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Original Article

Risk Factors for Perforation in Endoscopic Treatment for Early Colorectal Cancer: A Nationwide ENTER-K Study

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Background/Aims: Early colorectal cancer (ECC) is commonly resected endoscopically. Perforation is a devastating complication of endoscopic resection. We aimed to identify the characteristics and predictive risk factors for perforation related to endoscopic resection of ECC.

Methods: This nationwide retrospective multicenter study included patients with ECC who underwent endoscopic resection. We investigated the demographics, endoscopic findings at the time of treatment, and histopathological characteristics of the resected specimens. Logistic regression analysis was used to investigate the clinical factors associated with procedure-related perforations. Survival analysis was conducted to assess the impact of perforation on the overall survival of patients with ECC.

Results: This study included 965 participants with a mean age of 63.4 years. The most common endoscopic treatment was conventional endoscopic mucosal resection (n=573, 59.4%), followed by conventional endoscopic submucosal dissection (n=259, 26.8%). Thirty-three patients (3.4%) experienced perforations, most of which were managed endoscopically (n=23/33, 69.7%). Patients who undergo endoscopic submucosal dissection-hybrid and precut endoscopic mucosal resection have a higher risk of perforation than those who undergo conventional endoscopic mucosal resection (odds ratio, 78.65 and 39.72, $p<0.05$). Procedure-related perforations were not associated with patient survival.

Conclusions: Perforation after endoscopic resection had no significant impact on the prognosis of ECC. The type of endoscopic resection was a crucial predictor of perforation. Large-scale prospective studies are needed to further investigate endoscopic resection of ECC. **(Gut Liver 2025;19:95-107)**

Key Words: Colorectal neoplasms; Colonoscopy; Endoscopic mucosal resection; Intestinal perforation; Risk factors

INTRODUCTION

Early colorectal cancer (ECC) is defined as pathologic T1 colorectal cancer in which cancer cell infiltration is limited to the mucosa or submucosa, without distant metastasis, and regardless of regional lymph node involvement.[1] The principle of ECC treatment is to achieve complete cancerous tissue removal.[2,3] Although approximately 10%

of pathologic T1 colorectal cancers may require surgical intervention due to local lymph node involvement,[4,5] most patients with ECC can be effectively treated through endoscopic resection.

Currently, endoscopic resection is the standard initial treatment for ECC without lymph node metastasis. Resection techniques include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Generally, ESD is considered superior to EMR in both *en bloc* and complete resection.[6,7] After resection, vertical resection margin positivity (where cancer cells are observed at the vertical margin) indicates histologically incomplete resection, necessitating additional surgery because of the risk of local recurrence and lymph node metastasis.[8-10] Therefore, the emphasis is on achieving histologically complete resection through *en bloc* resection.[11,12]

The focus on *en bloc* resection for complete histological excision has led to more aggressive endoscopic treatment strategies, potentially increasing procedure-related complications. The types and frequencies of complications, such as bleeding, infection, and sedation-related issues, vary across studies;[13-15] among these, perforation should be avoided by endoscopists. Perforation rates range from approximately 0.8% to 3.0% in EMR and 4.0% to 16.0% in ESD, with a higher frequency observed in ESD.[16-18] Perforation can result in incomplete resection or discontinuation of endoscopic resection. To date, numerous studies have investigated risk factors associated with perforation such as tumor location, endoscopic morphology, and submucosal fibrosis; however, heterogeneity in conclusions due to differences in study population or methodologies,[19-21] along with limitations, such as small sample sizes or single-center designs, exists.[22] Furthermore, very limited data focus on procedure-related perforations following endoscopic treatment of ECC.

This study aimed to investigate the incidence and prognosis of procedure-related perforations during various endoscopic resection procedures for ECC treatment. Additionally, we explored potential risk factors predicting perforation occurrence before endoscopic treatment using a multicenter retrospective cohort study.

MATERIALS AND METHODS

1. Study population

The study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review boards of each participating medical center (approval number: VC18REDI0180). Written informed consent was waived. The ENTER-K (Early colorectal malignant Neoplasm Treated with Endoscopic Resection: Korean cohort study) cohort is a multi-institutional retrospective cohort involving 11 medical centers in the Republic of Korea, targeting 1,858 patients diagnosed with ECC over 12 years (January 2007 to December 2018). The study population included adults (1) aged ≥19 years, (2) who underwent endoscopic resection as the initial ECC treatment, and (3) who had sufficient data for analysis. Patients (1) unable to obtain a complete endoscopic resection, (2) who underwent surgical treatment without prior endoscopic resection, and (3) with insufficient medical records or endoscopic images for the analysis were excluded. Data from 965 patients were analyzed in the study, as shown in Fig. 1.

2. Clinical variable

Baseline characteristics of the study population, including sex, age at the time of the procedure, height, weight, alcohol consumption and smoking status, underlying diseases, and use of antiplatelet or anticoagulant agents were investigated. Preprocedural symptoms were classified into seven categories. Endoscopic reports and images were reviewed to determine the procedure types, size, location, and morphology of ECC, and endoscopic *en bloc* or complete resection. Additionally, the final pathological diagnosis, cancer lesion size, invasion depth and resected margin involvement were investigated. In addition to measurements of invasion depth, the Haggitt classification was also employed for assessing the extent of invasion. In this classification, Haggitt 0 refers to lesions where the invasion is restricted to the mucosa. Haggitt 1 refers to cases where the invasion has reached the submucosal layer but is confined to the polyp head. Haggitt 2 and 3 indicate that the cancer has invaded the neck and stalk of the polyp, respectively. Lastly, Haggitt 4 is defined by invasion that surpasses the stalk of the polyp, yet does not extend beyond the muscularis propria.[23] Deep submucosal invasion was defined as SM2, SM3, or Haggitt level 4 in the pathology reports.[4,24] The presence of lymphovascular or perineural invasion, as well as tumor budding, was determined based on the description in the pathology reports.

