ORIGINAL ARTICLE

Short-Term Outcomes of Endoscopic Submucosal Dissection in Patients with Early Gastric Cancer: A Prospective Multicenter Cohort Study

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Background/Aims: Endoscopic submucosal dissection (ESD) is an effective treatment for early gastric cancer (EGC) that has demonstrated a minimal risk of lymph node metastasis in retrospective studies. We sought to prospectively evaluate the short-term outcomes of ESD treatment in EGCs. **Methods:** A prospective multicenter cohort study of neoplasms 3 cm or less in diameter at endoscopic size evaluation was performed in 12 Korean ESD study group-related university hospitals and the National Cancer Center. Resected specimens were evaluated by the central pathologic review board. **Results:** A patient cohort (n=712) with a total of 737 EGCs was analyzed. The margin-free *en bloc* resection rate was 97.3%, and curative resection of 640 lesions (86.8%) was achieved. Lower curative resection rates were associated with lesions 2 to 3 cm in size prior to ESD compared with lesions 2 cm or less in size (78.6% vs 88.1%, respectively, p=0.009). Significant factors associated with noncurative resection were moderately or poorly differentiated histological type, posterior wall tumor location, tumor size larger than 3 cm, ulceration, and submucosal invasion. Delayed bleeding occurred in 49 patients (6.9%), and 12 patients (1.7%) exhibited perforations. **Conclusions:** ESD is an effective treatment with a high curative resection rate for EGCs that meets relatively conservative pre-ESD indications. Long-term survival outcomes should be evaluated in follow-up studies. **(Gut Liver 2016;10:739-748)**

Key Words: Stomach neoplasms; Endoscopy, gastrointestinal; Outcome assess; Prospective studies

INTRODUCTION

As the National Cancer Screening Program provides esophagogastroduodenoscopy for gastric cancer screening every 2 years, early gastric cancer (EGC) is increasingly detected in Korea.[1,2] The criteria without risk of lymph node metastasis in EGC were adopted as an absolute or expanded indication of endoscopic resection, and EGC meeting these criteria is treated with endoscopic submucosal dissection (ESD).[3] In recent years, ESD has become the primary endoscopic treatment for EGC because of higher *en bloc* and curative resection rates compared to endoscopic mucosal resection (EMR), although ESD has higher

rates of adverse events.[4-6] Moreover, ESD provides a better quality of life to patients compares with surgical treatment.[7]

In retrospective studies, long-term survival outcomes of ESD were excellent in patients with EGC meeting absolute or expanded indications.[8-12] Recent meta-analysis also showed that long-term mortality in the expanded indication group did not differ from those with conventional absolute indication group.[13] However, local recurrences or distant metastasis in EGC cases meeting the indications may occur.[14] Moreover, ESD outcomes from retrospective studies are based on pathological findings after resection and pre-ESD inclusion criteria are not usually defined, which might cause selection bias.[4] Also, patients who might have poor outcome could be selectively lost to follow up in retrospective studies. To overcome these limitations, prospective studies with clearly defined pre-ESD criteria and with minimal follow-up loss rates are necessary, but have not been reported yet.

Pathological diagnoses for gastric cancer may have significant inter-observer variations[15] and are subject to histological misclassifications.[16] Moreover, the pathological criteria of diagnosing gastric cancer in Western countries including Korea, which adopted the World Health Organization classification of tumors, slightly differ from the Japanese criteria.[17,18] Thus, it is uncertain whether the outcomes of ESD in other part of the world are compatible with Japanese outcomes.

In this study, we defined a prospective cohort to investigate long-term outcomes of ESD in the treatment of patients with EGC confirmed by a central pathological review. Herein, we preliminarily report short-term effectiveness and safety outcomes in the cohort.

MATERIALS AND METHODS

1. Study design

This is a multicenter, prospective cohort study to evaluate long- and short-term outcomes of ESD on EGC. From May 2010 to December 2011, patients who had planned ESD were prospectively enrolled from 12 university hospitals nationwide in Korea and the National Cancer Center. The minimum requirement for a center participating in the study was at least 20 ESD cases per year. This study was performed in collaboration with National Evidence-based Healthcare Collaborating Agency (NECA), which is the national research agency of Korea that was established to provide authentic and quality information about medical devices, medicines, and health technology through objective and reliable analyses.

