guidelines.^{2,4} Recurrence was diagnosed based on imaging studies or histopathological analysis.

Variable Evaluation

First, we evaluated the recurrence rate in patients who underwent additional surgery after curability C-2 ESD for EGC. Second, we evaluated the risk factors for recurrence in such patients. Based on previous reports about gastrectomy as the initial treatment for EGC,^{16–18} we evaluated the following factors: age, tumor size > 30 mm, undifferentiated type, lymphatic invasion, vascular invasion, and LNM. Sex (male) and location (lower third compared with the upper/middle thirds) were also evaluated. In addition, tumor depth (tumor invasion into the submucosa ≥ 500 μm from the muscularis mucosa [SM2] compared with tumor invasion into the submucosa < 500 μm from the muscularis mucosa or mucosa), ulceration (scar), and positive vertical margin (VM) were evaluated because these factors are associated with

curability C-2 ESD for EGC. We also evaluated the relationship between recurrence after additional surgery and the combination of the presence/absence of LNM and vascular invasion or lymphatic invasion. Furthermore, in the subgroup analysis, LNM status was subdivided into N0, N1, and N2/N3, according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system for gastric cancer.

Statistical Analysis

Data are presented as numbers and proportions for categorical variables, and median and interquartile range (IQR) for continuous but non-normally distributed variables. Recurrence after additional surgery was evaluated using the Kaplan–Meier method, and the difference in recurrence among patient groups was analyzed using the log-rank test. To account for multiple comparisons, p values in the log-rank test results were presented as those corrected using the Holm method. The Cox proportional hazards regression analysis was used to calculate univariate- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of recurrence after additional surgery. The assumption of the proportionality of hazards was checked using log-minus-log plots, which involved all evaluated factors as the covariates. Statistical significance was set at $p < 0.05$. All statistical analyses were performed by an independent statistician (NN) using SPSS version 23.0 for Windows (IBM Corporation, Armonk, NY, USA) and JMP Pro software version 14.1 for Windows (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Clinical and Histopathological Characteristics and Recurrence Pattern

Among the 1064 patients who underwent additional surgery after curability C-2 ESD for EGC, 14 experienced recurrence, with a median follow-up period of 5.6 years (IQR 4.6–7.3). The detailed clinical and histopathological characteristics of the enrolled patients, divided into those with and without recurrence, are shown in Table 1. In patients with LNMs, the median was 1 (IQR 1–2). The 5-year recurrence rate after additional surgery was 1.3% (electronic supplementary Fig. S1), and the median time to recurrence was 1.8 years (IQR 1.2–2.2). The most frequent recurrent site at the time of initial diagnosis was the lymph nodes, all of which were distant lymph nodes, followed by the liver (electronic supplementary Table S1). No local recurrence occurred in the enrolled patients.

Risk Factors for Recurrence After Additional Surgery

In the multivariate Cox analysis, LNM (HR 32.47; $p < 0.001$) was the highest risk factor for recurrence after additional surgery (Table 2). In addition, vascular invasion (HR 4.75; $p = 0.014$) was also an independent risk factor for recurrence; however, lymphatic invasion was not significantly associated with recurrence ($p = 0.885$).

The Role of Lymph Node Metastasis and Vascular Invasion for Recurrence After Additional Surgery

The 5-year recurrence rate in patients with both LNM and vascular invasion was 24.6% (Fig. 1a). By contrast, the 5-year recurrence rates in those with LNM but no vascular invasion, those with vascular invasion but no LNM, and those with neither LNM nor vascular invasion were 5.7%, 0.5%, and 0.3%, respectively (Fig. 1a). The site of first recurrence after additional surgery, according to LNM status and vascular invasion, is shown in electronic supplementary Table S2. Unlike vascular invasion, lymphatic invasion status did not affect the recurrence rate in patients with/without LNM (electronic supplementary Fig. S2).

Multivariate Cox analysis revealed that, considering patients with neither LNM nor vascular invasion as a reference, those with both LNM and vascular invasion had a high HR (119.32; $p < 0.001$) for recurrence after additional surgery (Table 3). Patients with LNM but no vascular invasion (HR 19.59; $p = 0.002$) also displayed a significant risk for recurrence after additional surgery.

