




ORIGINAL ARTICLE OPEN ACCESS

# Hybrid Versus Conventional Endoscopic Submucosal Dissection for Laterally Spreading Tumors (LSTs): A Retrospective Multicenter Study

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**Received:** 17 September 2024 | **Revised:** 11 November 2024 | **Accepted:** 19 November 2024

**Funding:** This work was supported by the National Youth Foundation of China (Research Grant 82200436) and the Key Project of Clinical Medical Research Special Fund of Zhejiang Medical Association (2024ZYC-Z04).

**Keywords:** colorectal adenoma | endoscopic submucosal dissection | hybrid endoscopic submucosal dissection | laterally spreading tumors

## ABSTRACT

**Background and Aims:** Endoscopic submucosal dissection (ESD) is an established treatment for laterally spreading tumors (LSTs). Hybrid ESD, a novel technique, is gaining popularity for colorectal neoplasms. This study aimed to compare hybrid ESD with conventional ESD for treating LSTs.

**Methods:** Data from patients with colorectal LSTs  $\geq 10$  mm who underwent ESD at six centers from May 2020 to April 2023 were analyzed retrospectively. The study assessed baseline characteristics, hospitalization costs, and outcomes (operative time, R0 resection rate, complications).

**Results:** 890 patients were included: 490 underwent conventional ESD and 400 hybrid ESD. Hybrid ESD showed significantly shorter procedure times and lower hospitalization costs compared to conventional ESD. However, the R0 resection rate and lifting sign positivity were lower with hybrid ESD. Subgroup analysis indicated potential cost savings and shorter operative times for lesions 10–30 mm with hybrid ESD, without compromising R0 resection rates. For lesions  $\geq 30$  mm, hybrid ESD had lower R0 resection rates despite cost savings.

**Conclusion:** Hybrid ESD offers a viable alternative to conventional ESD for LSTs sized 10–30 mm, reducing procedure duration and costs while ensuring R0 resection.

## 1 | Introduction

Lateral spreading tumors (LSTs), a distinctive subtype of colorectal tumors, originate in the colonic mucosa, predominantly

manifesting lateral superficial spread along the mucosal surface. LSTs seldom invade the deeper layers of the intestinal wall vertically, and the lesions typically exhibit a diameter of  $\geq 10$  mm [1]. Research indicates that ~17.2% of advanced colorectal cancers

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arise from LSTs, and ~20.9%–33.8% of LSTs progress to advanced-grade epithelial neoplasia [2, 3]. Currently, endoscopic resection stands as the preferred treatment method for colonic LSTs. This primarily includes endoscopic mucosal resection (EMR), endoscopic piecemeal mucosal resection (EPMR), conventional endoscopic submucosal dissection (ESD), and hybrid ESD [4]. For smaller diameter LST lesions, EMR demonstrates a high success rate in achieving complete removal in a single procedure, with low residual and recurrence rates. However, the complete removal of colonic LSTs larger than 20 mm proves challenging with EMR [5]. EPMR can be employed for the removal of colonic LSTs larger than 20 mm. Nevertheless, it may impact postoperative pathological integrity, potentially complicating the pathological diagnosis of infiltration depth and determination of resection margins [6]. ESD has the advantage of achieving complete en-bloc resection of lesions. Therefore, ESD is recommended as the primary treatment for lesions larger than 20 mm. However, ESD demands advanced technical skills, involves longer operative times, and the thin colonic wall increases the risk of bleeding and perforation during the procedure. Hybrid ESD, as an innovative endoscopic technique for treating colonic LSTs, allows for both en-bloc resection of lesions and is associated with lower procedural difficulty compared to conventional ESD [7, 8]. This study aims to compare the efficacy and safety of hybrid ESD and conventional ESD in the treatment of colonic LSTs. The primary objectives include a comprehensive comparison of R0 resection rates, procedural duration, surgical costs, as well as intraoperative and postoperative complications between hybrid ESD and conventional ESD. The findings are intended to provide compelling evidence for guiding strategic choices in the endoscopic treatment of LSTs.

