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Endoscopic submucosal dissection for gastric epithelial lesions: long-term results in a Spanish cohort

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ABSTRACT

Introduction: endoscopic submucosal dissection for gastric lesions (ESD-G) is a technique that allows en-bloc resection of early gastric tumors, with a cure rate similar to that of surgery but lower morbidity and mortality rates.

Objective: to assess total survival, disease-free survival and relapse rate during the course of disease in a Spanish cohort of patients undergoing ESD-G.

Material and methods: this was a prospective observational study of patients undergoing ESD-G from 2008 to 2015, with a follow-up ranging from six to 60 months. Recurrence at five years was analyzed using Kaplan-Meier curves and the results were compared according to several factors using the log-rank test. These included en-bloc *versus* piecemeal resection and R0 curative resection *versus* resection with affected

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lateral margins (LM+).

Results: a total of 35 patients undergoing ESD-G were assessed, with a median follow-up of 33.62 months. Four relapses were identified (11.4%) during this period, of which three were managed with repeat ESD-G. A histological specimen with LM+ was associated with a higher local relapse rate during follow-up (p = 0.06). Piecemeal resections had a higher relapse risk, although no statistically significant differences were identified (p = 0.49). No deaths from gastric cancer occurred and no gastrectomies due to persistent disease were performed during this period. The overall survival rate in our series was 94.3%.

Conclusions: ESD-G in our setting provides high long-term cure rates, while avoiding surgery. These results are similar to those reported by the European series and remain far removed from the cure and relapse rates obtained in Asian cohorts. Local relapse cases may be monitored with endoscopy.

Keywords: Gastric cancer. Endoscopic submucosal dissection. Survival. Gastric carcinoma. Long-term outcome.

INTRODUCTION

The incidence and mortality of gastric cancer has decreased over the past few decades on a worldwide scale (1). The higher incidence of this malignancy in areas such as Asia prompted the development of tools for detection and early management, which avoided surgery in a significant proportion of cases. Endoscopic submucosal dissection (ESD) for early gastric epithelial lesions has yielded good results in terms of curability in large series of patients, primarily in the Asian continent where it was first developed (2,3).

These results have been reproduced to a lesser extent in the western hemisphere, mainly due to a lower incidence of the disease and a more recent incorporation of the technique into the health systems elsewhere in the world. The goal of this study was to report the initial data on the long-term follow-up of gastric lesions resected with ESD (ESD-G) within the Spanish setting, as a first comparison with the wider European and Asian series involving expert endoscopists.

MATERIALS AND METHODS

Patient inclusion

This was a prospective observational study. Patients with gastric epithelial lesions identified with endoscopy and with an indication of ESD-G, were consecutively included from September 2008 to December 2015 at the following centers: Hospital Universitario 12 de Octubre, Hospital Rúber Juan Bravo and Hospital Universitario HM Sanchinarro, all in the Madrid region. Follow-up was extended to December 2018. Informed consent was obtained from all subjects and the study was approved by the Ethics Committee in our site (CEI 14/384; 29/9/2015).

Endoscopic equipment

Endoscopic procedures were performed with high-definition gastroscopes, with or without magnification (EG 590, EG 590 ZW, EG 600, EG 600 ZW), using the EPX-4400 and ELUXEO™ 7000 (Fujifilm, Tokyo, Japan) video processors. A chromoendoscopic study of the post-ESD scar was performed using a contrast stain (0.4% indigo carmine or 2% acetic acid) and/or a virtual approach (Fuji Intelligent Chromo Endoscopy, FICE). Flush knife BT™ (Fujifilm, Tokyo, Japan) and IT knife 2™ or IT nano™ (Olympus, Tokyo, Japan) scalpels were used for both the initial dissection and follow-up dissection for relapse (re-ESD). ICC 200 or VIO® 300D (ERBE, Tübingen, Germany) electrosurgical units, standard biopsy sampling forceps and argon plasma fulguration probes were also used.

Follow-up and event definition

Patient baseline characteristics were collected according to multiple variables. Patients with resected gastric epithelial lesions followed up for a minimum of six months to 60 months were considered for the analysis. The primary endpoint was disease-free survival at five years, defined as the absence of local or distant recurrence of the gastric neoplasm. Death from gastric malignancy and death from all causes were collected for the above assessment events, such as the need for gastrectomy during follow-up. Patients were regularly monitored at the outpatient clinic.