3. Types of endoscopic resection

The seven major categories of ECC treatment were conventional EMR, EMR with a cap, EMR with ligation, precut EMR, endoscopic piecemeal mucosal resection, ESD-hybrid, and conventional ESD. Conventional EMR involves submucosally injecting a solution (e.g., normal saline mixed with indigo carmine) lift the lesion. Subsequently, the protruded lesion is captured using an endoscopic snare, followed by excision using mechanical stress or diathermic current.[25,26] EMR with a cap involves applying a

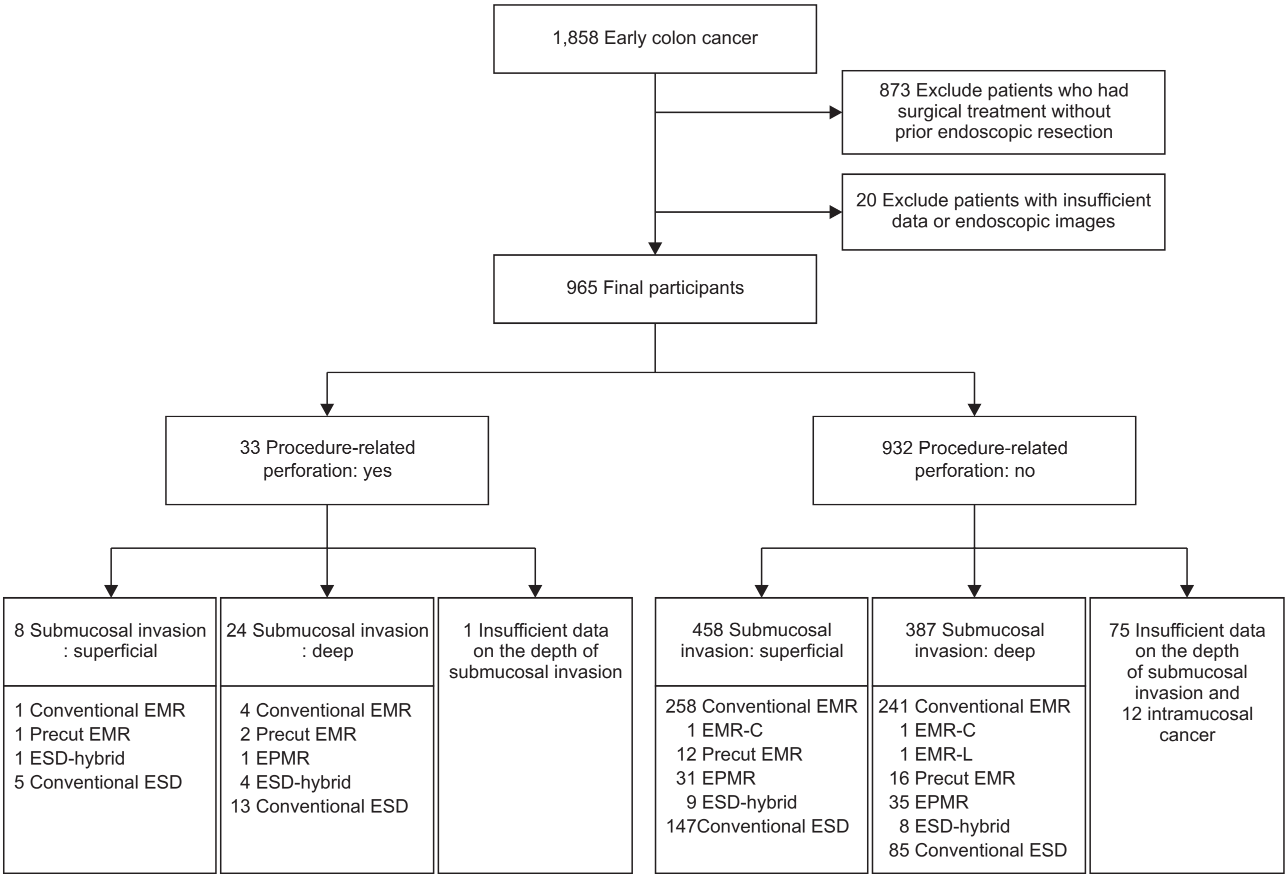


Fig. 1. The composition of the study population. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EPMR, endoscopic piecemeal mucosal resection; EMR-C, EMR with a cap; EMR-L, EMR with ligation.

transparent cap onto the scope during conventional EMR, whereas EMR with ligation entails submucosal injection followed by aspirating the lesion and ligating it using an elastic band.[27] Precut EMR is similar to conventional EMR but incorporates a circumferential incision before snaring.[28] Endoscopic piecemeal mucosal resection is an alternative method for achieving complete resection for large or flat lesions through multiple partial removal sessions.[29] Conventional ESD involves submucosal injection, precutting and submucosal dissection with electrosurgical knives, whereas ESD-hybrid represents a compromise between EMR and ESD by partial dissection of the submucosa and snaring of the remaining lesion for resection.[30]

4. Procedure-related perforation

Procedure-related perforations were categorized based on recognition timing during, within 6 hours after, or more than 6 hours after the procedure. In cases where perforations were identified after the procedure, the time taken for detection was determined by referencing medical records and endoscopic images. Additionally, we investigated detection methods and treatment approaches. The characteristics of the participants according to the presence of procedure-related perforation, factors related to the perforation occurrence, and the impact of perforation on overall survival were analyzed.

5. Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared using the Student t-test or Wilcoxon Mann-Whitney U test, whereas categorical variables were compared using the chi-square test or Fisher exact test. To explore variables related to the incidence of perforation, a univariate logistic regression analysis for each variable was performed, and a variable with a p-value <0.2 was selected for multivariate analysis. The final model of multivariate analysis was fitted using stepwise selection. Data from patients with missing values for the variables included in the model were not included in the multivariate analysis. The impact of each variable on procedure-related perforations is represented by odds ratios. The overall survival results were presented using a Kaplan-Meier plot, and potential differences in the survival period between the two groups were analyzed using the log-rank test. Statistical significance was set at p<0.05. All data analyses were conducted using R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Characteristics of the study patients

Detailed information on the demographic characteristics, medical histories, and medication histories of the patients is provided in Table 1. The mean age of the patients was 63.4 years, with 63.6% of them were females. Among the patients diagnosed with ECC, 364 (37.7%) presented with at least one symptom, most commonly hematochezia, followed by abdominal discomfort and pain, and positive findings on fecal occult blood test (Supplementary Table 1). Few patients exhibited symptoms of anemia or weight loss.

2. Endoscopic treatment for early colon cancer

Table 2 presents endoscopic findings and characteristics of the patients who underwent endoscopic resection. Of the study population, 686 (71.1%) underwent planned endoscopic resection after ECC was suspected or confirmed through diagnostic colonoscopy. The most commonly

Table 1. Baseline Characteristics of the Study Population

Characteristic	Total (n=965)
Age, yr	63.4±9.7
Male sex	351 (36.4)
Height, cm	162.6±8.6
Weight, kg	64.7±11.1
Body mass index, kg/m^2 (n=933)	24.4±3.4
<18.5	31 (3.3)
18.5 to <23.0	278 (29.8)
23.0 to <25.0	251 (26.9)
25.0 to <30.0	320 (34.2)
≥30.0	53 (5.7)
Alcohol consumption	
None	606 (62.8)
Social drinker	231 (23.9)
Heavy drinker	128 (13.3)
Smoking history	
Never smoker	665 (68.9)
Ex-smoker	144 (14.9)
Current smoker	156 (16.2)
Concomitant diseases	
Cardiovascular	118 (12.2)
Cerebrovascular	7 (0.7)
Hypertension	410 (42.5)
Diabetes	178 (18.4)
Dyslipidemia	63 (6.5)
Malignancy	103 (10.7)
Chronic renal disease	18 (1.9)
Chronic liver disease	39 (4.0)
ASA classification	
I	286 (29.6)
II	537 (55.6)
More than III	142 (14.7)
Antiplatelets/Anticoagulants	
Antiplatelets	176 (18.2)
Anticoagulants	18 (1.9)
Family history of colorectal cancer	44 (4.6)
History of colorectal polyps	93 (9.6)
CEA level before the treatment, ng/mL	2.2±2.2

Data are presented as mean±SD or number (%).
ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen.

