Review Article

Endoscopic resection for subepithelial lesions—pure endoscopic full-thickness resection and submucosal tunneling endoscopic resection

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Abstract: Endoscopic full-thickness resection (EFTR) and submucosal tunneling endoscopic resection (STER) are the frontier of therapeutic endoscopic. These two methods rely on the skillset and equipment of endoscopic submucosal dissection (ESD) while going beyond the boundaries of the gastrointestinal lumen. They are both representatives of natural orifice transluminal endoscopic surgery, with STER being a direct off-shoot of peroral endoscopic myotomy (POEM). Both techniques are designed for the removal of gastrointestinal tumors originating from the muscularis propria but tend to be used in different organs and come with respective challenges. In this review we will go over the history, indication, technique and literature of these two techniques.

Keywords: Endoscopic resection; natural orifice transluminal endoscopic surgery; gastrointestinal stromal tumor (GIST); leiomyoma; therapeutic endoscopy

Received: 22 March 2019; Accepted: 26 April 2019; Published: 25 May 2019.

doi: 10.21037/tgh.2019.05.01

View this article at: http://dx.doi.org/10.21037/tgh.2019.05.01

The field of interventional endoscopy has rapidly developed over the past decade, together with the genesis of the emerging field of Natural Orifice Transluminal Endoscopic Surgery (NOTES). Applications for gastrointestinal endoscopy is ever expanding and often go beyond the lumen of the gastrointestinal tract. Perforation, as defined by the ASGE lexicon (1), evidence of air or luminal contents outside of the GI tract, used to be a formidable word for any endoscopist but is now frequently performed during procedures such as Peroral Endoscopic Myotomy (POEM).

Treatment of gastrointestinal subepithelial lesions (SEL) is among the most exciting development of interventional endoscopy. SELs are commonly found incidentally during endoscopic procedures done for unrelated purposes. Insufficient data exists regarding their epidemiology, natural behavior or appropriate intervention. Majority of SELs detected in the upper gastrointestinal tract are gastrointestinal stromal tumors (GISTs), followed by leiomyoma, and more distantly, by other gastrointestinal mesenchymal tumors (GIMTs), neuroendocrine tumor (NET), granular cell tumor, glomus tumor, and various other pathologies. Majority of SELs detected in the rectum are SEL-mimicking epithelial tumors (oftentimes adenoma with scarring or adenocarcinoma) or NET and there is little data regarding the epidemiology of SELs in the colon due to its rarity. It is important to differentiate these pathologies, as GIST and NET have malignant potentials, for which relatively aggressive intervention or surveillance are recommended (2,3). Current NCCN guideline on GISTs recommends resection of all symptomatic lesions, any lesions that are ≥2 cm, or lesions that have high risk features under EUS. Annual surveillance is recommended for low risk GISTs (2). NET, meanwhile, has higher

malignant potentials. Some investigators advocate resecting all visible lesions. The minimal approach should be to resect tumors ≥1 cm in diameter. NET require surveillance similar if not more stringent than GIST (4,5). Lesions other than GIST or NET, in comparison, have much lower malignant potentials and a more relaxed surveillance approach is favored. Despite this, it is frequently difficult to determine the nature of a SEL based on morphology alone. The most commonly used tissue acquisition method, EUS-guided needle biopsy, has highly operator-dependent result, with literature reporting a diagnostic yield of less than 20% to higher than 90% (6). Treating all tumors as a 'potential GIST' can lead to excessive healthcare cost and cast emotional stress onto the patients.

Because of the aforementioned limitations in SEL management, methods have been developed to remove the SELs *en bloc* via flexible endoscopy both for histology diagnosis and as a therapy by itself. In this review we will discuss in depth two such methods, namely, pure Endoscopic Full Thickness Resection (pure EFTR) and Submucosal Tunneling Endoscopic Resection (STER). Both these methods can be performed without assistance of laparoscopy or equipment other than those routinely stocked in an interventional endoscopy unit.

Rationales for endoscopic resection

SELs are especially appropriate for endoscopic resection due to the following reasons:

(I) Unlike tumors of epithelial origin, SELs rarely exhibit a malignant potential when small and even when malignant, do no not metastasize via the lymph duct (7). A wide negative margin is not needed when resecting SELs (unlike when resecting epithelial tumors) as evidence from high quality trials showed no difference between survival after 'R1' and 'R0' resection in the absence of tumor rupture (8-10);

(II) Because these tumors are frequently found in critical locations such as the esophagus, esophagogastric junction, cardia and antrum, laparoscopic wedge resection is often not possible for tumor removal and more invasive organ resection is called for (11). This leads to a disruption of the natural anatomy of the gastrointestinal tract and is too radical for small low-risk SELs;

(III) Endoscopic removal of small SELs (less than 3–4 cm in the largest diameter) followed by purely endoscopic closure is well-tested and widely-performed in certain countries, is safe and can be done fairly quickly. 'Standby' of a surgical team is not routinely needed and the procedure can be performed in the endoscopic suite. Given the relatively low risk and low cost of this approach, early endoscopic removal can be favored over long-term surveillance when appropriate expertise is available in certain cases.

