

# Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a comparison study to surgery using propensity score-matched analysis

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## Abstract

**Background** Endoscopic submucosal dissection (ESD) has been accepted as a standard treatment in early gastric cancer (EGC) patients with negligible risk of lymph node metastasis. However, there are limited data regarding the long-term outcomes of ESD in comparison with surgery. This study aimed to compare the overall, recurrence-free, and metachronous cancer-free survival rates after ESD and surgery.

**Methods** From May 2003 to December 2007, 391 patients with 413 EGCs and 258 patients with 276 EGCs were treated by ESD and surgery, respectively. According to inclusion criteria, 288 patients in the ESD group and 173 patients in the surgery group were eligible for this study. Using propensity score matching, 88 patients were analyzed per group.

**Results** The overall survival rates were 92.0 % in the ESD group and 90.2 % in the surgery group. Local

recurrence was observed in five patients (1.7 %) in the ESD group and distant recurrence in one patient (0.6 %) in the surgery group. Metachronous gastric cancers were detected in 14 patients (4.9 %) in the ESD group, whereas no patient in the surgery group. Kaplan–Meier curves exhibited no significant differences in overall or recurrence-free survival between the two groups. However, metachronous cancer-free survival of the ESD group was significantly lower than that of the surgery group ( $p = 0.002$ ). In the ESD group, the late complication rate was significantly lower (0 vs. 6.8 %,  $p = 0.029$ ), and the duration of hospital stay was shorter (7.3 vs. 14.2 days,  $p < 0.001$ ), compared with the surgery group.

**Conclusions** The overall survival was similar between the ESD and surgery groups. Compared with surgery, the benefits of ESD included fewer late complications and shorter hospital stay duration.

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**Keywords** Early gastric cancer · Endoscopic submucosal dissection · Gastrectomy · Survival · Outcome

The prevalence of gastric cancer is high in Asia, especially in Korea and Japan [1]. Early gastric cancer (EGC) is defined as mucosal or submucosal cancer, regardless of regional lymph node metastasis [2]. The presence of lymph node metastasis has been reported to range from 2 to 18 % [3]. For this reason, radical gastrectomy with lymph node dissection was considered to be the only curative treatment. In EGC patients, the surgical outcome demonstrated excellent 5-year survival rates (>90 %) [4, 5].

Instead of surgery, endoscopic resection is recommended in selected EGC patients [6]. The standard indications include differentiated, intra-mucosal, elevated cancers <20 mm in size or depressed cancers <10 mm in size, without ulceration and lymph node metastasis. In 2000, EGC subgroups with negligible risk of lymph node metastasis were newly proposed on the basis of large-scale retrospective data [7, 8]. Thereafter, the results were adopted as expanded indications: (1) differentiated-type mucosal cancer without ulceration, regardless of tumor size; (2) differentiated-type mucosal cancer with ulceration  $\leq 3$  cm in diameter; (3) superficial (SM1; tumor infiltration into the submucosal layer <500  $\mu\text{m}$  from the muscularis mucosae) submucosal cancer  $\leq 3$  cm in diameter; (4) undifferentiated-type mucosal cancer without ulceration  $\leq 2$  cm in diameter.

Recently, endoscopic submucosal dissection (ESD) has resulted in high complete resection rates in EGC patients who met the expanded indications [9]. However, there are no comparative data available regarding the long-term outcomes following ESD and surgical gastrectomy. Therefore, this study aimed to evaluate the overall survival rate, tumor recurrence, and development of metachronous gastric cancers between patient groups treated with ESD versus surgery.

## Methods

### Patients and study design

From May 2003 to December 2007, a total of 391 patients with 413 EGCs were treated by ESD at a single, tertiary-care, academic medical center. We retrospectively reviewed the medical records and endoscopic and pathological reports of these patients. All patients underwent ESD according to the expanded indications. Of these, patients were excluded for the following reasons: EGC in a remnant stomach, additional surgery after ESD, or pathologically non-curative result based on resected ESD specimen.

During the same period, the surgery group included a total of 258 patients with 276 EGCs. For comparison with the ESD group, patients with EGC in a remnant stomach and deep submucosal cancer (SM2; tumor infiltration into the submucosal layer  $\geq 500$   $\mu\text{m}$  from the muscularis mucosae) were excluded. This study was approved by the institutional review board of the hospital (SCHUH 2014-07-010) and registered in ClinicalTrials.gov (NCT02216110).

### Endoscopic submucosal dissection and surgery

Before ESD, all patients underwent endoscopy, endoscopic ultrasonography (EUS), and computed tomography (CT) for assessment of tumor margin, depth of tumor invasion, and regional lymph node metastasis. ESD was performed under conscious sedation. For sedation, midazolam and/or propofol were administered intravenously, with cardiorespiratory monitoring. Initially, indigo carmine dye was sprayed onto the tumor to clarify the margin. Then, markings were made 10 mm outside the tumor margin using argon plasma coagulation (APC). After marking, a mixture of sodium hyaluronate with indigo carmine and epinephrine was injected into the submucosa outside the marking dots. Circumferential mucosal incision and submucosal dissection were performed using a Flex knife (Olympus, Tokyo, Japan) and/or IT knife (Olympus). During the procedure, immediate bleeding was treated by Coagrasper (Olympus). After ESD, chest and abdominal plain radiography were performed routinely for detection of gastric perforation. ESD-related bleeding was defined as one of the following: hematemesis, melena or bleeding proven by routine, second-look endoscopy within 24 h.

