Endoscopic Resection of Submucosal Lesions of the Upper GI Tract: Full-Thickness Resection (EFTR) and Submucosal Tunneling Resection (STER)

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Abstract

Gastrointestinal (GI) submucosal tumors (SMTs) represent a unique challenge to modern clinical practice. In spite of the variable resection techniques that are used

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to resect GI SMTs, there are no specific recommendations or guidelines for each modality of treatment. It is broadly accepted that asymptomatic small lesions <2 cm could be left for surveillance, while larger lesions >5 cm in diameter arising from muscularis propria (MP) are usually sent for surgery. In this chapter, we aim to discuss changing concepts in the management of SMTs. Expanding the criteria has been already addressed by many publications. These general trends suggest that smaller asymptomatic lesions can be effectively resected with a high safety profile, with a good impact on patients' health. Larger lesions that were not previously considered for endoscopic management are now being treated in highly qualified centers with endoscopy. Submucosal tunneling endoscopic resection (STER) is considered an ideal solution for SMTs, expanding the use of third-space endoscopy. STER is ideal for esophageal SMTs and is extended to involve cardial or even extraluminal lesions. Difficult locations and gastric SMTs can be managed with endoscopic full-thickness resection (EFTR), provided that the local experience and the available tools to close the defect are adequate.

Keywords

Submucosal tumors (SMTs) · Endoscopic mucosal resection (EMR) · Endoscopic submucosal dissection (ESD) · Endoscopic submucosal excavation (ESE) · Submucosal tunneling endoscopic resection (STER) · Endoscopic full-thickness resection (EFTR)

Introduction

Submucosal tumors (SMTs) include a wide range of lesions protruding from the wall of the gastrointestinal (GI) tract covered with intact mucosa [1]. They arise from any layer beneath the epithelium: muscularis mucosa, submucosa, muscularis propria, and serosa [2]. They are divided into tumors without malignant potential, such as mesenchymal tumors, lipomas, leiomyomas, schwannomas, desmoid tumors, duplication cysts, pancreatic rests, inflammatory fibroid polyps, and giant cell tumor, and those with malignant potential, which include glomus tumors, granular cell tumors, carcinoids, and GI stromal tumors (GISTs) [3].

SMTs are becoming more frequently encountered during clinical practice [4]. They are usually asymptomatic and accidentally discovered (0.3%) during endoscopy for unrelated causes [5]. GISTs are the most frequently found SMTs in the upper GI tract [6].

Endoscopic ultrasound (EUS) can help in better detailed visualization of SMTs: layer of origin, actual size, extraluminal extension, feeding vessels, high-risk features of malignancy and associated lymph node involvement [7]. EUS can also help in confirming a histopathological diagnosis through fine needle aspiration/biopsy and cytology as conventional endoscopic biopsies are usually of low benefit [8].

In the past, the mainstay of treatment was either watchful waiting for small asymptomatic SMTs or surgical excision for large complicated ones [9]. However, studies have surprisingly shown that after resecting small asymptomatic SMTs; 71% of them had malignant potential [10]. Thus, expanding the criteria of endoscopic resection is mandatory giving patients the chance of having a minimally invasive treatment.

Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is the conventional endoscopic resection techniques for superficial SMTs. Endoscopic submucosal excavation (ESE) [11] or endoscopic muscularis dissection (EMD) [12] is a more advanced form of ESD in which part of the muscularis propria is excised with the lesion. However, these techniques had the drawback of incomplete resection of the tumors.

With the innovation of the third-space endoscopy and expansion of endoscopic resection techniques, novel techniques had evolved to overcome the limitations of the conventional methods [13]. Submucosal tunneling endoscopic resection (STER) and endoscopic full-thickness resection (EFTR) are getting more attention due to their curative potential [14–17].

Indications of Endoscopic Management

In spite of the expanding endoscopic treatment options and the rising clinical attention to SMTs, there is still no consensus or guidelines.

There are some general practice approaches for the management of SMTs with overlapping, but not contradictory, criteria. It is obvious that management of SMTs depends on multiple intermingling factors such as: size, site, layer of origin, type of SMTs, vascularity, extraluminal extension, malignant features, patient preference, and local experience.

The American Society of Gastrointestinal Endoscopy (ASGE) consensus guideline stated that EUS should be done to all lesions regardless the size and then the intraluminal lesions were classified according to their layer of origin. Lesions arising from the fourth layer were then further classified according to the presence of symptoms and their size, where the cutoff value is 4 cm. Symptomatic or suspicious lesions more than 4 cm had to be referred to surgery, while those 2–4 cm can endoscopically resected (EFTR, STER) [18].

Symptomatic lesions originating from second or third layer which are hypoechoic and more than 2 cm should be resected with EMR or ESD, while those less than 2 cm can be removed by EMR. It also stated that benign-looking lesions (e.g., lipoma, duplication cyst...), hyperechoic, non-suspicious EUS features, asymptomatic and not increasing in size could be left for surveillance [18] (Algorithm 1).

Algorithm 1
ASGE Recommendations:

1. We suggest that EUS be used to further characterize indeterminate SMTs.
2. We suggest surveillance EUS for gastric GI stromal tumors <2 cm in size.

(continued)

3. We recommend surgery for gastric and colorectal GI stromal tumors >2 cm in size and those with high-risk features.
4. We recommend that rectal GI neuroendocrine neoplasms <1 cm in size may be managed by local endoscopic or transanal excision.
5. We suggest EUS for staging of rectal GI neuroendocrine neoplasms >1 cm. Endoscopic or transanal excision may be considered for rectal tumors 1–2 cm in diameter that do not invade the muscularis propria.
6. We recommend surgical resection for GI neuroendocrine neoplasms identified in the jejunum and ileum.
7. We recommend that asymptomatic leiomyomas do not require endoscopic surveillance or therapy unless symptomatic.
8. We recommend that GI lipomas do not require follow-up or therapy unless symptomatic.
9. We suggest that lesions arising from the muscularis propria be sampled with FNA or fine-needle biopsy for histologic evaluation.
10. We suggest that a firm, round subepithelial lesion with central umbilication along the greater curve of the antrum of the stomach be considered diagnostic for a pancreatic rest. Further investigation with EUS and follow-up is not required.
11. We suggest that lesions with malignant potential requiring treatment can be removed either endoscopically or surgically based on the type of lesion, size, location, patient preference, and available expertise.

Asian perspectives tend more to expand the criteria of endoscopic resection owing to the increased incidence of upper GI tract malignancies and to the higher experience in the endoscopic resection field [19].

The Chinese consensus expanded the criteria of resection to include the complicated SMTs (bleeding or obstruction), it also expanded for the small benign lesions of low malignant risk potentials that it should be removed according to the patient's preferences and compliance [20].

The Korean guidelines generally align with the Chinese consensus; however, it recommended removal of GIST whatever the size of the lesion or its malignant potential [21].

Chinese Consensus:
1. For tumors with malignant potential suspected by preoperative examination or pathologically confirmed through biopsy, endoscopic resection should be considered when technically possible.
2. Endoscopic resection is indicated for SMT with symptoms (e.g., hemorrhage and obstruction).