2. Patients

Pre-ESD inclusion criteria for patients and lesions were (1) adults aged at least 20 years old; (2) endoscopically-estimated lesion sizes ≤3 cm; (3) histologically well-differentiated or moderately differentiated adenocarcinoma or adenoma based on pathological evaluation of the biopsy specimen; (4) no endoscopic active or healing stage ulceration on the lesion; and (5) no evidence of lymph node metastasis on abdominal computed tomography (CT). Patients were ineligible if they (1) had history of cancer in other organs; (2) had a history of stomach surgery; (3) had a severe comorbid condition; (4) had a bleeding tendency; (5) were pregnant or possibly pregnant; or (6) were unable to provide informed consent.

3. Participant selection and follow-up

Informed consent was obtained from patients who were subjected to ESD for EGC or adenoma/dysplasia. Patients were enrolled if they fulfilled the requirements for eligibility according to the inclusion and exclusion criteria. Pathological evaluation after ESD was performed initially by a gastrointestinal pathologist at each participating center. Decisions about further treatment were made based on the pathologic results at each center. Follow-up periods were defined as 3 months, 6 months, 1 year, and yearly for 5 years after ESD, at which times endoscopy, abdominal CT, chest radiography, and laboratory tests were planned.

4. ESD procedure

ESD was performed under sedation with monitoring of cardiorespiratory function according to the standard procedure in each hospital, including marking, mucosal incision, and submucosal dissection with hemostasis. Detailed procedures and used devices were described in a previous study.[5]

Briefly, marking was made 2 mm outside of the lesion using the tip of an electrosurgical device or argon plasma coagulation. Then, various submucosal solutions were injected into the submucosal layer, and a circumferential mucosal incision was made using an electrosurgical knife according to the endoscopist's preference. Complete dissection of the submucosal layer is recommended, but snaring for resection was allowed after 50% of submucosal dissection was completed. Endoscopic hemostasis was performed for any oozing or exposed vessel both during and after the procedure. High-frequency generators (VIO 300D; ERBE, Tübingen, Germany) were used for the entire procedure.

5. Pathologic evaluation

Resected specimens were fixed in 10% neutral-buffered formalin and embedded into paraffin for histological evaluation. Sections (2-mm interval) were stained with hematoxylin and eosin. Diagnoses were made according to the World Health Organization classification of gastric cancer.[17] After the initial evaluation, slides of specimens were sent to an independent central pathology review board, which consisted of 16 specialists in gastrointestinal pathology who are members of the Korean Society of Pathologists. To make the final pathologic diagnoses, an agreement rate of 70% or more was required. Pathologic diagnoses composed the standard for primary out-

come evaluation and subgroup analyses.

6. Efficacy and safety assessments

Patients who had adenoma at central pathological review were excluded from the analysis. The primary outcome variables in this study are short-term outcomes of ESD and safety analyses. Short-term outcomes included histological complete resection rate, procedure time, treatments after ESD, and adverse event rates. Safety analyses included any adverse events and either death or life-threatening events associated with the procedure within 30 days of ESD. Long-term outcomes will be reported after the 5-year follow-up of the last enrolled patient, which is expected to be in December 2016.

Demographic data, clinical variables, lesion characteristics, and treatment-related variables were collected. *Helicobacter pylori* infection was evaluated by histological staining, rapid urease test, or noninvasive urea breath test.

7. Definitions

After evaluation of resected specimens, lesions were classified as complete or incomplete resection. In our protocol, complete resection was defined when an EGC was resected with tumor-free horizontal and vertical margins and was confirmed to be a differentiated-type carcinoma confined to the mucosal layer without lymphovascular invasion.

Curative resection was defined based on the Japanese Gastric Cancer Association (JGCA) recommendation for curability criteria. Lesions meeting the absolute or expanded indication and removed by *en bloc* resection with tumor-free horizontal margin and vertical margin were considered curative resection, if there was no lymphatic or venous invasion.[3] Absolute indica-

tions for ESD included mucosal differentiated-type histology carcinoma with the size ≤2 cm without ulcerative findings.[3] Condition for expanded indications were (a) differentiated-type histology mucosal cancer of tumor size >2 cm if ulcerative finding was negative; (b) differentiated-type histology mucosal cancer with tumor size ≤3 cm if ulcerative finding was present; (c) undifferentiated-type mucosal cancer with tumor size ≤2 cm without ulcerative finding; or (d) differentiated-type histology cancer with tumor size ≤3 cm without ulcerative finding if the lesion invaded superficial submucosal layer (<500 μm from the muscularis mucosae).[3]

Adverse bleeding events were defined as clinical symptoms including melena or hematemesis, or a 2 g/dL decrease in hemoglobin levels after the procedure. Perforation was categorized as frank or microperforation. Frank perforation was defined as a perforation noticed during the procedure by visualization of an intraperitoneal organ or visceral fat through a full-thickness laceration of the stomach wall. Microperforation was defined when recognized after the procedure by intraperitoneal free air on plain chest radiography or abdominal CT without frank perforation noticed during the procedure.