In the surgery group, distal subtotal gastrectomy, total gastrectomy, proximal gastrectomy, and segmental resection were performed according to the location and extent of the tumor. Also, D1 +  $\beta$  or D2 lymph node dissection was performed with gastric resection. During hospitalization, patients were managed according to a postoperative standardized protocol. Hospital discharge was determined in the absence of any complications.

### Pathological evaluation

According to the guidelines issued by the Japanese Gastric Cancer Association, an experienced gastrointestinal pathologist performed pathologic examination [10]. All resected specimens were immersed in 10 % formalin. Resected ESD specimens were fixed with pins, then sliced serially at 2-mm intervals, and embedded in a paraffin block. If the piecemeal resection was performed, all pieces were reconstructed carefully. Resected surgical specimens were prepared in the same manner and sliced serially at 4-mm intervals. The gross morphology was classified as

elevated, flat, or depressed. Tumor size, histologic type, depth of invasion, resection margin involvement, and lymphovascular invasion were evaluated. Histology was categorized as either differentiated type (well-differentiated or moderately differentiated adenocarcinoma) or undifferentiated type (poorly differentiated adenocarcinoma or signet-ring cell carcinoma). When the tumor consisted of both differentiated and undifferentiated types, the tumor was classified according to the quantitative predominance. Complete resection was defined when en bloc resection was achieved with tumor-free lateral and vertical margins. Curative resection was defined when all of the following conditions were fulfilled: en bloc resection, tumor-free lateral and vertical margins, superficial submucosal invasion of  $<500\ \mu\text{m}$  from the muscularis mucosae, and no lymphovascular invasion.

### Follow-up

After ESD or surgery, regular follow-up was recommended to all patients. In the ESD group, endoscopic examinations were scheduled at 2 months after initial ESD, then every 6 months for 2 years, and annually thereafter. During follow-up endoscopy, surveillance biopsy specimens of 1–3 pieces were routinely taken from the previous ESD scar and any suspicious lesions, to detect local recurrence or metachronous cancer. Abdominal CT and chest radiography were performed annually after ESD to evaluate lymph node or distant metastasis. In the surgery group, routine endoscopy and abdominal CT were scheduled at 6 months after gastrectomy and annually thereafter. For patients without follow-up visits, the survival data and cause of death were obtained from the National Cancer Registry database.

### Outcome data

The primary outcome of this study was overall survival. Secondary outcomes included tumor recurrence and the development of metachronous cancer and treatment-related complications. During follow-up, tumor recurrence was categorized as local, regional, or distant. Local recurrence was defined as a malignant tumor pathologically diagnosed at a previous ESD scar or surgically resection margin. Regional recurrence was defined as a tumor detected in the regional lymph nodes. Distant recurrence was defined as tumor metastasis in other organ sites. All cases of tumor recurrence were confirmed pathologically and/or by radiologic imaging. Metachronous cancer was defined as a new cancer detected in a different area of the stomach 1 year following the initial ESD or gastrectomy. Complications within and beyond 30 days after treatment were defined as early and late complications, respectively.

### Statistical analysis

To analyze the baseline characteristics of the patients, Student's *t* test was used for continuous data, whereas the  $\chi^2$  test and Fisher's exact test were used for categorical data. Because this study was designed retrospectively, there were potential confounding and treatment-related selection biases between the two groups. To balance the two treatment groups, we performed propensity score matching [11]. Propensity scores were calculated using a logistic regression model and the following covariates: age, sex, preexisting comorbidity, tumor location, tumor size, morphology, depth of invasion, and histology. For the assessment of bias reduction, we calculated absolute standardized differences of covariates before and after matching. An absolute standardized difference of  $<10\%$  suggests inconsequential residual bias.