Development of techniques

Endoscopic full-thickness resection

The pursuit for full-thickness tumor resection followed by surgical-level closure of the gastrointestinal wall using flexible endoscopy has been long. Numerous commercially-available or custom-designed devices have been tested (12-14). A patent search using 'gastric full thickness resection' returned >1,000 results, majority of which never reached the clinical phase. Two devices commonly used clinically today are the Over-the-Scope-Clip (OTSC®, Ovesco Endoscopy AG, Tubingen, Germany) and its second generation, Full-Thickness-Resection Device (FTRD®). A few relatively large studies on EFRD® from Europe reported using this device on a variety of indications, including difficult colorectal adenomas (15-20), gastric subepithelial tumors (21), and duodenal tumors (22). This device is useful as it offers a quick and easy-to-learn method to manage some challenging situations, such as early carcinoma or adenomas that have been previously manipulated or involve diverticulum or the appendiceal orifice. On the other hand, this technique is limited in tumor size (mostly <1 cm in the upper GI tract and <2 cm in the colorectum) and location (sharp bending of the endoscope can lead to clip deployment failure) (8). Non-R0 resection and adverse events are other concerns (17).

In comparison, a more versatile technique of 'pure' EFTR using endoscopic submucosal dissection (ESD) techniques and equipment have been reported (23,24). In contrast to device-assisted EFTR, pure EFTR is a 'cut then close' technique that constitutes dissecting the tumor around the capsule and completely remove the tumor from its attachment to the muscularis propria prior to closing the lumen defect. Major differences exist between device-assisted EFTR and pure EFTR. In this review we will focus on pure EFTR.

Submucosal tunneling endoscopic resection

STER is a direct offshoot of the endoscopic tunneling technique (25-27) and got wide clinical adoption while POEM became standard practice. First described in humans by Japanese and Chinese pioneer POEM centers in 2012 (28,29), STER (coined Peroral Endoscopic Tumor Resection, aka POET, by the Japanese center) utilizes the mucosa flap as a safety valve to prevent extravasation of lumen contents. One advantage of STER compared to EFTR is the relative easiness of closing the tunnel entrance compared to a full-thickness defect. One study compared outcomes of STER and EFTR for gastric GIST originating from the muscularis propria and found that patients who received EFTR had a longer suture time and needed more clips to close the gastric wall defect (30). However, we should note that the anatomical location most suitable for STER and EFTR are largely non-overlapping (see below).

Choice between pure EFTR and STER

When tunneling is feasible, STER is almost always the preferred technique as the mucosa flap entrance is easier to close than a full-thickness defect. The most suitable locations for a tunnel are those reachable by endoscopy in a straight line, i.e., the middle and lower esophagus, the gastroesophageal junction and gastric cardia, and less so the gastric antrum and rectum. Tumors larger than 3–4 cm in the shortest diameter are difficult to retract through the tunnel entrance sometimes and are difficult to operate on inside a confined space. Pure EFTR has more flexibility in terms of tumor morphology and location but should be avoided in the esophagus and certain locations of limited maneuverability of the endoscope and the suturing device, i.e., the gastric fundus and duodenum, unless done by very experience operators.

Indications and contraindications

No high-quality evidence or consensus exist on the appropriate indication or contraindication for endoscopic resection of SETs. The following patient eligibility criteria are used by the writers: (I) if the lesion is symptomatic; (II) GIST or suspected GIST >2 cm or with high risk EUS features; (III) NET; (IV) adenoma in transmural scars; (V) non-GIST mesenchymal tumors (e.g., Schwannoma, leiomyoma) that are non-symptomatic but are >2–3 cm in size, have rapid growth or high risk EUS/histologic features (e.g., central necrosis, nuclear atypia, high mitotic rate); (VI) undiagnosed lesions in younger patients for whom the risk of resection might be outweighed by the benefit of avoiding long-term surveillance. Patients are considered eligible for pure EFTR or STER as opposed to endoscopic submucosal excavation (ESE) or ESD if the tumor has significant muscularis propria involvement, has extraluminal component, or if full-thickness penetration of the gastrointestinal wall is expected for complete removal of the tumor.