8. Statistical analyses

Demographic information is presented as descriptive statistics. Efficacy measurements including complete or curative resection, and safety measurements are presented as percentages and 95% confidence intervals (CI). Multiple logistic regression analyses were performed to evaluate the associated factors for complete or curative resection. For all analyses, p<0.05 was considered statistically significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).
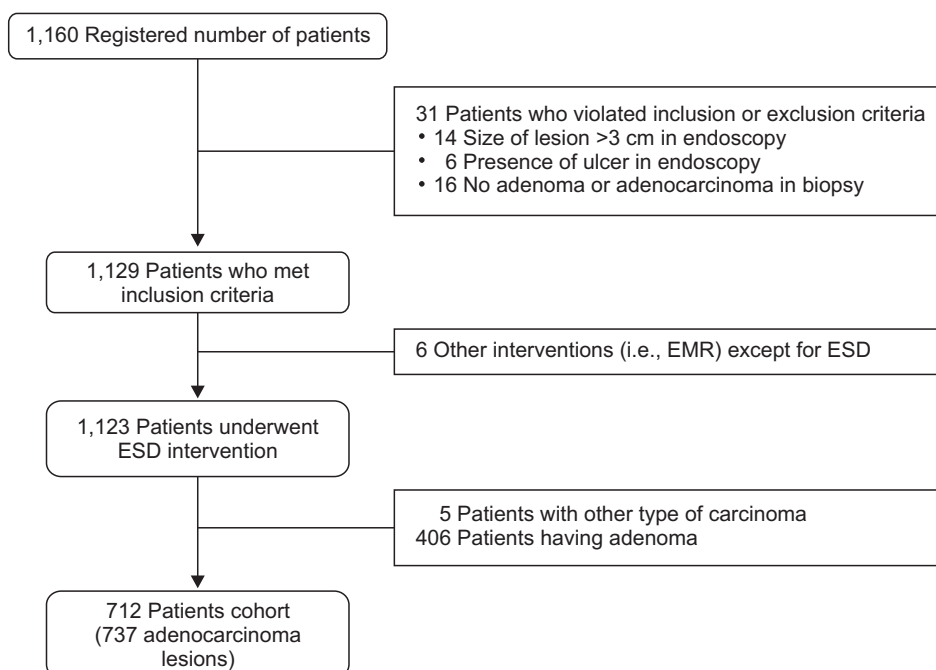

Fig. 1. Flow chart of participant selection.
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

9. Data integrity and confidentiality

All data were collected, recorded, and managed based on clinical research coordination platform (Velos Inc., Fremont, CA, USA) using electronic case report forms. For data consistency and accuracy, the institutions were regularly visited and source documents were checked. Confidential patient information was not collected. Access to the Velos system was restricted to authorized persons.

Table 1. Patient Characteristics (n=712)

Characteristic	No. of patients (%)
Gender	
Male	548 (77.0)
Female	164 (23.0)
Age, yr	62.8±9.2
<40	5 (0.7)
40–49	54 (7.6)
50–59	214 (30.1)
60–69	275 (38.6)
≥70	164 (23.0)
BMI, kg/m^2	24.2±2.8
<25	441 (61.9)
≥25	271 (38.1)
Smoking	
Never smoker	337 (47.3)
Ex-smoker	184 (25.9)
Current smoker	191 (26.8)
Drinking	
Never drinker	226 (31.7)
Ex-drinker	86 (12.1)
Current drinker	400 (56.2)
Cancer family history	
No	558 (78.4)
Yes	154 (21.6)
Stomach cancer family history	
No	613 (86.1)
Yes	99 (13.9)
Helicobacter pylori infection	
Negative	255 (35.8)
Positive	214 (30.1)
Unknown	243 (34.1)
Comorbidity	
Hypertension	238 (33.4)
Diabetes	69 (9.7)
COPD	2 (0.3)
Angina	8 (1.1)

