Safety of simultaneous endoscopic submucosal dissection for two large colorectal neoplasias in the same patient

Min Seob Kwak[1], Dong-Hoon Yang[2], Sung Wook Hwang[2], Jung Ho Bae[2], Jae Seung Soh[2], Seohyun Lee[2], Ho-Su Lee[2], Hyo Jeong Lee[2], Sang Hyoung Park[2], Byong Duk Ye[2], Jeong-Sik Byeon[2], Seung-Jae Myung[2], Suk-Kyun Yang[2]

[1]Department of Internal Medicine, Kyung Hee University College of Medicine, Kyung Hee University Hospital at Gang Dong, Seoul, Korea
[2]Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

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ABSTRACT

Background/Aims: Multiple large colorectal lesions requiring endoscopic submucosal dissection (ESD) are sometimes diagnosed during colonoscopy. We evaluated the feasibility and safety of ESD of two colorectal lesions in one session.

Materials and Methods: The lesions of 16 patients who underwent two ESD procedures in a single session (double ESD group) from November 2009 to July 2014 were matched with those of 64 patients who underwent a single ESD procedure (single ESD group) based on the size and location of the lesion and presence of submucosal fibrosis.

Results: The net ESD time per patient was longer in double ESD group than in single ESD group (104.0±36.2 vs. 59.1±39.2 min, p<0.001). The net ESD time per lesion tended to be shorter in double ESD group than in single ESD group (49.6±30.0 vs. 59.1±39.2 min, p=0.077). The en bloc resection and curative resection rates did not differ between double ESD and single ESD groups (93.8 % vs. 98.4%, p=0.262; 90.6 % vs. 84.4 %, p=0.534, respectively). The intra- and postprocedural bleeding rates were 12.5% and 0% in double ESD group and 15.6% and 3.1% in single ESD group, respectively. Perforation occurred in two (6.3%) in double ESD group and in six (9.4%) in single ESD group (p=0.715).

Conclusion: Compared with the single ESD, two simultaneous colorectal ESD procedures in a patient did not increase complications; the en bloc and curative resection rates were similar when performed a single ESD procedure and two simultaneous ESD procedures.

Keywords: Colorectal, neoplasia, endoscopic submucosal dissection

INTRODUCTION

Colonoscopic polypectomy can effectively prevent colorectal cancer and reduce colorectal cancer-related mortality rates (1,2). Endoscopic submucosal dissection (ESD) is a highly specialized form of polypectomy that enables the en bloc resection of large early colorectal neoplasias. However, ESD has a relatively higher risk of perforation than conventional endoscopic mucosal resection (EMR) (3,4). A recent meta-analysis has reported that the perforation rate was approximately 3-fold higher when performing ESD than when performing EMR (4). Moreover, because of technical difficulties, ESD usually takes more time, and several studies have reported that the mean procedure time was 2- or 3-fold longer in patients undergoing colorectal ESD (65.9-108.0 min) than in those undergoing conventional EMR (29-30 min) (5-7).

Multiple polypectomy procedures per session are common in clinical practice for managing synchronous polyps (8,9). Although the incidence of two or more synchronous large colorectal neoplasias is not well investigated, two or more ESD procedures may be required if a patient has multiple synchronous colorectal neoplasias that should be removed using ESD. A recent study has suggested that simultaneous ESD for synchronous gastric lesions is feasible and safe (10). In that study, the en bloc resection, curative resection, and complication rates were comparable between patients undergoing simultaneous gastric ESD and those undergoing the single ESD procedure (10). However, considering the longer procedure time and higher perforation risk when performing colorectal ESD than when performing both conventional EMR and gastric ESD (4,11), simultaneous colorectal ESD will be

ORCID IDs of the authors: M.S.K. 0000-0002-8988-7423; D.H.Y. 0000-0001-7756-2704; S.W.H. 0000-0002-6981-7575; J.H.B. 0000-0001-7669-1213; J.S.S. 0000-0003-1594-6029; S.L. 0000-0003-3992-801X; H.S.L. 0000-0003-3711-2180; H.J.L. 0000-0001-8300-3407; S.H.P. 0000-0002-5366-5749; B.D.Y. 0000-0001-6647-6325; J.S.B. 0000-0002-9793-6379; S.J.M. 0000-0003-0585-4016; S.K.Y. 0000-0003-2772-2575.

