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Comparison of endoscopic submucosal dissection and surgery for the treatment of gastric submucosal tumors originating from the muscularis propria layer: a single-center study (with video)

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Abstract

Introduction Endoscopic submucosal dissection (ESD) has been used for the treatment of gastric submucosal tumors (SMTs). This study aims to compare clinical outcomes of ESD versus laparoscopic wedge resection (LWR) for gastric SMTs.

Methods This is a retrospective cohort study. Patients with SMTs who underwent ESD or LWR were enrolled in this study at a university-affiliated hospital from January 2010 to October 2015. Preoperative endoscopic ultrasound and computed tomography were performed to determine origin of layer and growth pattern. Clinical outcomes including baseline demographics, tumor size, operation time, blood loss, hospital stay, cost, pathology and postoperative complications were compared.

Results From January 2010 to October 2015, 68 patients with SMTs received ESD and 47 patients with SMTs received LWR. There was no difference in age, gender, body mass index, origin of layer and proportion with symptoms between ESD group and LWR group. However, tumor size was significantly larger in the LWR group (37.1 mm) than in the ESD group (25.8 mm, $P = 0.041$). For patients with tumors smaller than 20 mm, ESD was associated with shorter mean operation time (89.7 ± 23.5 vs 117.6 ± 23.7 min, $P = 0.043$), less blood loss (4.9 ± 1.7 vs 72.3 ± 23.3 ml, $P < 0.001$), shorter length of hospital stay (3.6 ± 1.9 vs 6.9 ± 3.7 days, $P = 0.024$) and lower cost (2471 ± 573 vs 4498 ± 1257 dollars, $P = 0.031$) when compared with LWR. For patients with tumors between 20 mm and 50 mm, ESD was associated with shorter mean operation time (99.3 ± 27.8 vs 125.2 ± 31.5 min, $P = 0.039$), less blood loss (10.1 ± 5.3 vs 87.6 ± 31.3 ml, $P < 0.001$), shorter length of hospital stay (4.0 ± 1.7 vs 7.3 ± 4.5 days, $P = 0.027$) and lower cost (2783 ± 601 vs 4798 ± 1343 dollars, $P = 0.033$) when compared with LWR. There were no significant differences in terms of rates of en bloc resection, complete resection and complication and histological diagnosis regardless of tumor size.

Conclusions ESD can achieve similar oncological outcomes when compared with surgery for treatment of gastric SMT smaller than 50 mm.

Keywords Submucosal tumor · Endoscopic submucosal dissection · Laparoscopic wedge resection · Gastrointestinal stromal tumor · Surgery

Fan-Sheng Meng and Zhao-Hong Zhang have contributed equally to this work.

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In recent years, more and more gastric submucosal tumors (SMTs) are found incidentally during routine upper gastrointestinal (GI) endoscopies. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in upper GI tract, and GISTs have malignant potential, particularly those originating from the muscularis

propria (MP) layer. GISTs are commonly located in the stomach (50–60 %) and small intestine (20–40 %) [1].

Open gastrectomy has been established as standard treatment of choice. However, surgery is associated with high morbidities and mortalities and significantly impairs quality of life after surgery. Laparoscopic wedge resection (LWR) is less invasive than open surgery with lower complication rate and shorter hospital stay. However, excessive gastric tissue may be resected when LWR was applied for SMT with intraluminal growth pattern, resulting in postoperative gastric deformity [2]. It also has disadvantages when the tumor is located in the cardia [3].

Endoscopic submucosal dissection (ESD) is initially developed for the treatment of superficial GI cancer. Recently, ESD has been employed for the treatment of SMTs. Our endoscopy center has used ESD to treat gastric SMTs and yielded positive results. However, few researchers have compared the efficacy and safety of ESD with surgery for SMTs.

In this study, we retrospectively reviewed data from patients who underwent ESD or surgery for gastric SMTs to compare the efficacy, safety and feasibility of ESD with surgery.