Biopsy samples from all the lesions identified prior to planning the resection with ESD-G were obtained for histological assessment. Resected lesions were categorized according to morphological and histological characteristics (location, size, Paris classification [4], Vienna classification [5] and TNM). Curative resection was considered for lesions that met the criteria of the Japanese Gastric Cancer Treatment Guidelines (6) according to size, histological type, en-bloc resection, tumor surface ulceration status (UL+/-), absence of lymphovascular involvement, free lateral margins (LM-) and the absence of deep submucosal invasion (< 500 microns for gastric lesions). For piecemeal resected lesions, lateral margins were defined as "undetermined" (LMx) due to the impossibility of actual involvement measurements.

Endoscopic controls after resection were initially performed at three, six, nine and 12 months, and then once a year. A yearly computed tomography (CT) scan was performed for lesions with expanded criteria. A relapsing lesion was defined as the development of dysplastic tissue in the post-ESD scar area. Biopsy samples were taken from all scars, whether or not a macroscopic relapse was identified, both with white light and after directed chromoendoscopy with indigo carmine.

Statistical analysis

The MS-Access program (Microsoft Corp., Redmond, WA, USA) was used for data collection. The statistical analysis was performed using the IBM SPSS version 23.0 for Windows statistical software package (IBM Corp., Armonk, NY, USA). Discrete variables were expressed as percentages and continuous variables were expressed as the mean, standard deviation (SD) and range (or median and interquartile range for non-normal distribution variables). Factors associated with relapse risk were analyzed using Kaplan-Meier curves and comparisons were performed using the log-rank test. Patients followed up for less than six months post-ESD-G or without follow-up data were not included in the analysis. All authors had access to the final results of the study, which were reviewed and approved for the final manuscript.

RESULTS

A total of 52 ESD-G procedures were performed in 47 patients. Twelve lesions were excluded from follow-up. Two had an involved vertical margin (VM+) and therefore gastrectomy was indicated with a curative intent. Three resections had non-epithelial lesions, one hyperplastic lesion and two gastric neuroendocrine tumors. One patient had significant comorbidities and died early during the postoperative period, likely due to bronchoaspiration, even though the ESD procedure was performed with orotracheal intubation. Six patients were lost to follow-up (Table 1 and Fig. 1). Therefore, the final analysis included 35 subjects and 40 ESD-G procedures.

Lesions with endoscopic resection indication based on absolute or expanded criteria

Ten epithelial lesions met the absolute indication criteria for ESD (28.6%). These included guideline criteria: < 2 cm, differentiated histology and no ulceration, maximum invasion T1a. Based on expanded criteria, 24 lesions were resected (68.5%). This included 23 neoplasms larger than 20 mm with differentiated histology and UL and one neoplasm smaller than 20 mm with an undifferentiated histology and UL. Only one lesion (2.9%) was endoscopically excised outside the resectability criteria, which was a 27-mm undifferentiated carcinoma.

Lesions resected en bloc or piecemeal

En-bloc resection by ESD-G was used for 30 lesions (85.7%). Five lesions were excised piecemeal (14.3%). Therefore, histology could not establish lateral margin involvement status (LMx). The mean lesion size in histological specimens was 22 mm ± 4.47 mm overall and 26 mm ± 3.89 mm in lesions with expanded criteria.

Curative and non-curative resections

A total of 27 lesions (77.14%) met the curative criteria included in the Japanese Gastric Cancer Treatment Guidelines, which were en-bloc resection, free lateral and vertical margins and no lymphovascular invasion. Resections were deemed non-curative according to the following criteria: a) involved (R1) lateral margin (LM+) (2/35, 5.7%); b) piecemeal resection (LMx: 14.3%); and c) undifferentiated histology larger than 20 mm (2.9%). The initial resection was extended by re-ESD in the two cases with LM+.

Disease-free survival and relapse during follow-up

Follow-up data at 60 months were analyzed. The median follow-up was 33.62 months (range: 6-60 months). The mean number of monitoring endoscopies per patient was 4.42, with a median of 4.1. Disease-free survival rate at five years was 88.6%.

Four relapses were identified during this period (11.4%). Having individual patient preferences in mind, a repeat ESD was performed in three cases (8.57%) with a curative intent. Two had no evidence of disease relapse during follow-up after the repeat procedure. The third subject required ablation therapy (argon plasma fulguration) in successive monitoring visits due to persistent dysplastic tissue. One subject underwent argon gas fulguration at the relapse site as an initial treatment, with close endoscopic monitoring thereafter (Table 2).