Address for Correspondence: **Dong-Hoon Yang** E-mail: **dhyang@amc.seoul.kr**
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much more challenging than simultaneous gastric ESD or simultaneous colorectal EMR. To the best of our knowledge, little is known about the feasibility of simultaneous colorectal ESD for synchronous colorectal lesions; thus, in the present study, we aimed to assess the feasibility and safety of simultaneous ESD for synchronous colorectal neoplasias.

MATERIALS AND METHODS

Patients

From November 2009 to July 2014, 299 patients underwent colorectal ESD performed by a therapeutic endoscopist (D.H.Y.) at a tertiary medical center. Among them, 18 had multiple large colorectal neoplasias that required ESD. Two of these patients underwent ESD procedures in separate sessions: One had a 25-mm laterally spreading tumor (LST) and another had an extremely large (135 mm) LST; the other patient had an additional lesion that was missed at the first ESD. The remaining 16 patients underwent two ESD procedures in a single session (double ESD group) (Figure 1), and the other 281 patients underwent the single ESD procedure. The 32 lesions of the patients in double ESD group were matched with lesions removed in the single ESD procedure in a 1:2 ratio based on the size of the tumor, presence of submucosal fibrosis, and location of the tumor (rectum vs. above rectum); 64 patients were included in the control group (single ESD group). Figure 2 shows the flow chart of patient recruitment. The Institutional Review Board of Asan Medical Center approved this study, and all procedures were performed with informed consent.

Data collection and variable definition

Demographic and procedure-related variables, including the size of the lesion, location of the lesion, presence of fibrosis, procedure time, type of the procedure, intraprocedural bleeding, and perforation, were identified by reviewing the medical records and colorectal ESD database. The postprocedural clinical course and events, including postoperative hospital stay, postprocedural bleeding, delayed perforation, and postprocedural clinical course, were also reviewed. Each resected specimen was gently stretched and fixed onto a hard Styrofoam plate, and its length and width were measured. In cases of piecemeal or incomplete resection, the size was endoscopically determined using open biopsy forceps as a guide.