Contraindications for pure EFTR and STER include any contraindication for local resection (e.g., severe comorbidity or sign of metastasis). More specifically, tumor involvement and sometimes adjacency to large extra-luminal vessels is a contraindication for EFTR and STER (as compared to laparoscopic resection) as currently the ability of endoscopic hemostasis is limited by a lack of appropriate device and controlling bleeding from a large-diameter extra-luminal vessel is very difficult. There concerns aside, the size and location of the tumor that are fit for endoscopic resection has no fixed criteria but rather depends on the comfort level of the operator. However, we should note that tumors >3–4 cm in the shortest diameter often cannot be retracted from the mouth and tumors >5 cm in the longest diameter carry significantly higher risk of aggressive behavior and thus should probably be better resected surgically. Preoperative evaluation with contrast CT/ MRI for large tumors is essential to evaluate for large extra-luminal vessels and relation between tumor and extra-luminal structures.

Equipment, techniques and perioperative management

Equipment commonly used for pure EFTR and STER are the same as those used in ESD: single channel gastroscope for resection (GIF HQ 190, Olympus, MA, USA) and dual channel endoscope for suturing (CF 2T160L, Olympus, MA, USA), electrosurgical generator unit (Erbe, GA, USA), CO2 insufflator (UCR, Olympus, MA, US), injection needle (InjectorForce Max™, Olympus, MA, USA), electrosurgical knife (e.g., ITknife™, DualKnife™, Hooknife™, Olympus, MA, US; HybridKnife®, ERBE, MA, USA), hemostatic forceps (EndoJaw Hot™, Coagrasper™, Olympus, MA, USA), clips (e.g., Instinct™, Cook Medical, IN, USA; Resolution™, Boston Scientific, MA, USA), and endoscopic suturing system (OverStitch™, Apollo Endosurgery, TX, USA).

The writers (and anecdotally other US centers) routinely

use the endoscopic suturing device for pure EFTR cases, whereas the Chinese operators routinely use various clip and clip-assisted techniques, such as the omentum patch (23,31) and clip-endoloop technique (31-34) to close the defect. Closure of large defect with clips tend to be more cumbersome and less secure than suturing (35) and should be reserved for cases where suturing is not possible or available.

Pure EFTR constitutes the following steps (*Figure 1*): (I) submucosal injection of normal saline (or hetastarch) enhanced with a blue dye to delineate the tumor; (II) mucosa incision to access the submucosal working space; (III) submucosal dissection to expose the tumor; (IV) muscle fiber dissection along the capsule; (V) complete resection and tumor removal; (VI) mucosal defect closure.

STER is performed according to the following steps (*Figure 2*): (I) submucosal injection 1–2 cm proximal to the tumor; (II) submucosal tunneling above and around the tumor to separate the tumor from its covering mucosa; (III) muscle fiber dissection around and beneath the tumor to excavate the tumor from its attachment to the muscularis propria; (IV) complete resection and removal of the tumor; (V) tunnel entrance closure.

Prophylactic antibiotics covering enteric flora is administered at the start of the procedure and continued for a few days postoperatively. Cooperation with an experienced anesthesiologist is essential as once there is a full-thickness wall penetration, air tends to accumulate in the abdominal cavity, leading to a rise of the intra-abdominal pressure. Close monitoring of the peak airway pressure (as an indicator for the abdominal pressure) and prompt air venting either through the abdominal wall or by endoscopic suctioning are important. At our center, patients are kept on nil-per-mouth for at least 24 hours and undergo a barium swallow leak test prior to resuming po intake. Patients can be discharged once they can tolerate clears and if there is no symptoms or signs indicating a recovery out of ordinary.

Outcome

As of 2018 the majority of pure EFTR experience comes from China (23,24,30,33,34,36-46), reports out of China are few (31,47-49) (*Table 1*). Four studies that presented metrics of EFTR together with other techniques are not included in the table (24,50-52). Almost all studies are retrospective series and universally reported a technical success rate of (near) 100% and no recurrence, few if any clinically significant adverse events, and relatively short hospital stays (mostly 3–6 days). However, most studies did not report an *en bloc* resection rate and described the follow up scheme very briefly.

Similar to EFTR, almost all studies on STER are retrospective case series with scant follow up data (28,29,46,53-71) (*Table 2*). A recent meta-analysis compiled 12 STER studies in English literature up to Jun 2016 and found a pooled complete and *en bloc* resection rate of 98.1% and 94.9% respectively. The pooled estimates of gas-related and inflammation-related (including pleural and abdominal effusion) adverse events rate were 21.5% and 8.4%, respectively, and the pooled estimate of delayed bleeding rate was 2.2%. One prospective, open-labeled trial randomizing 66 patients with small esophageal submucosal tumors into STER and video-assisted thoracoscopic surgery (VATS) found shorter procedure time (44.5 *vs.* 106.5 min), lower cost (4,499 *vs.* 5,137 USD), less decrease in hemoglobin level (0.16 *vs.* 1.47 g/dL) and lower postoperative pain scores in the STER group and comparable perioperative clinical outcomes (complete resection rate, hospital times, and adverse events) between the two groups apart from a lower *en bloc* resection rate of STER for SET ≥2 cm (71.4% *vs.* 100%) (73). Because STER is mainly used in the esophagus or gastroesophageal junction, majority of the tumors included in published series are leiomyomas. Given the low malignant potential of leiomyomas and the generally short follow up/high loss-to-follow-up rate, it is not surprising that few recurrences (68,69,72,74,75) have been reported and there are questions whether these are real recurrences or residuals of incomplete primary resection.