(continued)

3. For benign tumors suspected by preoperative examinations or confirmed by pathological examination, endoscopic resection could be considered when patients cannot attend regular follow-up, tumors grow rapidly in a short period or patients have a strong preference for endoscopic treatment. After endoscopic resection for SMT, different treatment algorithms should be recommended according to pathological types:
   1. For benign lesions, such as lipoma and leiomyoma, postoperative routine treatment and follow-up are recommended.
   2. For SMT without malignant potential, such as well-differentiated rectal neuroendocrine tumors (NET) that are <1 cm, survival rate after complete resection is approximately 98.9–100% and the recurrence rate is extremely low. Therefore, routine follow-up is recommended when the margins were confirmed negative pathologically.
   3. Low-malignant-potential SMT, such as low-risk GIST, should be assessed by endoscopic ultrasonography or imaging every 6–12 months, and then managed according to clinical instructions.
   4. Medium/high-malignant-potential SMT, such as type 3 and type 4 gastric NET, colorectal NET that are >2 cm, and medium/high-risk GISTs, additional treatment is required according to the guidelines for each specific disease.

With regard to further expanding the criteria, there are some published studies about endoscopic resection of extraluminal SMTs even without laparoscopic assistance [22–24]. This suggests that local experience is one of the parameters that should be taken into consideration in the decisions of endoscopic resection of SMTs.

Submucosal Tunneling Endoscopic Resection (STER)

Since the introduction of natural orifice transluminal endoscopic surgery (NOTES), endoscopists can access the abdominal cavity (the second space) and perform therapeutic maneuvers [25]. To get access to the peritoneal cavity, a submucosal tunnel was intended to enable secure closure of the opening, using a submucosal endoscopy with mucosal flap safety valve (SEMF) [26]. While the original intent of submucosal tunneling was creation of a safe flap valve, the idea of tunneling has markedly evolved to utilizing the submucosa (third-space endoscopy) for direct therapies. Per-oral endoscopic myotomy (POEM) as treatment of achalasia [27] was one of the first major third-space endoscopy applications. Then tunneling extended to include G-POEM for refractory gastroparesis, submucosal tunneling endoscopic septum division [28] (also known as Z-POEM) for Zenker's diverticulum, and per-oral endoscopic tunneling (POET) for restoration of the esophageal lumen in cases of complete obstruction [29].

STER is part of this paradigm shift in endoscopy which is considered a disruptive innovation for endoscopic removal of SMTs. The nature of SMTs being submucosal had always been a challenge for endoscopists; however, this turned into an advantage to benefit from the endoscopic tunneling. STER was first introduced mainly for esophageal SMTs [14] and then extended to involve the gastric [30] and to a lesser extend to the rectal tumors [31].

Indications of STER

There are no sharp guidelines about when to use the STER versus other modalities; however, most studies and consensuses agreed that STER is best for SMTs which are symptomatic and > 2 cm in size. Still the upper limit of the size is the problem as some reviews state that the size of 3–3.5 cm is quite safe and applicable, while others extended the limit up to 5 cm [32, 33]. However, what matters is the cross-sectional diameter of the tumor, if the longitudinal diameter exceeds 5 cm and cross-sectional diameter is less than 3.5 cm, the SMT still can be treated by STER. Other factors usually involved are the patients' preferences and the local experience.

Absolute Indications

1. EUS and CT evidence of intraluminal growth tumor arising from muscularis propria
2. Diameter ≤ 5 cm (cross-sectional diameter of the tumor is mainly concerned due to the narrow space of the tunnel)
3. Tumor located in the mid esophagus, lower esophagus, or esophagogastric junction (EGJ)

Relative Indications

Significant extraluminal/exophytic growth SMTs arising from muscularis propria are considered as relative indications since STER procedures are more difficult to carry out.

Absolute Contraindications

1. Severe cardiopulmonary disease (ASA ≥ 3)
2. Coagulation disorders, thrombocytopenic disorders, or on anticoagulant or antiplatelet therapy which cannot be held or reversed
3. Pregnancy
4. Evidence of metastatic disease

Pre-Procedure Assessment

Before the procedure, routine EUS and computed tomography (CT) are performed in complementary pattern. They determine the size, possible layer of origin, margin, feeding blood vessels, growth pattern of the SMTs, extraluminal component, and to provide information regarding anatomic features of the adjacent structures and presence of metastasis [34].

Sometimes, EUS-guided FNA/B is obtained according to the indication to prove the histological diagnosis. However, the most challenging aspect in the diagnosis of SMTs by needle biopsy is the sampling error, which may miss focal areas of malignant changes [8].

STER Procedure

Equipment Required

A single-channel therapeutic water-jet scope is used during procedure. CO_2 insufflation must be used during STER procedure. A transparent cap is attached to the front of the endoscope. The patient is positioned in supine or left lateral and the procedure is carried out under general anesthesia with endotracheal intubation [14]. The most commonly used knifes are water-assisted knives, such as HybridKnife (ERBE, Tübingen, Germany) or injected Dual Knife (KD-655; Olympus, Tokyo, Japan); however, other knives can also be used according to the endoscopists' preference such as hook knife and IT knife (KD-611 and KD-620LR; Olympus, Tokyo, Japan). The presence of advanced electrosurgical unit is recommended (e.g., ERBE VIO 300 D). Coagulation forceps or at least hot biopsy forceps are necessary for the control of bleeding. Prophylactic intravenous antibiotics (second-generation cephalosporin) are given 30 min before procedure.

Procedure Steps (Fig. 1)

STER implies six important steps [14]:

Identification of the tumor: The tumor had to be accurately located. Sometimes it is challenging to locate, especially those in the cardia and fundus of the stomach. Submucosal injection of indigo carmine or methylene blue may be performed to help locate the tumor [30].

Submucosal injection and generating tunnel entry: A fluid cushion is created about 3–5 cm from the tumor. A longitudinal mucosal incision is done to generate tunnel entry. The initial mucosal incision can be about 1.5 cm in size to enable the entry of the scope meanwhile to maintain the endoscopic view with minimum gas insufflation. Later on, the mucosal incision may be increased to the size of the short dimension of the tumor to facilitate tumor retrieval.

Generating the tunnel: A submucosal tunnel extending 2 cm from the tumor is generated by dissecting between the submucosal and MP layers. The dissection plane should be maintained close to the MP to avoid mucosal injury. The tunnel should be sufficiently wide to ensure a satisfactory endoscopic view.

Dissection of the tumor: The tumor should be dissected at the MP layer without damaging the tumor capsule even if the MP and or serosal layers had to be cut completely.

Retrieval of the tumor: Small SMTs are easily extracted; however, for SMTs >35 mm is challenging. The tumor should be grasped with its longitudinal dimension parallel to the tunnel. If it is still difficult to extract from the tunnel opening or the

