



Propensity score-matched comparison of short-term and long-term outcomes between endoscopic submucosal dissection and surgery for treatment of early gastric cancer in a Western setting

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Received: 31 May 2018 / Accepted: 24 November 2018 / Published online: 3 December 2018
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Abstract

Background Endoscopic submucosal dissection (ESD) is a standard treatment option for early gastric cancer (EGC) in Asia; however, data about ESD efficacy in Western populations are limited. Furthermore, outcomes of EGC treatment after ESD or surgery have not been compared in Western cohorts. This study aimed to compare short-term and long-term results of ESD and surgery for EGC.

Methods This retrospective case–control study included patients with EGC treated in two largest cancer centers in Eastern Lithuania between 2005 and 2016. Propensity score nearest-neighbor 1:1 matching, based on clinicopathologic characteristics, was performed between patients who underwent ESD and surgery. The primary endpoint of the study was 5-year disease-free survival (DFS).

Results Of 260 eligible patients, 42 (16.1%) underwent ESD. After matching, two well-balanced groups consisting of 42 patients in each were analyzed. The operation time (83 vs. 151 min., $p=0.001$) and postoperative hospitalization stay (5.4 vs. 13.4 days, $p=0.001$) was significantly shorter in the ESD group. 5-year DFS rate was significantly higher in the surgery group (97.6% vs. 77.5%, $p=0.002$). However, this difference was reduced after exclusion of non-curative ESD cases (97.6% vs. 89.7%, $p=0.099$). There was no significant difference in 5-year OS rate between the study groups (73.8% vs. 69.0%, $p=0.599$).

Conclusions ESD might be an excellent alternative to surgery for EGC if curative resection is achieved. Non-curative ESD is associated with poor DFS and high rate of recurrence. Additional surgery should be recommended after non-curative ESD whenever treatment-associated risk is acceptable.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Surgery · West

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Early gastric cancer (EGC) is defined as gastric cancer in which tumor invasion is limited to the mucosa or submucosa, irrespective of the presence of lymph node metastasis (LNM). The LNM is a strong negative predictor of patients' prognosis. Therefore, gastrectomy with lymph node dissection has historically been the gold standard treatment for resectable gastric cancer [1, 2]. Surgery for EGC has shown excellent long-term outcomes, with 5-year overall survival exceeding 90% [3, 4]. However, radical surgery is associated with postoperative morbidity, mortality, and impaired quality of life [5–7]. Instead, local endoscopic resection (ER), including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has been suggested as an alternative treatment option for EGC associated with negligible risk of LNM. Nowadays, the endoscopic approach is accepted and is considered as a standard treatment option

for EGC meeting indications set by the Japanese gastric cancer treatment guidelines [8]. Many recent studies have compared ER with radical surgery for EGC treatment and have shown similar short-term and long-term outcomes [9–16]. However, all of these studies were conducted in Asian populations where the incidence of gastric cancer, including EGC, is higher than in the West. Additionally, the Western population is characterized by a higher BMI, older age, higher prevalence of proximal tumors and diffuse-type cancer [17]. Hence, while ESD is a widely accepted treatment of EGC in the East, its application and pertinency to Western cohorts is unclear. Furthermore, two recently published studies have suggested non-Asian race as a risk factor for LNM [18, 19]. Thus, the efficacy of ESD compared to surgical treatment of EGC in Western countries is an important issue to investigate.

While randomized controlled trials are the gold standard for comparing treatment outcomes, it is not always feasible to construct such studies due to lack of resources or ethical concerns. Propensity score matching analysis has been used to reduce selection bias in longitudinal observational studies and has been considered to mimic randomized controlled trials in which the effects of treatments are approximately randomized [20]. Therefore, to ensure suitable randomization in the evaluation of short and long-term outcomes in EGC patients who underwent ESD or surgery, we applied propensity score matching to equate the baseline clinicopathological characteristics of both studied groups.

Materials and methods

Ethics

Vilnius regional biomedical research ethics committee approval was obtained before this study was conducted. All study-related procedures were performed in accordance with the Declaration of Helsinki.