Table 2. Endoscopic and Pathologic Characteristics of the Study Population

Variable	Total (n=965)
Endoscopic features	
Diagnostic colonoscopy before the treatment	686 (71.1)
Imaging modalities for the early colon cancer: yes	907 (94.0)
CT scan	894 (92.6)
PET CT	19 (2.0)
MRI	7 (0.7)
Ultrasound	5 (0.5)
Type of procedure	
Conventional EMR	573 (59.4)
EMR-C	2 (0.2)
EMR-L	1 (0.1)
Precut EMR	34 (3.5)
EPMR (piecemeal)	72 (7.5)
ESD-hybrid	24 (2.5)
Conventional ESD	259 (26.8)
Work experience of the operator, yr	9.2±8.0
Endoscopic size of the lesion, mm	19.9±11.0
Conventional EMR	15.8±6.7
EMR-C	11.0±1.4
EMR-L	40.0±NA
Precut EMR	20.0±7.9
EPMR (piecemeal)	26.6±11.8
ESD-hybrid	25.6±7.6
Conventional ESD	26.0±13.2
Location of the lesion*	
Right colon	262 (27.2)
Left colon	457 (47.4)
Rectum	246 (25.4)
Paris classification (n=672)†	
IIa	45 (6.7)
Is	287 (42.7)
Isp	152 (22.6)
Ip	181 (26.9)
IIb, IIc or III	7 (1.0)
LST (n=285)‡	
LST-G-H	59 (6.2)
LST-G-MX	94 (9.8)
LST-NG-F	79 (8.3)
LST-NG-PD	53 (5.5)
En bloc resection	828 (85.8)
Complete resection (endoscopic)	901 (93.4)

Table 2. Continued

Variable	Total (n=965)
Pathologic features	
Pathology of the lesions	
Adenocarcinoma.	
Well differentiated	406 (42.1)
Moderate differentiated	536 (55.5)
Poorly differentiated	18 (1.9)
Mucinous adenocarcinoma	1 (0.1)
Micropapillary adenocarcinoma	1 (0.1)
Signet ring cell carcinoma	2 (0.2)
Neuroendocrine carcinoma	1 (0.1)
Pathologic size of the lesion (mm)	16.0±10.5
SM invasion, μm (n=877)	1,486±1,405
SM invasion group[§]	
Deep	411 (46.9)
Superficial	466 (53.1)
Haggitt level (n=36)	
Level 1	10 (27.8)
Level 2	9 (25.0)
Level 3	12 (33.3)
Level 4	5 (13.9)
Complete resection (pathologic)[ll]	626 (64.9)
Cancer lateral margin involvement	111 (11.5)
Cancer vertical margin involvement	123 (12.7)
Lymphovascular invasion	116 (12.0)
Perineural invasion	3 (0.3)
Tumor budding	144 (14.9)

Data are presented as number (%) or mean±SD.
CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; EMR, endoscopic mucosal resection; EMR-C, EMR with a cap; EMR-L, EMR with ligation; EPMR, endoscopic piecemeal mucosal resection; ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; LST-G-H, LST-granular-homogenous; LST-G-MX, LST-granoular-nodular mixed; LST-NG-F, LST-nongranular-flat elevated; LST-NG-PD, LST-nongranular-pseudodepressed; SM, submucosal.
*Right colon, from cecum to splenic flexure; Left colon, descending and sigmoid colon; [†]Lesions less than 10 mm; [‡]Lesions 10 mm or over; [§]Deep SM invasion: SM2-3 or Haggitt level 4; [ll]Not invaded by cancer or invasion of adenomatous tissue.

performed endoscopic resection technique for ECC was conventional EMR performed in 573 patients (59.4%), followed by conventional ESD in 259 patients (26.8%). The mean work experience of endoscopists was 9.2 years. The mean endoscopic size of the lesions was 19.9±11.0 mm, with the lesions most frequently located in the left colon (n=457, 47.4%). *En bloc* resection was performed in 828 patients (85.8%), and 93.4% was achieved complete resection in endoscopic evaluation.

3. Pathological findings of early colon cancer specimens

Most patients had well-to-moderately differentiated tumors, with a pathological mean size of 16.0±10.5 mm, which is smaller than visual measurement on colonoscopy.

Table 3. Characteristics of Perforated Cases

Variable	Total (n=965)
Perforation	33 (3.4)
Time of perforation detection	
Within 6 hr	18 (54.5)
After 6 hr	2 (6.1)
During the procedure	13 (39.4)
Confirmation of perforation	
Endoscopic	24 (84.8)
Imaging study	9 (15.2)
Combined bleeding	14 (42.4)
During the procedure	14 (100)
After the procedure	0
Treatment of perforation	
Conservative treatment	6 (18.2)
Endoscopic treatment	23 (69.7)
Surgery	4 (12.1)

Data are presented as number (%).

Approximately half of patients showed submucosal invasion depth of <1,000 μm. Pathologic complete resection was achieved in 626 patients (64.9%). Other pathological characteristics of the study population are presented in Table 2.

4. Procedure-related perforation

Thirty-three patients (3.4%) experienced procedure-related perforation (Table 3). Fifty-four point five percent of perforations were detected within 6 hours after the procedure, whereas 39.4% was identified during the procedure. Endoscopic confirmation of the perforation was possible in 84.8%. Site bleeding accompanying the perforation was noted in 14 (42.4%). Endoscopic treatment was performed in 23 patients (69.7%), and six (18.2%) recovered solely with conservative treatment. Surgery was required for four patients (12.1%): in three patients, perforation was detected on an abdominal X-ray performed within 6 hours after endoscopic resection, and surgery was immediately performed. One patient required surgery after an unsuccessful endoscopic closure. No immediate fatality after the perforation was noted.

5. Factors related to procedure-related perforation

The study population was categorized into the perforated and non-perforated groups, and demographic, endoscopic, and pathological variables were compared (Table 4, Supplementary Table 2). No significant differences in age, sex, body mass index, or medical history were observed. The proportion of receiving antiplatelet or anticoagulant medications was also comparable between two groups. The group with perforations had significantly more patients who underwent diagnostic colonoscopy before the planned resection (90.9% vs 70.4%, p=0.018). The perfo-

Table 4. Differences in Clinical Characteristics Depending on the Occurrence of Procedure-Related Perforation

Variable	No perforation (n=932)	Perforation (n=33)	p-value
Age, yr	63.4±9.8	63.2±9.7	0.934
Male sex	595 (63.8)	19 (57.6)	0.582
Body mass index, kg/m^2	24.5±3.4	23.8±2.8	0.299
Concomitant diseases			
Cardiovascular	113 (12.1)	5 (15.2)	0.802
Cerebrovascular	7 (0.8)	0	1.000
Hypertension	398 (42.7)	12 (36.4)	0.586
Diabetes	173 (18.6)	5 (15.2)	0.789
Dyslipidemia	62 (6.7)	1 (3.0)	0.639
Malignancy	100 (10.7)	3 (9.1)	0.990
Chronic renal disease	18 (1.9)	0	0.880
Chronic liver disease	37 (4.0)	2 (6.1)	0.881
Antiplatelets or anticoagulants	188 (20.1)	6 (18.2)	0.931
Diagnostic colonoscopy before procedure	656 (70.4)	30 (90.9)	0.018
Type of procedure			<0.001
Conventional EMR	568 (60.9)	5 (15.2)	
EMR-C	2 (0.2)	0	
EMR-L	1 (0.1)	0	
Precut EMR	31 (3.3)	3 (9.1)	
EPMR (piecemeal)	71 (7.6)	1 (3.0)	
ESD-hybrid	19 (2.0)	5 (15.2)	
Conventional ESD	240 (25.8)	19 (57.6)	
Work experience of the operator, yr	9.3±8.0	5.5±5.7	0.071
En bloc resection	801 (85.9)	27 (81.8)	0.679
Complete resection (endoscopic)	873 (93.8)	28 (84.8)	0.093
Endoscopic size, mm	19.6±10.7	28.1±15.4	0.004
Endoscopic morphology*			<0.001
Protruded	609 (65.3)	11 (33.3)	
Flat	58 (6.2)	2 (6.1)	
LST	265 (28.4)	20 (60.6)	
LST-G-H	56 (6.0)	3 (9.1)	
LST-G-MX	82 (8.8)	12 (36.4)	
LST-NG-F	76 (8.1)	3 (9.1)	
LST-NG-PD	51 (5.5)	2 (6.0)	
Location of the lesion†			0.827
Right colon	252 (27.0)	10 (30.3)	
Left colon	441 (47.3)	16 (48.5)	
Rectum	239 (25.6)	7 (21.2)	
Pathologic size, mm	15.8±10.2	23.8±13.4	0.002
SM invasion group (n=877)‡			0.002
Deep	387 (45.8)	24 (75.0)	
Superficial	458 (54.2)	8 (25.0)	
Complete resection (pathologic)†	613 (65.8)	13 (40.6)	0.001
Cancer involved lateral margin	100 (10.7)	11 (33.3)	<0.001
Cancer involved vertical margin	115 (12.3)	8 (24.2)	0.080

Data are presented as mean±SD or number (%).

EMR, endoscopic mucosal resection; EMR-C, EMR with a cap; EMR-L, EMR with ligation; EPMR, endoscopic piecemeal mucosal resection; ESD, endoscopic submucosal dissection; LST, laterally spreading tumor; LST-G-H, LST-granular-homogenous; LST-G-MX, LST-granoular-nodular mixed; LST-NG-F, LST-nongranular-flat elevated; LST-NG-PD, LST-nongranular-pseudodepressed; SM, submucosal.

*Protruded, Paris classification Ip, Isp or Is; Flat, Paris classification II or III; †Right colon, from cecum to splenic flexure; Left colon, descending and sigmoid colon; ‡Deep SM invasion: SM2-3 or Haggitt level 4.

rated group had a higher rate of precut EMR (n=3 [9.1%] vs n=31 [3.3%]), ESD-hybrid (n=5 [15.2%] vs n=19 [2.0%]), and conventional ESD (n=19 [57.6%] vs n=240 [25.8%]), whereas conventional EMR was performed frequently in the non-perforated group (n=5 [15.2%] vs n=568 [60.9%]). Operators in the perforated group had less experience than those in the non-perforated group, although this difference was not statistically significant (p=0.071). When categoriz-

Table 5. Details Regarding the Work Experience of the Operator

Years of experience	Work experience of the operator (n=463)	No perforation (n=448)	Perforation (n=15)	p-value
Experience, yr	9.2±8.0	9.3±8.0	5.5±5.7	0.071
≤5 yr	228 (49.2)	217 (48.4)	11 (73.3)	0.351
>5 to 10 yr	73 (15.8)	71 (15.8)	2 (13.3)	
>10 to 15 yr	60 (13.0)	60 (13.4)	0	
>15 to 20 yr	51 (11.0)	50 (11.2)	1 (6.7)	
>20 yr	51 (11.0)	50 (11.2)	1 (6.7)	
>7 yr of experience	198 (42.8)	196 (43.8)	2 (13.3)	0.038

Data are presented as mean±SD or number (%).

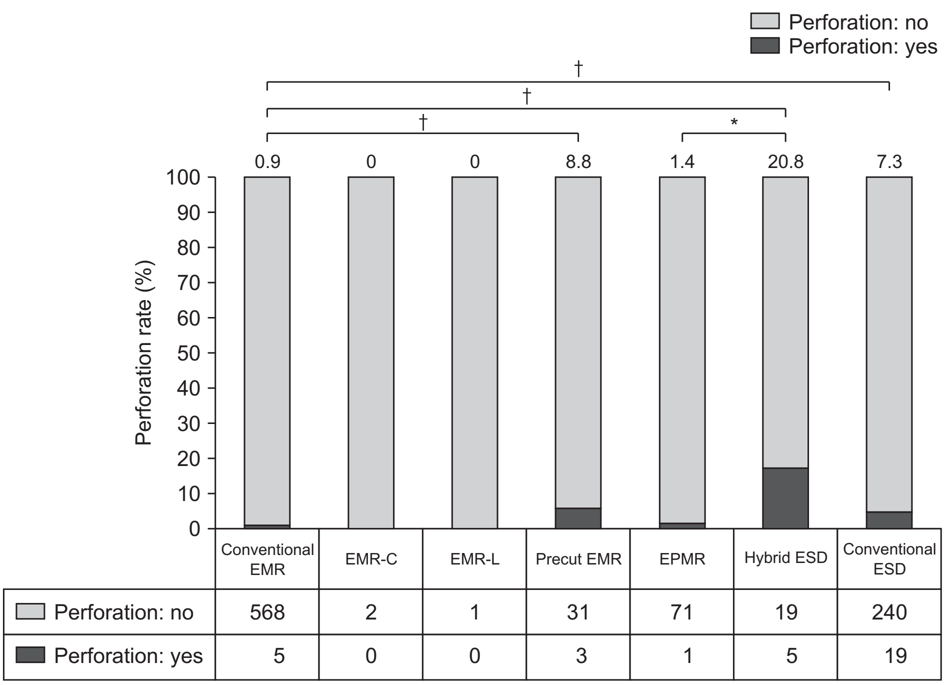


Fig. 2. Incidence of procedure-related perforation according to endoscopic treatment methods for early colorectal cancer. EMR, endoscopic mucosal resection; EMR-C, EMR with a cap; EMR-L, EMR with ligation; EPMR, endoscopic piecemeal mucosal resection; ESD, endoscopic submucosal dissection; *p<0.05, †p<0.01 in *post hoc* analysis.

ing work experience in 5-year intervals, the proportion of operators with 5 years or less of experience was higher in the perforated group, while the proportion with more than 10 years of experience was higher in the non-perforated group (Table 5). Notably, the proportion of operators with more than 7 years of experience was significantly higher in the non-perforated group (p=0.038).

The endoscopic size of lesions was larger in the perforated group (28.1±15.4 mm vs 19.6±10.7 mm, p=0.004). The proportion of laterally spreading tumors was higher in the perforated group (60.6% vs 28.4%, p<0.001). Pathological lesion size was also larger in the perforated group (23.8±13.4 mm vs 15.8±10.2 mm, p=0.002), with a higher proportion of deep submucosal invasion (n=24 [27.0%] vs n=387 [45.8%], p=0.002). The rate of complete pathological resection was lower in the perforation group (40.6% vs 65.8%, p=0.001). Recurrences, metastases, and metachronous cancers did not differ in both groups during the follow-up.

The incidences of procedure-related perforations among endoscopic resection methods are illustrated in Fig. 2. The most common method linked to perforation was hybrid ESD (5/24, 20.8%), followed by precut EMR (3/34, 8.8%) and conventional ESD (19/259, 7.3%). In the *post hoc* analysis, precut EMR, hybrid ESD, and conventional ESD exhibited higher rates of perforation compared to conventional EMR. Conventional ESD had similar perforation rates to other resection methods, except for conventional EMR.

The results of logistic regression analyses for the occurrence of perforation are presented in Table 6. The type of resection was categorized into five groups, combining conventional EMR, EMR with ligation, and EMR with a cap into an “EMR” group. The final multivariate model incorporated three variables: the type of resection, deep submucosal invasion, and operator’s working years. The group with deep submucosal invasion showed an odds ratio of approximately 5.71 compared to the superficial

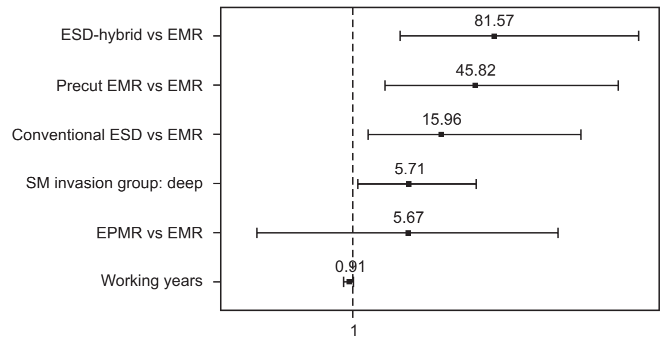
Table 6. Logistic Regression Analysis of the Occurrence of Procedure-Related Perforation

Variable	Univariate model (n=965)			Multivariate model (n=417)			Final model (n=417)		
	Estimate	OR (95% CI)	p-value	Estimate	OR (95% CI)	p-value	Estimate	OR (95% CI)	p-value
Age	−0.002	1.00 (0.96–1.04)	0.93						
Sex: male	0.263	1.30 (0.63–2.61)	0.46						
Body mass index	−0.057	0.94 (0.85–1.05)	0.30						
Hypertension: yes	−0.266	0.77 (0.36–1.55)	0.47						
Diabetes: yes	−0.244	0.78 (0.26–1.89)	0.62						
Working years	−0.085	0.92 (0.82–1.00)	0.09	−0.102	0.90 (0.79–1.00)	0.06	−0.098	0.91 (0.80–1.00)	0.05
Type of procedures*									
Precut EMR	2.403	11.05 (2.19–47.17)	<0.01	3.701	40.47 (4.36–895.36)	<0.01	3.825	45.82 (5.27–983.20)	<0.01
EPMR (piecemeal)	0.475	1.61 (0.08–10.16)	0.68	1.585	4.88 (0.18–135.07)	0.19	1.736	5.67 (0.22–148.59)	0.23
ESD-hybrid	3.403	30.05 (7.78–116.90)	<0.01	4.237	69.21 (6.59–1,662)	<0.01	4.401	81.57 (8.63–1,861)	<0.01
Conventional ESD	2.202	9.04 (3.59–27.52)	<0.01	2.608	13.57 (1.84–278.17)	0.01	2.770	15.96 (2.62–306.20)	0.01
Endoscopic size	0.048	1.04 (1.03–1.07)	<0.01	0.005	1.00 (0.95–1.05)	0.92			
Location of the lesion†									
Left colon	−0.090	0.91 (0.41–2.11)	0.83						
Rectum	−0.304	0.74 (0.26–1.95)	0.54						
Flat lesion vs protruded‡	0.647	1.91 (0.29–7.33)	0.41						
Laterally spreading tumor	1.354	3.87 (1.92–8.09)	<0.01	0.275	1.32 (0.39–4.51)	0.93			
Pathologic type§									
Adenocarcinoma, moderately differentiated	0.103	1.11 (0.55–2.32)	0.78						
Adenocarcinoma, poorly differentiated	0.573	1.77 (0.09–9.74)	0.59						
SM invasion group: deep‖	1.430	3.55 (1.64–8.52)	<0.01	1.770	5.87 (1.69–27.52)	0.01	1.742	5.71 (1.65–26.57)	0.01

Data from patients with missing values for the variables included in the model were excluded in the multivariate analysis, resulting in a final dataset of 417 patients for the analysis. The results are expressed as mean±SD or number (%).

OR, odds ratio; CI, confidence interval; EMR, endoscopic mucosal resection; EPMR, endoscopic piecemeal mucosal resection; ESD, endoscopic submucosal dissection; SM, submucosal.

*Compare each procedure type with the EMR group; †Compare with the location of right colon; ‡Flat lesion, Paris classification IIa, IIb, IIc or III; Protruded lesion, Paris classification Is, Isp, or Ip; §Compare with adenocarcinoma, well differentiated; ‖Deep SM invasion: SM2-3 or Haggitt level 4.



Variables	Estimate	SE	p-value	OR	Lower CI	Upper CI
ESD-hybrid vs EMR	4.4014	1.2538	<0.001	81.57	8.63	1,860.58
Precut EMR vs EMR	3.8247	1.2067	0.002	45.82	5.27	983.20
Conventional ESD vs EMR	2.7698	1.0952	0.011	15.96	2.62	306.20
SM invasion group: deep	1.7419	0.6855	0.011	5.71	1.65	26.57
EPMR vs EMR	1.7357	1.4409	0.228	5.67	0.22	148.59
Working years	−0.0981	0.0577	0.050	0.91	0.80	1.00

Fig. 3. Multivariate logistic regression analysis of factors associated with procedure-related perforation occurrence. ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; SM, submucosal; EPMR, endoscopic piecemeal mucosal resection; SE, standard error; OR, odds ration; CI, confidence interval.

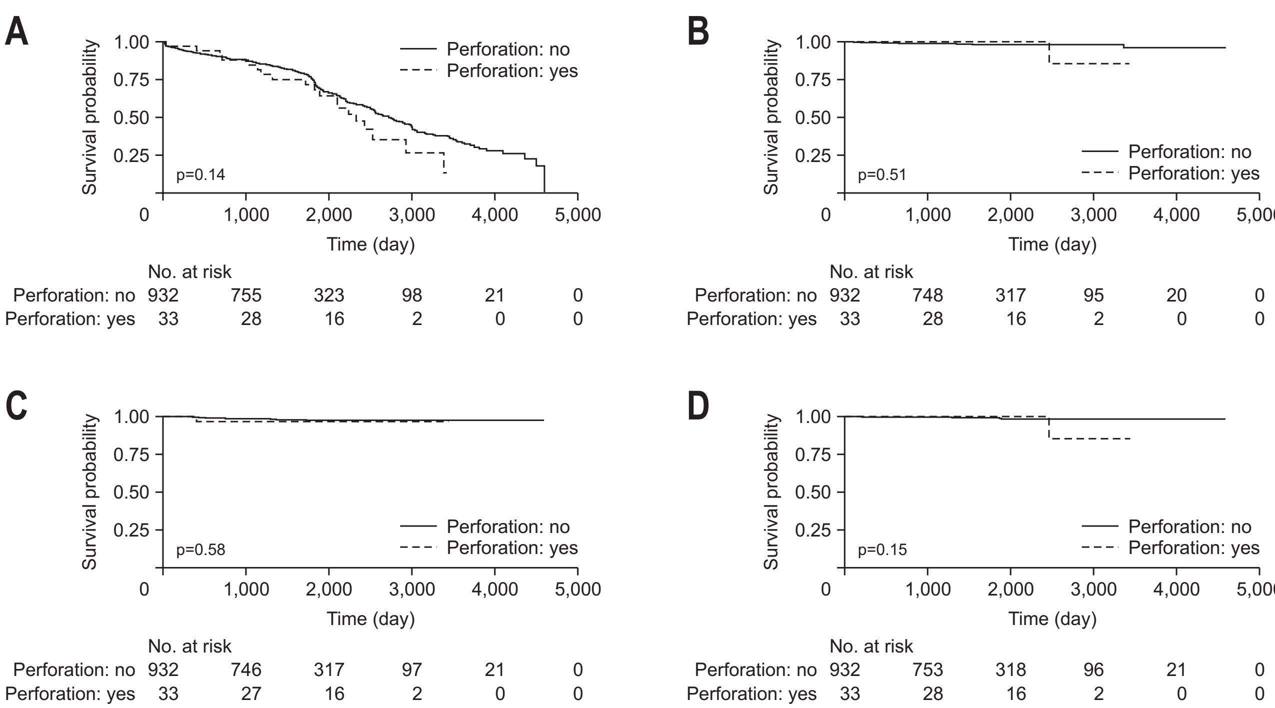


Fig. 4. Kaplan-Meier plots of the study population stratified by the presence of procedure-related perforation, (A) overall survival, (B) local recurrence, (C) distant metastasis, and (D) metachronous colorectal cancer.

invasion group (p=0.011). As the operator gained more experience, the risk of perforation during the procedure showed decreasing tendency (odds ratio, 0.91; 95% confidence interval, 0.80 to 1.00; p=0.054). The ESD-hybrid group showed the highest risk of perforation, followed by the precut EMR and ESD groups. Fig. 3 shows a summary of the final model.

6. Procedure-related perforation and prognosis

During the study period, there were a total of 27 deaths. The median follow-up period for the study population was 1,819 days. The occurrence of procedure-related perforations did not significantly affect the four prognostic outcomes: overall survival, local recurrence, distant recurrence, and metachronous colorectal cancer (Fig. 4). In perforated patients, age, sex, body mass index, methods for perforation confirmation, treatment modalities, and pres-

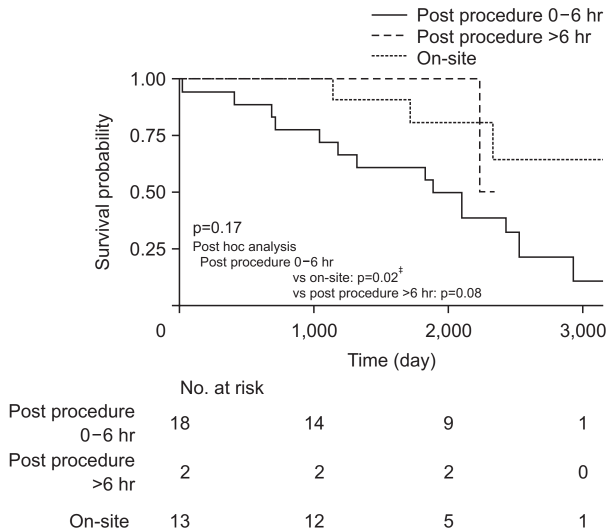


Fig. 5. Subgroup survival analysis for overall survival based on the timing of procedure-related perforation confirmation in perforated patients (*p<0.05).

ence of combined bleeding did not affect overall survival (Supplementary Fig. 1). No significant differences were also observed in the three-group comparison of the timing of perforation confirmation. However, *post hoc* analysis revealed a lower overall survival in the group where perforation was detected within 6 hours after the procedure compared to the on-site detection group (Fig. 5). Among the total deaths, there were five ECC-related deaths. There was no significant difference in disease-specific survival according to the occurrence of perforation (p=0.661) (Supplementary Fig. 2).

DISCUSSION

In this study, we assessed characteristics of procedure-related perforations during endoscopic treatment of ECC. The perforation rate of endoscopic resection for ECC is 3.4% in our study, which can be considered a favorable treatment outcome compared to previous literatures. Notably, traditionally recognized factors, such as lesion size, depth of invasion, and type of resection, were significantly associated with perforation, whereas variables reflecting preoperative conditions, such as age, sex, and comorbidities, did not exhibit a substantial association. The type of resection, deep submucosal invasion, and operators' work experience were significant variables in predicting the occurrence of perforation, with the relative importance of lesion size diminishing in the multivariate analysis.

ESD-hybrid offers the advantages of shorter procedure time, simpler procedure, and lower difficulty level compared to conventional ESD.[31] The reported incidence of procedure-related complications with ESD-hybrid is inconsistent, with some opinions suggesting a lower risk of complications, whereas others reporting similar rates of bleeding and perforation.[30,32] In our study, the perforation risk of ESD-hybrid group exceeded that of conventional ESD group. This may be attributed to inadequate submucosal dissection before snaring or inaccurate snaring along the precutting margin, resulting in excessive tissue capture and subsequent muscle layer injury. Deep submucosal invasion could be another reason for higher perforation risk of ESD-hybrid. Among patients who experienced perforation following ESD-hybrid, four (80%) had deep submucosal invasion, suggesting that ESD-hybrid may not be an optimal resection method for lesions with suspicious deep invasion.