The presence of LM+ in the histology specimen was associated with a higher local relapse rate during follow-up, with a trend towards statistical significance (p = 0.06). Piecemeal resections had a higher risk of relapse but no statistically significant differences were found (p = 0.49) (Fig. 2).

Overall survival in our series was 94.3%. No cases were recorded that required gastrectomy or met the guideline criteria, either expanded or LM+, and there were no deaths related to gastric malignancies. Two patients died from cerebrovascular accidents, which occurred nine and 14 months after endoscopic resection, respectively.

DISCUSSION

The present study involved the clinical and endoscopic follow-up of a cohort of 35 patients with gastric epithelial lesions resected by ESD-G. Our results suggest a high rate of disease-free survival at five years (88.6%), with endoscopic management for relapsing lesions in all cases. No gastrectomies were performed for advanced cancer disease and there were no cancer-related deaths.

ESD is a widely accepted technique in Asia for the curative management of early lesions in the gastrointestinal tract. In expert hands, it has demonstrated good outcomes in terms of complete resection and long-term survival (7-9). ESD avoids

surgery in many instances, with cure rates similar to those of gastrectomy and minor complications (10,11). Cumulative experience in other regions has contributed additional data to the large Asian series and provided further evidence in support of their well-known conclusions (12,13).

Data collection in our cohort paralleled the learning curve with the technique of four endoscopists (JCMG, JDT, AJdPG, SRM), as was previously reported by our team (14) (Fig. 3). This is an important factor when assessing local recurrence cases, as three met absolute indication criteria and yet no curative resection was initially achieved. Rescue endoscopic treatments were used in our cases (repeat ESD, argon plasma fulguration), which have demonstrated a good control of local recurrence in this scenario (15). Most local recurrences occurred in elderly patients with associated comorbidities. Available data regarding close endoscopic monitoring to avoid major surgery are favorable in this group of patients (16,17) based on clinical follow-up and histological specimen findings. Primarily, the absence of lymphatic invasion (18), which has proven to be an earlier risk factor for recurrence as compared to vascular invasion.

Most lesions in our series met the expanded criteria due to a size > 20 mm. In these indications, results regarding curative resection, local recurrence and long-term disease-free survival are similar to those of other series in our setting (19-22). Only two lesions were undifferentiated carcinoma histologically, one met the expanded criteria for cure and one fell outside the indication (27 mm, en-bloc resection, LM-, 23 months of follow-up, no relapse at the time of data analysis). For the latter, a conservative approach was selected because of the comorbidities of the patient (high surgical risk), a strategy that has shown acceptable outcomes with a more limited life expectancy (23,24).

Our cohort shows the initial evolution of this technique in our setting. Patients were included starting with the first procedure performed, data were collected prospectively for a protracted period of time (up to 60 months) in order to also assess the results of the clinical procedure, besides technical success.

Our study has a number of limitations. Firstly, the number of patients in follow-up during this period was small (n = 35) and inadequate to compare our results with those of the larger, previously reported series. Hence, no statistically significant causality

relationships were obtained between the variables. Secondly, there was no control group with patients undergoing surgery in order to compare morbidity and mortality rates. Further data are needed in our milieu to confirm the technical and clinical success of ESD for gastric epithelial lesions. At the time of writing this paper, a prospective, multicenter study on a nationwide scale is in its patient inclusion phase, with cases selected from 2016 onwards. This will provide more robust conclusions on the efficacy of this technique in our setting.

CONCLUSIONS

We report the first long-term follow-up data following the resection of gastric epithelial lesions using ESD in our country. The disease-free survival rate at five years was 88.6%. In the cohort of patients followed up after ESD (n = 35), no cases of gastrectomy with curative intent were found, no tumor progression cases were identified and there were no deaths from gastric cancer. ESD for gastric lesions offers good long-term clinical results, similar to those of European series, although still far removed from those reported by Asian expert teams. Further data are required to confirm this hypothesis in our setting.