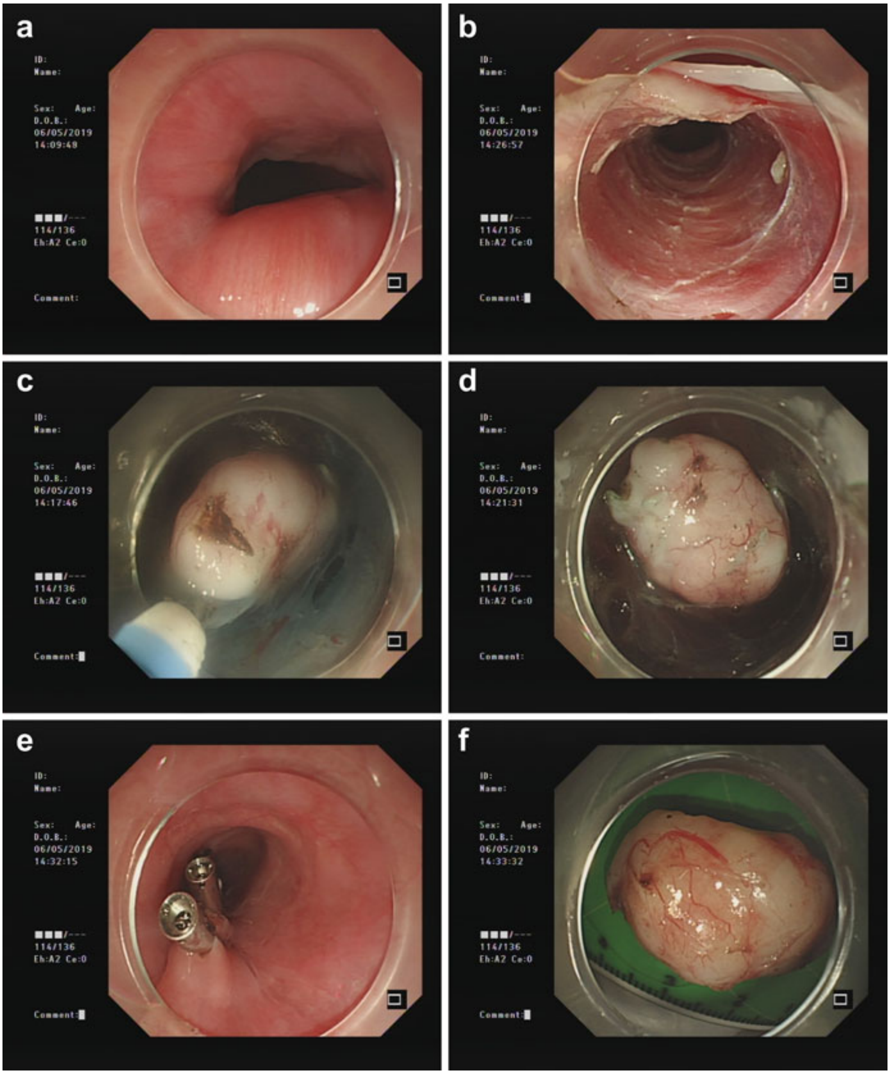

Fig. 1 STER (**a**) Identification of the tumor: an SMT located at the lower esophagus. (**b**) *Generating tunnel entry.* (**c**) *Generating the tunnel*. (**d**) *Dissection of the tumor*. (**e**) Closure of the mucosal entry. (**f**) The resected specimen

upper esophageal sphincter, the lesion can be cut down into pieces and extracted but this provided that the primary pathology is highly suggestive of a benign lesion [35]. An alternative approach is to generate a second "window," either in the area of the tumor or through a distal mucosal incision to facilitate en bloc extraction for large tumors [36].

Closure of the mucosal entry: Finally, the mucosal entry is sealed by several metallic clips or suturing.

STER at Different Situations

STER for esophageal and GEJ SMTs: The first STER case series was mainly for esophageal SMTs, as the tubular structure of the esophagus facilitates creating the tunnel. There is usually a decreased space to perform STER; hence, most experts recommend that maximum size should be 35 mm [30, 37]. But the fact is that this technique had extended to include larger and more difficult lesions. The maximum size that had been reported is 70 mm [38], but what matters is the cross-sectional diameter. Longitudinal size can be larger than the cross-sectional diameter.

STER for Gastric SMTs: Creating a tunnel in the stomach is usually challenging due to wide lumen, unfixed position, and thick mucosa. However, SMTs at the GEJ can typically be excised with STER, and some of the tumors in the fundus if they are close to the cardia by starting the tunnel in the lower part of the esophagus and dissecting across the cardia [39]. It is usually impossible to create a tunnel in the retroflexed position. There is a simple way to decide which maneuver is to be used to resect a SMT around the cardia. If the tumor is mostly seen from the lower esophagus, then STER is preferred; if the tumor is mostly seen in the fundus or occupies more than half circle in the cardia, direct resection by ESD technique is preferred. Figure 2 shows a gastric GIST resected by STER.

STER for rectal SMTs: The mucosa of the rectum is redundant with a tortuous lumen which makes it more difficult to create the tunnel than in the esophagus. There are few reports of successful excision of rectal SMTs with STER [31].

STER for multiple SMTs: Although it is quite rare to find multiple SMTs arising from the MP layer, there are some reported cases with multiple SMTs that could be all removed with STER [39–41]. Some were removed by creating a single tunnel when the patient had simultaneous esophageal and cardia lesions [42]. Others reported the presence of three lesions in the same time that were all removed by STER [43].

STER for extraluminal SMTs: STER is primarily indicated for intraluminal SMTs. However, in the era of third-space endoscopy and the insistence of stretching the limits, there are emerging data for extraluminal SMTs that were removed with STER [22]. Extraluminal SMTs or those with extraluminal extensions are considered a relative indication in expert hands. Taking advantage from tunneling, STER is considered optimum for these lesions. *Cai* et al. reported eight cases of SMTs with their size ranging from 20 to 39 mm with the main component of the tumors were extraluminal and they were successfully removed with STER [23]. The average procedure time was 67 min with median 3 days for hospital stay and no major events were recorded. *Li* et al. also reported resection of large mediastinal schwannoma, 20×25.7 mm with STER [44]. From the technical point, full thickness GI wall dissection is necessary to ensure en bloc tumor resection. A dual channel gastroscope is occasionally needed to extract the tumor into the submucosal tunnel using grasping forceps to prevent tumor displacement into the peritoneal cavity.

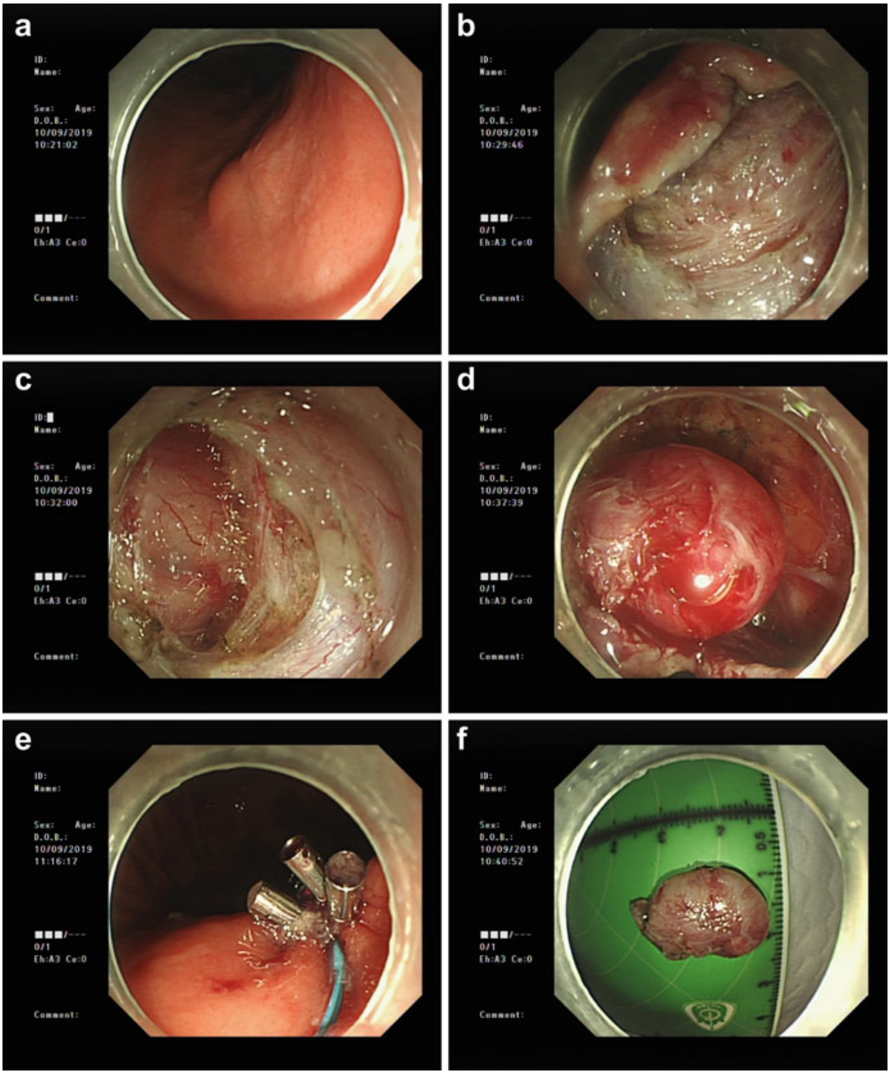

Fig. 2 Gastric STER. (**a**) An SMT was seen at the lesser curvature of gastric body. (**b**) Tunnel mucosal entry was made. (**c**) Dissection in the tunnel was done around the tumor. (**d**) The tumor was extraluminal growing to the abdominal cavity. (**e**) The mucosal entry was closed by clips and an endoloop. (**f**) The resected specimen

