ORIGINAL ARTICLE

The impact of experience on short- and long-term outcomes on gastric ESD: a western series

F. Catalano[1] · V. Mengardo[2] · A. Trecca[3] · A. Tomezzoli[4] · L. Rodella[1] · A. Cerofolini[1] · G. Verlato[5] · G. de Manzoni[2]

Abstract

Endoscopic submucosal dissection (ESD) represents the standard of care for early gastric cancer in Eastern countries. Nevertheless, in the West, this procedure is not widespread. Aim of the study was to confirm the feasibility and the efficacy of ESD in the West. A total of 60 ESD were performed between January 2005 and December 2014 by two expert endoscopists. The analysis, based on a retrospective collected database, was conducted by dividing the study period in three subgroups. Clinical and technical outcomes have been compared. Rates of complete, curative and en bloc resection did not significantly change among the study periods. Three cases of perforation occurred (5%), one in each period. The operation time significantly decreased from the second to the third period ($p < 0.001$). When adjusting for gender, tumor size and site in multivariable analysis, operation time decreased by nearly 90 min from the first to the second period, and by more than 3 h from the first to the last period. The median follow-up was 33 months. No cases of local or lymphnodal recurrence were detected during the study period. One patient presented a synchronous lesion, whilst four metachronous lesions have been discovered after a median follow-up of 11 months. Our experience supports the feasibility and safety of ESD in the West, if an adequate learning curve is accomplished. Long-term outcomes are comparable to the Eastern series.

Keywords ESD · Gastric cancer · Early gastric cancer · Western experience

Introduction

Endoscopic submucosal dissection (ESD) has been introduced in clinical practice in 1980 by Japanese endoscopists as a definitive, non-invasive treatment of early gastric cancer with negligible risk of lymph-node metastasis [1, 2]. Nowadays, in Japan, almost half of gastric tumors are successfully excised by ESD, with a 5-year survival rate close to 90% [3]. A national registry was created in 2011 among a total of 89 Japanese institutions. It analyzed a total of 3561 patients and compared the results of the two main endoscopic procedures, Endoscopic Mucosal Resection (EMR) and ESD, performed during the year 2004. En bloc resection rate and complete resection rate were higher in the ESD group, with a comparable incidence of complications between the two groups (0.3% in EMR group and 0.4% in ESD group) [4]. Due to a lower incidence of gastric tumors, Western countries have no screening programs. As a consequence, gastric tumors are often diagnosed in an advanced stage, and only a small amount of lesions are suitable for endoscopic dissection. Moreover, the learning curve of the ESD is longer than EMR, thus limiting the implementation of this procedure even in high-volume Western Upper GI centers [5]. According to the large Japanese experience, an endoscopist should complete 30–40 gastric ESD to achieve the learning curve [6, 7].

In 2009, we published a first experience of ESD in Europe, demonstrating its feasibility and safety in 12 patients [8].

✉ V. Mengardo
valentina.mengardo@gmail.com

1 Department of Emergency Surgical Endoscopy, Borgo Trento Hospital, Verona, Italy

2 General and Upper GI Surgery Division, University of Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy

3 Operative Units of Endoscopy, Usi Group, Rome, Italy

4 Department of Pathology, Borgo Trento Hospital, Verona, Italy

5 Department of Diagnostics and Public Health, University of Verona, Verona, Italy

The aim of this study was to confirm the feasibility of ESD in the West, reporting the short- and long-term outcomes of a high-volume center.

Materials and methods

We included all the patients treated with an ESD for gastric adenocarcinoma or high-grade dysplasia from January 2005 to December 2014 at two high-volume Units (Emergency Surgical Endoscopy Unit, Borgo Trento Hospital Verona and USI group, Rome). The first center performed 48 cases (80%) and the procedures were performed by 1 expert endoscopist while the other 12 cases were performed by 1 trainee endoscopist with support by expert 1. All information was retrospectively recorded.

