

Original Article



Clinical Outcomes of Endoscopic Submucosal Dissection for Early Gastric Cancer in Patients with Comorbidities

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ABSTRACT

Purpose: As the rate of endoscopic resection for early gastric cancer (EGC) has increased in patients with comorbid diseases, it is necessary to elucidate the efficacy of endoscopic submucosal dissection (ESD) for EGC in patients with comorbidities. This study aimed to analyze the clinical outcomes of ESD for EGC in patients with comorbidities.

Materials and Methods: A total of 969 patients with 1,015 lesions who underwent ESD for EGC at Seoul National University Hospital between 2010 and 2014 were analyzed. The short- and long-term clinical outcomes were evaluated according to the comorbidity status.

Results: Comorbidities were observed in 558 patients (57.6%). The comorbidity group had a higher proportion of patients using antithrombotic agents (29.5% vs. 0.9%; $P < 0.0001$). Although procedure-related complications (bleeding and perforation) were not significantly different between the two groups, the length of hospital stay was significantly longer (1.8 vs. 1.4 days, $P = 0.023$), while survival was significantly shorter in the comorbidity group (5-year overall survival rate: 90.5% vs. 97.2%, $P < 0.0001$; 5-year disease-specific survival rate: 97.9% vs. 100%, $P = 0.018$; 5-year disease-free survival rate: 83.4% vs. 89.2%, $P = 0.007$).

Conclusions: Gastric ESD can be performed in patients with comorbidities without increasing the risk of complications.

Keywords: Endoscopic submucosal dissection; Stomach neoplasms; Comorbidity

INTRODUCTION

According to the 2018 Global Cancer Observatory (GLOBOCAN) data, gastric cancer had the 5th highest incidence and 3rd highest mortality rate among all malignancies worldwide [1]. According to the 2018 National Cancer Information Center data, gastric cancer ranked first in terms of incidence but ranked 4th in terms of mortality among all malignancies reported in Korea [2]. Since the implementation of the Korean National Cancer Screening Program in 1999, the rate of gastric cancer detection by upper gastrointestinal endoscopy or barium study has been increasing [3].

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Author Contributions

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

Conflict of Interest

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

According to the Korean Practice Guidelines for Gastric Cancer 2018, endoscopic resection has been regarded as a definitive treatment modality for early gastric cancer (EGC) [4]. Endoscopic submucosal dissection (ESD) is a standard endoscopic treatment for EGC and is a minimally invasive procedure with negligible risk of recurrence rate, lymph node and/or distant metastasis, low post-procedural complication, and high en bloc resection rate [5-8].

Korea is a rapidly aging country, and the prevalence of chronic diseases is increasing. Worldwide, 41 million people die from chronic diseases every year, accounting for 71% of all deaths, while the annual number of deaths due to chronic diseases in Korea is 235,000 people, accounting for 80% of all deaths [9]. Of the patients diagnosed by a physician with at least one chronic disease in Korea, 68.7% were in their 50s, 83.7% were in their 60s, and 91.3% were in their 70s or older [10].

As the incidence of ESD for EGC has continuously increased, endoscopic procedures have also increased in older patients and/or those with comorbidities. In previous studies conducted in groups with comorbidities, the clinical outcomes were analyzed by dividing the patients using a physical severity assessment tool such as the Charlson Comorbidity Index or American Society of Anesthesiologists Physical Status (ASA-PS) classification system [11-13]. As a result, the short-term clinical outcomes were not significantly different between the groups; meanwhile, the comorbidity groups showed a higher mortality rate as a long-term clinical outcome.

In this study, we aimed to compare and analyze the procedure-related and non-related short- and long-term clinical outcomes that might affect the patients' general condition between the group with comorbidities and the previous healthy group, and the analyses were not limited to the patients classified according to the type of physical severity assessment tool.

