Predictors of long-term outcomes of endoscopic submucosal dissection of early gastric neoplasia in the West: a multicenter study

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ABSTRACT

Background This study aimed to determine long-term outcomes of gastric endoscopic submucosal dissection (ESD) in Western settings based on the latest Japanese indication criteria, and to examine predictors of outcomes and complications.

Methods Data were collected from consecutive patients undergoing gastric ESD at four participating centers from 2009 to 2021. Retrospective analysis using logistic regression and survival analysis was performed.

Results 415 patients were included (mean age 71.7 years; 56.4 % male). Absolute indication criteria (2018 guideline) were met in 75.3 % of patients. Median follow-up was 52 months. Post-resection histology was adenocarcinoma, high grade dysplasia, and low grade dysplasia in 49.9 %, 22.7 %, and 17.1 %, respectively. Perforation, early and delayed bleeding occurred in 2.4 %, 4.3 %, and 3.4 %, respectively. Rates of en bloc and R0 resection, and recurrence on first endoscopic follow-up were 94.7 %, 83.4 %, and 2.7 %, respectively. Relative indication (2018 guideline) for ESD was associated with R1 outcome ($P=0.02$). Distal location ($P=0.002$) and increased procedure time ($P=0.04$) were associated with bleeding, and scarring ($P=0.009$) and increased procedure duration ($P=0.003$) were associated with perforation. Recurrence-free survival at 2 and 5 years was 94 % and 83 %, respectively.

Conclusion This is the largest Western multicenter cohort and suggests that gastric ESD is safe and effective in the Western setting. A quarter of patients fell outside the new absolute indications for ESD, suggesting that Western practice involves more advanced lesions. We identified the predictors of complications, which should help to inform future Western practice and research.

Introduction

Gastric cancer is the fifth most common cancer worldwide and the sixth in Europe, and represents the third leading cause of cancer-related mortality globally [1]. Early gastric cancer (EGC) is defined as superficial cancer confined to the mucosa and submucosal layer, regardless of lymph nodes metastasis [2].

Endoscopic resection represents the main treatment modality in this group and provides an equally effective and minimally invasive approach compared with surgery [3]. The endoscopic submucosal dissection (ESD) technique was developed in Japan to meet the principles of onco-surgical resection of EGCs and

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overcome the drawbacks of endoscopic mucosal resection [3]. This minimally invasive technique has been widely practiced in East Asia and has become an accepted standard for the treatment of EGCs. However, the adoption of ESD in the West is still limited to a few referral centers [4].

The risk of lymph node metastasis is an important consideration for the indication of endoscopic resection for EGC. A large study in Japan evaluated the prevalence of lymph node metastasis in 5265 patients with EGC and found no risk of lymph node metastasis in patients with nonulcerated, well or moderately differentiated adenocarcinoma measuring < 30 mm, with depth of invasion up to < 500 µm into the submucosa and without lymphovascular invasion [5]. Another large study from Japan included 3843 patients with poorly differentiated gastric cancer who underwent gastrectomy with lymph node dissection, and identified lesion size of more than 20 mm, submucosal involvement, and presence of lymphovascular invasion as independent predictors of lymph node metastasis [6]. These two studies provided the base for the indication criteria for endoscopic resection of EGC in the Japanese guideline [3].

The latest Japanese guideline categorizes indications for endoscopic resection into three groups [3]. Absolute indications include differentiated (well to moderately differentiated), clinically intramucosal (T1a), nonulcerated lesions regardless of their size, and lesions ≤ 30 mm if ulcerated. The expanded indication category includes undifferentiated, nonulcerated, clinically intramucosal lesions ≤ 20 mm. The relative indication category is reserved for patients who do not fit either the absolute or expanded criteria but cannot undergo surgery because of clinical or other reasons.

A large volume of data demonstrating feasibility, efficacy, and safety of gastric ESD have been reported from East Asia [3, 7]. Moreover, several studies from the Far East have also shown good outcomes with the expanded criteria [7, 8]. However, data from Western endoscopy practice are still limited and come mostly from small series in single centers [9]. This raises questions about the generalizability of endoscopic resection in the West.

