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Clinical outcomes of early gastric cancer with lymphovascular invasion or positive vertical resection margin after endoscopic submucosal dissection

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Abstract
Background In early gastric cancer (EGC) cases with lymphovascular invasion or positive vertical margins after endoscopic submucosal dissection (ESD), additional radical gastrectomy is performed on principle. However, an additional surgery is often difficult to consider if the surgical approach itself is challenging or the patient refuses surgery. In such cases, only close surveillance is performed without additional surgical procedures. This study aimed to examine the difference in clinical prognosis of EGC cases with lymphovascular invasion or positive vertical margins after ESD either with or without surgery.
Methods We retrospectively studied 83 patients with lymphovascular invasion or positive vertical margins after ESD from July 2005 to November 2013.
Results Of the 83 patients, 45 (54.2 %) underwent radical additional gastrectomy (surgical group) and 38 (45.8 %) were under close surveillance without surgical or endoscopic treatments (close surveillance group.) The cancer-free survival period was 78.3 ± 3.4 months in the surgical group and 64.5 ± 4.6 months in the close surveillance group. The recurrence rates did not significantly differ between the 2 groups, at 7.9 % in the surgical group and 6.7 % in the non-surgical group.
Conclusions Close surveillance may be suggested as an option for EGC patients for whom a surgical approach is difficult, who exhibit a positive vertical margin after ESD, and who have no lymphovascular or deep submucosa invasion after ESD.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Incomplete resection · Lymphovascular invasion · Positive vertical margins

Detection rates of early gastric cancer (EGC) have been improving with the increase in widespread medical checkups and endoscopic examinations. These early detection rates are evident in South Korea where the proportion of EGC cases has recently increased to approximately 50 % of all detected cancers, as compared with less than 10 % in the early 1970s. Such an improvement in EGC detection has also highlighted the importance of endoscopic resection. In the past, indications for endoscopic resection, when compared with those for radical gastrectomy, were substantially limited, which was due to relative difficulties in predicting precise resection margin status and the possibility of overlooking lymph node metastasis. However, predicting lymph node metastasis has become possible with the development of advanced endoscopic and diagnostic technologies. Furthermore, adoption of endoscopic submucosal dissection (ESD) has ushered in a new era of broadened indications for endoscopic resection [1–3]. As ESD is now performed more frequently, interest regarding incomplete resection, a complication of ESD, has also increased. Despite performing ESD under the initial indication for this procedure, some cases manifest lymphovascular invasion or positive resection margins. When performing ESD without radical gastrectomy an incomplete resection is more commonly prescribed, which commonly happens in patients who are not good candidates for surgery due to poor overall health, presence of an

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associated disease, or the patient refusing surgery. In EGC cases with positive horizontal margins after ESD, additional ESD may be considered. By contrast, in cases with lymphovascular invasion or positive vertical margins, additional ESD is impossible; thus, additional radical gastrectomy is performed on principle. However, an additional surgery is difficult to consider if the surgical approach itself is challenging or the patient refuses surgery. In such cases, only close surveillance is performed without additional surgical procedures, but long-term clinical characteristics of EGC cases with lymphovascular invasion or positive vertical margins after ESD are rare. This research study aimed to examine EGC cases with lymphovascular invasion or positive vertical margins after ESD.

Patients and methods

Patients

From July 2005 to November 2013, 655 patients with EGC (61.6 % of all 1,064 patients who underwent ESD for gastric adenoma or EGC) were treated with ESD at KCCH in Korea. Among the 655 patients with EGC, 83 of the patients had lymphovascular invasion or positive vertical margins after ESD and were therefore enrolled in this study (Fig. 1). The medical records of all EGC patients who underwent ESD were reviewed retrospectively. The demographic characteristics of patients, endoscopic outcomes, and histopathological characteristics were assessed. The patients who have lymphovascular invasion or positive vertical margins after ESD for EGC were divided into two groups: surgical group and close surveillance group. We compared clinical outcomes between the surgery and close surveillance groups.

Indication for ESD

Endoscopy and abdominal computed tomography (CT) were performed in all patients before performing ESD to exclude lymph node metastasis or distant metastasis. The accepted extended indications for ESD are as follows: (1) differentiated mucosal cancer without ulcer and of any size, (2) differentiated mucosal cancer, with ulcer $\leq$3 cm in size, (3) differentiated submucosal cancer (sm1, $<$500 μm) $\leq$3 cm in size, and (4) undifferentiated mucosal cancer $\leq$2 cm in size. Based on the pre-ESD evaluation, ESD was performed for EGC that met the indication criteria. ESD was performed for EGC that did not meet the indication criteria when certain situations arose such as the overall health condition of the patient prevented them from being a good candidate for surgery, the patient having an associated disease, or the patient refusing surgery.