MATERIALS AND METHODS

Participants

This study was a retrospective review of the efficacy of ESD for EGC in patients with comorbidities. Patients who underwent ESD for EGC at Seoul National University Hospital between 2010 and 2014 were reviewed. The comorbidities were defined using the following International Classification of Diseases-10 codes: (1) hypertension (I10-I16), (2) diabetes (E08-E14), (3) chronic kidney disease (with the highest eGFR of <60 mL/min in the last two measurements) (N18), (4) chronic liver disease and viral hepatitis (K70-K77 and B15-B19, respectively), (5) coronary heart disease (I20-I25), (6) stroke and transient ischemic attack (I60-I67 and G45, respectively), and (7) cancers diagnosed in the last 5 years, excluding non-melanoma skin cancer (C00-C96 except C44, C4A, and C16). Patients with current pregnancy, history of previous gastrectomy or endoscopic resection, or missing data were excluded from the analysis.

This study was approved by the Institutional Review Board of Seoul National University Hospital (H-1912-067-1088) and was conducted in accordance with the Declaration of Helsinki.

ESD procedure

ESD was performed under conscious sedation using midazolam and/or propofol and cardiopulmonary monitoring. A standard single-channel endoscope (Olympus H260,

Olympus Optical) with a needle knife (KD-1 L; Olympus) and a forced 20-W coagulation current (VIO 300D; Erde, Tübingen, Germany) was used to create a 5 mm mark outside of the lesion. Then, a mixed solution of normal saline, diluted epinephrine (1:100,000), and indigo carmine was injected into the submucosal layer to create a submucosal cushion, and a small initial incision was made with a needle knife. Subsequently, circumferential mucosal incision and submucosal dissection were performed using an insulation-tipped knife (Kachu Technology Co. Ltd., Seoul, Korea). Finally, when bleeding occurred during and after the procedure due to a damaged vessel, a Coagrasper was used to cauterize the tip of the vessel. The procedure time was recorded from the start of mucosal marking to the end of hemostasis. Post-ESD bleeding was defined as one or more of the following signs of bleeding: hematemesis or melena, unstable vital signs, a reduction in the hemoglobin level by >2 g/dL, or a need for endoscopic hemostatic treatment after the completion of the procedure. The signs of bleeding observed within 24 hours were defined as immediate post-ESD bleeding, while those after 24 hours were defined as delayed bleeding. Perforation associated with the ESD procedure was diagnosed endoscopically during the procedure or as pneumoperitoneum on chest radiography.

Histopathological evaluation

According to the Japanese Classification of Gastric Carcinoma, the macroscopic types of EGC lesions were as follows: elevated (0-I and 0-IIa), flat (0-IIb), and depressed (0-IIc and 0-III); meanwhile, the locations of the lesions were divided into upper, middle, and lower parts [14]. The resected specimens were promptly stretched and pinned on a flat polystyrene board to prevent folding and fixed in 10% formalin. For histological evaluation, the fixed specimens were serially sectioned at 2-mm intervals. The histologic type, degree of differentiation, tumor size, invasion depth, tumor involvement in the margin, and lymphovascular invasion were assessed according to the JCGC. During the procedure, a biopsy specimen was taken from the antrum and body to evaluate the presence of *Helicobacter pylori* infection, mucosal atrophy, and intestinal metaplasia. Mucosal atrophy and intestinal metaplasia were histologically graded as 0 (none), 1 (mild), 2 (moderate), and 3 (marked), and grouped into none (0 and 1) and present (2 and 3) based on the Updated Sydney System [15].

En bloc resection was defined as resection of the tumor in one piece. The absolute histologic criteria for a curative resection were en bloc resection, absence of lymphovascular involvement, and presence of a differentiated mucosal cancer measuring 2 cm or less without ulceration. In addition, the expanded criteria for a curative resection were as follows: (1) differentiated mucosal cancer of >2 cm in diameter without ulceration, (2) differentiated mucosal cancers of ≤ 3 cm in diameter with ulceration, (3) differentiated minute submucosal cancers within 500 μ m of the muscularis mucosa and ≤ 3 cm in diameter, and (4) undifferentiated mucosal cancer ≤ 2 cm in diameter without ulceration. By contrast, a non-curative resection was performed in patients whose histological outcomes did not meet the above criteria.