In this study, we review the feasibility, effectiveness, and safety of endoscopic resection of early gastric neoplasia in a comprehensively characterized large cohort from four major endoscopy referral centers across Europe. We describe follow-up and outcomes based on the application of the most recent criteria set by the Japanese Gastroenterological Endoscopy Society [3]. We also aim to identify predictors of outcomes that can inform future Western practice.

Methods

Setting

This was an observational cohort study conducted in four European countries including Italy, UK, Switzerland, and Poland. The study was conducted as a part of an ESD research registry. Research ethics committee approval was obtained (approval number 16/ES/0074).

Data were collected on electronic endoscopy reporting systems and included patient demographics, lesion characteristics, procedure details, and outcomes of endoscopic treatment.

Description of lesions

All gastric lesions referred for ESD in participating centers were included. These included EGC, precancerous lesions (low grade dysplasia [LGD] and high grade dysplasia [HGD]), as well as other types (e. g. submucosal lesions).

All EGCs and precancerous lesions were referred for ESD based on pre-resection histology confirmation. These lesions were categorized based on clinical criteria (size of the lesion, ulceration etc.) into absolute, expanded, or relative indication for ESD according to the latest Japanese guideline [3]. All histological assessments (pre- and post-resection) were double reported in cases of cancer.

The morphology of the lesions was described based on the Paris classification [10]. Lesions in the distal gastric body, antrum, and pylorus were classified as distal, and lesions in the proximal gastric body, fundus, and cardia were regarded as proximal. Scarring was described when there were endoscopic features of mucosal and submucosal fibrosis but with a completely intact mucosal layer, whereas ulceration was described when the mucosal continuity was interrupted or broken (endoscopic) or when ulceration was histologically reported. All assessments were performed using high definition white-light imaging as well as enhanced imaging (i. e. narrow-band imaging, blue-light imaging).

Endoscopic resection techniques

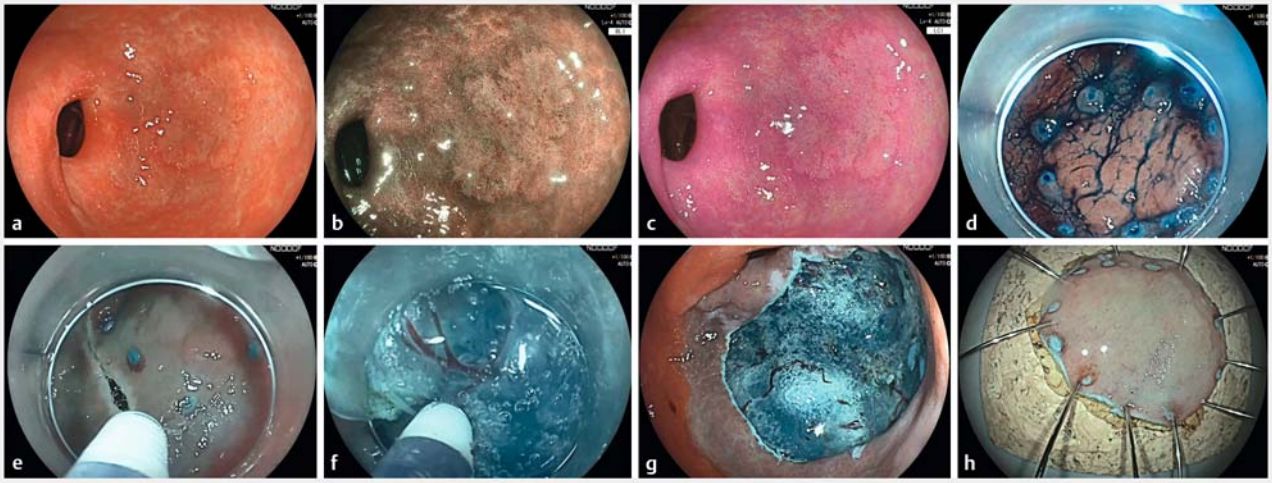
All endoscopic resection procedures were performed by expert endoscopists (A.R., P.Bh, S.Se., and M.F.K.). ESD techniques included conventional as well as pocket creation methods. In some cases, a hybrid technique was also used, described here as knife-assisted resection. ▶ **Fig. 1** illustrates the technical steps of the conventional ESD technique in the stomach.