Methods and patients

We retrospectively retrieved the data of all patients who underwent ESD at the endoscopy center of First Affiliated Hospital, Zhejiang University, China. One hundred and sixty-three patients with SMT received endoscopic therapy between January 2010 and October 2015; 95 patients received band ligation and polypectomy snare therapy and 68 patients with SMT originating from MP layer were consecutively enrolled in this study. The inclusion criteria were as follows: (1) intraluminal SMTs without ulceration; (2) the maximal size of the tumor was <5 cm, with no high-risk endoscopic ultrasound (EUS) properties, such as irregular border, cystic space and heterogeneous echogenicity; and (3) no evidence of lymph node metastasis.

Meanwhile, 47 patients with SMTs smaller than 50 mm received LWR in gastrointestinal surgery department at our hospital.

Before ESD and surgery, EUS examination was performed to determine the size, layer of origin, internal echogenicity and growth pattern of SMTs. Abdominal computed tomography (CT) scan with contrast was performed to determine growth pattern and to exclude possibility of distant metastasis.

Before ESD and surgery were performed, informed consent was obtained from all patients. In addition, patients were informed about the potential complications of the procedure, as well as the possibility of conversion to open surgery in the case of severe complications. This study was approved by the institutional review board of the hospital.

ESD procedure

ESD was performed as previously described [4]. All of the ESD procedures were performed with patients under general anesthesia, and tracheal intubation was performed for mechanical ventilation. The procedures were performed as follows: (1) Marking dots were placed circumferentially 2 mm away from the margin of lesion with argon plasma coagulation (APC; APC300, ERBE, Germany) probe (Fig. 1D). (2) Several milliliters of mixed solution (including 250 ml glycerol fructose, 5 ml indigo carmine and 2 ml epinephrine) was injected into the submucosal layer of the lesion with injection needle (NM-4L-1, Olympus, Tokyo, Japan) to fully lift the mucosal layer. (3) The mucosa was incised circumferentially outside the marking dots with a hook knife (KD-620LR, Olympus, Tokyo, Japan) or dual knife (KD-650Q/U, Olympus, Tokyo, Japan; Fig. 1E). (4) The submucosal tumor was peeled from MP layer with an insulated-tip (IT) knife (KD-610L, Olympus, Tokyo, Japan) or dual knife (Fig. 1F, G); the mixed solution was injected repeatedly during the procedure if necessary. (5) The artificial ulcer was cauterized with APC to prevent delayed bleeding (Fig. 1H). (6) Hybrid knife (ERBE, Tuebingen, Germany) was used for injection, cutting or hemostasis according to operators' habits and preferences. (7) If bleeding occurred during ESD, endoscopic hemostasis was performed with APC, hook knife, IT knife, hot biopsy forceps (FD-410LR, Olympus, Tokyo, Japan) or hemoclips. If perforation occurred, metal clips (HX-610-90, HX-610-135, Olympus, Tokyo, Japan; Resolution, Boston Scientific, Boston, USA) were used to occlude the perforation. Loop and clip technique was used if necessary.

Laparoscopic wedge resection

All surgeries were performed under general anesthesia, and tracheal intubation was performed. The patients' vital signs were monitored. Patients were placed in the reverse Trendelenburg position with their legs apart. A 10-mm curved incision was performed 3 mm below the umbilicus, Veress technique was used to achieve carbon dioxide pneumoperitoneum, and the pressure was maintained at 12–15 mmHg. Usually, a four- or five-port technique was used. A 10-mm trocar was placed into the curved incision as observation port, and 30° lens was then placed, and another four trocars (two of 10 mm and two of 5 mm) were inserted into the right costal margin, right anterior axillary line, left costal margin and left anterior axillary line; a total of five trocars were inserted and arranged in a V-shape. Ultrasound knife (Harmonic ACE36P, Johnson & Johnson, New Jersey,

