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PROCEEDINGS

ENDOSCOPIC TRANSMURAL RESECTION OF PREMALIGNANT AND MALIGNANT COLORECTAL LESIONS—CLOSING THE GAP BETWEEN ENDOSCOPY AND SURGERY

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ABSTRACT

INTRODUCTION: The evolution of interventional endoscopy and the current techniques and devices for the closure of wall defects with sizes up to 30 mm have enabled the developm minimally invasive endoscopic approaches for the treatment of early malignant and premalignant lesions in the gastrointestinal tract—endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The application of these current techniques has some limitations in lesions with significant submucosal fibrosis (frequently due to previous endoscopic treatment or taking biopsies) as well as in treating subepithelial lesions. Endoscopic full-thickness resection (EFTR) is a novel revolutionary technique in the management of subepithelial lesions, lesions invading the muscular layer, and lesions with significant submucosal fibrosis or with difficult endoscopic access due to anatomical location.

MATERIALS AND METHODS: We performed a retrospective analysis of a group of 12 patients with complex colorectal lesions unsuitable for standard endoscopic treatment for the period from April 2019 to May 2023. Our primary endpoint was technique efficacy defined as radical excision with clear resection margins. Our secondary endpoint was to evaluate the most common adverse events associated with EFTR.

RESULTS: In 100% of the cases, in the following histology report, we found radical excision of the lesion defined as clear margins. As for our secondary endpoint—evaluation of adverse events, we found a rate of 33.3% adverse events (in four of the patients), 3 events of bleeding, and one perforation. All of them were managed endoscopically.

CONCLUSION: The development of interventional endoscopy allows the application of minimally invasive treatment as a definitive treatment of complex colorectal lesions. Full-thickness resection and the option for transmural radical excision could be offered as an alternative to surgical treatment.

Keywords: *endoscopic full-thickness resection (EFTR), colorectal cancer (CRC), endoscopic submucosal dissection (ESD), adverse events (AE)*

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide. Fortunately, it is highly preventable due to changes in the modifiable risk factors, alongside the detection and removal of precancerous lesions. In 2023 a workgroup published a study about the burden of CRC on global health (1). According to the results, the burden of CRC is projected to increase to 3.2 million new cases and 1.6 mil-

lion deaths by 2040, with most cases predicted to occur in high or very high Human Development Index (HDI) countries. This all highlights the importance of the prevention of CRC. Key factors in prevention are screening programs for early CRC detection and endoscopic removal of precancerous lesions. Colonoscopic polypectomy suggests up to 53% reduction in mortality from CRC according to the results from the National Polyp Study (2). This defines endoscopy as a cornerstone in the prevention of cancer morbidity and mortality. The evolution of endoscopic techniques for the removal of lesions has expanded along with the advance in optical diagnosis. The evaluation of precise lesion characteristics such as location, size, histology, and depth of invasion prediction is essential for the selection of the optimal removal method. The current endoscopic techniques and the recommendations for their application are as follows: cold snare polypectomy for diminutive (< 5 mm) and small (6–9 mm) lesions, hot or cold snare polypectomy for non-pedunculated lesions with a size of 10–19 mm, endoscopic mucosal resection (EMR) for non-pedunculated lesions over 20 mm, and endoscopic submucosal dissection (ESD) for lesions over 20 mm with suspected submucosal invasion based on two main criteria of depressed morphology and irregular or nongranular surface pattern in order to provide en bloc resection for exact deep invasion evaluation (3,4). Unfortunately, some neoplastic lesions, including those involving the muscularis propria, cannot be adequately and safely treated with these techniques. With the development of novel endoscopic closure techniques and tools, endoscopic full-thickness resection (EFTR) has emerged as an alternative therapeutic option for the treatment of these lesions. Some current applications include removing subepithelial tumors (SETs) and epithelial neoplasia, extending deeper than the mucosa or associated with significant fibrosis (5).

The Technique

Endoscopic full-thickness resection involves the complete resection of the mucosa to the muscularis propria. It can be applied for the treatment of difficult-to-resect lesions, recurrent lesions with scar formation after previous endoscopic resections, and subepithelial tumors. Two general approaches to EFTR have been described: *exposed* and *non-exposed* EFTR. In exposed EFTR, the full-thickness resection is undertaken first, with subsequent closure of the defect. Further, the exposed technique is divided into tunneled exposed technique and non-tunneled exposed technique. In tunneled exposed technique, a mucosal incision is made distant to the lesion and a submucosal tunnel towards the targeted lesion is created by dissection of the submucosal layer. The lesion is then enucleated and removed through the tunnel and is used for subepithelial lesions. As the incision of the mucosa is distant from the excised lesion, full-thickness closure is not needed and only endoscopic clips or suturing devices can be used for closure of the mucosal defect. However, this technique cannot be applied to mucosal lesions but only in the management of subepithelial tumors. In the non-tunneled exposed technique, the approach is similar to ESD—fluid expansion of the submucosal layer with dissection in the submucosal layer, the dissection is then continued through the muscularis propria circumferentially around the lesion. With non-tunneled exposed EFTR, full-thickness closure must be performed. This technique may be used both for mucosal neoplasia and subepithelial tumors. Non-exposed EFTR is similar to surgical wedge resection. The bowel segment containing the targeted lesion is retracted into the lumen. This allows for approximation and subsequent secure fixation of 2 serosal surfaces by the use of various devices. The targeted lesion is isolated and then safely resected above the closed serosal layer (5). Devices that have been used to perform non-exposed EFTR include endoscopic suturing platforms and over-the-scope devices. Limitations of the technique include the paucity of available devices and the size of the resected lesions; EFTR can be safely and efficaciously performed in the resection of lesions up to 30 mm.

METHODS

Setting

A retrospective analysis of the patient database of a single tertiary referral center, Department of Interventional Gastroenterology at Acibadem City Clinic Tokuda University Hospital, was conducted. All patients provided written informed consent. An experienced therapeutic endoscopist (P.K.), certified for FTR and trained for ESD and EMR, performed all procedures.

Patients

We performed a retrospective analysis of a consecutive group of 12 patients treated in our center in the period April 2019 to May 2023. All patients had complex colorectal lesions unsuitable for standard endoscopic treatment. In all of these cases, EFTR was applied. The retrieved specimens were sent for pathology evaluation, including histology, grade of dysplasia, resection margins, and depth of vertical invasion for the lesions defined as cancer in the histology report.

AIM

Our primary endpoint was technique efficacy defined as radical excision with clear resection margins. Our secondary endpoint was to evaluate the most common adverse events, associated with EFTR.

RESULTS

For the period from April 2019 to May 2023, twelve EFTRs were performed using the non-exposed technique with the over-the-scope full-thickness resection device (FTRD) (Ovesco Endoscopy Tubingen, Germany) (Fig. 1).

Fig. 1. Ovesco colonic FTRD (Ovesco Endoscopy Tubingen, Germany).

The colonic FTRD consists of an applicator cap with a ready-to-use mounted FTRD clip, integrated hot snare, and thread. In the set is also a thread retriever for easy retrieval of the release thread, the endoscope sleeve with fixation tapes, and the FTRD hand wheel. The following steps are performed:

1. marking of the targeted lesion (Fig. 2.);
2. grasping and mobilizing the lesion (Fig. 3 and Fig. 4);
3. retraction of the lesion in the cap followed by applying a preloaded clip;

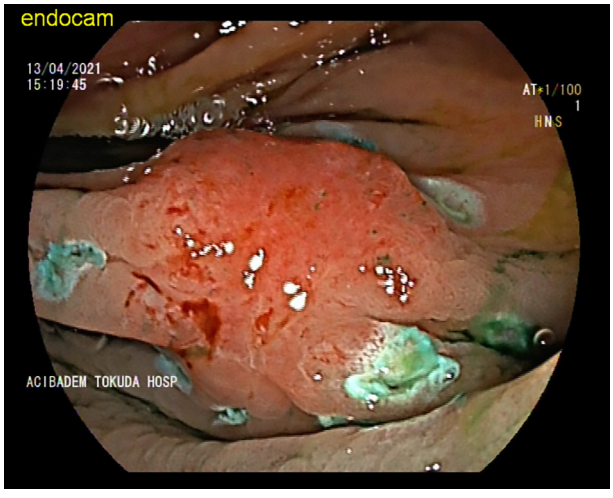

Fig. 2. Marking of the lesion with an FTRD marking probe.

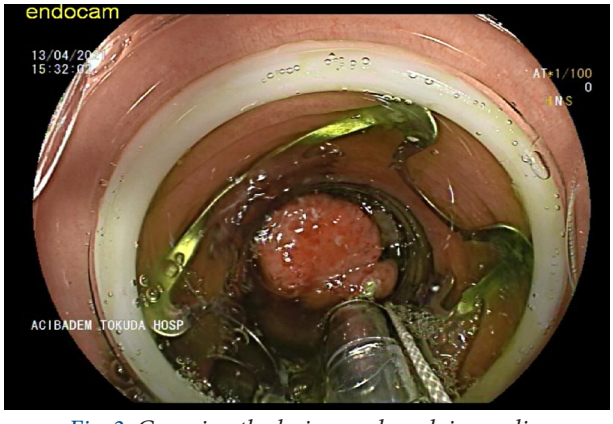

Fig. 3. Grasping the lesion and applying a clip.

Fig. 4. Grasping the lesion with forceps and retracting it in the cap, followed by an application of a clip.

4. resection of the lesion with a hot snare and retrieval of the specimen.

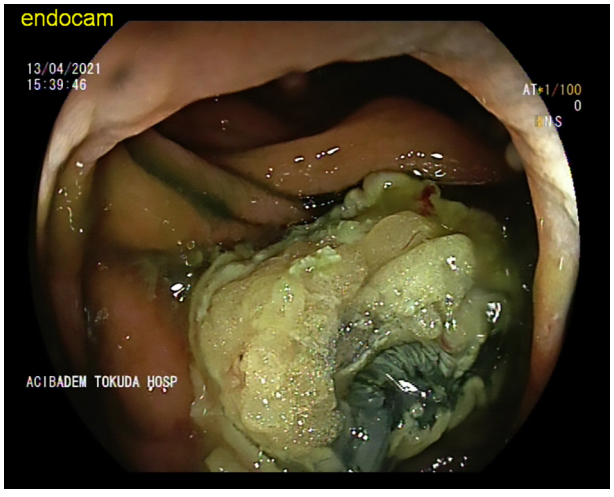

Fig. 5. Post-resection site with colon wall defect closed with preloaded clip.

Procedures

All of the patients were admitted to the hospital and had signed written informed consent. All of them underwent standard split-dose preparation with polyethylene glycol or polyethylene glycol combined with ascorbic acid. Intravenous sedation with Propofol, Midazolam, and Fentanyl was used. Patients were placed in the left lateral or supine position according to the location of the lesion. All of the patients received periprocedural antibiotic prophylaxis with Ceftriaxone and Metronidazole, followed by antibiotic treatment for up to seven days after the procedure. FTR was performed with a standard adult colonoscope Fujifilm and original FTRD (Ovesco Endoscopy, Tübingen, Germany) with carbon dioxide (CO2) insufflation. The colonoscope was advanced to the lesion which was marked by the FTRD marking probe. After that, the colonoscope was withdrawn and reintroduced with the FTRD set. The next step was grasping the lesion and pulling it into the cap by FTRD grasper, afterwards, the preloaded over-the-scope (OTS) clip was deployed. The last step was the resection of the lesion over the OTS clips by preloaded monofilamentous snare using pure cut mode 100–120 W (Olympus ESG-300). After that, the endoscope was introduced again to the location of the resection to check for complications. The extracted specimens were measured, fixed in formalin, and sent for pathology evaluation. Patients were kept nil by mouth for the day of the procedure and the day following the procedure, after that they received a soft diet.

Patient Group Characteristics

The baseline characteristics of the group were: male-to-female ratio of 11:1; mean age of 62 years. All concomitant diseases were evaluated (Table 1), as in some cases the concomitant comorbidity was the determinant factor for the choice of FTRD as a single curable technique. One of the patients (a 52-year-old male) had diffuse large cell B cell lymphoma with the stomach being the primal location. Due to his performance status and his refusal of surgery, FTRD was the only treatment modality for his colorectal lesion although the histology result of the resected lesion showed adenocarcinoma with a depth of invasion T3. He received chemotherapy for his hematological disease and was followed with scheduled colonoscopies and positron emission tomography/computed tomography (PET/CT) with no sign of recurrence of the colonic lesion. One of the patients (a 61-year-old male) had a previous subtotal colectomy with ileorectal anastomosis due to cancer of the sigmoid colon with polyposis syndrome. He refused surgery and FTRD was the choice of treatment for the rectal lesion which was found.

Lesion Characteristics

The average size of the removed lesions was 18 mm (18–38 mm). In 8 of the cases, previous endoscopic treatment was performed by pEMR, and FTR was performed in recurrent lesions. In 4 of the cases,

Table 1. Evaluation of concomitant diseases.

Type of Concomitant Disease	Total Number	Percentage of the Total Number
Arterial hypertension	9	75%
Atrial fibrillation	2	16.67%
Aortic valve insufficiency	1	8.33%
Heart surgery	1	8.33%
Chronic kidney injury	1	8.33%
Deep venous thrombosis	1	8.33%
Previous surgery for CRC	3	25%
Diffuse B cell lymphoma	1	8.33%
Diabetes	1	8.33%

FTR was the first choice of treatment. In one of these cases, FTR was performed due to a non-lifting sign phenomenon during an attempted pEMR, which is a sign of deep submucosal invasion. In 100% of the cases, the following histology report defined radical excision of the lesion both for vertical and horizontal margins. Lesion histology and location are presented in Table 2. All of the lesions were classified according to the Paris classification. The most common type was Is—in 7 patients (58.33%), followed by 0-Iia—2 cases (16.67%), and 0-IIa+Is, also in 2 cases (16.67%), and in one case the lesion was 0-IIa+IIc (8.33%).

Table 2. Lesion histology and localization.

Histology Result	Lesion Location
Tubular adenoma n = 2 (16.67%)	Rectum n = 5 (41.67%)
Villous adenoma n = 2 (16.67%)	Sigmoid colon n = 2 (16.67%)
Tubulovillous adenoma n = 2 (16.67%)	Transverse colon n = 3 (25%)
Sessile serrated adenoma n = 2 (16.67%)	Ascending colon n = 1 (8.3%)
Mucinous adenocarcinoma n = 1 (8.3%)	Cecum n = 1 (8.3%)
Adenocarcinoma T2 n = 1 (8.3%)	
Adenocarcinoma T3 n = 1 (8.3%)	
Adenocarcinoma in situ n = 1 (8.3%)	

