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# Clinical outcomes for patients with perforations during endoscopic submucosal dissection of laterally spreading tumors of the colorectum

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**Abstract**
*Background* Endoscopic submucosal dissection (ESD) for colorectal neoplasms is not widely performed because of the high risk of perforation. Perforations are divided into macroperforations and microperforations. Currently, there is a limited amount of clinical data on the outcome of patients with these types of perforations during colonic ESD. The aim of this study was to investigate the clinical outcome of patients who sustained colon perforations during ESD. We also compared the clinical outcome of patients with microperforations and those with macroperforations.
*Methods* This study enrolled 101 patients with colorectal laterally spreading tumors (LST) who underwent ESD. We retrospectively reviewed their medical records, including patient demographic data and the clinical, endoscopic, and pathologic features. In the cases where perforation had occurred, the course of hospital treatment was analyzed. All ESD-related perforations were divided into macroperforations and microperforations. A macroperforation was defined as a gross perforation that occurred during an ESD procedure and a microperforation was defined by free air visible on X-rays after the procedure.
*Results* Of the 101 enrolled patients, 9 (8.9 %) developed perforations. The most common tumor morphology was nongranular-type LST (5 of 9 cases, 55.6 %) based on endoscopic examination. Five patients had microperforations and four had macroperforations. All macroperforations were closed primarily by endoclips during ESD. The endoscopic characteristics did not differ between the groups. However, the length of hospital stay and the mean duration of NPO and antibiotic treatments were longer for microperforation patients. All patients had conservative nonsurgical management such as fasting, intravenous antibiotics, and nasogastric tube drainage.
*Conclusions* The clinical complications for microperforation patients were worse than those for macroperforation patients. However, the clinical prognoses of patients with perforations that occur during colonic ESD are favorable.

**Keywords** Colorectal laterally spreading tumor · Endoscopic submucosal dissection · Macroperforation · Microperforation · Perforation

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Endoscopic mucosal resection (EMR) is a useful therapeutic technique for adenoma and intramucosal or submucosal superficial (sm1, <1,000 μm from the muscularis mucosa) colorectal cancer because it is minimally invasive [1, 2]. However, it is difficult to perform en bloc resection for a colorectal tumor larger than 20 mm because of the physical limitation of the snare size [3, 4]. Piecemeal EMR can be used to remove large colorectal tumors. However, a precise histopathological diagnosis is difficult when using separate resected specimens obtained by piecemeal EMR.

Additionally, incomplete tumor removal and local recurrence are occasionally observed after EMR [5, 6]. Therefore, laparoscopy-assisted colectomy and transanal endoscopic mucosectomy have been accepted as the standard treatments for large colorectal tumors and early colorectal cancer throughout the world [7, 8].

An endoscopic submucosal dissection (ESD) has a high rate of en bloc resection for large colorectal tumors. ESD is also less invasive than an operation. Therefore, ESD was recently introduced as a new treatment modality for early colorectal cancer and large colorectal tumors. In treating gastric lesions, ESD is widely accepted as an alternative to surgery for complete resection [9, 10]. However, the colon wall is thinner than the gastric wall and there are many folds in the colorectum [11]. Therefore, ESD is not widely performed because of a greater level of technical difficulty, a longer procedure time, and an increased risk of complications such as perforation or bleeding [12, 13]. A perforation is likely to cause peritonitis that could require surgical treatment [11]. However, research examining the outcome of patients who sustained perforations during colon ESD procedures is limited.

All ESD-related perforations are divided into macroperforations and microperforations. A macroperforation is usually noted during the procedure and can be treated successfully with endoclips. However, microperforations are usually diagnosed by free air visible on X-rays after the procedure. Recently, Jeon et al. [14] reported the clinical outcomes of these two types of perforations from ESD in cases with gastric lesions. They found that the clinical prognosis and endoscopic characteristics between the patients with macroperforations and those with microperforations were similar. However, with colonic ESD, we have experienced a few cases with different clinical features between the two types of perforations. Presently, there is little information on the outcome of patients with microperforations or macroperforations that occur during colonic ESD.