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Table 1. Baseline characteristics of patients and lesions analyzed during follow-up

Characteristic (n = 35)	Total	Percentage (%)	SD
Sex (M/F)	19/16	54.3/45.7	
Age (SD)	69.9		(± 10.9)
ASA			
I-II	18/35	51.4	
III-IV	17/35	48.6	
Drugs			
OACs	6/35	17.1	
APDs	4/35	11.4	
Location			
Cardia	3/35	8.6	
Fundus	1/35	2.9	
Body	9/35	25.7	
Antrum/Incis	22/35	62.9	
Morphology			
0-Is	3/35	8.6	
0-IIa	7/35	19.9	
0-IIb	3/35	8.6	
0-IIc	8/35	22.9	
0-IIa+IIc	12/35	34.3	
0-III	2/35	5.7	
Histology			
Size (mm)	22 4/35	(10-31.2)	± 4.47
Vienna 3	29/35	11.4	
Vienna 4	11/35	82.9	
Vienna 4.1	6/35	31.4	
Vienna 4.2	3/35	17.2	
Vienna 4.3	9/35	8.5	

Vienna 4.4	2/35	25.8	
Vienna 5		5.7	
TNM	21/35		
T1a (M)	14/35	60	
T1b (SM)	14/35	40	
T1b1 (SM1)			

SD: standard deviation; OAC: oral anticoagulant; T1a: intramucosal tumor (M); T1b: submucosal tumor (SM); T1b1: submucosal tumor with invasion < 500 microns (SM1).

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Table 2. Characteristics of cases with local relapse

Case	*Age*	*Lesion*	*Histology*	*Resection*	*Post-ESD relapse*	*Initial treatment*	*Supplementary treatment*	*No. of endoscopies with relapse*	*Post-treatment follow-up*
1	80	0-IIa+IIc lower third 10 mm	Vienna 3	En-bloc	6 months	Argon plasma fulguration	No	1	CVA 9 months
2	81	0-IIa+IIc mid third 15 mm	Vienna 4	Piecemeal	12 months	Re-ESD	No	1	Control without dysplasia
3	80	0-IIa mid third 10 mm	Vienna 4	En-bloc	3 months	Re-ESD	Argon plasma fulguration	3	Control without dysplasia
4	67	0-IIa mid third 30 mm	Vienna 3	En-bloc	6 months	Re-ESD	No	1	Control without dysplasia

CVA: cerebrovascular accident.

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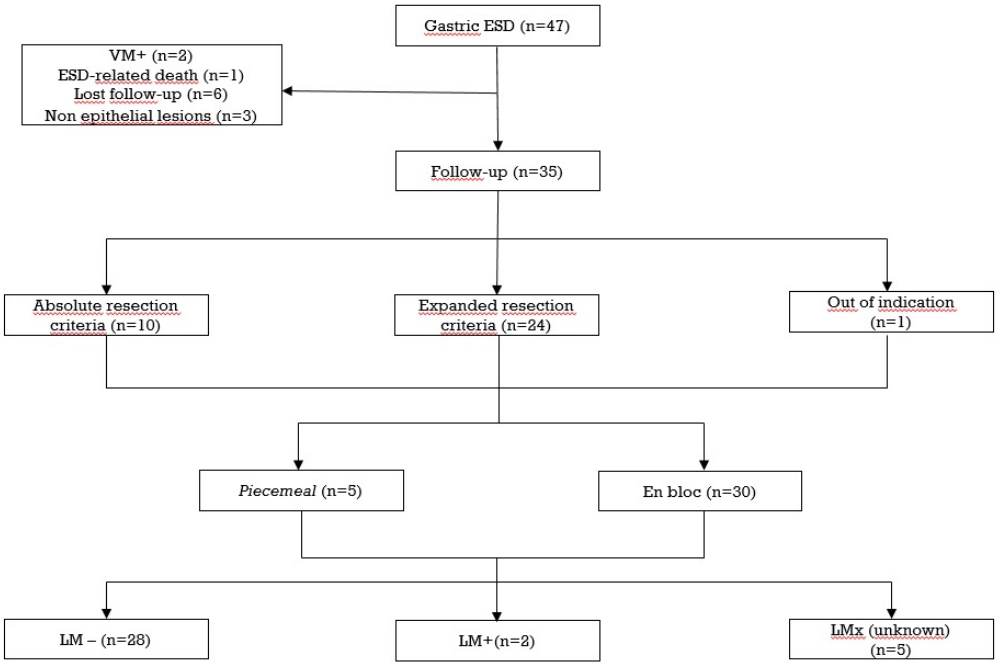

Fig. 1. Flowchart of G-ESD cases. VM: vertical margin; LM: lateral margin.

