Type of article: Case Report

Title: A Western single-center experience with endoscopic submucosal dissection for early gastrointestinal cancers

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Short running head: ESD know-how transfer from Japan

Abstract

Endoscopic Submucosal Dissection (ESD) has gained worldwide acceptance as a treatment for Early Gastrointestinal Cancers (EGICs). However, the management of these tumors in the Western world is still mainly surgical.

Our aim was to evaluate the safety and feasibility of ESD in a European center.

Based on the knowledge transferred by one of the most experienced Japanese Institutions, we conducted a pilot study on 25 consecutive patients with EGICs located in the esophagus (n=3), stomach (n=7), duodenum (n=1) and colon (n=14) at our tertiary center over a 2-year-period. Main outcome measurements were complete (R0), as were en bloc resection and management of complications.

R0 and en bloc resection rates were 100% and 84% respectively. There were 3 bleeding and 5 perforation cases. With a median follow-up of 15 months, 2 recurrences were observed.

ESD for early esophageal and gastric cancers is feasible and effective while colonic ESD requires more expertise.

Key words: Gastrointestinal Neoplasms; Endoscopic Submucosal Dissection; Endoscopic Gastrointestinal Surgery.

Introduction

In the era of minimal invasive therapy, ESD has gained wide acceptance in Asian countries for the treatment of EGICs [1-3].

In the West, ESD is rarely reported [4-8], both because of the apparent lower incidence of EGICs and of the much rarer usage of this technique.

We report a single center exploratory programme involving 25 cases of ESD for treatment of EGICs, performed at “Paride Stefanini” Surgical Department, University of Rome “La Sapienza”, Italy.

Case Reports

Twenty-five unselected consecutive patients (10 M, 15 F; mean age 70 years, range 47-88 years) with EGICs underwent ESD at our Institution from April 2007 to September 2009.

There were 3 esophageal, 7 gastric, 1 duodenal and 14 colonic lesions (Table 1). The mean size of the lesions was 25 mm (range 10-50 mm).

Inclusion criteria followed those of Oyama [9] for lesions of the esophagus; the extended Gotoda criteria for the stomach [10]; and Laterally Spreading Tumors (LSTs) greater than 20 mm in diameter [11] or Paris 0-II type lesions for the colon.

Preoperative Evaluation

The diagnostic endoscopy included contrast chromoscopy with 0.2% indigo carmine dye or 2.5% Lugol solutions, or Narrow Band Imaging (NBI) inspection, together with Magnifying Endoscopy (110 to 150x, Olympus GIFQ160Z or CFQ160Z). Histological assessment confirmed the lesions as Low Grade or High Grade Non Invasive Neoplasia (LGNIN or HGNIN).

All the patients were informed by oral and written explanation about the planned treatment. They were aware of the level of experience in ESD of the two operators (SC, PT). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and without any external financial support.

ESD technique

It-knife, Hook-knife or Dual-knife (Olympus Medical Systems Corp., Tokyo, Japan) were used for dissection (Olympus PSD-60, Endocut Mode, Effect 3, 60 to 80 Watt Cutting, 20 Watt Forced Coagulation), after multiple injections with saline and epinephrine solution (1:20000), stained with indigo-carmine, and further repeated injections of hyaluronic acid or 10% glycerol. An attachment cap was regularly used in order to facilitate the dissection.

In cases of failed en bloc removal, final excision was achieved using a polypectomy snare in a piecemeal fashion.

At the end, careful inspection of the ulcer site and coagulation of borders and visible vessels was routinely performed.

Outcomes and management

The main outcomes of the study were the feasibility of ESD, data on the percentage of en bloc and complete resection, and an indication of various possible complications.

Feasibility was indicated by the number of ESDs successfully accomplished.

All the patients were operated on in the operating theatre, under propofol sedation, with a surgical team available to treat possible complications not manageable endoscopically.

The following day, patients had plain abdominal x-rays to rule out perforation, and in the absence of bleeding signs, they were allowed a liquid diet 24-48 hours after the procedure. Proton pump inhibitors were routinely administered for 1 month in gastric-lesion patients only.

Follow-up

Follow-up (FU) with biopsies included a 1, 3 and 12-months examination.

Recurrence was defined as the presence of pathological tissue at the resection site.

