Hybrid and Conventional Endoscopic Submucosal Dissection for Early Gastric Neoplasms: A Multi-Center Randomized Controlled Trial
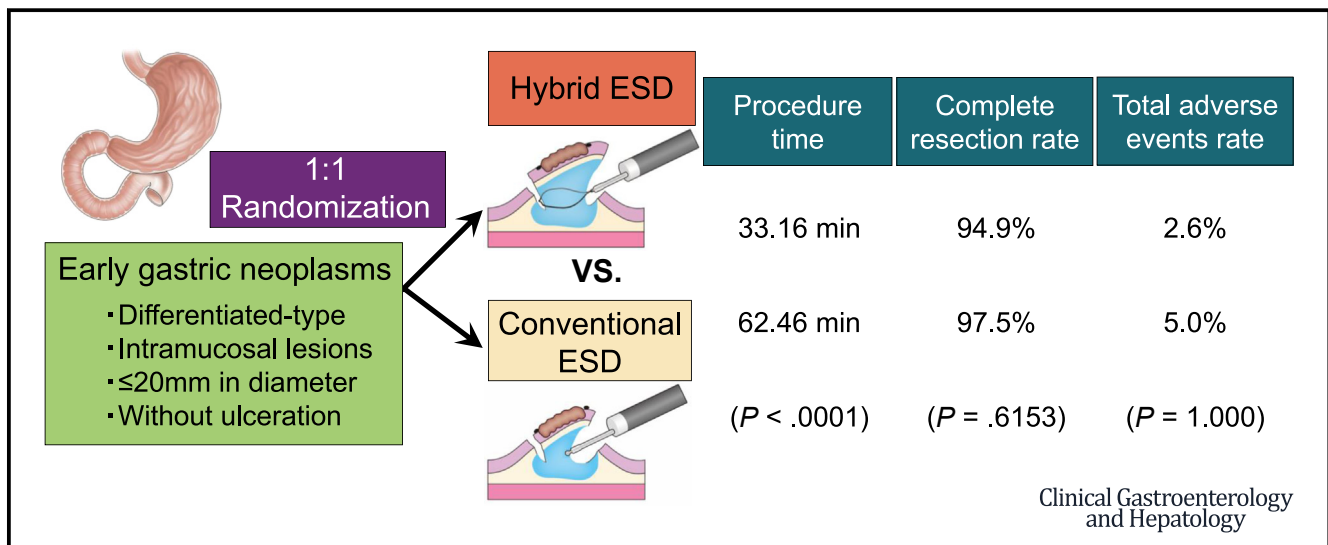
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ENDOSCOPY

Hybrid and Conventional Endoscopic Submucosal Dissection for Early Gastric Neoplasms: A Multi-Center Randomized Controlled Trial

Mitsuru Esaki,[1] Eikichi Ihara,[1,2] Yorinobu Sumida,[3,4] Hiroyuki Fujii,[5] Shunsuke Takahashi,[6] Kazuhiro Haraguchi,[7] Tsutomu Iwasa,[8] Shinichi Somada,[9] Yosuke Minoda,[1] Haruei Ogino,[1] Koshiro Tagawa,[10] and Yoshihiro Ogawa[1]

[1]Kyushu University, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Fukuoka, Japan; [2]Kyushu University, Department of Gastroenterology and Metabolism, Graduate School of Medical Sciences, Fukuoka City, Japan; [3]Kitakyushu Municipal Medical Center, Department of Gastroenterology, Kitakyushu, Japan; [4]National Hospital Organization Kyushu Medical Center, Department of Gastroenterology, Clinical Research Institute, Fukuoka, Japan; [5]National Hospital Organization Fukuokahigashi Medical Center, Department of Gastroenterology and Hepatology, Koga, Japan; [6]Fukuoka City Hospital, Department of Gastroenterology, Fukuoka, Japan; [7]Harasanshin Hospital, Department of Gastroenterology, Fukuoka, Japan; [8]Fukuokaken Saiseikai Futsukaichi Hospital, Department of Gastroenterology, Fukuoka, Japan; [9]National Hospital Organization Beppu Medical Center, Department of Gastroenterology, Beppu, Japan; and [10]Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka, Japan

	Procedure time	Complete resection rate	Total adverse events rate
Hybrid ESD	33.16 min	94.9%	2.6%
Conventional ESD	62.46 min	97.5%	5.0%
	(P < .0001)	(P = .6153)	(P = 1.000)

Early gastric neoplasms
- Differentiated-type
- Intramucosal lesions
- ≤20mm in diameter
- Without ulceration

1:1 Randomization

Clinical Gastroenterology and Hepatology

BACKGROUND & AIMS: Hybrid endoscopic submucosal dissection (H-ESD), which incorporates endoscopic submucosal dissection (ESD) with endoscopic mucosal resection, has been developed to make ESD technically easier. This study aimed to determine if H-ESD is superior to conventional ESD (C-ESD) for small early gastric neoplasms (EGNs).

METHODS: We conducted a multi-center, prospective, open-label, randomized controlled trial to compare the treatment outcomes of H-ESD and C-ESD (Hybrid-G Trial). Patients with differentiated type intramucosal EGN ≤20 mm in diameter and without ulceration were randomly assigned (1:1) to groups that underwent H-ESD or C-ESD. A single multi-functional snare, SOUTEN (ST1850-20, Kaneka, Medix, Tokyo, Japan), was used for H-ESD. The primary outcome was procedure time.

Secondary outcomes included mucosal incision time, time and speed of submucosal dissection, curability, and endoscopic procedural adverse events.

RESULTS:

A total of 39 and 40 patients underwent H-ESD and C-ESD, respectively. The procedure time of H-ESD was significantly shorter than that of C-ESD (33.16 min vs 62.46 min; H-ESD/C-ESD ratio: 0.53; 95% confidence interval, 0.41–0.69; $P < .0001$). There was no significant difference in mucosal incision time between the 2 groups; the time and speed of submucosal dissection of H-ESD were significantly shorter than those of C-ESD. No difference was observed between the 2 groups in other outcomes.

CONCLUSIONS:

H-ESD has significantly shorter procedure time than C-ESD, with high and comparable curability and safety for both H-ESD and C-ESD. H-ESD can be a good option for the endoscopic treatment of small EGNs. (UMIN Clinical Trials Registry, Numbers: UMIN000041244)

Endoscopic resection has been accepted as a less invasive treatment for early gastric neoplasms (EGNs).[1] Endoscopic mucosal resection (EMR) followed by endoscopic submucosal dissection (ESD) has been developed and applied to EGNs.[2] Current guidelines have permitted EMR and ESD for differentiated type intramucosal EGNs without ulceration ≤20 mm.[3,4] Comparative studies have shown that ESD achieved a higher degree of curability than EMR. However, ESD is technically challenging, with a longer procedure time and higher complication rates.[5,6] ESD is usually performed for EGN in Japan due to its high curability.[7] It is essential to reduce the technical difficulties of the ESD procedure to make it widely used, especially in Western countries.

