

# Three-Year Follow-Up Findings of Colorectal Neoplastic Patients Who Underwent Endoscopic Submucosal Dissection: A Single-Center Experience

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## Abstract

**Objective:** The removal of colorectal neoplastic lesions by endoscopic resection methods is recommended. These lesions could also be removed by endoscopic mucosal resection method. However, endoscopic mucosal resection is not ideal since it might leave residual neoplastic tissue and could not allow for a detailed histopathological evaluation. Most lesions could be removed by the endoscopic submucosal dissection method en bloc and it allows for adequate histological evaluation. In this study, we aimed to demonstrate whether endoscopic submucosal dissection is an ideal and safe method for the removal of colorectal neoplastic lesions.

**Methods:** The consecutive endoscopic submucosal dissection series of 70 patients who underwent colorectal endoscopic submucosal dissection between January 2018 and March 2022 at İnönü University, Faculty of Medicine Gastroenterology Clinic were reviewed. Non-invasive early cancers larger than 10 mm with low lymph node metastasis risk and premalignant lesions larger than 15 mm were included in the study. Adenocarcinoma inclusion criteria were good histological differentiation, no ulceration at the lesion base, no submucosal invasion (assessed by endoscopic ultrasound), and no lymph node involvement identified in computed tomography or endoscopic ultrasound. Age, gender, endoscopic submucosal dissection indications, procedure duration, instruments used, complications, hospitalization duration, follow-up after discharge, pathological findings, and post-endoscopic submucosal dissection endoscopic findings were collected retrospectively.

**Results:** All 70 cases who underwent endoscopic submucosal dissection were followed up by a single gastroenterologist for 36 months. Among the patients, 45 (64.2%) were female and 25 (35.8%) were male. Endoscopic submucosal dissection indications included intraepithelial lesions, high-grade dysplasia (n=30), low-grade dysplasia (n=16), neuroendocrine tumor (n=6), early-stage colorectal cancer (n=11), inflammatory polyp (n=2), and submucosal lesions [lipoma (n=2) and leiomyoma (n=3)]. The different types of lesions based on Paris classification are presented in Table 1. En bloc and piecemeal removal rates of the lesions with endoscopic submucosal dissection were 81.4% (57/70) and 18.6% (13/70), while pathologically complete and incomplete resection rates were 84.2% (59/70) and 15.8% (11/70), respectively. Perforation developed in 6 (8.5%) patients during the endoscopic submucosal dissection procedure. Three perforations developed in the rectum (2 Lateral Spreading Tumor [LST] and 1 early colonic cancer), 2 in the sigmoid colon (1 LST and 1 early colonic cancer), and 1 in the transverse colon (1 high-grade dysplasia). None of the colonic perforations required surgical intervention. All were closed with hemo-clips. Major bleeding was observed in 2 patients (2.8%). About 2 units of blood were transfused. Patients who developed major bleeding had early colon cancer and pseudo-depressed LST. Minor bleeding (1 cecum, 2 transverse colons, 2 sigmoid colons, and 12 rectums) developed in 17 (24.3%) patients.

**Conclusion:** In conclusion, as a center that just started to conduct advanced endoscopic procedures, our endoscopic submucosal dissection results were consistent with the literature. The analysis of the treatment, complications, and local recurrence pursuant to endoscopic submucosal dissection revealed satisfactory results when the endoscopic submucosal dissection was conducted with proper analysis of the lesions. All studies done on this topic, including this one, have shown good outcomes for the use of endoscopic submucosal dissection in suitable colorectal lesions, but there is a need to invest in more expertise and infrastructure to maximize the good outcomes of advanced endoscopic procedures.