In summary, current evidence supports the feasibility and safety of pure EFTR and STER as well as endorses its technical versatility (tumor size up to 6 cm; various locations such as the esophagus, gastric fundus and colon) but is not strong enough to endorse its long-term clinical success. However, we want to point out that given the low risk and slow growth of most SELs, proving long term success of these technique will be difficult since true recurrence probably takes years to detect and 'early recurrence' likely represents macroscopic residual of primary tumor or post-operative fibrotic changes, rather than microscopic residual secondary to a R1 margin, which is the primary concern for this type of endoscopic 'enucleation'. In addition, given the low risk of most of these tumors, long term surveillance has questionable utility after complete tumor resection and patient compliance for follow up can be an issue.

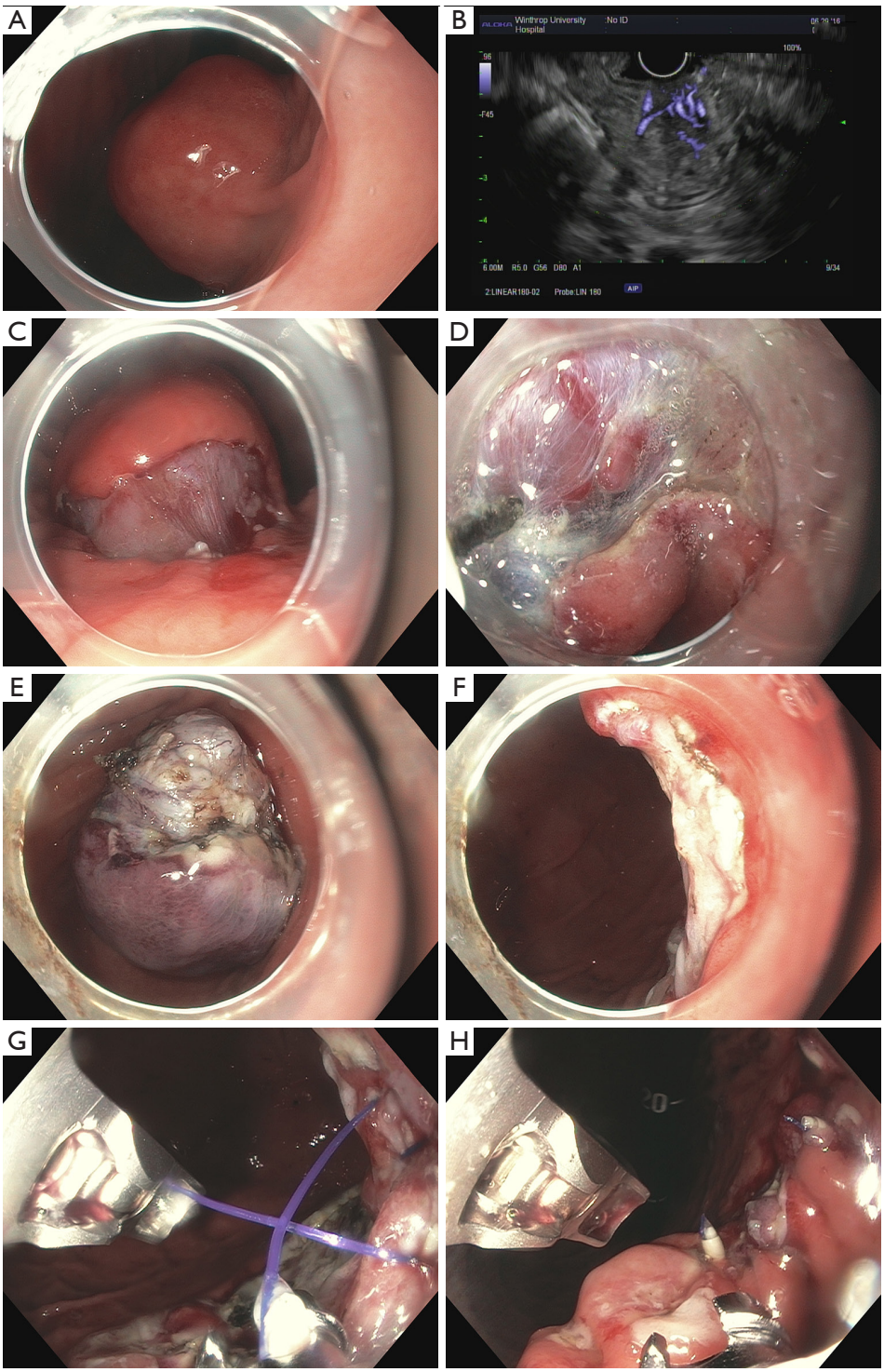

Figure 1 Steps for EFTR. (A) A 3 cm submucosal tumor was seen in the posterior wall of the distal gastric body; (B) endoscopic ultrasound showing abundant vessels inside the tumor; (C) mucosa incision and submucosal dissection exposed one side of the tumor, which seemed to originate from the deep muscularis propria; (D) a closer view showed large-caliber vessels coiling along the tumor capsule; (E) the resected tumor lying in the gastric fundus. A 'whirled' growth pattern was clearly seen at the tumor base, which is typical for GIST; (F) extraluminal fatty tissues can be seen through the dissection defect; (G,H) gastric wall defect closure with OverStitch. EFTR, endoscopic full-thickness resection; GIST, gastrointestinal stromal tumor.

