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RESEARCH ARTICLE

Clinical outcomes of endoscopic submucosal dissection for colorectal neoplasms: A single-center experience in Southern Taiwan

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Abstract

Background and aims

Endoscopic submucosal dissection (ESD) as an advanced endoscopic procedure can be considered for the removal of colorectal lesions with high suspicion of limited submucosal invasion or cannot be optimally removed by snare-based techniques. We aimed to analyze the clinical outcomes of ESD for colorectal neoplasms in our hospital.

Methods

We retrospectively enrolled 230 patients with 244 colorectal neoplasms who received ESD procedures from April 2012 to October 2020 at Kaohsiung Chang Gung Memorial Hospital. Clinicopathological data were collected by chart review. We also recorded ESD-related complications and clinical outcomes.

Results

The average age was 64 years old, with a mean follow-up time of 22.59 months. There was a loss of follow-up in 34 lesions. Most lesions were lateral spreading tumors of the non-granular type. The average ESD time was 51.9 minutes. Nine cases (3.7%) had procedure-related complications, including two intra-procedure perforations (0.8%) and seven delayed bleeding (2.9%) without procedure-related mortality. 241 lesions (98.8%) achieved en-bloc resection, while 207 lesions (84.8%) achieved R0 resection. Most lesions were tubulo-(villous) adenoma. Malignancy included 35 adenocarcinomas and 5 neuroendocrine tumors. No local recurrence was developed during follow-up. Multivariate analysis for long ESD time revealed significance in size $\geq 10 \text{ cm}^2$ and endoscopist's experience < 3 years. Pre-ESD endoscopic ultrasound revealed good prediction in discrimination of mucosal (sensitivity: 0.90) and submucosal lesion (specificity: 0.67).

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Conclusions

ESD for colorectal neoplasms is an effective and safe technique. Size $\geq 10 \text{ cm}^2$ and endoscopist's experience < 3 years were significantly associated with long procedure time. Pre-ESD EUS provided a good prediction for colorectal neoplasms in invasion depth.

Introduction

Adenomatous polyps are recognized as precursor lesions leading to the development of colorectal cancer (CRC). Complete colonoscopic removal of these polyps could prevent the occurrence and death from CRC [1, 2]. A well-known association exists between adenoma detection rates and interval CRC risk [3, 4]. However, local recurrence of colorectal tumors is a major problem after endoscopic resections. The risk factors for local recurrence are tumor size, depth of tumor invasion, high-grade dysplasia polyps, piecemeal resection, villous tumor components, and positive histopathological margin [5–7]. Nowadays, there are various endoscopic techniques for the resections of these premalignant colorectal neoplasms, such as polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD) [8]. EMR was developed as a less invasive endoscopic option for removing lesions that cannot be snared by conventional methods, such as sessile or flat neoplasms confined to the superficial layers [9]. However, EMR is not an ideal technique for larger lesions due to the higher possibility of piecemeal resection and local recurrence [10].

Compared to EMR, ESD allows a better rate of en-bloc resection and reduces the local recurrence rate [11]. However, ESD is technically demanding, time-consuming, cost-intensive, and has a higher procedure-related complication rate [12, 13]. Despite the advantages of ESD, western countries infrequently chose ESD over EMR based on the greater technical difficulty involved, longer procedure times, and increased risk of perforation [14]. While diagnosing invasion depth, the macroscopic type and growth type of the lesion influence the accuracy rate of deep submucosal invasion [8]. Thus, the appropriate diagnostic methods, like endoscopic observation and endoscopic ultrasonography (EUS), are quite important [8].

For the usefulness of ESD and the role of EUS in diagnosis, we aimed to analyze the clinical outcomes of ESD for colorectal neoplasms and the accuracy of pre-ESD EUS in our hospital retrospectively.

Materials and methods

We retrospectively reviewed 230 patients with 244 colorectal neoplasms who received colorectal ESD from April 2012 to October 2020 at Kaohsiung Chang Gung Memorial Hospital. None of these patients received previous EMR or polypectomy. Sixteen cases underwent biopsy only, which were unrelated to submucosal fibrosis during ESD. These colorectal lesions selected for ESD had morphological features, such as large broad-base or flat polyps, lateral spreading tumors, and submucosal tumors when EMR may result in piecemeal resection in advance. We chose ESD over EMR in some colorectal lateral spreading tumors less than 20 mm in cases of suspected lesions with limited submucosal invasion or difficult locations for en-bloc EMR, such as ileocecal valve, hepatic/splenic flexure, and sigmoid colon. We also performed an image-enhanced colonoscopy with a narrow band image and indigo-carmine dye spray as assistance to determine the invasion depth via NICE (NBI International Colorectal Endoscopic) and JNET (Japan NBI Expert team) classification [15, 16]. Lesions suspected of advanced submucosal invasion (NICE or JNET classification type 3) were excluded. The study protocol was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (IRB No.:202200582B0). The need for written informed consent was waived due to its retrospective, single-center nature.