ESD technique

ESD was performed by four experienced gastrointestinal endoscopists in KCCH. After identifying the target lesion, marking dots were made circumferentially at about 3–5 mm lateral to the margin of the lesion using a needle knife (Olympus Optical Co Ltd) or argon plasma coagulation. Once the marking dots were placed, a mixture of normal saline solution, epinephrine (1:1,000), and indigocarmine was injected into the submucosa around the lesion to lift it off the muscle layer. A circumferential mucosal incision was performed outside the marking dots to separate the lesion from the surrounding non-neoplastic mucosa. Direct dissection of the submucosal layer was

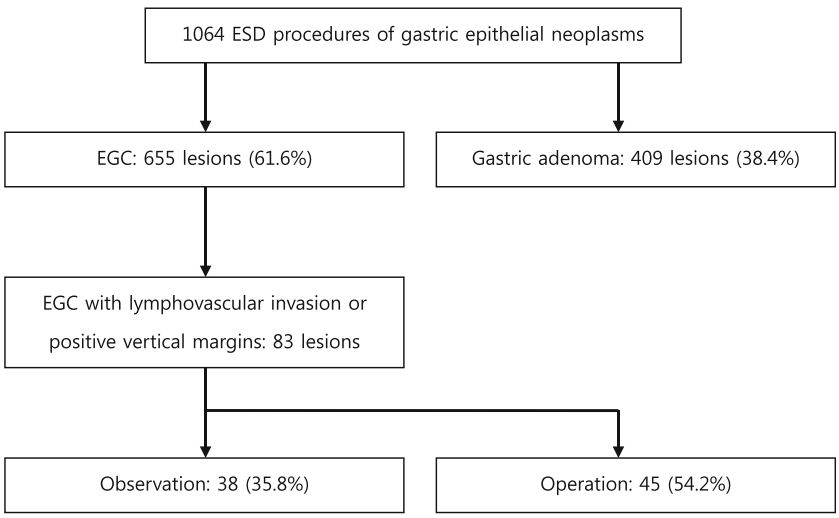

Fig. 1 Flowchart of the enrollment process. *EGC* Early gastric cancer, *ESD* endoscopic submucosal dissection

performed with one of the specified knives until complete removal was achieved. These steps were carried out using the needle knife (Olympus Optical Co Ltd) or IT knife (Olympus Optical Co Ltd) or Flex knife (Olympus Optical Co Ltd). Each resected specimen was immediately extended, fixed with pins, and then fixed in 10 % formaldehyde.

Follow-up

The patients were followed up with endoscopy and endoscopic biopsy 1 month after ESD. Endoscopy was performed every 3 months for the first year and every 6 months for the second year to check for local or metachronous recurrence. From the third year and beyond, endoscopy was performed annually. In addition, abdominal computed tomography (CT) and chest radiography were performed annually to detect extragastric recurrence.

Statistical analysis

All analyses were performed with Statistic Package for the Social Sciences (SPSS) version 13.0 (SPSS Inc. Chicago, IL, USA). The data were analyzed using Student's t test, Pearson χ^2 test, and Fisher's exact test. Long-term outcomes were calculated using the Kaplan–Meier method and analyzed using multiple logistic regression analysis. A p value of less than 0.05 was considered significant.

Results

Among 655 post-ESD EGC cases, 129 (19.7 %) did not meet the indication criteria for ESD. Histopathological analysis revealed that 83 patients (12.7 %: 51 men and 32 women; mean ± SD age, 67.5 ± 9.8 years) had lymphovascular invasion or a positive vertical margin. Of the 83 patients, 45 (54.2 %) underwent radical additional gastrectomy (surgical group) and 38 (45.8 %) were under close surveillance without surgical or endoscopic treatments (close surveillance group) (Fig. 1). The reasons that the patients in the close surveillance group were not operated were as follows: patients' refusal ($n = 26$), double primary cancer (concomitant cancer in a different part of the body; $n = 7$), coronary heart disease ($n = 2$), cerebrovascular disease ($n = 1$), liver cirrhosis ($n = 1$), and chronic kidney disease ($n = 1$). Table 1 compares the clinical characteristics, endoscopic outcomes, and histopathological characteristics between the surgery and close surveillance groups. The mean age of the close surveillance group was older than that of the surgical group (72.3 ± 8.3 vs. 63.5 ± 9.3 years; $p < 0.001$).

