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Hybrid endoscopic approaches for complex colorectal polyps with a non-lifting sign: the Greek experience

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Abstract

Background Hybrid approaches combining endoscopic full-thickness resection (EFTR) with conventional techniques (endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD]) have enabled the resection of difficult fibrotic colorectal adenomas exhibiting a "non-lifting" sign, and polyps in difficult positions. We present our cohort treated with either EMR+EFTR or ESD+EFTR as salvage hybrid endoscopic approaches for complex colorectal polyps not amenable to conventional techniques.

Methods Retrospective analysis included technical success, histological confirmation of margin-free resection, assessment of adverse events and follow up with histological assessment. All patients underwent follow-up endoscopy at least 6 and 12 months post-resection.

Results Fourteen patients underwent hybrid EFTR procedures (11 EMR+EFTR and 3 ESD+EFTR). Technical success was achieved in all cases where the full-thickness resection device (FTRD) was advanced to the site of the resection (100%). In 2 cases, the FTRD system could not be passed through the sigmoid colon because of severe chronic diverticulitis, subsequent fibrosis and stiffness. The mean lesion size in the EMR+EFTR group (41.7 mm; range 20-50 mm) was larger than the ESD+EFTR group (31.7 mm; range 30-35 mm). Six patients (42.9%) were histologically diagnosed with T1 carcinoma. The mean duration of hospitalization was 1.4 days. Follow-up endoscopy was available in all patients and no recurrence was observed with histological confirmation during a mean follow-up period of 15.4 months.

Conclusion Hybrid procedures appear to be safe and effective treatments for complex colorectal lesions not amenable to EMR, ESD or EFTR alone, because of the lesion size, positive non-lifting sign, and difficult positions.

Keywords Polyp, endoscopic submucosal dissection, endoscopic mucosal resection, endoscopic full-thickness resection, full-thickness resection device

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Conflict of Interest: None

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Introduction

Endoscopic resection of complex colorectal adenomas comprises endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD); the choice of technique depends on the characteristics of the polyp and local expertise [1,2]. The referral centers for advanced polypectomy face difficult and fibrotic colorectal adenomas in their daily clinical practice. A positive non-lifting sign represents either severe fibrosis due to previous endoscopic attempts at resection, or desmoplastic reaction in cases of T1 carcinomas, which transform the submucosal space to a compact area unable to expand with the injected material [3]. Endoscopic full thickness resection

(EFTR) with a full-thickness resection device (FTRD; Ovesco Endoscopy®, Tübingen, Germany) has enabled the resection of difficult non-lifting colorectal adenomas and early colorectal cancers, which cannot be separated from the muscular layer with submucosal injection [4-9]. Lesion size is the major limitation of this technique, restricted to a maximum size of 25 mm for the resected specimens, owing to the FTRD system's cap diameter. Larger lesions can be removed with ESD alone or with a combination of EFTR and other resection techniques, such as EMR and ESD [10,11]. Successful endoscopic resections of non-lifting colorectal adenomas combining piecemeal EMR with EFTR (hybrid EMR+EFTR) and ESD with EFTR (hybrid ESD+EFTR) have been reported in several limited series [10-14]. In contrast to EFTR alone, the efficacy and safety of hybrid EFTR have not yet been definitively established. In this case series, we present the first 2-center experience of hybrid EFTR in Greece, including not only EMR+EFTR cases, but also the application of ESD+EFTR in patients with large non-lifting colorectal adenomas not amenable to EMR, ESD or EFTR alone.