Various electrosurgical knives were used including Hybrid-Knife (Erbe Elektromedizin, Tübingen, Germany], and Dual Knife J, Flush Knife, Hook Knife, and IT Knife (all Olympus, Tokyo, Japan). Electrosurgical units used included Erbe VIO 300 D and Erbe VIO 3 (Erbe Elektromedizin).

The submucosal lifting solution varied slightly across different centers but generally comprised Gelofusine (B. Braun, Melsungen, Germany) or normal saline with indigo carmine dye (40 mg per 500 mL solution) and adrenaline (0.5–1.0 in 100:000).

The duration of the ESD procedure (in minutes) was recorded from the first submucosal injection to the complete removal of the lesion.

All procedures were performed under propofol sedation or general anesthesia. After endoscopic resection, most patients were admitted for overnight observation and discharged the following morning on high dose proton pump inhibitor therapy. These patients were followed up clinically and endoscopically as per standard protocol, which comprised 3-monthly gastroscopies in the first year, 6-monthly gastroscopies in the second year, and then annual surveillance for 5 years. Endoscopic fol-



▶ **Fig. 1** Technical steps of endoscopic submucosal dissection (ESD). **a** Subtle and flat early gastric cancer in the gastric antrum in high definition white-light imaging. **b,c** The same lesion in blue-light imaging (**b**) and linked color imaging (**c**). **d** Lesion markings seen with dye spray. **e** Mucosal incision using Dual Knife J (Olympus, Tokyo, Japan). **f** Submucosal dissection. **g** The ESD lesion base. **h** The fully dissected and pinned specimen. Histology from this lesion showed intramucosal carcinoma with clear radial and deep margins.

low-up included inspection and sampling of the resection scar to check for presence of residual or recurrent neoplasia.

Histological assessment

All resection specimens, but one, were retrieved, pinned (in cases of en bloc resection), and sent for histological assessment in a formalin solution. Histological examinations were performed by histopathologists with expertise in gastrointestinal neoplasia assessment and all cancers were double reported.

Adenocarcinoma cases were divided into intramucosal (pT1a) and submucosal (pT1b). The depth of submucosal invasion was measured from the muscularis mucosae and reported as either Sm1/Sm superficial (<500 µm from the muscularis mucosae) or Sm deep (>500 µm from the muscularis mucosae). Adenocarcinomas were described as differentiated (papillary adenocarcinoma, well differentiated, or moderately differentiated tubular adenocarcinoma) or undifferentiated (poorly differentiated adenocarcinoma and signet cell cancers).

Outcomes

The primary outcomes included rates of en bloc and R0 resection, and recurrence following endoscopic resection. Secondary outcomes included complications rates (early and delayed bleeding, perforation) and need for surgery. R0 resection was defined as an en bloc resection with no microscopically visible tumor cells at any of the margins. Resection was considered as R0 only if both lateral and deep margins were reported as R0. Recurrence on follow-up endoscopy was described as the presence of residual neoplasia around or within the previous endoscopic resection scar and confirmed by histopathological examination. Patients with evidence of metastasis on cross-sectional imaging were considered as having metastatic recurrence. Recurrence is reported according to European Society of Gastrointestinal Endoscopy (ESGE) criteria [11], British Society of Gastroenterology criteria [12], and the Japanese eCura classification [3].

Early bleeding was defined as bleeding within 24 hours of the procedure. Delayed bleeding was defined as bleeding after 24 hours but within 28 days of the procedure that was directly attributed to the endoscopic resection procedure, and resulted in hospital admission, significant hemoglobin drop (≥2 points), hemodynamic compromise, and/or need for endoscopic, radiological, or surgical intervention, or blood transfusion.