Among the 83 patients who exhibited lymphovascular invasion or positive vertical margins, 34 (41.0 %) met the indication criteria for ESD, whereas a large proportion (50/83, 59.0 %) of the patients did not. In the close surveillance group, more patients met the indication criteria (21/38, 55.3 %). However, in the surgical group, more patients did not meet the indication criteria (32/45, 71.1 %) ($p = 0.015$). In addition, of the 12 patients with confirmed EGC recurrences or postoperative lymph node metastasis, 1 patient (8.3 %) in the close surveillance group met the indication criteria.

In terms of histopathological evaluation, 44 patients exhibited lymphovascular invasion, 21 had a positive vertical margin, and 18 had both lymphovascular invasion and

Table 1 The baseline characteristics of 83 EGC patients with deep margin positivity and lymphovascular invasion after ESD

	Total ($n = 83$)	Observation ($n = 38$)	Operation ($n = 45$)	p-value
Sex				0.098
Male	51	27 (71.1 %)	24 (53.3 %)	
Female	32	11 (28.9 %)	21 (46.7 %)	
Age (mean)		72.3 ± 8.3	63.5 ± 9.3	0
Macroscopic type				0.092
Protruded	3	2 (5.3 %)	1 (2.2 %)	
Slightly elevated	25	16 (42.1 %)	9 (20.0 %)	
Flat	13	7 (18.4 %)	6 (13.3 %)	
Slightly depressed	38	12 (31.6 %)	26 (57.8 %)	
Excavated	4	1 (2.6 %)	3 (6.7 %)	
Indication				0.015
Indication	34	21 (55.3 %)	13 (28.9 %)	
Contraindication	49	17 (44.7 %)	32 (71.1 %)	
Depth				0.001
M	21	17 (44.7 %)	4 (8.9 %)	
SM1	17	7 (18.4 %)	10 (22.2 %)	
Deep SM	45	14 (36.8 %)	31 (68.9 %)	
Size (cm)				0.790
≤2	45	20 (52.6 %)	25 (55.6 %)	
>2	38	18 (47.4 %)	20 (44.4 %)	
Differentiation				0.517
Differentiated	68	30 (78.9 %)	38 (84.4 %)	
Undifferentiated	15	8 (21.1 %)	7 (15.6 %)	
Resection margin				0.156
LV (+)	44	22 (57.9 %)	23 (51.1 %)	
VM (+)	21	11 (28.9 %)	10 (22.2 %)	
LV (+) & VM (+)	18	5 (13.2 %)	12 (26.7 %)	
Recurrence	6 (7.2 %)	3 (7.9 %)	3 (6.7 %)	0.830

Early gastric cancer (EGC), endoscopic submucosal dissection (ESD), tumor infiltration into the submucosal layer <500 μm from the muscularis mucosa (SM1), tumor infiltration into the submucosal layer >500 μm from the muscularis mucosa (Deep SM), lymphovascular invasion (LV), vertical margin (VM)

a positive vertical margin. Among the 38 patients in the close surveillance group, 22 (57.9 %) exhibited lymphovascular invasion, 11 (28.9 %) a positive vertical margin, and 5 (13.2 %) both lymphovascular invasion and a positive vertical margin during post-ESD histopathological evaluation. Among the patients with lymphovascular invasion, 20 exhibited lymphatic invasion, 1 exhibited vascular invasion, and 1 exhibited both.

Among the 38 patients in the close surveillance group, 3 (7.9 %) exhibited gastric cancer recurrence, which was detected during the close surveillance period at 7.7, 12.2, and 33.0 months after ESD, respectively. All 3 patients exhibited lymphovascular invasion and one also had a positive vertical margin. In the patients who exhibited only a positive vertical margin, gastric cancer did not recur. Table 2 shows the characteristics of the 3 patients with EGC recurrences in the close surveillance group. One of the three patients had EGC recurrence at the ESD site 7.7 months after ESD. After refusal of the recommended surgery because of advanced age, the patient was lost to follow-up. The second case showed EGC in a region different from the original lesion site during the endoscopic examination performed 12.2 months after ESD. ESD was performed again because the patient refused surgery because of advanced age. The histopathological examination performed after the second ESD revealed a clear resection margin. No recurrence was observed in the follow-up 17 months later. The third case had EGC recurrence at the ESD site 33 months after ESD. ESD was performed again owing to liver cirrhosis and age-related high surgical risk. Post-ESD histological examination revealed a clear resection margin despite deep SM invasion. No recurrence was observed in the ongoing follow-up 13 months after surgery.