Materials and methods

Study design

This observational, retrospective study was conducted at 2 referral centers in Greece (Athens, Heraklion) from January 2020 through February 2022. We included consecutive patients who were diagnosed with colorectal adenomas not amenable to EMR, ESD or EFTR alone (non-lifting sign, size >25 mm) and underwent a hybrid EFTR (EMR+EFTR, ESD+EFTR). The study protocol was approved by the local Institutional Review Boards and written informed consent was obtained from all patients. In all cases, a complete colonoscopy prior to the combined endoscopic resection was performed with detailed lesion assessment. When the treating endoscopist assessed that a polyp could not be fully resected with EMR, ESD or EFTR alone, one of the hybrid EFTR techniques was selected according to the local expertise. Adenomas infiltrating the appendiceal orifice were also included in the study. T1 carcinomas were classified as low-risk—submucosal infiltration <1000 μm, no lymphovascular infiltration, no infiltration of blood vessels, G1 (well differentiated) or G2 (moderately differentiated), R0 resection, tumor budding 0-1—or high-risk—submucosal infiltration >1000 μm, lymphovascular infiltration, perineural invasion, G3 (poorly differentiated) or G4 (undifferentiated), R1/Rx resection, tumor budding >1—based on the risk for lymph node metastases [1,15,16]. The primary outcome was technical success in terms of complete macroscopic resection. Follow-up endoscopy, including at least 4 biopsies from the resection site, was scheduled at 6-12 month intervals after resection. All cases of T1 adenocarcinomas were discussed at multidisciplinary oncology meetings for further evaluation. Secondary outcomes were: (i) procedural time; (ii) adverse events; (iii) histological confirmation of margin-free resection; (iv) subsequent need for surgery; and (v) recurrence with histological assessment during endoscopic follow up. The severity of adverse events was graded by the changes in the plan of care, as recommended by the American Society for Gastrointestinal Endoscopy [17]. Specifically, clinical complications that required unplanned hospital admission or prolongation of hospital stay for ≤3 nights were considered as mild, whereas those that required prolongation of stay for 4-10 nights, admission to the Intensive Care Unit (ICU) for 1 night, transfusion and/or repeat endoscopy were regarded as moderate. Adverse events that ended in prolongation of stay for >10 nights, ICU admission for >1 night and/or surgery were considered as severe.

Statistical analysis

Procedural and patient data were collected and analyzed and were used exactly as presented by the contributing investigators, who were responsible for the accuracy of the data. Continuous variables were reported as mean, whereas categorical variables were expressed as frequencies and percentages (in parentheses) unless stated otherwise. No interim analysis was performed. Data recording was performed using Microsoft Excel 2016 for MacOs (version 15.21; Microsoft, Redmond, Washington). Statistical analyses were performed using SPSS (version 24.0; IBM, New York). Categorical data are expressed as percentages, whereas continuous data are reported as means with standard deviation. Categorical variables were compared using the corrected χ^2 or 2-sided Fisher's exact test. Continuous data were compared using the unpaired Student's *t* or Mann-Whitney test, as appropriate.

Salvage endoscopic resection techniques

All the procedures were performed by 2 endoscopists experienced in advanced polypectomy techniques (GT, GP), at referral centers in Athens and Heraklion, respectively. Colonoscopy and endoscopic resections were performed under moderate-to-deep sedation in the presence of an anesthetist. Every patient received a single dose of broad-spectrum antibiotic (tazobactam + piperacillin) during the procedure and antibiotics were continued in cases of post-procedural pain. Aspirin was not discontinued prior to resection, but all other anticoagulants and antiplatelets were held, as per European Society of Gastrointestinal Endoscopy and British Society of Gastroenterology guidelines [18]. Procedural time was measured from the first insertion of the scope until the final withdrawal.

First, the lesions were categorized as either benign or malignant, based on the established classifications for polyp

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morphology and surface patterns, such as the Paris classification, Japan NBI expert team classification (JNET) classification, and lateral spreading tumor (LST) classification [1]. White light endoscopy with standard (indigo carmine) and virtual chromoendoscopy (NBI) were used in order to exclude a deeply infiltrative adenocarcinoma. Nevertheless, when a non-lifting sign was suspected, a submucosal injection was performed in order to confirm whether the lesion could be elevated. In cases of a successful lift, a hybrid EFTR technique was attempted, according to local expertise and the endoscopist's preference. Specifically, at the referral center in Athens (GT), ESD was offered as the standard initial endoscopic procedure for the dissection of scarred and fibrotic polyps, while the hybrid EMR+EFTR strategy was selected from the beginning only for special positions, such as the appendiceal orifice and diverticulum. In contrast, at the referral center in Crete (GP), where ESD is not offered as a dissection option, the strategy involved EMR from the beginning, and hybrid EMR+EFTR for scarred lesions with a non-lifting sign or for polyps in specific locations.

