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# 대장직장 종양에 대한 내시경 점막하 절제술의 연대순 임상 결과와 학습 곡선

이상민, 김은수, 박경식, 조광범, 김동춘, 강유진, 이유진, 이정민, 최은성, 최재혁, 이호영
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## Chronological Outcomes and Learning Curve of Endoscopic Submucosal Dissection for Colorectal Tumors

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**Background/Aims:** Endoscopic submucosal dissection (ESD) is an effective procedure for *en-bloc* curative resection of the colorectal tumor. As it requires high technical skills and experience in therapeutic endoscopy, it is important to understand learning curve of ESD technique. The aim of this study was to retrospectively describe the clinical results of ESD and to evaluate learning curve for the ESD of colorectal tumors.
**Methods:** A total of 90 patients with 90 colorectal neoplasms, who had undergone ESD at a tertiary referral hospital from July 2009 to December 2012, were enrolled. The ESD was performed by a single endoscopist. All ESD cases were divided into three periods: first, cases 1-30; second, cases 31-60; and third, cases 61-90.
**Results:** The *en-bloc* resection rates in third period (100%) was significantly higher than that of the first (93.3%) and second period (80%) (p=0.025). The perforation rate in third period (0%) also significantly decreased compared with that of the first (13.3%) and second period (20%) (p=0.032). To calibrate the difference of tumor size among periods, proficiency was calculated, as the procedure time per specimen area (min/cm$^2$). The proficiency in third period (4.3) was significantly shorter than that of the first (16.8) and second period (10.2) (p=0.004).
**Conclusions:** The learning curve of colorectal ESD in our study shows that at least 60 cases of ESD have to be conducted to acquire sufficient skill of degree without perforation. **(Korean J Gastroenterol 2014;64:198-205)**

**Key Words:** Learning curve; Colon; Endoscopy; Dissection

## INTRODUCTION

Colorectal cancer is a global health problem and the fourth leading cause of death from cancer worldwide.[1] As most colorectal cancers are developed from adenomatous lesions through adenoma-carcinoma sequence, they can be prevented by colonoscopy with endoscopic resection at the stage of adenoma.[2] Sessile polyps and flat adenoma can be treated effectively by endoscopic mucosal resection (EMR) using a snare.[3] Although EMR using a snare is a simple and time-saving procedure, this method tends to remove colorectal tumors larger than 20 mm in a piecemeal manner.[4,5] Because it is difficult to determine the depth of invasion, lymphovascular invasion, and marginal involvement of tumors

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resected by endoscopic piecemeal resection, a precise pathologic evaluation is not possible to obtain.[6] Hence, it may result in relatively high incidence of local recurrence.

In an effort to resolve the problems associated with EMR, a new method, endoscopic submucosal dissection (ESD), has been developed.[7-9] ESD is an effective procedure for *en-bloc* resection and curative resection of large colorectal tumors that are difficult to resect by EMR.[10-13] However, it requires high-level technical skills and experience in therapeutic endoscopy. It also has a relatively higher rate of perforation and longer procedural time than EMR.[14,15] Therefore, it is important to understand the learning curve of the colorectal ESD technique in order to achieve good results with a tolerable complication rate. The aim of this study was to retrospectively describe the chronological clinical results of ESD and to evaluate the learning curve for ESD of colorectal tumors.

## MATERIALS AND METHODS

### 1. Patients

A total of 90 patients with 90 colorectal neoplasms, who had undergone ESD at Keimyung University Dongsan Hospital, Daegu, Korea from July 2009 to December 2012, were consecutively enrolled in our study. ESD was performed by a single endoscopist (E.S.K.), who had experienced approximately 2,000 colonoscopies, 200 colonic EMR, and 15 gastric ESD before starting colorectal ESD. In addition, he performed gastric ESD in 170 cases during the study period. Chronologically all ESD cases were divided according to three periods: first, cases 1-30; second, cases 31-60; and third, cases 61-90. In the first five cases, ESD was performed under the supervision of an expert endoscopist (K.B.C.) who was a regular staff member at our center. The institutional review board of our hospital approved this retrospective study (DSMC 2014-04-046-001).

