


# Implementation of endoscopic submucosal dissection in a country with a low incidence of gastric cancer: Results from a prospective national registry

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## Abstract

**Introduction:** Endoscopic submucosal dissection (ESD) has become the treatment of choice for early gastric malignancies. In recent years, the ESD technique has been implemented in Western countries with increasing use.

**Objectives:** To describe the results of gastric ESD in a Western country with a low incidence of gastric cancer.

**Patients and Methods:** The prospective national registry was conducted over 4 years in 23 hospitals, including 30 endoscopists. Epithelial and subepithelial lesions (SEL) qualified to complete removal with ESD were assessed. The technique, instruments, and solution for submucosal injection varied at the endoscopist's discretion. ESD was defined as difficult when: en-bloc resection was not achieved, had to be converted to a hybrid resection, lasted more than 2 h or an intra-procedural perforation occurred. Additionally, independent risk factors for difficult ESD were analyzed.

**Results:** Two hundred and thirty gastric ESD in 225 patients were performed from January 2016 to December 2019 (196 epithelial and 34 SEL). Most lesions were located in the lower stomach (111; 48.3%). One hundred and twenty-eight (55.6%) ESD were considered difficult. The median procedure time was 105 min (interquartile range [IQR]: 60–150). The procedure time for SEL was shorter than for epithelial lesions (90 min [45–121] vs. 110 min [62–160];  $p = 0.038$ ). En-bloc, R0, and curative resection rates were 91.3%, 75.2%, and 70.9%, respectively. Difficult ESD had lower R0 resection rates than ESD that did not meet the difficulty criteria (64.8% and 87.6%;  $p = 0.000$ , respectively). Fibrosis and poor maneuverability were

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independent factors associated with difficult ESD (OR 3.6, 95%CI 1.1–11.74 and OR 5.07, 95%CI 1.6–16.08; respectively).

**Conclusions:** Although the number of cases is limited, the results of this analysis show acceptable en-bloc and R0 rates in gastric ESD considering the wide variability in experience among the operators. Fibrosis and poor maneuverability were associated with more difficulty in completing ESD.

#### KEYWORDS

early gastric cancer, en-bloc, endoscopic resection, endoscopic submucosal dissection, gastric premalignant lesions, resection

#### Key summary

##### Summarize the established knowledge on this subject

- Endoscopic submucosal dissection (ESD) is the standard of care for treatment of early gastric cancers (GC). Due to a lower incidence of GC in European countries, the introduction of gastric ESD has been more gradual than in the East.
- ESD complications, technical and clinical success depend on the endoscopist's experience, the presence of submucosal fibrosis or invasive cancer, and poor access location.

##### What are the significant and/or new findings of this study?

- This study shows the results from a prospective nationwide registry of gastric ESD in a low GC incidence country. Despite a relative low number of cases, quite acceptable outcomes (en-bloc, R0 and curative resection of 91.3%, 75.2% and 70.9%, respectively) were observed considering the wide variability in experience among the operators.
- Difficult ESD were mainly associated with the presence of submucosal fibrosis and poor maneuverability; however, independent pre-procedural factors were not identified. There was a trend of association between ESD difficulty and the location of the lesion in the upper/middle stomach

## INTRODUCTION

Endoscopic submucosal dissection (ESD) has become the standard of care for the treatment of early gastric cancer (EGC).<sup>1</sup> The main advantage of ESD relies in its ability to achieve en-bloc instead of piecemeal resection regardless of the size of the lesion or presence of fibrosis. This minimally invasive treatment approach not only offers an excellent prognosis but also substantially improves the quality of life of patients with EGC.<sup>2,3</sup>

Despite the above, ESD is a highly demanding technique with a higher risk of perforation than standard EMR methods.<sup>4</sup> It requires a fully skilled endoscopist to ensure success and reduce adverse events; this entails specific training and an appropriate learning curve. Moreover, longer time slots, specific equipment, and infrastructure for adequate management of adverse events (i.e., possibility of admitting patients to ward, access to appropriate surgical teams, and/or interventional radiology) are required before starting an ESD.<sup>1,5</sup>