The first part of the combined resections, a standard piecemeal EMR or ESD technique, was performed with a view to reducing the lesion size at the periphery. The endoscopes used in the referral center of Athens were an Olympus PCF-H190TL colonoscope and a Fujifilm ELUXEO EC-760S-L colonoscope. The colonoscopes used in the referral center of Crete were the Olympus colonoscopes CF-H190L and PCF-H180AL. A solution of hydroxyethyl starch (Voluven) with epinephrine and indigo carmine was used for submucosal injection. Resection in EMR was performed with a 15 mm or 25 mm polypectomy snare (SnareMaster – Olympus®, Captivator II snare – Boston Scientific®), while an endoscopic needle-type knife was used for the ESD (Dual Knife – Olympus®). Afterwards, when the non-lifting area had been reduced in size to a maximum of 25 mm, EFTR was applied. The FTRD was fitted to the endoscope and the mounted colonoscope was advanced to the lesion. Firstly, the lesion was pulled carefully into the FTRD cap with the aid of the FTRD grasper. Secondly, the FTRD clip was deployed, and finally the tissue was removed with the integrated snare into the cap's distal end. After the removal of the FTRD cap and the collection of the specimen for analysis, the endoscope was then reinserted and the resection site was thoroughly inspected. All patients were admitted to the ward and remained fasting overnight. A clear liquid diet was commenced the following day, and they were discharged if no signs of peritonitis or bleeding were noted. The hybrid procedures are illustrated in Fig. 1-3 and Video 1.

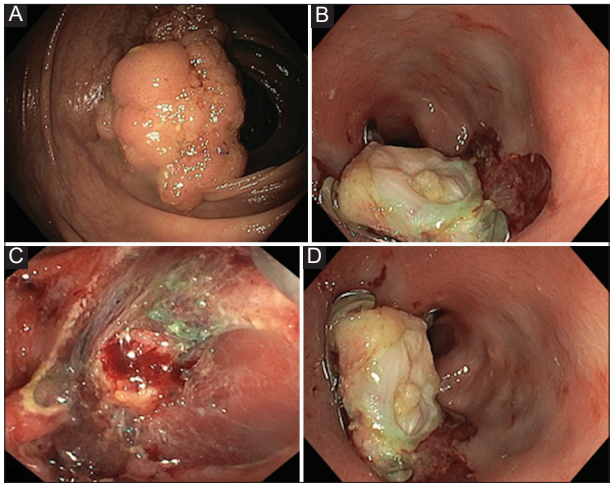

Figure 1 (A) A 30-mm Paris classification 0-Is lesion with a NICE classification 2 surface pattern, located in the ascending colon. (B) The polyp was firstly resected by piecemeal endoscopic mucosal resection (EMR) with an 8 mm central adenomatous remnant that was firm and impossible to resect with a snare-based technique. (C,D) Hybrid resection with EMR+endoscopic full-thickness resection with a full-thickness resection device was performed, with an endoscopically radical dissection