We divided the patients in three study periods to study the improving in both clinical and technical outcomes. The first period included patients treated from January 2005 until April 2007, the second one considered patients from May 2007 to April 2010 and the third one included the patients from May 2010 until the end of the study period. The first period included the initial experience on ESD of the two centers (Surg End 2009). We decided to divide all the patients treated from May 2007 until December 2014 in two different periods using as cutoff a retraining stage in Japan conducted by the two endoscopists in April 2010.

Technical outcomes included rate of en bloc resection, complete resection (R0), curative resection, post-operative complications (bleeding and perforation) and duration of procedure (starting from marking to complete removal or extraction of the lesion). The resection was defined "complete" when the deep and lateral margins of the specimen were free of tumor macroscopically and on histologic examination. Curative resection was defined, in our study, as complete resection when the standard criteria of Japanese Gastric Cancer Association were confirmed on histologic examination. Within oncological outcomes we considered recurrence rate, metachronous lesion rate and their onset time.

Patient selection and treatment

All the patients had a preoperative diagnosis of adenocarcinoma or high-grade dysplasia and preoperative staging that excluded lymph-nodal or distant metastasis. The standard imaging for preoperative staging included esophagogastroduodenoscopy, endoscopic ultrasonography (EUS) and staging thoracic-abdomen CT scan.

Patients that fulfilled the standard criteria of Japanese Gastric Cancer Association (JGCA) (well-differentiated intramucosal adenocarcinoma, less than 20 mm in diameter without any endoscopic findings of ulceration and no

clinical lymph-node metastasis) [9] have been included. We considered for endoscopic resection also patients with well-differentiated adenocarcinoma bigger than 2 cm without ulceration or lymphovascular invasion, as described in the expanded criteria of JGCA. Patients presenting other expanded criteria were not considered for endoscopic treatment [10]. All the patients signed informed consent for Upper Gastrointestinal Endoscopy (UGE) and therapeutic procedures.

ESD were performed according to the technique proposed by Hosokawa [11]. Briefly, the surgeon marked the mucosa at least 5 mm away from the tumor using a standard needle knife (Olympus Co., Tokyo, Japan) and then performed a submucosal injection with a saline solution mixed with epinephrine (0.04 mg/ml) and indigo carmine. The mucosa was then incised and the submucosal dissection was performed using an IT knife.

Histological staging and follow-up

All the resected specimens have been evaluated by an expert GI pathologist. Curative resection was defined when the standard JGCA criteria were confirmed, considering more than 2 cm in size as the only extended criteria accepted, lateral and vertical margins were free of cancer and no lymphatic or vascular invasion were detected. Surgical resection was indicated in case of non-curative resections.

Follow-up included UGE at 2, 6, and 12 months, and then annually. Abdominal US and chest X-ray were performed every 6 months.

Statistical analysis

Significance of differences among different periods was evaluated by the Kruskal–Wallis test. A non-parametric test used as the distribution of most variables was positively skewed and variability of most variables, such as tumor size and operation time, increased across subsequent periods. Multivariable analysis was accomplished by quantile regression, considering operation time as response variable, and gender, tumor size, tumor site, and calendar period as explanatory variables. Statistical analyses were performed using STATA 13.0 Statistics Software.

Results

Fifty-four patients were included with a total of 60 lesions: 12 lesions over 12 patients in the first period, 18 lesions over 16 patients in the second period and 30 lesions over 26 patients in the third one. Patients and disease characteristics, technical outcome and clinical long-term outcome are shown in Table 1.