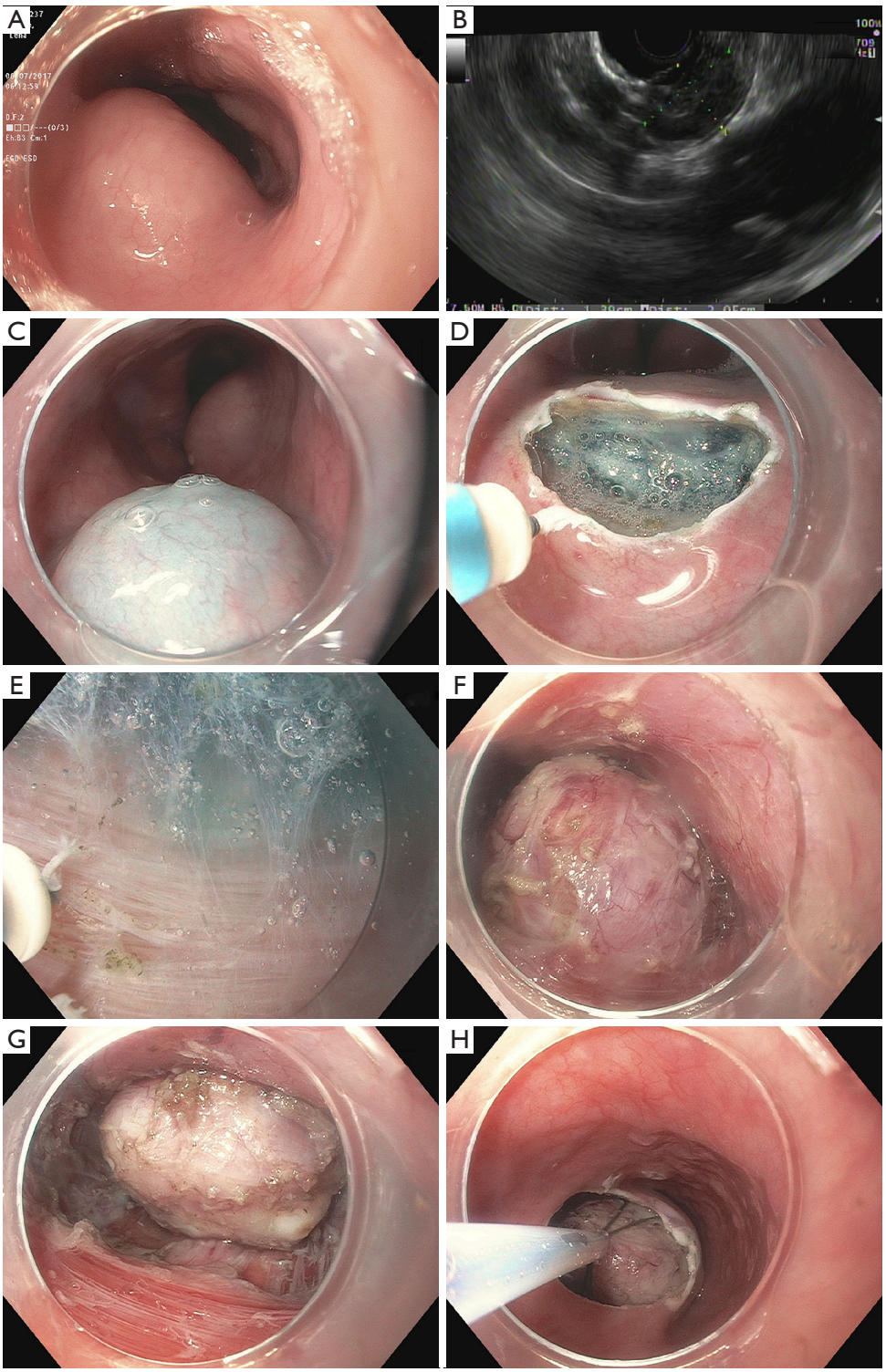

Figure 2 Steps for STER. (A) A submucosal bulge is seen in the mid-esophagus; (B) EUS showing a 2cm homogeneous hypoechoic tumor; (C) submucosal injection 2 cm above the cephalic end of the tumor; (D) mucosa incision; (E) submucosal dissection showing circular muscle of the esophagus; (F,G) further dissection exposed a firm and muscular tumor originating from the deep muscularis propria. The mediastinum can be seen under the tumor; (H) an ERCP web basket was used to retrieve the tumor. STER, submucosal tunneling endoscopic resection; EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography.

Table 1 Literature review on EFTR series

Study	Study period	Tumor location	N	Tumor size, mm	Operation time, min	Closure method	Technical success	*En bloc*	R0	LOS, day	csAE	Pathology	Recurrence	Follow–up, month
Zhou (23), *Surg Endosc*, 2011	Jul 2007–Jan 2009	Gastric	26	28 [12–45]	105 [60–145]	Clips	100%	100%	NA	5.5 [3–8]	None	16 GIST, 6 leiomyoma, 3 glomus, 1 Schwannoma	None	8 [6–24]
Xu (40), *Endoscopy*, 2013	Jul 2009–Jan 2012	Colon	19	18 [12–30]	67 [45–130]	Clips/ endoloop, purse–string, lap assist	95%	100%	100%	NA	2 localized peritonitis, 1 bleeding	9 leiomyoma, 4 GIST, 2 Schwannoma, 2 fibromatosis, 1 hamartoma, 1 granuloma	None	18 [6–36]
Feng (38), *J Laparoendosc Adv Surg Tech A*, 2014	Jan 2009–Oct 2012	Gastric	48	16 [5–48]	60 [30–270]	Clips	100%	NA	NA	[4–7]	None	43 GIST, 4 leiomyoma, 1 Schwannoma	None	12 [2–24]
Ye (33), *Surg Endosc*, 2014	Jan 2009–Dec 2012	Gastric	51	24 [13–35]	52 [30–125]	Clips, loops	98%	NA	NA	5.9 [3–9]	None	30 GIST, 21 leiomyoma	None	22.4 [1–48]
Huang (41), *World J Gastroenterol*, 2014	Jan 2010–Sep 2013	Gastric	35	28 [20–45]	90 [60–155]	Clips, omental patch	100%	NA	NA	6 [4–10]	None	25 GIST, 7 leiomyoma, 2 Schwannoma	None	6