Follow-up

After ESD, chest radiography was performed to confirm the presence of perforation. To prevent bleeding, a proton-pump inhibitor was injected intravenously after the procedure, and oral medication was prescribed for 6 weeks to promote ulcer healing. Eradication therapy was provided in patients with *H. pylori* infection. Follow-up surveillance endoscopy, abdominal computerized tomography, and chest radiography were performed every 6 months for 1 year and then annually thereafter.

Outcome assessment

In this study, local recurrence was defined as cancer recurrence at the treated site, synchronous recurrence when the cancer recurred at another site within 12 months, and metachronous recurrence when cancer recurred at another site after 12 months. Overall survival was measured from the date of ESD for EGC to the date of all-cause death. Disease-specific survival was measured from the time after surgery to the date of death associated with gastric cancer. Disease-free survival was measured from the date of ESD to the date of tumor recurrence, distant metastasis, or all-cause death. Tumor recurrence included local recurrence and occurrence of synchronous and metachronous gastric cancers. Patients who dropped out during follow-up were censored on the day of the last follow-up.

Statistical methods

Demographic information between the two independent groups were compared using the t-test and χ^2 test. Survival rates were calculated using the Kaplan–Meier method, while the two groups were compared using the log-rank test. All statistical tests were two tailed, and a P-value of <0.05 was considered significant. Multivariable regression analyses were used to analyze the comorbidities associated with long-term outcomes. Significant factors in the multivariable analysis were included in the multivariable logistic regression model. Statistical analyses were conducted using SPSS software, version 26 for Windows (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 969 patients with EGC underwent ESD, of whom 558 had comorbidities. The mean age was significantly higher in the group with comorbidities ($P < 0.0001$). The use of antithrombotic agents was more frequently observed in the group with comorbidities ($P < 0.0001$). Family history of gastric cancer was less frequent ($P = 0.008$) and the follow-up duration was significantly shorter in the group with comorbidities ($P = 0.003$). However, sex, histologic type of the lesion, histologic type by Lauren, tumor size, location, gross type, depth of tumor invasion, presence of ulcer, lymphovascular invasion, mucosal atrophy, and intestinal metaplasia did not significantly differ between the two groups (**Table 1**).

The most common comorbidity was hypertension, followed by diabetes, chronic liver disease, viral hepatitis, newly diagnosed cancer in the last 5 years (excluding non-melanoma skin cancer), coronary heart disease, stroke, transient ischemic attack, and chronic kidney disease (highest eGFR of <60 mL/min in the last two measurements).

Clinical outcomes of ESD

Procedure time, en bloc and curative resection, non-curative resection rates, and additional treatments for non-curative resection were not significantly different between the two groups. In addition, the recurrence rate ($P = 0.395$) and procedure-related complication rate ($P = 0.462$) were not significantly different. Although the incidence of procedure-related fever and aspiration pneumonia were not significantly different between the two groups, the length of hospital stay was significantly longer in the group with comorbidities ($P = 0.023$; **Table 2**).

Table 1. Baseline characteristics between the groups with and without comorbidities