Although not statistically significant, the perforated patients had less operator's working experience compared to non-perforated patients (5.5 years vs 9.3 years, p=0.071). Furthermore, endoscopists with more than 7 years of experience performed safer procedures with fewer perforations compared to those with less experience. These findings highlight the importance of experience and skill for safe endoscopic resection of ECC. There are previous studies indicating a close relationship between endoscopists' experiences and the complication occurrence. A recent cohort study reported significantly higher rates of muscularis propria damage and perforation following colorectal ESD in trainee groups compared to experts.[33] A meta-analysis for risk factors of perforation during colorectal ESD suggested that the risk is approximately 1.6 times higher among lesser experienced endoscopists.[22] Lesions suspected to be ECC typically require a more aggressive treatment approach than common adenomas, resulting in an increased risk of complications including perforation. Therefore, in future studies, proposing the optimal timing along the learning curve for safe endoscopic procedures of ECCs with minimizing complications appears to be a promising research topic.

The rate of perforation was higher in cases of deep submucosal invasion in our data, making dissection difficult and increasing perforation risk.[34,35] Contrary to these findings, free vertical resection margin from cancer was not significantly associated with perforation; rather, free lateral resection margin was fewer in the perforated group compared to non-perforation group. This can be attributed to several factors. First, a large lesion leads to an expanded resection burden, increasing the perforation risk and incomplete resection. Second, the endoscopist may no longer aim for complete resection due to the perforation and subsequent treatments such as endoscopic clipping. Third, perforation may be a byproduct of aggressive dissection for complete resection, rather than being directly associated with lateral margin positivity itself.

Non-perforated patients had a lower rate of diagnostic endoscopy before endoscopic resection compared to perforated patients (70.4% vs 90.9%, p<0.018). When ECC lesions were incidentally discovered during routine colonoscopy and excision is attempted on-site, there may be a preference for less invasive resection method compared to planned treatments. This preference was supported by the fact that EMR-based procedures were more commonly performed in patients who underwent on-site resection during diagnostic colonoscopy, rather than in therapeutic endoscopy cases of ECCs. In fact, the rate of prior diagnostic endoscopy in the EMR group is 59.4%, which is lower compared to 76.5%–91.9% in other treatment groups.

Procedure-related perforations did not have a significant impact on prognosis of ECC patients after the endoscopic resection. However, in the subgroup analysis for perforated patients, on-site identified group showed better overall survival compared to the group identified within 6 hours after the procedure. Delayed detection of perforation can lead to increased peritoneal contamination, infection, and a higher risk of surgical management and postoperative complications.[36-38] On-site identification of perforation allows for subsequent endoscopic closure, and if necessary, facilitates fast referral to a surgeon.[39] Surprisingly, perforated patients identified 6 hours post-procedure did not show inferior prognosis compared to other groups. This contradiction can be attributed to the rarity of cases in our study (2/33, 6.1%), leading to a lack of survival events during follow-up.

One strength of this study is the access to a large-scale cohort database derived from multiple referral hospitals, covering demographics, medical conditions, endoscopic and pathologic findings, and prognosis. Additionally, we investigated the risk of procedure-related perforation associated with various types of endoscopic resection currently used in clinical practice for treating ECC. However, our study also has limitations. Firstly, despite efforts to obtain as refined data as possible, this retrospective study analyzed data from 10 healthcare institutions over 12 years, resulting in inevitable heterogeneity within the cohort. Secondly, procedural details such as indications and techniques of each resection type, accessories or equipment could not be obtained from the cohort data. Future studies are needed to provide a clearer understanding of the impact of technical or equipment-related variables on the complications of endoscopic resection. Thirdly, we only evaluated overall survival as a general prognostic outcome; other clinical outcomes, such as hospital stay days, were unavailable. While several studies have reported prolonged hospital stays following perforations after endoscopic resection,[40-42] future research related to procedure-related perforation should assess indicators that consider the health and economic burdens as well as patient survival. Fourthly, we were unable to analyze the impact of submucosal invasion depth or fibrosis on the occurrence of perforations due to the lack of relevant data. To date, efforts have been made to evaluate the depth of submucosal invasion using endoscopic findings, combined with advanced techniques such as chromoendoscopy and image-enhanced endoscopy. Submucosal fibrosis has also been addressed as a crucial factor in previous literature on perforations during endoscopic resection. Future researchers should consider these variables as an important candidate predictor for procedure-related perforation. Lastly, we adopted SM2 and SM3 as the definition for deep submucosal invasion due to the limitations of our dataset, instead of the threshold of 1,000 micrometers typically applied in non-pedunculated polyps.

In conclusion, procedure-related perforations during endoscopic resection rarely occur and do not affect the prognosis, underscoring the safety as a modality for ECC treatment. The type of resection was the most critical factor in predicting the risk of perforation. Large-scale prospective studies for predicting the risk of complications of endoscopic resection will be needed to achieve safer and more effective treatment for ECC.

CONFLICTS OF INTEREST

H.J.L. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: I.H.J., H.G.K., Y.S.C. Data acquisition: I.H.J., H.G.K., Y.S.C., H.J.L., E.R.K., Y.J.L., S.W.H., K.O.K., J.L., H.S.C., Y.J., C.M.M. Data analysis and interpretation: I.H.J., H.G.K., Y.S.C. Drafting of the manuscript:

I.H.J. Critical revision of the manuscript: H.G.K., Y.S.C. All authors approved the final submission.