Three (6.7 %) of the 45 patients in the surgical group exhibited recurrence. Table 3 shows the characteristics of the 3 patients. All 3 patients exhibited deep submucosal (SM) invasion of more than 0.5 mm and a positive vertical margin after ESD, with one of the patients exhibiting accompanying lymphovascular invasion. All had undergone subtotal gastrectomy, and recurrences were detected at 12.0, 12.8, and 25.0 months during the close surveillance period after surgery. After surgery, no residual cancer was detected on the gastric walls in any of the 3 patients. However, 1 patient with lymphovascular invasion exhibited lymph node metastasis histopathologically.

No residual cancer within the gastric walls was found in the histopathological outcomes of the surgical group. However, 7 patients (15.6 %) in the group exhibited lymph node metastasis. The characteristics of the 7 patients with lymph node metastasis are described in Table 4. Histopathological outcomes showed deep SM invasion of more

Table 2 Characteristics of the three patients who experienced recurrence of EGC after ESD

	Case 1	Case 2	Case 3
Age/sex	74/M	84/F	82/F
Endoscopic findings			
Location	Angle (middle)	Antrum (middle)	Antrum (middle)
Size (cm)	0.75	3.75	1.3
Type	IIa	IIc + IIa	IIa
Histological findings			
Differentiation	Well	Moderately	Poorly
Depth	M	SM1	Deep SM
Margin	LV (+)	LV (+)	LV & VM (+)
DFS (month)	12.2	7.7	33.0

Early gastric cancer (EGC), endoscopic submucosal dissection (ESD), mucosa (M), tumor infiltration into the submucosal layer <500 μm from the muscularis mucosa (SM1), tumor infiltration into the submucosal layer >500 μm from the muscularis mucosa (Deep SM), lymphovascular invasion (LV), vertical margin (VM), disease-free survival (DFS)

Table 3 Characteristics of the three patients experienced recurrence of EGC after additional curative gastrectomy

	Case 1	Case 2	Case 3
Age/sex	60/M	74/M	61/M
Endoscopic findings			
Location	Antrum (middle)	Antrum (lower)	Body (middle)
Size(cm)	1.7 cm	6.5 cm	2.5 cm
Type	IIc	IIa + IIb	IIa + IIc
Histologic findings			
Differentiation	Moderately	Well	Moderately
Depth	Deep SM	Deep SM	Deep SM
Margin	VM (+)	LV & VM (+)	VM (+)
Radiologic findings	Non-specific	Non-specific	Non-specific
Surgical procedure	Subtotal gastrectomy	Subtotal gastrectomy	Subtotal gastrectomy
Histologic findings			
Remnant tumors	(−)	(−)	(−)
Node metastasis	(−)	(+)	(−)
DFS (month)	25	12	12.8

Early gastric cancer (EGC), tumor infiltration into the submucosal layer >500 μm from the muscularis mucosa (Deep SM), lymphovascular invasion (LV), vertical margin (VM), disease-free survival (DFS)

Table 4 Characteristics of seven patients who had lymph node metastasis in surgical specimens

Case	Age/sex	Histological findings (ESD)			CT findings	Remnant tumors	DFS (month)
		Differentiation	Depth	Margin			
1	69/F	Moderately	Deep SM	LV & VM (+)	Non-specific	(−)	3.0
2	67/M	Poorly	Deep SM	LV & VM (+)	Non-specific	(−)	58.6
3	61/M	Moderately	Deep SM	VM (+)	Non-specific	(−)	49.3
4	43/F	Poorly	Deep SM	VM (+)	Non-specific	(−)	48.3
5	74/M	Well	Deep SM	LV & VM (+)	Non-specific	(−)	12.0 recurrence
6	62/M	Poorly	Deep SM	LV (+)	Non-specific	(−)	48.2
7	74/M	Moderately	Deep SM	LV & VM (+)	Non-specific	(−)	25.2

Endoscopic submucosal dissection (ESD), tumor infiltration into the submucosal layer >500 μm from the muscularis mucosa (Deep SM), lymphovascular invasion (LV), vertical margin (VM), disease-free survival (DFS)

than 0.5 mm in all the patients. Of the 7 patients with lymph node metastasis, 5 previously exhibited lymphovascular invasion post-ESD treatment. As previously mentioned, 1 patient (14.3 %) had a recurrence during the observation period of 12 months after additional gastrectomy. Among the 38 patients without lymph node metastasis, 2 (5.3 %) experienced a recurrence. However, no difference in recurrence rate was observed between the group that had previously exhibited postoperative lymph node metastasis and the group that had no metastasis.