Variables	Previous healthy group (n=411)	Comorbidity group (n=558)	P-value
Age (yr)	60.8±9.7	66.3±9.2	0.0001
Sex, M:F	268 (65.4):142 (34.6)	380 (68.1):178 (31.9)	0.372
Comorbid diseases			
Hypertension		401	
Diabetes		178	
CKD		11	
CLD and viral hepatitis		73	
CHD		70	
Stroke and TIA		70	
Cancer		71	
Family history of gastric cancer	80 (19.6)	74 (13.3)	0.008
Use of antithrombotic agents	5 (0.9)	180 (29.5)	0.0001
H. pylori status			
Negative	88 (24.1)	125 (29.4)	0.020
Persistent	121 (33.2)	139 (32.7)	
Eradicated	127 (34.8)	111 (26.1)	
Unevaluated	29 (7.9)	50 (11.8)	
Histologic type			
Differentiated	377 (92.0)	519 (93)	0.535
Undifferentiated	33 (8.0)	39 (7.0)	
Histologic type by Lauren			
Intestinal	382 (93.4)	527 (95.3)	0.372
Diffuse	17 (4.0)	16 (3.1)	
Mixed	10 (2.6)	9 (1.6)	
Tumor size, mm	17.6±10.4	18.4±12.1	0.286
Location of tumor			
Upper	13 (3.2)	11 (2.0)	0.299
Middle	143 (35.0)	180 (32.3)	
Lower	253 (61.9)	366 (65.7)	
Gross type			
Elevated	59 (14.5)	73 (13.1)	0.242
Flat	67 (16.5)	73 (13.1)	
Depressed	281 (69.0)	410 (73.7)	
Depth of tumor invasion			
Mucosa	347 (84.8)	467 (83.8)	0.349
SM1	28 (6.8)	51 (9.2)	
SM2	34 (8.3)	39 (7.0)	
Ulcer	20 (11.6)	36 (13.9)	0.492
Lymphovascular invasion	26 (6.4)	38 (6.8)	0.779
Antral mucosal atrophy			
No	174 (49.4)	184 (45.0)	0.358
Yes	51 (14.5)	57 (13.9)	
Non-applicable	127 (36.1)	168 (41.1)	
Antral intestinal metaplasia			
No	173 (49.1)	202 (49.4)	0.559
Yes	178 (50.6)	207 (50.6)	
Non-applicable	1 (0.3)	0 (0.0)	
Body mucosal atrophy			
No	174 (49.6)	213 (52.1)	0.750
Yes	64 (18.2)	74 (18.1)	
Non-applicable	113 (32.2)	122 (29.8)	
Body intestinal metaplasia			
None	202 (57.5)	237 (58.1)	0.881
Mild	149 (42.5)	171 (41.9)	
Follow-up duration, mon	69.7±30.9	63.4±32.0	0.003

Values are presented as mean±standard deviation or number (%).

CKD = chronic kidney disease; CLD = chronic liver disease; CHD = coronary heart disease; TIA = transient ischemic attack.

Table 2. Clinical outcomes between the groups

Variables	Previous healthy group (n=411)	Comorbidity group (n=558)	P-value
Procedure time, min	21.5±15.8	20.6±17.9	0.435
En bloc resection	404 (98.8)	553 (99.6)	0.119
Curative resection	323 (78.8)	456 (81.7)	0.254
Non-curative resection	87 (21.2)	102 (18.3)	0.254
Additional treatment status			0.462
Surgery	22 (25.3)	34 (32.7)	
APC	4 (4.6)	6 (5.8)	
Follow-up	61 (70.1)	64 (61.5)	
Recurrence			0.395
Local recurrence	27 (7.5)	24 (5.0)	
Synchronous cancer	3 (0.8)	7 (1.5)	
Metachronous cancer	13 (3.6)	20 (4.2)	
Procedure related complication	47 (11.4)	75 (13.5)	0.462
Post-ESD bleeding	21 (5.1)	26 (4.7)	0.750
Perforation	5 (1.2)	5 (0.9)	0.627
Fever	29 (7.1)	51 (9.2)	0.243
Aspiration pneumonia	0 (0.0)	2 (0.4)	0.511
Hospital stay, days	1.4±0.73	1.8±4.11	0.023

Values are presented as mean±standard deviation or number (%).

APC = argon plasma coagulation; ESD = endoscopic submucosal dissection.

Survival analysis

The overall 5-year survival rate was 97.2% in the previous healthy group and 90.5% in the comorbidity group ($P < 0.0001$). The 5-year disease-specific survival rates were 100% and 97.9% ($P = 0.018$), while the 5-year disease-free survival rates were 89.2% and 83.4% ($P = 0.007$) in the previous healthy group and comorbidity group, respectively; these results showed that the survival rates were significantly lower in the comorbidity group (**Fig. 1**). The comorbidity factors significantly associated with worse overall survival on multivariate analysis were chronic liver disease, coronary heart disease, and cancers (**Table 3**).

DISCUSSION

Since ESD has been regarded as a safe therapeutic modality, its indication included patients with comorbidities, older age, and tumors. Patients with comorbidities tend to be older and use antithrombotic drugs more frequently according to their characteristics. As comorbidity or use of antithrombotic drugs might result in an increased risk of post-procedural complications and/or compromised survival, we aimed to compare the efficacy and safety of ESD between the previous healthy group and comorbidity group.