When LNM status was subdivided based on the 8th edition of the AJCC TNM staging system for gastric cancer, no patients with N1 disease but no vascular invasion (0/42) had recurrence during the follow-up duration (Fig. 1b). On the other hand, those with both N1 disease and vascular invasion, those with N2/N3 disease but no vascular invasion, and those with both N2/N3 disease and vascular invasion had 19.4%, 27.3%, and 42.9% recurrence in 5 years, respectively (Fig. 1b). The high risk of recurrence after additional surgery in these three categories was confirmed in multivariate Cox analysis (electronic supplementary Table S3). There was a significant interaction between the number of LNMs and vascular invasion for recurrence in the multivariate model (p for interaction = 0.030).

DISCUSSION

In this study, we revealed that the 5-year recurrence rate after additional surgery after curability C-2 ESD for EGC was 1.3%, and that LNM and vascular invasion were the independent risk factors for recurrence. In particular,

TABLE 1 Baseline characteristics of the enrolled patients

	No recurrence (<i>n</i> = 1050)	Recurrence (<i>n</i> = 14)
Age, years [median (IQR)]	69 (61–75)	72.5 (71–76)
Sex		
Male	826 (78.7)	10 (71.4)
Female	224 (21.3)	4 (28.6)
Location		
Upper	283 (27.0)	7 (50.0)
Middle	447 (42.6)	3 (21.4)
Lower	320 (30.5)	4 (28.6)
Macroscopic type		
Elevated/flat	260 (24.8)	9 (64.3)
Depressed	10 (1.0)	0 (0.0)
Mixed	780 (74.3)	5 (35.7)
Tumor size, mm [median (IQR)]	28 (19–40)	31 (21–42)
Invasive depth		
M	174 (16.6)	0 (0.0)
SM1	210 (20.0)	4 (28.6)
SM2	666 (63.4)	10 (71.4)
Histopathological type		
Differentiated	906 (86.3)	12 (85.7)
Undifferentiated	144 (13.7)	2 (14.3)
Lymphatic invasion		
Positive	423 (40.3)	9 (64.3)
Negative	627 (59.7)	5 (35.7)
Vascular invasion		
Positive	231 (22.0)	9 (64.3)
Negative	819 (78.0)	5 (35.7)
Ulceration [scar]		
Presence	272 (25.9)	5 (35.7)
Absence	778 (74.1)	9 (64.3)
Vertical margin		
Positive	186 (17.7)	7 (50.0)
Negative	861 (82.0)	7 (50.0)
Unclear	3 (0.3)	0 (0.0)
LNM ^a		
N0	975 (92.9)	3 (21.4)
N1	63 (6.0)	5 (35.7)
N2	10 (1.0)	6 (42.9)
N3a	2 (0.9)	0 (0.0)
N3b	0 (0.0)	0 (0.0)

Data are expressed as *n* (%) unless otherwise specified

^aBased on the 8th edition of the AJCC TNM staging system

IQR interquartile range, *M* tumor confined to mucosa, *SM1* tumor invasion into the submucosa < 500 μm from the muscularis mucosa, *SM2* tumor invasion into the submucosa ≥ 500 μm from the muscularis mucosa, *LNM* lymph node metastasis

patients with both LNM (N1–N3) and vascular invasion, as well as those with N2/N3 disease but no vascular invasion, had a high risk of recurrence.

According to the guidelines,^{1–4} additional surgery is the standard therapy in patients with curability C-2 ESD for EGC. However, there are no arguments for further treatment, such as adjuvant chemotherapy, after additional

TABLE 2 Risk factors for recurrence after additional surgery for patients with curability C-2 ESD for EGC

