BACKGROUND

Polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection are endoscopic procedures performed to remove superficial tumors involving the mucosa and submucosa of the gastrointestinal system (GI).\(^1\) The efficacy and safety of these techniques are hampered in the presence of non-lifting epithelial lesions due to severe fibrosis and scarring, subepithelial lesions (SELs) emerging from muscularis propria (MP), and complex lesions that are difficult to approach endoscopically or at high risk for complications such as bleeding and/or perforation.\(^2\)

Endoscopic full-thickness resection (EFTR) has emerged as an endoscopic resection technique for removing deep submucosal tumors (SMTs) in the GI wall.\(^3\)

Suzuki and Ikeda were the first to describe EFTR in 2001.\(^4\) There are three EFTR techniques: clip-assisted EFTR, standard (direct) resection of the lesion followed by defect closure (“exposed” EFTR), and lesion resection by submucosal tunneling (non-exposed EFTR).\(^5\) In this manuscript, we will discuss the technical characteristics, indications, safety, and outcomes of EFTR.

Full-Thickness Resection Device

The FTRD (Full-thickness resection device) system consists of a plastic cap (13 x 23mm) preloaded with an FTRD clip and a 14-mm poly filament polypectomy snare, as well as accessory equipment including a tissue grasper and a high-frequency marking device or probe (see Figure1). Before endo-mucosal full-thickness resection with FTRD, the marking probe is used. This high-frequency marking probe is used to tag the target lesion before applying the FTRD, enabling detection and complete excision of the target tissue easier (see Figures 2 & 3). In contrast to the majority of endoscopic polypectomy snares, the FTRD system’s snare does not progress through the working channel; instead, the shaft runs along the scope’s exterior side, protected by a plastic sheath, leaving the working channel available for instrumentation.\(^5\)
1. Clip-Assisted EFTR

Standard EFTR approaches entail the excision of a lesion followed by the closure of the defect with mechanical clips or endoscopic suturing devices. However, over-the-scope clip (OTSC) assisted EFTR is a newly developed “close then cut” technique for complete excision of epithelial and subepithelial lesions throughout the GI tract. This approach offers a potentially safer alternative that involves stabilizing and affixing the defect prior to resection of the target lesion.

Indications

Non-lifting epithelial lesions (e.g., adenoma) linked with significant fibrosis from earlier resection attempts, as well as SELs, such as neuroendocrine tumors, leiomyomas, some pancreatic rests, and gastrointestinal stromal tumors (GISTs) are potential indications for clip-assisted EFTR. In a recent meta-analysis involving eighteen studies with 730 patients, Brewer Gutierrez et al. reported a pooled overall histological full resection rate (R0) of 82%. Lesions included in this study were difficult/residual colorectal adenomas, adenomas that involved a diverticulum or the appendiceal orifice, early cancers, colorectal SELs, and upper gastrointestinal lesions. Perforation and hemorrhage occurred in 0.1 and 2% of patients, respectively. There were no EFTR-related deaths.

Technique

After identifying the target lesion, the circumference of each lesion is pre-marked with a high-definition marking probe using the coagulation setting. Following that, the scope is withdrawn, and the FTRD system is attached to it. After re-inserting the scope, the lesion is pulled inside the distal plastic cap using the appropriate grasper with the intention to pull all layers of the stomach or bowel wall. The FTRD clip is then deployed, and the electrocautery snare is engaged with monopolar current and used in a standard manner to excise the clip-captured tissue in full-thickness. The specimen is subsequently removed, leaving the intestinal wall closed by the OTSC.

Safety and Efficacy

In a prospective multicenter study involving 181 participants, the efficacy and safety of the FTRD system for the removal of colorectal lesions were reported. EFTR was technically successful in 89.5%, with a 76.9% R0 resection rate. The R0 resection rate was 77.7% in 127 individuals with complicated adenomas and benign histology. Unsuspected cancer was found in 14 of the lesions, while 15 of the lesions were primarily known as malignancies. R0 resection was achieved in 72.4% of the cases, while 8 more instances exhibited
profound submucosal infiltration >1000 m. As a result, only 13/29 patients were able to have curative resection (44.8%). R0 resection rate was 87.0% in the subgroup with subepithelial tumors (SETs) (n=23). In general, lesions < 2 cm had a greater R0 resection rate than lesions >2 cm (81.2% vs. 58.1%, p=0.0038). The rate of adverse events was 10%. Out of 181 patients, 10 experienced procedure-related moderate adverse events, such as hemorrhage, post-polypectomy syndrome which is defined as development of abdominal pain, fever, leukocytosis, and peritoneal inflammation in the absence of frank perforation, appendicitis (which was conservatively handled), and recurrent abdominal pain of unclear origin (5.5 percent ). 8 patients out of total 181 (4.5% ) developed severe adverse events which include perforation, appendicitis required laparoscopic appendectomy and enterocolonic fistula after EFTR. Benjamin Meier et al. in a multicenter retrospective study including 1,178 colorectal FTRD procedures reported an 80% R0 resection rate for difficult adenomas, early carcinomas, and subepithelial tumors. Full-thickness excision (visible of all layers of the colonic wall, including serosa, within the resection material) was histologically confirmed in 89.9% of the cases in the whole cohort. Compared to the rectum, the colon had a considerably greater rate of full-thickness resection (92.0% vs. 83.3%, P=0.0001). Histologically complete resection (R0) was accomplished in 80.0% of the whole cohort. There was no significant difference in
Endo-Mucosal Full-Thickness Resection