Table 1 Case series: clinical results of endoscopic procedures along the three study periods

	I period (2005–2007)*	II period (2007–2010)	III period (2010–2014)	P value
Lesions/patients	12/12	18/16	30/26	
Patients' characteristics				
Sex (male) n (%)	5 (42%)	13 (81%)	19 (73%)	0.075
Age, years (median, range)	72 (61–81)	70 (57–80)	75 (65–89)	0.055
Lesions' characteristics				
Lesion size, mm (median, range)	14 (8–26)	20 (15–45)	22 (15–60)	
Resection size, mm (median, range)	20 (16–31)	32 (30–60)	35 (27–75)	**< 0.001**
Site of lesion, n (%)				**0.051**
Cardias or fundus	–	3 (17%)	7 (23%)	
Body	**10 (83%)**	**6 (33%)**	8 (27%)	
Angulus	–	4 (22%)	5 (17%)	
Antrum	2 (17%)	5 (28%)	**10 (33%)**	
Type of lesion (Paris), n (%)				**0.012**
0–Is	–	3 (17%)	4 (13%)	
0–IIa	**6 (50%)**	**10 (56%)**	**21 (70%)**	
0–IIa+c	1 (8%)	3 (17%)	2 (7%)	
0–IIb	–	–	3 (10%)	
0–IIc	**5 (42%)**	2 (11%)	–	
Advanced histology post-resection, n (%)	5 (42%)	3 (17%)	14 (47%)	0.115
Histopathology				0.434
Low-grade dysplasia	2 (17%)	–	2 (7%)	
High-grade dysplasia	5 (42%)	5 (28%)	8 (27%)	
Intramucosal carcinoma	5 (42%)	11 (61%)	16 (53%)	
Submucosal carcinoma	–	–	3 (10%)	
Other histology	–	2 (11%)	1 (3%)	
Surgical outcomes				
Procedure time, min (median, range)				
Overall	205 (115–240)	198 (49–340)	80 (25–294)	**< 0.001**
Marking	12 (4–20)	8 (2–22)	6 (2–22)	**0.0165**
Circular incision	25 (18–33)	26 (11–50)	16 (5–56)	**0.019**
Submucosal dissection	172.5 (89–202)	164 (34–280)	57 (14–226)	**< 0.001**
En bloc resection, n (%)	11 (92%)	17 (94%)	28 (93%)	1.000
R0 resection, n (%)	11 (92%)	17 (94%)	27 (90%)	1.000
Curative resection, n (%)	11 (92%)	16 (89%)	25 (83%)	0.787
Complications				
Bleeding	1 (8%)	3 (17%)	5 (17%)	0.803
Perforations	1 (8%)	1 (6%)	1 (3%)**	0.771
Surgery (due to complication) n (%)	1 (8%)	1 (6%)	–	0.246
Long-term clinical outcomes				
Follow-up time (months) (median, range)	93 (132–87)	60 (84–61)	24 (1–51)	
Recurrence, n (%)	–	–	–	
Metachronous lesion, n (%)	3 (25%)***	2 (11%)	3 (10%)	0.475
Synchronous lesion, n (%)	–	–	1 (3%)	1.000
Time to metachronous, mo (median, range)	14 (2–62)	16 (2–48)	13 (2–24)	

P values were computed by Fisher's exact test for nominal variables, and by Kruskal–Wallis test for quantitative variables

Statistically significant values are in bold

*Data already published in Surg End 2009

**Conservative treatment

***Treated by EMR

Clinical-pathological features

More than half of the lesions (57%) were located within the body and in the upper third of the stomach. The majority of the lesions were non-polypoid type (89%). The diameter of the lesions progressively increased over the study period, with the largest lesion excised in the latter group, with a diameter of 60 mm (Figs. 1, 2).

Evaluation of the resected specimen showed a more advanced histology in comparison with clinical staging among the three groups with an overall value of 37% (Table 1).

Technical outcomes

The percentage of en bloc resections exceeded 90% throughout the study period. In addition, the percentage of complete and curative resections remained high in all the periods, as shown in Table 1.

Most of the operation time (78.7%) was indeed represented by submucosal dissection.