Guo (37), *Surg Endosc*, 2015	Oct 2013–Mar 2014	Gastric	23	12 [6–20]	40 [16–104]	Otsc	100%	NA	NA	3 [2–5]	2 localized peritonitis	19 GIST, 4 leiomyoma	None	3 [1–6]
Yang (39), *Surg Endosc*, 2015	Jun 2012–Apr 2014	Gastric	41	16±5.9	79±46	Otsc, clips	100%	NA	NA	5.4±1.1	None	33 GIST, 4 leiomyoma, 1 NET, 1 Schwannoma, 2 benign	NA	NA
Wang (43), *Surg Endosc*, 2016	Jan 2011–Dec 2013	Gastric	35	13±5	91±63	Clips, nylon band	100%	NA	NA	6.7±0.9	None	GIST	None	[1–72]
Lu (44), *Gastrointest Endosc*, 2016	Jan 2013 – Mar 2015	Fundus LC	62	[8–60]	25–180	Clips	98%	NA	NA	[4–6]	NA	44 GIST, 17 leiomyoma, 1 Schwannoma	None	[1–24]
Tan (30), *Surg Endosc*, 2017	Apr 2011–Jun 2016	Gastric	32	15.4±6.6	69±27	Clips	100%	97%	NA	6.4±2.0	None	GIST	None	23.8±18.6
Shi (46), *Surg Endosc*, 2017	Apr 2014–Feb 2015	Fundus	68	26 [20–35]	41 [23–118]	Clips, endoloops	100%	100%	NA	5.4 [3–9]	1 Mallory-Weiss, 1 bleeding	GIST	None	[3–13]
Wu (34), *Medicine*, 2018	Jun 2016–May 2017	Gastric	25	17±10 [5–45]	31±14	Clips, purse–string	100%	NA	NA	NA	None	21 GIST, 2 leiomyoma, 1 neuroma, 1 calcifying fibrous tumor	None	7 [1–11]
Shi[a] (45), *J Laparoendosc Adv Surg Tech A*, 2018	Jan 2015 – Dec 2016	Fundus	24, 24	8.8±3.3	11±3; 19±5	Clips/loops	NA	NA	NA	3.2±0.5; 3.2±0.5	NA	38 GIST, 10 leiomyoma	NA	NA
Andalib (47), *Surg Endosc*, 2018	Dec 2014–Apr 2016	Gastric	12	24 [10–50]	80 [17–180]	Clip, endoloops, sutures	100%	92%	NA	2.08	None	GIST	None	12 [6.5–24]

Summary metric is either median or mean. Range is presented in square brackets, standard deviation is presented after ±. [a], with *vs.* without dental floss traction. NA, not available; LC, lesser curvature; csAE, clinically significant adverse events; EFTR, endoscopic full-thickness resection; LOS, length of stay; GIST, gastrointestinal stromal tumor; OTSC, Over-the-Scope-Clip.

