

Clinical Outcomes of Endoscopic Submucosal Dissection in Patients under 40 Years Old with Early Gastric Cancer

Kyu Yeon Hahn^{1,2}, Sang Kil Lee^{1,2}, Chan Hyuk Park³, Hyunsoo Chung^{1,2}, Jun Chul Park^{1,2}, Young Hoon Youn^{2,4}, Jie-Hyun Kim^{2,4}, Sung Kwan Shin^{1,2}, Yong Chan Lee^{1,2}

Division of Gastroenterology, Department of Internal Medicine, Severance Hospital¹, Institute of Gastroenterology², Yonsei University College of Medicine, Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine³, Division of Gastroenterology, Department of Internal Medicine, Gangnam Severance Hospital⁴, Seoul, Korea

Background/Aims: The clinicopathologic features of gastric cancer in young patients are different from those of older patients. However, endoscopic submucosal dissection (ESD) is performed regardless of age. The purpose of this study was to characterize younger patients (≤ 40 years) who underwent ESD for early gastric cancer (EGC) and analyze the results of ESD.

Materials and Methods: From January 2006 to June 2014, 55 patients aged 40 years or younger with newly diagnosed EGC underwent ESD at two tertiary hospitals. The clinicopathologic features of EGC and clinical outcomes of ESD in these young patients were reviewed retrospectively.

Results: A total 55 patients with 57 EGC lesions underwent ESD. Female sex, superficial flat or depressed lesions, and undifferentiated histology were more common in younger patients than in older patients in our institutional ESD cohort. The *en bloc* resection rate was 92.7% and the complete resection rate was 94.5%. Although there was a high proportion of undifferentiated cancer in the younger patient group, the curative resection rate was 72.7%. Among 15 patients with non-curative resection, 4 patients underwent additional surgery and 1 patient underwent argon plasma coagulation at the ESD ulcer margin. Eight patients were placed under close surveillance without additional treatment, and no recurrent tumors developed, with a median follow-up period of 37.2 ± 23.6 months.

Conclusions: Younger EGC patients who underwent ESD showed the typical characteristics seen in younger patients with gastric cancer. ESD in younger EGC patients showed comparable outcomes to those in patients with undifferentiated EGC in general. (Korean J *Helicobacter* Up Gastrointest Res 2016;16:139-146)

Key Words: Young age; Early gastric cancer; Endoscopic submucosal dissection

INTRODUCTION

Although the incidence and mortality rates of gastric cancer are declining overall, it is still the major cause of cancer-related deaths worldwide.¹ Especially, in Korea and Japan, where gastric cancer is prevalent, gastric cancer screening is commonly conducted. In Korea, since a nationwide gastric cancer screening program was started in 1999 as part of the National Cancer Screening Program, persons 40 years or older have been undergoing biennial upper endoscopies or upper gastrointestinal series.² Owing to mass screening programs and recent improvements in diagnostic technique, early detection in

a resectable state followed by treatment of gastric cancer has increased and, therefore, the overall survival rates have increased.²

Until now, in patients < 40 years, routine gastric cancer screening is not recommended. Gastric cancer is predominantly diagnosed in older patients. Gastric cancer usually occurs in the sixth and seventh decades of life, and is considered to be an age-related disease.^{1,3} The incidence of gastric cancer in patients younger than 40 years ranges from 2.4% to 6.2%.³⁻⁶ The clinicopathologic features of gastric cancer in young patients are different from those in older patients. It is considered that higher proportion of young patients have a histologically poorly differentiated type of cancer, female predominance, more aggressive tumor behavior, and metastatic disease at the time of diagnosis than older patients.^{3,5,6} Owing to these features and the delayed diagnosis, it is believed that the prognosis of young patients is worse than that of older patients.

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Corresponding author: Sang Kil Lee
Division of Gastroenterology, Department of Internal Medicine, Severance Hospital, Institute of Gastroenterology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1996, Fax: +82-2-393-6884, E-mail: sklee@yuhs.ac

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A few studies on gastric cancer in patients aged 40 years or younger have been reported.⁶⁻¹⁰ Because most previous studies included young patients with early gastric cancer (EGC) and advanced gastric cancer, the enrolled young patients showed more advanced-stage and metastatic disease at the time of diagnosis. Owing to awareness about rapid progression in young patients, there are concerns about endoscopic treatment in young patients with EGC that met the expanded indication of endoscopic submucosal dissection (ESD). Furthermore, little is known about the prognosis of young patients with EGC at a stage early enough for curative endoscopic treatment.