The aim of this study was to examine the frequency and the clinical outcome of patients who experience colon perforation during ESD. We also compared the clinical outcome of patients with macroperforations and with that of patients with microperforations.

## Patients and methods

### Study protocol

This study enrolled 101 patients with colorectal tumors who underwent ESD at Konkuk University Medical Center, Seoul, Korea, between January 2008 and May 2011. We retrospectively reviewed their medical records, including patient demographics, clinical, endoscopic, and pathologic features, and hospital treatments. All patients were informed about the risks and benefits of ESD and provided written informed consent. The institutional review board of Konkuk University Medical Center approved this study.

The ESD was performed by two endoscopic specialists who were highly experienced. The indication for ESD at our center was colorectal epithelial neoplasia, precancerous adenomatous lesions, and adenocarcinoma. The lesions were identified by endoscopic laterally spreading findings with chromoendoscopy and endoscopic ultrasonography.

The colonoscopic appearance and location of the lesion were classified according to the Japanese Research Society classification scheme [15]. The location of a lesion was defined as right colon if it was proximal to and included the splenic flexure. A laterally spreading tumor (LST) was defined as a lesion 10 mm or larger with a low vertical axis that extended laterally along the interior luminal wall. The tumors were classified according to Kudo's classification scheme: LST-GH (granular and homogeneous), LST-GM (granular and nodular mixed), and LST-NG (nongranular). A histological assessment was made according to the World Health Organization classification of gastrointestinal epithelial neoplasia.

### Endoscopic submucosal dissection and perforation

The bowel was prepared by ingestion of 4 L doses of polyethylene glycol solution (Colyte-F; Taejoon Pharm, Seoul, Korea). Midazolam and meperidine were used for sedation and cardiorespiratory function was monitored during the procedure. A single-channel lower gastrointestinal endoscope (CF-260AI; Olympus Optical Co., Tokyo, Japan) with a transparent cap to tip was used in this study. Demarcation of the lesion was done by chromoendoscopy using indigo carmine mixed solution and narrow band imaging. The hyaluronic acid–epinephrine–indigo carmine mixed solution was injected to lift the submucosal layer using a 21–25-gauge injection needle. A circumferential incision in the mucosa was made with a Flex knife (Olympus, Tokyo, Japan). The tissue was dissected along the submucosal layer with a Flex knife after incising about two-thirds of the lesion. In a small number of ESD cases, the snare was used to cut in the final step. During ESD, endoscopic hemostasis was achieved with a coagrasper and/or hemoclip. The high-frequency generator used in this study was a VIO300D (Erbe Elektromedizin, Tübingen, Germany).

All patients underwent a simple abdominal X-ray immediately after the ESD and the next morning. Additionally, all laboratory testing was performed the day after ESD. There are two types of tissue perforations.

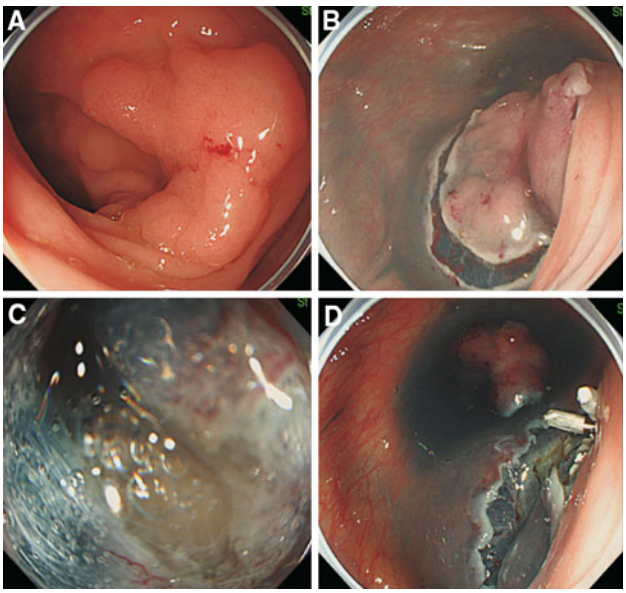


**Fig. 1** A case of macroperforation. **A** The 30 mm-diameter size and LST-NG-type tumor located in the hepatic flexure. **B** Circumferential incision with a Flex knife. **C** Direct endoscopic observation of mesenteric fat during submucosal dissection with a Flex knife. **D** Clipping state and ulceration after the submucosal dissection