Perforation was defined as a significant injury to the muscularis propria as noted by the endoscopist during the procedure, or as a result of clinical or radiological assessment demonstrating signs consistent with perforation.

Statistical analysis

Statistical analysis was performed using Stata software version 15.1 (StataCorp LLC, College Station, Texas, USA). The main objective of the analysis was to determine factors associated with the three primary outcomes (i.e. en bloc, R0, and recurrence rates) and to examine the effect of the indication criteria (i.e. absolute, expanded, or relative) on these outcomes. All outcomes were binary in nature. Logistic regression analysis was performed to identify any significant predictors. Significance levels and *P* values were two sided. Significance was regarded at $P<0.05$. Categorical variables were summarized by the number and percentage of patients in each category. Continuous variables were summarized by the mean and SD if found to be normally distributed, and the median and interquartile range (IQR) if not.

Calculations of the proportion of patients free from a recurrence during the follow-up period were calculated using Kaplan–Meier methods. Factors associated with the time to recurrence were evaluated using Cox regression.

Results

A total of 415 patients were included in the study (see **Fig. 1 s** in the online-only Supplementary material). Data on indication criteria based on the latest Japanese guideline (5th edition, 2018 [3]) and analysis of curative resection rates were obtained in 372 patients with epithelial lesions (LGD, HGD, and adenocarcinoma). Analysis of recurrence outcome was only performed on patients with complete endoscopic follow-up data (293 patients).

▶ **Table 1** summarizes patient demographics, general procedure details, and lesion characteristics, and ▶ **Table 2** shows the histological changes from pre-resection (biopsies) to post-resection specimens, as well as the histological staging details of adenocarcinomas. ▶ **Table 3** summarizes outcomes and complications. The results of the multivariate analysis are shown in ▶ **Table 4**.

Kaplan–Meier analysis estimated 2-year recurrence-free survival at 94 % but it dropped to 83 % at 5 years. A graphical illustration of the proportion of patients free from recurrence over the follow-up period is shown in ▶ **Fig. 2**. **Fig. 2 s** and **Fig. 3 s** show the Kaplan–Meier plots for time to recurrence by resection technique (ESD vs. knife-assisted resection) and margin status, respectively.

Discussion

This is one of the largest multicenter Western gastric ESD series with long-term follow-up data and the first study to identify predictors of long-term outcome in Western settings. We found that ESD was a safe and effective treatment, with rates of en bloc and R0 resection, and early and delayed recurrence of 94.7 %, 83.4 %, 2.7 %, and 3.2 %, respectively, and rates of early bleeding, delayed bleeding, and perforation of 4.3 %, 3.4 %, and 2.4 %, respectively. Only three cases of complications (two bleeding and one delayed perforation) needed radiological or surgical intervention and the rest were all amenable to endoscopic treatment, further demonstrating the safety of gastric ESD in the Western setting.

The outcomes reported in our study were not dissimilar to recently published large Western series. Ngamruengphong et al. published a large North American multicenter series and reported rates of en bloc and R0 resection, and recurrence of 92 %, 82 %, and 3.9 %, respectively, with perforation and delayed bleeding rates of 6.6 % and 2.6 %, respectively [13]. However, their median follow-up duration of 8 months was significantly lower than in our study and endoscopic follow-up was missing in a significant proportion (42.0 %) of patients [13]. Another Italian multicenter study by Manta et al. reported en bloc and R0 rates of 97.6 % and 89 %, respectively, with a recurrence rate of 6.2 % and curative rate in the EGC group of only 72.5 % [14]. The same study reported complications in 10.1 % of patients. However, this study also lacked data on long-term outcomes. The only published Western series with long-term outcomes [15, 16] were both single-center studies with a significantly smaller number of patients compared with the current study.

▶ **Table 1** Summary of patient demographics, general procedure details, and lesion characteristics (n = 415).