In the present study, therefore, we aimed to characterize young patients (aged 40 years or younger) who underwent ESD for EGC, and analyze the results of ESD.

MATERIALS AND METHODS

1. Patients

The prospective databases at two tertiary hospitals, Severance Hospital and Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea were reviewed retrospectively. From January 2006 to June 2014, 55 patients aged 40 years or younger with newly diagnosed EGC underwent ESD at the two tertiary hospitals. The demographic and clinicopathologic features and outcomes of the enrolled patients were reviewed by using the electronic medical record databases. Patients who underwent additional surgery directly after ESD or whose follow-up periods were less than a year were excluded in the long-term outcome analysis. The Institutional Review Board of Severance Hospital approved this study (IRB No. 4-2016-0537).

2. Indication for ESD and treatment protocol

EGC that met the expanded indication for ESD and curative resection was defined on the basis of the resected specimen according to the Japan Gastroenterological Endoscopy Society Guideline 2016, in collaboration with the Japanese Gastric Cancer Association.¹¹ Complete resection was defined when the resected specimens were cancer free in all lateral and vertical margins. The resection was considered as curative when all of the fol-

lowing conditions were fulfilled: *en bloc* resection, complete resection, no lymphovascular infiltration, and: (i) absolute indication; tumor size ≤ 2 cm, histologically differentiated type, intramucosal cancer without ulcerative lesion (UL[-]); (ii) expanded indication; (a) tumor size > 2 cm, histologically differentiated type, intramucosal cancer, UL(-); (b) tumor size ≤ 3 cm, intramucosal tumor, histologically differentiated type, UL(+); (c) tumor size ≤ 3 cm, histologically differentiated type, submucosal invasion (submucosa [SM] 1, $< 500 \mu\text{m}$ from the muscularis mucosa), UL(-); (d) tumor size ≤ 2 cm, histologically undifferentiated type, intramucosal tumor, UL(-).

Before ESD, all patients underwent esophagogastroduodenography (EGD) and abdominal CT for pre-ESD evaluation. ESD was performed in selected patients with EGC that met the expanded indication for ESD, when there was no evidence of lymph node metastasis in the pre-ESD evaluation. Patients with EGC beyond the pre-operative indication for ESD, and those who refused endoscopic treatment underwent surgery.

The ESD procedures were performed as described in our previous report.¹² After curative resection, the patients underwent surveillance EGD at 3, 6, 12, 18, and 24 months after ESD for detecting residual or recurrent tumors. After 24 months, surveillance EGD was performed every 12 months. In addition, abdominal CT was performed every 6 months for the first year and annually thereafter to detect lymph node metastasis or distant metastasis.

3. Definition

Any adverse events within 30 days and beyond after ESD were defined as acute and late complications. The type of recurrent gastric cancer was defined according to the time and site of recurrence. Recurrences at the previous ESD site within a year and after more than 1 year after the initial ESD were defined as residual disease and local recurrence. Synchronous and metachronous tumors were defined as recurrent tumors at a location other than the previous ESD site with a year and after > 1 year after the initial ESD. Recurrences at a distant lymph node, other solid organ, or carcinomatosis were defined as distant metastasis.

4. Statistical analysis

Statistical tests to compare the results included t-test, χ^2 test and Fisher's exact test. Mann-Whitney test was done for non-parametric variables. Continuous variables are expressed as mean \pm SD and categorical variables were expressed as numbers with percentage. $P < 0.05$ was considered statistically significant. All statistical analyses were performed by using IBM SPSS Statistics ver. 21.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline characteristics of the enrolled patients and lesions

The baseline characteristics of enrolled patients are shown in Table 1. From January 2006 to June 2014, a total of 55 patients aged 40 years or younger, with 57 lesions newly diagnosed as EGC, underwent ESD. The mean age of the enrolled patients was 37.6 \pm 3.3 years. Of these patients, 24 patients (43.6%) were women and 7 patients (12.7%) had a positive family history of gastric cancer in