Post-Procedure Care

Monitoring of post-procedure symptoms is essential such as fever, chest pain, dyspnea, cyanosis, bleeding, abdominal pain, guarding, or rigidity. Detection of early complications and subsequent prompt management is important in improving the outcome of the patients. Although there are no guidelines in this area, our practice is as follows. All patients are kept *nil per os* (NPO) for at least 24 h. Intravenous antibiotics should be continued, proton pump inhibitors (PPI) and I.V fluids are given. PPI should be continued orally for upper GIT SMTs for few weeks after. For rectal SMTs, it is important to maintain soft stools without straining in defecation. If patient remains asymptomatic on day 2, the diet is advanced to liquids and subsequently to full diet accordingly [31].

Adverse Events of STER

In general, STER is a safe procedure with a varying percentage of adverse events in expert hands. No STER-related deaths have been reported to date. Early detection and prompt management of these adverse events are essential for the outcome of the patients. In a large study of 290 patients who underwent STER, the overall adverse event rate was 23.4% (68/290, including 39 minor and 29 major adverse events). Major adverse events consisted of 9 cases of major pneumothorax, 3 mucosal injury, 5 major bleeding, 11 major effusion, and 1 esophageal-pleural fistula, which needed interventions [38]. This study demonstrated that irregular shape, the location of the tumor in the deep MP layer, increased procedure time, and air insufflation were risk factors for major STER-related adverse events.

Intra-Procedural Complications

Most of the intra-procedural complications are related to the gas diffusion especially after cutting the muscles. Other adverse events as bleeding, aspiration, or mucosal injuries could be also encountered.

Gas-related complications: Subcutaneous emphysema (SE), pneumoperitoneum, and to a lesser extent pneumothorax and mediastinal emphysema are the most frequently encountered complications during the procedure reaching up to 66.7% [45, 46]. These are related to gas diffusion specially after cutting the muscle; hence the use of CO_2 insufflation is a must due to its high absorbability. These can be detected during the procedure when the CO_2 sensor connected to the endotracheal tube starts to read elevated levels. At that time, hyperventilation or even pausing the procedure for some time can solve the problem. For pneumoperitoneum, it usually needs no intervention as it will be eventually absorbed. However, if tension develops that comprise the patient's vital signs, immediate venting with a percutaneous angiocath under water seal should be done. Pneumothorax is relatively a rare complication that will usually resolve spontaneously; however, chest drainage may be needed in compromised cases with lung collapse >30%. Some consider pneumothorax and pneumoperitoneum as a sequel rather than a true complication [47]. It is recommended to use an adjustable CO_2 insufflator, where the flow can be controlled, and the use of the lowest flow is required to maintain an open lumen. The endoscopists should minimize pressing on the air/CO_2 insufflation button especially after cutting the MP layer.

Bleeding: Intra-operative bleeding is usually mild and can be controlled with use of coagulation with the tip of the knife. However, major bleeding can rarely occur and can be controlled with coagulation forceps. It is essential to secure all bleeding blood vessel to avoid delayed bleeding. One of the most important steps in STER is to secure the tumor bed after resecting it through coagulating the potentially bleeders. The largest series had a rate of 1.7% (5/290) for major bleeding (>200 ml). All were managed endoscopically without blood transfusion [38]. Excessive coagulation should be avoided, as it can cause undesired mucosal injury.

*Mucosal injury: This is o*ne of the most unwanted complications of STER as it abolishes the idea of tunneling. It may be related to excessive coagulation or during dissection in narrow space between the tumor and the mucosa. Enough injection is required when dissecting close to the mucosa. Inspection of the surface of the tunnel is essential step before closing the tunnel opening, to detect any small lacerations and close them. Mucosal injuries are usually small and can be closed with clips while large areas may sometimes require stenting or suturing [48]. Unclosed mucosal injuries may lead to delayed perforation, leakage, or fistulas.

Post-Procedure Complications

Delayed or post-procedure complications are usually serious complications that are related to leakage and infection.

Fistula and leakage: This is the most challenging complications after STER. The valve-like manner in the tunneling technique functions to prevent fistula formation and subsequent leakage. However, a few cases were reported, <0.2%, for example, delayed esophageal-pleural fistula [38]. Leakage is usually managed with drainage of the collection (thoracic or abdominal) first, then endoscopic closure of the fistula opening with endoclips.

Infections: These include mediastinitis, peritonitis, or subphrenic infections. Monitoring of fever postoperatively is crucial for early detection of infections together with the presence of abdominal or chest pain. Upgrading antibiotics is recommended once fever (>38.5° C) is encountered. Few reported cases of post-procedure infection have been reported and are usually managed conservatively with antibiotics and or drainage [49]. No related mortalities have been encountered.

Pleural or mediastinal effusion: Most of the effusions are reactive, but clinically significant effusions are uncommon. Clinically significant pleural and mediastinal effusions were treated with antibiotics and/or drainage [38, 49].

Bleeding: Delayed bleeding is a potential concern, however no reported cases.

Pain: Postoperative pain is usually annoying to the patients especially chest pain. Prophylactic analgesics could be given just before the end of the procedure.

Patient Follow-Up

Patients are followed up with endoscopy at 3, 6, and 12 months after STER and annually thereafter to assess for residual tumor or tumor recurrence. For patients with tumors with malignant potential, a contrast enhanced CT is performed on an annual basis to rule out distant metastasis.

Clinical Outcomes of STER

The data of the main researches that tackled STER across the years are tabulated in Table.1. As shown in Table 1, the technical success of STER is ranging from 97% to 100%, while the en bloc resection rate ranges from 81% to 100%. It is recommended that STER should be done in a highly qualified center with experienced endoscopists in the third space era. The mean duration of the procedure ranges from 43 to 104 min with most of the studies around 1 hour. Most of the complications encountered are usually related to gas diffusion, but serious complications as esophageal-pleural fistula was only encountered once in a large study (1/290) [38]. The presence of residual tumor or recurrence was not experienced in literature (Table 1); this may be related to the nature of the tumor itself being capsulated and submucosal targeting to remove it with an intact capsule. Long-term outcome trials are few: the largest one included 180 patients with only 1 patient needing additional surgery, 2 patients lost for follow-up, and 177 patients had no recurrence after a mean follow-up period ranging from 28 to 51 months with mean of 36 months [50]. It is obvious that STER is an effective procedure with modest, manageable adverse events. However, randomized controlled trials are still needed to assess its efficacy and safety compared to other modalities including observation alone.