2. Standard EFTR (Exposed EFTR)

In contrast to clip-assisted EFTR, the standard EFTR approach is a “cut and then close” procedure that is generally utilized to remove gastric SELs from the MP. However, limited working space, limited mobility for defect closure, and substantial morbidity are associated with adverse events, including mediastinitis and fistula formation. Similarly, the use of traditional EFTR use in the colon is restricted due to an increased risk of perforation and inadequate defect closure.

**Indication**

Standard EFTR is best suited for gastric SELs < 3 cm arising from the MP. Although EFTR is technically viable for lesions larger than 3 cm, their extraction through the esophagus following *en bloc* resection can be harrowing, and the resulting esophageal wall defects may be difficult, if not impossible, to seal, increasing the risk of perforation.

**Standard EFTR Technique**

The procedure begins with lesion marking utilizing high-definition marking probe to place coagulation dots along the lesion’s periphery, followed by peripheral incision and lesion enucleation with breach of MP. Finally, an endoscopic suturing device is used to close the defect.

**Safety and Efficacy**

In a retrospective analysis, Jian G. et al.’s colleagues included 100 gastric SMTs excised using EFTR. Efficacy of EFTR was measured in terms of rates of *en bloc* resection and was achieved in 98 cases (98%). Ten patients (9.9%) experienced adverse events. Two patients developed intraoperative bleeding, one delayed bleeding, and seven patients had peritonitis. EFTR was ceased in one patient due to massive intraoperative bleeding, and conversion to laparoscopic surgery was necessary. One patient required laparoscopic surgery due to delayed bleeding, and other minor complications were resolved with conservative management. Overall tumor size > 3 cm was associated with difficult EFTR, which was defined as a procedure time ≥ 120 minutes and/or the occurrence of major adverse events, such as significant bleeding, abdominal pain, or peritonitis. Antonino G. et al., in their recent systematic review, evaluated 15 studies, mainly from Asia, reported 750 exposed-EFTR treated gastric SMTs. The complete resection and surgical conversion rate was 98.8% and 0.8%, respectively. The rate of major adverse events, including delayed bleeding, perforation, peritonitis, and infection, was 1.6%, 0.5%, 0.1%, and 0.9%, respectively. The rate of successful exposed EFTR and effective endoscopic defect closure was 98.3%.

Another retrospective study by Ye L.P et al. included a series of 726 patients who underwent resection of 733 upper subepithelial lesions (1-4 cm in size) originating from the muscularis propria via exposed EFTR and EFTR through submucosal tunneling. Adverse events including perforation (12.1%), immediate bleeding (1.8%), peritonitis (0.7%) and delayed bleeding (0.1%). Most lesions were leiomyomas (63%) and GISTs (34%) without residual lesions and a mean follow-up of 28 months. The major risk factors for incomplete resection were an extensive connection to the muscularis propria (p=0.007) and extraluminal growth (p=0.04).
Risk factors for perioperative perforation were large tumor size ($p=0.04$), extensive connection to muscularis propria ($p=0.01$) and extraluminal growth ($p=0.04$). Although conventional EFTR has been reported for resection of SELs in the colon, its safety profile limits its widespread usage at the moment, in large part due to the inability to consistently close the resection defect.

**Submucosal Tunneling Endoscopic Resection (STER)**

**STER Technique**

STER is a combination of peroral endoscopic myotomy and endoscopic submucosal dissection techniques. In this technique, a submucosal tunnel is constructed to serve as a working area for endoscope insertion and tumor excision. When compared to ESD, this method has a lesser chance of perforation since the integrity of the GI mucosa is preserved; it also provides better wound healing and a lower risk of infection. Furthermore, due to the deeper tumor origin, this technique is better suited for cancers coming from the muscularis propria layer, for which ESD resection is problematic.