Table 1. Baseline Characteristics of the Patients

Characteristic	Value
Patient	55
Lesion	57
Age (yr)	37.6 \pm 3.3
Sex	
Male	31 (56.4)
Female	24 (43.6)
Family history of gastric cancer in first degree relatives	
Absence	48 (87.3)
Presence	7 (12.7)
<i>Helicobacter pylori</i> infection	41 (74.5)
Comorbidity	
Hypertension	2 (3.6)
Cardiologic disease	1 (1.8)
Rheumatologic disease	2 (3.6)
Pulmonary tuberculosis	1 (1.8)
Pheochromocytoma	1 (1.8)
Other malignancy	3 (5.4)
Smoking history	27 (49.1)
Alcohol consumption	31 (56.4)
Symptom at the time of diagnosis	
Absence	35 (63.6)
Presence	20 (36.4)

Values are presented as number only, mean \pm SD, or n (%).

first-degree relatives. Forty-one patients (74.5%) had *Helicobacter pylori* infection, and successful eradication was performed. Three patients had malignancy in other organs (colon, thyroid, and cervix) at the time of diagnosis of gastric cancer. Of the enrolled patients, 49.1% had a history of smoking and 56.4% had a history of alcohol consumption. Among the 55 patients, 20 patients (36.4%) presented with symptoms at the time of disease detection. The most commonly presented symptoms were epigastric soreness and dyspepsia.

Table 2 shows the baseline characteristics of the lesions. Two patients had synchronous cancer at the time of diagnosis and underwent ESD in two different lesions. Among 57 lesions, 41 tumors (71.9%) were located at the lower third of the stomach. A large proportion of patients had flat or depressed lesions (48, 84.2%), lesions <2 cm (46, 80.7%), lesions with undifferentiated histology (37,

Table 2. Baseline Characteristics of the Lesions

Characteristic	Value
Patient	55
Lesion	57
Multiple initial early gastric cancer	2 (3.6)
Location	
Upper third	1 (1.8)
Middle third	15 (26.3)
Low third	41 (71.9)
Macroscopic appearance	
Elevated type	9 (15.8)
Flat or depressed type	48 (84.2)
Tumor size (cm)	
≤ 2	46 (80.7)
2~3	8 (14.0)
>3	3 (5.3)
Histology	
Adenocarcinoma well differentiated	10 (17.5)
Adenocarcinoma moderate differentiated	10 (17.5)
Adenocarcinoma poorly differentiated	3 (5.3)
Signet ring cell carcinoma	34 (59.6)
Differentiation	
Differentiated	20 (35.1)
Undifferentiated	37 (64.9)
Depth of invasion	
Mucosal invasion	54 (94.7)
Minute submucosal invasion (SM 1)	2 (3.5)
SM 2, deep submucosal invasion	1 (1.8)
Presence of ulcer	0

Values are presented as number only or n (%).
SM, submucosa.

64.9%), and intramucosal cancers (54, 94.7%). Especially, signet ring cell carcinoma was reported to be the most common histologic type (34, 59.6%) among the enrolled patients.

2. Short-term outcomes of ESD

The short-term outcomes of ESD are shown in Fig. 1 and Table 3. On the basis of the resected specimen, 16 lesions (29.1%) met the absolute indication, 29 lesions (52.7%) met the expanded indication and 10 lesions (18.2%) were beyond the indication for ESD. There was no diagnosis of lymphovascular infiltration. The rate of *en bloc* resection and complete resection was 92.7% and 94.5%, respectively. As a result, 40 patients (72.7%) underwent curative ESD. Of the 40 patients with curative resection, 14 patients with EGC met the absolute indication and 26 patients met the expanded indication for ESD. Of 15 patients with non-curative resection, 4 patients underwent additional surgery and 1 patient underwent endoscopic treatment (argon plasma coagulation at the lateral margin of the ESD scar). All of these four patients who underwent additional surgery were found to have no residual cancer and lymph node metastasis.

Seven patients reported acute complications after treatment. Five patients (9.1%) showed bleeding events and were treated successfully with endoscopic hemostasis.

Table 3. Short-term Outcomes of ESD

Variable	Value
ESD indication	
Absolute indication	16 (29.1)
Expanded indication	29 (52.7)
Beyond indication	10 (18.2)
Lymphovascular invasion	0
<i>En bloc</i> resection	51 (92.7)
Complete resection	52 (94.5)
Curative resection	40 (72.7)
Absolute indication	14 (35.0)
Differentiated EGCs in EI group	3 (7.5)
Undifferentiated EGCs in EI group	23 (57.5)
Acute complication	
Bleeding	5 (9.1)
Perforation	2 (3.6)
Additional treatment	
Endoscopic treatment	1 (1.8)
Surgery	4 (7.3)
Observation	8 (14.6)

Values are presented as n (%).
ESD, endoscopic submucosal dissection; EGC, early gastric cancer; EI, expanded indication.