A macroperforation is defined as a gross defect noted during the procedure with direct endoscopic observation of mesenteric fat, intraluminal organs, or space through the lesions (Fig. 1). A microperforation is identified by the presence of free air on the radiological finding after ESD (Fig. 2). Perforations confirmed during the procedure were managed immediately by endoscopic closure using hemoclips. A Levin tube was inserted if needed. Patients with perforations that were not seen during the ESD but were later identified by X-ray were closely monitored.

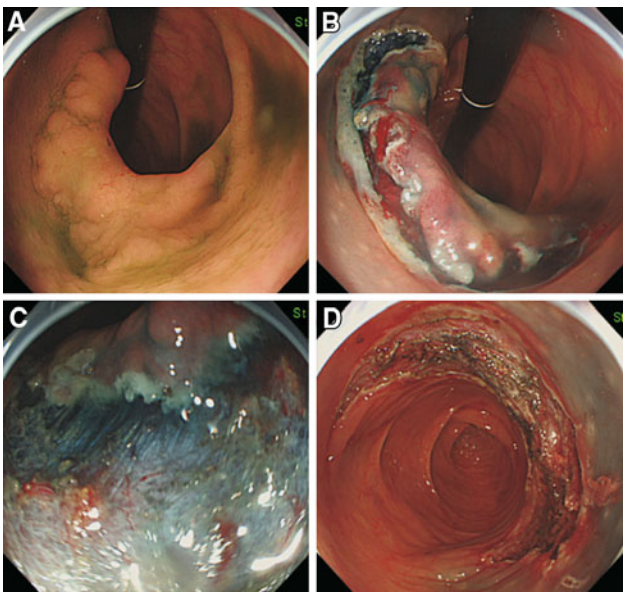


**Fig. 2** A case of microperforation. **A** The retroflexion view of 40 mm-diameter, LST-NG-type tumor located in the descending colon. **B** Circumferential incision with a Flex knife. **C** Submucosal dissection with a Flex knife. **D** Ulceration after the submucosal dissection

### Statistical analysis

Continuous variables were expressed as the mean ± standard deviation and categorical variables were presented as absolute values and percentages. The differences between groups were evaluated using the two-sample $t$ test for continuous data and the $\chi^2$ test for binary data. The SPSS ver. 17.0 (SPSS, Inc., Chicago, IL) was used for all analyses. $P < 0.05$ was considered statistically significant.

## Results

This study included 101 patients. The baseline characteristics of the patients and lesions are summarized in Table 1. The mean age of the patients was 63.75 ± 9.94 years (range = 40–86 years) and the male:female ratio was 1.53 (61:40). The mean size of the resected specimens was 26.27 ± 10.04 mm (range = 10–60 mm) and the mean procedure time was 56.32 ± 36.00 min (range = 10–205 min). Based on macroscopic examination, 9 cases were LST-GH type (8.9 %), 42 cases were LST-GM type (41.6 %), and 50 cases were LST-NG type (49.5 %). No correlation between patients without perforation and those with perforation with respect to disease type and lesion location was observed. The histological diagnosis was low-grade dysplasia in 50 cases (49.5 %), high-grade dysplasia in 23 cases (22.8 %), and carcinoma in 28 cases (27.7 %). A colonic perforation occurred during ESD in 9 patients (8.9 %). The tumor size was larger in the perforation group. The procedure time was longer for the perforation group. However, these differences were not significant ($P = 0.495$ and $P = 0.079$, respectively). Additionally, the perforation group was predominantly female (88.9 %). The majority of tumors with perforations were located on the right side of the colon.

Table 2 summarizes the clinical features of the perforation patients. All perforation patients were treated using nonsurgical management such as fasting, intravenous antibiotics, and nasogastric tube drainage. A fever above 37.8 °C occurred in four of the nine perforation patients (44.4 %). One patient developed a fever on the first day after perforation. The other patients developed fevers 2 days after the procedure. One patient had a fever for 5 days. On the day following perforation, six patients had leukocytosis higher than 9,000 $mm^{-3}$ (66.7 %). However, the leukocytosis resolved in all patients after 3 days. The presence of free air was found by X-ray in five patients.