Baseline characteristics of patients analyzed were age, gender, size of lesions, the gross appearance of lesions, location of lesions, pre-ESD endoscopic ultrasound results, types of anesthesia, ESD-related complications, and mean follow-up months. We used maximal length multiplied by maximal width to represent the size of the lesions. Furthermore, we analyzed the time of endoscopic submucosal resection.

Although EUS is not a routine exam before colorectal ESD in our hospital, pre-ESD EUS was performed for lesions with bigger sizes or central depression resulting in poor observation of the surface and micro-vascular pattern. EUS procedures were performed by two experienced endoscopists who have performed more than 2000 EUS procedures. Our EUS procedures used a miniature Probe (UM-2R; Olympus Medical Systems, Tokyo, Japan) and an ultrasound system (EU-ME2 Premier Plus; Olympus Medical Systems, Tokyo, Japan).

The ESD procedures (Fig 1) were performed under general sedation or non-sedation by five experienced endoscopists. The equipment used included flexible endoscopes with a distal cap and the HybridKnife[™] water-jet system (ERBE, Tubingen, Germany) or DualKnife-J[™] electrosurgical knife (Olympus, Tokyo, Japan). Submucosal injection included normal saline with Bosmin and indigo-carmine in ESD with Hybridknife and Glycerol with Bosmin and indigocarmine in ESD with DualKnife-J. We initially made a circumferential incision of the mucosal layer with an electrosurgical knife, followed by a dissection of the submucosa. In some cases, we used traction techniques to help with submucosal incisions. Hybrid-ESD was defined as resection completed using CaptivatorTM II Single Use Snare (Boston Scientific, Natick, MA, USA) after adequate submucosal dissection and circumferential incision. We performed direct coagulation for hemostasis with the electrosurgical knife or the Coagrasper™ Hemostatic Forceps (Olympus, Tokyo, Japan) during the procedure and after complete resection. Mucosal defects were closed with SureClip® (Micro-Tech, Nanjing, China). Sulcrafate gel was sprayed on the wound of ESD after adequate coagulation to observe the possible minor bleeder. Post-ESD specimens were sent for pathology and classified histologically based on WHO classification. R0 resection was defined as an en-bloc resection with histologically clear deep and peripheral margins.

For the efficiency of colorectal ESD, there was no consensus on the length of ESD procedure time. Most of our ESDs were done within 100 minutes, and we considered the experience in Japan [17]. Thus, we defined a long procedure time as more than 100 minutes.

Results

Patient characteristics and gross appearance of colorectal neoplasms

As shown in Table 1, 230 patients who underwent ESD for 244 lesions were included in this study (males: 67; mean age: 64.0 ± 9.1 years). The mean post-ESD observation period was 22.59 months, with a loss of follow-up in 34 lesions (13.9%). The mean tumor size in the 244 colorectal lesions was 7.83 ± 6.6 cm², and 23.8% (58/244) were larger than 10 cm². Regarding the tumor morphology, 89% were lateral spreading tumors (217/244; 9 were granular type, 150 were non-granular type, and 58 were mixed type), 9% (5/244) were polypoid lesions, and 2% (5/244) were submucosal tumors. The distribution of lesions was 67.2% (164/244), 23.4% (57/244), and 9.4% (23/244) at the right-side colon, left-side colon, and rectum, respectively.



(e)

Fig 1. Colorectal ESD procedure. (a) Chromoendoscopy with indigo carmine staining (b) Circumferential cutting (c) Submucosal dissection (d) Complete resection (e) Specimen fixation.

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Therapeutic and histopathological results of ESD for colorectal neoplasms

The ESD time was 51.9 ± 32.9 minutes (Table 2). Forty of 244 lesions (16.4%) were completed with hybrid ESD. Nine cases (3.7%) had procedure-related complications, including two minimal perforations (0.8%) closed by SureClip® successfully after the complete ESD procedure and 7 delayed bleeding (2.9%). Our minimal perforation was defined as muscle layer defect without observation of mesenteric fat or intra-peritoneum organ and pneumoperitoneum. All post-ESD bleeding ceased spontaneously after medical treatment and observation. There was