Data are presented as number (%) or mean±SD.
BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table 2. Characteristics of Adenocarcinoma Lesions according to Post-ESD Central Pathology (n=737)

Characteristic	No. of lesions (%)
Location of the lesion	
Lower 1/3	465 (63.1)
Middle 1/3	187 (25.4)
Upper 1/3	85 (11.5)
Circumferential location	
Anterior wall	148 (20.1)
Lesser curvature	282 (38.2)
Posterior wall	140 (19.0)
Greater curvature	167 (22.7)
Histologic type	
Papillary	5 (0.7)
Tubular adenocarcinoma, well differentiated	488 (66.2)
Tubular adenocarcinoma, moderately differentiated	226 (30.7)
Tubular adenocarcinoma, poorly differentiated	18 (2.4)
Histologic type by Lauren classification	
Intestinal	712 (96.6)
Diffuse	8 (1.1)
Mixed	17 (2.3)
Tumor size, cm	
≤2.0	545 (73.9)
2.1–3.0	128 (17.4)
>3.0	64 (8.7)
Depth of invasion	
Invades lamina propria of mucosa (pT1a)	367 (49.8)
Invades muscularis mucosa (pT1a)	252 (34.2)
Submucosal invasion	118 (16.0)
Type	
Depressed	395 (53.6)
Elevated	182 (24.7)
Flat	109 (14.8)
Unclassified	51 (6.9)
Horizontal resection margin involvement	
Present	2 (0.3)
Vertical resection margin involvement	
Present	13 (1.8)
Piecemeal resection	
Present	6 (0.8)
Microscopic ulceration	
Present	35 (4.7)
Lymphatic invasion	
Present	32 (4.3)
Venous invasion	
Present	2 (0.3)

ESD, endoscopic submucosal dissection.

10. Ethics statement

This study was reviewed and approved by the NECA Institutional Review Board (IRB) (NECAIRB09-013-1) and each local hospital's IRB. The protocol was registered at ClinicalTrials.gov (identifier number: NCT01132469). This study was conducted according to International Conference Harmonization/Good Clinical Practices, clinical regulatory guidelines, and the ethical statements of the Declaration of Helsinki.

RESULTS

1. Patient and lesion characteristics

Among the 1,160 patients registered for screening between May 2010 and December 2011, a total of 737 EGC lesions identified from 712 patients were included in this short-term outcome study (Fig. 1). Patient characteristics are presented in Table 1. Male patients composed 77% of the study population, and the mean age (standard deviation [SD]) was 62.8 (9.2) years.

The lesion characteristics are presented in Table 2. Although enrollment criteria were adenoma or differentiated-type intramucosal cancer of size 3 cm or smaller, several factors deviated from the initial assessments in terms of depth, size, and histologic type. Submucosal layer invasion was the most common deviation from pre-ESD assessment (16%). Horizontal or vertical resection margin involvement of the cancer was uncommon and noted only in two (0.3%) and 13 cases (1.8%), respectively. Lymphovascular invasion was noted in 32 lesions (4.3%) for lymphatic vessel invasion and in two lesions (0.3%) for venous invasion.

2. Efficacy evaluation

The *en bloc* resection rate was 99.2% (731/737) and the margin-free *en bloc* resection rate was 97.3% (717/737). Complete resection was obtained in 602 lesions (81.7%; 95% CI, 78.7%

Table 3. Curative Resection Rates according to Estimated Pre-ESD Lesion Size

Pathologic criteria	Pre-ESD size		
	Total (n=737)	≤2.0 cm (n=639)	2.1–3.0 cm (n=98)
Curative resection	640 (86.8)	563 (88.1)	77 (78.6)
Absolute indication	446 (60.5)	418 (65.4)	28 (28.6)
Expanded indication*			
Total	194 (26.3)	145 (22.7)	49 (50.0)
A	135	93	42
B	22	20	2
C	6	6	0
D	31	26	5
Noncurative resection	97 (13.2)	76 (11.9)	21 (21.4)
p-value[†]		0.009	