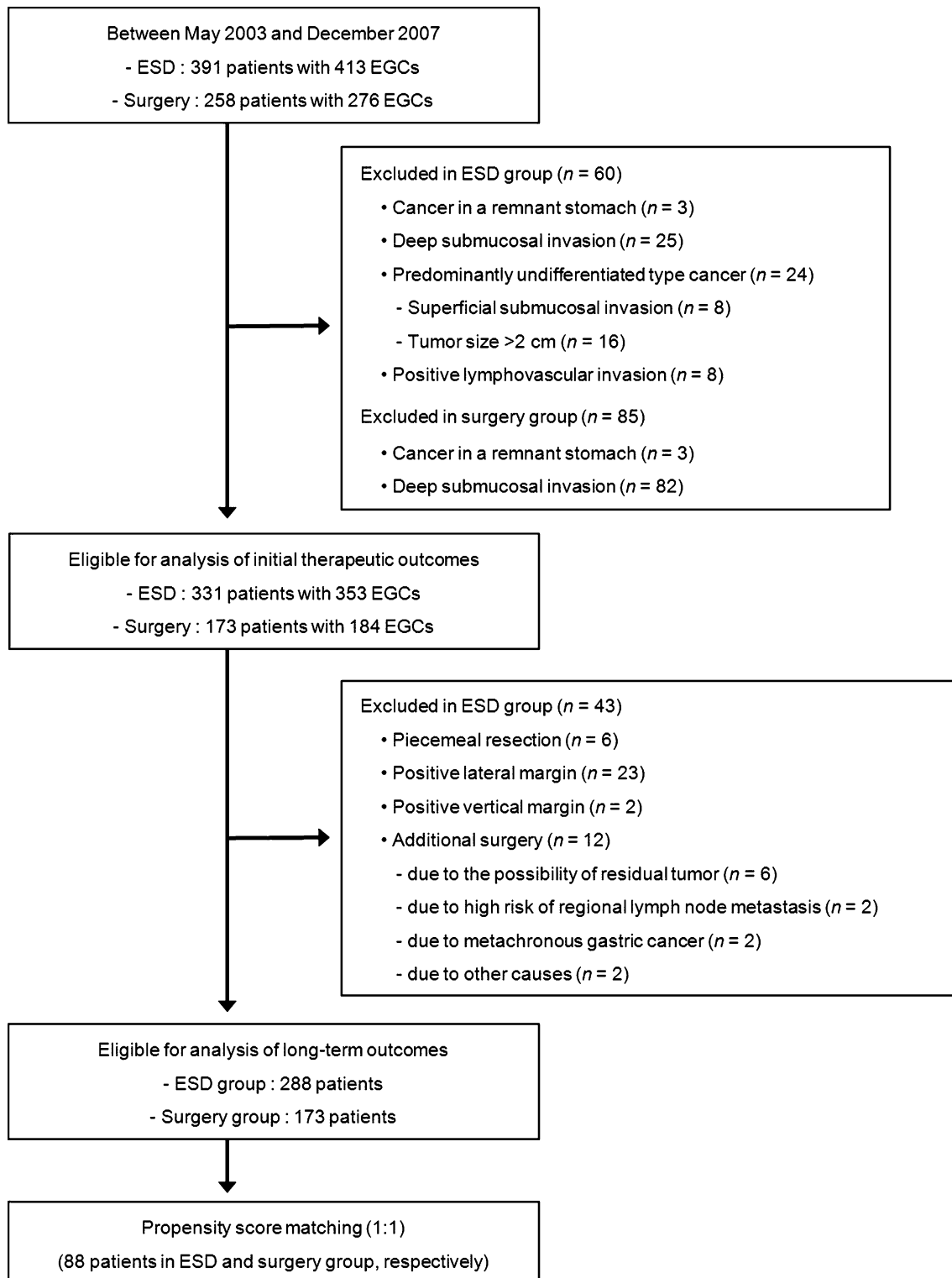
The Kaplan–Meier method and log-rank test were used to analyze the long-term outcomes including overall survival, recurrence-free, and metachronous cancer-free survival. *P* values  $<0.05$  were considered to be statistically significant. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA) and SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Figure 1 presents a flow chart of patient enrollment in this study. In the ESD group, 60 patients were excluded for the following reasons: cancer in a remnant stomach ( $n = 3$ ), deep submucosal invasion ( $n = 25$ ), predominantly undifferentiated-type cancer with submucosal invasion and/or  $>2\ \text{cm}$  in diameter ( $n = 24$ ), and positive lymphovascular invasion ( $n = 8$ ). In the surgery group, three patients with EGC in a remnant stomach and 82 patients with deep submucosal cancer were excluded from this study. Thus, a total of 331 patients with 353 EGCs in the ESD group and 173 patients with 184 EGCs in the surgery group were eligible for analysis of initial therapeutic outcomes.

In addition, 43 patients of ESD group were excluded due to piecemeal resection ( $n = 6$ ), positive lateral margin ( $n = 23$ ), positive vertical margin ( $n = 2$ ), and additional surgery after ESD ( $n = 12$ ). In the surgery group, all patients underwent curative gastric resection, such as distal subtotal gastrectomy ( $n = 146$ , 84.4 %), total gastrectomy ( $n = 24$ , 13.9 %), proximal gastrectomy ( $n = 2$ , 1.1 %), or segmental resection ( $n = 1$ , 0.6 %). Finally, a total of 288 patients in the ESD group and 173 patients in the surgery group were eligible for the analysis of long-term outcomes. Next, using propensity scores, ESD patients were matched



**Fig. 1** Flow chart presenting the inclusion of patients in this study. *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer

individually (1:1) to patients who underwent surgery, for a total of 176 patients (88 patients from each group).

The baseline characteristics of the patients are listed in Table 1. Before propensity score matching, the mean age

of the ESD group was higher than that of the surgery group ( $62.2 \pm 9.8$  vs.  $59.4 \pm 11.5$  years,  $p = 0.007$ ). Among preexisting comorbidities, the surgery group was more likely to have renal dysfunction ( $p = 0.021$ ). Notably,

there were significant differences between the two groups in terms of tumor characteristics. In the ESD group, the tumor was more frequently located in the lower third of the stomach ( $p < 0.001$ ). In the surgery group, the mean tumor size was larger, compared with the ESD group ( $24.9 \pm 13.7$  vs.  $16.6 \pm 8.9$  mm,  $p < 0.001$ ). Patients in the ESD group were more likely to have elevated type lesion, mucosal cancer, and differentiated-type cancer ( $p < 0.001$ ). However, all baseline characteristics after propensity score matching were similar between groups. Except for cardiovascular diseases, absolute standardized differences of all covariates were reduced to  $<10\%$  (Fig. 2).

### Therapeutic outcomes of endoscopic submucosal dissection

As given in Table 2, the rates of en bloc resection were  $94.6\%$  (334/353) in total patients;  $96.3\%$  (232/241) in the standard group and  $91.1\%$  (102/112) in the expanded group ( $p = 0.044$ ). Complete resection rates were  $90.1\%$  (318/353) in total patients;  $94.6\%$  (228/241) in the standard group and  $80.4\%$  (90/112) in the expanded group ( $p < 0.001$ ). In total, ESD-related complication rate was  $5.4\%$  (19/353). Bleeding, intra-luminal stricture, and perforation were observed in 15 patients ( $4.2\%$ ), 3 patients ( $0.8\%$ ), and 1 patient ( $0.3\%$ ), respectively. There was no significant difference of ESD-related complication between the standard and expanded groups ( $p = 0.132$ ).