Total: 230 patients (244 l	esions)
Patient characteristi	ics
Age (years), mean ± SD	64 ± 9.1
Gender (male), n (%)	67 (29.1%)
Mean follow-up times (months), mean ± SD	22.59 ± 22.35
Loss of follow-up, n (%)	34(13.9%)
Gross appearance of colorecta	l neoplasms
Size (cm ²), mean ± SD	7.83 ± 6.6
< 10 cm ² , n (%)	186 (76.8%)
\geq 10 cm ² , n (%)	58 (23.8%)
Morphology	
Lateral spreading tumor (LST), n (%)	217 (89%)
LST-G, Granular type, n (%)	9 (3.7%)
LST-NG, Non-Granular type, n (%)	150 (61.5%)
LST-MG, Mixed type, n (%)	58 (23.8%)
Polypoid lesions, n (%)	22 (9%)
Submucosal tumor, n (%)	5 (2%)
Location	
Right colon, n (%)	164 (67.2%)
Left colon, n (%)	57 (23.4%)
Rectum, n (%)	23 (9.4%)

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no procedure-related mortality. In this study, 241 lesions (98.8%) achieved en-bloc resection, while three cases (1.2%) converted to piecemeal EMR due to severe fibrosis. No local recurrence developed during follow-up (mean: 22.6 ± 22.35 months, minimum-maximum: 2–105 months), with loss of follow-up in 34 cases (13.9%).

The pathological features and results of 244 colorectal neoplasms are shown in Table 2, which comprised 204 (83.6%) premalignant neoplasms (159 were conventional polyps, and 45 were sessile serrated lesions) and 40 (16.4%) malignant neoplasms (35 were adenocarcinomas, and 5 were neuroendocrine tumors); 95.5% of tumor invasion depths were limited to the mucosal layer, while 10 lesions (4.1%) had submucosal invasion, and one (9.4%) had already invaded the muscle layer. Regarding the histopathological results, 207 lesions (84.8%) achieved R0 complete resection, and 37 lesions showed incomplete resection. Among the 37 cases without R0 resection, five (13.5%) were referred for further surgical interventions due to adenocarcinoma or high-grade dysplasia with submucosal invasion. One case of adenocarcinoma with submucosal invasion was lost to follow-up due to refusal of further surgical treatment. The remaining 31 cases included 26 cases of tubulo-(villous) adenoma and five intra-mucosal adenocarcinomas with mucosal margin involved by low-grade dysplasia. There was no local recurrence under endoscopic surveillance among these patients.

The efficiency of ESD and the accuracy of pre-ESD EUS

We further analyzed the efficiency of ESD (Table 3). ESD time of the rectal lesions was significantly longer than left and right colonic lesions (80.2 ± 45.1 , 43.7 ± 27.8 , and 50.8 ± 30.5 minutes, respectively, p<0.001). Regarding size, ESD lesions bigger than 10 cm² had significantly longer ESD times (69.0 ± 35.8 and 46.6 ± 30.1 , respectively, p<0.001). To analyze the influence of the endoscopist's experience, we divided the patients into three groups according to their years of experience: experience of < 3 years (2012-2014), experience of 3–5 years (2015-

Total: 2	30 patients (244 lesions)	
ESD therapeutic results		
ESD time (min), mean ± SD	51.9 ± 32.9	
Hybrid-ESD, n (%)	40 (16.4%)	
ESD complication, n (%)	9 (3.7%)	
Perforation, minor, n (%)	2 (0.8%)	
Delayed bleeding, n (%)	7 (2.9%)	
En-bloc resection, n (%)	241 (98.8%)	
Overall local recurrence, n (%)	0 (0%)	
Histopathological results		
Premalignant neoplasm	204 (83.6%)	
Tubulo-(villous) adenoma	159 (65.2%)	
Sessile serrated lesions	45 (18.4%)	
HGD/LGD	24/180 (9.8%/73.8%)	
Malignant neoplasm	40 (16.4%)	
Adenocarcinoma	35 (14.3%)	
NET, grade 1	5 (2%)	
Invasion depth		
Mucosal layer	233 (95.5%)	
Submucosa	10 (4.1%)	
Muscularis	1 (0.4%)	
R0 complete resection rate; n (%)	207 (84.8%)	

Table 2. Therapeutic and histopathological results of ESD for colorectal neoplasms.

ESD, endoscopic submucosal dissection; SD, standard deviation; HGD, high-grade dysplasia; LGD, low-grade dysplasia; NET, neuroendocrine tumor.

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2017), and experience of 5–7 years (2018–2020). Decreasing ESD procedure time (p<0.001) along with an accumulation of ESD experience was significantly identified (Fig 2).

