Recent advances in minimally invasive endoscopic approaches have pushed the boundaries of well-established resection techniques for therapeutic and diagnostic applications. Endoscopic full thickness resection techniques are a key development in the management of challenging epithelial and subepithelial lesions that are not amenable to conventional endoscopic resection methods and previously required a surgical approach. Endoscopic full thickness biopsy represents a paradigm shift in tissue acquisition and will enhance our understanding of the pathophysiology, and guide therapy, of gastrointestinal neuromuscular diseases, as well as other inflammatory and neoplastic conditions. This review highlights current tools and techniques available for endoscopic full thickness resection and biopsy, as well as outcomes from such interventions.

**Keywords:** Endoscopic Full Thickness Resection; Full Thickness Resection Device; Subepithelial Lesions; Submucosal Tunneling Endoscopic Resection.

**Therapeutic Applications**

**Rationale**

EFTR is increasingly being performed for the removal of select subepithelial and epithelial lesions that are not amenable to conventional resection techniques. For particular lesions, such as GI stromal tumors (GISTs), EFTR offers important diagnostic advantages over endoscopic ultrasound (EUS)–guided fine-needle aspiration or biopsy with regard to procurement of adequate material for definitive diagnosis. Although EFTR implies resection through all layers of the GI wall, in practice the term is also used to include removal of intramural lesions without complete breach of the gut wall (eg, resection of a tumor originating from the MP with preservation of the uninvolved adventitia or serosa). These partial thickness resections have been labeled “endoscopic muscularis dissection,” “endoscopic enucleation,” “endoscopic submucosal excision,” and “endoscopic muscularis excision,” to name a few, and are included under the umbrella term EFTR for the purpose of this review.

Conventional endoscopic pinch biopsies are non-diagnostic for neuromuscular disorders and other conditions that involve the deep layers of the GI tract. However, a safe and effective method that can capture the entire GI wall to include the MP has eluded us until the advent of endoscopic muscle biopsy techniques. In order to standardize nomenclature, we propose using the terms endoscopic full thickness biopsy (EFTB) and endoscopic full thickness resection (EFTR) to clearly differentiate between diagnostic and therapeutic applications, respectively.

**Abbreviations used in this paper:** GI, confidence interval; EFTB, endoscopic full thickness biopsy; EFTR, endoscopic full thickness resection; EUS, endoscopic ultrasound; FTRD, full thickness resection device; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; MP, muscularis propria; OTS, over-the-scope; SEL, subepithelial lesion; STER, submucosal tunneling endoscopic resection.
diagnosis and for determination of malignant potential (ie, mitotic index). Moreover, indefinite periodic examinations without definitive diagnosis are costly and emotionally burdensome for some patients, and the therapeutic value of EFTR in this setting cannot be overstated. According to the National Comprehensive Cancer Network guidelines, gastric GIST >2 cm should undergo resection, whereas treatment options for incidental GIST <2 cm without high-risk features on EUS include resection or surveillance. The surveillance approach, however, raises concerns about patient compliance, cost-effectiveness, risk associated with repeated endoscopic procedures, and delay in therapy of potentially malignant lesions.

Although endoscopic resection of SELs involving the MP was previously considered a contraindication owing to a high perforation rate, the refinement in resection tools and closure devices, as well as increased experience with EFTR techniques, have minimized this adverse event. In particular, confidence in closure has allowed full thickness resection and biopsy techniques to progress forward in a safe and effective manner. Furthermore, an intentional perforation is expected for some EFTR procedures and should not be viewed as an adverse event, as long as it can be sealed effectively intra-procedurally. In the era of EFTR, recategorization of adverse events for invasive procedures should be pursued to differentiate consequential and inevitable events from true adverse events impacting outcomes.

Relative to thoracoscopic or laparoscopic interventions, EFTR is the least invasive modality along the spectrum of minimally invasive procedures, and is better suited for the removal of SELs at particular locations, such as the esophago-gastric junction, where laparoscopic surgery is challenging. However, EFTR should be performed by appropriately trained advanced therapeutic endoscopists. Similar to other advanced resection procedures, such as peroral endoscopic myotomy for achalasia, no standardized protocol for training and assessment of competence is currently available. Future GI societal guidelines will be instrumental in directing training and evaluation of competence.

Pre–Endoscopic Full Thickness Resection Assessment

The location, size, and features of the lesion determine, for the most part, resectability and the type of EFTR procedure most suitable to accomplish the task. EUS plays an important role in identifying benign incidental lesions that do not necessitate resection (eg, duplication cyst, lipoma) and in characterizing SELs, including size, layer of origin, growth pattern (intra- vs extraluminal), involvement of adjacent structures and regional lymphadenopathy. Lesions with high-risk features on EUS that suggest malignancy (eg, irregular border, cystic spaces, heterogenous echotexture, and suspect lymph nodes) would preclude removal of these lesions via EFTR.