Data are presented as number (%).
ESD, endoscopic submucosal dissection.
*Curability criteria for the expanded indication included in the Japanese Gastric Cancer Association guidelines.[3] Curative A: size >2 cm, differentiated type, pT1a (muscularis mucosa or lamina propria), Ulcer (-). Curative B: size ≤3 cm, differentiated type, pT1a, Ulcer (+). Curative C: size ≤2 cm, undifferentiated type, pT1a, Ulcer (-). Curative D: size ≤3 cm, differentiated type, pT1b (submucosal invasion <500 μm); [†]Chi-square for noncurative resection.
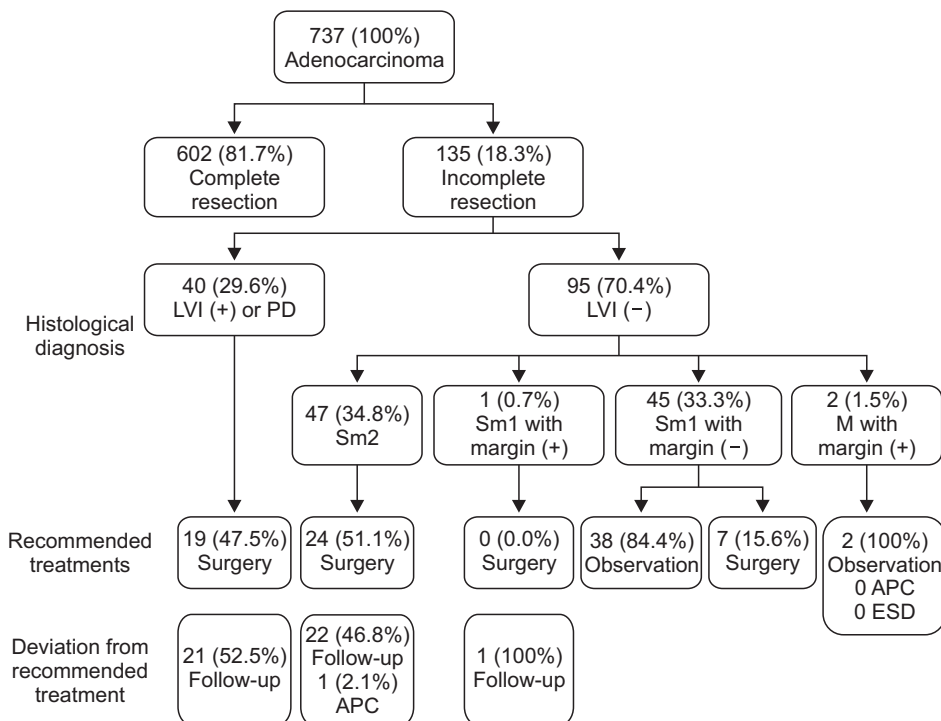

Fig. 2. Pathological and clinical outcomes after endoscopic submucosal dissection (ESD). Complete resection was defined when an differentiated type mucosal early gastric cancer (EGC) without lymphovascular invasion was resected with tumor free margins.
LVI, lymphovascular invasion; PD, poorly differentiated adenocarcinoma; Sm, submucosa; M, mucosa; APC, argon plasma coagulation.

Table 4. Risk Factors Associated with Noncurative Resection (n=737)