Complications

Minor bleeding was immediately treated with repeated injections of saline solution or with the Coagrasper forceps (Olympus Medical Systems Corp., Tokyo, Japan).

Perforation was defined as the endoscopic intraoperative diagnosis of a hole in the viscus, or the presence of free air the following day on plain x-ray, with or without clinical signs. All identified perforations were treated intraoperatively by clips apposition (Resolution Clip, Boston Scientific, Natick, MA, USA).

Histopathologic assessment

The specimens were fixed and orientated on a board. After fixation, the samples were sectioned at 2-mm intervals parallel to the closest resection margin to assess both lateral and vertical margins. Multiple histological sections (at least 10) were obtained from each paraffin block, stained with Hematoxylin-eosin.

Results

En bloc resection was feasible in 3/3 esophageal, 6/7 gastric, 1/1 duodenal and 10/14 colonic cases (overall 84%). Complete resection was achieved in all the en bloc procedures. Median operating time was 120 minutes (range 30-360 minutes). The median follow-up was 18 months (range 3-33 months).

Comparing to preoperative diagnosis, histological examination of the whole sample resulted in 6 up-stagings and 1 down-staging.

Overall, bleeding accounted for 12% and perforation for 20% of cases.

In one case occurred an esophageal substenosis.

Disease recurrence was present in 2 cases.

Discussion

Japanese experts recommend performing ESD on gastric lesions first, as they are technically easier to remove and exhibit a lower rate of complications compared to esophageal or colonic lesions [10, 12-14].

Nevertheless, it was decided to include all consecutive unselected cases referred to our Department. This was a research programme aimed at assessing the feasibility of ESD as an alternative treatment for EGICs in a University Hospital with an estimated catchment area of about 1.000.000 inhabitants.

SC attended the NCCH in Tokyo for 3 months, to gain practice before the first autonomous procedure. For the first month of his training, he observed at least 3-5 complete procedures per day performed by TG and his team. He then started to practise on isolated pig stomachs, performing about 3 ESDs per week. In the third month, he performed under the strict supervision of TG 3 ESDs in 3 patients with EGC. Throughout this period, he followed the team in all their clinical duties, including the management of complications.

PT has 26 years of experience in therapeutic and emergency endoscopy. He observed at least 30 videos of ESD performed by TG and his colleagues.

The first 3 procedures were performed by SC supervised by TG. Then, SC performed autonomously 14 procedures and assisted PT in performing 2 cases. The last 6 ESDs were performed by PT autonomously.

EGC is the most accepted indication for ESD worldwide. In Western countries, only a few series have been recently published with encouraging results [15-17].

Overall, we had a satisfactory en bloc and complete resection rate for upper GI cancers (90%), while it was lower for colonic series (72%).

In the literature, the perforation rate ranges between 1-10% [11, 18-21].

There was a high perforation rate in our small colonic series, probably because of the initial experience with ESD and the unselected cases. However, all of them were recognized at the time of operation, and subsequently clipped. Only 1 case received a EUS-guided needle decompression.

Only in 1 gastric case, surgery was required. It was the case of an 83-year-old patient with a large EGC (40 mm) at the beginning of our study. Twenty-four hours after the procedure, a small amount of free air was seen at the plain x-ray, but an emergency laparotomy failed to disclose evidence of perforation. The patient died 40 days later of respiratory insufficiency, presumably as a consequence of laparotomy.

Substenosis occurred after one esophageal ESD. It was a case of HGNIN within an 8 cm long segment of circumferential Barrett's esophagus and was effectively managed by endoscopic balloon dilation.

Recurrence was present in 1 giant (50 mm) recurrent antral hyperplastic polyp, responsible for severe anemia. Suspecting neoplastic progression, we performed an en bloc and complete ESD (Figure 3). At the 3-months-FU endoscopy again a 10 mm recurrence was noted. EUS was then performed without any clear explanation for this recurrence. This patient was retreated by a standard polypectomy and Argon Plasma Coagulation.

One gastric case was a solitary antral nodule, which was a recurrent localized mantle cell Lymphoma This patient, who had received chemotherapy (CHT) and bone marrow transplantation, was offered an ESD as alternative treatment to further CHT (Figure 4). She is disease free at the 6-month endoscopic control.