To detect the influence of factors on procedure time, we defined procedure time ≥ 100 min as a long ESD time. Univariate analysis showed that rectal lesions (odds ratio [OR]: 0.166; 95% confidence interval [CI]: 0.053–0.522, p = 0.002), lesion size ≥ 10 cm² ([OR]: 4.041; 95% CI:

Table 3. Analysis of the efficiency of ESD.

Factors	ESD time (mean ± SD, min)	P-value
Location		
Rectum	80.2 ± 45.1	< 0.001
Left-side colon	43.7 ± 27.8	
Right-side colon	50.8 ± 30.5	
Size		
$< 10 \text{ cm}^2$	46.6 ± 30.1	< 0.001
$\geq 10 \text{ cm}^2$	69.0 ± 35.8	
Endoscopist's experience		
< 3 years	81.4 ± 39.9	< 0.001
3–5 years	55.7 ± 26.6	
5–7 years	35.0 ± 22.4	

ESD, endoscopic submucosal dissection; SD, standard deviation.

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Endoscopist experience (Ex)

Fig 2. Analysis of ESD time according to endoscopist's experience.

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1.481–11.024, p = 0.006), and endoscopist's experience < 3 years ([OR]: 0.032; 95% CI: 0.004–0.257, p = 0.001) were factors significantly associated with a long procedure time (Table 4)

Multivariate analysis was considered for all variables showing significant differences in the univariate analysis. Multivariate analysis for long ESD time revealed significant differences regarding lesion size $\geq 10 \text{ cm}^2$ ([OR]: 8.010; 95%CI: 2.097–30.591, p = 0.002), and endoscopist's experience < 3 years (odds ratio [OR]: 0.020; 95% CI: 0.002–0.201, p = 0.001) (Table 5).

Furthermore, we analyzed the accuracy of the pre-ESD EUS exam for lesions with indistinguishable invasion depth based on endoscopic appearance. Among 48 patients (19.7%) who received pre-ESD EUS, there were six cases with discordance (12.5%), including two lesions (4.2%) suspected as intra-mucosal carcinomas under EUS with histological submucosal invasion and four lesions (8.3%) suspected as focal submucosal invasion under EUS with histological intra-mucosal carcinoma. Despite the discordances, pre-ESD EUS showed good prediction in discriminating mucosal (sensitivity: 0.90, positive predictive value: 0.90) and submucosal lesions (specificity: 0.67, negative predictive value: 0.90) (Table 6).

Discussion

Therapeutic result of ESD for colorectal neoplasms

EMR was the minimally invasive, organ-sparing endoscopic technique considered to remove benign and early malignant colorectal lesions before ESD [9]. Several studies have compared ESD to EMR. ESD provides higher curative rates with better rates of en-bloc resection and R0

Factors	Ν	OR	95%CI	P-value
Age: < 60 years vs. ≥ 60 years	244	1.804	0.501-6.490	0.367
Gender: male vs. female	244	1.680	0.530-5.325	0.378
Procedure-related complication	244	4.171	0.796-21.857	0.091
Size: $< 10 \text{ cm}^2 \text{ vs.} \ge 10 \text{ cm}^2$	244	4.041	1.481-11.024	0.006
Location	244			
Rectum	23	0.166	0.053-0.522	0.002
Left-side colon	57	1.607	0.337-7.670	0.552
Right-side colon	164	1.000	Ref.	
Morphology	244			
LST NG, non-granular type	150	1.000	Ref.	
LST MG, mixed type	58	0.763	0.249-2.355	0.635
LST-G, granular type	9		Not calculated	
Submucosal tumor	5		Not calculated	
Polypoid lesions	22	1.511	0.184-12.414	0.701
Histopathology	244			
Tubulo-(villous) adenoma	159	1.000	Ref.	
Sessile serrated polyps	45	1.418	0.296-6.799	0.662
Adenocarcinoma	35	0.382	0.120-1.129	0.104
NET, grade 1	5	Not calculated		
Invasion depth	244			
Mucosal layer	233	1.000	Ref.	
Submucosa	10	0.593	0.070-5.037	0.632
Muscularis	1	Not calculated		
R0 resection	244	1.935	0.593-6.318	0.274
Endoscopist's experience	244			
< 3 years	47	0.032	0.004-0.257	0.001
3–5 years	94	0.173	0.020-1.505	0.112
5–7 years	103	1.000	Ref.	

Table 4.	Univariate	logistic regres	ssion analysi	is for long	ESD time ((procedure time \geq 100 min)	

CI, confidence interval; ESD, endoscopic submucosal dissection; min, minute; LST, lateral spreading tumor; NET, neuroendocrine tumor; OR, odds ratio.