Endoscopic Full-Thickness Resection (EFTR)

EFTR is defined as resection of all the layers of the GI wall. It is described mainly for lesions that are not amendable for resection with the conventional endoscopic resection techniques such as EMR or ESD. These lesions could be SMTs arising from the MP layer, non-lifting adenomas, or recurrent adenomas with severe fibrosis [54]. In the past, these lesions were sent for surgical resection due to the inevitable risk of perforation. With the advance of the endoscopic techniques, closure devices and methods, these lesions could be endoscopically resected and hence came the idea of EFTR, saving the patient from unneeded surgery. Assisted laparoscopic resection was addressed in literature [55], but recently, free-hand EFTR can be used as single method [15]. It is well accepted that EFTR are usually classified into two types: the device-assisted EFTR in which a preloaded device is used to close the defect before resection and is called EFTRD (will be discussed in later chapters). While the second type is the free-hand EFTR, in which the lesions is totally removed leaving a defect behind, that should be subsequently closed [56, 57].

The ASGE described two different approaches for EFTR: exposed and nonexposed EFTR [58]. In exposed EFTR, the full-thickness resection is undertaken first, with subsequent closure of the defect. Exposed EFTR can be further classified into tunneled and non-tunneled techniques. In nonexposed EFTR, the bowel wall segment containing the lesion is invaginated toward the lumen to allow a secure serosa-to-serosa apposition before full-thickness resection. The closure is achieved before the resection with this approach, and thus the term "nonexposed" [59]. However, the

Table 1 Clinical outcomes of STER

Study	N	Mean size (range) (mm)	Site	Pathological diagnosis	Success (%)	En bloc (%)	Adverse events	Mean time (min)	Recurrence/ follow-up (m)
Xu et al. [14] (2012)	15	19 (13–30)	Esophagus (9) Cardia (3) Corpus (2) Antrum (1)	Leiomyoma (9) GIST (4) Glomus tumor (1)	100	100	Pneumoperitoneum (1) Pneumothorax (1)	78.7	0/6
Ye et al. [46] (2014)	85	19.2 (10–30)	Esophagus (60) Cardia (16) Corpus (9)	Leiomyoma (65) GIST (19) Calcifying fibrous tumor (1)	100	100	Pneumoperitoneum (4) Pneumothorax (6)	57.2	0/8
Wang et al. [33] (2015)	80	23.2 (10–55)	Esophagus (67) Cardia (16)	Leiomyoma (68) GIST (15)	100	97.6	Pneumothorax (1) Chest pain (3)	61.2	0/10.2
Chen T et al. [38] (2016)	290	21 (10–70)	Esophagus: Upper (13) Middle (96) Lower (90) Cardia (68) Stomach (23)	Leiomyoma (226) GIST (53) Schwannoma (5) Calcifying fibrous tumor (3) Glomus (3)	100	89.3	SE (61) Pneumothorax (22) Pneumoperitoneum (15) Effusion (49) Fistula (1) Diverticulum (1)	43	0/12
Chen et al. [50] (2017)	180	26 (20–50)	Esophagus (124) Cardia (43) Corpus (13)	Leiomyoma (146) GIST (28) Calcifying fibrous tumor (2) Schwannoma (2)	99.4	90.7	Pneumothorax (10) Major bleeding (2) Mucosal injury (2) Esophageal-pleural fistula (1)	45	0/36

Tu et al. [51] (2018)	119	19.4 (8–60)	Esophagus: Upper (10) Middle (58) Lower (51)	Leiomyoma (113) GIST (5) Granular cell tumor (1)	100	97.5	SE (9) Pneumothorax (6) Pneumoperitoneum (2) Perforation (9)	46.7	0/15
Cai et al. [23] (2018)	8	28 (20–39)	Extraluminal (8)	GIST (6) Schwannoma (1) Foregut cyst (1)	100	87.5	Pneumoperitoneum (5) Mucosal injury (1)	67	0/10
Xu et al. [52] (2019)	44	22.07	Esophagus (14) Cardia (14) Fundus (16)	Leiomyoma (31) GIST (10) Schwannoma (2) Lipoma (1)	100%	100	SE (12) Pneumothorax (6) Pneumoperitoneum (2)	104.9	0/17.5
Zhang et al. [53] (2019)	27	16.67 (8–40)	Esophagus Upper (1) Middle (15) Lower (11)	Leiomyoma (25) GIST (1) Schwannoma (1)	100	81.48	Fever (1)	84.05	0/22.4

tunneled exposed approach is like the STER procedure described above, in which the mucosa is requested to be intact and this is unusual to be described as EFTR.

Indications of EFTR

Due to the novelty and relative complexity of the procedure, it is still not broadly used for treatment of SMTs and no definite guidelines for it [60]. These are proposed indications and contraindications for EFTR for SMTs [56]:

Indications	
	SMTs $\leq$5 cm arising from the MP layer confirmed by EUS and CT, especially when the laparoscopic intervention could be difficult, provided that the devices required for closing the defect and the necessary experience are available
Contraindications	1. High surgical risk as severe cardiopulmonary diseases, coagulation disorders
	2. Features in preoperative imaging or pathology suggestive of aggressive behavior

Pre-Procedure Assessment and Equipment

Regarding the pre-procedure assessment, the same as mentioned above for STER. While the required settings also the same as mentioned above, however, for each type of EFTR, specialized instruments will be used accordingly targeting mainly the closure of the defect created. This will be mentioned in details with discussing each type thoroughly.

EFTR Techniques

Free-Hand EFTR

Free-hand EFTR is a complex technique that requires a highly experienced endoscopists and a fully equipped advanced endoscopy unit. Back-up surgery should be always available. EFTR constitutes the concept of “CUT and CLOSE.” The procedure starts by complete resection of the lesion violating the whole layers of the GIT. This results in a “HOLE” that should be efficiently closed to avoid leakage. Methods that were described in literature to close perforations are the key for EFTR.

STEPS of EFTR [16] (Fig. 3)

Step 1: For deep lesions or small lesions (<10 mm), several marking dots around the periphery of the lesion or one marking dot on the top of the lesion are made using either the tip of the electrosurgical knife or argon plasma coagulation (APC)