### Long-term outcomes of endoscopic submucosal dissection and surgery

Long-term outcomes of ESD and surgery for EGC patients are described in Table 3. The median follow-up period was 77 months (range 18–107 months) for the ESD group and 78 months (range 1–113 months) for the surgery group. In the ESD group, 23 patients died of various causes other than gastric cancer, including cardiovascular disease ( $n = 4$ ), lung cancer ( $n = 2$ ), rectal cancer ( $n = 1$ ), non-Hodgkin lymphoma ( $n = 1$ ), and unknown ( $n = 15$ ). In the surgery group, 17 patients died. Of these, one patient died of metastatic recurrence 17 months after subtotal gastrectomy, and the remaining patients died of other diseases, including cardiovascular disease ( $n = 2$ ), pancreas cancer ( $n = 1$ ), chronic lymphoid leukemia ( $n = 1$ ), intracranial hemorrhage ( $n = 1$ ), renal dysfunction ( $n = 1$ ), and other causes ( $n = 10$ ). The overall survival rates were  $92.0\%$  (265/288) for the ESD group and  $90.2\%$  (156/173) for the surgery group. In propensity score-matched patients, the overall survival rates were  $89.8\%$  (79/88) for the ESD group and  $90.9\%$  (80/88) for the surgery group.

Local recurrence was observed in five patients ( $1.7\%$ , 5/288) in the ESD group, all of whom showed no regional lymph node metastasis on abdominal CT. The median time until local recurrence was 24 months (range 20–30 months). One patient underwent gastrectomy for treatment of a locally recurrent tumor. The remaining four patients underwent endoscopic treatment including endoscopic mucosal resection (EMR;  $n = 2$ ) or APC ( $n = 2$ ). Of those who underwent repeated endoscopic treatment, no second local or regional recurrence occurred during follow-up (median 65 months; range 34–81 months). In one patient ( $0.6\%$ , 1/173) from the surgery group, tumor recurrence with para-aortic lymph node and liver metastasis was observed 13 months after subtotal gastrectomy. In propensity score-matched patients, recurrence-free survival rates were  $96.6\%$  (85/88) for the ESD group and  $100\%$  (88/88) for the surgery group.

Metachronous gastric cancers were detected in 14 patients ( $4.9\%$ , 14/288) in the ESD group. The median time between ESD and detection of metachronous cancer was 38 months (range 14–82 months). The mean size of metachronous gastric cancer was 15.0 mm, and all lesions were treated by EMR ( $n = 3$ ) or ESD ( $n = 11$ ). Of these, one patient had a third metachronous cancer that was also resected by ESD. In the surgery group, no patient had metachronous cancer of the remnant stomach. In propensity score-matched patients, metachronous cancer-free survival rates were  $96.6\%$  (85/88) for the ESD group and  $100\%$  (88/88) for the surgery group.

Kaplan–Meier curves were used to indicate the long-term outcomes of ESD and surgery in overall and propensity score-matched patients (Figs. 3, 4). In overall patients, there were no significant differences between the ESD and surgery groups in terms of overall survival ( $p = 0.565$ ) or recurrence-free survival ( $p = 0.252$ ). However, metachronous cancer-free survival was significantly lower in the ESD group compared with the surgery group ( $p = 0.002$ ). In propensity score-matched patients, there was no significant difference in overall survival ( $p = 0.691$ ) between the ESD and surgery groups. However, the ESD group showed a lower rate of recurrence-free ( $p = 0.073$ ) and metachronous cancer-free survival ( $p = 0.070$ ) compared with the surgery group.

### Complications and hospital stay

Table 4 provides detailed descriptions of treatment-related complications in propensity score-matched patients. In the ESD group, a total of seven patients (five with post-ESD bleeding, one with gastric perforation, and one with pneumonia) experienced early complications. All post-ESD bleeding was treated by endoscopic hemostasis. Gastric perforation was treated by endoscopic clips and conservative management. A patient with pneumonia



**Table 1** Baseline characteristics of patients before and after propensity score matching (1:1 matching)

Variable	Before matching			After matching		
	ESD group ( <i>n</i> = 288)	Surgery group ( <i>n</i> = 173)	<i>p</i> value	ESD group ( <i>n</i> = 88)	Surgery group ( <i>n</i> = 88)	<i>p</i> value
Age (year), mean ± SD	62.2 ± 9.8	59.4 ± 11.5	0.007	61.8 ± 9.8	61.3 ± 9.8	0.741
Male, no. (%)	203 (70.5)	115 (66.5)	0.367	63 (71.6)	62 (70.5)	0.868
Preexisting comorbidity, no. (%)						
Cardiovascular diseases	42 (14.6)	18 (10.4)	0.197	10 (11.4)	13 (14.8)	0.502
Respiratory diseases	1 (0.4)	3 (1.7)	0.151	1 (1.1)	1 (1.1)	>0.999
Liver dysfunction	6 (2.1)	1 (0.6)	0.264	2 (2.3)	1 (1.1)	0.623
Renal dysfunction	4 (1.4)	9 (5.2)	0.021	3 (3.4)	3 (3.4)	>0.999
Diabetes	36 (12.5)	17 (9.8)	0.384	9 (10.2)	8 (9.1)	0.799
Tumor location, no. (%)			<0.001			0.588
Upper third	21 (7.3)	17 (9.8)		12 (13.6)	11 (12.5)	
Middle third	80 (27.8)	93 (53.8)		38 (43.2)	35 (39.8)	
Lower third	187 (64.9)	63 (36.4)		38 (43.2)	42 (47.7)	
Tumor size (mm), mean ± SD	16.6 ± 8.9	24.9 ± 13.7	<0.001	21.8 ± 12.1	21.4 ± 10.1	0.808
Morphology, no. (%)			<0.001			0.632
Elevated	131 (45.5)	45 (26.0)		31 (35.2)	28 (31.8)	
Flat/depressed	157 (54.5)	128 (74.0)		57 (64.8)	60 (68.2)	
Depth of invasion, no. (%)			<0.001			0.562
Mucosa	268 (93.1)	136 (78.6)		73 (83.0)	70 (79.5)	
Submucosa, SM1	20 (6.9)	37 (21.4)		15 (17.0)	18 (20.5)	
Histology, no. (%)			<0.001			>0.999
Differentiated	280 (97.2)	104 (60.1)		80 (90.9)	80 (90.9)	
Undifferentiated	8 (2.8)	69 (39.9)		8 (9.1)	8 (9.1)	