Factor	Total no.	Curative resection		Univariate analysis			Multivariate analysis		
		No.	%	OR	95% CI	p-value	OR	95% CI	p-value
Age, yr									
<60	283	247	87.3		Ref (1)		–	–	–
61–70	283	248	87.6	0.968	0.589–1.592	0.899	–	–	–
≥71	171	145	84.8	1.23	0.714–2.121	0.4556	–	–	–
Gender									
Female	173	153	88.4		Ref (1)		–	–	–
Male	564	487	86.3	1.21	0.716–2.043	0.4771	–	–	–
BMI, kg/m^2									
0–25	456	392	86		Ref (1)		–	–	–
≥26	281	248	88.3	0.815	0.52–1.277	0.3721	–	–	–
Smoking									
Non-smoker	348	306	87.9		Ref (1)		–	–	–
Current smoker	201	168	83.6	0.966	0.557–1.672	0.9006	–	–	–
Ex-smoker	188	166	88.3	1.431	0.874–2.344	0.1541	–	–	
Drinking									–
Non-drinker	237	210	88.6		Ref (1)		–	–	–
Current drinker	412	351	85.2	0.886	0.399–1.968	0.7668	–	–	–
Ex-drinker	88	79	89.8	1.352	0.833–2.194	0.2226	–	–	–
Gastric cancer family history									
No	634	547	86.3		Ref (1)		–	–	–
Yes	103	93	90.3	0.676	0.339–1.348	0.2664	–	–	–
Helicobacter pylori infection									
Positive	262	240	91.6		Ref (1)			Ref (1)	
Negative	253	208	82.2	2.36	1.372–4.061	0.0019	2.464	0.902–6.73	0.0786
Unknown	222	192	86.5	1.705	0.953–3.050	0.0725	2.773	0.914–8.416	0.0717
Histologic type									
Papillary or well-	493	460	93.3		Ref (1)			Ref (1)	
Moderately differentiated	226	174	77	4.166	2.604–6.664	<0.0001	2.793	1.165–6.697	0.0213
Poorly differentiated	18	6	33.3	27.878	9.837–79.008	<0.0001	239.572	31.417–>999.999	<0.0001
Location									
Lower 1/3	465	410	88.2		Ref (1)			Ref (1)	
Middle 1/3	187	165	88.2	0.994	0.587–1.683	0.9819	0.442	0.16–1.222	0.1155
Upper 1/3	85	65	76.5	2.294	1.291–4.075	0.0046	0.411	0.131–1.289	0.1274
Circumferential location									
Lesser curvature	282	252	89.4		Ref (1)			Ref (1)	
Anterior wall	148	126	85.1	1.467	0.813–2.647	0.2035	1.56	0.497–4.902	0.4462
Posterior wall	140	113	80.7	2.007	1.14–3.532	0.0157	3.327	1.068–10.364	0.0381
Greater curvature	167	149	89.2	1.015	0.547–1.883	0.963	1.567	0.477–5.152	0.4592
Size, mm									
≤20	545	493	90.5		Ref (1)			Ref (1)	
21–30	128	106	82.8	1.968	1.146–3.379	0.0142	2.063	0.73–5.83	0.172
>30	64	41	64.1	5.319	2.963–9.548	<0.0001	28.654	7.053–116.411	<0.0001
Ulcer									
Not identified	702	618	88		Ref (1)			Ref (1)	
Present	35	22	62.9	4.347	2.111–8.954	<0.0001	14.076	2.236–88.612	0.0048
Depth of invasion									
Mucosa (T1a)	619	609	98.4		Ref (1)			Ref (1)	
Submucosa (T1b)	118	31	26.3	170.871	80.933–360.754	<0.0001	462.34	132.183–>999.999	<0.0001
ESD									
Without snare	660	574	87		Ref (1)		–	–	–
With snare	77	66	85.7	1.112	0.565–2.190	0.757	–	–	–
Gross type									
Depressed	395	341	86.3		Ref (1)		–	–	–
Elevated	182	151	83	1.296	0.801–2.098	0.2905	–	–	–
Flat	109	98	89.9	0.709	0.357–1.408	0.3256	–	–	–
Unclassified	51	50	98	0.127	0.017–0.933	0.0426	–	–	–

OR, odds ratio; CI, confidence interval; BMI, body mass index; ESD, endoscopic submucosal dissection.

to 84.4%), which was defined in our protocol as a differentiated adenocarcinoma limited to the mucosal layer with tumor-free margins in the resected specimen (Fig. 2). Among the incomplete resection cases (n=135), 50 (37.0%) were treated with further surgery, one case (0.7%) was treated with argon plasma coagulation, and 84 cases (62.2%) were not treated further (Fig. 2).

The mean (SD) duration of the procedure was 58.8 (40.2) minutes and ranged from 10 to 265 minutes. As lesion number increased, procedure duration also increased: 56.7 (38.6) minutes for one lesion and 91.2 (51.9) minutes for two lesions treated in a single ESD session.

3. Curative resection rates and further treatment

Curative resection criteria, including absolute and expanded indications suggested by the Japanese guidelines, were achieved in 640 lesions (86.8%; 95% CI, 84.2% to 89.2%) (Table 3).

Table 5. Adverse Events Occurring within 30 Days after the Procedure

	No. (%)
Bleeding	49 (6.9)*
Presenting symptom	
Hematemesis	36 (73.5)
Decrease in hemoglobin >2 g/dL	1 (2.0)
Melena	12 (24.5)
Timing	
0–24 hr	33 (67.3)
25–48 hr	10 (20.5)
49 hr–1 wk	6 (12.2)
>1 wk	0
Management of bleeding	
Endoscopic treatment	35
Conservative treatment	14
Perforation	12 (1.7)*
Type	
Frank	6 (50)
Micro	6 (50)
Management of perforation	
Clipping only	3 (25)
Surgery after clipping[†]	3 (25)
Conservative	6 (50)
Stenosis	
Cardia	1 (0.1)*
Cerebrovascular accident	
Infarct	1 (0.1)*
Infection (pneumonia or peritonitis)	0

*Percentage of the 712 patients; [†]Surgery after clipping was performed in the context of incomplete resection and not for the perforation itself.