Study design and patients

We reviewed data from 2 prospectively collected databases in two cancer care centers in Eastern Lithuania. ESD program for EGC treatment was implemented in Vilnius University hospital Santaros Clinics at 2006 and patients who underwent ESD for EGC between January 2006 and December 2016 were included in this study. Another center—National Cancer Institute did not have ESD program and all patients with gastric cancer underwent surgery. Since 2016, a significant number of patients who are candidates for ESD are sent to ESD centers. Therefore, to maintain a 10-year study period, patients who underwent surgery for EGC between January 2005 and December 2015 at the

National Cancer Institute were included. Choice of treatment center was made by personal patients' decisions. All patients were Caucasian. The exclusion criteria were (1) multiple or synchronous EGC and (2) history of gastric cancer treatment including neo-adjuvant chemotherapy. A flowchart of patient enrollment is demonstrated in Fig. 1. After exclusion of patients who met at least one exclusion criteria, 260 patients were included in the study and were divided into two groups according to the treatment method (surgery vs. ESD). Among these patients, propensity score matching analysis was performed to reduce the selection bias and to compare clinical outcomes between these groups. Forty-two patients in each group were matched by propensity score. The primary endpoint of the study was 5-year disease-free survival (DFS) rate. The secondary endpoints included 5-year overall survival (OS) rate, postoperative complication rate, operation time, and postoperative hospitalization time. OS was estimated from the date of surgery until death. DFS was defined as survival from the date of surgery to local, regional, or distant recurrence. Postoperative complications were defined as any deviations from a normal postoperative course during the hospitalization time. The severity of postoperative morbidity was classified according to Clavien–Dindo classification.

Preoperative evaluation and surgical procedures

Esophagogastroduodenoscopy with biopsy sampling was performed in all patients before surgery or ESD. Standard staging of the disease consisted of chest and abdomen CT scan. Additionally, endoscopic ultrasound was performed before ESD for more accurate evaluation of tumor invasion.

ESD was performed under general intravenous anesthesia. The standard ESD procedure at our institution begins with marking the lesion margins and injecting a saline solution containing epinephrine and methylene blue into the submucosal layer. A circumferential incision is made into the mucosa, and the submucosal layer is dissected. After specimen removal, endoscopic hemostasis is performed with hemoclips or hot biopsy forceps whenever bleeding or an exposed vessel is observed. An en bloc resection is defined as a single-piece resection. Histologically, complete resection included en bloc resection with microscopically negative horizontal and vertical margins. Curative resection was considered as proposed by Japanese gastric cancer treatment guidelines (histologically complete resection of a lesion not exceeding the expanded criteria for curative resection) [8].

The extent of gastrectomy depended on cancer localization in the stomach. In all cases patients underwent open surgery. Subtotal gastrectomy was performed whenever a sufficient proximal resection margin could be ensured; in other cases, total gastrectomy was performed. The standard lymphadenectomy was a D2 lymph node dissection