Results

Patients and lesions

Sixteen patients were included in the study. Combined interventions failed in 2 patients as a result of severe diverticular disease in fixed sigmoid colons, which impeded the advancement of the colonoscope fitted with the FTRD to the lesion. Finally, 14 hybrid resections (EMR+EFTR: 11, ESD+EFTR: 3) were analyzed. Patients were evenly men and women (7/7), and the mean age for all patients was 69.3 years. Indications for the combined resection were: (i) non-lifting sign (71.4%), due to repeated interventions after a failed previous polypectomy (28.5%) and advanced neoplasia (superficial infiltrative adenocarcinoma) (42.9%); or (ii) a difficult position (28.6%), such as the appendiceal orifice (14.3%) or diverticular region (14.3%). Most lesions were located in the right colon (50%). The median lesion size was 41.7 mm for combined EMR+EFTR resections and 31.7 mm for ESD+EFTR resections. According to the Paris classification, most cases were characterized as 0-IIa+c (35.7%) and IIa+Is (35.7%); based on the JNET classification, 71.4% of the lesions were described as 2B, including high-grade dysplasia (HGD) and superficially infiltrative adenocarcinomas. Tissue histology prior to the resection was available in all cases, revealing HGD in 57.1%, with no cases of invasive adenocarcinoma noted. Multiple biopsies (42.9%) and pretreatment with EMR (21.4%) were the most frequent reasons for a non-lifting sign and subsequent EFTR. The characteristics of patients and lesions are shown in Tables 1 and 2.

Procedural data

Technical success was 100%, with a complete macroscopic resection in all cases. Even though complete resection was achieved in all cases, R0 resection was established only for the ESD+EFTR procedures (n=3). Since the rest of the resected specimens were removed with piecemeal EMR+EFTR, R0 resection could not be microscopically

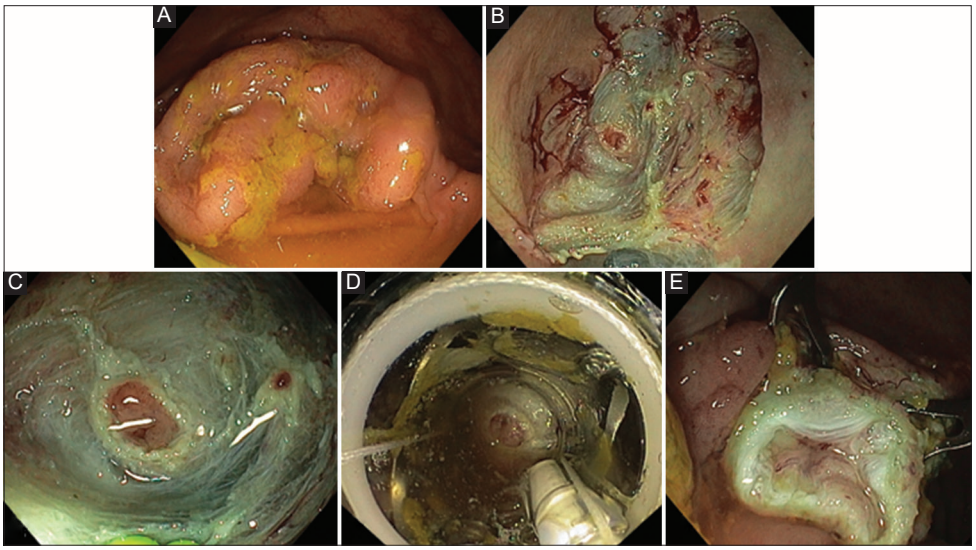

Figure 2 (A) A 25 mm Paris classification 0-IIa lesion with NICE classification 2 and Japan NBI expert team classification 2A, intruding into the appendix. (B) The part of the polyp extending to the cecum area was first resected by piecemeal endoscopic mucosal resection (EMR). (C) The remaining part of the lesion that intruded into the appendix was impossible to resect using conventional EMR. (D) A hybrid resection with EMR+endoscopic full-thickness resection was performed. (E) Defect of the technically demanding resection in a difficult position