Conclusions

Our study has many limitations: a limited and heterogeneous cohort, with and without prior endoscopic treatment, with and without neoplasia; 2 operators with a variable experience and learning curve; limited FU for several cases. However, we have demonstrated a successful cooperation and transfer of practical knowledge between 2 tertiary Institutions with hitherto differing therapeutic approaches.

Following this preliminary experience, ESD has been introduced in our hospital clinical practice as an experimental alternative treatment to surgery for early GI cancers.

In summary, we believe that:

- At least 30 procedures should be carefully observed for each location.

- At least 10 ESD should be performed on animal models before starting with patients (stomach only), and at least 3 initial procedures should be supervised by foreign experts;
- Colonic ESD should be performed in the lower rectum first; the right colon should be attempted only after adequate experience.
- Initial experiences should be performed in specialized centers. Caution is mandatory, and tight cooperation with a surgical team is advisable.

ESD for early esophageal and gastric cancers is feasible and effective.

Colonic ESD requires considerably more training due to the high risk of perforation and more cooperation with our expert Asian colleagues is needed to achieve the expertise appropriate for facing difficult lesions.

A more extended study is necessary to confirm the results of the small scale study presented here and more studies in the West are needed to identify full guidelines for the use of this technique.

Acknowledgments

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Figure legends

Figure 1

A: Early gastric cancer (0-IIa+IIc type, 15 mm), of the fundus, along the lesser curvature just below the cardia, after staining with indigo-carmine.

B: Residual ulcer after endoscopic submucosal dissection.

C: En bloc excised lesion fixed orientated on a board for the histopathologic assessment.

D: Well differentiated (G1) intramucosal ADC of intestinal type, vertical margins free of tumor (hematoxylin-eosin, original magnification 20X).

Figure 2

A: Laterally Spreading Tumor (non-granular type, 40 mm) of the sigmoid colon.

B: Dissection of the submucosal layer by It-knife.

C: En bloc excised lesion fixed orientated on a board for the histopathologic assessment.

D: Well differentiated (G1) adenocarcinoma. The lesion is largely intramucosal, with focal infiltration of the muscularis mucosae (hematoxilin-eosin, original magnification 10X).

Figure 3

A: Giant recurrent hyperplastic polyp of the gastric antrum, 50 mm, after staining with indigo-carmine.

B: Circumferential incision performed by Hook-knife around the polyp, outside the marking dots.

Figure 4

A: Solitary gastric nodule of recurrent localized mantle cell Lymphoma.

B: Submucosal dissection performed by It-knife.

C: En bloc excised lesion fixed orientated on a board for the histopathologic assessment (mucosal side).

D: En bloc excised lesion fixed orientated on a board for the histopathologic assessment (submucosal side).