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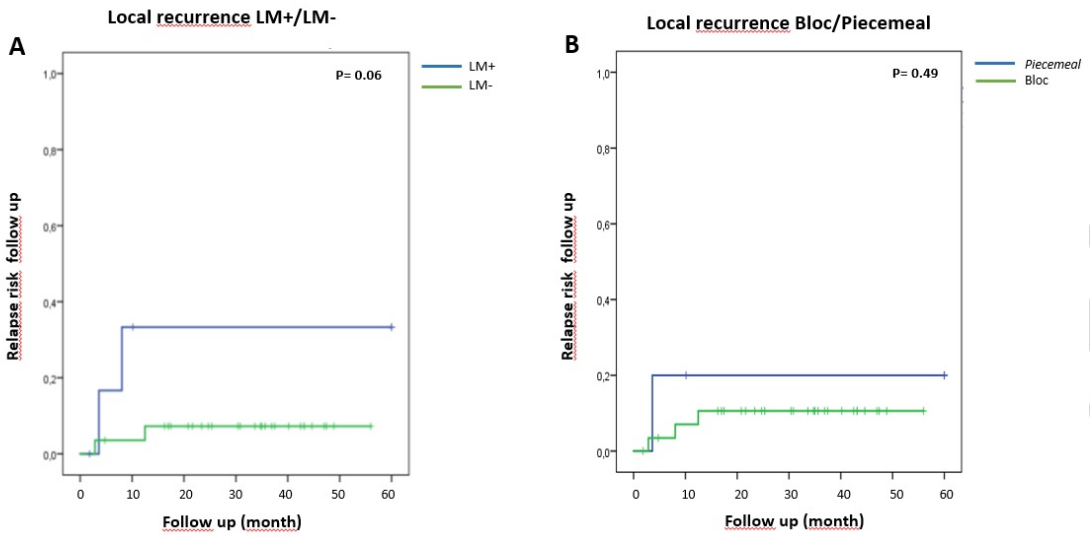

Fig. 2. Kaplan-Meier curves for recurrence risk stratification during five-years of follow-up. A. Relapse risk according to lateral margin status, affected (LM+) or free (LM-). B. Relapse risk according to resection type, en bloc or piecemeal.

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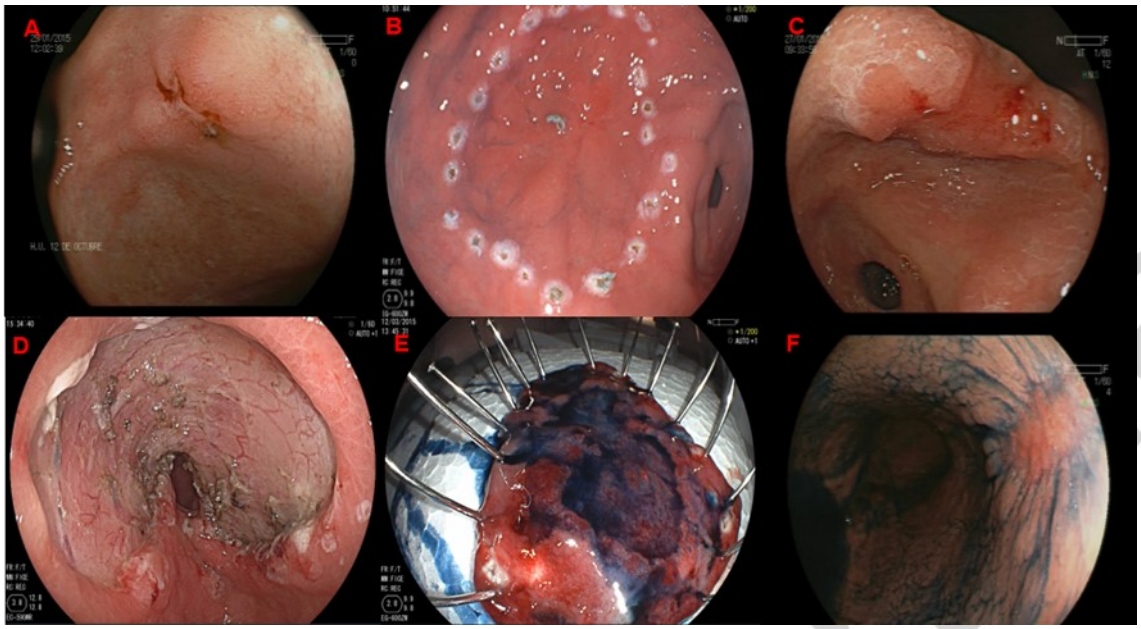

Fig. 3. Falta pie.