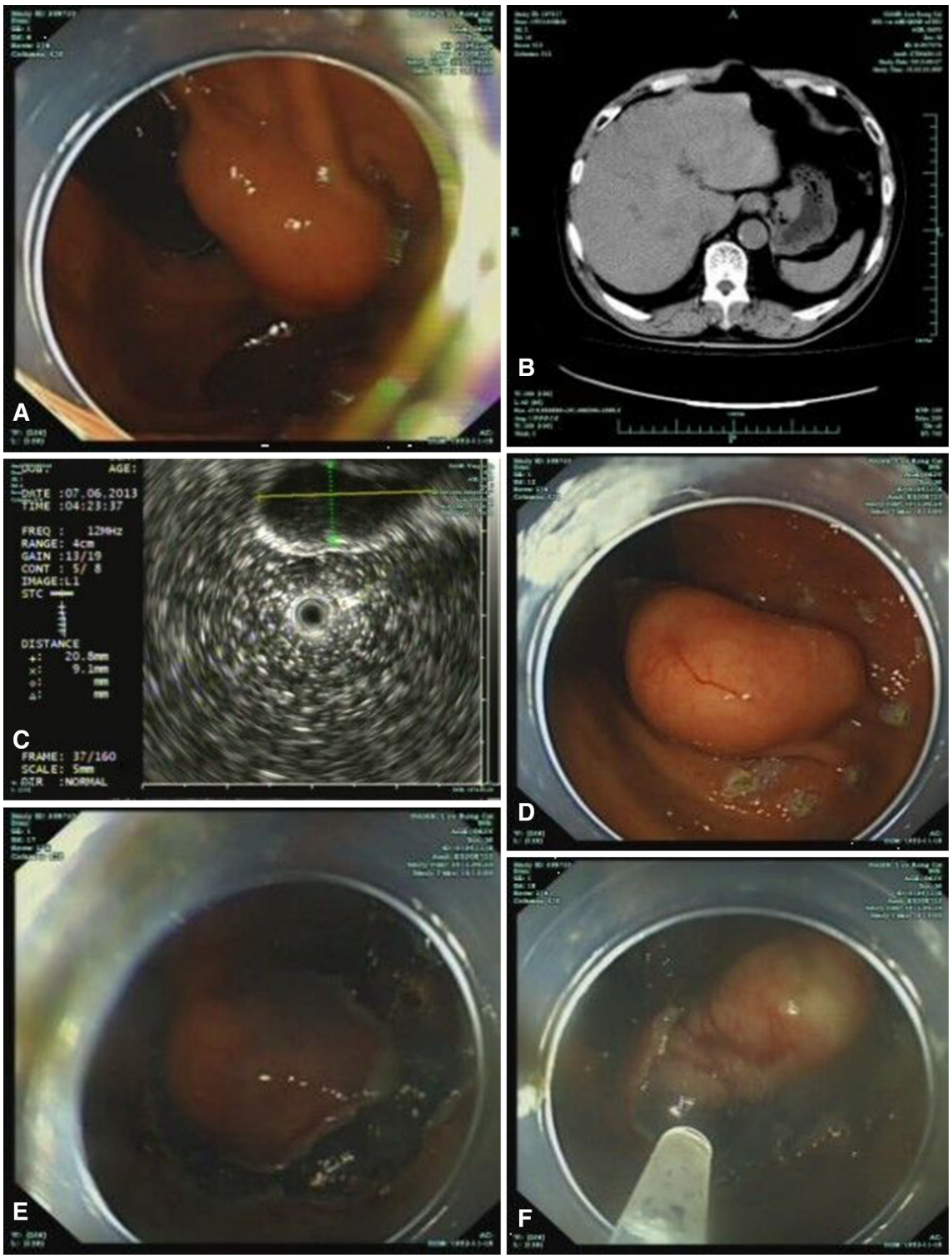

Fig. 1 ESD of gastric SMTs originating from the MP layer. **A** Endoscopic view of gastric SMTs. **B** CT evaluation of the same lesion. **C** EUS shows the tumor is originated from MP layer. **D** Marking dots circumferentially around the lesion. **E** Incision of the lesion circumferentially along the *marking dots* after submucosal injection. **F** Dissection of the lesion. **G** The completely resected tumor with an ESD technique. **H** The artificial wound surface was cauterized by APC