Variable	
Sex, n (%)	n = 415
▪ Female	181 (43.6)
▪ Male	234 (56.4)
Age at procedure, years	n = 415
▪ Mean (SD)	71.7 (10.5)
Indication criteria (5th version 2018)[1], n (%)	n = 372
▪ Absolute	280 (75.3)
▪ Expanded	1 (0.3)
▪ Relative	92 (24.7)
Indication criteria (4th version 2014)[2], n (%)	n = 372
▪ Absolute	104 (28.0)
▪ Expanded	175 (47.0)
▪ Outside	93 (25.0)
Resection technique, n (%)	n = 415
▪ ESD	371 (89.4)
▪ Knife-assisted resection	44 (10.6)
Procedure duration, minutes	n = 415
▪ Median (IQR)	90 (59–120)
Follow-up, median, (IQR), months	n = 415
▪ Median (IQR)	52 (29–82)
Presence of *H. pylori*, n (%)	n = 415
	28 (6.7)
H. pylori eradication, n (%)	n = 28
▪ Eradicated	26 (92.9)
▪ Not eradicated	2 (7.1)
Site, n (%)	n = 415
▪ Distal	209 (50.4)
▪ Proximal	206 (49.6)
Visible scarring	n = 415
▪ No	380 (91.6)
▪ Yes	35 (8.4)
Lesion size, mm	n = 415
▪ Median (IQR)	25 (20–40)
Paris classification, n (%)	n = 415
▪ Is	71 (17.1)
▪ IIa / IIb	162 (39.0)
▪ IIc	182 (43.9)

ESD, endoscopic submucosal dissection; IQR, interquartile range.
[1] 5th version 2018 [3].
[2] 4th version 2014 [31]

▶ **Table 2** Change in histology from pre-resection (on biopsy) to post-resection (n = 414), and the histological staging details of adenocarcinoma cases (n = 207).

Post-resection histology	Pre-resection histology (forceps biopsies)					
	Hyperplastic	LGD	HGD	Adenocarcinoma	Submucosal tumor	Total
Hyperplastic	8	3	0	0	1	12
LGD	0	59	12	0	0	71
HGD	0	27	59	8	0	94
Adenocarcinoma	0	12	90	105	0	207
Submucosal tumor	4	0	0	1	25	30
Total	12	101	161	114	26	414
Histological staging of adenocarcinomas (n = 207)					**n (%)**	
Depth of invasion						
▪ pT1a					136 (65.7)	
▪ Superficial submucosa					36 (17.4)	
▪ Deep submucosa					35 (16.9)	
Differentiation						
▪ Differentiated (well/moderately differentiated)					179 (86.5)	
▪ Undifferentiated (poorly differentiated/signet cells)					28 (13.5)	
Others						
▪ Signet cells					11 (5.3)	
▪ Lymphovascular invasion					30 (14.5)	

LGD, low grade dysplasia; HGD high grade dysplasia.

Our study results are also in line with data from large multicenter Japanese studies. Oda et al. reported a series of 655 patients, with an en bloc resection rate of 92.7 % and perforation rate of 3.6 % [17]. Another Japanese study included 485 early gastric neoplasms and found en bloc and R0 resection rates of 93.6 % and 85.4 %, respectively [18]. Another large series of 703 early gastric lesions from 30 Japanese centers reported a complete en bloc resection rate of 91.1 %–92.1 % in patients treated as per Japanese standard indication criteria, with perforation and delayed bleeding rates of 3.6 %–4.7 % and 0.0–0.26 %, respectively [19].

In contrast, single-center studies, both Western and Eastern, tend to report better outcomes [20–22]. These single-center series tend to mostly come from expert centers and reflect exceptionally high levels of technical skills; however, the possibility of selection bias cannot be completely excluded.

When compared with large series from the Far East [23–26], our R0 rate is slightly inferior, and this is possibly multifactorial. The learning curve for ESD can be lengthy and it may affect the procedure outcomes when endoscopists are still moving along this trajectory [27]. Moreover, this may also represent the challenges faced by Western endoscopists in accurately recognizing the margins of early gastric neoplasia, as the prevalence rate of this condition is still relatively low compared the rate in Asia [4]. Another issue might be that Western endoscopists tend to perform mucosal incision too close to the lesion margins, resulting in a diathermy artifact and subsequently overestimation of the lateral margin R1 rate.