### 2. Indication for ESD

ESD procedure can completely remove superficial colorectal neoplasms larger than 20 mm in diameter that might have a malignant potential without lymph node metastases. Rectal carcinoid tumors less than 20 mm can also be effectively removed by ESD.[16] Therefore, in this study, the indications for ESD included: (i) laterally spreading tumor (LST) of any type $>20$ mm; (ii) the protruded type of tumor $>20$ mm; and (iii) rectal carcinoid tumor, lesion $<20$ mm. LST or protruded type lesions with an irregular or non-structural shaped pit pattern accompanying a non-lifting sign were considered not suitable for ESD.[17]

### 3. ESD procedure

All patients took three liters of polyethylene glycol for bowel preparation one day before colorectal ESD. ESD was performed under unconscious sedation using intravenous midazolam and propofol.

All ESD were performed with single channel colonoscopies (CF-H260AI or CF-Q260AI; Olympus Optical Co. Ltd., Tokyo, Japan) and an air insufflation system. An attachment cap was used in order to facilitate dissection in all periods. The procedure sequence was submucosal injection, mucosal incision, and submucosal dissection with simultaneous hemostasis. Sodium hyaluronate or saline solution containing epinephrine (0.01 mg/mL) mixed with 0.8% indigo carmine was injected into the submucosal layer, just outside of the margin of the tumor in order to lift the lesions. Then, mucosal incision was made using a clear cut knife (I-type-1820; Finemedix Co. Ltd., Daegu, Korea). The clear cut knife or hook knife (KD-620LR; Olympus Optical Co. Ltd.) was used primarily for the submucosal dissection. If there was bleeding during the ESD procedure or the need to prevent delayed bleeding after the procedure, hemostasis was performed using hemostatic forceps (Coagrasper, FD-410LR; Olympus Optical Co. Ltd.). The high-frequency generator for electrical cutting and coagulation was VIO300D (ERBE Elektromedizin, Tübingen, Germany). The endocut mode was used for mucosal incision while swift coagulation mode was used for submucosal dissection.

### 4. Assessment of learning curve

We retrospectively reviewed the prospectively registered data of patients in order to assess the learning curve of colorectal ESD. We analyzed *en-bloc* resection rate, R0 resection rate, and perforation rate. R0 resection was defined as an *en-bloc* resection without tumor involvement to the lateral and vertical margins of the resected specimen in a pathologic diagnosis.[18] We used the proficiency that was calculated as the procedure time per specimen area (min/cm$^2$).[19] Complications related to ESD procedures such as perforation and

bleeding were also estimated. In addition, we sub-analyzed clinical outcomes of ESD for colorectal epithelial tumor only, excluding carcinoid tumor cases. As performing ESD in the right colon is challenging, it is important to know the learning curve of ESD in the right colon.[20] Therefore, we also analyzed clinical outcomes of ESD for right colon tumors.

### 5. Statistical analysis

All statistical analyses of the data were performed using PASW Statistics version 18 for Windows (IBM Co., Armonk, NY, USA). Categorical data were analyzed using the chi-square test or Fisher's exact test. Numerical data were analyzed by one way analysis of variance (ANOVA). p-value of $<0.05$ was considered statistically significant.

## RESULTS

The patient demographics and endoscopic characteristics of the lesion are described in Table 1. The mean age of the patients in each period was 59.1, 58.9, and 62.2 years, respectively. The majority of lesions in each period were located in the rectum (first: 66.7%, second: 56.7%, third: 43.3%), followed by right colon (first: 23.3%, second: 23.3%, third: 33.3%), and left colon (first: 10.0%, second: 20.0%, third: 23.3%). Based on macroscopic examination, LST was the most common type in all periods. Mean tumor size in each period was 20.9 mm, 24.9 mm, and 23.8 mm, respectively. No statistically significant difference in the demographics, location of tumors, macroscopic finding, and tumor size was observed among the three periods.