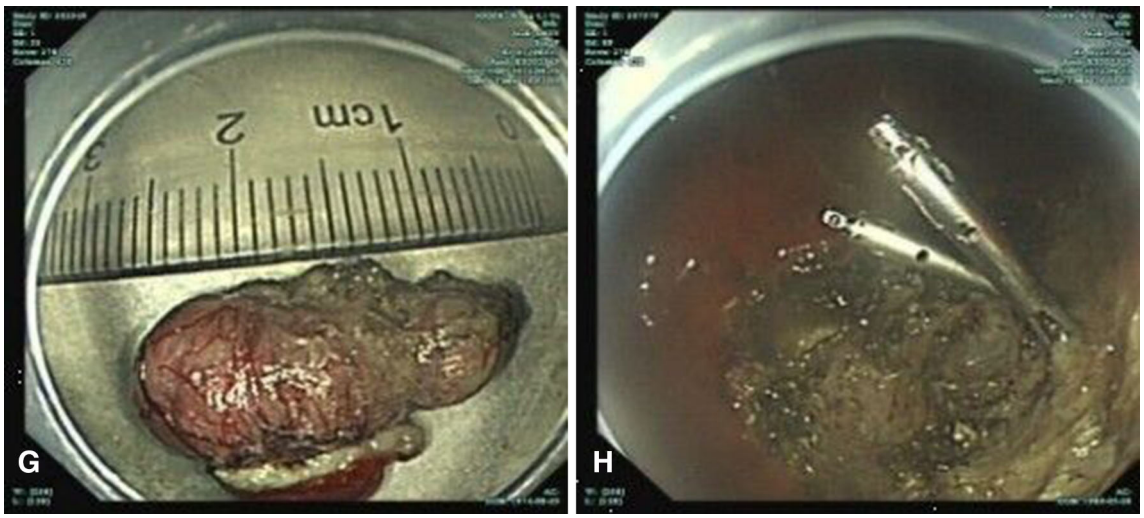

Fig. 1 continued

USA) was used to fully dissect stomach tissue around the tumor, and then, the tumor was lifted by clamping normal stomach tissue around tumor base with no-damage forceps. Gastroscopy was used intraoperatively to evaluate tumor localization if necessary. Laparoscopic linear stapling device (EC60, Johnson & Johnson, New Jersey, USA) was used to resect the tumor 20 mm away from the tumor base. Finally, the tumor was put into bag and extracted.

Those patients with large tumors with ulcer or hemorrhage, or tumors were located near the cardia or pylorus, proximal or distal gastrectomy was performed to prevent cardiac or pyloric stenosis.

En bloc resection was defined as the resection of tumors in one piece; complete resection was defined as an en bloc resection with tumor-free margins; operation time was defined as time length between start of operation and withdrawal of resected tumors; blood loss was defined as the amount of bleeding during operation; hospital stay was defined as the time from the date of ESD or gastrectomy to the discharge date; perforation was diagnosed as mesenteric fat or peritoneal space was seen during the procedure; massive bleeding was considered symptomatic bleeding with the need for blood transfusion or endoscopically uncontrollable bleeding with conversion to surgery.

Pathological evaluation

The resected samples were fixed in 10 % formalin solution and then sectioned for pathological evaluation. Immunohistochemical analyses of smooth muscle actin (SMA), desmin, CD117 (c-KIT), CD34, DOG1 and S-100 markers were performed to determine the tumor nature. Tumors that stained positive CD117 (c-KIT) or DOG-1 and CD34 were diagnosed as GISTs. Positive reactions for SMA and desmin were diagnosed as leiomyomas. Those lesions positive for S-100 were diagnosed as schwannoma. The risk potential of GISTs was determined in accordance with tumor size and mitotic index according to the National Institutes of Health consensus risk classification [5].

Postoperative management and follow-up

Oral diet was suspended for about 3 days for patients underwent ESD, and liquid diet was given after exsufflation for patients underwent LWR. Proton pump inhibitors (PPIs) and prophylactic antibiotics were administered intravenously for 3 days, and a PPI medication was then orally taken for another 8 weeks. When small perforation occurred, conservative treatment was employed, such as longer diet suspension, GI decompression and intravenous antibiotics.