Due to the low incidence of gastric cancer in Western countries, the introduction and availability of ESD has been gradual and less

widespread than in Asian countries such as Japan and South Korea.<sup>6</sup> A survey among European endoscopists clearly indicated that ESD was not common practice in Europe in 2010.<sup>7</sup> In this survey, only 20 centers provided data on gastric ESD, which was mainly performed by a single endoscopist. While in 2010 surgery was still considered the treatment of choice for EGC in the West, nowadays ESD is considered the standard of care<sup>1,5,8–13</sup> as confirmed by a new survey published in 2020 in which the results of gastric ESD are very similar to the reported in Eastern countries.<sup>14,15</sup>

Endoscopists without expertise or trainees, often cannot successfully complete the procedure or adequately manage adverse events, such as bleeding or perforation. In addition, difficult ESD is associated to a longer procedure time with the consequent impact on the organization of the Endoscopy Units. Kim et al. found that difficult ESD procedures are associated with the size of the lesion, its location, submucosal fibrosis, and submucosal invasive cancer.<sup>16</sup>

In this study, we present the results of gastric ESD in a Western country with low incidence of gastric cancer. As secondary objective, we assessed the risk factors associated with difficult gastric ESD.

## METHODS

### Spanish ESD Patient Registry

The Spanish ESD Patient Registry is a multicenter collaborative registry that collects data of procedures and outcomes of patients treated with ESD for early gastrointestinal neoplasia, preneoplastic lesions, and subepithelial lesions (SEL) in 23 hospitals (17 tertiary academic centers, 4 private, and 2 community centers) in Spain. Endoscopists were properly trained in ESD, most of them having visited Japanese expert centers as observer trainees. The registry did not mandate specific protocols for performing the procedure. Institutional review board approval was obtained from the Ethics Committee of each hospital and all patients provided written informed consent for inclusion in the registry. Consecutive patients were enrolled from January 2016 to December 2019 and only lesions planned to be completely removed by ESD were included.

### Lesion assessment

Epithelial lesions were characterized according to the Paris classification.<sup>17</sup> Lesion margins were assessed with chromoendoscopy (and near focus or magnification when available). Additionally, lesions were classified according to the Vienna classification at histology. SEL originated from submucosa were previously assessed with endoscopic ultrasound. The stomach was divided into upper (cardia, fundus, and body), middle (incisura), and lower (antrum) part.

### ESD procedures

ESD procedures were performed by 30 endoscopists, the majority under general anesthesia with endotracheal intubation. The tools selection (electrosurgical knives and solutions for the injection) depended on the endoscopist's discretion. ESD were performed following the different steps described elsewhere, with coagulation of exposed, nonbleeding vessels before completing the procedure. Pathologic specimens were pinned and submitted for histopathological analysis in formalin.

All patients were hospitalized for a variable period (1–5 days) and the proton pump inhibitors were administered for 8 weeks. Peri procedural antibiotics were not routinely used.

### Outcomes and definitions

ESD was considered difficult when en-bloc resection was not achieved, turned to hybrid resection, it lasted more than 2 h or an intraprocedural perforation occurred.

En-bloc resection was defined as the entire lesion resected in one piece and R0 (complete) when deep and lateral margins of the specimen were free of neoplasia. Curative resection was defined as

those R0 resections with no features of poor prognosis ( $\leq 500$   $\mu\text{m}$  of submucosal invasion, G1-2, and no lymphovascular invasion), it means, with low risk for local or distant recurrence that did not require further therapies. ESD was considered hybrid when the specimen was resected en-bloc with the help of a snare. A piecemeal resection was defined as a specimen removed in several fragments.

Intraprocedural bleeding was defined as oozing or jet bleeding requiring the use coagulation forceps (and/or clips, topic gel agents, etc.) or other nonendoscopic treatments such as interventional radiology or surgery. Delayed bleeding was defined as any of the following criteria: episode of hematemesis and/or melena, drop of 2 g/dl of the hemoglobin level, and suspicion of bleeding that required a new endoscopy after the completion of ESD and within 30 days.

Perforation was defined as deep mural injury with or without an obvious hole in the muscularis propria. Intraprocedural perforations were defined as those detected by the endoscopist during the procedure and which were managed either endoscopically (closure with through-the-scope or over-the-scope clips) or surgically. Delayed perforations were those not suspected during the procedure, diagnosed after the completion of ESD, and confirmed by imaging tests.

Submucosal fibrosis was generally described when a dense whitish or scar tissue was present at the submucosal space (Figure 1).