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resection compared to EMR [11, 18]. However, due to the high technical demand for ESD, the outcome of ESD as en-bloc and R0 resection rates varied according to the hospital and country. A Korean institute revealed high en-bloc and R0 resection rates of 97.1% and 90.5%, respectively [19]. Another single-center research in European showed relatively lower en-bloc (88.4%) and R0 resection rates (62.6%) [18]. In this study, the ESD resection results were

Table 5. Multivariate logistic regress	sion analysis for the long	ESD time (procedure time > 1	00 min).

Factors	Ν	OR	95%CI	P-value
Size: $< 10 \text{ cm}^2 \text{ vs.} \ge 10 \text{ cm}^2$	244	8.010	2.097-30.591	0.002
Endoscopist's experience	244			
< 3 years	47	0.020	0.002-0.201	0.001
3–5 years	94	0.162	0.018-1.476	0.106
5–7 years	103	1.000	Ref.	

CI, confidence interval; ESD, endoscopic submucosal dissection; min, minute. OR, odds ratio.

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Table 6. The accuracy of EUS.

		Histologic diagnosis		
		Mucosal lesion	Submucosa lesion/invasion	
EUS diagnosis	Mucosal lesion	38	2	
	Submucosal lesion/invasion	4	4	
		Sensitivity: 0.90	Specificity: 0.67	

EUS, endoscopic ultrasound.

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98.8% en-bloc resection rate and 84.8% R0 resection rate without local recurrence. These results are consistent with that in a Northeast Asian country, illustrating ESD's effectiveness in colorectal neoplasms.

As for the result of colorectal ESD in the same area with a similar background, Choo et al. revealed en-bloc resection rate (72.7%) and R0 resection rate (66.7%) with perforation rate (15.2%) when the ESD technique was newly developed in Southern Taiwan [20]. A study by Tseng et al. showed en-bloc resection rate (90.2%) and R0 resection rate (89.1%) with perforation rate (12%) [21]. Although the studies mentioned above vary, improvements in en-bloc resection rate, R0 resection rate, and complication rate were observed in our study, contributing to the accumulation of ESD experience and improvement of ESD training programs in Southern Taiwanese hospitals.

The complete removal of colorectal adenomas reduces the risk of CRC [22], and the significant risk factor for local recurrence was a positive histopathological margin [5]. Two Japanese long-term studies revealed five-year local recurrence rates of approximately 1.5%, which was related to piecemeal resection and incomplete histologic resection [23, 24]. In our study, there was no local recurrence during follow-up, showing the consistency of a lower recurrence rate of ESD with other studies. On the other hand, immediate referrals to further surgical intervention for lesions without en-bloc resection or malignancy with unclear submucosal resection margin might contribute to promising results in our study.

When it comes to complications, the higher risk of ESD perforation is one reason EMR is more popular than ESD in western countries [14]. A meta-analysis showed higher complication rates for ESD than EMR (5.7% vs. 1.4%) [11]. The most common complications reported in another meta-analysis were bleeding (0.75%) and perforation (4.2%) [25]. Despite the higher risk of perforation with ESD, several studies stated that most perforations, either microperforation or macro-perforation, could be treated with endoscopic clipping without needing further surgical intervention, consistent with our study [26]. In our study, the total procedure-related complication was 3.7%, including delayed minor bleeding (2.9%) and minimal perforations (0.8%) without procedure-related mortality. Although there were higher rates of complications for ESD compared to conventional snare techniques, most complications were treated during ESD or conservative post-procedure care in this study.

The efficiency of ESD

The longer procedure time compared to conventional snare-based techniques and EMR is another disadvantage of ESD [14]. We searched ESD outcomes from different countries as references. According to a single-center study in Japan, the mean ESD time was 46.4 minutes for 1199 lesions [17]. A study conducted by a Singapore group showed a mean time of 80.9 minutes with a median lesion size of 19.3 mm, showing that larger lesions require longer procedure times [27]. A study by a Korean group revealed a median time of 53.7 minutes for ESD, with a median lesion size of 21.1 mm [28]. A study in a western country had a median time of

105 minutes, with a median lesion size of 26 mm in 2011 [29]. Another recent study in a western country showed a median time of 82.7 minutes for ESD, with a median lesion diameter of 44.3 mm [30]. This study's average ESD procedure time was 51.9 minutes, with a median size of 7.83 cm², consistent with the study in a Northeast Asian country.