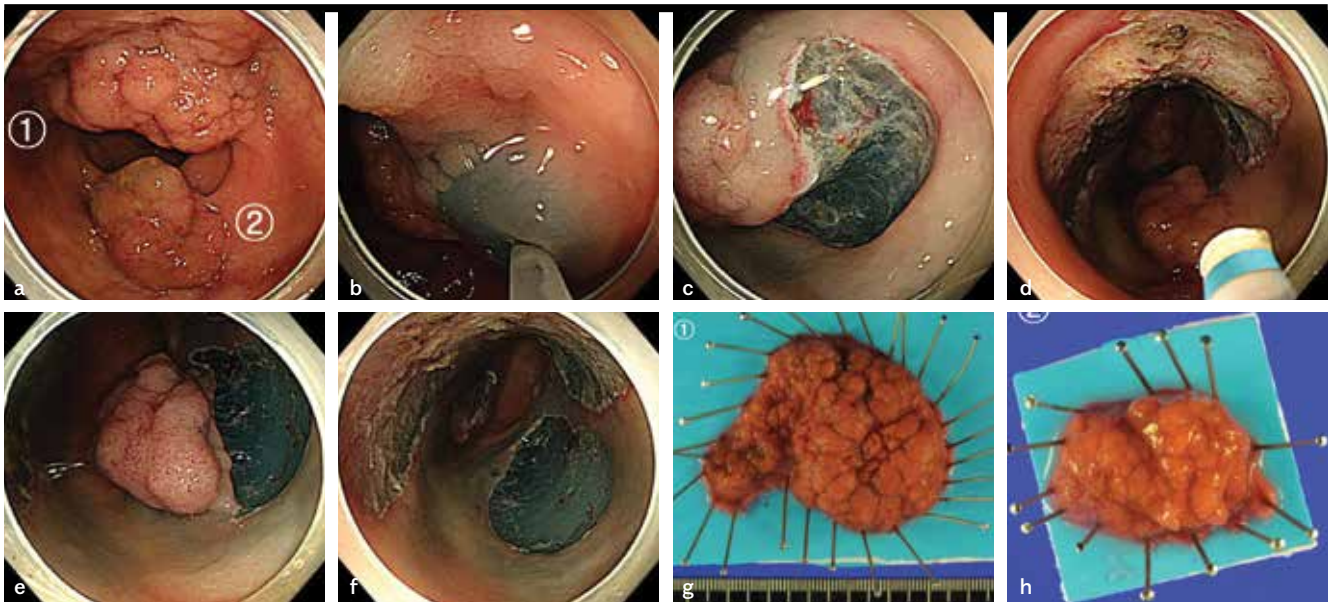

Figure 1. a-h. A representative patient with two synchronous laterally spreading tumors (LSTs). Two LSTs were identified in the rectum (a); After submucosal injection, the larger one was first removed using ESD (b-d); ESD was performed again to remove the smaller one (e); Finally, both lesions were removed completely in one session (f); Gross specimen of the larger lesion. The net ESD time was 73 min, and the lesion was 58×42 mm in size. A histologic examination revealed it to be a tubulovillous adenoma with high-grade dysplasia and clear resection margins (g); Gross specimen of the smaller lesion. The net ESD time was 16 min, and the lesion was 30×20 mm in size. Its histology revealed it to be a tubulovillous adenoma with high-grade dysplasia and clear resection margins (h)
LST: laterally spreading tumor; ESD: endoscopic submucosal dissection

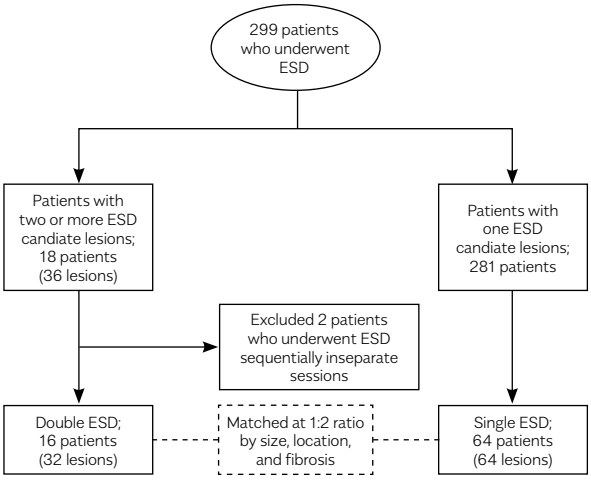

Figure 2. Flow chart of patient selection

The morphology of the lesions was categorized as sessile (Is lesions without a lateral growth pattern), granular LST (LST-G), and non-granular LST (LST-NG). Flat lesions (0-IIa, 0-IIa+Is, 0-Is+IIa, 0-IIc+IIa, or 0-IIa+IIb) based on the Paris classification system were designated as LST-G or LST-NG according to Kudo's descriptions (12-14). Superficial submucosal cancer refers to minimally invasive carcinoma with an infiltration depth of ≤1000 μm from the muscularis mucosa, whereas deep submucosal cancer is defined as massive invasive carcinoma with extensive submucosal invasion (>1000 μm below the muscularis mucosa) (15,16). The degree of submucosal fibrosis was determined based on the endoscopic characteristics observed at the time of submucosal local injection and dissection (17).

A blue transparent submucosal layer was defined as the absence of fibrosis; white web-like structures in the background of the blue submucosal layer were considered to be indicative of mild fibrosis, and white muscle-like structures without a definite blue transparent space in the submucosal layer were considered to be indicative of severe fibrosis. The "net ESD time per lesion" was defined as the time from submucosal injection to the complete removal of a lesion. The "net ESD time per patient" was the same as the net ESD time per lesion in the single ESD group but was defined as the sum of the net ESD time per lesion in the double ESD group. The mean dissection speed (cm^2/min) was calculated by dividing the area of the resected specimen by the procedure time. The largest diameter (length of the long axis) of the lesion was recorded as the size of the lesion. The area of the resected specimen was calculated using the formular for the area of an ellipse (area=π·long axis·short axis/4). Sedation-related hypoxemia was considered to be a decline in oxygen saturation to <85% in patients without underlying cardiopulmonary problems, and sedation-related hypotension was defined as a decline in blood pressure to <90/50 mmHg or >20% decrease in systolic blood pressure compared with that at baseline (18).