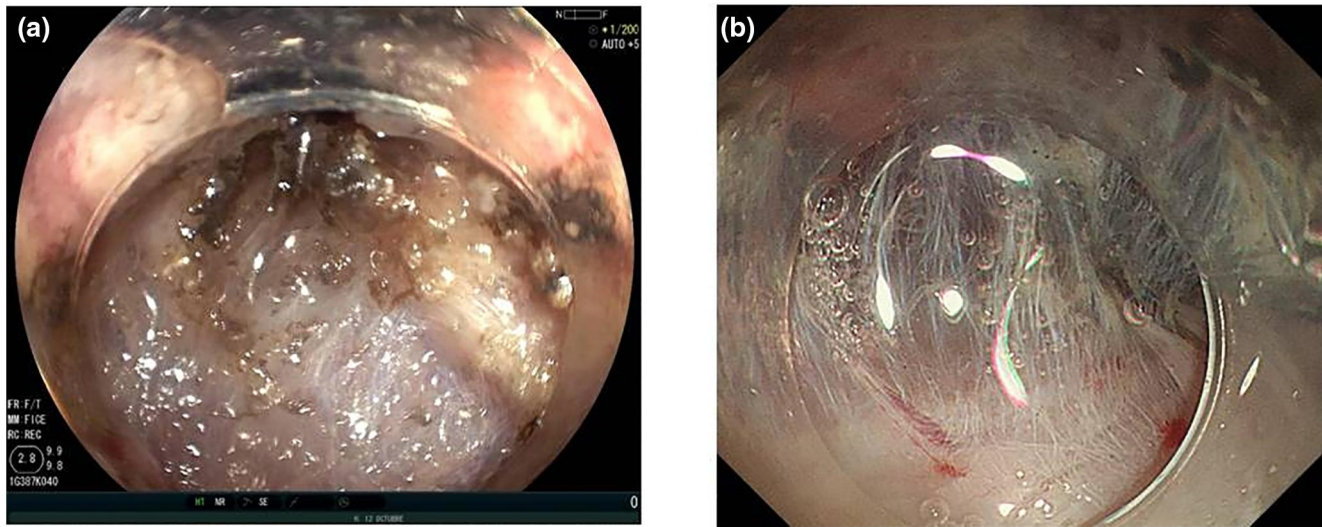
Maneuverability was considered good (good access to the lesion with a stable position and one-to-one movements with straight scope) or poor.

### Data collection

The registry included pre-procedural data such as demographics, comorbidities, chronic use of antiplatelet agents/anticoagulants, and any previous intervention for the lesion.

Procedural data were prospectively collected. This included: type of sedation (deep sedation or general anesthesia with endotracheal intubation), characteristics of the lesion (location, macroscopic morphology according to Paris classification<sup>17</sup>), technical aspects (i.e., type of knife and submucosal solution, use of traction systems), procedural time of each ESD step, the presence of fibrosis or fat in the submucosa, completeness of the resection (complete/incomplete, en-bloc or piecemeal resection), and intraprocedural adverse events. The estimation of the size of the lesion was not registered; instead, the diameter of the full specimen assessed by the pathologist after the resection was recorded. Post-procedural data included delayed adverse events and histology.

Personal and clinical data were codified, anonymously registered, and managed recorded on standardized case report forms and entered online in REDCap<sup>TM</sup> electronic data capture tools hosted at "i+12 Research Institute" of Hospital Universitario 12 de Octubre.<sup>18</sup> All authors had access to the study data and had reviewed and approved the final manuscript



**FIGURE 1** (a) A case of difficult endoscopic submucosal dissection. Submucosal fibrosis can be seen as dense whitish tissue in the submucosal space. (b) Normal submucosal space after injection of fluid. A thin penetrating vessel can be observed emerging from the muscular layer (down) whereas the mucosal flap is in the top of the image

## Statistical analysis

Efficacy outcomes and technical difficulty of ESD were analyzed in a per lesion basis whereas delayed adverse events were analyzed in a per patient basis. Continuous variables were presented as median plus interquartile range (25th and 75th percentiles; IQR) and were compared using the Mann–Whitney test. Dichotomous variables were expressed as frequencies (%) and were compared using Chi-square test.