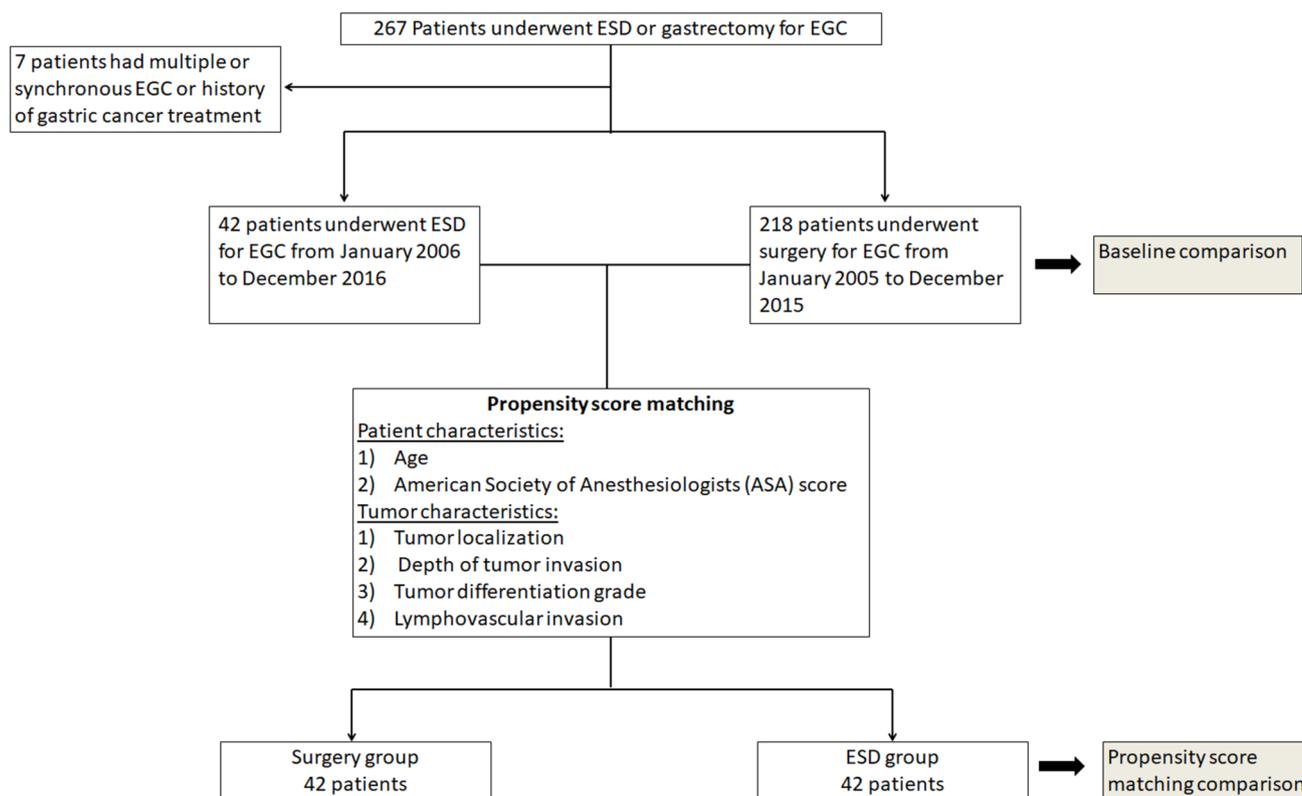


Fig. 1 Flowchart showing the patient selection process

which was performed as described in the 4th version of Japanese gastric cancer treatment guidelines [8]. D1 lymphadenectomy was performed in separate cases based on the individual decision of the operating surgeon. R0 resection, defined by no macroscopically and microscopically remaining tumor, was achieved in all cases.

Pathologic evaluation

Pathologic evaluation was performed at the National Center of Pathology, Vilnius, Lithuania. Pathologists specialized in gastric cancer analyzed all the specimens. Histological type of tumor was classified according to the World Health Organization and Lauren classifications. Slides were stained with hematoxylin-eosin for general evaluation. Tumor size, depth of invasion, lymphovascular involvement together with lateral and vertical margins were evaluated. The maximum diameter was used to determine tumor size. Lymphovascular invasion was defined as observable tumor spread through lymphatic vessels. Lymph nodes were identified in surgical samples and status of the nodes was evaluated after each node was examined microscopically.

Follow-up schedule

Esophagogastroduodenoscopy (EGD) was performed at 3, 6, and 12 months post-ESD and then annually for 5 years. Patients who underwent surgery received EGD twice a year for the first 2 years and then annually. Chest and abdominal CT were conducted annually in both groups. If patients underwent follow-up visits outside of the original study institutions, data were still obtained directly from the patient or their physicians by phone interview. The last follow-up data on death and recurrence were collected in December 2017. Two patients from the ESD group and one patient from surgery group were lost to follow-up.

Statistical analysis

All statistical analyses were conducted using the statistical program SPSS 22.0 (SPSS, Chicago, IL, USA). Continuous variables are presented as the mean \pm standard deviation or median with interquartile range. Categorical variables are shown as proportions. Propensity scores were determined by logistic regression model of covariates using six baseline variables: age, American Society of Anesthesiologists (ASA) score, tumor localization, depth of tumor invasion,

grade of tumor differentiation, and lymphovascular invasion. After propensity scores were calculated, patients in the ESD group were matched in a 1:1 ratio with the nearest neighbor from the surgery group. Comparison analysis of clinicopathological characteristics between ESD and surgery groups were analyzed by a 2-tailed *t* test, χ^2 test, or Fisher exact test. Overall and disease-free survival rates were analyzed by the Kaplan–Meier method and were compared by the log-rank test. Cox proportional hazard regression analysis was used to calculate multivariate-adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for DFS. In all statistical analyses, a *p* value of <0.05 was considered to be significant.

Results

Patients and baseline clinicopathologic characteristics

After propensity score matching analysis 42 patients who underwent ESD were matched with 42 patients who underwent surgery for EGC. Table 1 presents the baseline characteristics of the patients before and after propensity score matching. Significant differences between the ESD and surgery groups existed before the pairing. Patients in the surgery group were younger with a lower proportion

Table 1 Baseline clinicopathological characteristics in ESD and surgery groups before and after propensity score matching