Table 2 Literature review on STER series

Study	Study period	Tumor location	N	Tumor size	Operation time, min	Closure method	Technical success	*En bloc*	R0	LOS, day	csAE	Pathology	Recurrence	Follow–up, Month
Inoue (28), *Endoscopy*, 2012	NA	Esophagus, cardia	9	12 [12–30]	93 [84–365]	Clips	78%	100% [2/9 aborted]	100%	4 [4–16]	None	1 GIST, 5 leiomyoma, 1 aberrant pancreas	NA	NA
Gong (53), *Endoscopy*, 2012	Jun 2011–Nov 2011	Esophagus, cardia	12	19 [10–40]	48 [30–60]	Clips	100%	83%	NA	NA	2 PTX	7 GIST, 5 leiomyoma	NA	NA
Xu (29), *Gastrointest Endosc*, 2012	Jun 2010–Mar 2011	Esophagus, cardia, stomach	15	19 [12–25]	79 [25–130]	Clips	100%	100%	100%	3.8 [3–5]	1 PTX	5 GIST, 9 leiomyoma, 1 glomus tumor	None	1–6
Liu (54), *Surg Endosc*, 2013	Apr 2011–Jun 2012	Esophagus, cardia, stomach	12	19 [10–30]	78 [50–130]	Clips	100%	100%	100%	NA	4 PTX, 2 pleural effusion	2 GIST, 9 leiomyoma, 1 Schwannoma	None	5 [2–15]
Ge (55), *Endosc Ultrasound*, 2013	Oct 2009–Dec 2011	Esophagus	17	24 [12–50]	97 [60–150]	Clips	100%	NA	NA	NA	None	1 GIST, 16 leiomyoma	None	7 [3–13]
Wang (56), *Surg Endosc*, 2013	Nov 2009–Nov 2011	Esophagus	18	33 [21–45]	68	Clips	NA	NA	NA	2.3	3 bleeding	18 leiomyoma	None	17
Wang (57), *Surg Endosc*, 2014	Jul 2010–Aug 2012	GEJ	57	22 [6–35]	47 [15–120]	Clips	100%	100%	NA	2.7 [2–6]	5 PTX, 2 pleural effusion	7 GIST, 46 leiomyoma, 2 Schwannoma, 1 lipoma, 1 granular cell tumor	None	12 [6–24]
Ye (58), *Surg Endosc*, 2014	Aug 2011–Feb 2013	Esophagus, cardia, stomach	85	19 [10–30]	57 [30–115]	Clips	100%	100%	NA	5.9 [2–14]	6 PTX	19 GIST, 65 leiomyoma, 1 calcifying fibrous tumor	None	8 [2–19]
Lu[a] (59), *Surg Endosc*, 2014	Jan 2010–Jan 2014	Esophagus, cardia	45	12	84	Clips	100%	98%	98%	NA	None	3 GIST, 42 leiomyoma	None	9 ± 9
Lu (60), *Endoscopy*, 2014	Jan 2013–Apr 2014	Fundus	19	21 [8–50]	75 [40–100]	Clips	100%	NA	NA	NA	None	13 GIST, 6 leiomyoma	None	5
Lu (61), P*LoS One*, 2015	Jan 2012–	Stomach	47	14 [5–50]	79 [45–150]	Clips	96%	NA	NA	NA	None	36 GIST, 10 leiomyoma, 1 Schwannoma	None	11
Zhou (62), *World J Gastroenterol*, 2015	Aug 2012–Oct 2013	GEJ	21	23 [10–40]	63 [45–90]	Clips	100%	86%	NA	4.3 [3–7]	1 pleural effusion	6 GIST, 15 leiomyoma	None	6 [2–14]

Table 2 (*continued*)

Table 2 (*continued*)