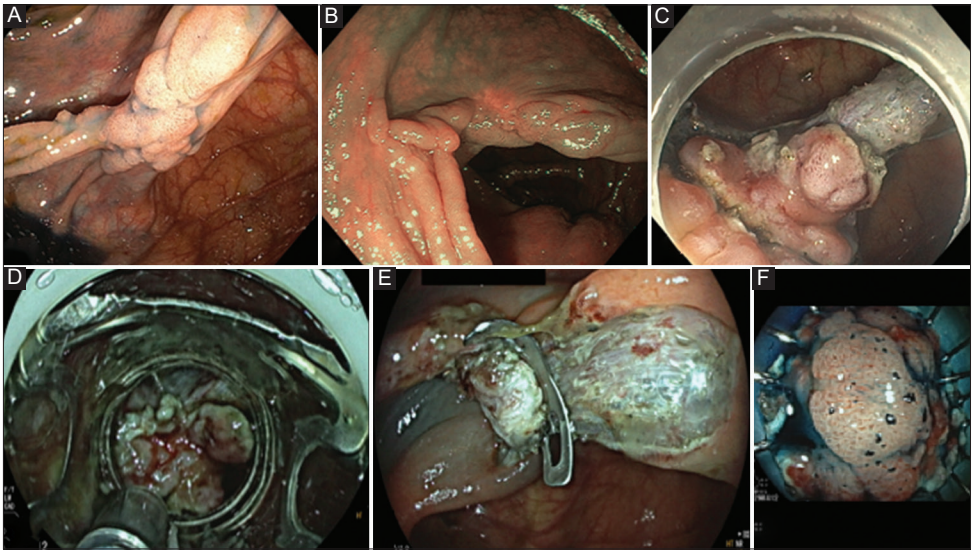

Figure 3 (A,B) A 20 mm severely fibrotic Paris classification 0-IIa+c, NICE classification 2 and lateral spreading tumor classification 2A polyp located in the ascending colon. Two previous endoscopic mucosal resections were unable to complete the resection and the polyp became scarred and fixed to the bowel wall. (C) The fibrosis and the difficult position of the polyp with poor access made completion of the resection with endoscopic submucosal dissection (ESD) alone technically infeasible. (D) A hybrid resection with ESD+endoscopic full-thickness resection was performed, and (E) the lesion was completely removed (R0 resection). (F) The resected specimen revealed an adenoma with high-grade dysplasia

proven. These cases were classified as Rx resections, and they underwent a comprehensive examination to check for any remaining tissue or signs of recurrence during the follow-up endoscopy. Mean procedural time was 53.8 min. Overall, histopathology showed T1 adenocarcinoma in 6 cases (42.9%). One patient treated with hybrid EMR+EFTR was diagnosed with a pT1SM2/G2 carcinoma (EFTR specimen) and pTis adenocarcinoma (piecemeal EMR specimen). This patient was further treated with colectomy, and histological analysis of the resected specimen did not reveal any residual tissue. For the remaining cases with low-risk T1 carcinomas, the endoscopic treatment was considered curative.

Adverse events

In total, 5 procedure-related adverse events occurred (35.7%) (4 mild, 1 moderate). Adverse events are shown in Table 3. All cases with a minor adverse event presented with post-procedural pain and no intervention was needed. The