We aimed to detect the influential factors of long procedure times. Although a study in Japan revealed fibrosis as a factor influencing long procedure times [17], there was no statistical significance in our study due to the limited cases of submucosal fibrosis. We, therefore, analyzed the possible factors, including location, size, and endoscopist's experience. According to Gotoda et al., performing at least 30 cases is required to be an experienced endoscopist in ESD procedures [31]. We thus classified our ESD procedure into three groups based on the endoscopist's experience. Initial analysis revealed that rectal lesions, bigger lesion size ≥ 10 cm^2 , and endoscopist's experience were significantly related to long procedure times (Table 3). Univariate analysis showed significance in rectal lesions, lesion size ≥ 10 cm², and endoscopist's experience < 3 years (Table 4). Multivariate analysis for long ESD time revealed significant differences in lesion size ≥ 10 cm² and endoscopist's experience < 3 years (Table 5). Considering the ESD experience in Japan, lesion size was demonstrated as a factor related to longer procedure time, which is consistent with our results but not endoscopist's experience [17]. Miyaguchi et al. compared experienced experts to trainees, while we compared the difference in ESD experience in the same group of endoscopists [17]. In our study, gradually decreasing ESD time along with accumulating ESD experience in clinical practice was significantly identified (Fig 2).

The accuracy of pre-ESD EUS

To evaluate the invasion depth of colorectal lesions, NICE and JNET classifications under chromoendoscopy with indigo carmine are widely used in clinical practice [15, 16]. The accuracy of deep submucosal invasion during ordinary or chromoendoscopic observation is around 70 to 80% [8]. According to current guidelines, EUS is not considered a routine examination before colorectal ESD [32]. A prospective study demonstrated that preoperative evaluation through EUS examination provided clues of possible pathological features and helped decide the treatment strategy [33]. The accuracy rate of EUS is approximately 80% in detecting deep submucosal invasion, which may help in diagnosis [8]. As diagnostic accuracy differs according to the macroscopic type and growth type of the lesion, appropriate diagnostic methods, such as endoscopic observation and EUS, should be combined depending on the situation [8]. In our experience, some circumstances lead to the poor observation of characteristics of these colorectal lesions, including lesions with bigger sizes or central depression. In these cases, the pre-ESD EUS results provided us with another aspect to determine the treatment plan. In our study, pre-ESD EUS revealed good prediction in discriminating mucosal (sensitivity: 0.90, positive predictive value: 0.90) and submucosal lesions (specificity: 0.67, negative predictive value: 0.90). The distortion of the lesions lead to the fuzzy boundary between the mucosa and submucosa, which might explain the discordances between EUS and histologic results.

Limitations

Our study had several limitations. First, it was a single-center retrospective study conducted by five endoscopists. Second, only 85.3% of patients received surveillance colonoscopy. The rate of lost follow-up is 14.7%; therefore, some local recurrence may be undetected. Third, we did not analyze the different knives used in ESD. Fourth, various traction methods emerged and were demonstrated to be efficacious in facilitating ESD by maintaining satisfactory traction

during dissection [34, 35]. We also used traction methods in the colorectal ESD. However, due to the limited number of cases, we did not analyze the efficacy of these traction methods in the current study.

Conclusions

Colorectal ESD is effective and relatively safe for colon mucosal lesions, lesions with possible superficial submucosal invasion, and lesions that snare-based techniques cannot optimally remove. This technique can allow high en-bloc resection rates and histologically R0 resection of large colorectal epithelial tumors and submucosal tumors with low complication rates. While considering the efficiency of ESD, lesion size $\geq 10 \text{ cm}^2$ and endoscopist's experience were significantly associated with long procedure time. Pre-ESD EUS can provide a good prediction for colorectal neoplasms with uncertain NICE and JNET classification under endoscopic appearance and chromoendoscopy.

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References

- Strum WB. Colorectal adenomas. N Engl J Med. 2016; 374: 1065–1075. https://doi.org/10.1056/ NEJMra1513581 PMID: 26981936.
- Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med. 2012; 366: 687–696. https://doi.org/10.1056/NEJMoa1100370 PMID: 22356322, PubMed Central PMCID: PMC3322371.
- Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014; 370: 1298–1306. https://doi.org/10.1056/ NEJMoa1309086 PMID: 24693890, PubMed Central PMCID: PMC4036494.
- Waldmann E, Kammerlander AA, Gessl I, Penz D, Majcher B, Hinterberger A, et al. Association of adenoma detection rate and adenoma characteristics With colorectal cancer mortality After screening colonoscopy. Clin Gastroenterol Hepatol. 2021; 19: 1890–1898. https://doi.org/10.1016/j.cgh.2021.04.023 PMID: 33878471.