**Keywords:** Endoscopic submucosal dissection, neuroendocrine tumor, premalignant colorectal neoplasm

## INTRODUCTION

It is recommended to remove early colorectal carcinomas (ECC) and colorectal premalignant lesions larger than 20 mm with endoscopic resection methods.<sup>1</sup> These lesions could be removed by endoscopic mucosal resection (EMR) and the piecemeal method. However, this method is not ideal

since it is prone to leaving residual neoplastic tissue. Furthermore, since the lesion is not removed en bloc, histopathological evaluation of the resection margins is difficult.<sup>2</sup> In the endoscopic submucosal dissection (ESD) method, most lesions could be removed en bloc.<sup>3</sup> Also, ESD method allows detailed histological evaluation of the surgical margin, submucosal, or lymphovascular invasion in resected lesions. Thus, the ESD method should be preferred in colorectal lesions and has been increasingly preferred.<sup>4</sup> We also retrospectively analyzed the patients who underwent ESD in our clinic due to colorectal neoplastic lesions. In this study, we aimed to demonstrate whether the method was ideal and safe for the removal of colorectal neoplastic lesions.

## METHODS

The consecutive ESD series of 70 patients who underwent colorectal ESD between January 2018 and March 2022 at Inonu University, Faculty of Medicine Gastroenterology Clinic were reviewed. The study was carried out with the approval of Inonu University Health Sciences Non-Interventional Clinical Research ethics committee (12.04.2022, 2022/3360). Non-invasive early cancers larger than 10 mm with low lymph node metastasis risk and premalignant lesions larger than 15 mm were included in the study. Adenocarcinoma inclusion criteria were good histological differentiation, no ulceration at the lesion base, no submucosal invasion (assessed by endoscopic ultrasound (EUS)), and no lymph node involvement identified in computed tomography (CT) or EUS. Age, gender, ESD indications, procedure duration, instruments used, complications, hospitalization duration, follow-up after discharge, pathological examinations, and post-ESD endoscopic findings were collected retrospectively. In the follow-up of the patients who underwent ESD, the patients who were surgically cured, who required repeat ESD, and who underwent surgery were analyzed and recorded. The research protocol was approved by the local ethics committee. Both verbal and written informed consent of the patients was obtained. This study was conducted in accordance with the ethical principles stipulated in the Declaration of Helsinki and good clinical practices.

## Equipment and Procedure

All of the ESD procedures were performed by a single surgeon who had 3 months of ESD training in 2016 (trained at Chun Hoon-jai, M.D. Ph.D. Departments of Gastroenterology & Hepatology Anam Hospital Seoul-Korea).

Before the ESD procedure, all lesions were examined with an optical magnification endoscope (EVIS EXERA III GIF-1TH190; Olympus, Tokyo, Japan) and colonoscope (CF-HQ190L; Olympus) with 1% Indigo Carmine in addition to magnification. Lesion size was determined with the comparison of the standard open-biopsy forceps and the lesion. The invasion depth of the lesions was determined

with echo-endoscopes (GF-UE160-AL5 Radial Array Ultrasound Gastrovideoscope; Olympus). Superficial lesions were classified as type I (protruding), type II (flat) a, b, c, and type III (excavated) according to the Paris classification system. Kudo pit classification was employed to characterize colonic lesions.

Endoscopic submucosal dissection procedure was performed in accordance with the standards. A 4 mm clear cap was attached to the tip of the endoscope (MH-588; Olympus Medical Systems, Tokyo, Japan) to facilitate optimal visualization of the region and to stabilize dissection. The lesion margins were marked with electrocautery (25 W soft coagulation) to determine the resection margin. A submucosal injection was then applied to separate the lesion from the mucosa. A special mixture (1 unit of 6% Voluven, Fresenius Kabi, 0.5 mL of epinephrine (1/10 000), 0.5% indigo carmine, and 1 unit of saline) was used in the injection. After adequate submucosal injection, an ESD knife (1.5 mm, dual knife; Olympus) was employed for a circumferential incision around the lesion extending into the submucosa. After the circumferential incision, submucosal dissection was done with the ESD blades (dual knife, hook knife; Olympus) to remove the lesion en bloc.