Subsequently, hybrid ESD (H-ESD) was developed to overcome technical difficulties.[8] H-ESD is a modified endoscopic technique that involves making a mucosal incision followed by partial submucosal dissection in the ESD portion and planned snaring in the EMR portion. Planned snaring eliminates the latter part of submucosal dissection and simplifies the ESD procedure. Initially, H-ESD required 2 devices: an electrosurgical knife for mucosal incision followed by partial submucosal dissection and an electrosurgical snare for snaring the submucosal layer. More recently, a single multi-functional snare, SOUTEN (ST1850-20, Kaneka Medix, Tokyo, Japan), has been developed (Supplementary Figure 1). SOUTEN, which is less expensive than conventional electrosurgical knives,[9] allows the completion of H-ESD with one device.

H-ESD seems superior to conventional ESD (C-ESD) for EGN, although evidence is lacking.[10,11] Furthermore, it remains to be determined whether SOUTEN is equivalent to conventional knives, especially in terms of the mucosal incision. We thus designed a multi-center, randomized controlled trial (RCT) to evaluate whether H-ESD using SOUTEN improves treatment outcomes compared with C-ESD in patients with intramucosal EGN ≤20 mm and without ulceration.

Methods

Study Design

We performed a prospective RCT in patients with EGN at 10 institutions in the Kyushu area of Japan between July 29, 2020, and August 4, 2021. Initially, patients were recruited from 9 institutions, and later, one more institution was added. We conducted the study in accordance with the Declaration of Helsinki and the guidelines of the Consolidated Standards of Reporting Trials. The protocol was approved by the Institutional Review Board of all institutions, including Kyushu University (IRB-No.20202005; July 28, 2020), and was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN000041244). The rationale and methodology of the study have been published, and the complete protocol is available online.[12] All authors had access to the study data and approved the final manuscript.

Patients

Patients aged ≥20 years who underwent ESD for EGN were eligible. The major inclusion criteria were lesions diagnosed using biopsy as gastric adenomas or adenocarcinomas and lesions diagnosed endoscopically as differentiated type intramucosal lesions of ≤20 mm in diameter and without ulceration. Clinical staging was conducted by conventional endoscopic images with white light image endoscopy, image-enhanced endoscopy, and indigo-carmine spray endoscopy. The observation by magnifying endoscopy with image-enhanced endoscopy and/or endoscopic ultrasound was additionally conducted when the extent and depth of the lesion could not be determined with a high degree of confidence by conventional endoscopy. The major exclusion criteria were: (1) patients with a history of gastric surgery; (2) patients on dialysis; and (3) patients requiring continuous administration of heparin during the perioperative period.

Randomization

Informed consent for participation and publication of the research was obtained from all patients before randomization. Enrolled patients were randomized in a 1:1 ratio with the web-based computer program for H-ESD or C-ESD procedures. Randomization was performed using dynamic balancing, which utilized the minimization method by tumor location (upper or middle third of the stomach vs lower third), tumor size (<10 mm vs ≥10 mm), and operators' experience with ESD (<30 vs ≥30 cases). The random sequence was stored in assignment tables managed by a third party blinded to this trial.

Endoscopic Equipment and Setting

The endoscopic procedure was performed with a Flush Knife (DK2620J, Fujifilm) or Dual Knife (KD-650, Olympus) in the C-ESD and a SOUTEN in the H-ESD. Either 0.4% of sodium hyaluronate or 0.6% of sodium alginate solution was used for submucosal injection,[13,14] Other details are described in the Supplementary Appendix.

Endoscopists

Each endoscopist in this study has been licensed to practice medicine in Japan for ≥2 years and has performed ≥500 endoscopies. Endoscopists with little experience in C-ESD and/or H-ESD using SOUTEN underwent hands-on training using a porcine model before participants in the trial.[15]

Endoscopic Procedure and Tissue Analysis

The details of each procedure are described elsewhere.[2,10,16] The common techniques are as follows: marking dots were made around the lesion with the

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What You Need to Know

Background

Hybrid endoscopic submucosal dissection (H-ESD) was developed to make ESD easier. However, whether H-ESD is superior to conventional endoscopic submucosal dissection (C-ESD) for the treatment of small early gastric neoplasms has yet to be determined.

Findings

H-ESD achieved a significant reduction in ESD procedure time compared with C-ESD, regardless of operator experience. High and comparable curability and safety were obtained for both H-ESD and C-ESD.

Implications for patient care

H-ESD can be a good option of the endoscopic treatment for small early gastric neoplasms.

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distal tip of the endo-knife or snare; a viscous solution was injected into the submucosal layer using the injection needle; a circumferential mucosal incision was made outside the marking dots; submucosal dissection was performed below the lesion (Figure 1, a). Snaring was applied during submucosal dissection in H-ESD to remove the lesion immediately (Figure 1, b; Supplementary Video 1). In C-ESD, submucosal dissection was continued until the lesion was completely removed (Figure 1, c; Supplementary Video 2). The resected specimens were sliced at 2-mm intervals for pathological analysis.

Outcomes

The primary outcome was to compare the procedure time between H-ESD and C-ESD. ESD procedure time was defined as the total time from the beginning of the mucosal incision to the completion of the tumor resection. The
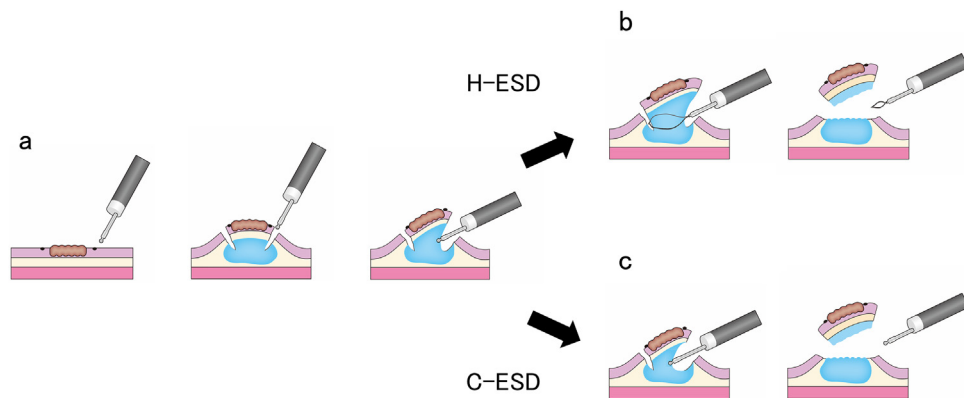
Figure 1. Procedures of H-ESD and C-ESD. *a-c*, Each step of procedures of H-ESD (*a, b*) and C-ESD (*a, c*) is shown. After marking dots were placed around the target lesion, the mucosal incision was conducted, followed by partial submucosal dissection (*a*). In H-ESD, the target lesion is retrieved by snaring the remaining submucosa after partial submucosal dissection (*b*). In C-ESD, submucosal dissection is continued until the target lesion is retrieved (*c*).

secondary outcomes included the time of mucosal incision, time and speed of the submucosal dissection, en-bloc/complete resection, endoscopic curability, volume of the injection solution used, thickness of the submucosal layer in the resected specimen, and the need for operator change during the procedure. The ESD procedure time was divided into the procedure time for the mucosal incision and submucosal dissection with snaring in H-ESD or without snaring in C-ESD. The dissection speed with snaring in H-ESD or without snaring in C-ESD was defined as the area of the resected specimen/the time of dissection (mm^2/min). En-bloc resection was defined as single-piece resection. Complete resection was defined as en-bloc resection with free vertical and horizontal margins. Curability is divided into endoscopic curability A, B, C–1, or C–2 according to the Japanese gastric cancer treatment guidelines.[4] Curative resection was considered as endoscopic curability A or B. The degree of the dissected submucosal layer before snaring was assessed in H-ESD.