All statistical tests were two-sided, and  $p$  values  $<0.05$  were considered statistically significant. Multiple logistic regression analysis was used in order to evaluate the strength of association between difficult ESD and significant variables using backward stepwise variable selection. The stepwise modeling procedure started with the full model and consisted in eliminating, for each step, the least statistically significant variable, thus re-computing the revised model. Candidate variables for inclusion in the model were those achieving a  $p$  value  $\leq 0.1$  in the univariable analysis. Odds ratios (ORs) and associated 95% confidence intervals (CIs) were used to quantify the level of association. Statistical analysis was performed using SPSS version 23 (IBM). Significance was regarded at  $p$  value  $< 0.05$ .

## RESULTS

### General

Over the course of 4 years, 230 gastric lesions in 225 patients were treated by ESD. One hundred and thirty (57.8%) patients were males with a median age of 71 (range 28–93) years. One hundred and nine (48.4%) had comorbidities and were ASA III or IV, 8 (3.6%) had a

coagulopathy and 75 (33.3%) were taking antiplatelet agents and/or anticoagulants. One hundred and ninety-six lesions were epithelial suspicious of EGC or gastric preneoplastic lesions and the rest ( $n = 34$ , 14.8%) were SELs. Most lesions were located in the lower stomach (111; 48.3%) and the most common morphology of epithelial lesions was nonpolypoid Paris 0-IIa (111/196, 56.6%; Table 1). Procedures were performed under general anesthesia and endotracheal intubation in 85% of cases. Hybrid knives with injection capability were used in 63.9% of procedures and the most common substance for submucosal injection was gelatin succinylated (30.4%) followed by glycerol (26.5%), saline (21.3%), and hydroxyethyl starch (17%), whereas hyaluronic acid was only used in a 2.6% of cases. Intra-procedural bleeding occurred in 86 (37.4%) lesions and was endoscopically managed in all cases (coagulation forceps in 62, clips in 17, and injection in 7).

The median number of ESD performed per endoscopist was 5 (IQR: 2–11.5). The median procedure duration was 105 min (IQR: 60–150 min) and the median size of the resected specimens in the pathology report was 35 mm (IQR: 25–48 mm). ESD for SELs was shorter than for epithelial lesions (90, IQR 45–121 min vs. 110, IQR 62–160 min;  $p = 0.038$ ). Table 2 shows different procedure times required for completing ESD based on the location and size of the lesions.

### ESD outcomes

A complete removal of the lesions was achieved in 226 (98.3%) cases. Reasons for incomplete resection were intraprocedural bleeding in one patient and extensive fibrosis in three patients. These four lesions were located in the proximal stomach. In 25 cases (10.9%), the procedure was turned into a hybrid ESD and 16 were piecemeal

**TABLE 1** Characteristics of the gastric lesions removed with endoscopic submucosal dissection

	All lesions N = 230	Epithelial lesions N = 196	Subepithelial lesion N = 34
Size (maximum diameter, mm) median (IQR)	35 (25–48)	35 (25–50)	27 (20–40)
Location, n (%)			
Cardia (upper)	14 (6.1%)	13 (6.6%)	1 (2.9%)
Fundus (upper)	5 (2.2%)	3 (1.5%)	2 (5.9%)
Body (upper)	71 (30.9%)	55 (28.1%)	16 (47.1%)
Incisura (middle)	29 (12.6%)	28 (14.3%)	1 (2.9%)
Antrum (lower)	111 (48.3%)	97 (49.5%)	14 (41.2%)
Paris classification, n (%)			
O-IIa	-	111 (56.6%)	-
O-IIb	-	14 (7.1%)	-
O-IIc	-	27 (13.8%)	-
O-IIa + O-II c	-	44 (22.5%)	-
Most advanced histology, n (%)			
Mucosal lesions			
Negative for neoplasia	-	14 (7.1%)	-
LGD	-	61 (31.1%)	-
HGD	-	42 (21.4%)	-
Noninvasive carcinoma	-	18 (9.2%)	-
Intramucosal carcinoma	-	34 (17.3%)	-
Submucosal invasive carcinoma	-	21 (10.7%)	-
Missing	-	6 (3%)	-
Subepithelial lesions			
Carcinoid	-	-	14 (41.2%)
Inflammatory fibroid polyp	-	-	8 (23.5%)
GIST	-	-	4 (11.8%)
Leyomioma	-	-	2 (5.9%)
Other	-	-	6 (17.6%)

resections (8 of them with the help of a snare). In two cases of en-bloc resection of epithelial lesions, the specimen could not be retrieved and in 35 of them the margins were positive (21 with vertical and 14 with affected horizontal margins). Histopathology of the lesions is shown in Table 1. Rates of en-bloc, R0, and curative resection were 91.3%, 75.2%, and 70.9%, respectively (Figure 2). Twenty-eight out of 225 patients (12.4%) presented a delayed bleeding. No delayed perforations were registered.