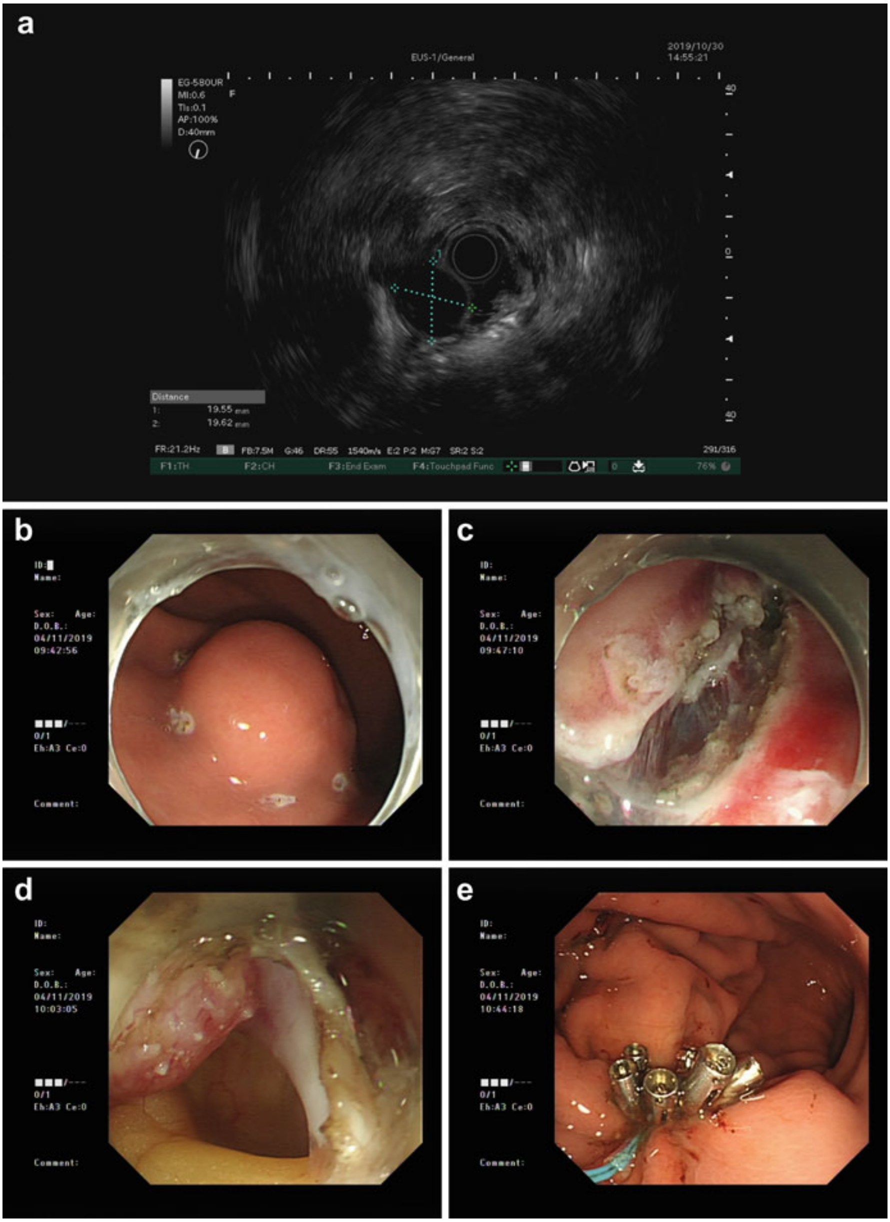

Fig. 3 (continued)

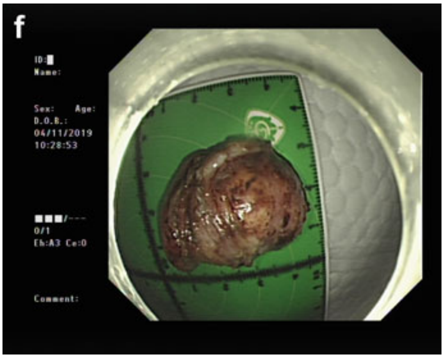

Fig. 3 **EFTR** (**a**) EUS found an SMT originating from the MP layer. (**b**) Several marking dots around the periphery of the lesion. (**c**) Incision was made along the marking dots. (**d**) Full-thickness resection was made with whitish tissue showing the serosa and yellowish tissue showing omentum. (**e**) The full-thickness defect was closed using purse-string closure technique. (**f**) The resected specimen

catheter because the location may become vague after submucosal injection. Otherwise, marking can be omitted.

Step 2: A submucosal injection of a mixture of 100 ml of normal saline with 1 ml of indigo carmine to create a protective submucosal "cushion" to prevent deep thermal injury during tumor resection.

Step 3: A circumferential mucosal incision is made along the contour of the SMT. Another option is to perform mucosal excision to unroof the SMT.

Step 4: Submucosal and sub-tumoral dissection is performed surrounding the tumor capsule to ensure a complete en bloc resection of the tumor. Meticulous care must be taken to avoid interruption of the tumor capsule. All visible vessels must be coagulated, and prompt hemostasis must be achieved to avoid accumulation of blood in the GI lumen or in the peritoneal cavity after tumor resection. To avoid losing the specimen into the peritoneal cavity, a snare can be used for the final cut of the lesion and immediate specimen retrieval after resection. Use a double-channel endoscope with grasping forceps inserted into one channel to grasp the lesion while the electrosurgical knife is inserted into the second channel to excise the lesion. Also, a suture attached to a clip applied to the mucosal surface of the lesion [61].

Step 5: Once the tumor is enucleated, the closure of excisional wall defect can be performed using various available methods as described below depending on the size of the GI wall defect. The diameter of the wall defect can be reduced by air suction to assist in closure of the defect. Continuous CO_2 insufflation must be avoided to prevent pneumoperitoneum and regular suction of content within the GI lumen is vital to avoid spillage of fluid and blood into the abdominal cavity. Throughout the procedure, care is taken to constantly monitor the patient's positive end expiratory pressure (PEEP) and for clinical signs of raised intra-abdominal pressure. When necessary, a 20-gauge needle is inserted under aseptic technique directly into the abdominal cavity to relieve pneumoperitoneum during and after the procedure.

Closure of iatrogenic wall defect: This is the most challenging step in EFTR. Cautious should always be taken to avoid unnecessary dissection, leaving a large gap.

Metallic clips closure: There are a variety of metallic clips available in clinical practice to close GI wall defects. Endoluminal metallic clips have been widely used in clinical practice for closure of GI wall defects, anastomotic fistulas, small perforations after endoscopic resection, and hemostasis. It is recommended that metallic clips are generally used to close elongated wall defect that are less than 2 cm in cross-sectional diameter. However, in certain locations (e.g., gastric fundus), endoscopic suction can reduce the size of the wound, and thus 2 cm is not a definite maximum diameter for metallic clips closure method.

Over-the-scope clip (OTSC) system (OTSC, OVESCO Endoscopy AG, Tübingen): It had been developed primarily for bleeding GI ulcers but its role had been expanded to closing the defects. OTSC can be used grasp more tissue and close wider defects. It consists of a cap with a preloaded clip and a hand wheel for clip release that utilizes the working channel of the endoscope [61]. Its setup is like a band ligation device and the clip resembles a bear claw when deployed. There are 3 cap-diameter options (11 mm, 12 mm, and 14 mm) and cap depths of either 3 mm or 6 mm. Three variations in clip teeth configuration are available: type a (blunt teeth primarily for compression), type t (small spikes on teeth for compression and anchoring), and type gc (spikes on elongated teeth for gastric wall closure) (Fig. 4a) [62]. Auxiliary devices such as a double grasping forceps (Twin Grasper, OVESCO Endoscopy AG, Tübingen) (Fig. 4b), a three-hook anchoring device (anchor OVESCO Endoscopy AG, Tübingen) (Fig. 4c), or simple suction into the mounted plastic cap were also assessed by the endoscopist. The rate of OTSC for closure of perforations is around 90% [63]. Guo et al. used a combination of OTSC system and metallic clips to completely close the resected opening and reported promising results [64].

The Padlock clip (Fig. 5): It is a star-shaped nitinol ring with six inner needles that is preloaded on a cap. It has radial compression technology that facilitates circumferential tissue apposition. The clip is available in two sizes: The standard Padlock fits a 9.5–11-mm diameter endoscope, while the Padlock Pro-Select fits an 11.5–14-mm endoscope. Both clips have a cap diameter of 11 mm that allows for atraumatic intubation, particularly via the oral route, and the cap depth or tissue chamber increases along with the diameter of the endoscope. The trigger wire for clip deployment is located alongside the endoscope's shaft, freeing the working channel for passage of accessories and suction of luminal contents [65]. The clip is deployed using a simple push button. It is postulated that the Padlock system offers more grasp of the tissue, so no need for an auxiliary accessory. Failure of clip deployment may be a result of capturing too large a volume of tissue and/or angular location of lesions that hinder the trigger mechanism for clip release.