Electrocautery with a high-frequency generator (ESG-300, Olympus) was employed in the ESD procedure. After the region was marked, a circular area was incised around the lesion that left a clean margin of at least 5 mm with the electrocautery (BlendCut, 30 W, effect 2 and soft coag., 50 W, effect 3). After the incision, the dissection stage was initiated with the previously prepared submucosal injection mixture. A dual knife and adequate electro mode (power coag., 30 W, effect, 2) were employed in dissection. Hemostatic grasper (Coagrasper, 4 mm and 6.5 mm, Olympus) and appropriate electrocautery mode (soft coag., 50 W, pulse, 3) were used to stop active bleeding during the ESD procedure or for bleeding prophylaxis. All ESD procedures were performed under deep sedation. Anesthesia was given by the anesthesiologist using midazolam, propofol, and fentanyl. During the anesthesia, electrocardiogram, blood pressure, and oxygen saturation were monitored.

## Definitions and Follow-Up Strategies

The resected lesions were examined by pathologists specialized in gastrointestinal lesions. En bloc resection was defined as the removal of the whole lesion. Piecemeal resection was defined as the partial resection of the lesions that could not be removed en bloc.

Recurrent lesion was defined as the recurrence of neoplastic tissue in the same region within the first 6 months after the ESD. In cases of perforation, hemo-clips were used. Minor bleeding was considered as endoscopic control of bleeding that occurred during the resection of the lesion. Major bleeding was defined as bleeding that required blood transfusion and led to hemodynamic instability.

R0 resection was defined as the cases where dysplastic lesion was at least 2 mm away from the vertical and lateral borders of the resected ESD material. R1 resection was accepted as the presence of neoplastic cells at the lateral and vertical borders of the ESD material. Surgery was planned for patients who were reported to have undifferentiated or signet ring cell carcinoma submucosal-lymphovascular invasion by the pathologists. All patients were hospitalized after the ESD procedure, and the first follow-up endoscopy was conducted on the third day. Subsequent endoscopic follow-ups were conducted after 3 and 6 months. Then, annual follow-up endoscopy was done.

## MAIN POINTS

- Today, the incidence of colonic pre-neoplastic lesions is increasing.
- Minimally invasive endoscopic procedures are increasingly used for the removal of these lesions.
- It has less time, less complications, and lesser hospitalization rate as an alternative to surgery for removing colonic lesions by endoscopic submucosal dissection (ESD) procedure.
- Since the recurrence rates in the follow-up of lesions removed by ESD procedure are acceptable, the use should be increased.

### Statistical Analysis

A continuous variable median was used to analyze the data. Descriptive statistics were calculated and presented as medians and ranges or inter-quartile ranges for continuous variables and percentages for categorical variables. Statistical Package for Social Sciences version 16.0 for Windows (Chicago, Ill, USA) was employed in statistical analysis.

### RESULTS

Colon ESD procedure was performed on 70 cases. All cases were followed up by a single gastroenterologist for 36 months. Forty-five (64.2%) patients were female and 25 (35.8%) were male. The patient's mean age (standard deviation) was 46.2 ( $\pm 16.5$ ).

Endoscopic submucosal dissection indications included intraepithelial lesions, high-grade dysplasia (n=30), low-grade dysplasia (n=16), neuroendocrine tumor (NET) (n=6), early-stage colorectal cancer (n=11), inflammatory polyp (n=2), and submucosal lesions [lipoma (n=2) and leiomyoma (n=3)]. The typology of lesions according to Paris classification is presented in Table 1. En bloc and piecemeal lesion removal rates in ESD were 81.4% (57/70) and 18.6% (13/70), while pathologically complete and incomplete resection rates were 84.2% (59/70) and 15.8% (11/70), respectively.

Two pseudo-depressed LSTs in the recto-sigmoid region in the colon, 8 granular type LSTs, 2 NETs, and a submucosal lesion (lipoma) in the transverse colon were resected with the piecemeal method. Eleven patients were referred to the surgery department due to the submucosal invasion and surgical margin positivity in 3 out of 11 ECC cases, submucosal invasion in 2 out of 6 NET cases, impossibility of the resection of the submucosal lesion in the transverse colon due to the size of the lipoma, surgical margin, and invasion positivity in 4 out of 30 patients with high-grade dysplasia due to intraepithelial adenoma, and submucosal invasion in 1 out of 16 patients with low-grade dysplasia. Two rectal LST patients were referred to surgery after the observation of local recurrence in the sixth-month follow-up colonoscopy.