### Risk factors for difficult ESD

One hundred and twenty-eight (55.6%) ESD were considered difficult: procedure time >2 h in 77 (33.4%), hybrid ESD in 25 (10.9%), en-

bloc resection not achieved in 20 (8.7%), and perforation in 6 (2.6%). Difficulty was translated into lower rates of en-bloc, R0 and curative resection (Table 3).

In the univariate analysis, the nonlifting sign, location in the upper/middle stomach, poor maneuverability, fibrosis, submucosal fat, and intraprocedural bleeding were associated with a more difficult ESD (Table 4). Difficulty was not related with experience of the endoscopist (53.2% and 65.2% difficult ESD in endoscopists with <10 or ≥10 procedures;  $p = 0.093$ ). The presence of fibrosis and poor maneuverability were independent factor associated with difficult ESD (OR 3.60, 95%CI 1.10–11.74,  $p = 0.034$  and OR 5.07, 95%CI 1.60–16.08,  $p = 0.006$ ; respectively [Table 4]). We did not identify any independent predictive variable that could be assessed before starting the procedure.



**TABLE 2** Time (minutes) required for completing ESD based on type, location, and size of the resected lesion

Location Size		Lower stomach	Middle stomach	Upper stomach
≤35 mm <sup>a</sup>	N	65	13	49
	Median	85	89.5	97.5
	IQR	50–120	56.2–117.5	41.2–128.2
>35 mm	N	46	16	41
	Median	97	170	145
	IQR	64–150	112.5–238.7	98.2–240

Note: Cells display three different colors corresponding to different median times: less than 90 min, 90–100 min, and more than 120 min. Time tends to increase from the upper left to the lower right.

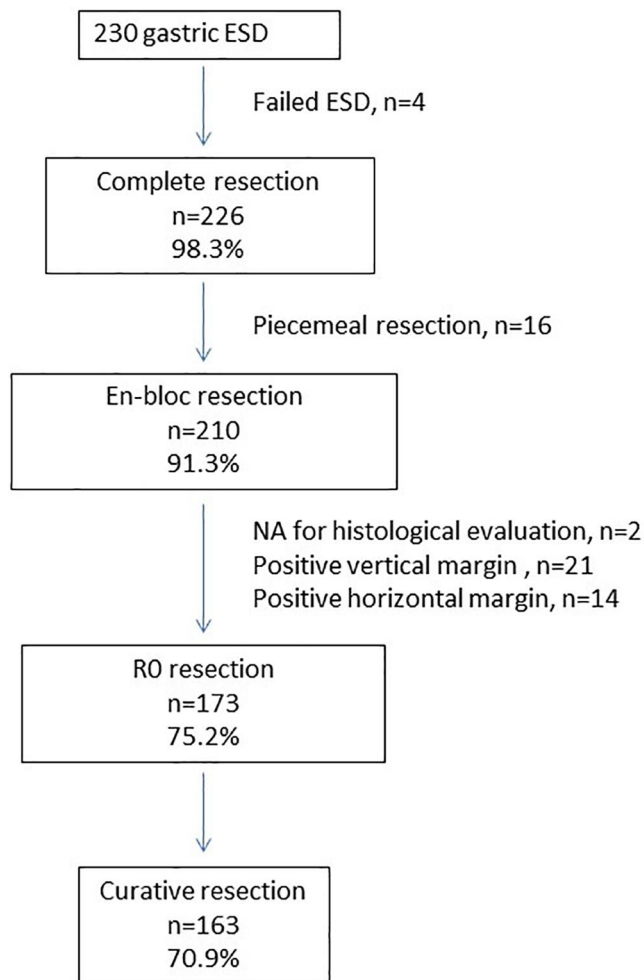
<sup>a</sup>Median of size of lesions included in the registry.

## DISCUSSION

In this study, we present the experience with gastric ESD in Spain, with rates of complete endoscopic resection, en-bloc, histological R0, and curative resection of 98.3%, 91.3%, 75.2%, and 70.9%, respectively. Despite the relatively low number of cases compared to other series in the East, our outcomes are very similar to those published in other Western reports.<sup>1,5,8–13</sup> Spain is considered a low-incidence area for gastric cancer,<sup>6</sup> which could explain that only 230 procedures were performed in 4 years.