Outcomes of the Procedure

Primary outcome measures were technical success rate and curative resection rate, defined as R0 resection rate (both for lateral and vertical margins) according to the following pathology report. The secondary outcome was the evaluation of the rate of adverse events. All patients were scheduled for follow-up, but it was performed in 7 patients. The average period of endoscopic follow-up was 310 days (184–366). During these endoscopies, in one of the patients, macroscopic signs of recurrence were found in the post-resection site, followed by resection of the found lesion with a cold snare. The histology report showed recurrent adenoma in the cicatrix. The next endoscopy in this patient was performed 10 months later and showed no signs of recurrence. In all the other patients who were followed up, there were no macroscopic signs of recurrence. Biopsy samples were taken from the site of the resection and the surrounding mucosa, in all the cases—with negative for recurrence histology. In 8 of the cases, previous endoscopic treatment was performed by pEMR, and FTR was performed in the recurrent lesions. In 4 of the cases, FTR was the first choice of treatment. In one of these cases, FTR was performed due to a non-lifting sign phenomenon during an attempted pEMR, which is a sign of deep submucosal invasion. In eight cases, en bloc resection of the lesion was performed with FTRD, with the removed specimen containing all layers of the bowel wall. In one of the cases, there was a failure to resect the lesion en bloc, and resection of the remnant fragments was performed with a hot snare. In this case, the lesion was in a region of previous pEMR and there was a lot of fibrosis in this segment of the colon. Despite this, radical excision of the lesion was confirmed by the pathological report. In three of the cases, hybrid resection was performed. The sizes of the lesions were 50 mm, 38 mm, and 35 mm in the third case. Reduction of the size up to 25 mm was achieved with pEMR of the peripheral parts of the lesion. Full-thickness resection was then performed on the central part of the lesions. All resected specimens were sent for pathology evaluation. In all of these cases, the histological report confirmed radical excision with clear both horizontal and vertical margins.

Complications occurred in four patients, or 33.3%. All of the events were treated endoscopically with no need for surgery or transfer to the intensive care unit. All of the cases were defined as mild according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon for an adverse event (1). There was no need for blood transfusion and no drop of the hemoglobin level by more than 20 g/L was found. The overall hospital stay was not prolonged by more than 3 days. There were 3 cases of post-procedure bleeding. In two of the cases, the bleeding was within the first 24 hours following the procedure, the third one was in the first 48 hours. In all three cases, second urgent endoscopy was performed with endoscopic hemostasis with hemostatic forceps (Olympus Coagrasper FD-411UR) using an electrosurgi-

cal unit (Olympus ESG-300) with Softcoag 60W effect 3 settings. There were no rebleeding events. One case of perforation was found—in the first patient in whom we used FTRD. In the second look, endoscopy malposition of the OTS clip led to the discovery of a defect of the bowel wall with a size of 25 mm. The defect was closed with another over-the-scope clip and two hemostatic clips. The patient was kept nil by mouth for two days, and antibiotic therapy was given. There were no signs of peritonitis and he was discharged on the fourth day following the procedure.

DISCUSSION

Full-thickness resection is a novel advanced technique for endoscopic resection of early colorectal neoplastic lesions not suitable for standard polypectomy or EMR. The indications for FTR are similar to the ESD indications: basically lesions with suspected deep mucosal invasion or superficial invasion of the submucosa, lesions with non-lifting caused by submucosal fibrosis due to previous endoscopic treatment or previous biopsies, local residual neoplasia after previous endoscopic treatment. Endoscopic submucosal dissection, on one hand, is a well-established method but on the other, there are concerns about the high risk of complications, the long learning curve, and the fact that the specimen contains only part of the submucosa, so the deep submucosal invasion cannot be evaluated. Full-thickness resection has the advantages of shorter procedure time, lower rate of complications, does not require as extensive training as ESD, and, due to the fact that the resected specimen contains all layers of the colon wall, allows for better staging of invasive cancerous lesions. The main disadvantages of the procedure are the cost of the devices and the limitations of the extent of curative resection—up to 30 mm. In our study we had one patient with a depth of invasion T2 and one with T3. In both cases the patients did not go for surgical treatment and FTR was the only treatment modality. One of the patients was followed up by PET CT and endoscopies and did not show any signs of recurrence. The other patient was lost to follow-up.

CONCLUSION

Full-thickness resection offers a new alternative endoscopic approach to the treatment of colorectal lesions, not amenable to standard endoscopic techniques such as EMR and ESD. It can be offered as an alternative to surgical treatment in selected cases due to the option for transmural radical excision with the advantages of a less invasive nature, shorter hospital stay, high level of efficiency, and a good safety profile. Unfortunately, there are still scarce data so further research including randomized trials is necessary to determine the efficacy and safety of FTR.

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