Perforation was defined as an endoscopically identified mural defect in the colorectum or pneumoperitoneum/pneumoretroperitoneum identified in chest and abdomen roentgenograms or computed tomography images (19). Significant intraprocedural bleeding was defined as bleeding that occurred during endoscopic resection that interrupted submucosal dissection and eventually required endoscopic hemostasis using hemostatic forceps or hemoclips. Postprocedural bleeding was defined as hematochezia and/or melena that occurred after the completion of endoscopic resection and required endoscopic hemostasis. Post-ESD electrocoagulation syndrome was defined as localized abdominal tenderness without evidence of perforation, which occurred at least 3 h after ESD and was accompanied with fever (≥37.2°C) or abnormal inflammatory responses (leukocytosis or elevated C-reactive protein levels [≥0.6 mg/dL]). En bloc resection was defined as complete resection in one piece, and histologically complete resection was defined as the absence of tumor cells at the resection margins of the specimen and successful en bloc resection.

Indications for endoscopic submucosal dissection

Endoscopic treatment for colorectal tumors was indicated for an adenoma and intramucosal or superficial submucosal colorectal cancer. The main indications for colorectal ESD were as follows: (1) large lesions (>20 mm in diameter) that are technically difficult to resect en bloc with conventional EMR and (2) lesions of any size that are likely to be superficial submucosal cancers.

Endoscopic submucosal dissection

An endoscope (GIF-H260, GIF-Q260J, CF-H260AI, CF-H260AL, CF-HQ290I, or PCF-Q260AL, CF-FH260AZI, or CF-H260AZL; Olympus Co., Tokyo, Japan) with a water-jet instrument and a transparent hood was used. Mucosal incision and submucosal dissection were performed using a fixed flexible snare knife (Kachu Technology Co., Seoul, Korea) or a dual knife (Olympus Co., Tokyo, Japan). For submucosal lifting, a sodium hyaluronate solution (Hyal®; Shinpoong Co., Seoul, Korea or Endo-Ease®; Un-

imed Co., Seoul, Korea) diluted 1:3 with a 1:100,000 epinephrine-normal saline solution was used. Hemostatic forceps (Coagrasper; Olympus Co., Tokyo, Japan) were used to control bleeding. A VIO300D (ERBE, Tubingen, Germany) electrosurgical generator was used. A mucosal incision was made with Endo-Cut Q (effect, 2; duration, 2; interval, 6). Submucosal dissection was performed using forced coagulation (effect 2, 40W). Hemostasis was performed with soft coagulation (effect 7, 80W). Before starting ESD, endoscopist-directed sedation was started using a combination of midazolam (0.05 mg per kg, maximal dose for sedation initiation=3 mg) and pethidine (25-50 mg). During ESD, sedation was maintained using repeated doses of midazolam (0.5-1 mg per additional dose) and a small amount of propofol was added if the sedative effect of midazolam was unsatisfactory. The target level of sedation was "mild sedation" in the American Society of Anesthesiologists (ASA) classification (20).

Outcome measures

The primary outcome was the incidence of complications, such as delayed bleeding or perforation. The overall midazolam dose used for the procedure, sedation-related hypoxemia/hypotension, en bloc resection rate, histologic complete resection rate, net ESD time per patient, net ESD time per lesion, mean dissection ESD speed, fasting period after ESD, and hospitalization period after ESD were compared between the two groups.

Statistical analysis

Data analyses were performed with Statistical Package for Social Sciences (SPSS) software version 21.0 for Windows (IBM Corp.; Armonk, NY, USA). Statistical differences were analyzed using two-tailed Student's *t*-test for continuous variables and two-tailed χ^2 test or Fisher's exact test for categorical variables. p-values of <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the patients

Of the 299 patients who underwent colorectal ESD performed by a single endoscopist at our hospital, 18 (6%) had multiple large colorectal neoplasias that needed ESD for en bloc resection. Of these 18 patients, 16 underwent two ESDs for the resection of colorectal neoplasms. For the case-control analysis, 64 lesions in the single ESD group were randomly matched to the 32 lesions in the 16 patients in the double ESD group patients according to tumor size (±5 mm), tumor location (rectum vs. above rectum), and the presence of submucosal fibrosis. The mean age and gender distribution did not differ between the two groups; the mean size of the lesions (28.3±12.1 mm in the double ESD group, 28.3±11.7 mm in the single-ESD group, p=0.949) also did not differ.