For SELs arising from the MP, assessment of the degree of lesion attachment with this layer may predict completeness of tumor resection. In one study, successful R0 resection (negative deep and lateral margins) was predicted by the observation of only narrow or no lesion attachment with the underlying fourth hypoechoic layer (MP) at EUS (odds ratio, 35.0; 95% confidence interval [CI], 3.7–334.4; \( P = .001 \)). Other factors, such as tumor location, histopathology, and size, were not statistically associated with complete resection. It should be noted, however, that EUS was only 73% accurate in determining the tumor’s layer of origin, and so the intended resection approach based on EUS findings may need to be altered at the time of the procedure.

In addition to EUS, computed tomography is recommended for evaluation of SELs because the combination of these techniques was superior to EUS alone at predicting the endoscopic maneuvers needed for lesion resection in a randomized trial. In the presence of large SELs (>3 cm), computed tomography is indicated for assessment of metastasis or invasion beyond the gut wall.

Endoscopic Full Thickness Resection Techniques

Clip-Assisted Endoscopic Full Thickness Resection

In general, EFTR involves resection of a lesion followed by defect closure using mechanical clips or endoscopic suturing. Over-the-scope (OTS) clip-assisted EFTR is an emerging “close then cut” technique that can provide full thickness resection of epithelial and subepithelial lesions throughout the GI tract, a potentially safer alternative that involves securing the defect before resection.

Indications. Select non-lifting epithelial lesions (eg, adenoma) that are associated with severe fibrosis from prior attempts at resection and small SELs, including neuroendocrine tumors and GISTs, may be considered for clip-assisted EFTR. The size of the lesion that can be targeted with this technique is dependent in part on the diameter of the OTS cap utilized. In general, OTS clip-assisted EFTR is suitable for lesions that are <1 cm in the upper GI tract and <2 cm in the colorectum. Clip-assisted resection for lesions within the appendiceal orifice and in the presence of a native appendix should be avoided due to risk of provoking appendicitis. The role of OTS clip-assisted EFTR for early T1 cancers and lesions >2 cm in size deserves further study.

Devices and techniques. Both non-dedicated and dedicated OTS clip devices have been used for clip-assisted EFTR.

Non-dedicated devices. The 2 non-dedicated OTS clip devices include the Padlock clip (US Endoscopy, Mentor, OH) and the OTSC (Ovesco Endoscopy AG, Tübingen, Germany). The Padlock clip is a star-shaped nitinol ring with 6 inner needles that is premounted on a cap. It has proprietary radial compression technology that facilitates circumferential tissue apposition (Figure 1A). The clip is available in 2 sizes: the Standard Padlock fits a 9.5- to 11-mm diameter endoscope while the Padlock Pro-Select fits an 11.5- to 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. The clip is deployed using a simple push button. 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.

The OTSC system consists of a cap with a premounted clip and a hand wheel for clip release that utilizes the working channel of the endoscope (Figure 1B). Its setup is similar to 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). For OTSC-assisted EFTR in the upper GI tract, we typically use the 12/6 type t clip on a therapeutic channel endoscope, which allows passage of devices for tissue anchoring and retraction, as well as providing secure closure. In the colon, either the 12/6 or 14/6 type t clip can be used, depending on access to and size of the lesion.

OTS clip-assisted EFTR uses the “no hole” concept in order to prevent overt perforation and contamination of the peritoneal cavity. The OTS clip is advanced to the target lesion, which is retracted into the cap using a tri-pronged tissue retraction device (OTSC Anchor; Ovesco Endoscopy AG) or grasping forceps, followed by clip deployment. Suction of the lesion into the cap should be performed judiciously, given the risk of extraluminal organ entrapment. The pseudopolyp of tissue created is then resected via an electrosurgical snare (Figure 2 and Video Clip 1). The Padlock clip has an ideal flat configuration, allowing ease of snare positioning and resection of tissue above the clip. Resection with the OTSC device can be more difficult due to its concave geometry. The snare often entraps the corners of the clip and cannot be placed close to the base of the pseudopolyp, which can lead to incomplete resection. If snare access to the pseudopolyp lesion is difficult, an electrosurgical knife (eg, Hook knife; Olympus Corp., Tokyo, Japan) can be used for resection.

A submucosal fluid injection before resection is not required. Based on our experience, this limits the volume of tissue that can be retracted into the cap and subsequent R0 resection. Successful entrapment of the entire lesion into the cap depends on pliability of the lesion and, thus, fibrosis and overt inflammation can compromise lesion capture and resection.