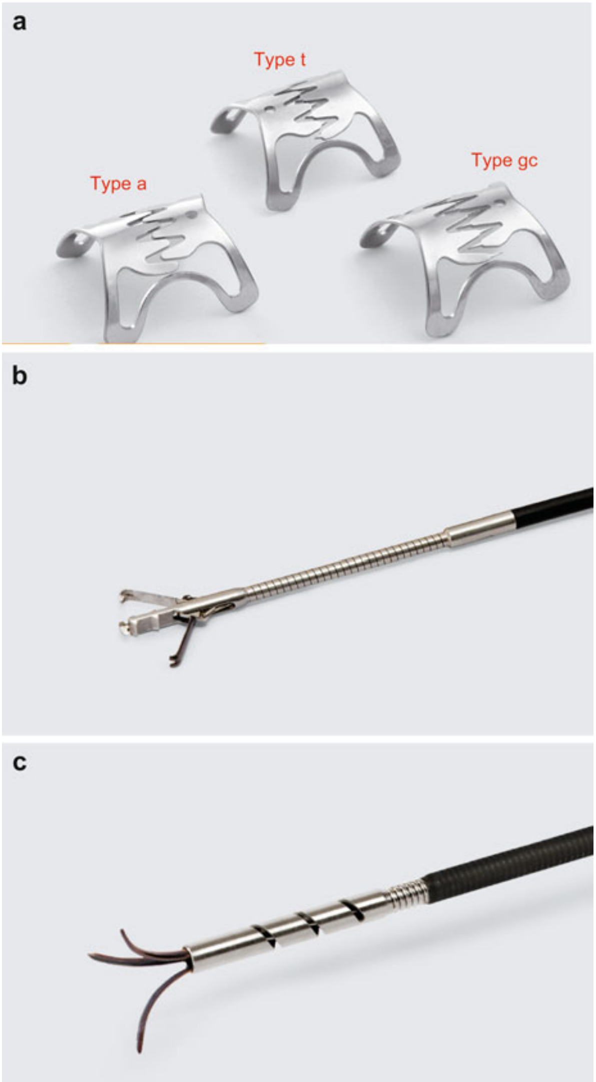

Fig. 4 OTSC system. (Photo credit: OVESCO Endoscopy AG, Tübingen, Germany). (**a**) Different types of clips. (**b**) A double grasping forceps. (**c**) A three-hook anchoring device

Purse-string closure technique (metallic clips combined with endoloop): Matsuda first introduced the metallic clips combined with endoloop snare to close EMR defects successfully [66]. This technique can be divided into two ways:

Linear closure: This is applicable for small defects with a single endoloop and two metallic clips anchoring over the proximal and distal edges of the defect to close.

Purse-string closure: This way is suitable for large defects. It uses a single endoloop and about five to six metallic clips gathering mucosa around the defects to the center to close [67]. This technique has many variations; the commonly used

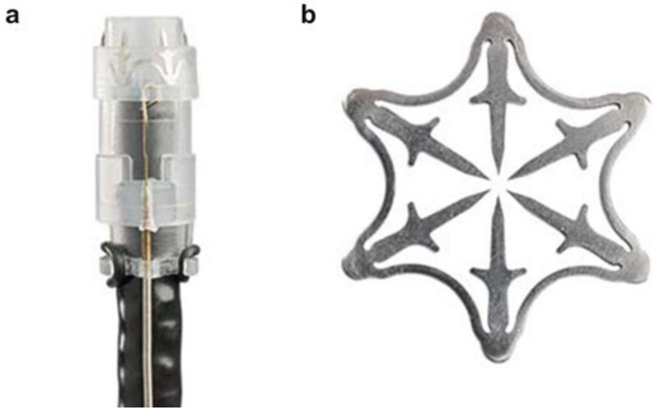

Fig. 5 The Padlock clip. (Photo credit: STERIS America, Mentor, OH, USA)

maneuver was performed by a double-channel gastroscope, introducing endoloop through one channel and metallic clips through other channel. For centers without double-channel gastroscope, single-channel method can be used with a specially designed loop (Fig. 6) (LeClamp™, LEOMED, Changzhou, China).

Endoscopic suturing devices: There are limited numbers of endoscopic suturing devices. The first one is Apollo OverStitch suturing device that was approved in 2011 by the Food and Drug Administration and is used for closure of fistulas and perforations, oversewing ulcers, and bariatric endoscopy in the United States [68]. This device is a single-use device that is mounted onto a double-channel gastroscope. This device enables both interrupted or continuous suture application and allows full-thickness suturing as well as tissue approximation or plication in the gastrointestinal tract. OverStitch has been found to successfully close post-ESD mucosal defects in a clinical setting, while also closed gastric perforations following EFTR in porcine models [68, 69].

Double-armed bar suturing system (DBSS) (Fig. 7) developed by Mori et al. that can be applied using single-channel endoscope and provides the same suturing strength to surgical hand-sewn sutures. It is applied to the tip of the scope, and it has two arms: the first one has a suturing surgical thread, and the second arm with the puncture needle is moved by handle movement of the device. Mori et al. demonstrated that there was no significant difference in leaking between the hand-sewn and DBSS, but that both hand-sewn and DBSS were able to withhold higher burst pressures when compared to the OTS clip arm [70].

Full-Thickness Resection Device Assisted

This technique constitutes the concept of "close and cut," which implies the closure of the expected defect followed by resection. This technique results in safe resection, as no hole is left and no exposure to the peritoneal cavity. For more details about this technique, readers can refer to later chapters in this book.

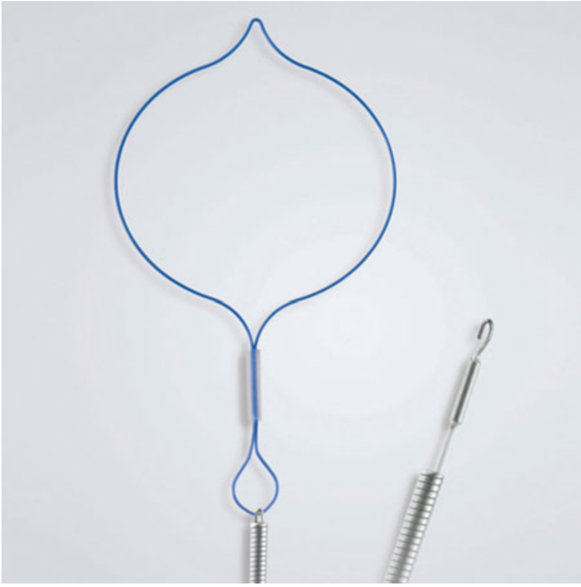

Fig. 6 The detachable loop. (Photo credit: LeClampTM, LEOMED, Changzhou, China)

Post-Procedure Care

Post-procedure care is crucial. All patients are kept strictly NPO after EFTR and nursed in a Semi-Fowler's position. A nasogastric (NG) tube is recommended to decompress the stomach and to detect early post-procedure bleeding, and vital signs and abdominal signs are monitored closely. At our center, a third-generation cephalosporin is used for the first three postoperative days. Oral proton pump inhibitors are prescribed for 2 months to protect gastric mucosa in patients with upper GI lesions. The NG tube is typically removed after 48 hours if there is no sign of bleeding or worsening of abdominal pain. The patients are started on a liquid diet and gradually upgraded to a soft and then finally to a normal diet prior to discharge from hospital.

Complications of EFTR

The complications of EFTR is similar to STER with some complications may be of increased frequency in EFTR: peritonitis, leakage, bleeding, and adjacent organ injury. It is vital to avoid fluid or blood escaping into the peritoneal cavity to reduce the risk of post procedure peritoneal infection that can lead to serious complication such as peritoneal adhesions and intra-abdominal abscess.