SM1 tumor infiltration into the submucosal layer <500 μm from the muscularis mucosae

ESD endoscopic submucosal dissection, SD standard deviation

improved after antibiotic treatment. In the surgery group, early complications occurred in five patients. Among the surgical complications (*n* = 2), intra-luminal bleeding occurred in one patient, and hemostasis was achieved by surgical intervention. One patient with intra-abdominal abscess was managed by antibiotic treatment. Among the medical complications (*n* = 3), one patient with pleural effusion was treated by percutaneous drainage, and one with acute renal failure and one with cerebral infarction recovered after conservative management. In terms of early complication rates, there was no significant difference between the ESD and surgery groups (8.0 % [7/88] vs. 5.7 % [5/88], respectively; *p* = 0.550).

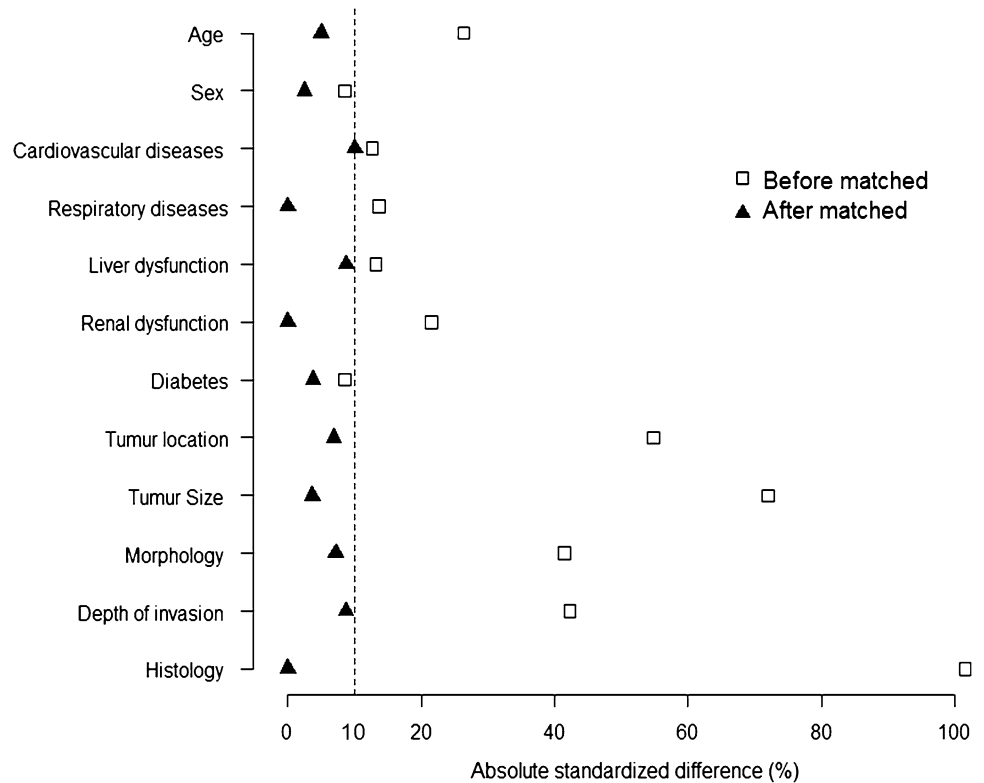
After hospital discharge, there were no late complications in the ESD group, whereas six patients in the surgery group experienced late complications (one with anastomotic stricture, two with intestinal obstruction, two with marginal ulcer, and one with gastric stasis). Anastomotic stricture was treated by endoscopic balloon dilation. One patient with intestinal obstruction underwent adhesiolysis after

conservative management had failed. The remaining four patients were managed by conservative treatment. There was a significant difference in late complication rates between the ESD and surgery groups (0 % [0/88] vs. 6.8 % [6/88], respectively; *p* = 0.029). The mean hospital stay duration was significantly shorter in the ESD group, compared with the surgery group (7.3 ± 2.9 vs. 14.2 ± 8.4 days, respectively; *p* < 0.001).

## Discussion

Before the ESD era, gastrectomy was the treatment of choice for EGC patients, and the long-term survival rate was >90 %. Recently, several studies have reported highly favorable 5-year overall and disease-specific survival rates in EGC patients who underwent curative ESD [12, 13]. However, there are limited data regarding the long-term outcomes of ESD in comparison with surgery.