The first report on the experience of a European country in gastric ESD was published in 2009. It was a retrospective single center study performed in Portugal with 19 patients that showed histological R0 and en-bloc rates of 79% and 89%, respectively.<sup>11</sup> Since then, more series have been published (most of them retrospective and with a maximum of three endoscopists) showing a clear improvement between the oldest and most recent studies. Whereas studies performed before 2011 included less than 100 patients with an R0 and en-bloc rates of 64%–89% and 79%–90%, recent studies include more than 100 patients with rates between 87%–92% and 83%–95%, respectively.<sup>10–13,19–22</sup> These studies confirm that the prevalence of EGC remains low in most non-Eastern countries since the rate of inclusion of cases is still low, requiring between 3 and 12 years for treating less than 200 patients.

An adequate training is the main prerequisite for a safe and effective ESD.<sup>5</sup> In early reports from Europe, gastric ESD was performed by endoscopists without a standard learning program, usually in a self-taught manner followed by a short visit to Japan as observer trainee.<sup>12</sup> Spanish endoscopists have performed a variable and non-systematic training that includes hands-on courses<sup>23</sup> and visits as observer trainee to Japan and other European and Spanish hospitals with a high volume of cases. Moreover, all endoscopists performing ESD in Spain have expertise in advanced diagnostic endoscopy, proficiency in EMR techniques and management of adverse events as recommended by the ESGE.<sup>5,24,25</sup> However, despite the experience in colonic EMR and that all



**FIGURE 2** Flow chart

lesions were evaluated with chromoendoscopy, in this analysis the lesion was not properly delineated, resulting in positive horizontal margins in 14 cases, thus stressing the importance of an accurate evaluation and delineation of the lesions (in our series, the R0 would have increased up to 81.3%).

Another important aspect for achieving proficiency in ESD is the continuous training. In this regard, the Spanish Society of Digestive Endoscopy promotes educational activities among its members.<sup>26</sup> Only seven of the 30 endoscopists met the requirement to perform a minimum of 25 ESD per year as recommended by the ESGE.<sup>5</sup> Moreover, most of those with less than five cases have either stopped doing ESD or are starting after having been trained by a senior endoscopist in the same center.

Besides the experience, for successful ESD it is mandatory to predict the degree of technical difficulty before starting the procedure. As shown in our study, difficult ESD is associated with an incomplete or noncurative resection. Difficult ESD procedures entail more device exchanges for tissue elevation, more bleeding, and more time. This certainly has significant implications in most health care environments because of the associated cost. Therefore, when a

**TABLE 3** Therapeutic outcomes according to the ESD difficulty

	All ESD N = 230	Difficult ESD N = 128	Not difficult ESD N = 97	p value
Complete endoscopic resection rate, n (%)	226 (98.3%)	124 (96.9%)	97 (100%)	0.079
En-bloc resection rate, n (%)	210 (91.3%)	108 (84.4%)	97 (100%)	0.000
R0 resection rate, n (%)	173 (75.2%)	83 (64.8%)	85 (87.6%)	0.000
Curative resection rate, n (%)	163 (70.9%)	76 (58.4%)	82 (84.5%)	0.000

Abbreviation: ESD, endoscopic submucosal dissection.