## 2 | Methods

### 2.1 | Patients

This study involved a multicenter retrospective analysis of 890 consecutive patients with a colorectal LST > 10 mm who underwent endoscopic treatment at 6 medical centers (The Second Affiliated Hospital, College of Medicine, Zhejiang University; The Affiliated Jinhua Hospital, Zhejiang University School of Medicine; First Affiliated Hospital of Huzhou University; The Second Hospital of Jiaxing; Jinhua People's Hospital; Lanxi People's Hospital) between May 2020 and April 2023. The inclusion criteria are as follows: (1) age  $\geq$  18 years of any sex; (2) lesion size of > 10 mm; (3) The lesion does not extend beyond the submucosal layer on preoperative endoscopic ultrasound. Patients meeting any of the following exclusion criteria are ineligible for this study: (1) patients who require continued perioperative heparinized infusion; (2) plasma prothrombin time > 14s; (3) patients with inflammatory bowel disease (IBD); (4) patients on dialysis.

### 2.2 | Description of Endoscopic Procedures

#### 2.2.1 | The Conventional ESD Technique

Each endoscopist participating in this study is a licensed medical professional in China with at least 2 years of experience and has performed a minimum of 500 endoscopies. The patient was administered intravenous general anesthesia prior to endoscopy, during

which a transparent cap was inserted along the lumen. Narrow-band imaging (NBI) technology and indigo carmine staining were employed for lesion localization, sizing, and assessment of extent. Submucosal injection of methylene blue solution at various sites was performed, followed by periphery incision using a dual knife. The submucosal injection was administered multiple times, followed by the utilization of an IT knife for submucosal separation and gradual excision of the lesion. In cases of significant bleeding at the wound site, electrocoagulation hemostatic forceps were employed for hemostasis. Additionally, deep peeling of local tissue necessitated the use of a metal titanium clip for clamping, while exposed blood vessels were managed with electrocoagulation to achieve hemostasis. If endoscopy proves ineffective, surgical intervention should be considered. In terms of specimen processing, the specimen should be flattened on a fixed plate, with the oral and anal sides clearly marked, the size measured, and then fixed in formalin solution prior to examination.

#### 2.2.2 | The Hybrid ESD Technique

The submucosal injection and circumferential incision of the Hybrid ESD were performed as described above. Subsequently, snaring was conducted post-submucosal dissection utilizing a polypectomy snare for complete lesion removal. Careful attention was paid during excision to avoid muscle layer penetration and to control cutting speed in order to mitigate the potential for hemorrhage and perforation. The subsequent steps of the procedure closely followed the conventional ESD methodology outlined previously. A hybrid ESD procedure for colon LST is shown in Figure 1.

### 2.3 | Study Variables

Collect data on two sets of demographic characteristics among patients (specifically, sex and age), as well as details regarding the lesions (including size, location, morphological classification, and histological findings), operative time, rate of R0 resection, and the occurrence of complications such as intraoperative bleeding, delayed bleeding, perforation, and additional colectomy.

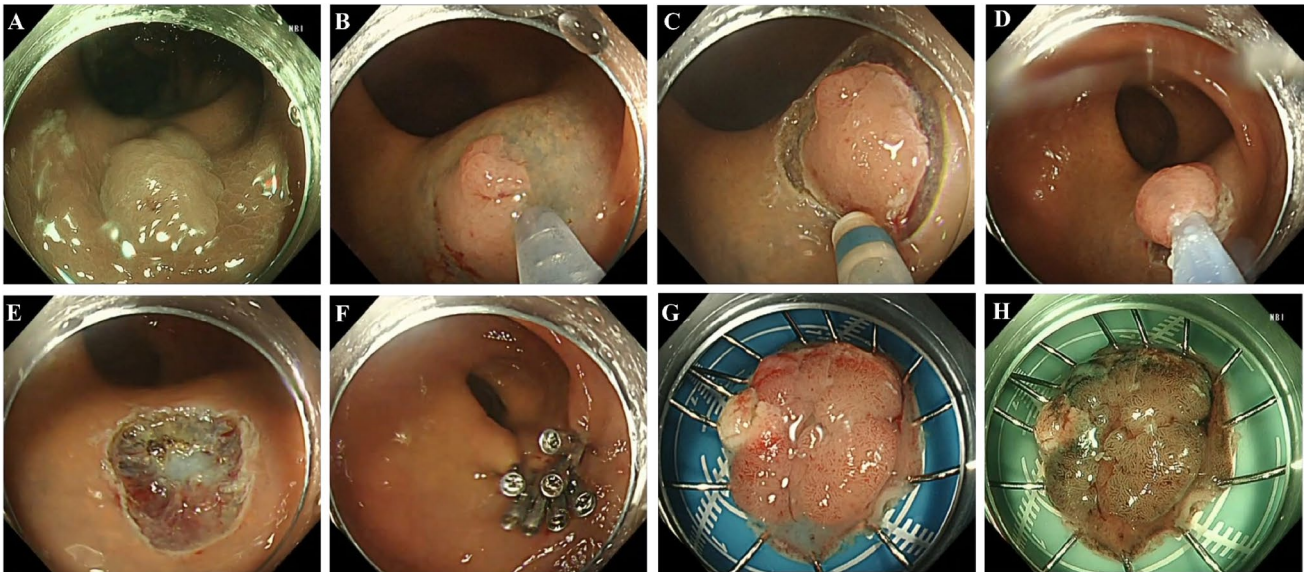
### 2.4 | Statistical Analysis

Analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean  $\pm$  standard deviation (SD) or median (interquartile range) and categorical numbers with percentages. Comparisons between each two groups were conducted using a two-tailed Student's *t*-test. Categorical data were expressed as percentages (%), and comparisons were made using the chi-square test. A two-sided *p*-value of less than 0.05 was considered statistically significant.

## 3 | Results

### 3.1 | Baseline Characteristics of Patients and Lesions

A total of 890 patients were included in this study, of which 490 were in the conventional ESD group and 400 were in the hybrid ESD group. Significant differences were found between



**FIGURE 1** | A hybrid endoscopic submucosal dissection procedure for colon laterally spreading tumor (LST). (A) Colon LST assessment using narrow-band imaging (NBI). (B) Submucosal injection of methylene blue solution. (C) Peripheral incision with a dual knife. (D) A snaring resection was employed to excise the lesion. (E) Post-resection defect. (F) The defect was sealed using clips. (G) The specimen was excised in its entirety. (H) Assessment of the specimen with NBI.

the conventional and hybrid ESD groups in age ( $62.7 \pm 10.1$  vs.  $58.6 \pm 11.6$  years,  $p < 0.001$ ), history of hypertension (26.7% vs. 16.0%,  $p < 0.001$ ), and lesion size ( $26.1 \pm 13.8$  vs.  $17.0 \pm 6.3$  mm,  $p < 0.001$ ). Additionally, there were no statistically significant differences in gender, BMI, atrial fibrillation, coronary artery disease, cerebrovascular accident, diabetes mellitus, chronic liver disease, chronic kidney disease, or history of tumor (Table 1).

### 3.2 | Clinical Outcomes

Clinical outcomes between conventional ESD and hybrid ESD were compared in Table 2. Statistical analysis indicated significant differences between the two groups across various parameters, including the R0 resection rate (98.8% vs. 96.8%,  $p = 0.038$ ), positivity of the lifting sign (99.8% vs. 97.3%,  $p = 0.001$ ), use rate of Seton (10.8% vs. 1.3%,  $p < 0.001$ ), postoperative pyrexia rate (8.0% vs. 2.0%,  $p < 0.001$ ), operative time ( $[93.5 \pm 61.4]$  vs.  $[54.0 \pm 32.9]$  min,  $p < 0.001$ ), and hospitalization costs (13438.4 [11514.0, 16029.2] vs. 11402.3 [9661.6, 13083.1] CNY,  $p < 0.001$ ). However, the study found no statistically significant differences in the incidence rates of immediate bleeding and perforation, delayed bleeding and perforation, positive surgical margins, vascular infiltration, and additional colectomy (all  $p > 0.05$ ).

### 3.3 | Sub-Group Analysis for Different Sizes of Lesion

The results of subgroup analysis by lesion size are summarized in Table 3. When the lesion size falls within the range of 10 to less than 20 mm, there were no statistically significant differences in the rates of R0 resection or procedural complications between the conventional ESD and hybrid ESD groups.

However, operative time ( $[45.7 \pm 21.1]$  vs.  $[75.2 \pm 44.2]$  min,  $p < 0.001$ ), and hospitalization costs (12865.0 [11160.0, 14368.0] vs. 11265.4 [9451.3, 12810.4] CNY,  $p < 0.001$ ) were significantly reduced in the hybrid ESD group. When the lesion size was between 20 and 30 mm, there were no statistically significant differences in the rates of R0 resection, immediate bleeding and perforation, delayed bleeding, and perforation or operative time between the two groups. However, the rate of postoperative pyrexia (1.0% vs. 6.4%,  $p < 0.001$ ) and hospitalization costs (12795.2 [11005.8, 14988.9] vs. 11265.4 [9451.3, 12810.4] CNY,  $p < 0.001$ ) were significantly lower in the hybrid ESD group. For lesions  $\geq 30$  mm, there were no significant differences in procedural complications or operating time between the two groups, but hospitalization costs were significantly lower in the hybrid ESD group (15871.2 [13031.1, 18563.1] vs. 12990.8 [11464.7, 15828.5] CNY,  $p = 0.008$ ). In addition, the R0 resection rate was lower in the hybrid ESD group compared to the conventional ESD group (84.6% vs. 98.6%,  $p = 0.005$ ).

## 4 | Discussion

Colorectal LSTs are a distinct lesion subtype characterized by a heightened propensity for malignancy. These lesions predominantly exhibit lateral growth patterns, as opposed to vertical growth. The current therapeutic approaches for managing colorectal LSTs encompass EMR, conventional ESD, EPMR, and traditional surgical interventions [9, 10]. Surgical resection has been the conventional approach for treating lesions. However, the challenge of detecting lesions beyond the intestinal wall in cases of lateral growth of LSTs necessitates preoperative localization or intraoperative endoscopic assistance, thereby complicating the surgical procedure. Furthermore, the disadvantages of significant surgical trauma and prolonged recovery time have led to an increasing preference for endoscopic surgery as a primary treatment

**TABLE 1** | Patient characteristics and clinicopathological features of the LST per treatment group.

Variable	ESD (n = 490)	Hybrid ESD (n = 400)	p
Mean age (year, ± SD)	62.7 ± 10.1	58.6 ± 11.6	< 0.001
Male (%)	263 (53.7%)	193 (48.3%)	0.121
BMI (kg/m <sup>2</sup> )	23.0 ± 3.1	23.2 ± 3.2	0.300
Atrial fibrillation	2 (0.4%)	3 (0.8%)	0.662
Coronary arterial disease	12 (2.4%)	10 (2.5%)	0.564
Hypertension	131 (26.7%)	68 (17.0%)	< 0.001
Cerebral stroke	3 (0.6%)	4 (1.0%)	0.390
Diabetes mellitus	43 (8.8%)	17 (4.3%)	0.005
Chronic liver disease	12 (2.4%)	12 (3.0%)	0.381
Chronic kidney disease	6 (1.2%)	1 (0.3%)	0.102
Tumor history	25 (5.1%)	22 (5.5%)	0.453
Lesion size (mm)	26.1 ± 13.8	17.0 ± 6.3	< 0.001
Localization, n (%)			
Cecum	51 (10.4%)	44 (11.0%)	
Ascending	129 (26.3%)	138 (34.5%)	
Hepatic flexure	20 (4.1%)	43 (10.8%)	
Transverse	96 (19.6%)	82 (20.5%)	
Descending	30 (6.1%)	24 (6.0%)	
Sigmoid	60 (12.2%)	42 (10.5%)	
Rectum	104 (21.2%)	27 (6.8%)	
Histological type, n (%)			
Adenoma	18 (3.7%)	20 (5.0%)	
Tubular adenoma with low-grade dysplasia	157 (32.0%)	146 (36.7%)	
Tubular adenoma with high-grade dysplasia	64 (13.1%)	35 (8.8%)	
Villous adenoma with low-grade dysplasia	12 (2.4%)	2 (0.5%)	
Villous adenoma with high-grade dysplasia	3 (0.6%)	0 (0.0%)	
Tubular villous adenoma with low-grade dysplasia	32 (6.5%)	14 (3.5%)	
Tubular villous adenoma with high-grade dysplasia	47 (9.6%)	10 (2.5%)	
Hyperplastic	11 (2.2%)	25 (6.3%)	
Serrated lesions	109 (22.2%)	131 (32.9%)	
Cancer	37 (7.6%)	15 (3.8%)	
Morphologic classification, n (%)			
GH	127 (25.9%)	102 (25.6%)	
GM	179 (36.5%)	78 (19.5%)	
NG F	148 (30.2%)	202 (50.6%)	
NG PD	36 (7.3%)	17 (4.3%)	

Abbreviations: ESD, endoscopic submucosal dissection; Hybrid ESD, electrocautery snaring as final step of endoscopic submucosal dissection; LST, laterally spreading tumor; LST-GH, LST-homogeneous type; LST-NG F, LST at-elevated type; LST-NG PD, LST-pseudo-depressed type; LST-NM, LST-nodular mixed type; M, intramucosal adenocarcinoma; SM-d, carcinoma with deep submucosal invasion ≥ 1000mm; SM-s, carcinoma with shallow submucosal invasion < 1000mm.

**TABLE 2** | Clinical outcomes per treatment group.

Variable	ESD (n = 490)	Hybrid ESD (n = 400)	p
R0 resection (%)	484 (98.8%)	387 (96.8%)	<b>0.038</b>
Lifting sign (+), n (%)	489 (99.8%)	389 (97.3%)	<b>0.001</b>
Seton, n (%)	53 (10.8%)	5 (1.3%)	<b>&lt;0.001</b>
Positive surgical margins, n (%)	4 (0.8%)	2 (0.5%)	0.373
Vascular infiltration, n (%)	2 (0.4%)	4 (1.0%)	0.297
Immediate complications			
Bleeding (%)	2 (0.4%)	3 (0.3%)	0.686
Perforation (%)	3 (0.6%)	0 (0.0%)	0.117
Additional colectomy (%)	8 (1.6%)	6 (1.5%)	0.874
Delayed complications			
Bleeding (%)	10 (2.0%)	11 (2.8%)	0.488
Perforation (%)	2 (0.4%)	1 (0.3%)	0.686
Pyrexia (%)	39 (8.0%)	8 (2.0%)	<b>&lt;0.001</b>
Operative time (min)	93.5 ± 61.4	54.0 ± 32.9	<b>&lt;0.001</b>
Hospitalization costs (M (Q <sub>1</sub> , Q <sub>3</sub> ), CNY)	13438.4 (11514.0, 16029.2)	11402.3 (9661.6, 13083.1)	<b>&lt;0.001</b>

Abbreviations: ESD, endoscopic submucosal dissection; Hybrid ESD, electrocautery snaring as final step of endoscopic submucosal dissection.

modality, with surgical resection becoming a secondary option for cases where endoscopic surgery is not feasible or unsuccessful [11]. EMR is typically employed for the removal of colorectal lesions smaller than 20 mm in size. Lesions larger than 20 mm necessitate R0 resection, a task that EMR is unable to accomplish, thus requiring the use of EPMR. However, EPMR is often associated with incomplete histopathological evaluation and a notable recurrence rate. Conventional ESD demonstrates superior outcomes, with a recurrence rate of 6.3% for EPMR versus no reported cases of recurrence after an average follow-up period of 12.2 months for conventional ESD [12]. Studies have demonstrated that conventional ESD can effectively achieve full resection of colorectal tumors larger than 20 mm, yielding R0 resection rates ranging from 89% to 92%. However, there exists a potential risk of perforation. Furthermore, the conventional ESD procedure is characterized by its complexity, technical difficulty, prolonged duration, high equipment demands, and necessitates the involvement of highly experienced physicians for successful completion [13, 14]. Hybrid ESD involves the utilization of an electric knife to meticulously incise the perimeter of a lesion, partially dissect the submucosal layer, and subsequently ensnare the entire lesion with a snare. Subsequently, electrocoagulation and electrocautery are employed to manage the resulting wound. The primary benefit of this technique is its ability to facilitate the removal of lesions with greater ease, while concurrently mitigating the risks of perforation and secondary infections [10].

The findings of our research indicate that the R0 resection rate and positivity of the lifting sign were significantly higher in the conventional ESD group compared to the hybrid ESD

group. However, the utilization rate of Seton, incidence of postoperative pyrexia, operative time, and hospitalization costs were significantly higher in the conventional ESD group than in the hybrid ESD group. A subsequent subgroup analysis revealed that there was no statistically significant difference in the rates of R0 resection and procedure complications between the two groups for lesions with a size of 10 to less than 20 mm. However, the hybrid ESD group demonstrated a significantly shorter surgical time and lower hospitalization costs compared to the conventional ESD group. In lesions with a size of 20 to less than 30 mm, the postoperative pyrexia rate in the hybrid ESD group was significantly reduced. However, for lesions equal to or greater than 30 mm in size, the R0 resection rate of the hybrid ESD group was significantly lower compared to the conventional ESD group. These findings suggest that for lesions smaller than 30 mm, hybrid ESD may be a preferable treatment option due to its ability to reduce operative time without compromising the R0 resection rate and lower hospitalization costs. Conversely, for lesions equal to or greater than 30 mm, conventional ESD demonstrates an advantage in achieving R0 resection.

Conventional ESD technology, particularly submucosal dissection technology, is noted for its complexity compared to hybrid ESD technology. Novices often encounter difficulties in maintaining control, which can result in prolonged treatment times and an increased risk of complications such as bleeding and perforation. R0 resection of lesions can be challenging. In cases where the lesion size is less than 30 mm, hybrid ESD may offer a viable alternative by minimizing complications, ensuring complete lesion removal, reducing operative time, and reducing hospitalization costs.

TABLE 3 | Clinical outcomes of different lesion size.

Variable	10 ≤ Lesion size < 20 (mm) (n = 430)			20 ≤ Lesion size < 30 (mm) (n = 290)			Lesion size ≥ 30 (mm) (n = 170)		
	ESD (n = 158)	Hybrid ESD (n = 272)	p	ESD (n = 188)	Hybrid ESD (n = 102)	p	ESD (n = 144)	Hybrid ESD (n = 26)	p
R0 resection (%)	157 (99.4%)	269 (98.9%)	0.532	185 (98.4%)	96 (94.1%)	0.052	142 (98.6%)	22 (84.6%)	<b>0.005</b>
Immediate complications									
Bleeding (%)	1 (0.6%)	0 (0.0%)	0.367	1 (0.5%)	0 (0.0%)	0.648	0 (0.0%)	1 (3.8%)	0.153
Perforation (%)	0 (0.0%)	0 (0.0%)		1 (0.5%)	0 (0.0%)	0.648	2 (1.4%)	0 (0.0%)	0.717
Delayed complications									
Bleeding (%)	2 (1.3%)	4 (1.5%)	0.612	2 (1.1%)	5 (4.9%)	0.055	6 (4.2%)	2 (7.7%)	0.353
Perforation (%)	0 (0.0%)	0 (0.0%)		1 (0.5%)	0 (0.0%)	0.648	1 (0.7%)	1 (3.8%)	0.283
Pyrexia (%)	7 (4.4%)	5 (18%)	0.104	12 (6.4%)	1 (1.0%)	<b>0.026</b>	20 (13.9%)	2 (7.7%)	0.307
Operative time (min)	75.2 ± 44.2	45.7 ± 21.1	<b>&lt;0.001</b>	81.4 ± 40.5	62.6 ± 36.8	0.067	129.4 ± 82.2	106.7 ± 55.4	0.296
Hospitalization costs (M (Q <sub>1</sub> , Q <sub>3</sub> ), CNY)	12865.0 (11160.0, 14368.0)	11265.4 (9451.3, 12810.4)	<b>&lt;0.001</b>	12795.2 (11005.8, 14988.9)	11265.4 (9451.3, 12810.4)	<b>&lt;0.001</b>	15871.2 (13031.1, 18563.1)	12990.8 (11464.7, 15828.5)	<b>0.008</b>

Abbreviations: ESD, endoscopic submucosal dissection; Hybrid ESD, electrocautery snaring as final step of endoscopic submucosal dissection; LST, laterally spreading tumor.

## 5 | Conclusions

Hybrid ESD has demonstrated efficacy in the surgical management of colorectal LSTs, though it exhibits a diminished rate of R0 resection for lesions exceeding 30 mm in diameter compared to conventional ESD. The size of the lesion has a significant impact on the complexity and success rate of R0 resection in hybrid ESD procedures. In conclusion, the results of this investigation suggest that hybrid ESD could serve as a feasible substitute for conventional ESD by guaranteeing comprehensive lesion eradication, diminishing surgical duration, and reducing hospitalization expenses for colorectal LSTs between 10 and 30 mm in diameter.

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### Acknowledgments

We thank all the investigators and subjects who participated in this project.

### Conflicts of Interest

The authors declare no conflicts of interest.

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