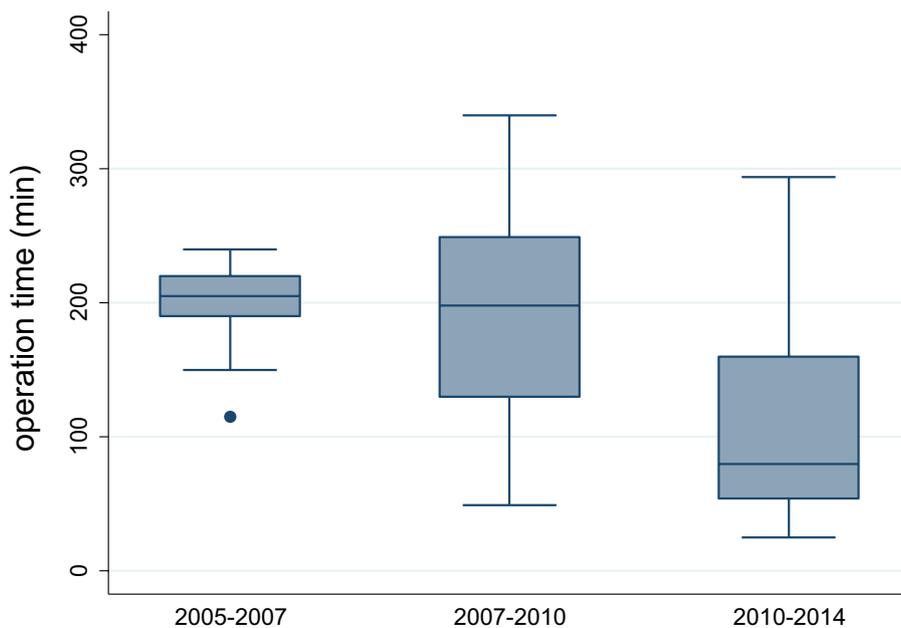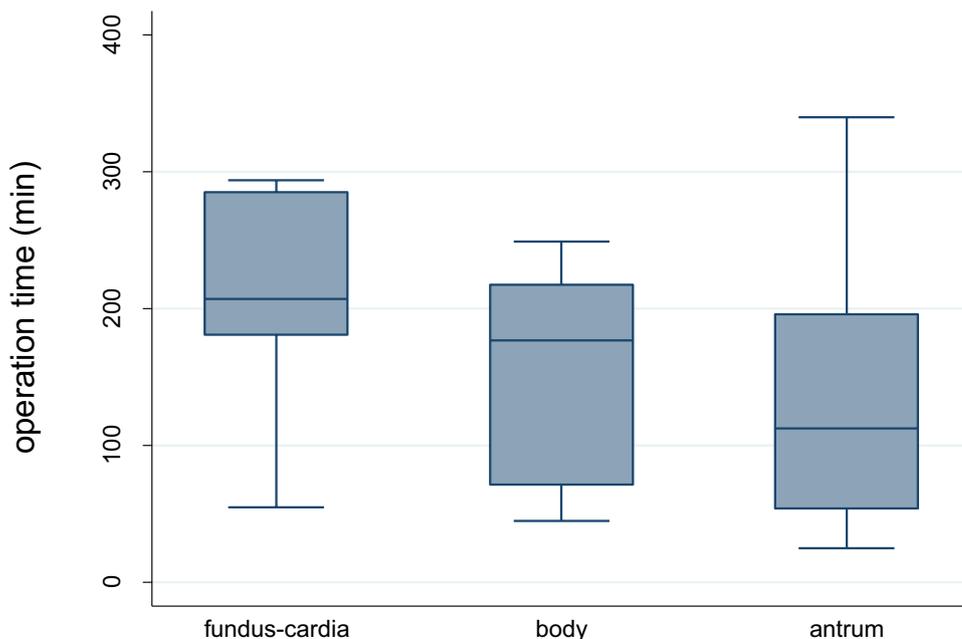**Fig. 1** Operation time as a function of time period