Our data show a significant discrepancy between pre- and post-resection histology, with a significant number of LGDs upgraded to HGDs (26.7 %) and adenocarcinomas (11.9 %), as well as HGD lesions being upgraded to adenocarcinoma (55.9 %) after ESD. This indicates that pre-resection biopsy results can be misleading and supports findings from other studies [28]. This is particularly relevant as most of the initial detection work and discussion with patients is usually performed by general endoscopists who rely heavily on histology-driven management decisions. This discrepancy is a reminder that all early gastric neoplasia lesions, including LGD, should be referred to specialist centers for expert assessment and decision making.

The treatment strategy in patients with noncurative resection in this cohort was varied and based on many factors. Patients who were fit and willing to undergo surgery were referred for surgical treatment. Patients who were not fit or not willing to undergo surgery were followed up endoscopically and radiologically; if recurrence was found during surveillance, they were counseled about endoscopic or surgical treatment based on their fitness and views. A small proportion of patients opted to have no further treatment or surveillance. All decisions were discussed in the multidisciplinary team meetings,

▶ **Table 3** Outcomes and complications of endoscopic resection of early gastric neoplasia.

Outcomes	n (%)
En bloc	n = 415 393 (94.7)
R0 margins	n = 415 346 (83.4)
Recurrence (on 1st endoscopy follow-up)	n = 293 8 (2.7)
Delayed recurrence (after 1st endoscopy follow-up)	n = 285 9 (3.2)
Curative resection rate (ESGE criteria[1])	n = 372
▪ Curative	282 (75.8)
▪ Noncurative	90 (24.2)
Curative resection rate (BSG criteria[2])	n = 372
▪ Curative	270 (72.6)
▪ Noncurative	102 (27.4)
Curative resection rate (eCura classification[3])	n = 372
▪ A	254 (68.3)
▪ B	12 (3.2)
▪ C-1	16 (4.3)
▪ C-2	90 (24.2)
Complications	
Bleeding	n = 415
▪ Early	18 (4.3)
▪ Delayed	14 (3.4)
Management of bleeding	n = 32
▪ Conservative PPI	5 (15.6)
▪ Endoscopic	25 (78.1)
▪ Radiologic	1 (3.1)
▪ Surgical	1 (3.1)
Transfusion required	n = 32 9 (28.1)
Perforation	n = 415 10 (2.4)
Management of perforation	n = 10
▪ Endoscopic	9 (90.0)
▪ Surgery	1 (10.0)

ESGE, European Society of Gastrointestinal Endoscopy; BSG, British Society of Gastroenterology; PPI, proton pump inhibitor.
[1] ESGE criteria [11].
[2] BSG criteria [12].
[3] eCura classification [3].

▶ **Table 4** Multivariate analysis of factors associated with outcomes and complications.

Factors and variables	OR (95 %CI)	*P* value
Factors associated with non-en bloc status		
Ulceration		
▪ No	1	0.03
▪ Yes	3.52 (1.14–10.9)	
Resection technique		
▪ ESD	1	<0.001
▪ Knife-assisted resection	27.3 (10.1–74.1)	
Factors associated with R1 status		
Indication (2018 criteria[1])		
▪ Absolute	1	0.02
▪ Relative	3.89 (1.22–12.4)	
Scarring		
▪ No	1	0.008
▪ Yes	3.99 (1.43–11.2)	
Ulceration		
▪ No	1	0.02
▪ Yes	2.79 (1.18–6.61)	
Post resection histology		
▪ Deep submucosal invasion	8.52 (7.06–56.9)	<0.001
Factors associated with noncurative resection (ESGE criteria[2])		
Lesion size, mm	1.41 (1.00–1.97)	0.05
Ulceration		
▪ No	1	0.006
▪ Yes	17.6 (2.31–134)	
Indication (2018 criteria[1])		
▪ Absolute	1	<0.001
▪ Relative	316 (58.6–1699)	
En bloc resection		
▪ Yes	1	0.08
▪ No	14.7 (0.75–286)	
Margins		
▪ R0	1	<0.001
▪ R1	250 (37.9–1648)	
Factors associated with noncurative resection (Japanese eCura classification[3])		
Site		
▪ Distal	1	0.04
▪ Proximal	2.24 (1.02–4.94)	
Paris classification		