**TABLE 4** Independent predictive factors for difficult ESD

	Difficult ESD N = 128 (%)	Not difficult ESD N = 97 (%)	OR (95%CI)	p value <sup>a</sup>	Adjusted OR (95%CI)	p value <sup>b</sup>
Anesthesiologist, n (%)						
No	13 (10.2%)	1 (1.0%)	<b>0.09 (0.01–0.72)</b>	<b>0.005</b>	0.25 (0.26–1.46)	0.238
Yes	115 (89.8%)	95 (97.9%)				
Endoscopist experience, n (%)						
<10 ESD	45 (35.2%)	24 (24.7%)	0.60 (0.33–1.09)	0.093	0.80 (0.33–1.92)	0.623
10 or more	83 (64.8%)	73 (75.2%)				
Nonlifting sign, n (%)						
No	44 (84.6%)	41 (100%)	0.55 (0.49–0.62)	0.008	NV	NV
Yes	8 (15.4%)	0 (0%)				
Location, n (%)						
Lower	50 (39.1%)	58 (59.8%)	<b>2.32 (1.35–3.97)</b>	<b>0.002</b>	1.61 (0.78–3.32)	0.189
Middle/Upper	78 (60.9%)	39 (40.2%)				
Maneuverability, n (%)						
Good	73 (58.4%)	70 (82.3%)	<b>3.32 (1.71–6.44)</b>	<b>&lt;0.001</b>	<b>5.07</b>	<b>0.006</b>
Poor	52 (40.6%)	15 (17.7%)			<b>(1.60–16.08)</b>	
Fibrosis, n (%)						
No	41 (32%)	75 (78.1%)	<b>7.57 (4.11–13.94)</b>	<b>&lt;0.001</b>	<b>3.60</b>	<b>0.034</b>
Yes	87 (68%)	21 (21.9%)			<b>(1.10–11.74)</b>	
Submucosal fat, n (%)						
No	62 (73%)	65 (98.5%)	<b>24.11 (3.16–183.98)</b>	<b>&lt;0.001</b>	NV	NV
Yes	23 (27%)	1 (1.5%)				
Use of any type of traction, n (%)						
No	94 (81.7%)	85 (91.4%)	2.37 (0.99–5.64)	0.046	0.34 (0.57–2.13)	0.254
Yes	21 (18.3%)	8 (8.6%)				
Intraprocedural bleeding, n (%)						
No	57 (44.5%)	82 (84.5%)	<b>6.80 (3.54–13.06)</b>	<b>&lt;0.001</b>	1.36 (0.30–6.60)	0.681
Yes	71 (55.5%)	15 (15.5%)				

Abbreviations: ESD, endoscopic submucosal dissection; NV, not valuable.

<sup>a</sup>Univariable analysis.

<sup>b</sup>Multivariable analysis.

difficult ESD is expected, appropriate preparation must be considered, including consultation with more experienced endoscopists.

Fibrosis in the submucosal space has been reported as a factor for difficulty in other series.<sup>16</sup> To overcome difficult ESD procedures, several endoscopic knives and accessories have been developed including hybrid knives with injection capability or lifting devices.<sup>27,28</sup> The use of any type of traction (clips, fishing line, rubber band, etc.) may also be helpful.<sup>27</sup> These alternatives can be used depending on the operator's preference and the individual circumstances of each case.

Intraprocedural bleeding is difficult to avoid and occurs in almost all ESD.<sup>29</sup> In our definition, we did not include the bleeding that stops spontaneously or is easily managed with the endoscopic knife. Although a bleeding that requires other endoscopic treatments such as coagulation forceps or clip placement can be tough to control, prolongs the duration of the procedure and makes the dissection more difficult, it is not considered an adverse event. On the other hand, a difficult ESD due to severe fibrosis or poor maneuverability can also lead to more bleeding episodes due to an impaired visibility or uncontrolled movements.

Most of variables associated with difficult gastric ESD (such as fibrosis, poor maneuverability, or submucosal invasive cancer) cannot be determined before starting the procedure.<sup>16,30,31</sup> We did not identify any independent pre-procedural factor that predicted a difficult gastric ESD. However, there was an association between difficulty and location in the upper/middle stomach in the univariate analysis. As expected, ESD of lesions located in the upper and middle stomach was also associated with longer procedural time, especially in the case of epithelial lesions.

The main strength of our study is the representation of the real practice of ESD in Spain with a registry that included consecutive cases performed by multiple operators with variable level of training. To our knowledge, this is the only registry published in Europe in which all endoscopists performing ESD in the country have participated.

The present study has some limitations. First, the relatively low number of included cases precluded from drawing solid conclusions and recommendations about pre-procedural factors that could be considered prior to a gastric ESD. Second, the estimation of the lesion size was not recorded, and we only have the diameter of the full specimen assessed by the pathologist after the resection; then, we could not use this variable to predict difficulty before starting the procedures. Third, similarly with the size, we did not record the presence of ulceration before the resection. Correct diagnosis of ulceration may be difficult, especially when biopsies are taken previously or after proton pump inhibitor treatment.

In conclusion, the results of this prospective Spanish registry show an acceptable en-bloc and histological R0 rates in gastric ESD considering the wide variability in experience among the operators. Submucosal fibrosis and poor maneuverability were associated with more difficulty for completing ESD.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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