Granular laterally spreading tumor was the most common morphologic type (56.3% in the double ESD group vs. 51.5% in the single ESD group, p=0.361). Three lesions (9.4%) in the double ESD group and six lesions (9.4%) in the single ESD group had severe submucosal fibrosis. The baseline characteristics of the patients and lesions are listed in Tables 1 and 2, respectively.

Procedure-related complications

The incidence of intraprocedural bleeding was noted in the double ESD (12.5%) and single ESD (15.6%) groups (p=0.768). Postprocedural bleeding occurred in three patients in the single ESD group (3.1%) and in none of the patients in the double ESD group (p=0.551), whereas colonic perforation occurred in six patients (9.4%) in the single ESD group and in two patients (6.3%) in the double ESD group (p=0.715). Post-ESD electrocoagulation syndrome developed in two patients and in one patient in the single and double ESD groups, respectively (p=0.493), and all of them spontaneously improved within 2 days after ESD (Table 3). There was no incidence of delayed perforation in either group. All patients improved after conservative management without any surgical intervention.

Sedation and sedation-related complications for endoscopic submucosal dissection

The total dose of midazolam administered during the procedure was nearly the same in both groups (4.5±1.5

Table 1. Clinical characteristics of the study patients

Patient characteristics	Double ESD group (n=16)	Single ESD group (n=64)	p
Male, n (%)	11 (68.8)	45 (70.3)	0.903
Age, mean (SD), years	67.8 (7.4)	64.3 (9.7)	0.144
Medical comorbidity, n (%)†	4 (25.0)	24 (37.5)	0.397
Previous abdominal or pelvic surgery, n (%)	2 (12.5)	11 (17.2)	0.999
Prior antiplatelet use, n (%)	4 (25.0)	10 (15.6)	0.463

†Diabetes mellitus, hypertension, ischemic heart disease, and chronic kidney disease

SD: standard deviation; ESD: endoscopic submucosal dissection

Table 2. Characteristics of lesions in the double and single ESD groups

Characteristics of lesions	Double ESD group (n=16)	Single ESD group (n=64)	p
Size, mean±SD, mm	28.3±12.1	28.3±11.7	0.949
Location, n (%)			1.000
Above rectum	19 (59.4)	38 (59.4)	
Rectum	13 (40.6)	26 (40.6)	
Morphology, n (%)			0.361
LST-G	18 (56.3)	33 (51.5)	
LST-NG	10 (31.2)	17 (26.6)	
Is	4 (12.5)	14 (21.9)	
IIa	0 (0.0)	0 (0.0)	
Histopathology			0.852
Non-neoplastic†	2 (6.3)	0 (0.0)	
Adenoma	11 (34.4)	20 (31.3)	
CIS or mucosal cancer	16 (50.0)	37 (57.7)	
Superficial SM cancer	0 (0.0)	2 (3.1)	
Deep SM cancer	0 (0.0)	4 (6.3)	
SSA	3 (9.4)	1 (1.6)	
Fibrosis, n (%)			1.000
Severe	3 (9.4)	6 (9.4)	
Absent or mild	29 (90.6)	58 (90.6)	

†Two LST-like lesions that the initial histology from forceps biopsies suggested to be neoplasia were revealed to be benign non-neoplastic lesions in the final histological analysis after ESD

SD: standard deviation; ESD: endoscopic submucosal dissection; LST-G: granular laterally spreading tumor; LST-NG: non-granular laterally spreading tumor; CIS: carcinoma in situ; SM: submucosal; SSA: sessile serrated adenoma

mg in the double ESD group vs. 4.4±1.3 mg in the single ESD group, p=0.760) (Table 3). During ESD, one patient in the double ESD group and eight patients in the single ESD group needed oxygen supplementation because of mild hypoxia (p=0.679) (Table 3). However, no patient experienced significant hypotensive crisis in either group.

Short-term therapeutic outcomes of endoscopic submucosal dissection

En bloc resection was achieved in 30 (93.8%) lesions in patients in the double ESD group and in 62 (98.4%) lesions in patients in the single ESD group (p=0.262) (Table 3). The histologic complete resection rate was 90.6% in the double ESD group and 84.4% in the single ESD group (p=0.534). The net ESD time per patient was significantly longer in the double ESD group than in the single ESD group (104.0±36.2 min vs. 59.1±39.2 min, p<0.001). However, the net ESD time per lesion did not significantly differ between the groups (49.6±30.0 min in the double ESD group vs. 59.1±39.2 min in the single ESD group, p=0.077) (Table 3). The mean dissection speed of ESD (cm^2/min) was 1.2±0.8 in the double ESD group and 1.1±0.8 in the single ESD group (p=0.625). The mean length of postoperative hospitalization was 1.5 days in both groups, ranging from 1 to 5 days in the double ESD group and from 1 to 4 days in the single ESD group (p=0.755) (Table 3).

DISCUSSION

In this single hospital-based, retrospective series, 6% of the patients who underwent ESD had two or more candidate lesions suitable for ESD. However, considering potential selection bias, the incidence of synchronous large colorectal neoplasias that are potential candidates for ESD may be much lower than that indicated by our current results, although synchronous colorectal adenomas observed during screening colonoscopy were found to be very common in previous studies (2,21). Therefore, patients presenting with two or more candidate lesions suitable for ESD may be uncommon in clinical practice, but if encountered, endoscopists should decide how to remove the lesions and whether to remove them in a single session or in separate sessions.

In our current study, 16 of the 18 patients with two candidate lesions suitable for ESD underwent simultaneous ESD in a single session. Given that a large size of a lesion, its non-rectal location, and submucosal fibrosis may influence the difficulty of colorectal ESD and procedure-related outcomes, such as en bloc resection rate, procedure time, and complications (22-24), we matched double ESD cases with single ESD cases according to the size and location of lesions and the presence of submucosal fibrosis for case-control analysis. Procedure-related complications were compared between the two groups. The frequency of intraprocedural bleeding that interrupted submucosal dissection was not different between the two groups (12.5% in the double ESD group and 15.6% in the single ESD group). Postprocedural bleeding occurred only in patients in the single ESD group (3.1%), but there was no statistical difference between the two groups. We also found that simultaneous ESD for two colorectal le-

Table 3. Comparison of sedation-related variables, procedure outcomes, complications, and short-term postprocedural clinical course between the double and single ESD groups

Characteristics of lesions	Double ESD group (n=16)	Single ESD group (n=64)	p
Sedation-related variables			
Total dose of midazolam, mean±SD, mg	4.5±1.5	4.4±1.3	0.760
Additive propofol, n (%)	1† (6.3%)	3† (9.4%)	
Transient hypoxemia during ESD, n (%)	1 (6.3)	8 (12.5)	0.679
Procedure outcomes			
En bloc resection, n (%)	30 (93.8)	62 (98.4)	0.262
Curative resection, n (%)	29 (90.6)	54 (84.4)	0.534
Net ESD time per patient, mean±SD, min	104.0±36.2	59.1±39.2	<0.001
Net ESD time per lesion, mean±SD, min	49.6±30.0	59.1±39.2	0.077
Dissection speed, mean±SD, cm2/min	0.1±0.1	0.1±0.1	0.625
Complication, n (%)			
Intraprocedural bleeding per lesion	4 (12.5)	10 (15.6)	0.768
Postprocedural bleeding per lesion	0 (0.0)	2 (3.1)	0.551
Perforation per lesion	2 (6.3)	6 (9.4)	0.715
Post-ESD electrocoagulation syndrome per patient	1 (6.3)	2 (3.1%)	0.493
Postprocedural clinical course			
Fasting period after ESD, mean±SD, days	1.3±0.6	1.1±0.5	0.106
Hospitalization period after ESD, mean±SD‡, days	1.5±0.8	1.5±0.9	0.755

†One patient in the double ESD group needed 70 mg of propofol in addition to 5 mg of midazolam, and three patients in the single ESD group needed 10 mg of propofol in addition to 4-6 mg of midazolam

‡Six patients were excluded from this analysis; one patient in the double ESD group, four patients in the single ESD group with requested consultation for ESD from another department, and one patient in the single ESD group underwent additional surgery due to the presence of synchronous cancer