The mean ESD procedure duration for per square cm lesion and the total mean procedure duration were 25.1 and 126 minutes, respectively. The mean resected lesion area in the colon was 5.88 cm<sup>2</sup>.

Forty-six lesions in the colon that underwent ESD were adenomas (2 tubulovillous adenomas with high-grade dysplasia (HGD) in the cecum, 3 tubulovillous adenomas with HGD, 2 tubular adenomas with low-grade dysplasia (LGD) in the transverse colon, 6 tubulovillous adenomas with HGD, 5 adenomas of LGD, 2 tubular in the sigmoid colon, 14 tubulovillous adenomas, 3 tubular adenomas, 9 adenomas of LGD in the rectum), 6 carcinoid tumors (rectum), 11 early colon cancers (7 rectum, 3 sigmoid colon, and 1 cecum), 5 SMLs (1 cecum, 2 transverse colons, and 2 rectums), and 2 inflammatory polyps (2 rectum) (Table 2). Early-stage colon cancers were classified as IIa+IIc based on Paris classification.

### Safety

Six (8.5%) patients developed perforation during the ESD procedure. Three perforations developed in the rectum (2 LST and 1 ECC),

**Table 1. Colorectal Lesion Typology Based on Paris Classification**

	Ia	IIa	IIb	IIa+IIc
Colon	2 <sup>1</sup>	48 <sup>2,3</sup>		20 <sup>4</sup>

<sup>1</sup>Two lesions are inflammatory polyps; <sup>2</sup>five lesions are submucosal; <sup>3</sup>18 lateral spreading tumor cases; <sup>4</sup>pseudo-depressed lateral spreading tumor in 4 cases.

**Table 2. Cases of Endoscopic Submucosal Dissection of Colonic Lesions**

Location	Histology	Count
Cecum	HGD (TVA)	2
	SML	1
	ECC	1
Transverse colon	HGD (TVA)	3
	LGD (TA)	2
	SML	2
Sigmoid colon	HGD (TVA)	6
	LGD (TA)	5
	TA	2
	ECC	3
Rectum	HGD (TVA)	14
	LGD TA	9
	ECC	7
	TA	3
	NET	6
	INF POL	2
	SML	2
Lesion size (mean, cm <sup>2</sup> )	5.88 cm <sup>2</sup>	
Procedure duration (average-min)	126 min (25.1 min/cm <sup>2</sup> )	

HGD, high-grade dysplasia; LGD, low-grade dysplasia; NET, neuroendocrine tumor; ECC, early colonic cancer; SML, submucosal lesion; INF POL, inflammatory polyp; TA, tubular adenoma; TVA, tubulovillous adenoma.

2 in the sigmoid colon (1 LST and 1 ECC), and 1 in the transverse colon (1 HGD). None of the colonic perforations required surgical intervention. All were closed with hemo-clips. Patients with perforation were hospitalized for about 12 days. Stenosis was not observed in any patient post-ESD. Major bleeding developed in 2 patients (2.8%). The bleeding was in the rectum in 2 patients and received about 2 units of blood. Patients who developed major bleeding were early colon cancer and pseudo-depressed LST cases. Minor bleeding (1 cecum, 2 transverse colons, 2 sigmoid colons, and 12 rectums) developed in 17 (24.3%) patients. Complications are presented in Table 3.

### DISCUSSION

Endoscopic resection procedures have improved with the advances in endoscopy. After EMR, the ESD procedure was developed, especially in the Far East, to resect larger lesions with the endoscopic approach. This procedure was also accepted by Western endoscopists and became globally popularized.<sup>5</sup> Advanced endoscopic procedures have been performed in our center for the last 5 years. We aimed to present clinical outcome ESD data for colorectal premalignant and non-invasive early gastrointestinal cancer treatment in our center.