**Fig. 2** Absolute standardized differences in baseline characteristics before and after propensity score matching



**Table 2** Initial therapeutic outcomes of endoscopic submucosal dissection in the standard and expanded groups

Outcomes, no. (%)	Total (n = 353)	Standard group (n = 241)	Expanded group (n = 112)	p value
En bloc resection	334 (94.6)	232 (96.3)	102 (91.1)	0.044
Complete resection	318 (90.1)	228 (94.6)	90 (80.4)	<0.001
Incomplete resection	35 (9.9)	13 (5.4)	22 (19.6)	<0.001
Positive lateral margin	33 (9.3)	13 (5.4)	20 (17.8)	
Positive vertical margin	2 (0.6)	0	2 (1.8)	
ESD-related complications	19 (5.4)	10 (4.1)	9 (8.0)	0.132
Bleeding	15 (4.2)	8 (3.3)	7 (6.2)	
Intra-luminal stricture	3 (0.8)	2 (0.8)	1 (0.9)	
Perforation	1 (0.3)	0	1 (0.9)	

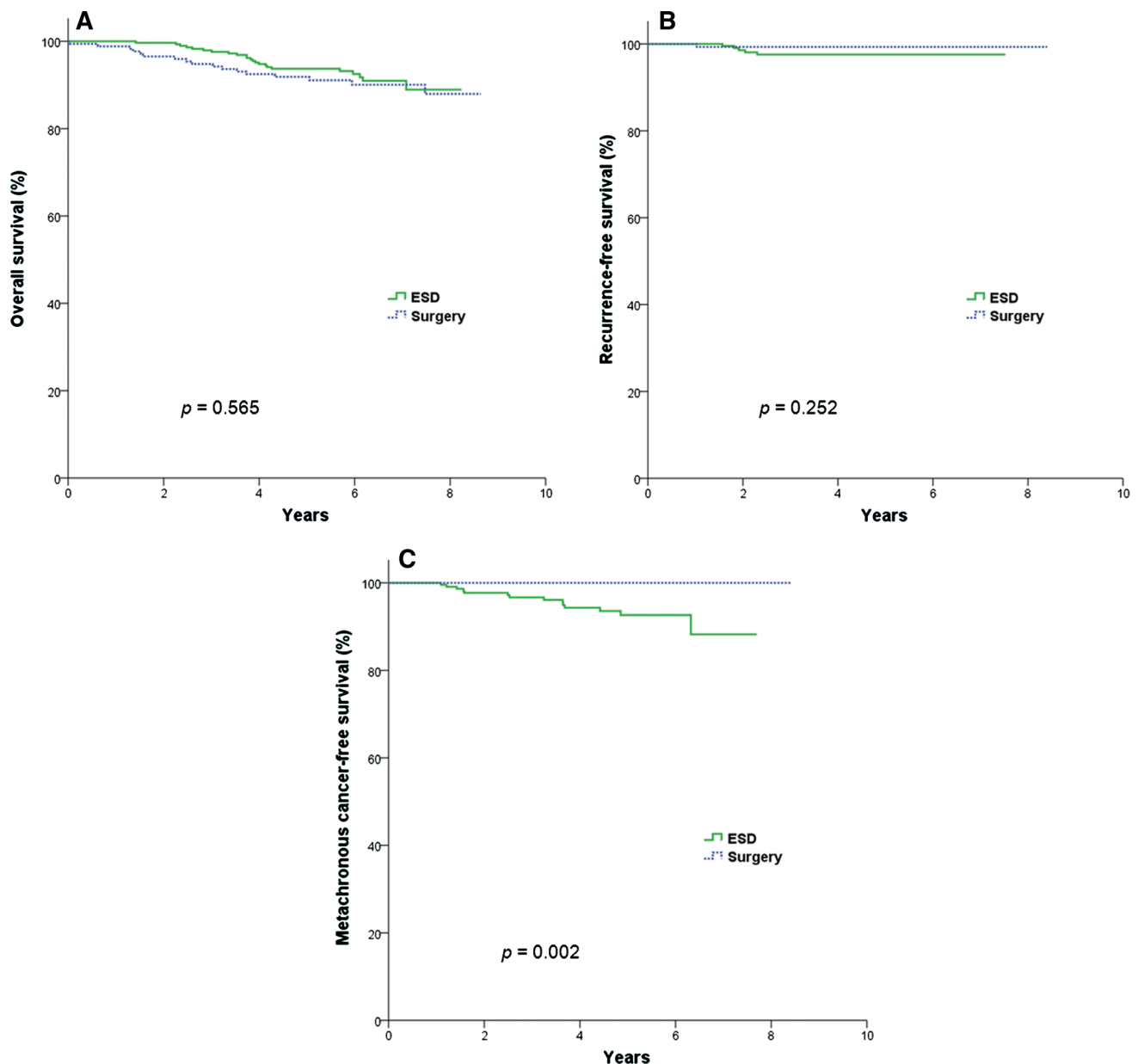
**Table 3** Long-term outcomes of endoscopic submucosal dissection and surgery

	Overall patients		Propensity score-matched patients	
	ESD group (n = 288)	Surgery group (n = 173)	ESD group (n = 88)	Surgery group (n = 88)
Death, no. (%)	23 (8.0)	17 (9.8)	9 (10.2)	8 (9.1)
Recurrence, no. (%)	5 (1.7)	1 (0.6)	3 (3.4)	0
Metachronous gastric cancer, no. (%)	14 (4.9)	0	3 (3.4)	0

ESD endoscopic submucosal dissection

In EGC, larger tumor size, deeper invasion, and undifferentiated-type histology are associated with the presence of lymph node metastasis [7]. Because the ESD technique

allows removal of only the primary tumor along the submucosal layer, patients with possible lymph node metastasis were excluded from the ESD group of our study.