ESD: endoscopic submucosal dissection; SD: standard deviation

sions in one patient did not significantly increase the perforation rate (6.3% in the double ESD group and 9.4% in the single ESD group). Given that the perforation rate in the initial 250 colorectal ESD procedures performed by the endoscopist (D.H.Y.) was 8%, the perforation rate in the single ESD group might be less influenced by potential bias from the selection of matched controls (25). The perforation rate in the double ESD group seems to be acceptable, considering that all perforations could be treated without surgery. Although the perforation rates ranged between 5.5% and 10.0% in earlier Japanese studies (26,27) and between 5.3% and 20.4% in Korean studies (28-32),_ENREF_22 recent Japanese data have shown reduced perforation rates (2.3%-4.9%) (3,33,34). Therefore, we expect that increased experience in performing ESD and advances in devices for performing ESD will reduce perforation rates in both single and double ESD groups in the future.

Next, therapeutic outcomes in the double and single ESD groups were assessed. The en bloc resection and curative resection rates were 93.8% and 90.6% in the double ESD group and 98.4% and 84.4% in the single ESD group, respectively, and there were no statistically significant differences between the two groups. Tanaka et al. (35) summarized therapeutic outcomes after reviewing 13 single institution-based colorectal ESD datasets reported between 2007 and 2011._ENREF_29 The overall en bloc resection and histological R0 resection rates in that study were 90.5% (2740/3028; range, 61%-98.2%) and 76.9%

(1385/1801; range, 58%-95.6%), respectively. In addition, a prospective Japanese multicenter study reported an 88% en bloc resection rate and 89% curative resection rate (3). Therefore, we consider that immediate therapeutic outcomes in the double and single ESD groups were comparable with those previous studies and were clinically acceptable, although subsequent studies should be performed to evaluate recurrence rates in both groups.

Although the frequency of hemorrhage and rate of perforation and immediate therapeutic outcomes were similar between the two groups, the procedure time in the double ESD group was necessarily longer than that in the single ESD group. A prolonged procedure time itself can be a potential obstacle for endoscopists who perform simultaneous ESD in a single session because it can induce the paradoxical movement of the colon that makes the procedure more difficult (36). Therefore, the expected procedure time and an endoscopist's skill level should be taken into consideration before performing simultaneous ESD for colorectal lesions. Moreover, a prolonged procedure time may entail repeated doses of sedative drugs, possibly leading to an overdose of the sedative drug. Despite a longer procedure time in the double ESD group than in the single ESD group, the total dose of midazolam administered during the procedure was not different between the two groups and the total dose of midazolam administered in the double ESD group was in accordance with that administered in previous studies (37,38).

Although a small proportion of patients experienced mild oxygen desaturation during the procedure, they improved only just oxygen supplementation via a nasal prong. No patient experienced hypotensive crisis. In our present study, to avoid midazolam overdose, the starting and maintenance doses of midazolam were strictly regulated by considering the target level of sedation (mild sedation in the ASA classification), and the sedation level was monitored by a specially trained nurse on a regular basis. This sedation-focused protocol might be helpful to enable ESD to be performed without serious sedation-related complications, even with a long procedure time.

Our study had several limitations. First, it was based on retrospective data from only one expert endoscopist in a tertiary referral hospital. Therefore, the observed incidence of two or more candidate lesions suitable for colorectal ESD should not be generalized, and the results of the comparative analysis of the double and single ESD groups can be biased. However, to minimize potential selection bias, we matched lesions by their size and location and by submucosal fibrosis data. Given the findings from the high-quality endoscopist in the high-volume single center, the generalization of our findings should be further evaluated in multicenter trials, which may minimize bias related to procedural quality. Second, because of the retrospective design of our analyses, we were unable to obtain data on paradoxical bowel movement during the procedure, which is considered to be one of the most important factors affecting the difficulty of colorectal ESD (22). Third, our sample size was too small to provide conclusive data on the feasibility and safety of two ESD procedures. However, to the best of our knowledge, our current study is the first to investigate the feasibility of two ESD procedures, and it is hoped that our findings will prompt further larger studies.

In conclusion, patients who undergo two ESD procedures in one session have similar short-term therapeutic outcomes than those who undergo a single ESD procedure in terms of complication, en bloc resection, and curative resection rates. Additional studies should be conducted to determine the conditions that affect patient suitability for double ESD procedures in more detail.

Ethics Committee Approval: Ethics committee approval was received for this study from Institutional Review Board of Asan Medical Center (Decision No: 2014-1129).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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