	Before matching			After matching		
	ESD group (<i>n</i> =42)	Surgery group (<i>n</i> =218)	<i>p</i>	ESD group (<i>n</i> =42)	Surgery group (<i>n</i> =42)	<i>p</i>
Age (mean ± SD)	72.0 ± 10.9	65.5 ± 12.3	0.001	72.0 ± 10.9	72.3 ± 8.0	0.874
Sex, <i>n</i> (%)						
Male	24 (57.1%)	117 (53.7%)	0.737	24 (57.1%)	24 (57.1%)	0.999
Female	18 (42.9%)	101 (46.3%)		18 (42.9%)	18 (42.9%)	
BMI (mean ± SD)	27.6 ± 7.6	25.9 ± 4.9	0.534	27.6 ± 7.6	26.3 ± 5.4	0.541
ASA score, <i>n</i> (%)						
1–2	15 (35.7%)	128 (58.7%)	0.006	15 (35.7%)	17 (40.5%)	0.653
3–4	27 (64.3%)	90 (41.3%)		27 (64.3%)	25 (59.5%)	
Tumor localization, <i>n</i> (%)						
Upper 3rd	11 (26.2%)	14 (6.4%)	0.001	11 (26.2%)	4 (9.5%)	0.050
Middle 3rd	11 (26.2%)	125 (57.3%)		11 (26.2%)	20 (47.6%)	
Lower 3rd	20 (47.6%)	79 (36.2%)		20 (47.6%)	18 (42.9%)	
Tumor invasion, <i>n</i> (%)						
Mucosal	35 (83.3%)	99 (45.4%)	0.001	35 (83.3%)	36 (85.7%)	0.999
Submucosal	7 (16.7%)	119 (54.6%)		7 (16.7%)	6 (14.3%)	
Lauren classification, <i>n</i> (%)						
Intestinal type	35 (94.6%)	123 (59.7%)	0.001	35 (94.6%)	35 (97.2%)	0.225
Mixed type	2 (5.4%)	19 (9.2%)		2 (5.4%)	0 (0.0%)	
Diffuse type	0 (0.0%)	64 (31.1%)		0 (0.0%)	1 (2.8%)	
Tumor differentiation grade, <i>n</i> (%)						
Well differentiated	25 (59.5%)	44 (20.2%)	0.001	25 (59.5%)	22 (52.4%)	0.369
Moderately differentiated	16 (38.1%)	70 (32.1%)		16 (38.1%)	16 (38.1%)	
Poorly differentiated	1 (2.4%)	104 (47.7%)		1 (2.4%)	4 (9.5%)	
Ulceration, <i>n</i> (%)						
Present	8 (19.5%)	78 (35.9%)	0.001	8 (19.5%)	3 (7.1%)	0.116
Absent	33 (80.5%)	139 (64.1%)		33 (80.5%)	39 (92.9%)	
Lymphovascular invasion, <i>n</i> (%)						
Present	2 (4.8%)	30 (13.8%)	0.127	2 (4.8%)	1 (2.4%)	0.999
Absent	40 (95.2%)	188 (86.2%)		40 (95.2%)	41 (97.6%)	
Tumor size, <i>n</i> (%)						
< 2 cm	39 (92.9%)	105 (48.4%)	0.001	39 (92.9%)	19 (46.3%)	0.001
2–3 cm	3 (7.1%)	52 (24.0%)		3 (7.1%)	9 (22.0%)	
> 3 cm	0 (0.0%)	60 (27.6%)		0 (0.0%)	13 (31.7%)	

Significant *p* values are highlighted in bold

of severe comorbidities. A higher proportion of patients in ESD group had tumors located in the upper third of the stomach, while submucosal tumor invasion, poor differentiation, diffuse-type cancer, ulceration, and wider tumors were more common in the surgery group. After propensity score matching groups were more balanced. Mean propensity scores were 0.39 ± 0.22 and 0.34 ± 0.18 in ESD and surgery groups, respectively, $p = 0.290$. After pairing, patients in both groups were comparable according to various patient-related characteristics such as age, sex, BMI, ASA score, and also, according to multiple tumor-related characteristics: depth of invasion, histological type, differentiation grade of the tumor, ulceration, and lymphovascular invasion. However, even after propensity score matching, tumors exceeding 2 cm in diameter were more common in the surgery group.

Treatment and short-term outcomes

Table 2 shows short-term outcomes after surgery or ESD for EGC. In the surgery group, 10 (23.8%) patients underwent

total gastrectomy and 32 (76.2%) subtotal gastrectomy. Operation and postoperative hospitalization times were significantly shorter in the ESD group. Postoperative complications occurred for 7 (16.7%) patients in each group. In the ESD group, 2 (4.8%) patients had infectious complications, 3 (7.1%) patients had postoperative bleeding, and 2 (4.8%) patients had a perforation. Endoscopic hemostasis was successful in all hemorrhagic episodes. Both cases of perforation were treated with open or laparoscopic surgery. Four of 7 complications in the surgery group were mild and classified as grade II complications according to Clavien–Dindo. Two (4.8%) patients were re-operated due to fecal or biliary peritonitis, which in both cases were not associated with anastomotic insufficiency. One patient (2.4%) died during the postoperative course as a result of acute cardiopulmonary insufficiency. All patients in the surgery group underwent radical (R0) surgery. In the ESD group, en bloc and histologically complete resection were achieved in 38 (92.7%) and 32 (78.0%) cases, respectively. However, after the histological examination of specimens, only 30 (71.4%) procedures were classified as curative. Figure 2 shows