Study	Study period	Tumor location	N	Tumor size	Operation time, min	Closure method	Technical success	*En bloc*	R0	LOS, day	csAE	Pathology	Recurrence	Follow–up, month
Li (63), *Surg Endosc*, 2015	Apr 2011–Mar 2014	Cardia, lesser curvature, greater curvature	32	23 [10–50]	52 [25–125]	Clips	100%	100%	NA	3.9 [2–9]	3 PTX, 3 pleural effusion, 1 subphrenic infection	11 GIST, 18 leiomyoma, 1 fibrous tumor, 1 glomus tumor, 1 Schwannoma	None	6–32
Zhang (64), *Indian J Cancer*, 2015	Jun 2011–Jun 2014	Esophagus, cardia, lesser curvature	49	15 [8–35]	40 [20–75]	Clips	100%	100%	NA	4 [2–9]	2 PTX, 2 pleural effusion	49 leiomyoma	None	18 [3–36]
Wang (72), Eur *J Gastroenterol Hepatol*, 2015	Oct 2011–May 2014	Esophagus, cardia	83	23 [10–55]	61 [25–160]	Clips	100%	98%	NA	5.4 [3–10]	1 PTX	15 GIST, 68 leiomyoma	None	10
Tan[b] (65), *Surg Endosc*, 2016	Jan 2010–Dec 2014	Esophagus	18	41	75	Clips	NA	89%	NA	6	None	18 leiomyoma	NA	NA
Chen (66), *Endoscopy*, 2016	Jan 2011–Aug 2013	Esophagus, GEJ, stomach	290	21 [10–70]	43 [15–200]	Clips	NA	89%	NA	3.5 [2–22]	29 complications requiring interventions	53 GIST, 226 leiomyoma, 5 Schwannoma, 3 calcifying fibrous tumor, 3 glomus tumor	NA	NA
Tang (67), *Gut Liver*, 2017	Jan 2012–Jan 2015	Esophagus, cardia, stomach	70	19 [10–40]	49 [30–150]	Clips	NA	96%	NA	5.8 [3–10]	2 PTX	11 GIST, 59 leiomyoma	None	18
Chen (68), *Ann Surg*, 2017	Jun 2011–May 2013	Esophagus, stomach	180	26 [20–50]	45 [15–200]	Clips	NA	90.6%	NA	3.2 [2–22]	10 PTX/pleural effusion, 2 bleeding, 1 fistula	28 GIST, 146 leiomyoma, 4 Schwannoma, 2 calcifying fibrous tumor	None	36 [28–51]
Mao (69), *Dis Esophagus*, 2017	Jan 2012–Dec 2014	Cardia	56	18 [10–32]	42 [20–65]	Clips	100%	100%	NA	4.9 [2–9]	8 PTX, 5 pleural effusion	10 GIST, 45 leiomyoma, 1 fibrous tumor	None	25 [7–42]
Zhou[c] (70), *World J Gastroenterol*, 2017	Aug 2012–Dec 2015	Esophagus, cardia, stomach	HO 34, HK 49	HO 19.7 [10–40]; HK 19.3 [8–40]	HO 57.2 [30–150]; HK 41.3 [15–120]	Clips	NA	HO 94%; HK 100%	NA	HO 5.6 [3–10]; HK 5.8 [3–10]	4 perf 1 bleeding	13 GIST, 69 leiomyoma, 1 lipoma	None	HO 27±6, HK 26±4
Zhang (71), *Endoscopy*, 2017	2015–2017	Lower esophagus, fundus near cardia, GEJ	10	43 [12–50]	80 [45–150]	Clips	100%	90%	NA	NA	None	1 GIST, 9 leiomyoma	NA	NA

[a], retrospective, compared to ESE; [b], retrospective, compared to VATS; [c], retrospective, Hook knife (HO) *vs*. HybridKnife (HK). Significant adverse event, gas-related adverse events including subcutaneous emphysema, pneumoperitoneum and atelectasis are not included here since they are common and mostly don't require any intervention. Fever resolved after short-course of antibiotics is not included either. STER, submucosal tunneling endoscopic resection; LOS, length of stay; GEJ, gastroesophageal junction; PTX, pneumothorax.

Summary

The management of low-risk gastrointestinal subepithelial tumors is an involving field. The risk-benefit balance might shift to favor a more aggressive early-resection approach rather than long-term surveillance as new techniques and equipment got more widely used and operators get more comfortable with the new concepts. Numerous studies have shown the technical feasibility and safety of pure EFTR and STER in resecting these tumors. Future research is needed regarding the long-term result of these techniques and more tailored tools are needed were further breakthrough to be made.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Stavropoulos is a consultant for Boston Scientific and Olympus and receives an honoraria from ERBE USA; Dr. Zhang, Dr. Modayil and Dr. Criscitelli have no conflicts of interest to declare.

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doi: 10.21037/tgh.2019.05.01
Cite this article as: Zhang X, Modayil R, Criscitelli T, Stavropoulos SN. Endoscopic resection for subepithelial lesions—pure endoscopic full-thickness resection and submucosal tunneling endoscopic resection. Transl Gastroenterol Hepatol 2019;4:39.