- Murakami T, Yoshida N, Yasuda R, Hirose R, Inoue K, Dohi O, et al. Local recurrence and its risk factors after cold snare polypectomy of colorectal polyps. Surg Endosc. 2020; 34: 2918–2925. https://doi. org/10.1007/s00464-019-07072-7 PMID: 31482353.
- Komeda Y, Watanabe T, Sakurai T, Kono M, Okamoto K, Nagai T, et al. Risk factors for local recurrence and appropriate surveillance interval after endoscopic resection. World J Gastroenterol. 2019; 25: 1502–1512. <u>https://doi.org/10.3748/wjg.v25.i12.1502</u> PMID: <u>30948913</u>, PubMed Central PMCID: PMC6441916.
- Facciorusso A, Di Maso M, Serviddio G, Vendemiale G, Spada C, Costamagna G, et al. Factors associated With recurrence of advanced colorectal adenoma After endoscopic resection. Clin Gastroenterol Hepatol. 2016; 14: 1148–1154.e4. https://doi.org/10.1016/j.cgh.2016.03.017 PMID: 27005802.
- Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, et al. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc. 2020; 32: 219–239. https://doi.org/10.1111/den.13545 PMID: 31566804.
- ASGE Technology Committee Hwang JH, Konda V Abu Dayyeh BK, Chauhan SS Enestvedt BK, et al. Endoscopic mucosal resection. Gastrointest Endosc. 2015; 82: 215–226. https://doi.org/10.1016/j.gie. 2015.05.001 PMID: 26077453.
- Belderbos TD, Leenders M, Moons LM, Siersema PD. Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. Endoscopy. 2014; 46: 388–402. https://doi.org/10.1055/s-0034-1364970 PMID: 24671869.
- Fujiya M, Tanaka K, Dokoshi T, Tominaga M, Ueno N, Inaba Y, 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. https://doi.org/10.1016/j.gie.2014.07.034 PMID: 25592748.
- Dumoulin FL, Hildenbrand R. Endoscopic resection techniques for colorectal neoplasia: current developments. World J Gastroenterol. 2019; 25: 300–307. <u>https://doi.org/10.3748/wjg.v25.i3.300</u> PMID: 30686899, PubMed Central PMCID: PMC6343101.
- Kim ER, Chang DK. Management of complications of colorectal submucosal dissection. Clin Endosc. 2019; 52: 114–119. <u>https://doi.org/10.5946/ce.2019.063</u> PMID: 30959586, PubMed Central PMCID: PMC6453857.
- Uraoka T, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection: is it suitable in western countries? J Gastroenterol Hepatol. 2013; 28: 406–414. <u>https://doi.org/10.1111/jgh.12099</u> PMID: 23278302.
- Hayashi N, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc. 2013; 78: 625–632. <u>https://doi.org/10.1016/j. gie.2013.04.185</u> PMID: 23910062.
- Sano Y, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Dig Endosc. 2016; 28: 526–533. https://doi.org/10.1111/den.12644 PMID: 26927367.
- Miyaguchi K, Tashima T, Terada R, Jinushi R, Nakano Y, Katsuda H, et al. A retrospective cohort study of factors influencing long procedure times in colorectal endoscopic submucosal dissection. Scand J Gastroenterol. 2021; 56: 1255–1263. Epub 20210729. https://doi.org/10.1080/00365521.2021. 1958000 PMID: 34320880.
- Sauer M, Hildenbrand R, Oyama T, Sido B, Yahagi N, Dumoulin FL. Endoscopic submucosal dissection for flat or sessile colorectal neoplasia > 20 mm: A European single-center series of 182 cases. Endosc Int Open. 2016; 4: E895–E900. https://doi.org/10.1055/s-0042-111204 PMID: 27540580, PubMed Central PMCID: PMC4988858.
- Lee EJ, Lee JB, Lee SH, Kim DS, Lee DH, Lee DS, et al. Endoscopic submucosal dissection for colorectal tumors—1,000 colorectal ESD cases: one specialized institute's experiences. Surg Endosc. 2013; 27: 31–39. https://doi.org/10.1007/s00464-012-2403-4 PMID: 22729707.
- Choo C-H YH-H, Yang C-W, Chen Y-Y, Su W-W, Soon M-S. Short-term outcomes of endoscopic submucosal dissection for colorectal neoplasms in a single medical center. Adv Dig Med. 2015; 2: 54–60. https://doi.org/10.1016/j.aidm.2015.01.002
- Tseng MY, Lin JC, Huang TY, Shih YL, Chu HC, Chang WK, et al. Endoscopic submucosal dissection for early colorectal neoplasms: clinical experience in a tertiary medical center in Taiwan. Gastroenterol Res Pract. 2013; 2013: 891565. Epub 20130225. https://doi.org/10.1155/2013/891565 PMID: 23533391, PubMed Central PMCID: PMC3596899.
- Robertson DJ, Greenberg ER, Beach M, Sandler RS, Ahnen D, Haile RW, et al. Colorectal cancer in patients under close colonoscopic surveillance. Gastroenterology. 2005; 129: 34–41. <u>https://doi.org/10. 1053/j.gastro.2005.05.012</u> PMID: 16012932.