The clinicopathological outcomes according to treatment period are summarized in Table 2. The histological diagnosis was adenoma in 38 cases (42.2%), adenocarcinoma in 30 cases (33.3%), and carcinoid tumor in 19 cases (21.1%). The majority of adenocarcinoma cases were intramucosal cancer (23, 76.7%). On the basis of 1,000 μm, submucosal cancer was divided according to shallow and deep invasion. There were three patients with adenocarcinoma of deep invasion and two of them were managed by subsequent surgical operation. The other patient refused to undergo surgery. No difference with respect to pathology was observed among the three periods.

**Table 1.** Patient Demographics and Endoscopic Characteristics of the Lesions by Treatment Period

| Characteristic | 1st period | 2nd period | 3rd period | p-value |
|---|---|---|---|---|
| Age (yr) | 59.1 (36-79) | 58.9 (41-76) | 62.2 (35-81) | 0.538 |
| Gender (n, male:female) | 14:16 | 18:12 | 21:9 | 0.183 |
| Comobidity | | | | |
| Hypertension | 12 (40.0) | 12 (40.0) | 9 (30.0) | 0.650 |
| Type 2 DM | 8 (26.7) | 3 (10.0) | 5 (16.7) | 0.236 |
| CLD | 2 (6.7) | 0 (0.0) | 1 (3.3) | 0.770 |
| CVD | 0 (0.0) | 0 (0.0) | 2 (6.7) | 0.326 |
| CRD | 2 (6.7) | 1 (3.3) | 0 (0.0) | 0.770 |
| Others[a] | 2 (6.7) | 3 (10.0) | 2 (6.7) | 1.000 |
| Location of tumors[b] | | | | 0.426 |
| Right colon | 7 (23.3) | 7 (23.3) | 10 (33.3) | |
| Left colon | 3 (10.0) | 6 (20.0) | 7 (23.3) | |
| Rectum | 20 (66.7) | 17 (56.7) | 13 (43.3) | |
| Endoscopic diagnosis | | | | 0.314 |
| LST-G | 11 (36.7) | 15 (50.0) | 14 (46.7) | |
| LST-NG | 3 (10.0) | 4 (13.3) | 8 (26.7) | |
| Polypoid | 6 (20.0) | 3 (10.0) | 4 (13.3) | |
| Carcinoid | 10 (33.3) | 8 (26.7) | 4 (13.3) | |
| Tumor size, long axis (mm) | 20.9 (9-40) | 24.9 (10-55) | 23.8 (9-45) | 0.359 |
| Duration per ESD (day) | 16.5 | 13.1 | 12.1 | |

Values are presented as mean (range), n (%), or mean only.
Chronologically all cases were divided according to three periods: first period, cases 1-30; second period, cases 31-60; third period, cases 61-90.
Type 2 DM, type 2 diabetes mellitus; CLD, chronic liver disease; CVD, cardiovascular disease; CRD, chronic renal disease; LST-G, laterally spreading tumor-granular type; LST-NG, laterally spreading tumor-nongranular type; ESD, endoscopic submucosal dissection.
[a]First period: uterine cervical cancer, stomach cancer; second period: stomach cancer, hypothyroidism; third period: stomach cancer.
[b]Right colon: cecum, ascending colon, transverse colon; left colon: descending colon, sigmoid colon.

**Table 2.** Clinicopathological Outcomes by Treatment Period

| | 1st period | 2nd period | 3rd period | p-value |
|---|---|---|---|---|
| Pathology | | | | 0.217 |
| Adenoma | 11 (36.7) | 13 (43.3) | 14 (46.7) | |
| Adenocarcinoma | 8 (26.7) | 9 (30.0) | 13 (43.3) | |
| Intramucosal cancer | 6 (20.0) | 6 (20.0) | 11 (36.7) | |
| Submucosal cancer | | | | |
| Shallow (<1,000 μm) | 1 (3.3) | 2 (6.7) | 1 (3.3) | |
| Deep (≥1,000 μm) | 1 (3.3) | 1 (3.3) | 1 (3.3) | |
| Carcinoid tumor | 9 (30.0) | 8 (26.7) | 2 (6.7) | |
| Others[a] | 2 (6.7) | 0 (0.0) | 1 (3.3) | |
| Procedure time, min | 39 (10-100) | 31.5 (8-133) | 15 (5-100) | 0.034 |
| *En-bloc* resection | 28 (93.3) | 24 (80.0) | 30 (100.0) | 0.025 |
| R0 resection[b] | 27 (90.0) | 21 (70.0) | 27 (90.0) | 0.056 |
| Perforation | 4 (13.3) | 6 (20.0) | 0 (0.0) | 0.032 |