Fig. 2 Operation time as a function of tumor site

Eight patients had a non-curative resection (13%). Four cases failed due to technical reasons: macroperforation occurred in two cases, intraoperative specimen rupture occurred in one case due to the large size of the specimen, and it was not possible to proceed to the dissection in one case due to no lifting sign and a severe fibrosis of the cardia lesion. All the four patients underwent surgical treatment. Other four failed due to histological criteria: one undifferentiated cancer, two deep submucosal invasions (sm3) and one lympho-vascular invasion. These lesions were comprised in Gotoda's expanded criteria; gastrectomy was proposed to each patient, but it was accepted by only one of them. In this case, histological examination on the surgical specimen was negative for cancer and the follow-up of 18 months was disease-free. Follow-up of the three patients who refused surgery was negative, respectively, at 84, 35 and 12 months.

In addition to the already mentioned two cases of perforation, one other micro-perforation occurred in one procedure and was successfully managed by endoclip positioning.

Postoperative bleeding occurred in nine patients (15%): one case in the first group (8%), three cases in the second (17%) and five cases in the third (18%). All the patients were successfully treated endoscopically and did not require any blood transfusion.

Size of resected tumors significantly increased from the first period (median 2 cm, interquartile range 1.7–2.5 cm) to the second period (3.2 cm, 3.1–4 cm), while remaining stable (3.5 cm, 3–3.9 cm) in the third period ($p < 0.001$) (Table 1).

Conversely, operation time, significantly decreased from the second to the third period ($p < 0.001$) (Fig. 1). Of note, this reduction was mainly due to a decrease of the time required for submucosal dissection, but also time for marking the lesion and performing the circular incision significantly decreased (Table 1).

Tumors arising from cardia-fundus required more prolonged interventions than the other tumors, although the difference was not significant ($p = 0.095$) in univariable analysis (Fig. 2).

Multivariable analysis

In multivariable analysis, tumor size, tumor site and calendar period emerged as independent determinants of operating time ($p < 0.05$) (Table 2). According to the quantile regression, operating time increased on average by 47 min when tumor size increased by 1 cm, and by 71 min when the tumor was located in the fundus rather than in the antrum. If gender, tumor size and site had remaining constant over time, operation time would have decreased by nearly 90 min from the first to the second period, and by more than 3 h from the first to the last period.

Table 2 Multivariate analysis: changes in operation time (min) as a function of gender, size, tumor site, and calendar period

	Multivariable analysis	
	HR (95% CI)	P value
Sex (female/male)	− 1.0 (− 39.5 to 37.5)	0.959
Size (per 1 cm increase)	46.7 (28.9–64.5)	**< 0.001**
Tumor site		
Antrum	1 (ref)	
Fundus	71.0 (19.9–122.1)	**0.007**
Body	23.3 (− 17.1 to 63.8)	0.252
Calendar period		
2005–2007	1 (ref)	
2008–2010	− 88 (− 149.6 to − 27.1)	**0.006**
2011–2015	− 188 (− 245.4 to − 131.3)	**< 0.001**

Coefficients and p values were estimated by a quantile regression, controlling for all the other variables in the model

Statistically significant values are in bold

Clinical long-term outcome

The median follow-up was of 33 months. No cases of local or lymphnodal recurrence were detected during the follow-up in all the three study groups.

In the second period, two patients presented a metachronous lesion, while in the third period one patient presented both synchronous and metachronous lesions and other two patients presented a metachronous lesion. The four metachronous lesions were discovered after a median follow-up of 11 months; the incidence of 15% is similar to that of eastern series.