Safety assessments included intraoperative/delayed perforation, delayed bleeding, and the number and duration of hemostasis using a hemostatic device. Adverse events (AEs) that occurred during admission were assessed. Subgroup analyses were conducted according to the lesion location, lesion size, operator's experience, and pathological ulceration (presence/absence). The association between the procedure time and each factor was investigated.

The other definitions are presented in detail in the Supplementary Appendix.

Sample Size

The sample size was calculated based on the primary endpoint for testing the superiority of H-ESD over C-ESD. While comparing H-ESD and C-ESD treatment outcomes for EGN, the common logarithmically converted procedure times for H-ESD and C-ESD were (mean ± standard deviation) 1.244 ± 0.228 minutes and 1.578 ± 0.225 minutes, respectively.[10] We estimated the required sample size by assuming a reduction of 0.2 (37%) in the log-scale of the procedure time between the H-ESD and C-ESD and a common standard deviation of 0.3 for the 2 groups. Based on this, 74 patients (37 × 2) were required to ensure a statistical power of 80% for a *t* test with a significance level of 0.05. Considering a 10% dropout, 41 patients were required in each group to complete the trial.

Statistical Analysis

The primary analysis included the full analysis set. To address the skewed distribution, a logarithmic transformation was used for the ESD procedure time, mucosal incision time, and submucosal dissection time. The primary and secondary outcomes with continuous variables (except hemostatic number and time) were compared between the 2 groups using analysis of covariance with randomization stratification (location, size, and ESD experience) as covariates. These continuous variables were expressed as the least-square mean (LSM) with a 95% confidence interval (CI). The LSM ratio with 95% CI or the LSM difference with 95% CI was shown in the analysis of covariance. Furthermore, hemostatic numbers and time were compared using the Wilcoxon test, and secondary outcomes with categorical data were compared using the Fisher exact test. Continuous variables in baseline characteristics, hemostatic number, and time were presented as median with an interquartile range. In subgroup analyses, ESD procedure time was compared between the 2 groups for each subgroup, including 3 factors: randomization, stratifications, and pathological ulceration. If the subgroup factor was one of the covariate factors of randomization stratification, the analysis excluded the subgroup factor from covariates.

A 2-sided *P*-value of < .05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC).

Results

The flow chart showing the patient enrollment in the study is presented in Supplementary Figure 2. Eighty-two patients were enrolled and randomized during the study period. The modalities used for preoperative diagnosis are shown in Supplementary Table 1. Among these, 79 patients were included in the safety analysis set (SAS) population. Three patients were excluded; two declined to continue participating, and one was not treated due to poor health. The full analysis set and per-protocol set were identical to the SAS. Finally, 40 patients were allocated to the C-ESD and 39 to the H-ESD. A central review was performed on all patients, and all patients underwent ESD according to the assigned treatment method. The baseline characteristics, including 3 covariate factors of randomization stratification in the enrolled patients, were similar between groups (Table 1; Supplementary Table 2).

Primary Outcome

The primary outcome, ESD procedure time, was 33.16 minutes (95% CI, 27.40–40.14 minutes) for H-ESD and 62.46 minutes (95% CI, 51.76–75.38 minutes) for C-ESD (Figure 2). ESD procedure time in H-ESD was significantly shorter than in C-ESD (ratio of H-ESD/C-ESD, 0.53; 95% CI, 0.41–0.69; *P* < .0001).

Secondary Outcomes

The secondary outcomes are shown in Table 2. The mucosal incision time was not significantly different between the groups (ratio of H-ESD/C-ESD, 1.07; 95% CI, 0.79–1.45; *P* = .6773). However, the submucosal dissection time of H-ESD was significantly shorter than that of C-

Table 1. Baseline Characteristics of Enrolled Patients

	H-ESD n = 41	C-ESD n = 41	All
Gender			
Male	24 (58.5)	25 (61.0)	49 (59.8)
Female	17 (41.5)	16 (39.0)	33 (40.2)
Age, y	76.0 [73.0–80.0]	76.0 [68.0–82.0]	76.0 [71.0–81.0]
Location			
Upper or middle	19 (46.3)	19 (46.3)	38 (46.3)
Lower	22 (53.7)	22 (53.7)	44 (53.7)
Location			
Upper	5 (12.2)	2 (4.9)	7 (8.5)
Middle	14 (34.1	17 (41.5)	31 (37.8)
Lower	22 (53.7)	22 (53.7)	44 (53.7)
Position			
Greater curvature	12 (29.3)	11 (26.8)	23 (28.0)
Lessor curvature	12 (29.3)	16 (39.0)	28 (34.1)
Anterior wall	7 (17.1)	4 (9.8)	11 (13.4)
Posterior wall	10 (24.4)	10 (24.4)	20 (24.4)
Tumor size (long axis), mm			
0–9	20 (48.8)	21 (51.2)	41 (50.0)
≥10	21 (51.2)	20 (48.8)	41 (50.0)
Long axis, mm	10 [7.0–15]	9 [8.0–12.0]	9.5 [7.0–15.0]
Short axis, mm	8 [6.0–10]	8 [6.0–12.0]	8 [6.0–12.0]
Shape			
Protruded	25 (61.0)	23 (56.1)	48 (58.5)
Flat	2 (4.9)	0 (0)	2 (2.4)
Depressed	14 (34.1)	17 (41.5)	31 (37.8)
Mixed	0 (0)	1 (2.4)	1 (1.2)
ESD skill			
0–29	18 (43.9)	19 (46.3)	37 (45.1)
≥30	23 (56.1)	22 (53.7)	45 (54.9)

Note: Continuous data are presented as median [IQR], and categorical data are presented as number (%).
C-ESD, Conventional endoscopic submucosal dissection; ESD, endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range.

ESD (ratio, 0.35; 95% CI, 0.26–0.48; P < .0001). Furthermore, the submucosal dissection speed of H-ESD was significantly greater than that of C-ESD (difference between H-ESD and C-ESD, 24.01 mm²/min; 95% CI, 14.80–33.22; P < .0001). En-bloc resection was achieved
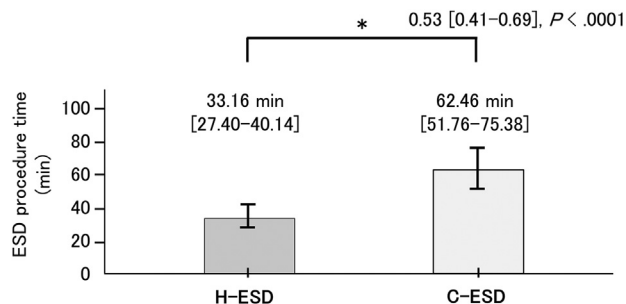

Figure 2. Comparison of ESD procedure time as a primary outcome between H-ESD and C-ESD. The panel shows the LSM value of ESD procedure time with 95% CI in each group. P-value and LSM ratio with 95% CI are calculated by comparing the ESD procedure times between H-ESD and C-ESD, using analysis of covariance with randomization stratification (location, size, and ESD skill) as covariates. *Significant difference.

in all cases for both groups. Both complete resection and curative resection rates were also quite high in both groups with no significant difference (complete resection rate, 94.9% vs 97.5%; P = .6153; curative resection rate, 92.3% vs 97.5%; P = .3589). No significant between-group differences in the thickness of the submucosal layer were noted. Snaring was achieved in 61.5% of cases who underwent H-ESD before the submucosal dissection was half completed. The total volume of submucosal injection used in H-ESD was significantly smaller than that in C-ESD (difference, −12.1 mL; 95% CI, −17.3 to −6.8 mL; P < .0001). No significant between-group difference in the rate of operator change was noted. In C-ESD, the treatment outcomes based on the type of needle knife are shown in Supplementary Table 3. The procedure time with flush knife was significantly shorter than that with dual knife.

Safety

Safety was assessed for the SAS population (Table 3). The frequency of total AEs was <5% in all patients, 2.6%

Table 2. Secondary Outcomes

	H-ESD n = 39	C-ESD n = 40	Ratio/difference of LSM [95% CI]	P-value
Time of mucosal incision				
LSM, *min* [95% CI]	14.92 [11.99–18.55]	13.99 [11.29–17.34]	1.07 [0.79–1.45]	.6773
Time of submucosal dissection				
LSM, *min* [95% CI]	16.22 [13.03–20.20]	45.76 [36.88–56.78]	0.35 [0.26–0.48]	< .0001
Speed of submucosal dissection				
LSM, *min* [95% CI]	34.38 [27.81–40.96]	10.37 [3.90–16.85]	24.01 [14.80–33.22]	< .0001
En bloc resection				
n (%)	39 (100)	40 (100)	–	–
Complete resection				
n (%)	37 (94.9)	39 (97.5)	–	.6153
Endoscopic curability				
A	35 (89.7)	39 (97.5)	–	–
B	1 (2.6)	0 (0)		
C–1	2 (5.1)	1 (2.5)		
C–2	1 (2.6)	0 (0)		
Curative resection				
A + B	36(92.3)	39(97.5)		.3589
The thickness of the submucosal layer				
LSM, *min* [95% CI]	990.5 [791.0–1189.9]	854.9 [658.6–1051.2]	135 [−143 to 415]	.3371
Degree of partial submucosal dissection				
0–1/3	13 (33.3)	–	–	–
1/3–1/2	11 (28.2)	–		
1/2–2/3	6 (15.4)	–		
2/3–1	9 (23.1)	–		
The viscous solution used in submucosal injection				
Sodium hyaluronate	29 (74.4)	28 (70.0)	–	.8027
Sodium alginate	10 (25.6)	12 (30.0)		
The total volume of submucosal injection				
LSM, *min* [95% CI]	18.9 [15.1–22.6]	31.0 [27.3–34.6]	−12.1 [−17.3 to −6.8]	< .0001
Operator's change				
None	33 (84.6)	29 (72.5)	–	.2742
Partial	6 (15.4)	11 (27.5)		
Complete	0 (0)	0 (0)		

C-ESD, Conventional endoscopic submucosal dissection; CI, confidence interval; H-ESD, hybrid endoscopic submucosal dissection; LSM, least square mean; ESD, endoscopic submucosal dissection.

in H-ESD, and 5.0% in C-ESD without significant difference. Intraoperative perforation occurred in one case in H-ESD. Endoscopic closure with clips was completely achieved after the ESD procedure, which prevented peritonitis. No delayed perforation occurred in either group. In contrast, delayed bleeding occurred in 2 cases in C-ESD. Endoscopic hemostasis was successfully performed in both. There was no significant difference in each of the AEs between the 2 groups. All AEs were resolved by the end of the trial, and none led to the discontinuation of the trial.

The intraprocedural hemostasis with hemostatic forceps was required in 21 cases (52.5%) in C-ESD, whereas it was required in 14 cases (35.9%) before snaring and 7 cases (17.9%) that had bleeding just after snaring in H-ESD. No significant between-group differences in the number and time of intraprocedural hemostasis cases were noted. Complete hemostasis was achieved in all hemostatic procedures.

Sub-group Analyses

Supplementary Tables 4 to 6 and Figure 3 show the outcomes of the subgroup analyses. Ulceration was diagnosed on pathological assessment only in 5 cases because lesions with ulceration endoscopically diagnosed were not included in this study. Therefore, analysis for lesions with ulceration was not conducted. The reduction in ESD procedure time was noted in both factors in all prespecified subgroups, including lesion location, lesion size, ESD skill, and operators.

Table 3. Adverse Events and Endoscopic Hemostasis

	H-ESD n = 39	C-ESD n = 40	P-value
Total adverse events n (%)	1 (2.6)	2 (5.0)	1.000
Intraoperative perforation n (%) [95% CI]	1 (2.6) [0.1–13.5]	0 (0) [0–8.8]	.4937
Delayed perforation n (%) [95% CI]	0 (0) [0–9.0]	0 (0) [0–8.8]	–
Delayed bleeding n (%) [95% CI]	0 (0) [0–9.0]	2 (5.0) [0.6–16.9]	.4937
Usage of hemostatic forceps during ESD (During ESD), n (%) (Total), n (%)	14 (35.9) 21 (53.8)	21 (52.5) 21 (52.5)	.1759 –
Number of hemostasis Median [IQR]	0 [0–1]	1 [0–2]	.1725
Time of hemostasis Median, *min* [IQR]	0 [0–1]	0.8 [0–4]	.1395

C-ESD, Conventional endoscopic submucosal dissection; CI, confidence interval; ESD, endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range.

Discussion

In this multicenter, prospective RCT, we have shown that the procedure time of H-ESD was significantly shorter than that of C-ESD for EGN. Furthermore, high curability and low complication rates were achieved in H-ESD as well as in C-ESD.

ESD allows en-bloc resection by dissecting the submucosal layer with an electrosurgical knife.[2] However, ESD is more difficult than EMR. It is expected to shorten the procedure time by applying planned snaring in ESD, namely H-ESD, whereas curative effects should be confirmed.[15] Two retrospective studies about H-ESD for EGN showed high curability in H-ESD as well as C-ESD; however, controversial results were obtained for the procedure time.[10,11] One study failed to show a significant difference in the procedure time between H-ESD and C-ESD. Therefore, we conducted a prospective, multicenter comparative study sufficiently powered to assess the procedure time as the primary outcome. As a result, H-ESD achieved a significantly shorter procedure time than C-ESD. In detail, the mucosal incision time did not differ; however, the submucosal dissection time of H-ESD was significantly shorter than that of C-ESD, which indeed contributed to the reduction of the total procedure time. The reduction in the procedure time (46.9%) of H-ESD was more than we had expected (37%).

We have shown that the curability of H-ESD was as high as that of C-ESD, although it was reported that EMR has less curability than ESD. Importantly, there was no significant difference in the thickness of the submucosal layer, indicating that H-ESD allows us to retrieve a sufficient depth of the lesion. A few AEs were observed, where delayed bleeding occurred only in the C-ESD. H-ESD may result in less thermal damage to the submucosal layer than C-ESD.

It was ideal to use 2 conventional devices in H-ESD, including a needle-type knife and a snare, which are designed for mucosal incision followed by submucosal dissection and retrieval of the lesion by snaring, respectively. In this trial, a multi-functional snare, SOUTEN, was used in the H-ESD procedure, considering the cost reduction advantage of using a single device. As a result, all H-ESD-associated procedures can be completed with a single device, SOUTEN. Indeed, SOUTEN was as effective as the conventional needle-type knives in the mucosal incision procedure. Importantly, this indicates that the main findings of this study can still be applied to H-ESD using 2 separate conventional devices (needle knife and snare) applied for each segment of the procedure.
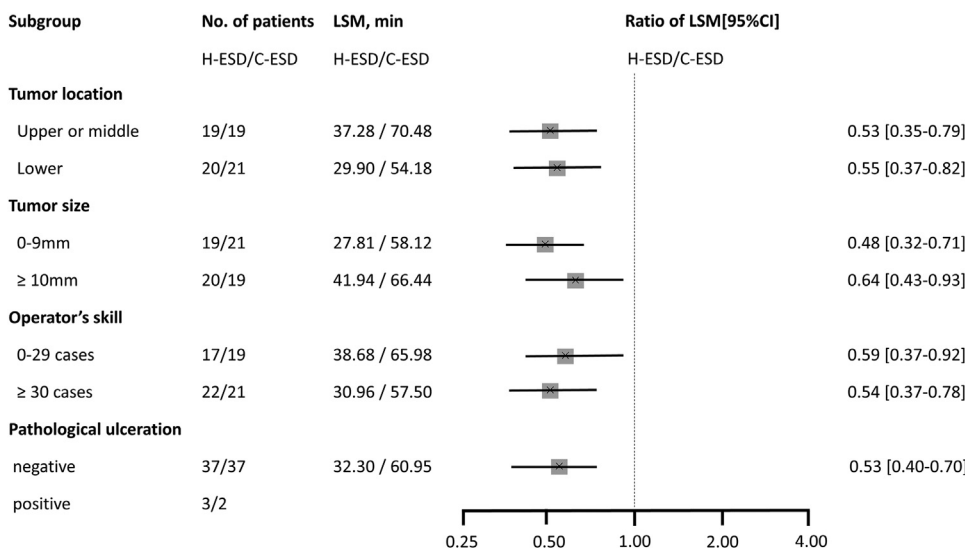
Subgroup	No. of patients H-ESD/C-ESD	LSM, min H-ESD/C-ESD		Ratio of LSM[95%CI] H-ESD/C-ESD
Tumor location				
Upper or middle	19/19	37.28 / 70.48		0.53 [0.35-0.79]
Lower	20/21	29.90 / 54.18		0.55 [0.37-0.82]
Tumor size				
0-9mm	19/21	27.81 / 58.12		0.48 [0.32-0.71]
≥ 10mm	20/19	41.94 / 66.44		0.64 [0.43-0.93]
Operator's skill				
0-29 cases	17/19	38.68 / 65.98		0.59 [0.37-0.92]
≥ 30 cases	22/21	30.96 / 57.50		0.54 [0.37-0.78]
Pathological ulceration				
negative	37/37	32.30 / 60.95		0.53 [0.40-0.70]
positive	3/2			

0.25   0.50   1.00   2.00   4.00

Figure 3. Subgroup analysis of primary outcomes according to the lesion location, lesion size, operator's experience, and pathological ulceration. ESD procedure times were compared between H-ESD and C-ESD for each of the 4 subgroups (location, size, ESD skill, and pathological ulceration), using analysis of covariance with randomization stratification (location, size, and ESD skill).

Herein, we focused on lesions for which EMR/ESD was absolutely indicated, namely the differentiated mucosal neoplasms within 20 mm without ulceration. Tumor location, size, and operator skills were selected as allocation factors for randomization, considering their influences on the outcomes. The stratified analysis based on each factor has shown that H-ESD is superior to C-ESD in any factor, indicating that H-ESD can be performed for all enrolled lesions. However, the findings of this study cannot be directly applied to lesions >20 mm and lesions with ulceration because such lesions were excluded from this study. In this trial, snaring before the half-completion of submucosal dissection was conducted in 61.5% of H-ESD based on the operator's judgment. Therefore, H-ESD could be applied to lesions >20 mm and/or lesions with ulceration when a large proportion of the submucosal dissection is completed prior to snaring the small residual undissected submucosal plane, and/or a larger snare is developed. These points should be clarified in future studies.

Although the institutions participating in this study were all in Japan, where ESD is commonly performed, almost one-half of the lesions were treated by non-experts. We conducted a sub-analysis of treatment outcomes based on the operator's experience (Supplementary Tables 5 and 6). The superiority of H-ESD over C-ESD in the ESD procedure time with high curability and low complication rate was obtained for experts with an experience of performing ≥30 ESDs and nonexperts with an experience of performing <30 ESDs. This result indicates that H-ESD may achieve a relatively quick learning curve with high curability and shorter procedure time. The hybrid technique may reduce the barriers to introducing ESD-associated procedures, including mucosal incision and submucosal dissection in areas where ESD has not been widely performed.

Several assistive methods during submucosal dissection have been developed to make the ESD procedure easier. Traction is reportedly one of the major assistive methods. Large RCTs, however, showed that the traction technique shortened the procedure time in esophageal ESD but failed to show it in gastric ESD.[17,18] Therefore, C-ESD did not use any assistive methods represented by traction in this trial. According to the findings of this study, snaring is a better assistive method than the traction technique for the enrolled EGNs. Significant synergy effects between traction and snaring in ESD have been reported.[19] This combined assistive method may further improve the treatment outcomes of H-ESD.

This study has some limitations. First, target lesions were limited to differentiated type intramucosal EGN without ulceration that were ≤20 mm. Second, the institutions participating in this study were all in Japan. Third, each operator in this study decided the timing of snaring. A precise rule for the timing should be determined to standardize the H-ESD procedure in the future. Fourth, the ESD procedure time of C-ESD with a Flush Knife was significantly shorter than that with Dual Knife. The water jet function through the Flush Knife might affect the treatment outcomes. Considering that SOUTEN is not equipped with a water jet function, the presence or absence of the water jet function did not affect the primary outcome that H-ESD was superior to C-ESD in the procedure time with other favorable outcomes. Fifth, the injection solution was not standardized in our trial, but either 0.4% of sodium hyaluronate or 0.6% of sodium alginate solution was used in this trial, both of which are approved for use by the Japanese insurance system. There was no significant difference in the proportion of viscous solution selected between the 2 treatment groups. Additionally, a previous study demonstrated the noninferiority of 0.6% sodium alginate against 0.4% sodium hyaluronate in esophageal and gastric ESD.[14] Therefore, the solution had little effect on the treatment outcomes in our opinion.

In conclusion, we performed a multi-center, prospective RCT to compare H-ESD and C-ESD treatment outcomes for patients with differentiated-type EGNs ≤20 mm in diameter and without ulceration. We found that H-ESD, even when performed by inexperienced operators, allows significantly shorter procedure time compared with C-ESD, with comparable and high curability and safety between the 2 techniques.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.10.030.

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Correspondence
Address correspondence to: Eikichi Ihara, Kyushu University, Department of Gastroenterology and Metabolism, Graduate School of Medical Sciences, Fukuoka, Japan. tel: +81-92-642-5286. e-mail: ihara.eikichi.167@m.kyushu-u.ac.jp.

Supplemental Appendix

Endoscopic Equipment and Setting

Patients underwent endoscopic submucosal dissection (ESD) with a procedural single-channel endoscope (GIF-Q260J, Olympus, Tokyo, Japan; EG-450-RD5, Fujifilm, Tokyo, Japan). A disposable hood (Elastic touch, Top, Tokyo, Japan; D-201-11804, Olympus) was attached to the distal tip of the endoscope to ensure an unobstructed field of view. The submucosal injection was performed with an injection needle. If hemostasis could not be completed only with endo-knives, hemostasis forceps, including Coagrasper (FD-410LR, Olympus), Coagrasper G (FD-412LR, Olympus), RAICHO (RC-1900, Kaneka Medix), RAICHO 2 (RC1550-2, Kaneka Medix), and HemoStatY (H-S2518, Pentax, Japan), were used.

Definitions

a. The thickness of the submucosal layer was assessed just below the center of the lesion in the resected specimen.

b. Handover of the procedure to another operator was allowed if experienced endoscopists considered the handover clinically desirable for reasons such as prolonged procedure time >60 minutes, massive uncontrollable bleeding, or the occurrence of perforation during an ESD procedure.

c. The degree of the dissected submucosal layer before snaring in hybrid endoscopic submucosal dissection (H-ESD) was divided into 0 to 1/3, 1/3 to 1/2, $^1/_2$ to 2/3, and 2/3 to 1.

d. During the ESD procedure, intraoperative perforation was diagnosed when mesenteric fat or intra-abdominal space was observed with a stomach wall defect.

e. Delayed perforation was diagnosed when free air was detected on x-ray or computed tomography scans after the ESD procedure was completed.

f. Delayed bleeding was defined as clinical evidence of bleeding after the ESD procedure requiring endoscopic hemostasis or a blood transfusion.

g. The number of hemostasis using hemostatic forceps before retrieving the lesion was counted.

h. The duration of hemostasis was defined as the cumulative time from the appearance of the hemostatic forceps on the endoscopic monitor to the completion of hemostasis.

i. The safety analysis set was defined as the enrolled patients for whom the study treatment was provided.

j. The full analysis set was defined as the enrolled patients excluding the following patients: (1) those who did not receive study treatment; (2) those who had serious noncompliance with ethical guidelines; and (3) those with missing primary endpoint data.

k. The per-protocol set was defined as patients included in the full analysis set, excluding the following patients: (1) those who did not meet the inclusion criteria; and (2) those who showed significant deviations from the study protocol.
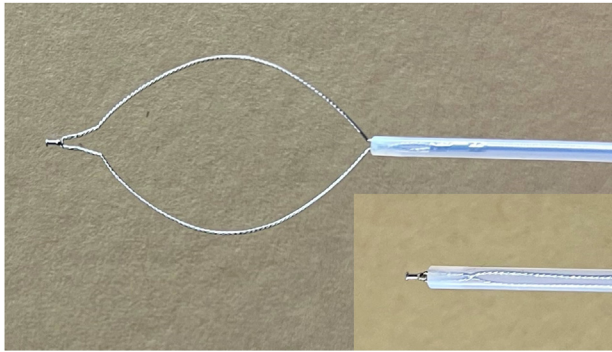
Supplementary Figure 1. Image of the multi-functional snare, SOUTEN (ST1850-20, Kaneka, Medix, Tokyo, Japan).
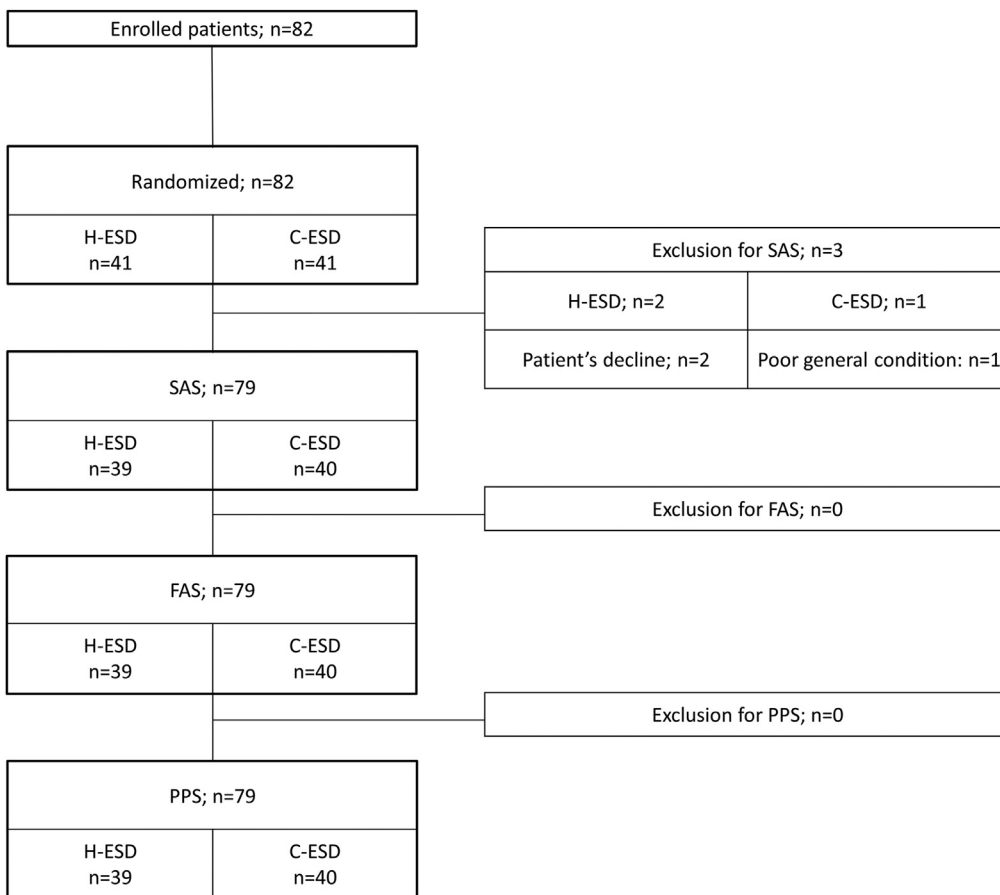
Supplementary Figure 2. Flow chart of enrolled patients in Hybrid-G Trial. A flow chart of enrolled patients in the Hybrid-G Trial is shown.