Table 3. Multivariable logistic regression analysis of comorbidities associated with overall survival

Variables	Odds ratio (95% CI)	P-value
Hypertension	1.06 (0.66–1.71)	0.814
Diabetes	1.33 (0.77–2.28)	0.305
CKD	2.50 (0.82–7.58)	0.106
CLD and viral hepatitis	2.49 (1.30–4.79)	0.006
CHD	2.61 (1.35–5.05)	0.005
Stroke and TIA	1.39 (0.66–2.96)	0.388
Cancer	4.18 (2.31–7.58)	0.0001

CI = confidence interval; CKD = chronic kidney disease; CLD = chronic liver disease; CHD = coronary heart disease; TIA = transient ischemic attack.

Clinical Outcomes of ESD for EGC

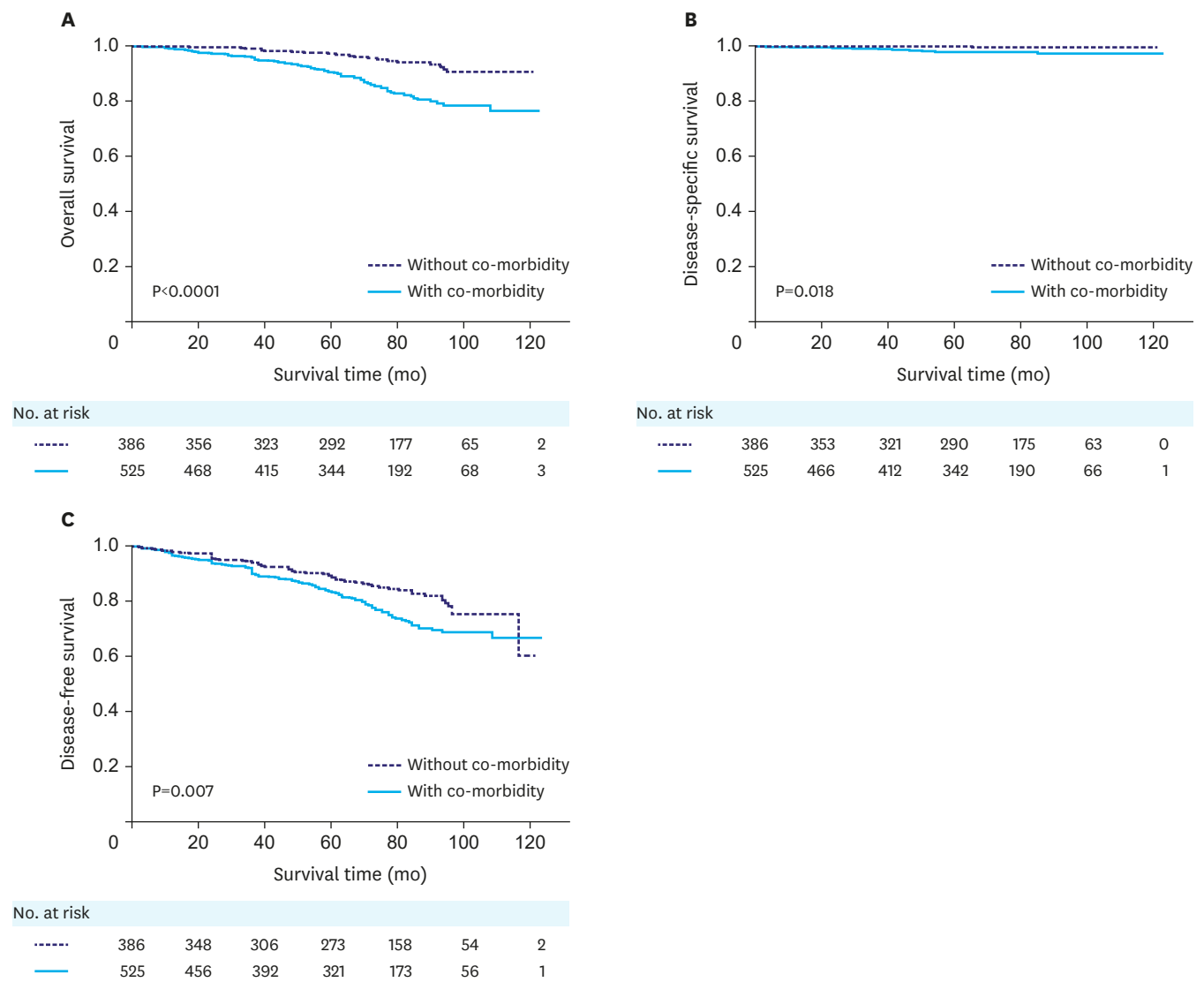


Fig. 1. Kaplan-Meier plots for (A) overall survival, (B) disease-specific survival, and (C) disease-free survival in all the patients.

