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Hybrid resection with ESD and FTRD: Could this be a rescue treatment in the presence of severe submucosal fibrosis?

1. Introduction

Endoscopic submucosal dissection (ESD) is currently the endoscopic procedure of choice for the treatment of gastrointestinal neoplasms as it allows en bloc resection and accurate histological evaluation of the lesions and results in a low rate of local recurrence [1]. ESD, a time-consuming technique, requires specific training and a high level of skill in order to be safely performed. The presence of fibrosis makes the procedure more difficult and it is associated with low complete resection rates during colorectal ESD [1,2]. Factors that may predict the degree of submucosal fibrosis include tumour size, histology, depth of invasion, and pit pattern [2]. The FTRD® (full thickness resection device; Ovesco Endoscopy, Tübingen, Germany) is an over-the-scope device that allows EFTR with a clip-and-cut technique. In Europe, it was granted the CE Mark and the approval for lower gastrointestinal (GI) tract resection in September 2014 [3]. We describe the first hybrid technique case series using endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR) with FTRD (Fig. 1) in patients with severe fibrosis in order to achieve en bloc resection.

2. Patients and methods

From December 2017 to September 2018, 28 consecutive patients with colorectal lesions were referred for ESD to our tertiary center; five of them underwent combined ESD and EFTR. Previous biopsies revealed high-grade dysplasia in two patients and carcinoma in situ in one patient. Written informed consent was obtained from all patients. The data were collected retrospectively. Before resection, the lesions were characterized using white light and narrow band imaging (NBI) or blue laser imaging (BLI). All procedures were performed under deep sedation with propofol. ESD was performed using a HybridKnife, a new system that combines electrosurgical technology with a water-jet system (ERBEJET2; ERBE, Tübingen, Germany). A transparent hood was attached to the tip of the endoscope (short ST hood; Fujifilm Medical Co). A VIO generator (VIO 300D and VIO3; ERBE) was used. A saline solution containing epinephrine (0.01 mg/ml) and minimal indigo carmine was used in all cases. Circumferential cutting and submucosal dissection were performed by using the T-type HybridKnife or the I-type HybridKnife. Severe fibrosis was defined as the appearance of a white muscular structure without a blue transparent layer in the submucosa, as previously reported [1]. In the presence of severe fibrosis, the ESD procedure was interrupted (Fig. 2C). Then, the colonoscope with the mounted FTRD was advanced to the lesions (Fig. 2D). Once the colonoscope had reached the lesion with partial resection, the lesion was pulled into the cap by using the FTRD grasper (Ovesco Endoscopy) until the muscular layer was visible inside. After OTSC deployment, the lesion was resected with a preloaded snare; subsequently the specimen was put in the cap and extracted with the scope. The resection site was again inspected for complications (Fig. 2E). In the presence of diverticula or colonic shrinkage, a colonoscopy with a prOVE CAP (Ovesco Endoscopy, Tübingen, Germany), a cap similar in size to the FTRD cap, was performed in order to evaluate the accessibility of the target lesion. Histological classification was performed according to the Vienna staging system for epithelial neoplasms of the gastrointestinal tract [4]. Information about size, margins and other criteria for malignant polyps were provided.

The patients were hospitalized for 2 nights and monitored. The patients were started on clear liquids 24 h after the procedure once signs of bleeding or peritonitis had been excluded. The patients were scheduled for a follow-up endoscopy at 3 and 6 months after the procedure. In the absence of residual or recurrent adenoma, as determined by using white light and BLI, we performed biopsies of the scar.

3. Results

All lesions were resected successfully with the FTRD (Table 1). We did not observe any immediate or delayed perforations. The lesions were located in the sigmoid colon (n = 1), the transverse colon (n = 1) and the ascending colon (n = 3). The mean diameter of the resection specimens was 27.8 mm (range 25–31 mm). The mean age of the patients was 68.8 years (range 57–77 years). The mean procedure time was 127.4 min (range 90–165 min). Histology confirmed full-thickness resection in all cases. Complete (R0) resection was achieved all cases. Histological evaluation showed two adenomas with high grade dysplasia, one of adenocarcinoma T1/G2/SM1, one adenocarcinoma T1/G1/SM2 and one adenocarcinoma T1/G2/SM3; this latter patient underwent surgical resection: histopathology demonstrated pT1N0. At 3 months follow-up colonoscopy we were able to observe a spontaneous clip dislocation in three out of four patients. We did not observe any local recurrence in four patient at three months. Six months follow-up is available in only two patients and none of them showed disease recurrence.

4. Discussion

ESD is not widely used in colorectal lesions because of the technical difficulty, the risk of perforation and the resultant peritonitis and the greater time required to carry out the procedure. Difficulties in ESD result in incomplete en bloc resection and perforation. The presence of fibrosis has been demonstrated to be related to perforation, and severe fibrosis is related to incomplete resection. Yoshida et al. showed that severe fibrosis was the most important risk factor for incomplete resection [5]. A recent report showed that submucosal invasion and carcinomatous histology were independent risk factors for severe fibrosis [2]. According to previous studies, a wide range of perforation rates has been found in the presence of fibrosis, from 1.4% to 14% [6]. This great variability may be due both to the incomplete lift of the tumour after submucosal injection in cases where fibrosis is present and the inadequately secured dissection margin. EFTR with FTRD has been shown to be a valid technique to treat non-lifting lesions [7–9]. This device, using a clip-and-cut technique, reportedly allows a full-thickness and complete resection of lesions up to 3 cm in size; however, in our previous study, the maximum diameter of the EFTR specimens was 42 mm [7]. Previous literature data described a hybrid EFTR for the resection of large non-lifting colorectal lesions [10]; how-

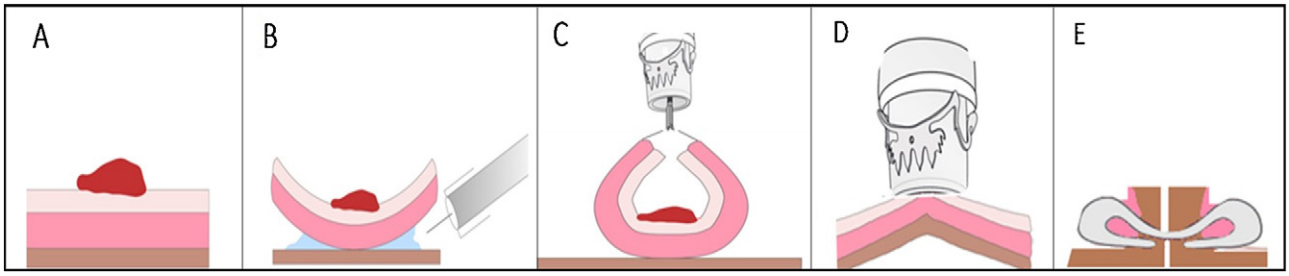

Fig. 1. Schematic illustration of the hybrid ESD–EFTR technique. A: lesion; B: endoscopic submucosal dissection of the lesion until fibrosis area; C: grasping the margins of lesion with a FTRD grasper; D: pulling the lesion into the cap of the FTRD; E: resection site.

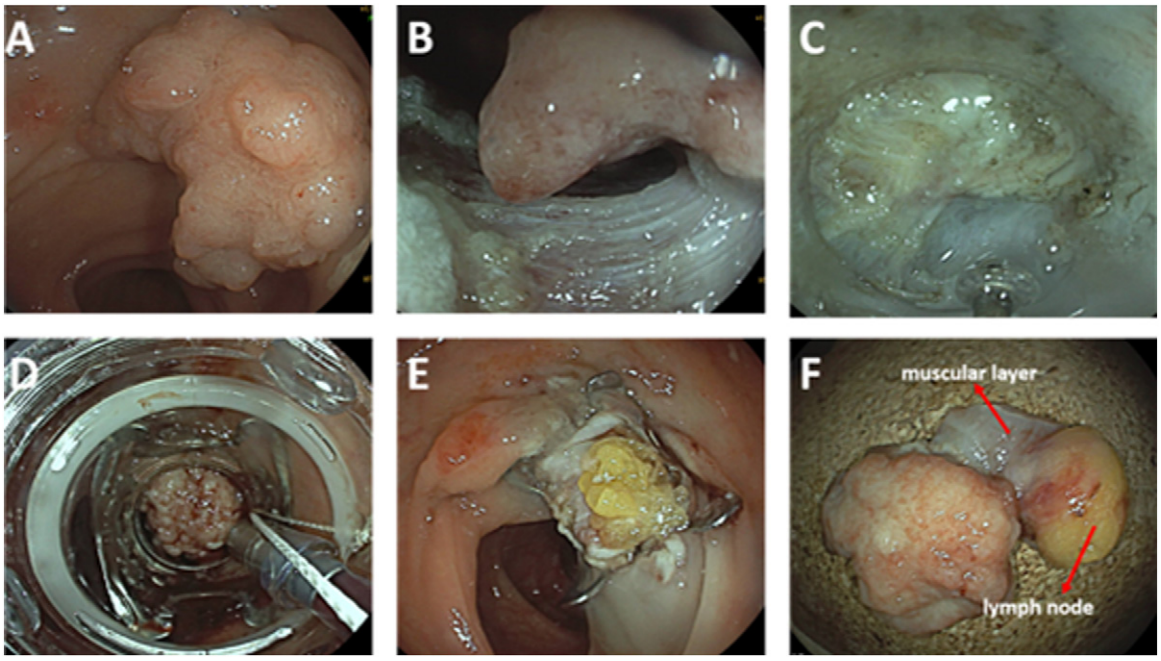

Fig. 2. Hybrid ESD–EFTR of lesion Paris: 0-Is in the sigmoid colon. A: image of the lesion; B: resection site during endoscopic submucosal dissection; C: severe fibrosis; D: the lesion reached by FTRD; E: over-the-scope clips (OTSC) completely closing the full-thickness resection site; F: full-wall resection specimen with lymph node presence.

Table 1
Patient and lesion characteristic, and outcomes following hybrid endoscopic resection.

Patient	Age	Sex	Lesion location	Lesion size (mm)	Classification	Size of the EFTR specimen (mm)	Histology	R0 resection	EFTR resection	Adverse events	Follow-Up (3 months)
1	76	M	Ascending colon	30	LST-NG-F	25	ATV-HGD	Yes	Yes	None	No residual
2	57	M	Sigmoid colon	35	Paris: 0-Is	27	T1/G2/SM3	Yes	Yes	None	NA
3	65	M	Ascending colon	30	LST-G Paris: 0-IIa	31	AT-HGD	Yes	Yes	None	No residual
4	69	M	Ascending colon	25	Paris: 0-Is	28	T1/G2/SM1	Yes	Yes	None	No residual
5	77	F	Transverse colon	35	Paris: 0-Is	28	T1/G1/SM2	Yes	Yes	None	No residual

M, male; F, female; LST-NG-F: laterally spreading tumor non granular flat; LST-G: laterally spreading tumor granular type; ATV-HGD, adenoma tubulo-villosum with high grade dysplasia; AT-HGD, tubular adenoma with high grade dysplasia; T1, the cancer has grown through the muscularis mucosa into the submucosa; NA: the patient did not receive follow-up endoscopy according to elective surgery.

ever, the proposed approach does not allow en bloc resection of the lesion, making histological evaluation not as precise as the ESD or the standard EFTR. Recently, Lupu et al. described a single case of the hybrid endoscopic submucosal dissection using a full-thickness resection device to perform the en bloc resection of a large adenoma deeply invading the appendix [11]. In this case the hybrid technique was used to extend the cutoff size for the FTRD. The goal of our study was to complete ESD and achieve en bloc resection in cases where the presence of severe fibrosis does not allow it. To date, this case series is the first in the literature to propose this hybrid technique as a rescue therapy. The major limitation of FTRD is the cap size, which makes it difficult to reach the lesion and represents the main size threshold of the lesion that can be incorporated. In our limited experience with this technique, we have observed that the lesion, when partially dissected, allows the selective grip of the margins with the FTRD grasper. This results in complete resection of the lesion, but makes it more difficult to "feel" the traction of the lesion and, in some cases, makes the releasing OTSC and resection a "blind sequence".