Table 2 Short-term outcomes of ESD and surgery groups after propensity matching

	ESD group ($n=42$)	Surgery group ($n=42$)	<i>p</i>
Operation time (min \pm SD)	83 \pm 47	151 \pm 47	0.001
Postoperative hospitalization time (days \pm SD)	5.4 \pm 3.1	13.4 \pm 6.6	0.001
Postoperative complication rate, <i>n</i> (%)	7 (16.7%)	7 (16.7%)	0.999
Clavien–Dindo, <i>n</i> (%)			
I–II	2 (4.8%)	4 (9.5%)	
III–IV	5 (11.9%)	2 (4.8%)	
V	0 (0.0%)	1 (2.4%)	
Surgical treatment efficacy			
Radical (R0) surgery, <i>n</i> (%)	–	42, (100%)	
Retrieved lymph nodes (mean \pm SD)	–	19.31 \pm 7.57	
Lymph node metastasis, <i>n</i> (%)	–	2, (4.8%)	
En bloc resection, <i>n</i> (%)	38, (92.7%)	–	
Histologically complete resection	32, (78.0%)	–	
Curative resection	30, (71.4%)	–	

Significant *p* values are highlighted in bold

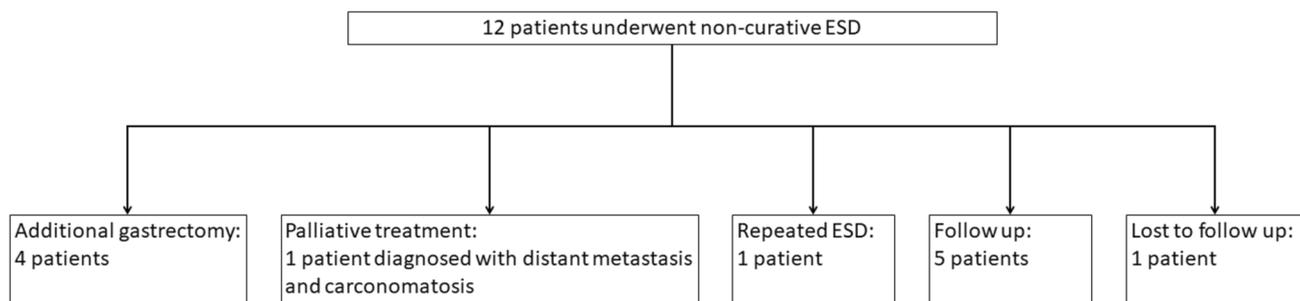


Fig. 2 Flowchart showing additional treatment after non-curative ESD

additional treatment tactics of 12 patients who underwent non-curative ESD.

Survival outcomes

The mean and median length of follow-up was 38 ± 34 and 28 (Q3:60–Q1:9) months for the ESD group and 52 ± 36 and 42 (Q3:74–Q1:30) months for the surgery group. Figure 3 represents disease-free and overall survival comparison between the study groups. Patients in the surgery group had significantly higher 5-year DFS (97.6% vs. 77.5%, $p=0.002$) (Fig. 3a). Exclusion of patients with non-curative ESD reduced the difference of DFS between the surgery and ESD groups. Five-year DFS was 89.7% in the curative ESD group and 97.6% in the surgery group, $p=0.099$ (Fig. 3c). In total, 9 (21.4%) patients from the ESD group and 1 (2.4%) patient from the surgery group ($p=0.014$) had a recurrence of gastric cancer during the follow-up period. Eight (19.0%) patients from the ESD group and 1 (2.4%) patient from the surgery group had local recurrences, which were successfully treated with repeated ESD or surgery. One (2.4%) patient from the ESD group was diagnosed with distant metastasis and carcinomatosis. Overall, 8 of 10 patients who experienced recurrence did so within 36 months after initial treatment. The rate of recurrence after non-curative ESD 5/11 (45.5%) was significantly higher compared to the rate after curative ESD 3/29 (10.3%), $p=0.007$. Furthermore, Cox proportional hazards regression model showed non-curative ESD as an independent risk factor for the decline of DFS (Table 3). Despite the differences between ESD and surgery groups according to the DFS, OS did not differ significantly between the study groups. Five-year OS was 73.8% and 69.0% ($p=0.599$) in the ESD and surgery groups, respectively (Fig. 3b). Furthermore, we did not find significantly different 5-year OS rate even when we compared groups of patients who underwent curative and non-curative ESD (66.7% vs. 76.7%, $p=0.581$) (Fig. 3e).