Table 1. Description of cases

Patient			Lesion				Procedure				Outcomes		
Case (no)	Age (y)	Sex	Type	Major diameter (mm)	Histology	Location	Time (min)	Resection	Complications	Management	Histopathologic result	Follow up (mo)	Recurrence
1	70	M	0-IIb	20	HGNIN	Body	60	R0 En bloc			HGNIN	33	
2	65	F	0-IIb	20	HGNIN	Body	50	R0 En bloc			HGNIN	33	
3	67	M	0-IIa	25	HGNIN	Antrum	90	R0 En bloc			HGNIN	33	
4	83	M	0-IIa+IIb	40	HGNIN	Antrum	360	R0 Piecemeal (snare)	Perforation	op. surgery	pTis G1	†	
5	74	F	G-LST	40	HGNIN	Left colon	120	R0 Piecemeal (snare)	perforation, delayed bleeding	clipping, conservative	HGNIN	27	Yes
6	70	F	G-LST	40	HGNIN	Sigmoid colon	180	R0 Piecemeal (snare)			HGNIN	24	
7	64	F	0-IIa	15	HGNIN	Cecal fundus	30	R0 En bloc + lap. appendectomy	perforation	clipping, lap. surgery	HGNIN	23	
8	63	M	0-IIa+scar	10	HGNIN	Rectum	60	R0 En bloc			HGNIN	21	
9	79	M	0-IIa+IIc	15	HGNIN	Fundus	90	R0 En bloc	immediate bleeding	It-knife, Coagrasper	pT1 G1	21	
10	72	M	NG-LST	20	LGNIN	Transverse colon	50	R0 En bloc			LGNIN	21	
11	80	F	NG-LST	20	LGNIN	Cecum	180	R0 piecemeal (It-knife)			LGNIN	18	
12	81	F	Ip	50	Hyperplasia	Antrum	150	R0 En bloc	immediate bleeding	It-knife, Coagrasper	Hyperplasia	18	Yes
13	76	F	NG-LST	40	HGNIN	Sigmoid colon	240	R0 En bloc			pTis G1	14	
14	88	F	0-I	20	HGNIN	Esophagus	240	R0 En bloc			pT1 G2	14	
15	47	F	G-LST	20	LGNIN	Right colon	180	R0 En bloc	perforation	clipping, decompressive puncture	LGNIN	13	
16	66	M	0-IIc	20	HGNIN	Esophagus	120	R0 En bloc			LGNIN	12	
17	61	F	0-I	15	Mantle Cell Lymphoma	Antrum	60	R0 En bloc			Mantle Cell Lymphoma	11	
18	58	F	NG-LST	30	LGNIN	Sigmoid colon	150	R0 En bloc			LGNIN	9	
19	69	M	G-LST	40	LGNIN	Rectum	240	R0 En bloc			LGNIN	8	
20	64	F	0-IIa	12	HGNIN	Esophagus	90	R0 En bloc	substenosis	balloon dilation	HGNIN	7	
21	66	F	0-IIa	12	LGNIN	Duodenum	90	R0 En bloc			LGNIN	6	
22	81	F	G-LST	30	LGNIN	Right colon	110	R0 En bloc			HGNIN	4	
23	57	M	G-LST	25	LGNIN	Right colon	240	R0 En bloc			LGNIN	3	
24	62	M	G-LST	25	LGNIN	Right colon	180	R0 En bloc	perforation	clipping	HGNIN	3	
25	74	M	G-LST	20	LGNIN	Rectum	120	R0 En bloc			LGNIN	3	

HGNIN, High Grade Non Invasive Neoplasia; LGNIN, Low Grade Non Invasive Neoplasia; G-LST, Granular type Laterally Spreading Tumor; NG-LST, Non Granular type Laterally Spreading Tumor.

Figure

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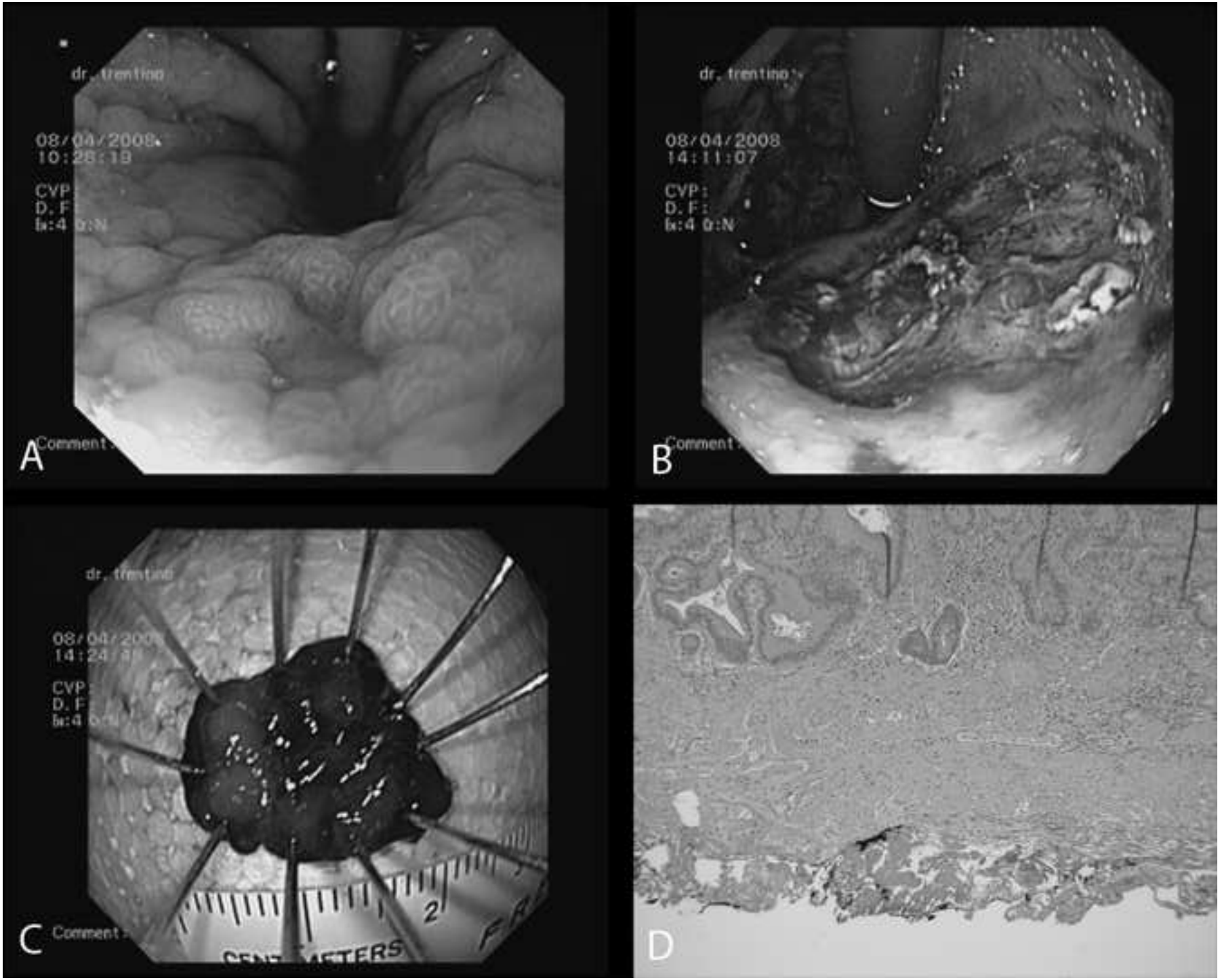