▶ **Table 4** (Continuation)

Factors and variables	OR (95 %CI)	*P* value
▪ Is	1	0.04
▪ IIa/IIb	0.22 (0.06–0.73)	
▪ IIc	0.29 (0.09–0.93)	
Ulceration		
▪ No	1	0.04
▪ Yes	3.05 (1.07–8.69)	
Indication for ESD (2018 criteria[1])		
▪ Absolute	1	<0.001
▪ Relative	45.4 (19.4–106)	
En bloc resection		
▪ Yes	1	<0.001
▪ No	71.6 (12.5–410)	
Factors associated with bleeding		
Site		
▪ Distal	1	0.002
▪ Proximal	0.28 (0.12–0.63)	
Procedure time, hours	1.55 (1.03–2.33)	0.04
Paris classification (for early bleeding)		
▪ Is	1	0.04
▪ IIa/IIb	1.02 (0.10–10.1)	
▪ IIc	4.46 (0.57–35.2)	
Ulceration (for delayed bleeding)		
▪ No	1	0.02
▪ Yes	3.90 (1.24–12.3)	
Factors associated with perforation		
Procedure time, hours	4.77 (1.71–13.2)	0.003
Lymphovascular invasion		
▪ No	1	0.004
▪ Yes	4.46 (0.57–35.2)	
Age at time of procedure, years[4]	2.96 (0.99–8.88)	0.05
Scarring		
▪ No	1	0.009
▪ Yes	19.6 (2.09–183)	
Factors associated with time to recurrence	**HR (95 %CI)**	
Resection technique		
▪ ESD	1	0.001
▪ Knife-assisted resection	7.07 (2.29–21.8)	
Margins		
▪ R0	1	<0.001
▪ R1	9.60 (3.45–26.7)	

OR, odds ratio; ESD, endoscopic submucosal dissection; ESGE, European Society of Gastrointestinal Endoscopy; HR, hazard ratio.
[1] 2018 criteria [3].
[2] ESGE criteria [11]
[3] eCura classification [3]
[4] OR given for a 10-unit increase in predictor variable.

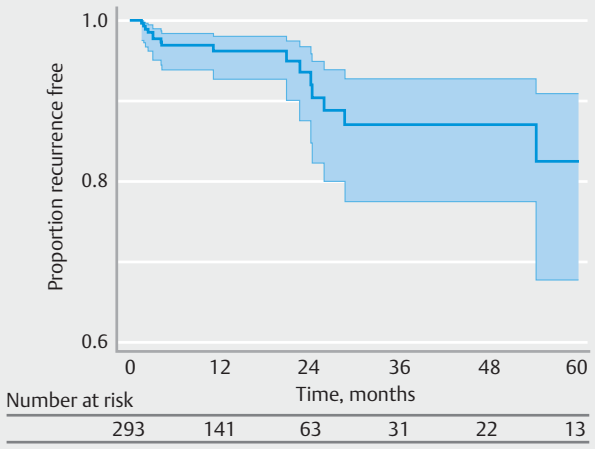
and patient's views and expectations were considered. **Table 1 s** summarizes management of patients with noncurative resection.

Our multivariate analysis showed that performing gastric ESD for relative criteria, as per the latest Japanese guideline, was a predictor of R1 resection (odds ratio [OR] 3.89, $P=0.02$). Lesions in this category are generally challenging and difficult to resect. Despite this, we did not see a significant increase in recurrence or complication rates in this group of patients on multivariate analysis. Although our data demonstrated good overall outcome in this group, these results should be interpreted with caution, as the endoscopists involved in this series were highly experienced.