**Dedicated device.** A dedicated full thickness resection device (FTRD; Ovesco Endoscopy AG) has been available in Europe since 2014 and was approved for use in the United States in 2017 for colorectal EFTR (Supplementary Figure 1). The FTRD system enables one-step EFTR after placement of a modified OTS clip with an integrated electrosurgical snare. The FTRD is affixed to a colonoscope (recommended diameter 11.5–13.2 mm) and consists of a modified OTSC (14 mm) premounted on a clear cap that has a larger depth (23 mm) and diameter (21 mm). A 13-mm snare is integrated within the cap, with its catheter and handle running alongside the endoscope shaft through a transparent plastic sheath.

The border of the target lesion is usually marked with coagulation dots using argon plasma coagulation or an electrosurgical knife. The lesion is retracted into the cap similar to the technique utilized with the non-dedicated OTS clip devices. After clip deployment, immediate snare resection ensues.

Technical challenges of the FTRD system include advancing the device to the target lesion due to increased friction along the plastic-wrapped endoscope, and the large cap which impairs the field of view and flexibility of the endoscope’s tip. Visualization of the entrapped lesion within the long cap before snare resection can be impaired, leading to potential incomplete resection. Snare dysfunction and failed clip deployment with resultant immediate perforation may also occur. Tissue fibrosis, right-sided colonic lesions, and lesions >30 mm are risk factors for incomplete resection.11

**Efficacy and safety.** In our case series, clip-assisted EFTR using both Padlock clip and OTSC was performed in...
the stomach, duodenum, rectosigmoid colon, and appendiceal orifice status post-appendectomy without adverse events. The mean procedure time was 53 ± 21 minutes. The mean size of the resected specimens was 11 ± 3 mm and R0 resection was achieved in all cases.12 Similarly, other case series have reported on clip-assisted EFTR using the OTSC device primarily for the removal of colorectal lesions, such as non-lifting or recurrent adenomas not amenable to standard polypectomy techniques, SELs (eg, carcinoid tumors), and lesions in difficult locations (eg, appendiceal orifice or within a diverticulum).13,14 The utilization of the Padlock clip in a series of 26 patients with colorectal lesions resulted in an R0 resection and adverse event rates of 73% and 12%, respectively (Table 1).15

A large European prospective multicenter trial encompassing 181 patients reported on the efficacy and safety of the FTRD system for the removal of colorectal lesions.11 Lesions up to 30 mm in diameter were included and a subgroup analysis showed that the R0 resection rate dropped from 81.2% for lesions ≤2 cm to 58.1% for lesions >2 cm in size (P = .0038). The R0 resection rate was also lower for lesions with submucosal infiltration and scarring from prior endoscopic resection (45%–57%). The rate of adverse events approximated 10% (Table 1).

Although the FTRD system is not approved for use in the upper GI tract due to risk of iatrogenic tear and perforation, especially at the cricopharyngeus and pyloric ring, a case series of 4 patients reported that esophageal intubation was feasible with the assistance of balloon dilation to 18 mm to facilitate passage of the device.16 Additional studies that have reported on outcomes related to the FTRD system are summarized in Table 1.17–19

**Standard Endoscopic Full Thickness Resection**

In contrast to clip-assisted EFTR, the standard EFTR technique is a "cut then close" procedure primarily used for the removal of gastric SELs originating from the MP. This technique is ill-advised in the esophagus or duodenum due to limited working space, restricted maneuverability for defect closure, and serious morbidity associated with adverse events related to these organs, such as mediastinitis and fistula formation. Similarly, its use is limited in the colon due to a heightened risk of leak and peritonitis, and unreliable defect closure.

A "close then cut" EFTR approach has been described whereby transmural sutures are placed underneath the lesion before resection using endoscopic suturing devices intended for other indications (eg, GERDX; G-Surg GmbH, Seeon-Seebuck, Germany and Plicator; NDO Surgical, Mansfield, MA).1 This approach is not popular due to device restrictions or unavailability.

**Indications.** With regard to lesion size, gastric SELs <3 cm arising from the MP are most suitable for standard EFTR. Although EFTR is technically feasible for lesions >3 cm, their extraction through the esophagus after en-bloc resection can be problematic and the resultant gastric wall defects may be difficult to close with risk of postoperative gastric leaks.20

In our opinion, SELs that have a broad (>50%) and deep attachment to the MP on EUS are a challenge to resect due to a higher likelihood of developing clinically significant intra procedural adverse events, such as tension pneumoperitoneum, as well as delayed adverse events, such as postoperative leak. Moreover, the creation of a large defect during the procedure results in escape of insufflated gas,
leading to collapse of the operative field and hampering the resection. If EFTR is entertained for such lesions, they should be removed by a highly skilled operator who can manage adverse events, such as tension pneumoperitoneum, and has access to robust closure devices, such as endoscopic suturing.

Although EFTR is feasible for an SEL with growth that is predominantly extraluminal, measures should be taken to avoid dropping the resected specimen in the peritoneal cavity. Laparoscopic wedge resection is a more efficient and preferred approach for a readily accessible lesion that exhibits extraluminal protrusion on imaging studies.