**Table 1** Baseline characteristics of patients who underwent colonic ESD with or without perforation

| | All patients ($n = 101$) | Patients without perforation ($n = 92$) | Patients with perforation ($n = 9$) | $P$* value |
|---|---|---|---|---|
| Age (years) [mean ± SD (range)] | 63.75 ± 9.94 (40–86) | 63.82 ± 8.84 (40–86) | 63.00 ± 13.16 (46–80) | 0.833 |
| Sex (M:F) | 61:40 | 73:39 | 8:1 | 0.010 |
| Macroscopic type [$n$ (%)] | | | | 0.886 |
| LST-GH | 9 (8.9) | 8 (8.7) | 1 (11.1) | |
| LST-GM | 42 (41.6) | 39 (42.4) | 3 (33.3) | |
| LST-NG | 50 (49.5) | 45 (48.9) | 5 (55.6) | |
| Tumor location [$n$ (%)] | | | | 0.120 |
| Right colon | 38 (37.6) | 32 (34.8) | 6 (66.7) | |
| Left colon | 35 (34.7) | 32 (34.8) | 3 (33.3) | |
| Rectum | 28 (27.7) | 28 (30.4) | 0 (0.00) | |
| Tumor size (mm) (mean ± SD) | 26.27 ± 10.04 | 26.04 ± 10.01 | 28.67 ± 10.48 | 0.495 |
| Histology [$n$ (%)] | | | | 0.926 |
| Low-grade dysplasia | 50 (49.5) | 45 (48.9) | 5 (55.6) | |
| High-grade dysplasia | 23 (22.8) | 21 (22.8) | 2 (22.2) | |
| Carcinoma | 28 (27.7) | 26 (28.3) | 2 (22.2) | |
| Procedure time (min) (mean ± SD) | 56.32 ± 36.00 | 54.19 ± 32.05 | 78.11 ± 36.51 | 0.079 |

* $P$ value between patients without perforation and patients with perforation

There were six patients with abdominal pain that required analgesics. The mean duration of fasting was 4.1 ± 1.5 days. The mean duration of intravenous antibiotic use was 6.0 ± 2.0 days. Nasogastric decompression was provided for three patients. The patients began oral feeding regardless of the presence of free air if the symptoms and signs improved. Pneumoperitoneum remained in all the patients with radiographic evidence of free air before diet initiation and discharge. The mean length of the hospital stay was 8.3 ± 2.1 days. Of the nine cases of colonic perforation, five were microperforations and four were macroperforations. All macroperforations were closed primarily with endoclipping during ESD (Fig. 1); only one patient with a macroperforation had free air visible on X-ray. Conversely, all of the patients with a microperforation had free air visible on X-ray (Fig. 3). The short-term clinical outcomes for the patients with microperforations and macroperforations are summarized in Table 3. There was no difference in the baseline and endoscopic characteristics between the microperforation and macroperforation groups. However, the length of hospital stay, mean duration of NPO, and antibiotic use were longer in the microperforation group than in the macroperforation group. Additionally, the development of fever was more common in the microperforation group but there was no significant difference between the two groups.

## Discussion

In the present study we examined the clinical outcomes of patients following ESD for colonic LST and found that the perforation rate was 8.9 %. Moreover, the patients who sustained a perforation were successfully managed with no surgical intervention. In addition, we compared the clinical course and prognosis of patients with microperforations and macroperforations.