Among the 45 patients in the surgical group, 4 (8.9 %) had EGC invasion limited to mucosa (M), 9 (20.0 %) had mucosa invasion of less than 0.5 mm (SM1), and 32 (71.1 %) had deep SM invasion of more than 0.5 mm. Lymph node metastasis was absent, with EGC limited to M and SM1. Among the 32 patients who exhibited deep SM invasion, 7 (21.9 %) exhibited lymph node metastasis. However, no discrepancy in lymph node metastasis rate was observed between SM1 and deep SM invasion within the surgical group. Furthermore, among the 35 patients who had undergone surgery for lymphovascular invasion post-ESD treatment, 5 (14.3 %) had confirmed lymph node metastasis, but the incidence rate did not significantly differ from that in the group without lymphovascular invasion.

Among the 45 patients in the surgical group, 38 (84.4 %) exhibited well-differentiated gastric cancer and 7 (15.6 %) exhibited poor differentiation gastric cancer. Among the 38 patients with well-differentiated EGC, 4 (10.5 %) exhibited lymph node metastasis after surgery. Among the 7 patients with poorly differentiated EGC, 3 (42.9 %) exhibited lymph node metastasis. Poor differentiation of EGC correlates with a higher rate of lymph node metastasis ($p = 0.030$). Poorly differentiated EGC was 6.4 times more likely to show lymph node metastasis than well-differentiated EGC.

The cancer-free survival period was 78.3 ± 3.4 months in the surgical group and 64.5 ± 4.6 months in the close surveillance group. The recurrence rates did not differ significantly between the 2 groups, at 7.9 % in the surgical group and 6.7 % in the non-surgical group (Fig. 2).

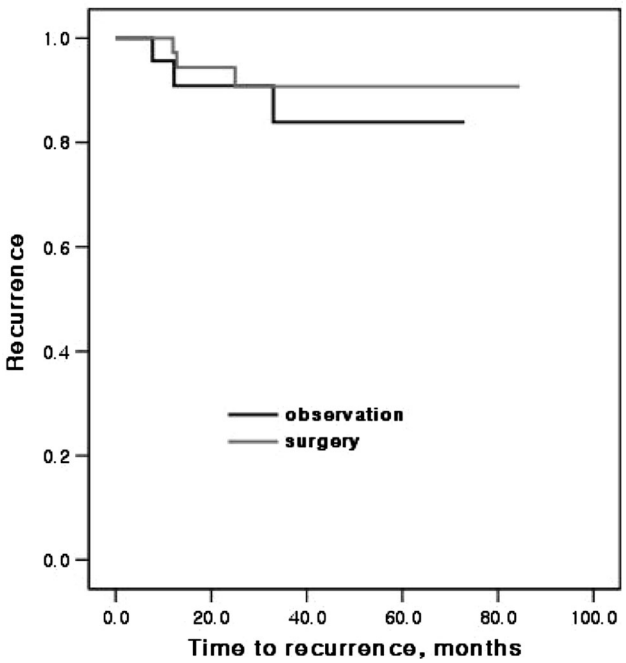

Fig. 2 Kaplan–Meier analysis of local recurrence according to additional treatment after non-curative endoscopic submucosal dissection of early gastric cancer

Discussion

As advances in medical imaging and endoscopic technologies today have enabled accurate diagnosis and precision in procedures, the use of ESD as a treatment option for EGC is becoming more popular. ESD is relatively less invasive than traditional surgery and presents sound advantages such as improved quality of life, organ preservation, and cost effectiveness. ESD is increasingly used even when a lesion does not meet the indication criteria in

patients with a high risk associated with radical gastrectomy, such as elderly patients and patients with accompanying diseases, or in patients who refuse operation. Additionally, incomplete resection after ESD is also becoming more frequent, thus warranting appropriate treatment.

Recent studies on prognosis and treatment of EGC cases with positive horizontal margins have been published. In cases with positive horizontal margins, additional operation or re-ESD is recommended with a confirmation rate higher than 20 % after incomplete resection [4–12]. However, if the risk of lymph node metastasis is low, close surveillance is also recommended [13–16].