The use of EFTR with full thickness breach of the gut wall for removal of early gastric cancer is controversial because of the risk of iatrogenic peritoneal tumor seeding via contact with and transplantation of cancer cells.21

Devices and techniques. The EFTR procedure is performed under general anesthesia with endotracheal intubation and antibiotic prophylaxis. Carbon dioxide is used for insufflation instead of ambient air to reduce the risk of clinically significant gas-related adverse events. Lavage of the stomach with a dilute antibiotic solution before EFTR is optional.

The standard EFTR technique is an extension of endoscopic submucosal dissection with utilization of similar devices and accessories. The procedure involves a series of steps, including marking of the lesion periphery, mucosal incision, lesion enucleation, hemostasis, and defect closure (Supplementary Figure 2 and Video Clip 2).

Lesion marking consists of placement of coagulation dots along the periphery of the lesion using argon plasma coagulation or the tip of an electrosurgical knife. A circumferential mucosal incision is usually performed after submucosal fluid injection, although incisional variants include longitudinal and cross incisions to facilitate defect closure.20 The various injection solutions used for the submucosal fluid lift contain either saline or a viscous agent (eg, hydroxypropyl methylcellulose) mixed with a dye (eg, indigo carmine, methylene blue), with or without dilute epinephrine. Tissue dissection is performed around and underneath the lesion with intent to accomplish en-bloc resection. Because it is difficult to assess R0 resection for SELs as opposed to epithelial lesions, the aim is to enucleate the lesion with its pseudocapsule intact. A variety of electrosurgical knives are available for this purpose, with the selection of a particular knife or knives determined primarily by operator preference. In many cases, a combination of knives is required to enable dissection in a forward (non-insulated tip knife) as well as pull (insulated tip knife) motion. A snare can also be used to complete en-bloc resection of a partially dissected lesion that remains on a small pedicle. A lesion that is tightly adhered to the deep MP and serosa requires intentional through-and-through perforation for complete removal. As the resection reaches near completion, and depending on the size of the underlying perforation, the lesion may require grasping by an accessory passed through a double-channel endoscope so it does not fall into the peritoneal cavity. A dedicated hemostatic forceps (Coagrasper; Olympus Corp, Tokyo, Japan) is

| Table 1. Case Series (n ≥ 20) of Clip-Assisted Endoscopic Full Thickness Resection |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| First author, year              | Patients, n     | OTS clip type | Lesions          | Procedure time, min, mean (range) | R0 resection rate, % | Technical success rate, % | Procedure time, min, mean (range) | Recurrence/residual rate, % (mean follow-up, mo) |
| Backes, 2017                    | 26 (Padlock)    |                | Colorectal: 15 adenomas, 2 SEL, 3 diagnosis | 43 (NA) | 100 | 10 (4–20) | 11 (6) |
| Schmidt, 2015                   | 25 (FTRD)       |                | Colorectal: 20 adenomas, 2 SEL | 12 (2 perforations; 1 bleeding) | 73 | 12 (2 PPS; 1 bleeding) | 20 (4) |
| Schmidt, 2017                   | 181 (FTRD)      |                | Colorectal: 143 adenomas, 15 SEL | 80 | 75 | 12.5 (6 perforations; 5 FCD; 1 perforation) | 69.2 (3) |
| Valli, 2017                     | 60 (FTRD)       |                | Gastro/intestinal: 53 Adenoma | 150 (5–177) | 80 | 24 (10–35) | 60 (15–177) |
| Andrisani, 2017                 | 20 (FTRD)       |                | Colorectal: 4 adenomas, 9 SEL | 115 (10–42) | 100 | 26 (10–42) | 50 (NA) |

FCD, failed clip deployment; NA, not available; PPS, post-polypectomy syndrome.
essential for control of active bleeding and prophylactic coagulation of visible vessels during the procedure. Depending on the size, accessibility, and viability of the margins of the defect, the latter can be closed with through-the-scope clips with or without endoloop reinforcement, OTS clips, or endoscopic sutting (OverStitch; Apollo Endosurgery, Austin, TX). Pulling of omentum through the defect before clip or suture closure (omentum patch) is beneficial when technically feasible.

Of note, gas-related events, such as subcutaneous emphysema, pneumothorax, and pneumoperitoneum, may occur, particularly when full breach of the gut wall is required during cut-then-close EFTR procedures. Unless symptomatic, these occurrences should not be construed as adverse events. Due to its rapid absorption, the judicious use of CO₂ insufflation instead of ambient air has minimized the risk of adverse events related to air under tension.