The ESD procedure is a feasible endoscopic method for treating colorectal tumors because it can provide en bloc specimens for pathologic diagnosis. Nevertheless, because colorectal ESD is technically difficult to perform and the risk of complications such as perforation is high, it is not currently the standard therapeutic method for treating colorectal tumors. Recently, various techniques, devices, endoscopes, and peripheral equipment for performing colorectal ESD have been developed and improved [12]. The number of perforations decreased dramatically using these techniques and the safety of this procedure has increased [12, 16]. A number of studies that examined the clinical outcomes of colorectal ESD patients have reported a wide range of perforation rates (1.4–10.4 %) [16–18]. The rate of complications has decreased over time [12]. Although perforations occurred, surgical intervention was not necessary in most cases. The appropriate use of

**Table 2** Characteristics in the cases with perforation

| No. | Age | Sex | Tumor type | Location | Size (mm) | Time (min) | Perforation type | Free air | WBC ($mm^{-3}$) | Fever (>37.8 °C) | Abdominal pain | Antibiotics (days) | NPO (days) | Hospital stay (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 60 | F | LST-NG | D colon | 25 | 56 | Micro | Yes | 7,800 | Yes | Yes | 5 | 4 | 8 |
| 2 | 80 | F | LST-NG | T colon | 30 | 97 | Macro | No | 10,190 | No | No | 5 | 3 | 6 |
| 3 | 64 | F | LST-NG | A colon | 18 | 94 | Macro | No | 7,700 | No | No | 2 | 2 | 5 |
| 4 | 58 | F | LST-GM | Cecum | 50 | 107 | Macro | Yes | 88,400 | Yes | Yes | 5 | 5 | 12 |
| 5 | 51 | F | LST-NG | D colon | 40 | 150 | Micro | Yes | 10,200 | Yes | Yes | 5 | 5 | 8 |
| 6 | 51 | F | LST-NG | D colon | 25 | 57 | Micro | Yes | 12,200 | Yes | Yes | 6 | 6 | 10 |
| 7 | 77 | M | LST-NG | Hepatic flexure | 20 | 60 | Macro | No | 7,250 | No | No | 3 | 3 | 8 |
| 8 | 80 | F | LST-GM | A colon | 20 | 45 | Micro | No | 18,400 | No | Yes | 3 | 3 | 9 |
| 9 | 46 | F | LST-GM | A colon | 30 | 37 | Micro | Yes | 16,400 | No | Yes | 6 | 6 | 9 |

*D colon* descending colon, *A colon* ascending colon, *T colon* transverse colon

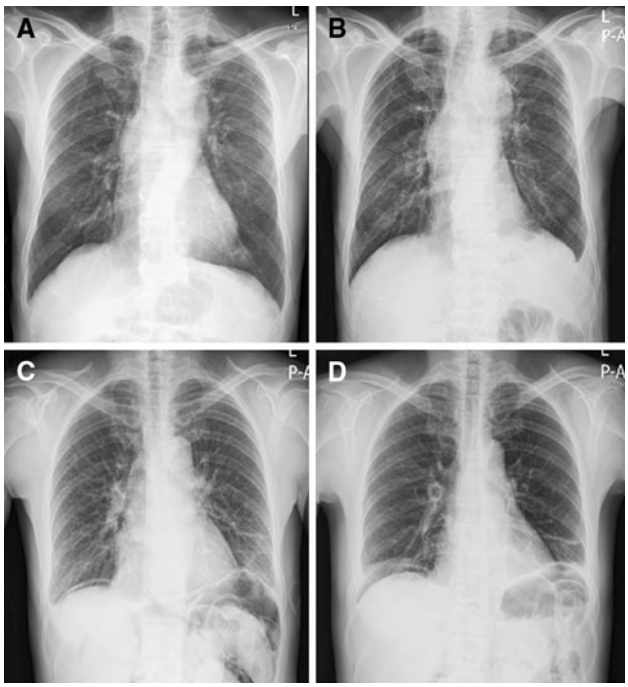


**Fig. 3** Chest X-ray images in a case of macroperforation (**A**, **B**) and a case of microperforation (**C**, **D**). In the case of macroperforation, there was no free air on the chest X-ray 1 day after ESD (**A**) and before discharge (**B**). In the case of microperforation, pneumoperitoneum was noticed on the chest X-ray 1 day after ESD (**C**) and remained until discharge (**D**)

clipping and the clean bowel from preparation may lead to a benign clinical course [2, 18]. In our study, the perforation rate was 8.9 % and all the perforations developed during ESD were successfully repaired using nonsurgical approaches without further endoscopic treatment. This is consistent with the results of previous studies [16–18]. The perforation rate also has been decreasing because of improvement in the endoscopist's skills [11]. In this study, no peritoneal dissemination was observed in the nine patients with perforation during a median (range) follow-up period of 32 months (range = 10–50 months). However, emergency surgery may be still required in some cases, and the risk of peritoneal seeding should also be considered. These factors suggest that the incidence of perforation should be minimized.