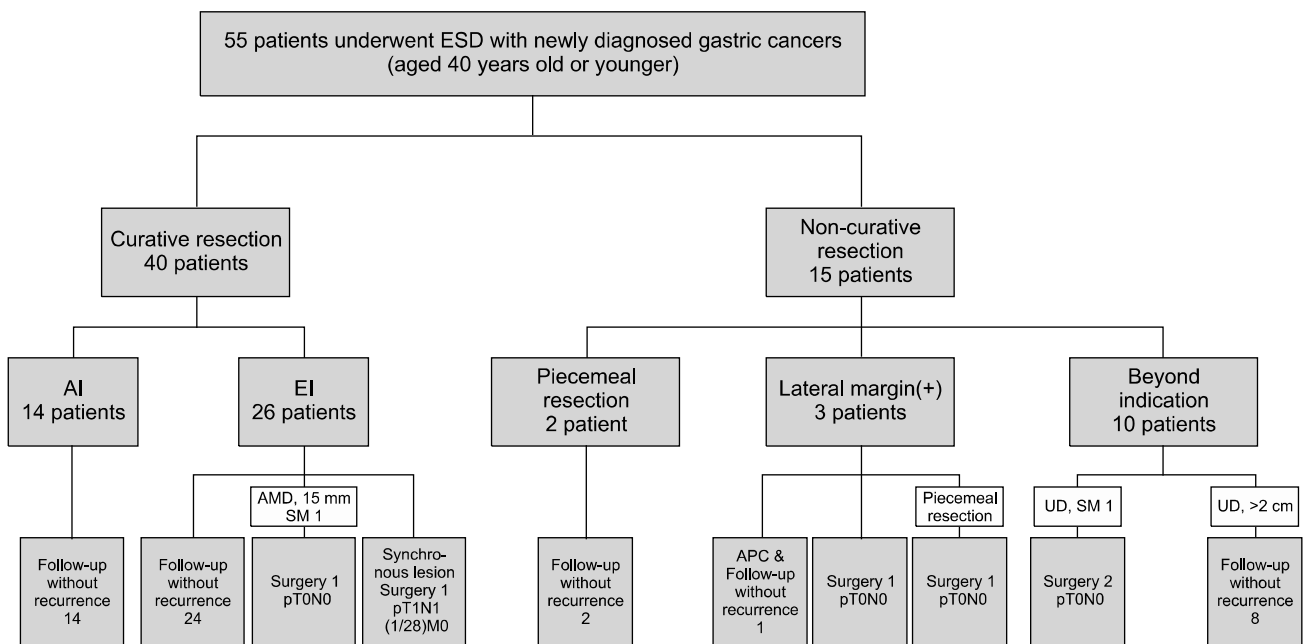


Fig. 1. Flow chart of enrolled patients. ESD, endoscopic submucosal dissection; AI, absolute indication; EI, expanded indication; AMD, adenocarcinoma; APC, argon plasma coagulation; UD, undifferentiated histology; SM, submucosa.

Two patients (3.6%) showed perforation at the time of the ESD procedures and were treated by using endoscopic clips.

3. Long-term outcomes of ESD

Table 4 and Fig. 1 show the long-term outcomes of ESD. A total 47 patients were included in the long-term outcome analysis. Patients who underwent additional surgery directly after ESD or those whose follow-up period was less than a year were excluded from the analysis. The median follow-up period of the enrolled patients was 37.2 ± 23.6 months. To date, none of the patients had developed delayed complications.

One patient with synchronous cancer diagnosed at 3 months after the initial ESD underwent additional gastrectomy and lymph node dissection. This patient was a 40-year-old man with EGC that met the expanded indication for ESD (signet ring cell histology, 6-mm intramucosal cancer, without ulcerative findings), and underwent curative ESD. At the first surveillance endoscopic examination after the initial ESD, he was found to have synchronous cancer and underwent gastrectomy. He underwent R0 resection and his cancer was diagnosed as stage IB EGC (T1aN1M0).

Among the 15 patients with non-curative resection, 2 patients with piecemeal resection did not undergo additional treatments and were undergoing regular surveillance examination at our institution without evidence of recurrence. One patient with only one lateral margin pos-

itive resection underwent argon plasma coagulation at the lateral margin of ESD scar and showed no recurrence. Eight patients with non-curative resection because of lesions that were beyond the indication with complete resection did not undergo additional treatments and are under close follow-up at our institution. To date, none of these nine patients had developed recurrent gastric cancer.