**Efficacy and safety.** In a recent systematic review of 6 studies that encompassed 204 patients with 208 gastric SELs originating from the MP, the overall success rate for EFTR was 96.8%, with mean procedure times ranging from 37 to 105 minutes and mean lesion sizes ranging from 12.1 to 34 mm. A low rate of adverse events was reported (6%), including abdominal distention, fever, and localized peritonitis, all managed conservatively. The majority of lesions consisted of GISTs and leiomyomas with no recurrence on limited follow-up.²²

A large series of 726 consecutive patients who underwent resection of 733 upper GI SELs (1–4 cm in size) originating from the MP combined both standard EFTR (n = 536) and EFTR via submucosal tunneling (n = 197) in the analysis. The complete resection rate was 97.1%, with a mean procedure time of 49.2 ± 14.3 minutes. Adverse events developed in 12.9% of cases, including perioperative perforation (12.1%), perioperative bleeding (1.8%), localized peritonitis (0.7%), and delayed bleeding (0.1%). The majority of resected lesions were leiomyomas (62.9%) and GISTs (34.1%) without residual lesion at a mean follow-up of 28 months. Risk factors for incomplete resection were extensive connection of the tumor to the MP layer (P = .007) and extraluminal growth (P = .048). Risk factors for perioperative perforation were larger tumor size (<2.0 cm vs 2.1–3.0 cm vs >3.0 cm; P = .021), extraluminal growth (P = .046), and extensive connection to the MP (P < .001).²³

In one retrospective study, EFTR (n = 35) compared favorably to laparoscopic resection (n = 33) of gastric GISTs, particularly for lesions <2 cm, with regard to rates of en-bloc resection and adverse events.²⁴

Conventional EFTR for resection of SELs in the colon has been reported, but its safety profile precludes its routine use currently, in large part due to the inability to close the resection defect reliably.²⁵,²⁶

**Endoscopic Full Thickness Resection via Submucosal Tunneling**

The tunneling technique was inspired by developments in submucosal endoscopy,²⁷ natural orifice transluminal endoscopic surgery²⁸ and peroral endoscopic myotomy for achalasia.²⁹ Coined as STER (submucosal tunneling endoscopic resection), the technique is utilized for the removal of select SELs arising from the MP with an overlying intact mucosa.²⁹,³⁰ The intent of STER is to preserve the mucosal layer overlaying the lesion in order to reduce the risk of leak, secondary infection, and stricture formation at the resection site.³¹ Peroral endoscopic tumorectomy is another term used to describe STER in the upper GI tract.

**Indications.** STER is suitable for tumors originating from the MP with an intact overlying mucosa and without high-risk EUS features, as described previously. Lesions that are <3.5 cm in size are generally amenable to STER. Although technically feasible, the removal of larger lesions is associated with technical difficulties, a lower rate of en-bloc resection, and an increased risk of adverse events.³¹–³⁴

The creation of a submucosal tunnel is more readily accomplished in the relatively straight and tubular structures of the mid-distal esophagus and gastric cardia, and so tumors at these locations are the most suitable targets for STER. Lesions in a high cervical esophageal location are not appropriate for STER due to space restrictions in establishing a submucosal tunnel. The performance of a submucosal tunnel is also challenging in non-cardia regions of the stomach³⁵ and rectum,³⁶ owing to their anatomic configurations, distensibility, and mucosal hypertrophy. A wandering tunnel can easily be created in the capacious stomach, and gastric mucosal hypertrophy can inhibit effective submucosal fluid lift for tunnel formation.

**Devices and techniques.** Similar to standard EFTR, the STER procedure is performed under general anesthesia with endotracheal intubation and antibiotic prophylaxis. CO₂ insufflation is essential to minimize the risk of clinically significant gas-related adverse events.

The technical steps for STER (Figure 3 and Video Clip 3) in the upper GI tract are as follows:

1. Placement of a submucosal fluid cushion and initiation of a mucosal incision (mucosotomy) using an electrosurgical knife approximately 5 cm above the proximal margin of the target lesion. A 2-cm longitudinal mucosotomy is typically performed, but variations in mucosotomy configuration have been described.³⁷

2. Passage of a cap-fitted endoscope through the mucosotomy site and creation of a submucosal tunnel that extends 1–2 cm distal to the lesion to provide sufficient working space for resection of the tumor. Submucosal tunneling is accomplished using an electrosurgical knife with intermittent injection of a solution that typically consists of normal saline and a dye (indigo carmine or methylene blue), with or without dilute epinephrine. The submucosal dissection stays close to the MP layer to avoid mucosal injury and to expose the tumor.

3. Tumor enucleation with intent to achieve removal of the lesion en bloc. Similar to standard EFTR, a variety of electrosurgical knives can be used to dissect the
tumor from the surrounding normal submucosa and MP. A partial or full thickness resection of the MP is performed based on the degree of attachment of the lesion to the MP, with the goal to avoid rupture of the tumor pseudocapsule and unnecessary breach of the esophageal adventitia or gastric serosa. For a lesion that arises from the deep MP and adherent to the adventitial or serosal layer, a full thickness resection that includes the lesion, its underlying MP, and adventitia or serosa is performed. A snare can be
used to complete the resection en bloc once the dissected lesion remains on a small pedicle. The resected tumor is then extracted using a retraction device (e.g., OTSC Anchor) or retrieval net. The mucosotomy site may need to be extended to enable extraction of large lesions. The Coagrasper hemostatic forceps is typically used for control of active bleeding or prophylactic coagulation of visible vessels during the procedure.