Values are presented as n (%) or median (range).
Chronologically all cases were divided according to three periods: first period, cases 1-30; second period, cases 31-60; third period, cases 61-90.
[a]First period: chronic colitis, granular cell tumor; third period: atypical cells.
[b]*En-bloc* resection without tumor involvement to the margins of the resected specimen.

The *en-bloc* resection rate was significantly higher in the third period (100%) compared with that of the first (93.3%) and second period (80%) (p=0.025). The R0 resection rates in each period were 90.0%, 70.0%, and 90.0%, respectively (p=0.056). The perforation rate also showed significant improvement in the third period (0%) compared with that of the first (13.3%) and second period (20%) (p=0.032). All perforation cases were treated by endoscopic clipping and conservative management, including intravenous antibiotics and nothing per mouth without the surgical intervention.

Significant difference in the median procedure time was observed among the three periods (39 min, 32 min, and 15 min, p=0.034). To calibrate the difference of tumor size among periods, proficiency was calculated, as the procedure time divided by specimen area (min/cm$^2$). The learning curve of proficiency is shown in Fig. 1. Proficiency decreased over time and the proficiency was significantly shorter in the third period (4.3) compared with that of the first (16.8) period and second (10.2) period (p=0.004).

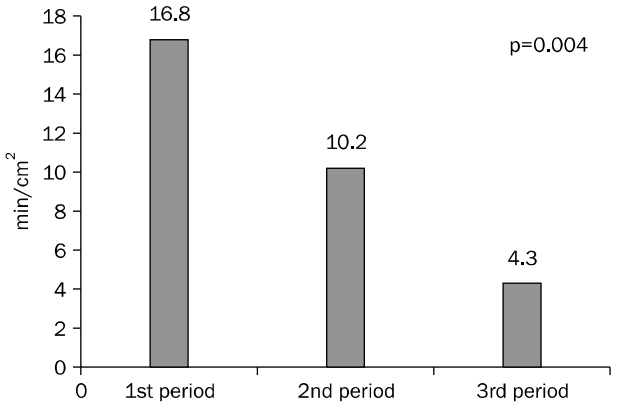


**Fig. 1.** Learning curve of procedure time per specimen area (min/cm$^2$). The values represent mean proficiency in each period.

Excluding carcinoid tumors, we sub-analyzed clinical outcomes for colorectal epithelial tumors only. Mean tumor size in each period was 25.6 mm, 30.2 mm, and 26.9 mm. No significant difference in R0 resection rate (first, 85%; second, 63.6%; third, 88.5%) was observed among the three periods. However, *en-bloc* resection rate was significantly higher in the third period (100%) compared with that of the first (90.0%) and second period (72.7%) (p=0.008). The proficiency also showed significant improvement in the third period (4.2) compared with that of the first (12.7) and second period (7.4) (p=0.02). The perforation rate was significantly better in the third period (0%) compared with that of the first (20.0%) and second period (27.3%) (p=0.008) (Table 3).