Discussion

Despite the common use of ER as a treatment option for EGC in the East, Western countries have been slow to accept such an approach. It has been speculated if Western institutions could achieve ESD results comparable to those reported from leading Asian institutions [21]. Besides a few recent studies demonstrating favorable outcomes similar to those achieved in Asia, data on ESD efficacy in Western populations are limited [21–24]. Additionally, these studies have limitations such as lack of data of long-term results or a high percentage of study participants with non-cancerous lesions. Also, all of these studies reported outcomes after ER, but none of them compared ESD with surgery. To our

best knowledge, our study is the first study comparing short-term and long-term outcomes of ESD and surgery for EGC in a Western cohort of patients.

In short-term outcome analysis, we found that ESD achieved significantly better perioperative outcomes regarding shorter operative time and shorter postoperative hospitalization. The mean procedure duration of ESD was 83 min and was closely comparable to times reported in large Western studies as well as those in Eastern regions [23, 25]. The superiority of ESD according to shorter operative time and postoperative hospital stay has previously been shown by Chiu et al. [9], where authors retrospectively compared 74 patients with severe dysplasia or EGC treated by ESD to 40 patients treated by gastrectomy in China. In contrast to this study and findings of a systematic review [25], we did not find a lower rate of postoperative complications after ESD. In our study, the postoperative complications occurred for 7/42 (16.7%) patients in each group. The severity of complications in both groups was also comparable. Complications requiring only pharmacological treatment were observed in 4/42 (9.5%) and 2/42 (4.8%) patients in the surgery and ESD groups, respectively. An endoscopic intervention for management of complications was necessary only for postoperative bleeding, which occurred after 3 (7.1%) ESDs. The postoperative bleeding rate found in our study is close to rates reported in various Asian and Western studies reporting delayed bleeding rates between 1.6 and 7% [22, 23, 26]. Two (4.8%) patients from each group had complications requiring surgical treatment. In the surgery group, both patients underwent re-operation for postoperative peritonitis, while in the ESD group, surgery was necessary for management of perforations. In one case, it was intraoperative perforation and the patient underwent surgery after unsuccessful initial endoscopic management, and in another case, it was delayed perforation. Likewise, the perforation rate after ESD in our study is also comparable to findings in other studies. According to recent reports, perforation follows 2.2% to 9.7% of ESDs in Eastern cohorts and 1.8% to 10% in Western cohorts [22, 23, 25]. Therefore, we believe that the discrepancy in postoperative complications between our findings and Asian studies are influenced by the relatively low rates of postoperative morbidity after surgery and relatively high proportion of complications requiring only pharmacological treatment in the ESD group of our study.

Postoperative death was registered only in the surgery group of our study in which 1/42 (2.4%) patient died during the postoperative period. The postoperative mortality rate in the propensity-matched surgery group represents the entire cohort very well since our previous report demonstrated a 1.8% mortality rate after surgery for EGC in the non-matched cohort [27]. We failed to show the risk of postoperative mortality after ESD. However, it should be taken into consideration that our study cohort was relatively