The follow-up strategy was based on histological reports. The patients who underwent ESD were followed up with endoscopy at 1, 3 and 6 months after ESD. EUS was performed 3 months after ESD and was then repeated yearly. The patients who underwent laparoscopic surgery received first endoscopy at 3 months after surgery and then repeated yearly.

Statistical analysis

Demographic data, therapeutical outcomes and complications were analyzed with SPSS 19.0 software (SPSS Inc., Chicago, USA). Continuous data were expressed as mean ± standard deviation (SD). A Chi-square test or Fisher's exact test was used for comparison of categorical

data, and Student's t test was used for comparison of continuous data. A P value <0.05 was considered statistically significant.

Results

From January 2010 to October 2015, 68 patients with SMTs underwent ESD and 47 patients with SMTs were treated with LWR. The mean tumor size in the LWR group (37.1 mm) was significantly larger than that in ESD group (25.8 mm, $P = 0.041$). There was no significant difference in age, gender distribution, BMI, tumor site, tumor origin and proportion of patients with symptoms between the two groups ($P > 0.05$; Table 1).

Comparison of clinical outcomes between ESD and LWR

For patients with tumors smaller than 20 mm, ESD was associated with shorter mean operation time (89.7 ± 23.5 vs 117.6 ± 23.7 min, $P = 0.043$), less blood loss (4.9 ± 1.7 vs 72.3 ± 23.3 ml, $P < 0.001$), shorter length of hospital stay (3.6 ± 1.9 vs 6.9 ± 3.7 days, $P = 0.024$) and less cost (2471 ± 573 vs 4498 ± 1257 dollars, $P = 0.031$) when compared with LWR. There were no significant differences in terms of conversion to open surgery, tumor rupture, rates of en bloc resection, complete resection and complication and histological diagnosis (Table 2).

For patients with tumors between 20 and 50 mm, ESD was associated with shorter mean operation time (99.3 ± 27.8 vs 125.2 ± 31.5 min, $P = 0.039$), less blood loss (10.1 ± 5.3 vs 87.6 ± 31.3 ml, $P < 0.001$), shorter length of hospital stay (4.0 ± 1.7 vs 7.3 ± 4.5 days, $P = 0.027$) and less cost (2783 ± 601 vs 4798 ± 1343 dollars, $P = 0.033$) when compared with LWR. There were no significant differences in terms of conversion to open surgery, tumor rupture, rates of en bloc resection, complete resection and complication and histological diagnosis (Table 3).

The overall complication rate was not significantly different between ESD group and LWR group (8/68 vs 11/47, $P = 0.098$; Table 4). Five patients developed perforations and 3 patients developed bleeding in ESD group. The main complications of ESD were perforation and bleeding, 1 patient was converted to open surgery because of massive bleeding, and the rest of complications were managed endoscopically.

Discussion

GISTs are the most common SMTs in the stomach, which have prevalence of 0.4 % during routine endoscopies [6]. GISTs originate from the interstitial Cajal cells. These cells have myogenic and neurogenic potential and could be found within the mesenteric plexus, submucosa and MP of the GI tract [7]. GISTs are characterized by mutations of c-KIT or PDGFR [8, 9]. Although only 10–30 % GISTs are clinically malignant [10], all GISTs carry malignant potential [8]. According to the guidelines of National Comprehensive Cancer Network, all GISTs larger than 2 cm should be resected, and the management strategy for GISTs smaller than 2 cm is resection or surveillance [11]. However, the surveillance approach is associated with

Table 1 Comparison of baseline demographics and tumor pathology

	ESD group ($n = 68$)	LWR group ($n = 47$)	P value
Age	58.5 ± 7.3	57.1 ± 6.9	0.897
Gender (male/female)	28/40	20/27	0.883
BMI	25.1 ± 3.7	25.9 ± 4.2	0.843
Tumor size (mm)	25.8 ± 9.7	37.1 ± 12.3	0.041
Tumor site			0.779
Gastric fundus	27	20	
Gastric corpus	29	22	
Gastric antrum	7	3	
Gastric cardia	5	2	
Origin			0.437
Superficial MP layer	54	40	
Deeper MP layer	14	7	0.897
Patients with symptoms	31	22	