4. Closure of the mucosotomy site can be accomplished with clip placement or endoscopic suturing.

**Efficacy and safety.** Reports on the efficacy and safety of STER are mostly retrospective in nature with relatively short-term follow-up. The en-bloc resection rates range from 78% to 100% and the rates of adverse events vary widely (0%–67%) because asymptomatic gas-related events, such as subcutaneous emphysema and pneumoperitoneum without tension, are also included as adverse events in some series. In the largest case series published to date, the overall incidence of STER-related adverse events was 23.4% (68 of 290), but only 10% of procedures (29 of 290) required intervention.

Table 2 summarizes the outcomes of STER from the larger case series (n > 50). A meta-analysis of 28 studies that encompassed 1041 patients and 1085 lesions reported a pooled complete resection and en-bloc resection rates of 97.5% (95% CI, 96.0%–98.5%) and 94.6% (95% CI, 91.5%–96.7%), respectively. The pooled estimates for gas-related adverse events were 14.8% (95% CI, 10.5%–20.5%) for subcutaneous emphysema and pneumoperitoneum without tension, and 6.8% (95% CI, 4.7%–9.6%) for pneumothorax. The pooled prevalence of perforation was 5.6% (95% CI, 3.7%–8.2%). The recurrence rate was 0% in all studies except in one report (2.7%).

Three studies have compared STER to video-assisted thoracoscopic surgery for the resection of esophageal tumors arising from the MP. Although the en-bloc resection and adverse event rates were similar in both groups, STER was associated with less postoperative pain, lower estimated blood loss, decreased procedure time, and shorter length of hospital stay. One study that compared STER to standard EFTR for the resection of gastric GISTs showed no difference in technical or patient outcomes, although the non-tunneling approach required a longer procedure time and a greater number of clips to close the gastric wall defect. These comparative studies, however, are limited by their retrospective nature and inherent bias. Randomized controlled trials and long-term follow-up studies are needed to determine the effectiveness of STER relative to other endoscopic and surgical methods.

**Post-Procedural Care and Follow-Up**

Post-procedural management and length of hospital stay vary according to institutional protocol. In our practice and after an uneventful EFTR procedure in the upper GI tract, patients are observed in hospital for 24 hours and kept nil per os until a contrast swallow study the following day confirms absence of leak. For colonic resections, the need for a post-procedural imaging study, such as computed tomography, is dictated by the patient’s clinical course. Patients are typically maintained on a gradual liquid to soft diet for 1 week, with resumption of a normal diet thereafter.

The optimal follow-up scheme after EFTR is not established. Benign lesions and those with an extremely low risk of malignancy, such as leiomyomas and neural tumors (e.g., schwannoma), that were completely resected do not necessarily require follow-up. Lesions with malignant potential, such as GISTs, require follow-up with endoscopy/EUS and/or cross-sectional imaging despite complete resection until long-term data suggest otherwise.

In patients who underwent OTS clip-assisted EFTR, biopsy of the post-resection site within and outside the clip is strongly recommended during follow-up, even in the presence of a benign-appearing scar to ensure any recurrent or residual lesion is identified. OTS clips are generally no longer present in about 75% of patients at follow-up. If a clip requires removal, this can be achieved using a dedicated cutting device or argon plasma coagulation, as long as the clip is not deeply embedded in tissue.

**Diagnostic Applications**

**Rationale**

The availability of large tissue specimens allows for both qualitative and quantitative analysis of multiple cell types. The role of EFTB is still evolving and its targets include the diagnosis of neuromuscular-based disorders, as well as challenging inflammatory or neoplastic processes. The pathophysiology of several GI conditions, including functional dyspepsia, idiopathic gastroparesis, and chronic intestinal pseudo-obstruction, remains largely unknown. There is increasing evidence to support an underlying heterogeneous neuromuscular pathology in many of these conditions. The acquisition of MP to include the intermuscular layer allows for evaluation of the myenteric plexus and interstitial cells of Cajal networks that lie within this layer, which may shed light on the etiology and potential therapy for these disorders.