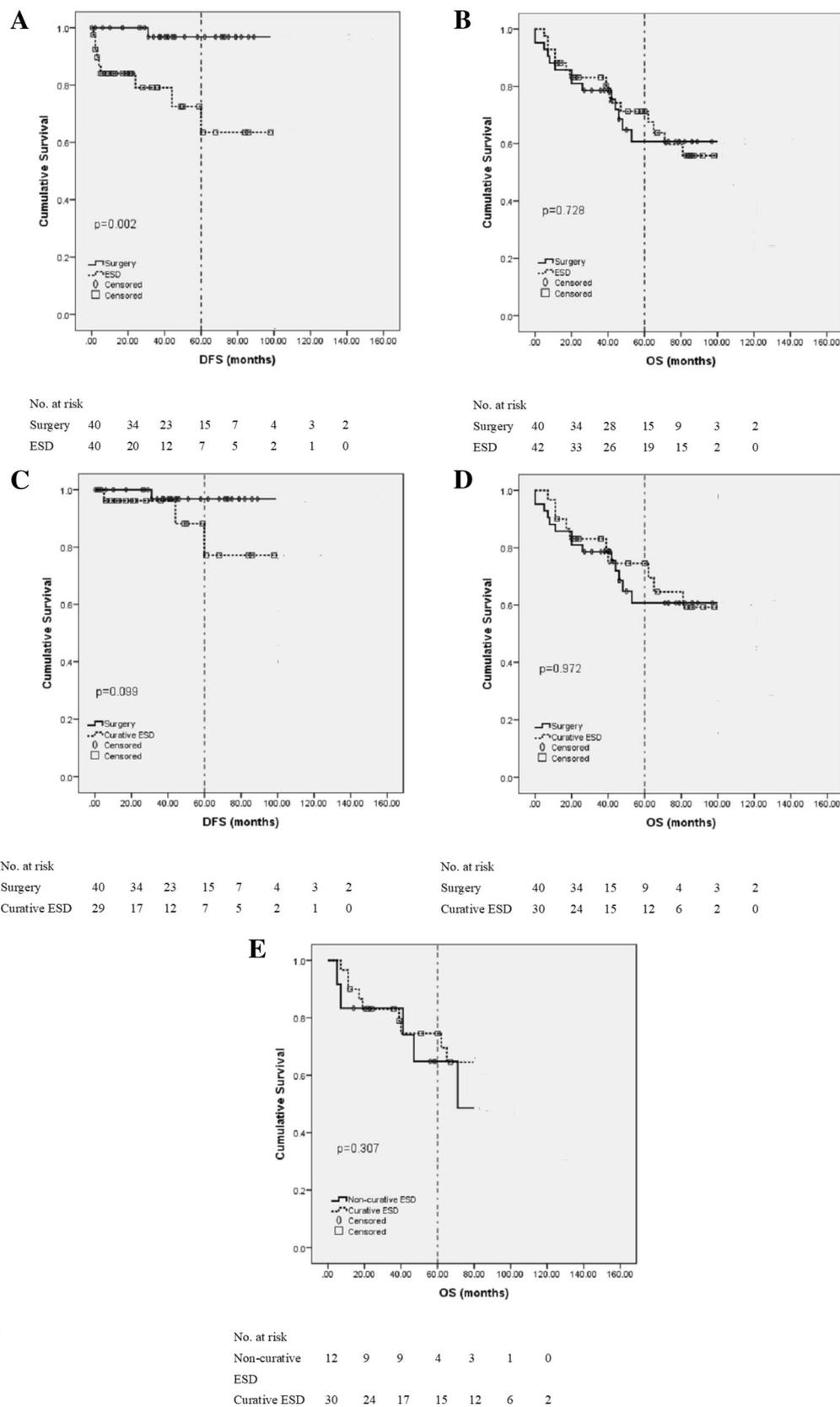


Fig. 3 Comparison of long-term outcomes in propensity-matched groups. **A** DFS in ESD and surgery groups. **B** OS in ESD and surgery groups. **C** DFS in curative ESD and surgery groups. **D** OS in curative ESD and surgery groups. **E** OS in curative ESD and non-curative ESD groups

Table 3 Multivariate Cox regression analysis for disease-free survival in patients with EGC

Factor	HR (95% CI)	<i>p</i> value
Age	0.96 (0.89–1.04)	0.380
Gender		
Female	1	0.126
Male	0.27 (0.05–1.44)	
Tumor characteristics		
pT1a, differentiated-type, ≤2 cm, U1–	1	0.940
(1) pT1a, differentiated-type, >2 cm, U1–	1.29 (0.14–11.74)	
(2) pT1a, differentiated-type, ≤3 cm, U1+		
(3) pT1a, undifferentiated-type, ≤2 cm, U1–		
(4) pT1b (SM1), differentiated-type, ≤2 cm, U1–		
Exceeding above-mentioned criteria	1.00 (0.08–11.97)	
Treatment		
Radical surgery or curative ESD	1	0.001
Non-curative ESD	41.79 (7.21–242.17)	

Significant *p* value is highlighted in bold

low and mortality risk could have been underestimated, as previous reports have shown mortality rates reaching up to 3.3% [21].

We found that all patients who underwent surgical treatment for EGC had radical surgery. This finding confirms the results published in many Asian studies, where the reported rate of radical resection after surgery was 100% [25]. In contrast to excellent results of surgery according to radicality, en bloc resection was achieved in 38/42 (92.7%) and histologically complete resection in 32/42 (78.0%) patients in the ESD group. The en bloc and histologically complete resection rates of our study were comparable with previous reports from different regions of the world [21–24, 26]. After histological examination of the specimens, 2 (4.8%) patients had an EGC which exceeded expanded criteria for curative ER and only 30/42 (71.4%) ESDs were classified as curative resections. In a multivariate Cox regression analysis, we revealed non-curative ESD as a risk factor for a decline in DFS. We believe that the relatively high rate of non-curative ESDs explains our finding of significantly higher 5-year DFS in the surgery group. In contrast to our results, a total of 1331 Asian patients were summarized in a systematic review comparing ER and surgery for EGC, and no differences regarding recurrence were found between the surgery and ER groups [25]. Therefore, we analyzed DFS in ESD and surgery groups after exclusion of the patients who underwent non-curative ESD. As expected, exclusion blunted the significant differences.