Among 97 noncurative lesions, additional curative surgery was performed for 41 lesions (42.3%). Curative resection rates were significantly lower in lesions that were 2 to 3 cm at the pre-ESD estimation compared to lesions 2 cm or less (78.6% vs 88.1%, respectively, p=0.009).

In multivariate analyses, significant factors associated with noncurative resection were moderately- or poorly-differentiated histologic type, posterior wall location of tumor, tumor size larger than 3 cm, presence of ulceration, and submucosal invasion (Table 4). *H. pylori* infection negative status shows trend to the risk of noncurative resection (odds ratio, 2.46; 95% CI, 0.90 to 6.73).

4. Adverse events and safety assessment

Delayed bleeding occurred in 49 patients (6.9%) and was the most common adverse event (Table 5). Among delayed bleeding cases, 67% occurred within 24 hours. Management of ESD bleeding was successful in 35 cases by endoscopic hemostasis using electrocautery, argon plasma coagulation, or clipping. Other cases were treated conservatively, and any interventions such as surgery or transarterial embolization were not needed.

Twelve patients (1.7%) had perforation. Six cases of gross perforations were closed successfully with clipping, but three cases required additional surgery due to incomplete resection. Six cases of microperforation were treated conservatively and recovered uneventfully.

One case of stenosis was found after ESD, which occurred 4 weeks after ESD for a cardiac lesion. The stenosis improved after balloon dilation. One case of cerebral infarct occurred 8 days after ESD, but no other serious adverse event including infection or procedure-related mortality was found within 30 days of ESD.

DISCUSSION

In this prospective cohort study, we evaluated the effectiveness and safety of ESD for the treatment of EGC, which was estimated at the pre-ESD evaluation to be within the absolute indications except for the estimated lesion size of 3 cm or smaller. In this predefined group with EGC, we confirmed that complete resection and curative resection rates were as high as those of previous retrospective studies. Our data also confirmed that ESD is a safe technique in terms of adverse events, which could be managed endoscopically or conservatively.

In this study, the margin-free *en bloc* resection rate was 97.3% and horizontal margin-positive cases were 0.3%, which are better than previous Korean retrospective data of 90.1% and 2.6%, respectively.[5] These findings might reflect increasing ESD experience among endoscopists. A previous study recruited patients when ESD had just been introduced and was not yet popular in Korea.[5] ESD is a technically challenging procedure and requires a learning curve of approximately 30 cases to obtain a

good performance.[19,20] Our current study enrolled participants in 2010 to 2011 when most participating endoscopists had extensive experience with ESD technique.

Our study found that the complete resection rate was 81.7%. Previous studies considered *en bloc* margin-free resection only or without lymphovascular invasion as the criterion for complete resection.[21,22] Our definition of complete resection, however, is rather strict and we considered submucosal tumors or undifferentiated-type histology as incomplete resection because these conditions may not be completely free of lymph node metastasis.[23,24] Our previous retrospective study that applied the same criteria showed a complete resection rate of 87.7%, which seems higher than our study.[5] The main difference results from the submucosal invasion rate, which was 16% in our study compared to 7.4% in the retrospective study. Because our definition of complete resection is conservative, we performed analyses according to Japanese expanded criteria (JGCA 2010 guideline).[3] Our curative resection rate of 86.8% was comparable to those reported in the literature, which were as high as 82.7% to 93.4%.[21,22,25]

In this study, we included gastric lesions smaller than 3 cm because (1) ESD can provide technically successful tumor removal; (2) there is a high chance of curative resection in terms of an expanded indication, even if minute submucosal invasion or ulceration was found in the resected specimen;[3] and (3) although the current Korean national health insurance system reimburses ESD only for absolute indication, a 2 to 3 cm lesion may indicate ESD if the patient pays by themselves. In our *post hoc* analyses, a clinically-estimated lesion size of 2 to 3 cm before ESD was significantly associated with lower curative resection rates (78.6%). Because approximately 20% of such ESD cases required additional surgery, it is necessary to provide patients with careful explanation before ESD, that additional surgery might be required due to significant discrepancies between pre- and post-ESD pathological diagnoses.[26] A large number of these patients, approximately 58% in our study, did not undergo additional surgery and might compromise their long-term survival.[27]