**Indications**

STER is appropriate for tumors arising from the MP with an intact overlying mucosa and no high-risk EUS characteristics. STER is usually effective for lesions less than 3.5 cm in diameter. Resection of larger lesions can be associated with technical problems, a lower probability of en bloc resection, and a higher risk of adverse events, including bleeding, mucosal laceration, and perforation.

**Contraindications**

STER should not be performed if the mucosa is ulcerated. SMTs with irregular borders are more likely to be malignant and more challenging to resect using STER. There is a significant risk of perforation, persistent fistula development, and secondary infection when removing lesions involving a deep part of the muscularis propria.

**The Steps Involved in STER**

1. **Identification of Tumor**
   The first step of STER involves tumor identification. Injection of indigo carmine or methylene blue may be performed to help locate the tumor and guide the direction of subsequent tunneling.

2. **Submucosal Injection**
   A fluid cushion is subsequently generated through a submucosal injection of fluid, usually a saline solution with indigo carmine or methylene blue, 2-5cm from the SMT. Sometimes, epinephrine is added to the solution.

3. **Generating Tunnel Entry**
   To create an entrance to the submucosal tunnel, a mucosectomy is performed, with the orientation of the incision being left to the operator.

4. **Tunnel Generation**
   An electrosurgical knife is used to guide the endoscope through the incision. To further distinguish the submucosal and muscularis layers, a dye such as indigo carmine or methylene blue with or without epinephrine with saline as an injectate is utilized as the scope progresses to prevent damage while expanding the tunnel mucosa. To provide enough working area, the tunnel should be extended approximately 2 cm beyond the distal edge of the SMT.

5. **Tumor Dissection and Removal**
   Various electrosurgical knives may be employed for a partial or full-thickness resection, depending on the degree of attachment of the lesion to the muscularis propria. It is recommended to avoid unnecessary breach of the adventitia or the serosal layer during an en bloc excision. The resected tumor is then extracted using a retraction device such as an endoscopic anchoring device, a rat-tooth forceps, or a retrieval net.

**Efficacy and Safety**

Chen et al., in a retrospective study, evaluated 180 patients with upper gastrointestinal submucosal tumors undergoing STER and reported a 90.6% en bloc resection rate. The overall complication rate was 8.3%. Pneumothorax and hydrothorax occurred
in 10 patients (5.5%), clinically significant bleeding occurred in 2 patients (1.1%), the mucosal injury occurred in 2 patients (1.1%), and an esophageal-pleural fistula occurred in 1 patient (0.6%).

Xiu-He Lv et al. published a meta-analysis showing pooled complete resection and en bloc resection rates for SMTs undergoing STER was 95.5% and 94.6%, respectively. The most common complications related to STER were pneumothorax and bowel perforation. The pooled rate of subcutaneous emphysema and pneumomediastinum was 14.8%. The rate for pneumothorax was 6.1% and 6.8% for pneumoperitoneum. Additionally, the pooled rate of perforation was 5.6%. Only a few cases of bleeding were reported in only two studies.22

Li et al. found a 98.6% en bloc resection rate in their retrospective study of 74 patients who underwent STER for esophageal SMTs lesions. Perforation was reported in only one patient as an intraoperative adverse event. Pneumothorax and pneumoperitoneum were postoperative complications noted in 9 individuals.23 Mao et al., in their prospective study of 56 patients, reported a 100% rate of en bloc resection. Only 9 patients experienced adverse events, including pneumothorax, pleural effusion, and pneumoperitoneum.24 Chen et al., in their retrospective study of 290 patients with upper gastrointestinal SMTs treated by STER, reported an 89.3% en bloc resection rate. The overall incidence of complications was 23.4% (68/290).10.0% of procedures (29/290) required intervention for complications. Major bleeding occurred in 5 patients (1.7%). Pleural effusion occurred in 49 patients, including 9 patients who developed pneumothorax.25 Wang et al., in their prospective study of 80 patients undergoing STER, reported a 97.6% en bloc resection rate. Complications included chest pain, subcutaneous emphysema, and pneumothorax in 8.75% (7/80) of cases, and all of them resolved with conservative therapy.26

**CONCLUSION**

Although EFTR technology is still in development, it is a less invasive technique when compared to surgery for specific neoplastic lesions. The development of reliable closure devices and the adoption of appropriate indications will continue to make EFTR more feasible. In addition, it will help patients minimize their financial, physical, and psychological burdens.

Although the published results to date are encouraging, prospective comparative studies are required to determine the long-term effectiveness and safety of EFTR.

**References**


Answers to this month’s crossword puzzle: