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Clinical study of submucosal tunneling endoscopic resection and endoscopic submucosal dissection in the treatment of submucosal tumor originating from the muscularis propria layer of the esophagus

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Abstract

Herein, we aimed to evaluate the clinical value and safety of transendoscopic submucosal tunnel tumor resection (STER) and endoscopic submucosal dissection (ESD) for the resection of esophageal submucosal intrinsic muscle tumors. We retrospectively analyzed the clinical data of 68 patients with esophageal submucosal intrinsic muscle tumors treated with STER (STER group, n = 38, March 2018 to January 2020) or ESD (ESD group, n = 30, January 2017 to January 2020) at the First People's Hospital of Lianyungang to compare the treatment efficacy, hospitalization time and costs, and postoperative complications between the 2 groups. All 68 cases were of single lesions. The mean operative duration was shorter in the STER group (53.39 ± 11.57 min) than in the ESD group (68.33 ± 18.52 min, $P < .05$). The postoperative hospital stay duration was significantly shorter in the STER group (5.86 ± 1.01 days; $P < .05$) than in the ESD group (8.2 ± 3.4 days, $P < .05$). The mean hospitalization cost was significantly lower in the STER group than in the ESD group (12,468.8 + 4966.8 yuan vs 17,033.3 ± 4547.2 yuan; $P < .05$). Only 1 case of intraoperative perforation occurred in ESD group. There were no other complications in both groups. The wound healed in both groups, and no residual or recurrent tumors were detected during the follow-up period. Both STER and ESD can be used for the treatment of esophageal intrinsic muscular layer (MP) tumors, and STER is safer and more efficient for lesions with a diameter <3.5 cm.

Abbreviations: ESD = endoscopic submucosal dissection, MP = muscular layer, POME = transoral endoscopic myotomy, SMT = submucosal tumor, STER = submucosal tunneling endoscopic resection.

Keywords: endoscopic resection, endoscopic submucosal dissection, esophageal neoplasms, submucosal tunneling, therapeutic endoscopy

1. Introduction

A submucosal tumor (SMT) is a tumor of the gastrointestinal tract that originates from the tissue underneath the mucosal layer. Such tumors are relatively more prevalent in the upper gastrointestinal tract. With the widespread use of ultrasound, gastrointestinal endoscopy techniques, and instruments, the SMT detection rate has been greatly improved. Although most tumors of the intrinsic muscular layer (MP) of the esophagus are benign, the biological behavior is difficult to determine for some of these lesions, and they may have some malignant potential,[1–4] particularly if they originate from the intrinsic MP or are large-sized SMTs, which are attributes that strongly suggest a malignant potential.[5,6] Infiltration can be definitively ruled out only after endoscopic resection. In the past, surgical resection was the accepted treatment for most patients;[7] however, postoperatively, patients require long-term follow-up, which may increase the financial burden and psychological stress of patients. Studies have shown that higher levels of education, age, medical occupation, and history of cancer may influence patients'

YZ, JW, and SZ contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The experimental protocol was developed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Lianyungang Hospital, Jinzhou University (no. ZD201929), all methods were carried out in accordance with relevant guidelines and regulations. Patients were fully informed of the surgical risks and complications before the surgery, and all patients signed the informed consent form for treatment.

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decision in seeking treatment.[8,9] Anxiety and frustration, lack of knowledge, and financial challenges are major barriers that keep patients from availing cancer prevention treatments, thus leading to rapid progression of the disease.[3] Therefore, endoscopic techniques are currently preferred over surgical resection of submucosal esophageal tumors. This study investigates two endoscopic techniques, one of which is endoscopic submucosal dissection (ESD), which is a commonly used method for treating SMT. ESD allows for direct endoscopic debridement of the tumor and offers a high rate of complete resection and low recurrence rates with low chances of their remaining any residual tumor.[3] However, tumors originating from the intrinsic MP require total resection, which makes ESD surgery prone to complications, such as perforation. The other approach is submucosal tunneling endoscopic resection (STER), which is a modified endoscopic technique based on ESD and is gradually incorporated for the treatment of esophageal SMT.[1,2] In 2012, inspired by transoral endoscopic myotomy (POME), STER was first developed for the removal of esophageal SMT originating from the MP layer.[10] This technique creates a surgical space between the mucosal layer and the MP layer through an artificial tunnel; this approach maintains the integrity of the mucosa and prevents perforation.[11] The submucosal tunneling technique was originally described by Sumiyama as an access point for natural orifice oral endoscopic procedures.[12] This technique was later improved by Pasricha and Inoue, who started using submucosal tunnels as a working space for endoscopic myotomy in patients with cardia loss retardation.[13–15]

We herein retrospectively analyze and report the case data of ESD and STER treatment on SMT of the intrinsic MP of the esophagus in our hospital in recent years.

2. Methods

2.1. General data

We performed a retrospective analysis of patients who visited the First People's Hospital of Lianyungang from January 2017 to January 2020. Herein, we included 933 cases of submucosal esophageal tumors diagnosed by electrogastroscopy and endoscopic ultrasonography (EUS). A total of 659 cases were diagnosed as having an esophageal mucosal layer SMT, and 288 cases were diagnosed as having an esophageal intrinsic muscle layer SMT. A total of 68 patients with intrinsic muscular SMT who underwent endoscopic treatment were included in the study. A total of 68 cases (mean age, 64 ± 11 years), comprising 35 men and 33 women, were included in the study. There were 38 cases in the STER group, with a male:female ratio of 21:17 and an age range of 42 to 79 years. There were 30 cases in the ESD group, with a male:female ratio of 14:16 and an age range of 45 to 83 years. Tumor size ranged from 1.0 to 3.0 cm (mean tumor size: 1.9 cm). For all patients, the diagnosis was established by endoscopy with intact mucosa on the surface of the lesion, CT examination with no peripheral or distant lymph node metastasis, or ultrasound gastroscopy with clear signs of lesion boundary, texture, and liquefaction. The groups did not statistically significantly differ in terms of gender composition, average age, and tumor size ($P > .05$). Patients were fully informed of the surgical risks and complications before the surgery, and all patients signed the informed consent form for treatment. The experimental protocol was developed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Lianyungang Hospital, Jinzhou University (no. ZD201929). All methods were carried out in accordance with relevant guidelines and regulations.

2.2. Endoscopist experience

Dr Shuxian Zhang, Deputy Chief Physician, is a doctoral candidate skilled in endoscopic treatment with ultrasound endoscopy (EUS), ESD, and STER, among others. Endoscopy for 10 years.

Dr Weiping Ju, Deputy Chief Physician, is skilled in endoscopic treatment of gastrointestinal, hepatobiliary, and pancreatic diseases. More than 20 years in endoscopy.

Dr Xuyang Liang, deputy chief physician, specializes in endoscopic sclerosis and ligation of esophagogastric fundic varices, screening for early cancers of the digestive tract, endoscopic submucosal dissection of early cancers (ESD), and STER and ERCP for common bile duct stones and biliary stricture diseases. Endoscopy for 10 years.

Dr Yunliang Sun, Deputy Chief Physician, is a doctoral candidate skilled in gastroenteroscopic techniques and endoscopic interventions for various gastrointestinal diseases. Endoscopy for 14 years.

Dr Shengxiang Lv, Deputy Chief Physician, a doctoral student skilled in the treatment of gastrointestinal polyps and other endoscopic treatments. Endoscopy for 18 years.

Dr Qing-Yun Kong, Chief Physician, is a doctoral candidate having worked on more than 100,000 cases of gastroscopy and is skilled in endoscopic treatments, such as ERCP, ESD, balloon dilation treatment for cardia loss, and STER. More than 30 years in endoscopy.

Dr Zhang Zhimei, Chief Physician, is a doctoral candidate specializing in endoscopic treatment of gastrointestinal, hepatobiliary, and pancreatic diseases. Endoscopy for 15 years.

Dr Kun Wang, an attending physician, is a postgraduate student skilled in endoscopic diagnosis and treatment, small intestine microscopy, and capsule endoscopy technology. Endoscopy for 9 years.

2.3. Evaluation of lesions

The size, source level, and growth type of lesions were preoperatively determined by gastroscopy and EUS. Because of the difficulties associated with endoscopically removing tumors measuring >3.5 cm, we selected cases with tumor sizes of 1.0 to 3.5 cm. All tumors were SMTs originating from the intrinsic MP having intact surface mucosa and no liquefied necrosis. Surgery was recommended for cases wherein EUS revealed a tumor measuring >3.5 cm and difficult-to-resect extra-cavernous growth-type lesions.

2.4. Instruments

Olympus 260J gastroscope, UM2000 endoscopic ultrasound system, UM-3R ultrasound probe, NM-4L-1 injection needle, KD-620U dual knife, KD-612L IT-nano knife (Olympus, Tokyo, Japan), NJ minimally invasive ROCC-D-26-195-C harmonic clamp [Micro-Tech (Nanjing) Co., Ltd., Nanjing, China], FD-1U-1 thermal biopsy forceps (Olympus, Tokyo, Japan), ERB E ICC-200 high-frequency generator, APC300 [ERBE ELEKTROMEDIZIN GMBH Aerobic (Shanghai) Medical Equipment Co., Shanghai, China], NOE342217-G disposable polypectomy device with a transparent cap, CO_2 air pump, and injection pump (Olympus, Tokyo, Japan) (Fig. 1).

2.5. Treatment

The patients were instructed to discontinue anticoagulation or antiplatelet aggregation drugs, such as aspirin and clopidogrel, for 1 week before surgery and to not have food or water for at least 8 hours before surgery. All patients were asked to lay in the left lateral position and anesthetized by tracheal intubation by a physician with extensive experience in endoscopy. The operation of ESD was conventional. The procedure of STER was as follows: First, a mixture of 5 mL indigo carmine + 1 mL epinephrine + 100 mL glycofructose was injected under the mucosa on the side of the mouth at a distance of 5.0 cm above the tumor

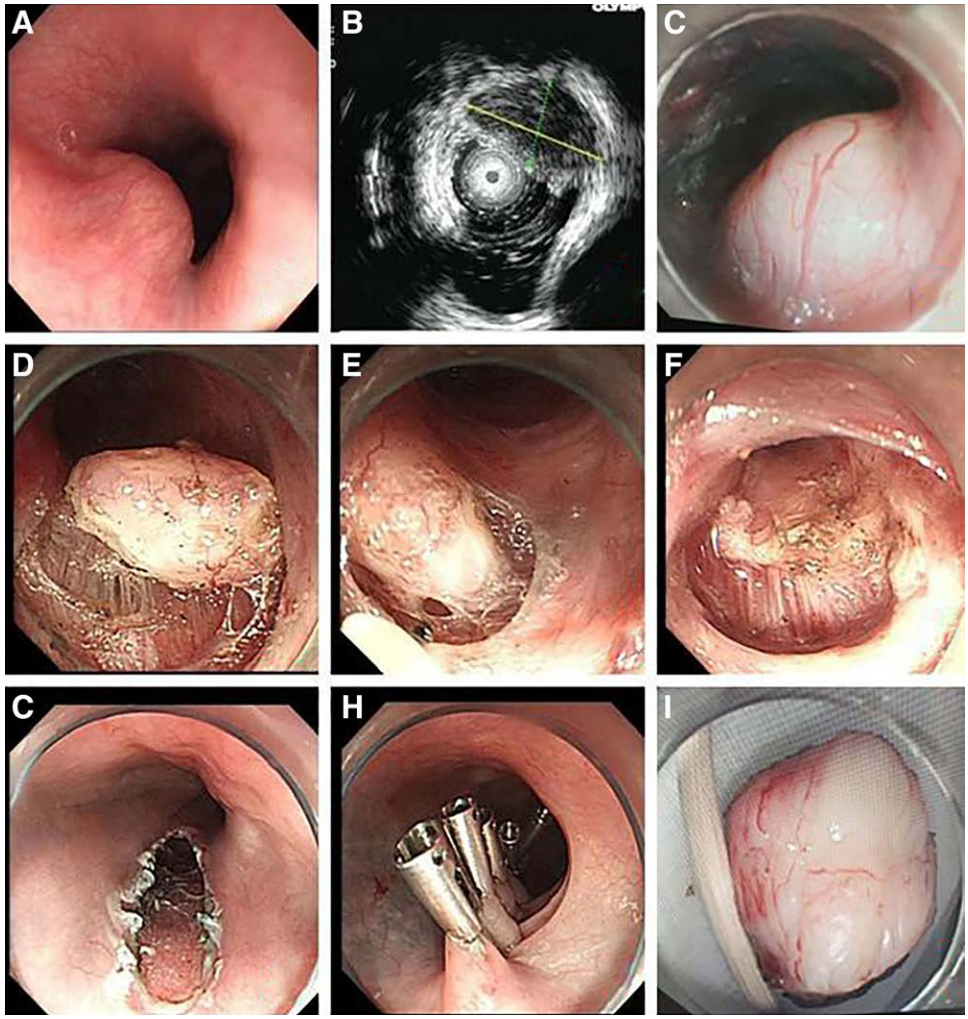

Figure 1. Transendoscopic STER for submucosal intrinsic esophageal muscle tumor. (A) White light endoscopy shows a bulging submucosal esophageal lesion. (B) Ultrasound endoscopy shows that the lesion originates from the intrinsic MP of the esophagus and has clear borders. (C) The close relationship between the tumor and the MP seen after entering the tunnel. (D and E) Peeling along the periphery of the tumor. (F) Trauma after tumor resection. (G) Entrance to the tunnel after tumor peeling. (H) Metal titanium clip to close the tunnel. (I) Resected specimen. MP = muscular layer, STER = submucosal tunnel tumor resection.

until the mucosa was clearly elevated. Next, dual-knife longitudinal incision of the mucosal layer and submucosal layer was performed, and a tunnel entrance with a length of about 1.5 to 2.0 cm was built. The submucosal tissue was separated, and the tunnel was entered with an endoscope between the mucosal layer and the intrinsic muscle layer. With the mucosal layer gradually peeling off as the endoscope was advanced, the tumor was reached, and separation of the submucosal layer was continued till 1.0 to 2.0 cm below the tumor. Then, a dual-knife was used to gradually separate the tumor body from the intrinsic muscle layer, and with bleeding or exposed blood vessels clamped by hemostatic forceps to stop or avoid bleeding, complete separation of the tumor body was achieved, and the tumor was removed. Thereafter, after the absence of any active bleeding was confirmed by observation, the endoscope was withdrawn from the tunnel, and the tunnel entrance was closed with a metal titanium clip. Finally, the tumor size was measured. The tumor was photographed and then immersed in 4% formalin and sent for pathological and immunohistochemical examination (Fig. 1).

2.6. Postoperative management and follow-up

Patients in both groups were fasted for 24 hours postoperatively and prescribed bed rest. They were provided gastrointestinal decompression for 72 hours if necessary, depending on the resection of the lesion. The patients were administered proton pump inhibitors, antibiotics to prevent infection, and electrolytes for rehydration; they were administered symptomatic treatment and closely monitored for signs and symptoms of vomiting blood, black stool, chest pain, and subcutaneous emphysema. Hemoglobin and platelet counts were quantified; C-reactive protein levels were checked, and temperature changes were closely monitored. For patients with intraoperative perforation or bleeding and endoscopic metal clip sutures, the fasting time was extended appropriately. To prevent delayed perforation or pneumothorax, chest CT scans and other examinations were performed if deemed necessary. All resected lesions were sent for pathological examination to determine the nature of the lesions and to confirm complete resection. Electronic gastroscopy was repeated at 3, 6, and 12 months postoperatively to observe wound healing and ensure that there is no recurrence of the disease. Moreover, chest and abdominal CT was repeated to exclude distant metastases during the follow-up period.

2.7. Statistical analysis

Considering that the age and gender of the two groups may not be balanced, which can interfere with the results, we conducted

a 1:1 propensity score matching (PSM) using the matchit package in R language, and the incorporated matching variables included age, gender, and a caliper value of 0.2 times the standard deviation of the log propensity score. The age and sex of the two groups were compared before and after matching to evaluate the balance. The following variables were used as outcome variables: length of stay, cost of hospitalization, duration of surgery, number of titanium clips, number of bleeding cases, and number of complete resections. These variables were compared between groups before and after matching. Data analysis was performed using R software (version 4.2.1) https://cran.r-project.org/src/base/R-4/. Bilateral *P* values of <.05 were considered to indicate statistically significant differences.

3. Results

3.1. Lesion characteristics

Among the 68 cases of esophageal SMT, the lesion was located in the upper esophagus in 1 case (1.47%), in the middle esophagus in 29 cases (42.65%), and in the lower esophagus in 38 cases (55.88%). Moreover, 62 cases (91.17%) showed predominantly intraluminal growth, whereas 6 cases (8.82%) showed intraluminal extraluminal growth. All lesions originated from the intrinsic MP of the esophagus. Postoperative pathology and immunohistochemistry revealed 13 cases (34.2%) of mesenchymal tumors and 25 cases (65.7%) of smooth muscle tumors in the STER group and 11 cases (27.5%) of mesenchymal tumors and 19 cases (47.5%) of smooth muscle tumors in the ESD group; there was no statistically significant difference in the pathological composition between the two groups (*P* > .05).

3.2. Surgical treatment

In the 68 cases of SMT of the intrinsic MP of the esophagus, the lesions were successfully resected endoscopically. The mean operative duration was 53.00 min [46.50 min; 60.00 min] in the STER group, and the number of titanium clips used was 4.00 [4.00; 5.00]. The postoperative hospital stay duration was 6.00 [5.00; 6.75] days. The overall hospital cost was 12,047.02 yuan [9145.06 yuan; 13,281.32 yuan]. In the ESD group, the operative time was 67.50 min [54.00 min; 83.75 min] (*P* < .05), the number of titanium clips was 3.00 [3.00; 4.00], the length of hospital stay was 7.00 [6.00; 9.50] days (*P* < .05), and the hospital cost was 16,640.68 yuan [13,119.59 yuan; 20,039.21 yuan] (*P* < .05; Table 1). Compared with patients in the ESD group, patients in the STER group had shorter operative times, lower hospital costs, and shorter hospital stays, and the differences were statistically significant (all, *P* < .05). The whole resection rate and complete resection rate were both 100.0% (38/38) in the STER group and 86.7% (26/30) and 100% (30/30), respectively, in the ESD group.

3.3. Comparison of the patient characteristics and treatment outcomes between ESD and ESTD groups before and after PSM

Before PSM, the length of hospital stay was greater in the ESD group than in the STER group (6 days vs 7 days). The cost of hospitalization was greater in the ESD group than in the STER group (16,640.68 yuan vs 12,047.02 yuan). The operating time was greater in the ESD group than in the STER group (67.50 min vs 53.00 min). After PSM, the age and gender distribution of the two groups were balanced (*P* > .05), whereas the length of hospital stay, hospital cost, and operating time remained greater in the ESD group than in the STER group. After PSM, the age and gender distribution of the two groups were balanced (*P* > .05l; Table 2); however, the length of hospital stay, hospitalization cost, and operation time remained significantly greater in the ESD group than in the STER group (all *P* < .05; Table 1), which is consistent with the results before PSM. There were no significant differences between the two groups in all other variables analyzed.

3.4. Complications

Among the 30 patients treated with ESD, one patient presented with delayed bleeding, which was successfully stopped postoperatively. No other patient showed any other complication. One patient in the STER group presented with subcutaneous emphysema, which resolved after conservative treatment, and there were no complications, such as bleeding or perforation. During the follow-up period, endoscopic review of both groups showed good wound healing, and there no local recurrence of the lesion or distant metastasis was noted.

Table 1

Comparison patient and lesion characteristics between the ESD and STER groups before and after groups propensity score matching.

	Before PSM (n = 68)			After PSM (n = 38)		
	0	1	*P* overall	0	1	*P* overall
	N = 38	N = 30		N = 19	N = 19	
Hospital stay (d)	6.00 [5.00; 6.75]	7.00 [6.00; 9.50]	<.001	5.00 [5.00; 6.00]	8.00 [6.00; 10.00]	<.001
Hospitalization cost (yuan)	12,047.02 [9145.06; 13,281.32]	16,640.68 [13,119.59; 20,039.21]	<.001	12,543.01 [9086.28; 13,859.52]	16,349.23 [12,914.25; 19,994.11]	.020
Operative duration (min)	53.00 [46.50; 60.00]	67.50 [54.00; 83.75]	.001	50.00 [41.50; 55.00]	67.00 [57.00; 86.50]	.001
Titanium clip	4.00 [4.00; 5.00]	3.00 [3.00; 4.00]	.001	4.00 [4.00; 5.00]	3.00 [3.00; 4.00]	.008
Whole block resection			.034			.486
No	0 (0.00%)	4 (13.33%)		0 (0.00%)	2 (10.53%)	
Yes	38 (100.00%)	26 (86.67%)		19 (100.00%)	17 (89.47%)	
Bleeding			.441			>.99
No	38 (100.00%)	29 (96.67%)		19 (100.00%)	19 (100.00%)	
Yes	0 (0.00%)	1 (3.33%)		0 (0.00%)	0 (0.00%)	

ESD = endoscopic submucosal dissection, PSM = propensity score matching, STER = submucosal tunnel tumor resection.

Table 2

Comparison patient gender age characteristics between the ESD and STER groups before and after groups propensity score matching.

	Before PSM (n = 68)			After PSM (n = 38)		
	0	1	*P* overall	0	1	P overall
	N = 38	N = 30		N = 19	N = 19	
Sex			1.000			1.000
Male	17 (44.74%)	14 (46.67%)		12 (63.16%)	11 (57.89%)	
Female	21 (55.26%)	16 (53.33%)		7 (36.84%)	8 (42.11%)	
Age	56.87 ± 8.96	61.40 ± 10.26	0.061	59.21 ± 6.43	59.53 ± 8.02	0.894

ESD = endoscopic submucosal dissection, PSM = propensity score matching, STER = submucosal tunnel tumor resection.

4. Discussion

SMTs of the esophagus are usually detected during endoscopy. Most smooth muscle tumors in the esophagus originate in the smooth muscle layer of the lower two-thirds of the esophagus.[9,11,16,17] Currently, there are many techniques used for the endoscopic resection of SMT in the upper gastrointestinal tract, such as EMR, ESD, and STER.[18]

In our group of 68 patients having esophageal SMT, postoperative pathology suggested smooth muscle tumors in 44 patients (64.7%) and mesenchymal tumors in 24 patients (35.3%). Therefore, to obtain an accurate and complete pathological diagnosis, early excision of SMT is essential. STER is used for the treatment of larger SMTs. It is performed endoscopically by creating a tunnel in the space between the submucosa and the intrinsic MP. The greatest advantage of STER is that it maintains the integrity of the gastrointestinal mucosa. This minimizes complications, such as perforation and secondary infection, and allows complete resection of the tumor. It also helps effectively avoid complications of gastrointestinal fistula and secondary thoracic and mediastinal infections.[10] In addition, Lv et al[19] reported that injecting carbon dioxide gas during the surgery reduces gas-related complications, such as pneumothorax. Furthermore, Maeda et al[20] reported that blowing carbon dioxide gas instead of air during esophageal ESD offered a significantly reduced incidence of postoperative mediastinal emphysema.[21] According to our findings, the whole resection rate and complete resection rate did not significantly differ between the STER group and the ESD group, suggesting that both techniques are suitable for the resection of the SMT located in the intrinsic MP of the esophagus. However, STER is associated with a shorter operative duration, shorter hospital stay, and lesser hospital costs, which greatly reduced the financial burden on patients. However, the sample size of patients with resected intrinsic esophageal muscle tumor was relatively small in this study, and the tunneling technique has been performed for a relatively short period as well; therefore, the long-term efficacy and long-term complications of STER remain unpredictable, and its clinical value needs to be studied further in larger samples. STER is performed by creating a submucosal tunnel 5 cm away from the tumor, and through this tunnel, the tumor is completely removed from the intrinsic MP. Conversely, conventional ESD involves resection of the tumor directly through the mucosa on the surface of the lesion. Therefore, ESD is associated with a relatively large trauma, and a part of the intrinsic muscle layer is removed as well in the process, thus making it difficult to completely close the surgical site using a metal titanium clip. Conversely, STER has a relatively small trauma, and with the mucosal layer and intrinsic muscle layer intact, the tunnel can be closed completely, thus enabling superior postoperative wound healing, shorter hospital stay, and lower costs in the STER group than in the ESD group. Notably, 4–6 clips are usually required to close the tunnel entrance postoperatively; accordingly, more titanium clips were used in the STER group than in the ESD group. Conversely, in the ESD group, titanium clips were used only when the wound was perforated or if thermal hemostatic forceps cannot be used. Generally, fewer clips (1–2 clips) were required. ESD reportedly has high complication rates, requires a longer operative duration, and requires extensive training and professional proficiency.[8,22–25] ESD is generally less efficient for SMT with deep MP layers and offers a low rate of complete resection (64%–75%) and a high incidence of perforation (≤20%).[11,26,27] One case in the ESD group developed black stool 24 hours postoperatively, which improved after endoscopic hemostasis. In contrast, only one case of subcutaneous emphysema occurred in the STER group, and there was no postoperative bleeding. These findings establish that STER can provide effective mucosal vascular management under direct vision during surgery, thereby reducing intraoperative and postoperative bleeding. This may have been caused by friction of the gastric tube, irritation of the wound by gastric reflux, and incomplete closure of the wound. STER endoscopic technique allows complete closure of the tunnel. This avoids any irritation from gastric reflux, thus reducing the incidence of delayed bleeding.[3,28] In a randomized controlled trial, it was noted that the lack of a plasma membrane layer can easily cause perforation after the resection of deeper intrinsic esophageal myxomatous tumors; furthermore, owing to a narrower esophageal lumen and greater wall tension in such cases, titanium clips cannot completely and effectively close the perforation, making the individuals prone to developing postoperative complications and even requiring surgical intervention.[29] Studies have shown that the application of some new methods and materials, for example, a newly invented injectable "thermogel as a novel submucosal injectable substance can reduce the incidence of complications in ESD. It has been acknowledged as the ideal injectable material for creating a higher submucosal mucosa and maintaining a longer lifetime. In this way, it minimizes the occurrence of mucosal perforation.[30–32]

In conclusion, our study shows that STER can safely and effectively treat submucosal intrinsic esophageal muscle tumors with fewer complications, such as bleeding and perforation, while offering the advantages of shorter hospital stay, lower hospital costs, and lesser trauma than ESD.

4.1. Limitations

In this study, all tumors measuring 1.0 to 3.5 cm in diameter were selected for the study. Since we introduced ESD technology earlier in our hospital, we have some experience in endoscopic surgical treatment before introducing the new technology in order to better perform STER technology. The operation was performed by senior and experienced physician, which, if performed by a relatively inexperienced physician, would have caused the accuracy of the results and compromised the broad applicability of the method.

Author contributions

All authors read and approved the final manuscript.
Yue Zhang: Project development, data analysis, and manuscript writing and editing.
Jing Wen: Project development, data analysis and collection, and manuscript writing.
Xiao Qiao: Project development, data collection, and operation treatment.
Shuxian Zhang: Project development, data collection, and operation treatment.
Xuyang Liang: Project development, data collection, and operation treatment.
Ling Ren: Project development, data collection, and operation treatment.
Lu Wang: Project development, data collection, and operation treatment.
Yunliang Sun: Project development, data collection, and operation treatment.
Shouying Li: Project development, data collection, and operation treatment.
Kun Wang: Project development, data collection, and operation treatment.
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Formal analysis: Jing Wen, Ling Ren, Xiao Qiao, Yue Zhang.
Methodology: Shengxiang Lv.
Project administration: Jing Wen, Kun Wang, Ling Ren, Lu Wang, Shengxiang Lv, Shouying Li, Shuxian Zhang, Xiao Qiao, Xuyang Liang, Yue Zhang, Yunliang Sun.
Resources: Kun Wang, Lu Wang, Shouying Li, Shuxian Zhang, Xuyang Liang, Yunliang Sun.
Writing – original draft: Jing Wen, Ling Ren, Xiao Qiao, Yue Zhang.
Writing – review & editing: Jing Wen, Shengxiang Lv, Xiao Qiao, Yue Zhang.

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