**Techniques and Outcomes**

**Preclinical Setting.** We initially described the “no hole” (close then cut) technique for the collection of duodenal and rectal muscle biopsies in a survival porcine model with the intent to avoid overt perforation. Duodenal EFTB was performed using a single resection method, whereby a targeted site in the duodenum was retracted in its entirety into the cap of a Padlock clip using the OTSC Anchor tissue retraction device, followed by clip deployment. The duodenal pseudopolyp was then resected using a hot snare. An alternative to the tri-pronged retraction device is utilization of a grasping forceps to potentially minimize entrapment of extraluminal surrounding structures. Rectal EFTB was achieved using a double resection clip-assisted technique similar to gastric EFTB, as described later. In our study, the mean procedure times...
<table>
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<th>Mean/median procedure time, min (range)</th>
<th>En-bloc resection rate, %</th>
<th>Adverse events(^a) (rate, %)</th>
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<td>Subcutaneous emphysema and pneumomediastinum (21) Thoracic effusion (17) Pneumothorax (8) Pneumoperitoneum (5) Major bleeding (2) Mucosal injury (1) Esophagopleural fistula (0.3) Infection (4) Perforation (1)</td>
<td>0 (10)</td>
<td>68 leiomyomas 15 GISTs</td>
</tr>
<tr>
<td>Chen, 2016</td>
<td>290</td>
<td>Esophagus (199) EGJ (68) Stomach (23)</td>
<td>21 (10–70)</td>
<td>43 (15–200)</td>
<td>89.3</td>
<td>Subcutaneous emphysema and pneumomediastinum (21) Thoracic effusion (17) Pneumothorax (8) Pneumoperitoneum (5) Major bleeding (2) Mucosal injury (1) Esophagopleural fistula (0.3) Infection (4) Perforation (1)</td>
<td>NA</td>
<td>226 leiomyomas 53 GISTs 5 schwannomas 3 glomus tumors 3 calcified fibrous tumors</td>
</tr>
<tr>
<td>Li, 2017</td>
<td>74</td>
<td>Esophagus (74)</td>
<td>18.9</td>
<td>56</td>
<td>98.6</td>
<td>Subcutaneous emphysema and pneumomediastinum (21) Thoracic effusion (17) Pneumothorax (8) Pneumoperitoneum (5) Major bleeding (2) Mucosal injury (1) Esophagopleural fistula (0.3) Infection (4) Perforation (1)</td>
<td>2.7 (20)</td>
<td>67 leiomyomas 7 GISTs</td>
</tr>
<tr>
<td>Mao, 2017</td>
<td>56</td>
<td>Cardia (56)</td>
<td>18</td>
<td>42</td>
<td>100</td>
<td>Subcutaneous emphysema, pneumoperitoneum, pneumothorax, pleural effusion (15)</td>
<td>0 (25)</td>
<td>45 leiomyomas 10 GISTs 1 fibroid tumor 87 leiomyomas 1 fibrous tumor 1 lipoma</td>
</tr>
<tr>
<td>Du, 2017</td>
<td>89</td>
<td>Esophagus (89)</td>
<td>16 (10–60)</td>
<td>40 (12–142)</td>
<td>78.7</td>
<td>Subcutaneous emphysema, pneumomediastinum, pneumothorax (9) Fever (9) Pain (5) Mucosal injury (3) Pneumothorax/effusion (6) Bleeding (1) Perforation (1) Esophagopleural fistula (0.3)</td>
<td>0 (6)</td>
<td></td>
</tr>
<tr>
<td>Chen, 2017</td>
<td>180</td>
<td>Esophagus (124) EGJ (43) Stomach (13)</td>
<td>22 (20–50)</td>
<td>45 (15–200)</td>
<td>90.6</td>
<td>Subcutaneous emphysema, pneumomediastinum, pneumothorax (9) Fever (9) Pain (5) Mucosal injury (3) Pneumothorax/effusion (6) Bleeding (1) Perforation (1) Esophagopleural fistula (0.3)</td>
<td>0 (36)</td>
<td>146 leiomyomas 28 GISTs 4 schwannomas 2 calcified fibromas</td>
</tr>
</tbody>
</table>

EGJ, esophagogastric junction; NA, not available.

\(^a\)Subclinical gas-related events were included as adverse events in some studies.
were 23.7 ± 2.5 minutes and 13.25 ± 2.8 minutes for duodenal and rectal biopsies, respectively. The mean diameters of the duodenal and rectal specimens were 13.25 ± 4.3 mm and 12.5 ± 1.7 mm, respectively. No adverse events occurred.58

Gastric full thickness biopsy in a survival porcine model using a novel endoscope mounted circular cutter and anchor (Cook Endoscopy, Winston-Salem, NC) was described by Fritscher-Ravens et al.59 The rotating blades of the cutter resected the gastric wall without use of electrosonurgy and the resultant defect was closed using either an OTSC or T-tags (author’s workshop and Ethicon Endosurgery, Cincinnati, OH). The mean procedure time for the full thickness resection and defect closure was 17.9 minutes and the mean specimen diameter was 9.1 mm. Minor bleeding was reported in some animals.