Meanwhile, if lymphovascular invasion or a positive vertical margin is present after ESD, surgical treatment is the only acceptable standard treatment, as an additional endoscopic procedure is not an option [4]. The number of cases that are inappropriate for surgical operation owing to the aforementioned reasons is increasing, but not many studies have been performed in this regard. The present study conducted a relatively long-term monitoring and comparative analysis of clinical progress between EGC patients who underwent gastrectomy (surgical group) and EGC patients under close surveillance without additional surgery (close surveillance group) upon detection of lymphovascular invasion or a positive vertical margin post-ESD for EGC. In this study, 83 patients (12.7 % of overall) exhibited lymphovascular invasion or positive vertical margins after ESD for EGC. Analysis of the surgical and close surveillance groups showed no significant discrepancies in the recurrence rate between the 2 groups (6.7 and 7.9 %, respectively). In addition, the sustained close surveillance period before recurrence was longer than 60 months for both groups, which again showed no significant discrepancy. Furthermore, in the patients with M cancer or SM1 with a positive vertical margin, recurrence or lymph node metastasis was not detected. This proves that the probability of recurrence or lymph node metastasis was low. Furthermore, viable tumor cells were not detected in the cross-sectional view of excised tissue samples owing to electrocoagulation effects during resection for most of the cases with positive vertical margins. Based on these findings, close surveillance may be suggested as an option for EGC patients for whom surgical approach is difficult, who exhibit a positive vertical margin, and who have no lymphovascular or deep SM invasion.

Lee et al. reported that when additional gastrectomy was performed for patients with positive resection margins post-ESD, 84.6 % of the patients exhibited no residual cancer [17]. Koide et al. also reported that 94.4 % of patients who underwent gastrectomy for incomplete resection post-ESD exhibited no residual cancer [18]. Other studies reported that in long-term close surveillance of EGC patients who underwent gastric resection for incomplete resection, no lymph node or remote metastasis was found [16]. Similarly, in our studies, residual cancer in the gastric walls was not detected in the patients who underwent additional gastrectomy, of whom 84.4 % had no signs of lymph node metastasis. Despite 20 % of the patients not meeting the indication criteria, the fact that the incidence of residual cancer and lymph node metastasis was similar to that in other studies suggests that the ESD success rate in our hospital is also similar to that in other hospitals. The relatively high incomplete resection rate of 12.7 % is thought to be due to the large number of patients included in the study who did not meet the indication criteria.

The total number of recurrent cases in this study was 6 (7.3 %). Even after accounting for the cases with lymph node metastasis, the number is 12 (14.5 %) in total. Therefore, residual cancer or remote metastasis is considered rare even in cases with lymphovascular invasion or positive vertical margins post-ESD. These data may prove useful in evaluating the prognoses of patients who have undergone radical gastrectomy and those who have not.

Our study has several limitations. First, it was a retrospective study conducted in a single institution and with a small number of patients. Such limitations may lead to issues of selection bias and heterogeneous patient group. In this study, lymph node metastasis was detected in the resected tissue samples from 7 patients in the surgical group but was not detected in those from the patients in the close surveillance group. This may imply that the clinician had included more patients with relatively poor prognoses in the surgical group. However, prospective studies with close surveillance groups that exclude the current standard surgical treatment could not be performed. Moreover, despite the lack of surgical treatment that allows for radical removal of lesion sites and nodes, the fact that the surgical and close surveillance groups showed similar recurrence rates may have significant clinical implications. Second, a high proportion of EGC patients did not meet the indication criteria. At 12.7 %, the incidence of lymphovascular invasion or positive vertical margins post-ESD seems relatively high. As mentioned earlier, this is believed to be due to the relatively high inclusion rate (19.7 %) of lesions that did not meet the indication criteria compared with other studies. Considering that procedures are frequently performed outside the indication criteria, the results of this study are expected to bear more significance in the future.

In conclusion, the patients who were under close surveillance without additional surgical treatment for lymphovascular invasion or positive vertical margins after ESD had similar recurrence rates to those who underwent surgical resection. As such, close surveillance may be considered for EGC cases with positive vertical margins

but no lymph node metastasis or deep SM invasion for which surgical treatment is impossible. However, due to the limitations of this study being a single-institute retrospective research, additional large-scale studies that include multiple institutions are needed to confirm our results.

Disclosures Geum Youb Noh, Ha Ra Ku, Youn Joo Kim, Su Cheol Park, Jin Kim, Chul Ju Han, Yu Chul Kim, Ki Young Yang have no conflicts of interest or financial ties to disclose.

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