DISCUSSION

In this study, we analyzed the lesions and demographic characteristics of young patients who underwent ESD for EGC. We found that young EGC patients who underwent ESD showed similar typical characteristics to those of young gastric cancer patients, such as a lower male-to-female sex ratio, relatively high rates of positive family history of gastric cancer in first-degree relatives, and high incidence of poorly differentiated type histology.

Compared with previous studies,^{3,6,9,10,13} there were no significant differences between young gastric cancer patients with all-stage and early-stage disease in demographic characteristics, such as female predominance and higher proportion of positive family gastric cancer history in first-degree relatives, in our study. Gastric cancer is more common in male patients, with a high male-to-female sex ratio (1.62:1~2:1).¹ However, most previous studies on young gastric cancer patients showed a female predominance, with a lower male-to-female sex ratio (0.54:1~1.26:1).^{3,6,9,10,13} The male-to-female sex ratio of young gastric patients who underwent ESD was 0.77:1 in our study. This corresponds to findings in young gastric patients with not only advanced stage but also early stage of disease. Furthermore, relatively higher rates of positive family history of gastric cancer in first-degree relatives and lower rates of smoking history and alcohol consumption were similar characteristics between young gastric cancer patients with all-stage and early-stage disease. Although there was no obvious evidence of familial aggregation, a positive family history of gastric cancer in first-degree relatives is a known risk factor for developing the disease.^{14,15} Especially, a positive family history of gastric cancer correlates with younger age,¹⁵ and the rate of positive family history of gastric cancer in young gastric

Table 4. Long-term Outcomes of ESD

Variable	Value ^a
Patient	47
Median follow-up periods (mo)	37.2 ± 23.6
Delayed complication	0
Type of recurrence	1 (2.1)
Residual disease	0
Local recurrence	0
Synchronous tumor	1 (2.1)
Metachronous tumor	0
Distant metastasis	0

Values are presented as number only, median±SD, or n (%). ESD, endoscopic submucosal dissection.

^aThe cases which underwent surgery directly after the ESD or whose follow-up periods of less than 1 year were excluded.

cancer patients ranged from 5.9% to 19.3%.^{3,6,10,13} Like other studies on young gastric cancer patients including those with advanced-stage gastric cancer, relatively higher rates of young patients with early-stage disease (12.5%) had a positive family history of gastric cancer in first-degree relatives, and less than half the patients had a smoking history and about half of the patients had a history of alcohol consumption.

In previous studies, tumors located in the middle third, with a flat or depressed morphology, of the diffuse type according to Lauren's classification, and with undifferentiated type histology were more common in young gastric cancer patients than in older patients.^{3,6,10,13} Similarly, tumors with a flat or depressed morphology and undifferentiated type histology were common in young gastric patients who underwent ESD. The predominance of the undifferentiated type of cancer was one of the significant characteristics in young gastric cancer patients not only with advanced-stage but also those with early-stage disease. In this study, among 37 patients with the undifferentiated type of cancer, 34 patients presented signet ring cell carcinoma, except 3 patients with poorly differentiated adenocarcinoma. Even though we are not able to verify the exact evidence of these findings, this corresponds to previous reports that the predominance of signet ring cell in young gastric cancer patients (68% in 92 patients, 40 years of age or younger).⁴ Unlike the characteristics of advanced-stage cancer patients, the percentage of tumors located in the lower third for patients at the early stage were 71.9%, which was higher than that reported in Japan,^{3,6} China,¹⁰ and Korea.⁹ The percentages of tumors located in the middle and upper thirds were reported 41.4% and 20.1% in Japan,⁶ similar to that reported in China (60.0% in the middle and upper thirds).¹³ The tumors of young gastric cancer patients at an advanced stage were located more commonly in the upper or middle third, compared with that in young EGC patients who underwent ESD.