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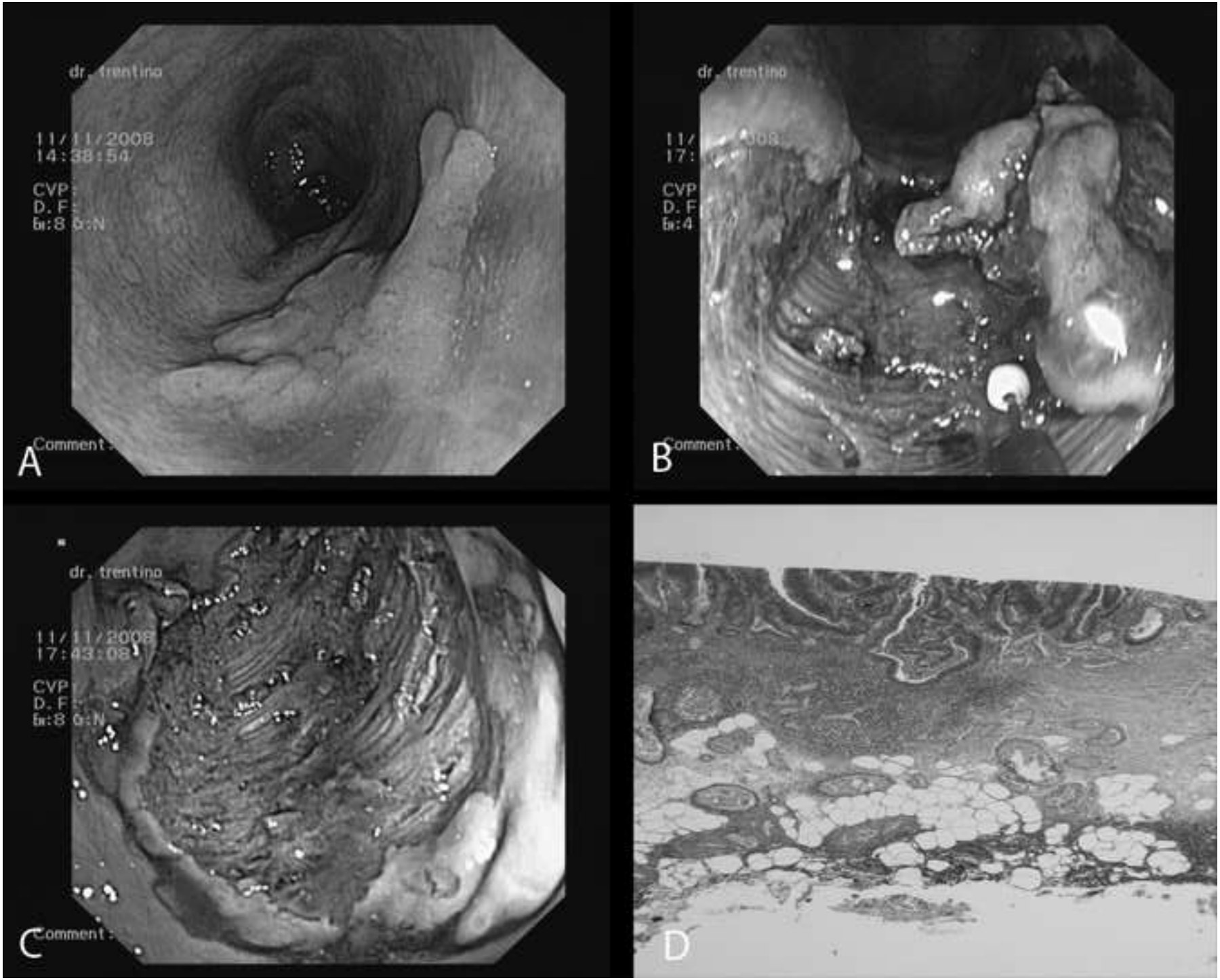