ESD endoscopic submucosal dissection, *LWR* laparoscopic wedge resection, *BMI* body mass index, *MP* muscularis propria

Table 2 Comparison of clinical outcomes between ESD group and LWR group for the treatment of gastric submucosal tumors (≦20 mm)

	ESD group ($n = 28$)	LWR group ($n = 14$)	P value
Mean operation time (min)	89.7 ± 23.5	117.6 ± 23.7	0.043
Mean blood loss (ml)	4.9 ± 1.7	72.3 ± 23.3	<0.001
Mean hospital stay (days)	3.6 ± 1.9	6.9 ± 3.7	0.024
Mean cost ($)	2471 ± 573	4498 ± 1257	0.031
Conversion to open surgery	0	0	–
Tumor rupture	0	0	–
En bloc resection	28	14	–
Complete resection	28	14	–
Complication	3	2	0.736
Bleeding	1	1	
Perforation	2	0	
Gastric emptying disorder	0	1	
Histological diagnosis			0.875
GIST	21	10	
Leiomyoma	6	3	
Schwannoma	1	1	
Follow-up (months)	11.7 ± 2.7	10.9 ± 4.3	0.651

ESD endoscopic submucosal dissection, *LWR* laparoscopic wedge resection

Table 3 Comparison of clinical outcomes between ESD group and LWR group for the treatment of gastric submucosal tumors (20–50 mm)

	ESD group ($n = 40$)	LWR group ($n = 33$)	P value
Mean operation time (min)	99.3 ± 27.8	125.2 ± 31.5	0.039
Mean blood loss (ml)	10.1 ± 5.3	87.6 ± 31.3	<0.001
Mean hospital stay (days)	4.0 ± 1.7	7.3 ± 4.5	0.027
Mean cost ($)	2783 ± 601	4798 ± 1343	0.033
Conversion to open surgery	1	0	–
Tumor rupture	0	0	–
En bloc resection	39	33	–
Complete resection	39	33	–
Complication	5	9	0.400
Bleeding	2	3	
Perforation	3	0	
Infection	0	1	
Postprocedural adhesion	0	1	
Anastomosis site stricture	0	1	
Gastric emptying disorder	0	3	
Histological diagnosis			0.847
GIST	28	21	
Leiomyoma	10	10	
Schwannoma	2	2	
Follow-up (months)	12.9 ± 5.1	11.1 ± 3.7	0.845

ESD endoscopic submucosal dissection, *LWR* laparoscopic wedge resection

issues of patient compliance, cost-effectiveness, emotional strain of bearing a tumor and delayed diagnosis of malignancy [12].

Previously, gastric SMTs are removed by open surgery [13]. However, open surgery is associated with longer operation time and hospital stay and higher complication rate. Quality of life will be significantly impaired, and the risk of remnant gastric cancer may increase [14].

LWR is less invasive with lower morbidity and mortality. However, it is sometimes difficult to determine a

Table 4 Comparison of overall complication rate between ESD group and LWR group for the treatment of gastric submucosal tumors

	ESD group ($n = 68$)	LWR group ($n = 47$)	P value
Massive bleeding	1	2	
Delayed bleeding	2	2	
Perforation	5	0	
Infection	0	1	
Postprocedural adhesion	0	1	
Anastomosis site stricture	0	1	
Gastric emptying disorder	0	4	
Small stomach syndrome	0	0	
Total	8	11	0.098

ESD endoscopic submucosal dissection, *LWR* laparoscopic wedge resection

precise lesion location, leading to excessive resection of gastric wall, particularly when the tumor is small and has intraluminal growth pattern.

Endoscopic resection of SMTs includes band ligation, snare polypectomy and ESD. The main disadvantage of band ligation is that specimens are not available for pathological analysis and risk evaluation, and snare polypectomy could be only suitable for small superficial SMTs. ESD is a minimally invasive treatment modality for early gastric cancer. In recent years, ESD has been applied for the treatment of gastric SMTs. Many studies have demonstrated that ESD has high efficacy and safety for the treatment of gastric SMTs [15–17]. ESD can preserve the whole stomach and maintain the integrity of normal GI function, so patients can have fewer complications and better quality of life.