Although ESD is the recommended treatment for differentiated intramucosal tumors larger than 2 cm,[3] tumor size larger than 3 cm is associated with compromised complete resection rates.[28,29] In our multivariate analyses similar to previous reports, tumor size larger than 3 cm is a significant risk factor for noncurative resection.[30] In addition, significant factors associated with noncurative resection include poorly-differentiated histologic type, presence of ulceration, and submucosal invasion as previously reported, and those factors were already reflected in the expanded criteria for ESD.[3,31,32] Tumor location at upper part of stomach was associated with noncurative resection in the univariate analysis as previously reported.[30,32] However, it lost significance when considered with posterior wall location, which maintained its significance even after adjustment. This result was similar to recent report, which showed posterior wall location of tumor was the more significant factor than upper location probably due to technical difficult and poor visual field.[33] Unfavorable outcomes in *H. pylori*-negative cases might be partly explained by the previous finding that *H. pylori* eradication changes tumor morphology by flattening the superficial-elevated type lesion and covering the tumor with normal epithelium. This makes the tumors indistinct at the time of endoscopic detection.[34] Poorer prognoses in gastric cancer patients having *H. pylori*-negative status were also reported even after surgical treatment.[35] Future studies should examine the mechanism of different outcomes according to *H. pylori* status. Currently, the association of noncurative resection and moderately-differentiated histology is not well-understood and future study is needed to confirm our finding.

Perforation and bleeding rates were comparable to those of previous retrospective studies. Oda *et al*.[36] reviewed 28 papers that included 300 or more ESD cases, and reported that perforation rates ranged from 1.2% to 5.2%, and delayed bleeding rates were between 0% and 15.6%. Our rates of adverse events were in agreement with those reported in the literature, and endoscopic or conservative management was successful without the need for emergency intervention. One patient with a cardiac lesion developed stenosis within 4 weeks of ESD. Endoscopic balloon dilation was successful in this patient, but the procedure does have a risk of perforation.[37,38] Steroid use or pre-emptive ballooning should be considered in cases with risk factors for post-ESD stenosis.[39]

Our study has several advantages. First, this was a multicenter prospective study. Most data about the effectiveness and safety of ESD are from retrospective studies, which have the limitations of selection bias, recall bias, and high follow-up loss.[16] Thus, the retrospective outcome results must be confirmed by prospective studies. To the best of our knowledge, patient enrollment in a Japanese prospective observational study for ESD began in 2010 to evaluate long- and short-term outcomes.[40] The study results have yet to be reported after a 5-year follow-up.

Another important strength of our study is that an independent central pathology review board composed of pathologists who specialize in gastrointestinal tumors performed pathological evaluation for ESD specimens. It is well known that interobserver variations in diagnoses of gastric tumors are high, even among specialists.[15] The importance of a central pathology review for ESD cases was also presented in a case of EGC within the expanded indication of distant metastasis, which turned out to be a case beyond the expanded indication.[16] Furthermore, there was a large discrepancy between Western and Japanese pathologists in diagnoses of gastric lesions, with a κ-value of only 0.16. This discrepancy could be largely resolved by the introduction of the Vienna classification of gastrointestinal epithelial neoplasia.[15] Because Korean pathologists have Western viewpoints in the diagnosis of gastric lesions and follow the

Vienna classification,[41] our study suggested that ESD outcome data were excellent even when used Western pathological criteria

Our study has the following limitations. First, these data are from high-volume centers and the endoscopists are experts in ESD. This might overestimate the efficacy and safety of ESD, and our results might not be applicable to novice endoscopists from low-volume centers. Various *in vivo* or *ex vivo* training programs and live case observations will help Western endoscopists become competent in ESD procedures.[42] Second, various ESD devices were used according to the endoscopist's preference. We think this might result in more acceptable outcomes, as there are no significant performance differences for ESD knives.

In conclusion, our prospective study confirmed previous retrospective data that ESD is an effective treatment for EGC with excellent short-term outcomes in terms of effectiveness and procedure-related adverse events, particularly for EGCs estimated within the absolute indications. However, long-term outcome evaluation regarding survival and cancer recurrence in this selected EGC cohort is necessary.

CONFLICTS OF INTEREST

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

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