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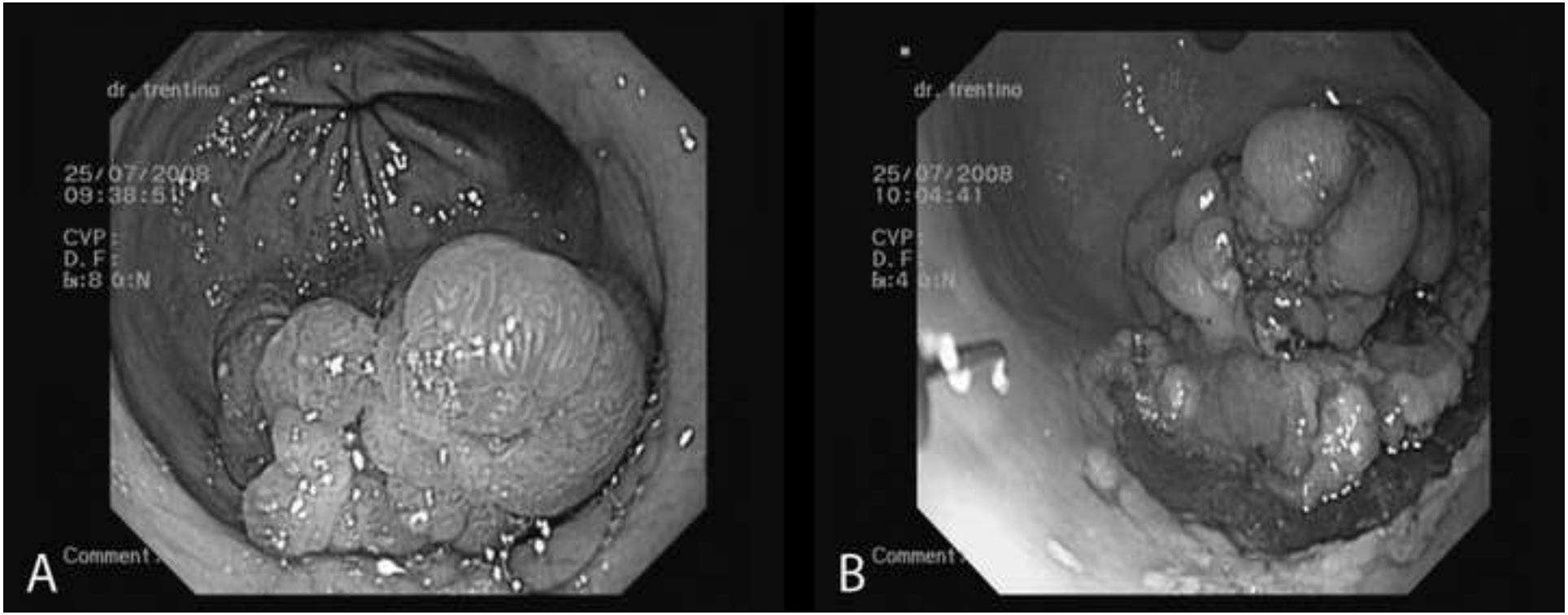