This is the first study to compare the clinical outcome of microperforation and macroperforation patients with colorectal tumors. Macroperforations were closed immediately by clipping, and the ESD was completed successfully. Only one patient with a macroperforation developed pneumoperitoneum after ESD. A fever was observed in only one patient with pneumoperitoneum. Conversely, microperforations are the result of injury to the proper muscle layer during precutting or submucosal dissection and air under tension in the colorectal wall may pass through the hole [14]. Pneumoperitoneum developed after

**Table 3** The baseline characteristics and short-term clinical outcome in patients with microperforations and macroperforations

| | Microperforation ($n = 5$) | Macroperforation ($n = 4$) | $P$ value |
|---|---|---|---|
| Age (years) (mean ± SD) | 57.60 ± 13.50 | 69.75 ± 10.47 | 0.184 |
| Sex (M:F) | 0:5 | 1:3 | 0.236 |
| Macroscopic tumor type [$n$ (%)] | | | 0.595 |
| LST-GM | 2 (40.0) | 1 (25.0) | |
| LST-NG | 3 (60.0) | 3 (75.0) | |
| Tumor location [$n$ (%)] | | | 0.058 |
| Right colon | 2 (40.0) | 4 (100.0) | |
| Left colon | 3 (60.0) | 0 (0.0) | |
| Tumor size (mm) (mean ± SD) | 28.0 ± 7.58 | 29.5 ± 14.64 | 0.847 |
| Histology [$n$ (%)] | | | 0.347 |
| Low-grade dysplasia | 2 (40.0) | 3 (75.0) | |
| High-grade dysplasia | 1 (20.0) | 1 (25.0) | |
| Carcinoma | 2 (40.0) | 0 (0.0) | |
| Procedure time (min) (mean ± SD) | 69.00 ± 46.03 | 89.50 ± 20.44 | 0.439 |
| Mean duration of NPO (days) | 4.80 ± 1.30 | 3.25 ± 1.26 | 0.118 |
| Length of hospital stay (days) | 8.80 ± 0.84 | 7.75 ± 3.10 | 0.485 |
| Free air, present [$n$ (%)] | 4 (80.0) | 1 (25.5) | 0.099 |
| Fever [$n$ (%)] | 3 (60.0) | 1 (25.5) | 0.294 |
| Abdominal pain [$n$ (%)] | 5 (100.0) | 1 (25.0) | 0.048 |
| Intravenous antibiotics (days) | 5.0 ± 1.23 | 3.75 ± 1.50 | 0.210 |
| Levin tube [$n$ (%)] | 3 (60.0) | 0 (0.0) | 0.058 |
| WBC ($mm^{-3}$) (mean ± SD) | 13,000 ± 4,366 | 8,385 ± 1,294 | 0.077 |

ESD in all the patients with microperforations. The mean duration of NPO, antibiotics usage, and hospital stay were longer for microperforation patients than for macroperforation patients. All the patients in which a Levin tube was used had microperforations, and leukocytosis occurred at a higher rate in microperforation patients than in macroperforation patients. Our results demonstrate that the clinical course of patients with microperforations is longer and more severe than that for patients with macroperforations. However, this finding is not statistically significant because of the small number of cases.

This study has the limitations associated with a retrospective single-center analysis study. The number of perforations was small due to the low rate of perforation. In addition, our study does not provide data on the survival benefits of endoscopic treatment of perforations compared to surgery.

In summary, the perforation rate was less than 9 % during colonic ESD in this study. All of the perforations developed during ESD were successfully treated without a surgical procedure or further endoscopic treatment. Compared with patients who developed macroperforations, the patients with microperforations required a longer duration of antibiotic treatment and had a longer hospital stay. Nevertheless, the clinical prognoses for perforations that occur during colonic ESD are favorable.

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