Discussion

Gastric cancer is the fifth most frequent cancer and the 3rd cause of death for cancer in the world [12] with a higher incidence in Asian countries [13]. Endoscopic skills in the diagnosis of early stage of the disease prompt Japanese endoscopists to propose endoscopic resections as the first-line treatment for early neoplastic lesions in Eastern countries. Due to a higher incidence of gastric cancer and to the extensive use of screening programs, Eastern countries routinely perform ESD for early gastric tumors and defined the standard and advanced criteria for endoscopic resection. Data coming from the National Cancer Center Hospital, Tokyo, have resulted in abandon of EMR by Japanese endoscopists since 2002 [14] according to two large series meta-analyses that showed higher rates of en bloc (92% vs 52%, respectively) and R0 (82–92% vs 42–43%, respectively) resections and less local recurrence (0.8% vs 5.0–6.4%, respectively) after ESD procedure

Fig. 3 Incidence of surgical versus endoscopic treatment of high grade dysplasia and early gastric cancers treated in Verona (years 2005–2014)
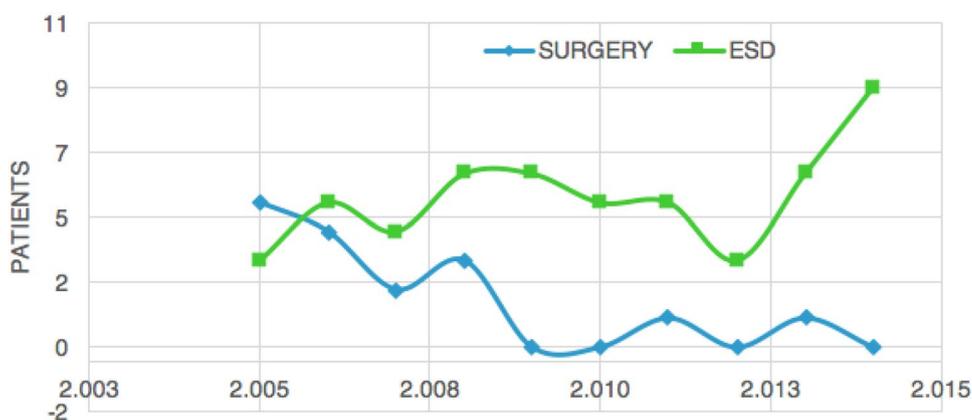
[15, 16]. In western countries, a lower incidence of early gastric cancer resulted in a more limited experience in endoscopic resection, and the majority of the series published reported mainly mucosal resections. In the last few years, some European centers published their experience on ESD, but data are still limited [7, 17–21] and often included procedures on the entire gastrointestinal tract [7, 21, 22]. These studies focused on the feasibility of ESD in the West, but only few reported long-term outcome and complication rate [19–21]. These papers suggest that ESD in the West has the same outcomes compared to the Eastern experience.

In our previous study, we focused on the feasibility of ESD in a high-volume Upper GI center [8]. In this series of patient, we analyzed the impact of experience on short- and long-term outcomes.

During the observation period indications expanded, as suggested by the significant increase in tumor size. Nonetheless, operation time significantly decreased, along with the surgeon learning curve. In multivariable analysis, the effect of the learning curve was largely amplified: if gender, tumor size and site had remaining constant over time, operation time would have decreased by nearly 90 min from the first to the second period, and by more than 3 h from the first to the last period.

Of note, in the resected specimen, we found four lesions comprised in Gotoda's expanded criteria. Only one of these patients underwent surgery; the other three patients that refused, had a negative long-term follow-up. Similar results have been recently published by Probst et al. [22]. They analyzed the long-term survival between ESD for standard criteria and ESD for expanded criteria (48.6%), finding comparable results.

Another interesting data in our study regards the upstaging at the final histology. These data confirm the difficult preoperative staging in the West, that does not include the predictive criteria of deep submucosal invasion proposed by Eastern endoscopist and the not correct use of target biopsy [23, 24].

In conclusion, our experience suggests that ESD in the West is feasible in centers that can guarantee an adequate learning curve for the endoscopist. After its introduction in our department, we evidenced a significant increase of ESD versus surgery for early gastric lesions (Fig. 3), as already described by the wider Eastern experience [25]. An adequate learning curve and the respect of severe oncological criteria seem the key points to achieve satisfactory clinical results to propose even in Western countries the endoscopic treatment as the treatment of choice for superficial neoplastic lesions of the stomach [26, 27].

Compliance with ethical standards

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