We also sub-analyzed the results of the right colon ESD. No significant difference in *en-bloc* resection rates (first, 71.4% [5/7]; second, 71.4% [5/7]; third, 100% [10/10]), R0 resection rates (first, 71.4% [5/7]; second, 57.1% [4/7]; third, 80.0% [8/10]) and perforation rates (first, 42.9% [3/7]; second, 28.6% [2/7]; third, 0% [0/10]) was observed among the three periods. However, the proficiency of the right colon ESD was significantly shorter in the third period (3.6) compared

**Table 3.** Clinicopathological Outcomes by Treatment Period in Colorectal Epithelial Tumors

| | 1st period | 2nd period | 3rd period | p-value |
|---|---|---|---|---|
| Tumor size, long axis (mm), mean (range) | 25.6 (20-40) | 30.2 (21-55) | 26.9 (20-47) | 0.199 |
| Procedure time (min), median (range) | 51.6 (15-100) | 47.4 (8-133) | 27.7 (5-100) | 0.023 |
| *En-bloc* resection, n (%) | 18 (90.0) | 16 (72.7) | 26 (100.0) | 0.008 |
| R0 resection[a], n (%) | 17 (85.0) | 14 (63.6) | 23 (88.5) | 0.124 |
| Perforation, n (%) | 4 (20.0) | 6 (27.3) | 0 (0.0) | 0.008 |
| Proficiency (min/cm$^2$), mean only | 12.7 | 7.4 | 4.2 | 0.02 |

Chronologically all cases were divided according to three periods: first period, 20 cases; second period, 22 cases; third period, 26 cases. [a]*En-bloc* resection without tumor involvement to the margins of the resected specimen.

with that of the first (15.1) and second (6.4) period (p=0.034).

## DISCUSSION

The results of our study demonstrated that the proficiency of the novice in performing colorectal ESD improved significantly without serious complications. Competent and expert level of technical skill was achieved after 60 cases of colorectal ESD represented by *en-bloc* resection and perforation rate.

The ESD procedure was initially developed for early gastric neoplasm, which was difficult to remove by EMR.[21] ESD facilitates complete *en-bloc* resection and leads to lower recurrence rate than EMR.[14] However, colorectal ESD procedure requires high-level technical skills and significant experience in therapeutic endoscopy compared with gastric ESD because it has a relatively higher risk of complication due to anatomical characteristics of the colon.[16] Therefore, it is important to understand the learning curve of colorectal ESD.

Learning curves of colorectal ESD have been evaluated in several studies. Sakamoto et al.[22] demonstrated that colorectal ESD can be performed without serious complications by trainee endoscopists after a certain degree of preparatory training and experience with 30 cases. Hotta et al.[19] used a measurement: the procedure time divided by square centimeter of specimen area (min/cm$^2$) for evaluating the learning curve. After 40 procedures, the proficiency improved significantly with the measurement. The current study was also conducted with this measurement, and the proficiency improved significantly in the third period compared with that of the first and second period. In other words, the endoscopist had to experience at least 60 cases of colorectal ESD procedure before performing ESD with a stable level of technical competency. However, the number of cases of threshold in the current study was higher than that of previous Japanese studies. There are several plausible explanations for this various number of cases required for good colorectal ESD from different studies. First, the duration of guidance by the experienced endoscopist differed between studies. The study by Hotta et al.[19] included 20 ESD cases guided by an expert while only five cases were included in the current study. In another Japanese study, the trainee experienced all colorectal ESD with the assistance of an expert. If the cases were assisted by experts during the trainee's performance of the procedure, it might affect clinical outcomes favorably.[18] Second, different endoscopic equipment for ESD was used in each study. A former Japanese study used a pediatric-type colonoscope (PCF-Q260JI; Olympus Optical Co.) with a built-in water jet system and a carbon dioxide insufflation system while we used a conventional colonoscope with an air insufflation system. A small diameter pediatric-type colonoscope with good maneuverability might be useful for the situation requiring retroversion of the scope and water-jet function is convenient for bleeding control, particularly in a large tumor that is accompanied by many nutrient vessels.[23] In addition, carbon dioxide insufflation has been suggested to be effective during colorectal ESD.[24] Despite no definite evidence of the impact of these equipments on the ESD procedure, the diverse clinical outcomes of each study might be attributed to the various devices used in different settings.