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SUPPLEMENTARY MATERIALS

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REFERENCES

1. Kashida H, Kudo SE. Early colorectal cancer: concept, diagnosis, and management. Int J Clin Oncol 2006;11:1-8.
2. Buccafusca G, Proserpio I, Tralongo AC, Rametta Giuliano S, Tralongo P. Early colorectal cancer: diagnosis, treatment and survivorship care. Crit Rev Oncol Hematol 2019;136:20-30.
3. Park CH, Yang DH, Kim JW, et al. Clinical practice guideline for endoscopic resection of early gastrointestinal cancer. Clin Endosc 2020;53:142-166.
4. Ichimasa K, Kudo SE, Miyachi H, Kouyama Y, Misawa M, Mori Y. Risk stratification of T1 colorectal cancer metastasis to lymph nodes: current status and perspective. Gut Liver 2021;15:818-826.
5. Fujino S, Miyoshi N, Kitakaze M, et al. Lymph node metastasis in T1 colorectal cancer: risk factors and prediction model. Oncol Lett 2023;25:191.
6. Fujiya M, Tanaka K, Dokoshi T, et al. Efficacy and adverse events of EMR and endoscopic submucosal dissection for the treatment of colon neoplasms: a meta-analysis of studies comparing EMR and endoscopic submucosal dissection. Gastrointest Endosc 2015;81:583-595.
7. Arezzo A, Passera R, Marchese N, Galloro G, Manta R, Cirocchi R. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. United European Gastroenterol J 2016;4:18-29.
8. Park J, Kim HG, Jeong SO, et al. Clinical outcomes of positive resection margin after endoscopic mucosal resection of early colon cancers. Intest Res 2019;17:516-526.
9. Nishimura T, Oka S, Kamigaichi Y, et al. Vertical tumor margin of endoscopic resection for T1 colorectal carcinoma affects the prognosis of patients undergoing additional surgery. Surg Endosc 2022;36:5970-5978.
10. Zaffalon D, Daca-Alvarez M, Saez de Gordoa K, Pellisé M. Dilemmas in the clinical management of pT1 colorectal cancer. Cancers (Basel) 2023;15:3511.
11. Fuccio L, Repici A, Hassan C, et al. Why attempt en bloc resection of non-pedunculated colorectal adenomas? A systematic review of the prevalence of superficial submucosal invasive cancer after endoscopic submucosal dissection. Gut 2018;67:1464-1474.
12. Zhang QW, Dai ZH, Wang XY, Gao YJ, Ge ZZ, Li XB. Influence of early colorectal cancer component on the positive margins after endoscopic resection: a retrospective study. BMC Cancer 2022;22:120.
13. Saito I, Tsuji Y, Sakaguchi Y, et al. Complications related to gastric endoscopic submucosal dissection and their managements. Clin Endosc 2014;47:398-403.
14. Ferlitsch M, Moss A, Hassan C, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017;49:270-297.
15. Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: current developments. World J Gastroenterol 2019;25:300-307.
16. Burgess NG, Bassan MS, McLeod D, Williams SJ, Byth K, Bourke MJ. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. Gut 2017;66:1779-1789.
17. Keihanian T, Othman MO. Colorectal endoscopic submucosal dissection: an update on best practice. Clin Exp Gastroenterol 2021;14:317-330.
18. Yoshida N, Yagi N, Naito Y, Yoshikawa T. Safe procedure in endoscopic submucosal dissection for colorectal tumors focused on preventing complications. World J Gastroenterol 2010;16:1688-1695.
19. Hong JY, Kweon SS, Lee J, et al. Risk factors for procedure-related complications after endoscopic resection of colorectal laterally spreading tumors. Medicine (Baltimore) 2018;97:e12589.
20. Yang CW, Hung HJ, Chen PJ. Risk factors for perforation during colorectal endoscopic submucosal dissection. Adv Dig Med 2023;10:206-214.
21. Lee EJ, Lee JB, Choi YS, et al. Clinical risk factors for perforation during endoscopic submucosal dissection (ESD) for

large-sized, nonpedunculated colorectal tumors. Surg Endosc 2012;26:1587-1594.
22. Santos JB, Nobre MR, Oliveira CZ, et al. Risk factors for adverse events of colorectal endoscopic submucosal dissection: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2021;33:e33-e41.
23. Bujanda L, Cosme A, Gil I, Arenas-Mirave JI. Malignant colorectal polyps. World J Gastroenterol 2010;16:3103-3111.
24. Saraiva S, Rosa I, Fonseca R, Pereira AD. Colorectal malignant polyps: a modern approach. Ann Gastroenterol 2022;35:17-27.
25. Castro R, Libânio D, Pita I, Dinis-Ribeiro M. Solutions for submucosal injection: what to choose and how to do it. World J Gastroenterol 2019;25:777-788.
26. Lenz L, Martins B, Andrade de Paulo G, et al. Underwater versus conventional EMR for nonpedunculated colorectal lesions: a randomized clinical trial. Gastrointest Endosc 2023;97:549-558.
27. Park SJ. Tips and tricks for better endoscopic treatment of colorectal tumors: usefulness of cap and band in colorectal endoscopic mucosal resection. Clin Endosc 2013;46:492-494.
28. Yoshida N, Inoue K, Dohi O, Itoh Y. Precutting EMR with full or partial circumferential incision with a snare tip for the en bloc resection of difficult colorectal lesions. VideoGIE 2018;3:378-380.
29. Fujiya M, Moriichi K, Saitoh Y, Watari J, Kohgo Y. Endoscopic piecemeal resection is a practical option to cure colorectal tumors. Dig Endosc 2009;21 Suppl 1:S28-S30.
30. Wang XY, Chai NL, Zhai YQ, et al. Hybrid endoscopic submucosal dissection: an alternative resection modality for large laterally spreading tumors in the cecum? BMC Gastroenterol 2021;21:203.
31. McCarty TR, Bazarbashi AN, Thompson CC, Aihara H. Hybrid endoscopic submucosal dissection (ESD) compared with conventional ESD for colorectal lesions: a systematic review and meta-analysis. Endoscopy 2021;53:1048-1058.
32. Okamoto K, Muguruma N, Kagemoto K, et al. Efficacy of hybrid endoscopic submucosal dissection (ESD) as a rescue treatment in difficult colorectal ESD cases. Dig Endosc 2017;29 Suppl 2:45-52.
33. Zorron Cheng Tao Pu L, Yamamura T, Nakamura M, et al. Learning curve for mastery of colorectal endoscopic submucosal dissection: perspectives from a large Japanese cohort. JGH Open 2020;4:611-616.
34. Kaosombatwattana U, Yamamura T, Limsrivilai J, et al. Preoperative endoscopic predictors of severe submucosal fibrosis in colorectal tumors undergoing endoscopic submucosal dissection. Endosc Int Open 2019;7:E421-E430.
35. Kim EK, Han DS, Ro Y, Eun CS, Yoo KS, Oh YH. The submucosal fibrosis: what does it mean for colorectal endoscopic submucosal dissection? Intest Res 2016;14:358-364.
36. Oh JE, Shim SG. Colonoscopic perforation: a 10-year experience in single general hospital. Korean J Gastroenterol 2009;54:371-376.
37. Park JY, Choi PW, Jung SM, Kim NH. The outcomes of management for colonoscopic perforation: a 12-year experience at a single institute. Ann Coloproctol 2016;32:175-183.
38. Castellví J, Pi F, Sueiras A, et al. Colonoscopic perforation: useful parameters for early diagnosis and conservative treatment. Int J Colorectal Dis 2011;26:1183-1190.
39. Gweon TG, Yang DH. Management of complications related to colorectal endoscopic submucosal dissection. Clin Endosc 2023;56:423-432.
40. Pissas D, Ypsilantis E, Papagrigoriadis S, Hayee B, Haji A. Endoscopic management of iatrogenic perforations during endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for colorectal polyps: a case series. Therap Adv Gastroenterol 2015;8:176-181.
41. Chow CW, Fung TL, Chan PT, Kwok KH. Endoscopic submucosal dissection for colorectal polyps: outcome determining factors. Surg Endosc 2023;37:1293-1302.
42. Yoon JY, Kim JH, Lee JY, et al. Clinical outcomes for patients with perforations during endoscopic submucosal dissection of laterally spreading tumors of the colorectum. Surg Endosc 2013;27:487-493.