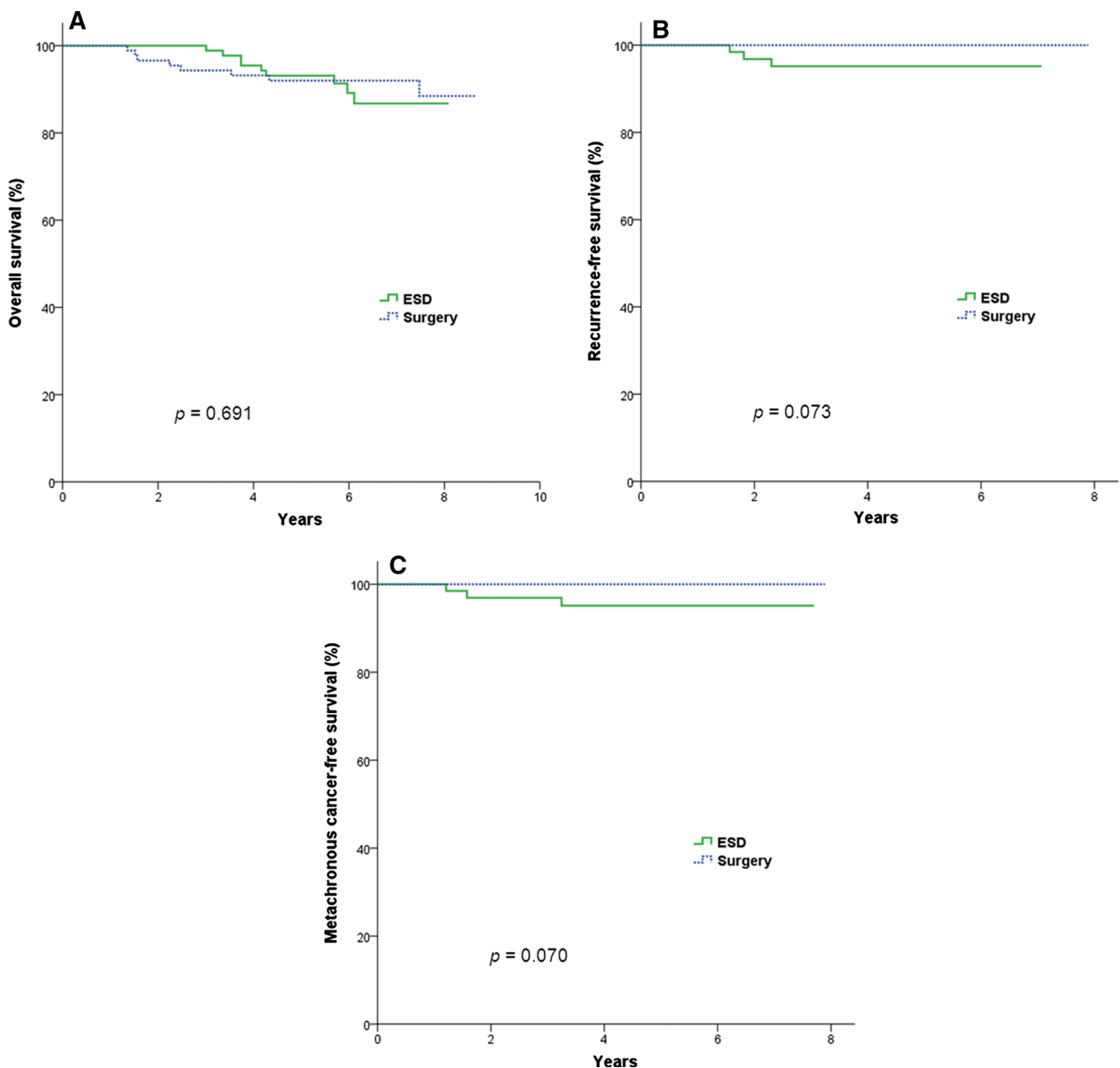
**Fig. 3** Kaplan–Meier curves for outcomes of endoscopic submucosal dissection and surgery in overall patients: overall survival (A), recurrence-free survival (B), and metachronous cancer-free survival (C). *ESD* endoscopic submucosal dissection

Thus, there were significant differences in the baseline characteristics between the ESD and surgery groups. By propensity score matching, new patient groups were generated, and tumor characteristics affecting treatment outcome were balanced through bias reduction. As a result, the overall survival of the ESD group was similar to that of the surgery group.

Although ESD may achieve curative resection of EGC, the remnant background mucosa still has a high risk of multiple cancers [14–16]. During follow-up after endoscopic resection, the detection rate of metachronous gastric cancer has been reported to range from 8.2 % to 14 %. In a

large-scale study, metachronous cancers were observed in 5.2 % of patients who underwent curative ESD of EGC. Almost all metachronous cancers were treated curatively with repeat endoscopic resection (96.2 %, 50/52). In our study, surveillance endoscopy was performed at least annually, and the detected lesions were appropriate for endoscopic resection. Although the ESD group showed a higher incidence of metachronous gastric cancer when compared with the surgery group (4.9 vs. 0 %), all lesions were treated completely by endoscopic resection. In Korea and Japan, annual or biannual endoscopic surveillance is recommended after endoscopic treatment for EGC [17, 18].