The trainee endoscopist must have a certain degree of eligibility to achieve a sufficient self-completion for submucosal dissection. This includes skillful insertion of the colonoscope without looping, EMR, and bleeding or perforation control with clips. Before performing the colonic ESD, experience in gastric ESD is also required, since gastric ESD is relatively easy to perform and removal of lesions is less time-

consuming. Trainees with gastric ESD experience showed better self-completion rate and satisfactory clinical outcomes in the introductory period of colorectal ESD compared to those without gastric ESD experience.[18] In the current study, the novice had competent skills in therapeutic procedures and management of complications (2,000 colonoscopies, 200 colonic EMR, and 15 gastric ESD) before starting colorectal ESD.

Piecemeal resection is associated with high incomplete resection rate and local recurrence rate.[4,7] ESD enables performance of *en-bloc* resection and allows a low recurrence rate. Therefore, *en-bloc* resection rate is also an important factor in evaluating colorectal ESD skills. The *en-bloc* resection rate in several clinical studies concerning the efficiency and safety of ESD in the colon and rectum was 80-98.6%.[11,12,25-29] The current study showed an *en-bloc* resection rate of 91.1%, similar to previous studies, and especially 100% in the third period after performing 60 cases of ESD.

In the meantime, ESD has a relatively high perforation rate compared with EMR. In particular, because of the tenuity of the colorectal wall, colorectal ESD has a higher risk of perforation than gastric ESD.[30] Several studies reported perforation rates of 1.4-10.4% in colorectal ESD.[31] The majority of cases were treated successfully by conservative management without emergency surgery and small perforations were closed by endoscopic clipping.[15,32] Compared with previous studies, our study shows a relatively high perforation rate in the first and second periods. However, the endoscopist was able to treat all perforation cases by endoscopic clipping and conservative management without surgical intervention. Furthermore, in the third period, the perforation rate was down to 0%. Delayed perforation as a serious complication after ESD was demonstrated in several studies, with rates ranging from 0.3-0.7%.[25,26,33] No case of delayed perforation was verified in our study.

Of particular interest, clinical outcomes including both perforation and *en-bloc* resection rates in the second period were worse than those of the first period. Although the reason for the poor outcomes in the second period was unclear, we postulated that the accumulation of experiences of colorectal ESD during the first period might cause the operator to perform relatively drastic submucosal incision and dissection in the following second period.

In the current study, ESD was performed not only for colorectal epithelial tumors but also carcinoid tumors. All 22 cases of carcinoid tumor were located in the rectum and mean tumor size in the three periods was 11.4 mm, 10.3 mm, and 14.5 mm, respectively. All carcinoid tumors were removed by complete *en-bloc* resection without complications of perforation or hemorrhage. In general, EMR was the treatment of choice for small rectal carcinoid tumors. However, histologically completeness of resection is difficult for EMR, because the majority of carcinoid tumors were not confined to the mucosa, but extended to the submucosa.[34] Therefore, ESD that can dissect tumors directly along the submucosal layer can be an effective treatment for carcinoid tumors.[25] Several studies reported that ESD could be a feasible and safe procedure for treatment of carcinoid tumors showing good clinical outcomes.[34-38]

Our study has several limitations. First, the study was a retrospective analysis. Although there could be a possibility of selection bias, there was no significant difference in variables among the three groups. Second, we included cases of carcinoid tumor in the study. Due to the small tumor size, carcinoid tumors could be relatively easily removed by ESD, compared to colorectal epithelial tumors. Therefore, the clinical outcomes such as proficiency and procedure time in our study might be greater than those of previous reports.[19,22] As colorectal epithelial tumors in our study were relatively smaller than those of previous reports, they would also affect the clinical outcomes.[19] The third limitation is that the study was designed for just one endoscopist in a single center. However, it is not easy to conduct a multicenter study with multiple endoscopists because there might be heterogeneity in basic skill and ability to acquire the procedure among endoscopists from different institutes. Therefore, our study can provide a good example for endoscopists just beginning the colorectal ESD. Nevertheless, competence in therapeutic procedures and ability to manage complications should be a prerequisite in training for colorectal ESD.

In conclusion, the ESD procedure can be performed safely, although it requires high-level technical skills. The learning curve of colorectal ESD in our study shows that be performed in at least 60 cases in order to acquire sufficient skill of degree without perforation.

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