Stomach cancer is the most common cancer among Korean men aged 35–64 years and women aged 65 years and older, and its incidence rate increases with age [2]. The mean age in the comorbidity group was higher than that in the previous healthy group, which might have resulted from the common distribution of comorbidities in older patients. In a previous study, the en bloc resection and complication rates in patients aged >75 years were not significantly different from those of younger patients [16]. In another study, short-term clinical outcomes such as adverse events and curability did not differ between the 80-year age group with frailty and the 80-year age group without frailty [17]. However, the long-term clinical outcomes were worse in patients with frailty than in those without frailty. Moreover, procedure time, length of hospital stay, procedure-related complications, en bloc and complete resection rate, and delayed bleeding were not significantly different between the older group (>80 years old) and the non-older group [18]. However, the procedure time with preventive hemostasis was significantly higher in the older group. Based on these data, ESD is considered a safe procedure even for the older group.

Antithrombotic drugs such as antiplatelets and anticoagulants have been increasingly used worldwide to reduce and prevent thromboembolic events in patients with cerebrovascular and cardiovascular diseases. Among the patients included in this study, cardiovascular diseases such as hypertension, stroke, TIA, and coronary heart disease were the most common comorbidities, and the number of patients using antithrombotic agents was significantly higher in the comorbidity group. Although post-procedural bleeding might be higher in the comorbidity group with frequent use of antithrombotics, no significant difference was observed in the risk of complications between the two groups, which might have resulted from the disappearance of the risk of adverse events due to the discontinuation of antithrombotic therapy during the time of ESD. Moreover, the use of antiplatelet or thienopyridine did not increase the risk of bleeding after ESD in previous retrospective studies [19,20].

In terms of the short-term clinical outcomes, no significant differences were found in the procedure time, en bloc resection rate, curative resection rate, and procedure-related complications between the two groups. No significant differences were also observed in the procedure time, en bloc resection rate, curative resection rate, and complication between the high-risk with comorbidities group and the low-risk without comorbidities group based on the Charlson Comorbidity Index [11]. In addition, the short-term outcomes such as aspiration pneumonia, arrhythmia, delirium, and ischemic heart attack were not significantly different between the group with comorbidities and that without comorbidities according to the ASA-PS classification system [12,13]. However, the length of hospital stay was lengthened in the comorbidity group due to the additional management of underlying diseases.

In terms of long-term clinical outcomes, the mean follow-up duration was significantly lower in the comorbidity group. As the 5-year overall survival and disease-free survival rates were significantly associated with the status of comorbidities, the follow-up duration might be influenced by the survival rate based on the status of comorbidities as well as EGC itself. In a previous study, the 5-year overall survival was significantly lower in the group with severe comorbidities than in the group with no or mild comorbidities [13].

This study has several limitations. First, this was a retrospective study conducted at a single center. A prospective study might be beneficial to further evaluate the validity of ESD for EGC in patients with comorbidities. However, this study presents reliable results with a higher number of patients than the previous studies. Second, most of the comorbidities were confirmed by taking the patient's history. Therefore, there was a possibility of classification bias in this study. Third, the comorbidities were not divided by disease severity. Therefore, the results could not be stratified by disease severity, which might affect the short- and/or long-term clinical outcomes.

In conclusion, ESD could be performed with a comparable risk of complications, even in patients with comorbidities. In conclusion, the long-term outcomes of gastric ESD for patients with comorbidities were worse than those without comorbidities, resulting in lower long-term survival rates. ESD can be performed with a comparable risk of complications, even for patients with comorbidities.

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