In previous studies, the prognosis of young patients was poorer and the survival rate was lower than those of older patients.^{16,17} The poor prognosis in young patients was believed to be a result of the higher proportion of patients with advanced-stage disease at the time of diag-

nosis, as well as their rapid progression compared with older patients. However, a few subsequent studies reported that the prognosis and survival rate were not significantly different between young and older patients after matching for tumor stage.^{3,13,18} Furthermore, the prognosis and survival rate of young patients after curative resection were better than those of older patients.^{5-7,9,13} Owing to awareness about aggressive tumor biology and rapid progression in young patients with gastric cancer, there were concerns about endoscopic local treatment in young patients with EGC, even for those that met the expanded indication for ESD. In the past, physicians and patients tended to choose surgery over ESD because of concerns about rapid progression and the possibility of recurrence of gastric cancer. Moreover, the higher proportion of the undifferentiated type histology caused physicians to hesitate about performing ESD for young patients. In our study, the curative resection rate of the enrolled patients was 72.7%. There were 10 patients with EGC beyond the indication for ESD based on the resected specimen after ESD. Most previous studies reported the curative resection rate of patients with EGC that met the expanded indication after excluding the patients with EGC beyond the indication for ESD.^{12,19,20} As with a previous method of data analysis, of 45 patients with EGC that met the expanded indication for ESD, 40 patients (88.9%) underwent curative resection in the present study. Even though there was a possibility of over-estimation due to small sample size, the curability in young patients was comparable to that in older patients.

The reported curative resection rate for EGC with undifferentiated type histology ranged from 61.9% to 90.7%.^{21,22} In a previous study at our institution, the curative resection rate was 75.9% in the undifferentiated histology group.¹² In the present study, all 10 patients with EGC beyond the indication for ESD had undifferentiated type histology. Two patients were found to have submucosal invasion, and the other eight patients had intramucosal cancer >20 mm. Two patients with submucosal invasion underwent additional surgery and were found to have no residual cancer and lymph node metastasis. Other eight patients with intramucosal cancer >20 mm had EGC with signet ring cell carcinoma. The size of the

lesion ranged from 21 to 44 mm, and the mean lesion size was 24.4 mm. Eight patients with EGC beyond the indication for ESD because of the large size of the lesion did not undergo additional treatment because patients refused additional surgery. To date, they are under close follow-up at our institution, and none have developed recurrent gastric cancer.

For young patients, the period of surveillance examination in their lifetime is longer than that of older patients. The cost and burden of lifelong surveillance cause hesitations about choosing ESD over surgery. A previous study at our institution reported that the annual incidence was 0.84% for recurrence at the previous ESD site and 2.48% for recurrence in the stomach other than the ESD site after curative resection.²³ Furthermore, scheduled endoscopic surveillance at least once in a year might help detect recurrent lesions at a stage early enough to allow for endoscopic treatment. Young patients after curative ESD should undergo strict scheduled endoscopic surveillance in their lifetime to detect early-stage recurrent gastric cancer. Further prospective studies are needed to compare between ESD and surgery with regard to the improvement of quality of life and the burden of lifelong surveillance examination in young patients.

Our study has several limitations. First, it had a retrospective design and there was a possibility of selection bias. However, to minimize the bias, we used the prospective collected databases at two tertiary hospitals. All patients who underwent ESD at two tertiary hospitals were enrolled in prospective observational ESD cohort. We reviewed the databases of young patients among this ESD cohort, retrospectively. Second, the follow-up duration of the enrolled patients was not long enough to evaluate the overall and disease-specific survival rates in young patients with EGC. However, in a previous study at our institution, the rates of recurrent tumors within 2 and 3 years after ESD were 73.05% and 87.23%, respectively.²³ Also, previous studies about surgery cases reported that the rate of recurrent gastric cancer within 2 and 3 years after gastrectomy were 68~75% and 89~90%, retrospectively.²⁴⁻²⁶ Even though recurrent gastric cancer can be developed 5~10 years after ESD, the median follow-up period of >3 years (37.2±23.6 months) was not short to

identify the incidence of recurrent gastric cancer in young patients. However, to evaluate the overall and disease-specific survival rates for young patients with EGC after curative resection, a lifetime observation study is needed in this study cohort.

In conclusion, young EGC patients who underwent ESD have similar characteristics to young EGC patients in general and the overall performance and outcomes of ESD in younger EGC patients seem to be comparable to those of general ESD for EGC. This finding implies the clinical efficacy of ESD in these patients after early diagnosis, and ESD can be optimal treatment for young patients with EGC met the expanded indication of ESD. If gastric cancer can be detected early enough to allow young patients to undergo ESD, this will also have a significant clinical meaning. For the oncologic safety, more long-term data and well-designed clinical trials are needed to support our findings.

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