**Table 3. ESD Complications and Anatomic Distribution of the Complications**

	Minor Bleeding	Major Bleeding	Perforation
Cecum	1(1 HGD)		
Transverse colon	2 (1 SML, 1 LGD)		1(1 HGD)
Sigmoid colon	2 (1 ECC, 1 HGD)		2 (1 LST, 1 ECC)
Rectum	12 (3 ECC, 6 LST, 1 INF POL, 1 NET, 1 SML)	2(1 ECC, 1 LST)	3 (2 LST, 1 ECC)
Total	17	2	6

HGD, high-grade dysplasia; LGD, low-grade dysplasia; NET, neuroendocrine tumor; ECC, early colonic cancer; SML, submucosal lesion; INF POL, inflammatory polyp; LST, lateral spreading tumor; ESD, endoscopic submucosal dissection.

It was not possible to resect large lesions en bloc with the previous EMR technique. En bloc resection of larger lesions reduces recurrence at the lesion site. Also, en bloc resection allows better pathological assessment of the lesion. R0 resection provides more accurate evaluation of the lesion. The ESD technique solves this problem to a great extent.<sup>6</sup> In a study where local recurrence and complete resection rate of colorectal lesions larger than 20 mm in EMR and ESD were compared, it was determined that ESD was superior to EMR based on the primary endpoints.<sup>7</sup> Since the median size of the colorectal lesions in this study was 5.88 cm<sup>2</sup>, ESD was preferred for better local recurrence rates and complete resection outcomes.

In a study conducted in Japan where the effectiveness of ESD was investigated in colorectal lesions, the en bloc resection and surgical margin negativity rates were reported as 91.5% and 70.5%, respectively. In the same study, the perforation development and local recurrence in follow-ups were 5% and 1.7%, respectively.<sup>8</sup>

In this study, the en bloc resection rate was 81.4%, and surgical margin negativity rate was 84.2%. Our en bloc rate was lower when compared to the literature. This was due to the fact that our center has recently started to perform the procedure. Our surgical margin negativity rate was lower. This could be due to our high selectivity in the selection of lesions amenable to ESD with ease.

Endoscopic mucosal resection and ESD procedures could lead to undesired complications such as perforation (0% and 0.1%-0.4%). This complication could be treated with hemo-clips, Over The Scope Clio, or endoscopic suturing methods. The number of patients who underwent surgery was quite low.<sup>9</sup> Also, the rate of patients who experienced major bleeding due to complications was 1.4%-1.7% in EMR and 1.5%-2.8% in ESD.<sup>10</sup> In the current study, the perforation and major bleeding rates were 8.5% and 2.8%, respectively. Our perforation rates were higher when compared to previous studies. However, none of our patients underwent surgery. All the patients were successfully managed endoscopically and were discharged. Our bleeding rates were consistent with the literature. Comparison of these data suggested that ESD is a safe procedure in the management of colorectal lesions.

Endoscopic resection of early-stage colorectal carcinomas is safe and the results are acceptable. Local recurrence rate of colorectal cancers without lymph node metastasis and submucosal invasion and with en bloc ESD resection is between 0% and 3%.<sup>11,12</sup> Local recurrence was observed in 2 (18.1%) out of 11 patients with early-stage colorectal cancer in the present study. These patients were then referred to surgery. These data suggest that ESD resection is safe for patients with early-stage colorectal cancer. Although the recurrence rate was high in the present study, these patients could be managed with proper follow-up programs.

In conclusion, as a center that has just started to perform advanced endoscopic procedures, our ESD results were consistent with the literature. The analysis of our ESD outcomes based on treatment, complications, and local recurrence revealed satisfactory results when the lesions were evaluated comprehensively before the ESD procedure.

All studies done on this topic, including this one, have shown good outcomes for the use of ESD in suitable colorectal lesions, but there is a need to invest in more expertise and infrastructure to maximize the good outcomes of advanced endoscopic procedures.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of İnönü University (Date: April 12, 2022, Decision No: 2022/3360).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

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