**Fig. 4** Kaplan–Meier curves for outcomes of endoscopic submucosal dissection and surgery in propensity score-matched patients: overall survival (A), recurrence-free survival (B), and metachronous cancer-free survival (C). *ESD* endoscopic submucosal dissection

In patients with *Helicobacter pylori*-infected stomach, eradication therapy may reduce the occurrence of metachronous gastric cancers [19].

In this study, five patients in the ESD group had local tumor recurrence despite curative resection of primary EGC. At the time of initial ESD, all patients showed differentiated-type mucosal ( $n = 4$ ) or superficial submucosal ( $n = 1$ ) cancer. Of these, three EGCs were resected en bloc. In the remaining two EGCs, piecemeal resection (two pieces) was performed, and resected specimens were properly reconstructed by an expert endoscopist. The

lateral and vertical margins showed no tumor positivity. In our endoscopy unit, routine biopsies of ESD-induced scars are performed for early detection of local recurrence. A previous study reported no local recurrence observed in completely resected EGCs during follow-up [20]. Risk factors associated with local recurrence after ESD include incomplete resection with margin positivity and/or piecemeal resection [21]. In this regard, local tumor recurrence in this study was considered to be uncommon. We suggest that the ESD-induced artificial ulcer was healed with highly inflamed mucosa, and a new malignant lesion might

**Table 4** Complications associated with endoscopic submucosal dissection and surgery

	ESD group ( <i>n</i> = 88)	Surgery group ( <i>n</i> = 88)	<i>p</i> value
Early complications, no. (%)	7 (8.0)	5 (5.7)	0.550
Post-procedural bleeding	5	1	
Intra-abdominal abscess	0	1	
Gastric perforation	1	0	
Pneumonia	1	0	
Pleural effusion	0	1	
Acute renal failure	0	1	
Cerebral infarction	0	1	
Late complications, no. (%)	0	6 (6.8)	0.029
Post-procedural stricture	0	1	
Intestinal obstruction	0	2	
Marginal ulcer	0	2	
Gastric stasis	0	1	

ESD endoscopic submucosal dissection

occur at the same scar site. Further investigation may be necessary to determine whether surveillance biopsy of ESD scars should be performed routinely.

A recent study reported the effectiveness and favorable long-term outcomes of ESD for local recurrence after previous endoscopic resection [22]. In our study, it was difficult to perform secondary ESD due to severe submucosal fibrosis caused by previous ESD. Instead, four patients underwent EMR or APC as additional treatment of local recurrence. Among them, there was no second local or regional recurrence during a median follow-up of 65 months. However, further studies are needed to confirm the efficacy and safety of EMR or APC for the treatment of local recurrence.

The major complications of ESD are bleeding and perforation [23]. In a study by Choi et al., the rates of ESD-related bleeding and perforation were 5.2 and 0.4 %, respectively [9]. All patients were treated by coagulation device and endoscopic clipping. A multicenter Korean study reported rates of delayed bleeding, significant bleeding, and perforation of 15.6, 0.6, and 1.2 %, respectively [24]. Except for two patients, most complications (98.9 %, 172/174) were managed with endoscopic treatment. In the current study, ESD-related complications (five delayed bleeding and one perforation case) were acceptable and managed successfully without surgical intervention.

EGC treatment through surgery is performed under general anesthesia, and patients experience postoperative pain and abdominal scarring. In some patients, surgical intervention can be required for management of postoperative complications. Early complications of gastrectomy for EGC treatment can include bleeding, anastomotic leakage, intra-abdominal abscess, and perioperative medical diseases [25]. Late complications include anastomotic

stenosis, anastomotic ulcer, and intestinal obstruction. In the current study, two patients in the surgery group underwent surgical intervention due to intraluminal bleeding and intestinal obstruction. In contrast, patients in the ESD group showed a shorter length of hospital stay and no complications after hospital discharge.

Although treatment efficacy and safety are important, quality of life is relevant to oncologic outcomes in cancer patients. Following gastrectomy, many patients experience dyspepsia, diarrhea, and eating restriction [26]. In particular, patients who undergo total gastrectomy have functional problems, such as fatigue and weight loss [27]. In contrast, ESD has the major advantage of removing only the tumor and preserving the stomach. A recent study reported that endoscopic treatment for EGC provided a better quality of life, as compared with surgery [28].

This study has several limitations. First, the baseline patient characteristics were significantly different among overall patients. However, application of the propensity score-matching method allowed balancing of the ESD and surgery groups in this retrospective study. Second, some patients did not receive surveillance endoscopy due to loss to follow-up, although their survival was confirmed through the National Cancer Registry. Consequently, the incidence rate of metachronous cancer may be higher than that reported in this study. Third, the *H. pylori* infection status of enrolled patients was not evaluated, although *H. pylori* might influence the development of metachronous gastric cancers after ESD. Fourth, this single-center study included 20 submucosal invasive cancers and eight undifferentiated-type cancers, and the numbers of patients may have been insufficient to analyze the long-term outcomes. In the future, a multicenter large-scale study is needed to confirm our results.

In conclusion, ESD was an effective treatment with preservation of the stomach in selected EGC patients. The overall survival was similar between the ESD and surgery groups. Compared with surgery, the benefits of ESD were fewer late complications and shorter hospital stay duration. Furthermore, regular surveillance endoscopy after ESD is essential for the detection of local tumor recurrence and metachronous cancers.

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#### Compliance with ethical standards

**Disclosures** Jun-Hyung Cho, Sang-Woo Cha, Hyun Gun Kim, Tae Hee Lee, Joo Young Cho, Weon Jin Ko, So-Young Jin, and Suyeon Park have no conflicts of interest or financial ties to disclose.

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