Some studies confirmed that fact that EFTR had an increased incidence of peritonitis and leakage when compared to STER. Also, hospital stay was prolonged

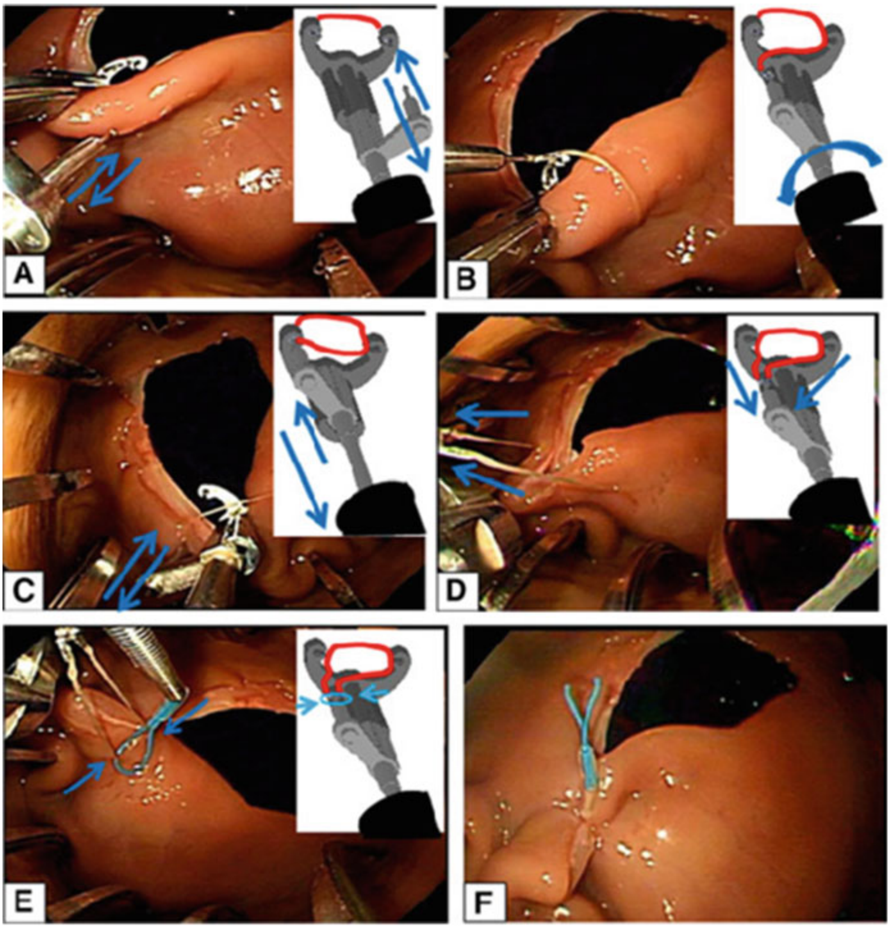

Fig. 7 Double-armed bar suturing system (DBSS) (©Mori H. et al. Surg Endosc 28 (2):683–690. https://doi.org/10.1007/s00464-013-3266-z)

in EFTR [71]. Bleeding in EFTR was shown to be higher when compared to STER, as hemostasis is somehow difficult to be achieved [72]. An important consideration of using STER is the location of the SMT. A submucosal tunnel is harder to accomplish in certain parts of the gastrointestinal tract, which would make EFTR a more reasonable option.

Clinical Outcome of EFTR

Clinical outcomes of full-thickness resection as shown in Table 2 seem to be promising. The technical success is almost 100%, meanwhile the en bloc resection rate ranges from 87% to 100%. It is evident that it was done to different

Table 2 Clinical outcomes of EFTR

Study	N	Site	Mean size (mm)	Pathological diagnosis	Time (min)/closure	Success	R_0	Adverse events	Recurrence/follow-up (m)
Zhou et al. [16] (2011)	26	Gastric	28 mm	GIST (16) Leiomyoma (6) Glomus tumor (1) Schwannoma (1)	105/metallic clips	100%	100%	No	0/8 m
Shi et al. [67] (2013)	20	Gastric	14.7 m	GIST (12) Leiomyoma (4) Schwannoma (2) Granular cell tumor (1) Ectopic Pancreas (1)	NA/purse-string	100%	100%	Pain and fever (5)	0/3–12 m
Feng et al. [73] (2014)	48	Gastric	15.9 mm	GIST (43) Leiomyoma (4) Schwannoma (1)	59.7/metallic clips	100%	100%	Distension (5)	2,6,12, and 24 m
Sarker et al. [74] (2014)	8	Duodenal Gastric Esophagus	13.4 mm	NET Granular cell tumor	NA/OTSC	100%	87.5%	0	0/8 m
Yang et al. [75] (2015)	41	Gastric	16.3 mm	GIST (33) Leiomyoma (4) NET (1) Ectopic pancreas (1) Schwannoma (1) Hyaline degeneration (1)	78.8/OTSC or metallic clips	100%	100%	Abdominal pain, fever, dysuria, vomiting (9)	–

Guo et al. [64] (2015)	23	Gastric	12.1	GIST (19) Leiomyoma (4)	40.5/OTSC	100%	100%	Peritonitis (2)	0/3 m
Lu et al. [76] (2016)	62	Gastric		GIST (44) Leiomyoma (17) Schwannoma (1)	80/clips	97%	97%	Fever and abdominal pain (12)	0/9
Shi et al. [77] (2017)	68	Gastric	26	GIST	41/clips, purse string	100%	100%	Bleeding, Mallory-Wiess tear	0/13
Tan et al. [71] (2017)	32	Gastric	15.4	GIST	69/clips	100%	97%	0	0/23.8
Andalib et al. [78] (2018)	12	Gastric	24	GIST	80/clips, purse string, suturing	100%	92%	0	0/12 m
Shichijo et al. [79] (2019)	8	Gastric	20	GIST	67.5/clips, purse string, OTSC	100%	100%		0/NA

histopathological tumors including GIST, schwannoma, leiomyoma, and granular cell tumors. There was no mortality related to EFTR, and no severe complications were reported. The complications resulted were mainly fever and abdominal pain which could be considered as a localized form of peritonitis. The duration of the procedure varied among the studies ranging from 45 min to 105 min, which is still in the accepted range. The presence of residual tumor or recurrence was not noted. The following data showed that EFTR could be an effective and safe method for technically difficult SMTs saving the patient from surgery. EFTR is a free-hand technique, enabling precise full resection of the lesions as well as closure of the defects with variable methods under complete supervision of the endoscopist. Some closure devices such as the suturing device are very expensive and are not widely available; however, the purse-string technique using the endoloop and metallic clips had offered a convenient substitution. Meanwhile, EFTR studies were mainly retrospective. So, prospective randomized controlled trials including larger number of patients are required comparing the different closure techniques.

Comparing Different Modalities

The presence of multiple and variable endoscopic resection techniques for SMTs increases the options for endoscopists to solve the SMTs puzzle. Comparing these different modalities should be available to validate which is the best solution for SMTs.

Comparing ESD with STER: Few studies retrospectively compared both techniques. It was found that regarding the efficacy and safety of both, there was no significant difference. However, the STER patients had less operative time, shorter hospital stay, and increased rate of incision healing.

Comparing ESE to STER: It was found that both techniques were effective, but for the gas-related complications, it was much lower with STER.

Summary and Conclusion

With the advances in both endoscopic techniques and accessory tools, clinical practice is shifting its schema of endoscopic resection for submucosal tumors arising from muscularis propria. STER is ideal for esophageal SMTs and is now extended to involve cardial or even extraluminal lesions. Gastric SMTs can be managed with endoscopic full-thickness resection (EFTR), provided that the local experience and the available tools to close the defects are adequate. Large multicenter prospective studies are still awaited to show more evidence of these techniques.

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