We conclude that this technique could be a rescue approach for "difficult" ESD, reducing the risk of incomplete resection and complications, particularly for lesions located in the ascending colon where FTRD performance is certainly favoured by the greater wall motility. Moreover, this technique could widen the limits of the

application of the FTRD, even if, unlike the technique proposed by Meier and colleagues [10], the volume of the lesion is bigger than the cap, which increases the risk of incomplete resection. Prospective studies are needed to further evaluate the efficacy, safety, rate of recurrence and long-term outcomes of this novel resection technique.

Conflict of interest

None declared.

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Low-dose biologics to treat inflammatory bowel disease. Ready for prime time?

Dear Editor

I read with interest the paper by Pouillon et al. on adalimumab dose de-scalation in patients with inflammatory bowel disease (IBD) [1]. The authors show that in approximately 2/3 of patients with both ulcerative colitis (UC) and Crohn's disease (CD) adalimumab dose can be successfully de-escalated from the typical every 2 week schedule to every 3 week schedule. They report that inactive disease at magnetic resonance imaging and/or endoscopy in the year before adalimumab dose de-escalation significantly decreased the risk of failure.

This is an excellent study — with results consistent with those previously published by Van Steenbergen et al. [2] and with those of our own earlier dose titration study in patients with post-operative relapse of CD [3]. In the latter study patients were treated prophylactically with infliximab 5 mg/Kg after surgery to prevent disease relapse. After three years of treatment – with patients in complete clinical, endoscopic and biochemical remission – infliximab was stopped and a colonoscopy performed immediately before the next scheduled infusion. In patients showing endoscopic recurrence infliximab was immediately re-started at a dose of 1 mg/Kg. After six months the patients underwent colonoscopy which showed persistence of inflammation in all. The infliximab dose was then escalated to 2 mg/Kg which was insufficient to re-induce endoscopic remission in most patients at six months. Therefore, the dose was increased to 3 mg/Kg — which restored and maintained mucosal integrity in all patients in the long term (1 year). A subgroup of these patients was later tested for infliximab trough levels (TL) and antibodies to infliximab (ATI) [4]. Although most patients had infliximab TL lower than recommended therapeutic values [5] and a number of them had low-titer ATI they all continued to remain in full endoscopic and clinical remission after 3 years on 3 mg/Kg infliximab — i.e. on a dose 40% less than standard, a reduction similar to that reported by Pouillon et al. [1]. Adalimumab TL were measured in a minority of patients in the Pouillon study so it is unclear whether they impacted on the risk of failure. Per authors' discussion, absent TL in patients in remission have been reported to be associated with low risk of relapse in those stopping therapy. However it is worth noting that patients successfully managed with adalimumab every three weeks were those with minimal or no inflammation at time of dose de-escalation. Hence those patients had a low disease burden just like patients with initial post-operative relapse after surgery. Taken together these observations do suggest that disease burden is a more rationale and practical target of disease management than TL [6]. As such it is possible that some patients (bearing a very low disease burden) can be managed with an even greater dose de-escalation. In our own study, mucosal integrity in a few patients could be reestablished with infliximab 2 mg/Kg — a reduction of 60% of the standard dose [3]. However that study was small and it is unclear whether such dose reduction could be used to manage CD patients who have never undergone surgery. Another interesting issue raised by this study is whether patients who were maintained in remission on adalimumab every 3 weeks could have been managed with a lower dose/longer interval from the outset. Clearly this can only be speculated upon. It is indeed possible that low disease burden patients (including those in the Pouillon study) might respond well to low initial medication doses. Early dose finding studies with anti-TNF agents in IBD patients were conducted in long standing disease [7] — when any medical therapy may be only marginally effective. Hence, it is possible that only "high" doses – which became the standard recommended doses – might have shown efficacy in those early studies. Later, we learned to treat IBD (especially CD) with anti-TNF agents at an earlier time — when patients are more responsive [8]. Hence, doses lower than those currently recommended might indeed be effective in a number of patients even at disease presentation. By contrast, if only standard doses are effective at presentation the persistence of remission after dose de-escalation must find different explanations. One possible explanation is that induction of remission with biologics might reset the immune system and re-establish partial immunological tolerance. This has