Supplementary Table 1. Usage of Modality for the Preoperative Diagnoses of Early Gastric Neoplasms

	H-ESD (n = 41), n (%)	C-ESD (n = 41), n (%)	All, n (%)
WLI			
Use	41 (100)	41 (100)	100 (100)
Non-use	0 (0)	0 (0)	0 (0)
IEE			
Use	41 (100)	41 (100)	100 (100)
Non-use	0 (0)	0 (0)	0 (0)
Indigo carmine			
Use	41 (100)	41 (100)	100 (100)
Non-use	0 (0)	0 (0)	0 (0)
ME with IEE			
Use	31 (75.6)	34 (82.9)	65 (79.3)
Non-use	10 (24.4)	7 (37.5)	17 (20.7)
EUS			
Use	6 (14.6)	4 (9.8)	10 (12.2)
Non-use	35 (85.4)	37 (90.4)	72 (87.8)

ESD, Endoscopic submucosal dissection; EUS, endoscopic ultrasound; H-ESD, hybrid endoscopic submucosal dissection; IEE, image-enhanced endoscopy; ME, magnifying endoscopy; WLI, white light imaging endoscopy.

Supplementary Table 2. Baseline Characteristics of Enrolled Patients in SAS/FAS/PPS

	H-ESD (n = 39)	C-ESD (n = 40)	All
Gender			
Male	23 (59.0)	25 (62.5)	48 (60.8)
Female	16 (41.0)	15 (37.5)	31 (39.2)
Age, y			
Median [IQR]	77.0 [73.0–81.0]	75.5 [68.0–82.0]	76.0 [72.0–81.0]
Location			
Upper or middle	19 (46.3)	19 (46.3)	38 (46.3)
Lower	22 (53.7)	22 (53.7)	44 (53.7)
Location			
Upper	5 (12.8)	2 (5.0)	7 (8.9)
Middle	14 (35.9)	17 (42.5)	31 (39.2)
Lower	20 (51.3)	21 (52.5)	41 (51.9)
Position			
Greater curvature	12 (30.7)	11 (27.5)	23 (29.1)
Lessor curvature	11 (28.2)	16 (40.0)	27 (34.2)
Anterior wall	7 (18.0)	4 (10.0)	11 (13.9)
Posterior wall	9 (23.1)	9 (22.5)	18 (22.8)
Tumor size (long axis), mm			
0–9	19 (48.7)	21 (52.5)	40 (50.6)
≥10	20 (51.3)	19 (47.5)	39 (49.4)
Long axis, mm			
Median [IQR]	10 [7.0–15]	9 [7.25–12.0]	9 [7.0–12.0]
Short axis, mm			
Median [IQR]	8 [6.0–10]	8 [5.25–11.5]	8 [6.0–10.0]
Shape			
Protruded	24 (61.5)	22 (55.0)	46 (58.2)
Flat	2 (5.1)	0 (0)	2 (2.5)
Depressed	13 (33.3)	17 (42.5)	30 (38.0)
Mixed	0 (0)	1 (2.5)	1 (1.3)
ESD skill			
0–29	17 (43.6)	19 (47.5)	36 (45.6)
≥30	22 (56.4)	21 (52.5)	43 (54.4)

Note: Continuous data are presented as median [IQR], and categorical data are presented as number (%).
C-ESD, Conventional endoscopic submucosal dissection; ESD, endoscopic submucosal dissection; FAS, full analysis set; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range; PPS, per-protocol set; SAS, safety analysis set.

Supplementary Table 3. Treatment Outcomes in C-ESD Based on the Type of Needle-knife

	Flush knife (n = 12)	Dual knife (n = 28)	Ratio/difference of LSM [95% CI]	*P*-value
ESD procedure time LSM, *min* [95% CI]	45.21 [34.32–59.57]	71.19 [59.74–84.83]	0.64 [0.46–0.89]	.0090
Time of mucosal incision LSM, *min* [95% CI]	10.48 [7.56–14.54]	15.83 [12.86–19.49]	0.66 [0.45–0.98]	.0413
Time of submucosal dissection LSM, *min* [95% CI]	32.86 [23.14–46.67]	52.01 [41.61–65.02]	0.63 [0.41–0.97]	.0346
Speed of submucosal dissection LSM, *min* [95% CI]	12.08 [7.80–16.35]	10.22 [7.50–12.94]	1.86 [−3.32–7.03]	.4711
En-bloc resection n (%)	12 (100)	28 (100)	–	-
Complete resection n (%)	12 (100)	27 (96.4)	–	1.0000
Endoscopic curability A B C–1 C–2	12 0 0 0	27 0 1 0	– 	-
Curative resection A + B	12	27	–	1.0000
The thickness of the submucosal layer LSM, *min* [95% CI]	874.7 [574.7–1174.8]	856.0 [665.2–1046.9]	18.7 [−343.9–381.3]	.9172
The total volume of submucosal injection LSM, *min* [95% CI]	24.1 [15.9–32.4]	33.8 [28.5–39.0]	−9.7 [−19.6–0.3]	.0567
Operator's change None Partial Complete	11 1 0	18 10 0	– 	.1244
Total adverse events n (%)	0 (0)	2 (7.1)	–	1.0000
Intraoperative perforation n (%) [95% CI]	0 (0.0) [0.0–26.5]	0 (0.0) [0.0–12.3]	–	-
Delayed perforation n (%) [95% CI]	0 (0.0) [0.0–26.5]	0 (0.0) [0.0–12.3]	–	-
Delayed bleeding n (%) [95% CI]	0 (0.0) [0.0–26.5]	2 (7.1) [0.9–23.5]	–	1.0000
Usage of hemostatic forceps during ESD During ESD, n (%) Total, n (%)	5 (41.7) 5 (41.7)	16 (57.1) 16 (57.1)		.4945 .4945
Number of hemostasis Median [IQR]	0.0 [0.0–1.0]	1.0 [0.0–3.0]		.1315
Time of hemostasis Median, *min* [IQR]	0.0 [0.0–1.0]	1.5 [0.0–5.0]		.0749

C-ESD, Conventional endoscopic submucosal dissection; CI, confidence interval; ESD, endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range; LSM, least square mean.