	Person-years	No. of events	Univariate		Multivariate ^a	
			HR (95% CI)	<i>p</i> Value	HR (95% CI)	<i>p</i> -Value
Age						
Per 1 year	6424	14	1.08 (1.00–1.15)	0.040	1.04 (0.96–1.12)	0.331
Sex						
Male	5066	10	0.69 (0.22–2.19)	0.687	0.64 (0.17–2.40)	0.508
Female	1358	4	1 (Reference)		1 (Reference)	
Location						
Lower	1998	4	0.92 (0.29–2.94)	0.891	0.72 (0.20–2.62)	0.613
Upper/middle	4426	10	1 (Reference)		1 (Reference)	
Tumor size, mm						
> 30	2777	7	1.29 (0.45–3.68)	0.635	1.02 (0.32–3.27)	0.980
≤ 30	3647	7	1 (Reference)		1 (Reference)	
Invasion depth						
SM2	4070	10	1.46 (0.46–4.65)	0.525	0.41 (0.10–1.63)	0.205
M/SM1	2355	4	1 (Reference)		1 (Reference)	
Histopathological type						
Undifferentiated	892	2	1.06 (0.24–4.73)	0.940	0.71 (0.14–3.62)	0.681
Differentiated	5532	12	1 (Reference)		1 (Reference)	
Lymphatic invasion						
Positive	2549	9	2.69 (0.90–8.03)	0.076	0.92 (0.28–3.04)	0.885
Negative	3875	5	1 (Reference)		1 (Reference)	
Vascular invasion						
Positive	1360	9	6.31 (2.12–18.84)	0.001	4.75 (1.38–16.39)	0.014
Negative	5065	5	1 (Reference)		1 (Reference)	
Ulceration (scar)						
Presence	1698	5	1.56 (0.52–4.66)	0.424	2.04 (0.59–7.02)	0.260
Absence	4726	9	1 (Reference)		1 (Reference)	
Vertical margin						
Positive	1118	7	4.60 (1.61–13.11)	0.004	2.63 (0.77–9.01)	0.124
Other	5306	7	1 (Reference)		1 (Reference)	
LNM						
Presence	500	11	43.34 (12.09–155.39)	< 0.001	32.47 (8.20–128.56)	< 0.001
Absence	5924	3	1 (Reference)		1 (Reference)	

^aAdjusted for all factors shown in this table

ESD endoscopic submucosal dissection, EGC early gastric cancer, HR hazard ratio, CI confidence interval, SM2 tumor invasion into the submucosa ≥ 500 μm from the muscularis mucosa, M tumor confined to mucosa, SM1 tumor invasion into the submucosa < 500 μm from the muscularis mucosa, LNM lymph node metastasis

surgery because clinicians, particularly physicians, believe that additional surgery is almost sufficient for preventing recurrence in patients with curability C-2 ESD for EGC. In fact, the 5-year CSS after additional surgery was 98.6–98.8% in such patients.^{8,9} However, some patients experience recurrence even after additional surgery, and which patients are at high-risk for recurrence after additional surgery has not yet been elucidated because of the very small number of cases with recurrence. Since this

multicenter study included more than three times as many patients as the largest study to date,⁹ we attempted to identify high-risk patients for recurrence after additional surgery.

The present study highlights two clinical implications: the identification of independent risk factors for recurrence after additional surgery, and that of high-risk patients for recurrence by combining two risk factors. First, this study revealed that the independent risk factors for recurrence

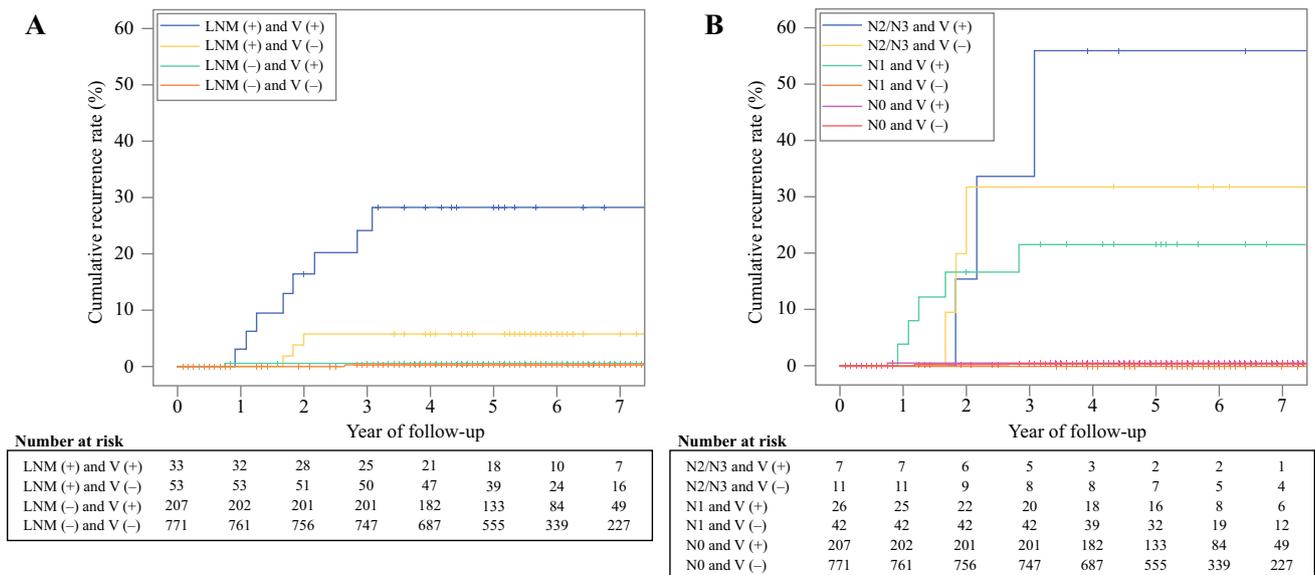


FIG. 1 Recurrence after additional surgery in patients with curability C-2 ESD for EGC, according to LNM status and vascular invasion. **a** Presence/absence of LNM and vascular invasion. Recurrence after additional surgery in patients with both LNM and vascular invasion (24.6% in 5 years) was significantly higher than in patients with LNM but no vascular invasion (5.7% in 5 years) [$p = 0.025$]. **b** LNM status, based on the AJCC TNM staging system, and vascular invasion. The 5-year recurrence rates after additional surgery in those with both N1

disease and vascular invasion, those with N2/N3 disease but no vascular invasion, and patients with both N2/N3 disease and vascular invasion were 19.4%, 27.3%, and 42.9%, respectively, which were significantly higher than in patients with N1 disease but no vascular invasion (0.0%) [$p = 0.024$, $p = 0.005$, and $p < 0.001$, respectively]. *AJCC* American Joint Committee on Cancer, *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer, *LNM* lymph node metastasis, *V* vascular invasion

TABLE 3 Risk for recurrence after additional surgery in patients with curability C-2 ESD for EGC, according to LNM status and vascular invasion

	Person-years	No. of events	Univariate		Multivariate ^a	
			HR (95% CI)	p value	HR (95% CI)	p value
LNM (+) and vascular invasion (+)	170	8	103.79 (22.03–489.06)	< 0.001	119.32 (20.84–683.14)	< 0.001
LNM (+) and vascular invasion (-)	330	3	21.90 (3.66–131.09)	0.001	19.59 (2.87–133.65)	0.002
LNM (-) and vascular invasion (+)	1190	1	1.88 (0.17–20.73)	0.606	2.25 (0.19–27.12)	0.524
LNM (-) and vascular invasion (-)	4735	2	1 (Reference)		1 (Reference)	

^aAdjusted for age, sex, location, tumor size, invasion depth, histopathological type, lymphatic invasion, ulceration (scar), and vertical margin *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer, *LNM* lymph node metastasis, *HR* hazard ratio, *CI* confidence interval

after additional surgery, which occurred at a rate of 1.3% in 5 years, were LNM and vascular invasion. According to previous studies regarding gastrectomy as an initial treatment for gastric cancer, the recurrence rate after surgery for submucosal gastric cancers ranged from 1.1 to 4.8%.^{11,17,19–25} In addition, LNM was reported as the most important risk factor for recurrence after surgery for EGC,^{16,17} while vascular invasion was an independent risk factor for metachronous liver metastasis after surgery for EGC.²⁴ Our study results are consistent with these previous studies, and we confirmed that LNM and vascular invasion

are important factors for recurrence when additional surgery is performed in patients with curability C-2 ESD for EGC.

Second, and more important, we found that patients with both LNM and vascular invasion had a much higher risk for recurrence after additional surgery in patients with curability C-2 ESD compared with the other categories. Although the 5-year recurrence rate in the enrolled patients was only 1.3%, the recurrence rate in patients with both LNM and vascular invasion was 24.6%. By contrast, only 0.5% of patients with vascular invasion but no LNM developed recurrence in the 5 years following additional surgery even though vascular invasion was an independent

risk factor for recurrence after additional surgery. In a further subgroup analysis, we found a difference in the recurrence rate according to LNM status (N0, N1, N2/N3) in patients with no vascular invasion. Interestingly, the 5-year recurrence rate was 27.3% in such cases with N2/N3 diseases, in contrast to the finding that no such cases with N1 disease recurred during the follow-up duration. To our knowledge, no studies, including those regarding gastrectomy as an initial treatment for EGC, have demonstrated these findings. Therefore, these study results provide new proposals in selecting treatment strategies for patients who undergo additional surgery after curability C-2 ESD for EGC. One of these proposals is that patients with both LNM (N1–N3) and vascular invasion, as well as those with N2/N3 disease but no vascular invasion, would be candidates for adjuvant chemotherapy, such as S-1 monotherapy for 1 year,²⁶ after additional surgery (Fig. 2). By contrast, based on the very small risk of recurrence in those patients without LNM, regardless of vascular invasion status, as well as those with N1 disease but no vascular invasion, these patients would be candidates for observation without further treatment after additional surgery (Fig. 2).

These findings also confirmed the importance of additional surgery for patients with vascular invasion after ESD for EGC, which is recommended in the guidelines.^{1–4} Our previous study revealed that vascular invasion was one of the significant risk factors for LNM in patients with C-2 ESD for EGC, although its significance was near borderline.¹³ However, since vascular invasion is considered to have a hematogenous route for metastasis,²⁴ chemotherapy may have been more appropriate than additional surgery for such patients. In the present study, the small risk of recurrence in those with vascular invasion but no LNM does not support this hypothesis. In addition, although LNM status largely affects the recurrence rate in patients with vascular invasion, it is impossible to identify LNM

	N0 ^a	N1 ^a	N2/N3 ^a
Vascular invasion (+)	0.5%	19.4%	42.9%
Vascular invasion (–)	0.3%	0.0%	27.3%

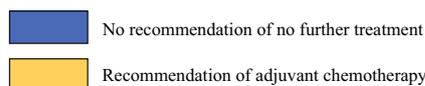


FIG. 2 Proposals for the recommendation of adjuvant chemotherapy after additional surgery in patients with curability C-2 ESD for EGC, based on the 5-year recurrence rate. Patients with both LNM (N1–N3) and vascular invasion, as well as those with N2/N3 disease but no vascular invasion, may be candidates for adjuvant chemotherapy after additional surgery for curability C-2 ESD of EGC. ^aBased on the 8th edition of the AJCC TNM staging system. *AJCC* American Joint Committee on Cancer, *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer

status without a gastrectomy with lymph node dissection. Thus, additional surgery may have two aspects: curative treatment, and the identification of high-risk patients for recurrence. Although it is difficult to reach a definitive conclusion because this study did not compare additional surgery with chemotherapy, these findings suggest that additional surgery and, if necessary, adjuvant chemotherapy may be appropriate as a treatment for patients with vascular invasion in ESD for EGC.

There is a discrepancy between the National Comprehensive Cancer Network (NCCN) guidelines and the Japanese guidelines in the treatment strategy after surgery for EGC (which corresponds to pT1 gastric cancer) with LNM. In the Japanese guidelines,^{2,4} adjuvant chemotherapy is recommended for gastric cancer with pStage II/III, except pT1 and pT3(SS)N0 cases. However, there are no recommendations for EGC with LNM in the Japanese guidelines;^{2,4} therefore, the management of such patients after surgery depends on the clinicians and patients. According to the NCCN guidelines,²⁷ adjuvant chemotherapy is recommended for EGC patients with LNM who do not receive preoperative therapy. The results of this study agree with the statement in the NCCN guidelines in that patients with N2/N3 disease are candidates for adjuvant chemotherapy. However, in patients with N1 disease, vascular invasion status may be an indicator for adjuvant chemotherapy.

Although the present study has the strength of including the largest cohort to date, several limitations should be noted. First, there is selection bias for determining the treatment strategy after curability C-2 ESD for EGC. However, it is difficult to overcome this limitation because of the ethical issue of randomization of treatment methods after curability C-2 ESD for EGC. Second, this study did not investigate the residual cancer in the surgical specimen. Third, the use of immunostaining for the evaluation of lymphatic and vascular invasions depended on the individual institutions. Lastly, the number of events (recurrences) was small, which can cause a type I error in the analysis. To overcome these limitations, a well-designed, prospective, nationwide multicenter study is required.

CONCLUSIONS

This multicenter study with the largest cohort to date revealed that the 5-year recurrence rate after additional surgery after curability C-2 ESD for EGC was 1.3% and that the combination of LNM and vascular invasion led to a high risk of recurrence. In addition, patients with N2/N3 disease but no vascular invasion had a high risk of recurrence. Thus, adjuvant chemotherapy may reduce

recurrence and improve the prognosis in such patients. However, further studies are warranted to validate our results and the effect of adjuvant chemotherapy on these patients.

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REFERENCES

- Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47:829–54.
- Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer*. 2017;20:1–19.
- Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer. *Dig Endosc*. 2016;28:3–15.
- Japanese Gastric Cancer Association. Gastric cancer treatment guideline. 5th ed. [in Japanese]. Tokyo: Kanehara; 2018.
- Ito H, Inoue H, Ikeda H, et al. Surgical outcomes and clinicopathological characteristics of patients who underwent potentially noncurative endoscopic resection for gastric cancer: a report of a single-center experience. *Gastroenterol Res Pract*. 2013;2013:427405.
- Yang HJ, Kim SG, Lim JH, et al. Predictors of lymph node metastasis in patients with non-curative endoscopic resection of early gastric cancer. *Surg Endosc*. 2015;29:1145–55.
- Kikuchi S, Kuroda S, Nishizaki M, et al. Management of early gastric cancer that meet the indication for radical lymph node dissection following endoscopic resection: a retrospective cohort analysis. *BMC Surg*. 2017;17:72.
- Kawata N, Kakushima N, Takizawa K, et al. Risk factors for lymph node metastasis and long-term outcomes of patients with early gastric cancer after non-curative endoscopic submucosal dissection. *Surg Endosc*. 2017;31:1607–16.
- Suzuki H, Oda I, Abe S, et al. Clinical outcomes of early gastric cancer patients after noncurative endoscopic submucosal dissection in a large consecutive patient series. *Gastric Cancer*. 2017;20:679–89.
- Toyokawa T, Ohira M, Tanaka H, et al. Optimal management for patients not meeting the inclusion criteria after endoscopic submucosal dissection for gastric cancer. *Surg Endosc*. 2016;30:2404–14.
- Suzuki S, Gotoda T, Hatta W, et al. Survival benefit of additional surgery after non-curative endoscopic submucosal dissection for early gastric cancer: a propensity score matching analysis. *Ann Surg Oncol*. 2017;24:3353–60.
- Hatta W, Gotoda T, Oyama T, et al. Is radical surgery necessary in all patients who do not meet the curative criteria for endoscopic submucosal dissection in early gastric cancer? A multi-center retrospective study in Japan. *J Gastroenterol*. 2017;52:175–84.
- Hatta W, Gotoda T, Oyama T, et al. A scoring system to stratify curability after endoscopic submucosal dissection for early gastric cancer: “eCura system”. *Am J Gastroenterol*. 2017;112:874–81.
- Hatta W, Gotoda T, Oyama T, et al. Is the eCura system useful for selecting patients who require radical surgery after noncurative endoscopic submucosal dissection for early gastric cancer? A comparative study. *Gastric Cancer*. 2018;21:481–9.
- Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer*. 2011;14:101–12.
- Saka M, Katai H, Fukagawa T, Nijjar R, Sano T. Recurrence in early gastric cancer with lymph node metastasis. *Gastric Cancer*. 2008;11:214–8.
- Youn HG, An JY, Choi MG, Noh JH, Sohn TS, Kim S. Recurrence after curative resection of early gastric cancer. *Ann Surg Oncol*. 2010;17:448–54.
- Kim SM, An JY, Lee J, Sohn TS, Kim S. Adjuvant chemotherapy versus chemoradiotherapy versus surgery alone for early gastric cancer with one or two lymph node metastasis. *Ann Surg Oncol*. 2018;25:1616–24.
- Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. *Cancer*. 1993;72:3174–8.
- Lee HJ, Kim YH, Kim WH, et al. Clinicopathological analysis for recurrence of early gastric cancer. *Jpn J Clin Oncol*. 2003;33:209–14.
- Ikeda Y, Saku M, Kishihara F, Maehara Y. Effective follow-up for recurrence or a second primary cancer in patients with early gastric cancer. *Br J Surg*. 2005;92:235–9.
- Japanese Gastric Cancer Association Registration Committee, Maruyama K, Kaminishi M, et al. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. *Gastric Cancer*. 2006;9:51–66.
- Isobe Y, Nashimoto A, Akazawa K, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer*. 2011;14:301–16.
- Ishida M, Morita S, Saka M, Fukagawa T, Taniguchi H, Katai H. Metachronous liver metastasis from early gastric cancer. *J Gastrointest Surg*. 2012;16:837–41.
- Nashimoto A, Akazawa K, Isobe Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer*. 2013;16:1–27.
- Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357:1810–20.
- National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology (NCCN guidelines). Gastric Cancer. Version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed 4 May 2019.

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