In our study, the mean tumor size SMTs in ESD group was 25.8 mm (range 11–50 mm), and it is significantly smaller than those in LWR group (37.1 mm, $P = 0.041$). Histological analysis revealed that 49 SMTs were GISTs, 21 GISTs were considered very low risk and 28 GISTs were low risk.

In our study, the en bloc resection rate and complete resection rate of ESD for SMTs were 98.5 %, respectively, consistent with previous reports [7, 16, 18, 19]. GISTs are encapsulated in a fibrous capsule. Preserving the integrity of the capsule with gentle manipulation can completely resect the tumor.

ESD was associated with shorter operation time and hospital stay, less blood loss and cost than LWR ($P < 0.05$). The mean operation time in our study was 91.3 min (range 55–115 min), similar to previous studies [7, 16, 18, 19]. We found that tumors located in the gastric fundus were more time-consuming, because retroflexion of endoscope results in difficult manipulation of the IT knife. And tumors arise from deep MP layer may consume more time to dissect the tumor.

Noteworthy, complication rate was not significantly different between ESD group and LWR group in both smaller than 20 and 20–50 mm categories. And the overall complication rate was not significantly different between the two groups. The main complications of ESD are perforation and bleeding. Ohta et al. [20] demonstrated that lesions in the upper stomach and lesions larger than 20 mm were independent risk factors for perforation during ESD. Previous studies have reported an occurrence of perforation ranging from 0 to 20 % [12, 15, 17]; our study has shown perforation rate was 7.4 % (5/68), consistent with previous reports. SMTs originating from deep MP layer have higher incidence of perforation than those from superficial MP layer; this result may be explained by the fact that tumors arising from MP layer usually tightly attached to the gastric serosa. Therefore, the integrity of gastric wall may be difficult to maintain.

Perforations occurred in this study were small and closed by metallic clips. Loop and clip technique was used if necessary. Recently, a new device called over-the-scope clip (OTSC) which can achieve full-thickness closure of GI tract is brought to the market, and OTSC system can provide a simple, safe and reliable approach to occlude GI perforations.

Bleeding is another main complication of ESD, and much more time is consumed for hemostasis during ESD. Massive bleeding during ESD is life-threatening, and endoscopists should pay more attention to hemostasis. The bleeding rate in our study is 4.4 % (3/68), similar to previous reports [12, 21]. If bleeding happened during ESD, operation is difficult to continue because of vague vision. Therefore, measures should be taken to prevent bleeding. Minute vessels could be directly coagulated by APC or IT knife, and larger vessels could be treated with hot biopsy forceps. Once bleeding occurred, APC, hot biopsy forceps, clips or hybrid knife could be used for hemostasis. After resection of tumors, small visible vessels on wound surface

were cauterized with APC, and clips were used to occlude vessels if necessary.

Recently, a new technique developed from ESD, called submucosal tunneling endoscopic resection (STER), has been introduced for the treatment of upper GI SMTs originating from MP. Some studies have reported high efficacy and safety of STER for upper GI SMTs [22–24]. Another new technique called laparoscopic and endoscopic cooperative surgery (LECS) is developed for gastric SMTs, and some institutions have reported promising results [14, 25, 26]. However, both STER and LECS are developing, and their indications should be well established in the future.

There are several limitations in this study. First, it was a retrospective analysis. Second, the sample size was small. Third, our hospital is a tertiary referral center in China, and our results may not be extrapolated to other institutes. Fourth, the follow-up time was too short to determine long-term results. Therefore, large, randomized, control trial is required to confirm our results.

In conclusion, ESD appears as effective and safe as surgery for gastric SMTs. ESD could be the first-line treatment for intraluminal growth SMTs smaller than 5 cm without malignancy. However, ESD is technically challenging, and it should be performed in tertiary centers by experienced endoscopists.

Compliance with ethical standards

Disclosures Drs. Fan-Sheng Meng, Zhao-Hong Zhang, Yan-Yun Hong, De-Jian Li, Jie-Qiong Lin, Xin Chen and Feng Ji have no conflicts of interest or financial ties to disclose.

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