Supplementary Table 4. Subgroup Analyses of This Study

	LSM, *min* [95% CI]	Ratio of LSM [95% CI]	*P*-value
Location			
Upper or middle			
H-ESD, n = 19	37.28 [28.10–49.45]	0.53 [0.35–0.79]	.0031
C-ESD, n = 19	70.48 [53.22–93.34]		
Lower			
H-ESD, n = 20	29.90 [22.55–39.63]	0.55 [0.37–0.82]	.0047
C-ESD, n = 21	54.18 [40.83–71.88]		
Size, *mm*			
0–9			
H-ESD, n = 19	27.81 [20.65–37.45]	0.48 [0.32–0.71]	.0006
C-ESD, n = 21	58.12 [44.46–75.96]		
≥10			
H-ESD, n = 20	41.94 [32.02–54.94]	0.63 [0.43–0.93]	.0209
C-ESD, n = 19	66.44 [50.53–87.35]		
ESD skill			
0–29			
H-ESD, n = 17	38.68 [27.90–53.61]	0.59 [0.37–0.92]	.0216
C-ESD, n = 19	65.98 [48.85–89.10]		
≥30			
H-ESD, n = 22	30.96 [24.05–39.84]	0.54 [0.37–0.78]	.0014
C-ESD, n = 21	57.50 [44.39–74.50]		
Ulceration			
Absence			
H-ESD, n = 37	32.30 [26.60–39.23]	0.53 [0.40–0.70]	< .0001
C-ESD, n = 37	60.95 [50.17–74.04]		
Presence			
H-ESD, n = 2	–	–	-
C-ESD, n = 3	–		

C-ESD, Conventional endoscopic submucosal dissection; CI, confidence interval; ESD, endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; LSM, least square mean.

Supplementary Table 5. Treatment Outcomes in Operators With an Experience of Performing 0 to 29 ESDs

	H–ESD (n = 17)	C–ESD (n = 19)	Ratio/difference of LSM [95% CI]	P-value
ESD procedure time LSM, *min* [95% CI]	38.68 [27.90–53.61]	65.98 [48.85–89.10]	0.59 [0.37–0.92]	.0216
Time of mucosal incision LSM, *min* [95% CI]	17.82 [11.99–26.49]	14.49 [10.06–20.87]	1.23 [0.71–2.12]	.4469
Time of submucosal dissection LSM, *min* [95% CI]	18.90 [13.69–26.10]	47.99 [35.66–64.58]	0.39 [0.25–0.61]	.0002
Speed of submucosal dissection LSM, *min* [95% CI]	26.24 [18.21–34.28]	10.78 [3.38–18.17]	15.47 [4.38–26.55]	.0077
En-bloc resection n (%)	17 (100)	19 (100)	–	-
Complete resection n (%)	16 (94.1)	19 (100)	–	.4722
Endoscopic curability A B C–1 C–2	15 0 1 1	19 0 0 0	– 	-
Curative resection A + B	15	19	–	.2159
The thickness of the submucosal layer LSM, *min* [95% CI]	916.5 [677.6–1155.4]	954.1 [734.3–1174.0]	−37.6 [−367.0 to 291.8]	.8175
Degree of partial submucosal dissection 0–1/3 1/3–1/2 1/2–2/3 2/3–1	3 7 1 6	– – – –	– 	-
The total volume of submucosal injection LSM, *min* [95% CI]	19.7 [13.0–26.3]	32.5 [26.4–38.7]	−12.9 [−22.1 to −3.7]	.0077
Operator's change None Partial Complete	12 5 0	12 7 0	– 	.7317
Total adverse events n (%)	1 (5.9)	1 (5.3)	–	1.0000
Intraoperative perforation n (%) [95% CI]	1 (5.9) [0.1–28.7]	0 (0.0) [0.0–17.6]	–	.4722
Delayed perforation n (%) [95% CI]	(0.0) [0.0–19.5]	0 (0.0) [0.0–17.6]	–	-
Delayed bleeding n (%) [95% CI]	0 (0.0) [0.0–19.5]	1 (5.3) [0.1–26.0]	–	1.0000
Usage of hemostatic forceps during ESD During ESD, n (%) Total, n (%)	 5 (29.4) 10 (58.8)	 12 (63.2) 12 (63.2)		 .0543 1.0000
Number of hemostasis Median [IQR]	0.0 [0.0–1.0]	1.0 [0.0–3.0]		.0554
Time of hemostasis Median, *min* [IQR]	0.0 [0.0–1.0]	1.5 [0.0–5.0]		.0926

C-ESD, Conventional endoscopic submucosal dissection; CI, confidence interval; ESD, endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range; LSM, least square mean.

Supplementary Table 6. Treatment Outcomes in Operators With an Experience of Performing ≥30 ESDs

	H-ESD (n = 22)	C-ESD (n = 21)	Ratio/difference of LSM [95% CI]	P-value
ESD procedure time				
LSM, min [95% CI]	30.96 [24.05–39.84]	57.50 [44.39–74.50]	0.54 [0.37–0.78]	.0014
Time of mucosal incision				
LSM, min [95% CI]	13.99 [10.74–18.23]	13.17 [10.04–17.28]	1.06 [0.72–1.56]	.7517
Time of submucosal dissection				
LSM, min [95% CI]	15.33 [11.07–21.21]	42.20 [30.23–58.90]	0.36 [0.23–0.58]	< .0001
Speed of submucosal dissection				
LSM, min [95% CI]	39.54 [29.04–50.03]	10.25 [−0.52–21.02]	29.29 [14.11–44.47]	.0004
En-bloc resection				
n (%)	22 (100)	21 (100)	–	-
Complete resection				
n (%)	21 (95.5)	20 (95.2)	–	1.0000
Endoscopic curability				
A	20	20	–	-
B	1	0		
C−1	1	1		
C−2	0	0		
Curative resection				
A + B	21	20	–	1.0000
The thickness of the submucosal layer				
LSM, min [95% CI]	1038.7 [725.0–1352.5]	687.1 [365.2–1009.1]	351.6 [−102.3 to 805.5]	.1253
Degree of partial submucosal dissection				
0–1/3	10	–	–	-
1/3–1/2	4	–		
1/2–2/3	5	–		
2/3–1	3	–		
The total volume of submucosal injection				
LSM, min [95% CI]	19.1 [14.6–23.7]	28.0 [23.3–32.7]	−8.9 [−15.5 to −2.3]	.0099
Operator's change				
None	21	17	–	.1853
Partial	1	4		
Complete	0	0		
Total adverse events				
n (%)	0 (0)	1 (4.8)	–	1.0000
Intraoperative perforation				
n (%) [95% CI]	0 (0.0) [0.0–15.4]	0 (0.0) [0.0–16.1]	–	–
Delayed perforation				
n (%) [95% CI]	0 (0.0) [0.0–15.4]	0 (0.0) [0.0–16.1]	–	–
Delayed bleeding				
n (%) [95% CI]	0 (0.0) [0.0–15.4]	1 (4.8) [0.1–23.8]	–	.4884
Usage of hemostatic forceps during ESD				
During ESD, n (%)	9 (42.9)	9 (40.9)		1.0000
Total, n (%)	11 (50.0)	9 (42.9)		.7626
Number of hemostasis				
Median [IQR]	0.0 [0.0–1.0]	0.0 [0.0–1.0]		.9783
Time of hemostasis				
Median, min [IQR]	0.0 [0.0–1.0]	0.0 [0.0–3.0]		.7862

C-ESD, conventional endoscopic submucosal dissection; CI, confidence interval; ESD, endoscopic submucosal dissection; H-ESD, hybrid endoscopic submucosal dissection; IQR, interquartile range; LSM, least square mean.