Moreover, multivariate analysis showed that hybrid resection technique, described here as knife-assisted resection, was a strong predictor for recurrence (hazard ratio 7.07, 95 %CI 2.29–21.8; $P=0.001$), and for piecemeal resection (OR 27.3, 95 %CI 10.1–74.1; $P\leq0.001$). Our results would therefore caution against the use of hybrid techniques for the resection of gastric neoplasia. Procedure time was found to be significantly correlated to both risk of bleeding (OR 1.55, $P=0.04$) and perforation (OR 4.77, $P=0.003$); however, we cannot be certain whether bleeding was responsible for the prolonged time or whether the prolonged procedure played a role in increasing the risk of bleeding. Furthermore, multivariate analysis showed distal location to be correlated to increased risk of bleeding ($P=0.002$); this is similar to data from some cohorts from East Asia [29, 30].

Lack of complete endoscopic follow-up data for all study patients represents a major limitation in most of the published Western literature on gastric ESD. Our study was no exception, as 29.4 % of patients in our series did not have complete endoscopic follow-up data post-ESD. To overcome this limitation, we performed a stringent recurrence-free survival analysis. Rather than simply measuring frequency, this type of analysis also involves a time-to-event element and deals with the issue of data censoring, which is loss to follow-up in this case.

This survival analysis showed a 2- and 5-year recurrence-free survival of 94 % and 83 %, respectively. We believe that the drop in predicted recurrence-free survival from 94 % at 2 years to 83 % at 5 years could potentially be the worst-case scenario but is a statistically robust way of allowing for the variable follow-up and lack of follow-up in some of our cases. This is also supported by other findings in this study, which demonstrated that



▶ **Fig. 2** Kaplan–Meier curve showing the proportion of recurrence-free patients over the follow-up period. At 2 and 5 years, 94 % and 83 % of patients were free from recurrence, respectively.

nine patients (3.2 %) developed recurrence after their first endoscopic follow-up compared with eight patients (2.7 %) who were found to have recurrence on first endoscopic follow-up, suggesting that recurrence rates can go up with longer follow-up. The predicted late recurrence is more in line with the R0 rate (83.4 %) and curative resection rate (75.8 % based on ESGE criteria) in our study. As we detailed above, the R0 and noncurative resection rates in our study were not very different from other large Western series, so we believe other studies' reliance on simply measuring the frequency of recurrence could have underestimated their recurrence rates. This highlights the importance of longer-term follow-up data and the use of the best statistical methods to address the variable follow-up data in studies such as these. The practical message here would be that these patients should stay under expert follow-up for 5 years.

This study represents the first Western series using the latest Japanese guideline (5th edition [3]). **Table 2 s** summarizes the differences between the latest and previous versions of the Japanese guidelines, and distribution of patients in this cohort based on these guidelines. Based on this latest guideline, all but one of the lesions that were previously (4th version) listed under expanded criteria (175, 47.0 % of patients) have been moved to absolute criteria category. The majority of our lesions would have fallen under the expanded or outside of criteria category according to the old (4th edition) guideline. However, when applying the new guideline, almost 75 % of our patients came under the absolute indication category, with only one patient in the expanded criteria group and almost 25 % of the patients meeting the relative indication criteria. Our data suggest that Western endoscopists have already been performing a lot of ESD on patients with lesions that fall beyond the absolute indications either by old or new guidelines. One of the important reasons could be later diagnosis of these lesions in the West compared with in the East.

The limitations of our study are similar to those of previously published series from the East and West, where lack of follow-up, selection bias, and high expertise can overestimate positive outcomes. We have tried to address some of these limitations by a multicenter design, longer follow-up, and by performing recurrence-free survival analysis.

In conclusion, this large multicenter European study demonstrated the feasibility and safety of gastric ESD even in patients outside of the latest Japanese absolute criteria. However, more effort needs to be made to improve R0 in the West. Despite this accumulating evidence, numbers are still not as large as those seen in the Far East, indicating that gastric ESD in the West should remain restricted to the few expert referral centers in order to achieve good outcomes. Our data also suggest that knife-assisted snare resection and other similar hybrid techniques should be avoided in the stomach.

Competing Interest

The authors declare that they have no conflict of interest.

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