Full thickness biopsies in the sigmoid colon were reported by Neunlist et al.60 in a non-survival porcine model using a band ligation device. The pseudopolyp of colonic wall created by the band was resected and the resultant perforation sealed using an OTSC. Although adequate tissue specimens were obtained, leak tests showed incomplete closure in half of the resection sites, leading the investigators to opine that an optimal and safe EFTB procedure in the colon needed to be identified before translation into clinical practice.

Clinical Setting

We initially reported on the clinical feasibility of gastric EFTB using the “no hole” approach, a concept we introduced in 2008 to prevent the risk of leak and subsequent peritonitis.2,61 Given the relative thickness of the gastric wall, EFTB was a 2-step procedure using a double-resection, clip-assisted technique (Supplementary Figure 3). A site was identified along the anterior wall of the gastric body, an ideal location both from a safety (avoidance of the gastroepiploic and gastric vessels) and ease of performance perspective. EFTB is best avoided in patients with a history of extensive abdominal surgery and/or radiation therapy given the increased risk of extraluminal entrapment of adjacent organs. In a small study of 3 patients with idiopathic gastroparesis, the mean procedure time was 25.7 ± 6 minutes and the mean length of muscle resected was 10.3 ± 1.5 mm. There were marked decrease in myenteric neurons and severe decrease in interstitial cells of Cajal seen across the muscle layers, which are considered hallmark features of gastroparesis. Adverse events consisted of transient abdominal pain which was treated conservatively.6 Although gastric EFTB remains a new procedure and appropriate caution must be exercised as with any novel technology, the minimally invasive procurement of a full thickness specimen for histochemical characterization may have a significant impact on patient care, including guidance on immunosuppressive therapy.

Diagnostic rectal EFTB using the FTRD system was recently reported in a small series of 4 patients with chronic obstruction and colonic dilation.1 The mean diameter of the resected samples was 21 mm and the mean procedure time was 12 minutes. There were no adverse events. Histologic diagnoses ranged from aganglionosis to hypoganglionosis and eosinophilic leiomyositis. The thickness of the rectal wall and tissue sampling below the peritoneal reflection make the rectum a suitable location for EFTB. Studies are needed to assess safety of EFTB above the rectum.

Post-Procedural Care and Follow-Up

Post-procedure pain occurs in the majority of patients after EFTB, akin to post-polypectomy syndrome, and can be managed with short-term analgesics. Patients should be maintained on clear liquids for 24 hours post-procedure. Diet can be advanced as tolerated thereafter. The utility of post-procedure antibiotic prophylaxis is unclear. In patients undergoing gastric EFTB, high-dose acid suppression therapy for 8 weeks is recommended.

Conclusions

The role of endoscopy for full thickness tissue acquisition and lesion resection is in a state of evolution. Advances in endoscopic resection and closure techniques have enabled transmural interventions to be performed that were the purview of the surgeons. Although results published thus far are promising, prospective comparative studies are needed to assess long-term efficacy and safety of these techniques. The learning curve is steep but, in experienced hands, EFTR represents a viable option for the removal of select lesions in the least invasive fashion. In some cases, a multidisciplinary approach is envisaged and a combined laparoscopic-endoscopic procedure may be best to optimize outcomes in terms of efficient lesion removal and safety.62–64 Lastly, reimbursement and dedicated Current Procedural Terminology codes commensurate to the complexity and effort required for the performance of EFTR are warranted as these procedures become standard of care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at http://dxdoi.org/10.1053/j.gastro.2018.02.020.

References

cell types, including myenteric neurons and interstitial cells of Cajal in patients with idiopathic gastroparesis: a feasibility study (with video). Gastrointest Endosc 2016; 84:512–517.


33. Li QY, Meng Y, Xu YY, et al. Comparison of endoscopic submucosal tunneling dissection and thoracoscopic...


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Conflicts of interest
The authors disclose no conflicts.
Figure 1. (A) FTRD system (Ovesco Endoscopy AG, Tübingen, Germany); (B) FTRD cap with preloaded clip and integrated snare.

Supplementary Figure 2. Standard EFTR. (A) Large 3-cm GIST in the gastric body; (B) peripheral incision; (C) lesion enucleation with breach of MP (arrow); (D) post-resection defect with view of serosal layer; (E) closure of defect with endoscopic suturing device; and (F) appearance post-endoscopic stitching of defect.
Supplementary Figure 3. Endoscopic full thickness biopsy of the stomach. (A) Endoscopic mucosal resection using the band ligation approach to expose the underlying MP; (B) creation of a MP pseudopolyp using a tri-pronged anchor for tissue retraction into the cap of a Padlock clip, followed by clip deployment; (C) resection of pseudopolyp of muscle above the clip using hot snare; (D) effective closure of the biopsy site confirmed by visible closure without disruption, sustained gastric distension with CO_2 insufflation, and absence of radiopaque contrast leakage into the peritoneal cavity under fluoroscopy.