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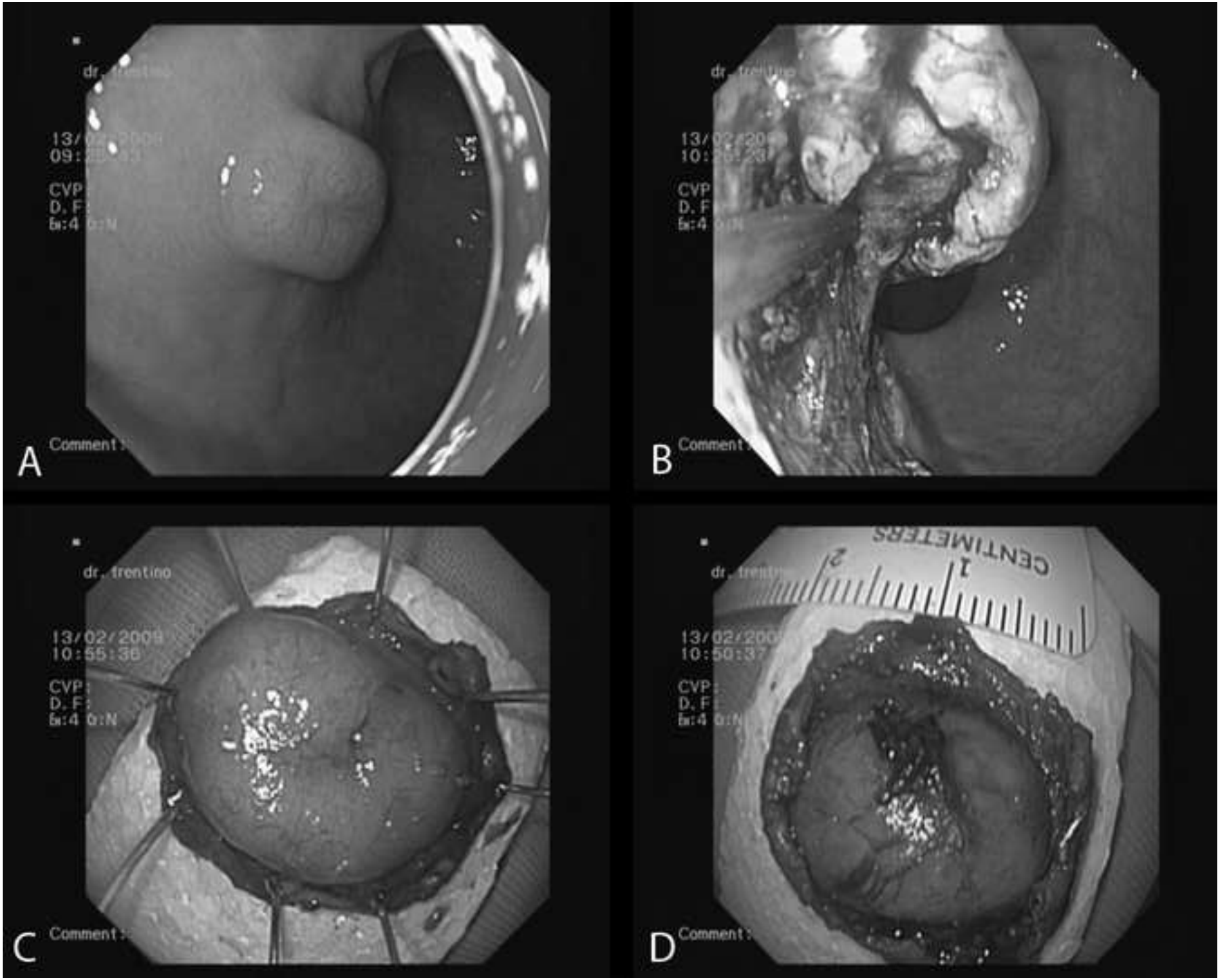

***Mini-abstract (less than 30 words)**

Mini Abstract

Based on the know-how transfer by a Japanese Institution to a European center, encouraging results are coming from a pilot study of 25 patients with EGICs treated with ESD.