- Shigita K, Oka S, Tanaka S, Sumimoto K, Hirano D, Tamaru Y, et al. Long-term outcomes after endoscopic submucosal dissection for superficial colorectal tumors. Gastrointest Endosc. 2017; 85: 546– 553. https://doi.org/10.1016/j.gie.2016.07.044 PMID: 27475492.
- Yamada M, Saito Y, Takamaru H, Sasaki H, Yokota T, Matsuyama Y, et al. Long-term clinical outcomes of endoscopic submucosal dissection for colorectal neoplasms in 423 cases: a retrospective study. Endoscopy. 2017; 49: 233–242. https://doi.org/10.1055/s-0042-124366 PMID: 28107766.
- 25. Akintoye E, Kumar N, Aihara H, Nas H, Thompson CC. Colorectal endoscopic submucosal dissection: a systematic review and meta-analysis. Endosc Int Open. 2016; 4: E1030–E1044. https://doi.org/10. 1055/s-0042-114774 PMID: 27747275, PubMed Central PMCID: PMC5063641.
- Yoon JY, Kim JH, Lee JY, Hong SN, Lee SY, Sung IK, 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. https://doi.org/10.1007/s00464-012-2462-6 PMID: 22806523.
- Tai YS, Chia CL, Tan KY. Endoscopic submucosal dissection of colonic lesions: first 50 cases at a local institution. Singapore Med J. 2019; 60: 508–511. https://doi.org/10.11622/smedj.2019130 PMID: 31663098, PubMed Central PMCID: PMC6875821.
- Kim JH, Baek IH, Kim KO, Jang HJ, Baik GH, Lee CK, et al. Usefulness and feasibility of endoscopic submucosal dissection for colorectal tumor: a nationwide multicenter retrospective study in Korea. J Gastrointest Oncol. 2016; 7: 924–930. https://doi.org/10.21037/jgo.2016.06.08 PMID: 28078115, PubMed Central PMCID: PMC5177587.
- Farhat S, Chaussade S, Ponchon T, Coumaros D, Charachon A, Barrioz T, et al. Endoscopic submucosal dissection in a European setting. A multi-institutional report of a technique in development. Endoscopy. 2011; 43: 664–670. https://doi.org/10.1055/s-0030-1256413 PMID: 21623560.
- Spychalski M, Włodarczyk M, Winter K, Włodarczyk J, Dąbrowski I, Dziki A. Outcomes of 601 colorectal endoscopic submucosal dissections in a single western center: is right colon location still a major concern? Surg Laparosc Endosc Percutan Tech. 2021; 31: 578–583. https://doi.org/10.1097/SLE. 000000000000940 PMID: 33935259.
- Gotoda T, Friedland S, Hamanaka H, Soetikno R. A learning curve for advanced endoscopic resection. Gastrointest Endosc. 2005; 62: 866–867. https://doi.org/10.1016/j.gie.2005.07.055 PMID: 16301027.
- Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, Repici A, Vieth M, De Ceglie A, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015; 47: 829–854. https://doi.org/10.1055/s-0034-1392882 PMID: 26317585.
- Yue W, Liu Y, Huang J, Jiang X, Liu J. Colorectal laterally spreading tumours : subtype evaluation by EUS and BLI and outcome of ESD. Acta Gastroenterol Belg. 2019; 82: 19–26. [Epub 2019/03/20]. PMID: 30888749.
- Abe S, Wu SYS, Ego M, Takamaru H, Sekiguchi M, Yamada M, et al. Efficacy of current traction techniques for endoscopic submucosal dissection. Gut Liver. 2020; 14: 673–684. <u>https://doi.org/10.5009/gnl19266</u> PMID: 31887810, PubMed Central PMCID: PMC7667936.
- Albouys J, Dahan M, Lepetit H, Charissoux A, Guyot A, Pioche M, et al. Double-clip traction could be superior to the pocket-creation method with cylindrical cap for colonic ESD: a randomized study in an ex vivo model. Surg Endosc. 2021; 35: 1482–1491. https://doi.org/10.1007/s00464-020-08171-6 PMID: 33398562.