The necessity of additional treatment after non-curative ER for EGC has been widely discussed. Many recent studies have failed to show significant differences in disease-specific survival (DSS) in groups with or without additional surgery after non-curative ESD [28–30]. These previous studies did have limitations such as data from a single institution, a relatively small sample size, and significant clinicopathologic

differences between the groups. The clear benefit of additional surgery after non-curative ESD was shown in a large multicenter propensity score-based retrospective analysis published by Suzuki et al. [20]. In this Japanese study, patients who underwent additional surgery showed a significantly higher rate of DSS and OS compared to the patients who only received follow-up care. This study found that additional surgery reduced the risk of gastric cancer-related death by one-third. However, the difference in DSS rates was narrow. Thus, the authors suggested that risk stratification systems to improve the selection of candidates for surgery are necessary to achieve the most favorable outcomes. In our institutions, the decision between additional surgery and follow-up after non-curative ESD is based on patient's age, physical status, and comorbidities. These factors affect the risk of operation and life expectancy. In our study, we were not able to compare the outcomes between patients who underwent additional treatment or received only follow-up care after non-curative ESD, because the total number of non-curative ESDs was low. However, we found a major difference in the recurrence rate after non-curative ESD (5/11, 45.5%) compared to curative ESD (3/29, 10.3%). Moreover, one patient receiving follow-up after non-curative ESD was diagnosed with distant metastasis and carcinomatosis. Therefore, we think that surgery should be highly recommended after non-curative ESD whenever surgery-related risk is acceptable.

Although DFS was significantly better in the surgery group, OS did not differ between the two groups in this study. Unexpectedly, even the non-curative ESD group did not show considerably worse OS. Several factors might be responsible for these results. First, the non-curative ESD group was rather small, and a significant number of patients (5/12, 41.6%) from this group underwent additional surgery during the first 6 months after initial ESD. Second, 8 of 9

patients who were diagnosed with the recurrent disease after primary ESD were radically treated either with repeated ESD or surgery. Radical treatment or recurrence resulted in complete cure of cancer, and probably later EGC did not have an impact on OS. Third, according to the latest World Health Organization report published in 2015, life expectancy in Lithuania is 73.6 years, and the mean age of patients in both groups exceeded 72 years. Therefore, we can assume that OS is mainly affected by general health status and natural mortality rates of the cohort. This feature of our cohort also explains the differences between OS rates found in our study and those reported in Asia, where 5-year OS after ER and surgery for EGC is 97.5% and 97.0%, respectively [16].

The present study has several limitations. First, it is retrospective design study in which patients were not randomly assigned to ESD or surgery groups. To reduce the selection bias, we performed propensity score matching analysis. Even with the use of this statistical method, a significant difference remained between the two groups regarding tumor size. Wider tumors were more frequent in the surgery group, and this difference may have negatively biased outcomes against the surgery group. Nevertheless, the surgery group showed significantly higher 5-year DFS rate and comparable OS rate. Second, the number of patients who underwent non-curative ESD was low. Therefore, we could not compare the outcomes of additional surgery or only follow-up in these patients. Third, the total number of patients in our study was relatively low, especially compared to similar studies performed in Asia. However, due to the low prevalence of EGC in Western countries, only large international multicenter studies can overcome this limitation. Despite all flaws, we managed to show differences between the two treatment groups in the first study comparing ESD and surgery for EGC in a Western setting.

In conclusion, curative ESD might be an excellent alternative to surgery for EGC, because of shorter operation and hospitalization time and comparable long-term outcomes. However, the rate of recurrence after ESD is significant. Therefore, careful surveillance after endoscopic treatment is needed. As non-curative ESD leads to a poor DFS rate, additional surgery should be recommended for these patients whenever treatment-associated risk is acceptable.

Acknowledgements R.B. and A.B. contributed equally to this article. This study did not receive any funding. At the time of submission, abstract based on the same dataset as this article is prepared for submission to the European Society of Surgical Oncology (ESSO) 38th congress.

Compliance with ethical standards

Disclosures All authors—R.Bausys, A.Bausys, J.Stanaitis, I.Vysniauskaite, K.Maneikis, B.Bausys, E.Stratilatovas, and K.Strupas—have no conflicts of interest or financial ties to disclose.

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