Table 1 Patient and lesion characteristics

Patient	Age	Sex	Lesion Size (mm)	Lesion Location	Classification	Histology prior to resection	Complexity of polyp	Pretreatment	Type of hybrid approach
1	67	F	30	Ascending colon	0-Is, JNET:2B	HGD	Non-lifting sign	1-2 biopsies	EMR + EFTR
2	63	M	40	Splenic flexure	0-IIa+Is, JNET:2B, G-Type (Mixed)	HGD	Non-lifting sign	Multiple biopsies	EMR + EFTR
3	80	M	30	Ascending colon	0-IIa+c, JNET:2B, G-Type (Homogenous)	LGD	Non-lifting sign	Recurrent adenoma, prior EMR	ESD + EFTR
4	76	M	35	Sigmoid colon	0-IIa+c, JNET:2B, NG-Type (depressed)	HGD	Non-lifting sign	Multiple biopsies	ESD + EFTR
5	74	F	40	Sigmoid colon	0-IIa+Is, JNET:2B, G-Type (Mixed)	HGD	Non-lifting sign	Multiple biopsies	EMR + EFTR
6	65	F	25	Appendiceal orifice	0-IIa, JNET:2A, NG-Type (flat elevated)	LGD	Difficult position: appendiceal orifice	1-2 biopsies	EMR + EFTR
7	78	M	30	Sigmoid colon	0-IIa+c, JNET:2A, NG-Type (flat elevated)	HGD	Non-lifting sign	Multiple biopsies	EMR + EFTR
8	70	F	30	Sigmoid colon	0-IIa+c, JNET:2B, NG-Type (depressed)	LGD	Difficult position: diverticulum	1-2 biopsies	ESD + EFTR
9	56	F	20	Sigmoid colon	0-Is, JNET:2A	LGD	Non-lifting sign	Recurrent adenoma, Prior EMR	EMR + EFTR
10	58	M	35	Descending colon	0-Is, JNET:2B	HGD	Difficult position: diverticulum	Multiple biopsies	EMR + EFTR
11	59	M	40	Appendiceal orifice	0-IIa+Is, JNET:2A, G-Type (Mixed)	LGD	Difficult position: appendiceal orifice	1-2 biopsies	EMR + EFTR
12	66	F	45	Ascending colon	0-IIa+Is, JNET:2B, G-Type (Mixed)	HGD	Non-lifting sign	Multiple biopsies	EMR + EFTR
13	73	M	50	Hepatic flexure	0-IIa+Is, JNET:2B, G-Type (Mixed)	LGD	Non-lifting sign	1-2 biopsies	EMR + EFTR
14	85	F	20	Rectum	0-IIa+c, JNET:2B, NG-Type (depressed)	HGD	Non-lifting sign	Recurrent adenoma, Prior EMR	EMR + EFTR
15	78	F	25	Cecum	0-IIa+c, JNET:2A, G-Type (Homogenous)	HGD	Non-lifting sign	Recurrent adenoma, Prior EMR	ESD EFTR failure
16	66	F	30	Appendiceal orifice	0-IIa, JNET:2A, NG-Type (flat elevated)	LGD	Difficult position: appendiceal orifice	Multiple biopsies	EMR EFTR failure

JNET, Japan NBI expert team classification; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EFTR, endoscopic full-thickness resection; G, granular type; NG, non-granular type

Table 2 Patient data

Number of patients (n=14)	
Sex, n (%)	
Male	7 (50)
Female	7 (50)
Age (years), mean (range)	69.3 (56-85)
Location of lesion, n (%)	
Right colon	5 (35.7)
Left colon	6 (42.9)
Rectum	1 (7.1)
Appendiceal orifice	2 (14.3)
Classification, n (%)	
Paris 0-Is	3 (21.4)
Paris 0-IIa	1 (7.1)
Paris IIa+c	5 (35.7)
Paris IIa+Is	5 (35.7)
JNET 2A	4 (28.6)
JNET 2B	10(71.4)
LST-G, homogenous	1 (7.1)
LST-G, mixed	5 (35.7)
LST-NG, flat elevated	2 (14.3)
LST-NG, pseudodepressed	3 (21.4)
Lesion size (mm), mean (range)	33.9 (20-50)
EMR lesion size	41.7 (20-50)
ESD lesion size	31.7 (30-35)
Histology before resection, n (%)	
Tubular adenoma with LGD	4 (28.6)
Tubular adenoma with HGD	5 (35.7)
Tubulovillous adenoma with LGD	1 (7.1)
Tubulovillous adenoma with HGD	3 (21.4)
Sessile serrated adenoma with LGD	1 (7.1)
Indication for EFTR, n (%)	
Non-lifting sign	10(71.4)
Recurrent adenoma	4(28.5)
Suspected T1 carcinoma	6 (42.9)
Difficult position	4 (28.6)
Appendiceal orifice	2 (14.3)
Diverticulum	2 (14.3)
Pretreatment, n (%)	
EMR	3 (21.4)
Multiple biopsies	6 (42.9)
None	5 (35.7)

JNET, Japan NBI expert team classification; LST-G, lateral spreading tumor, granular type; LST-NG, lateral spreading tumor, non-granular type; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EMR, endoscopic mucosal resection

nature of the pain was related to the thermal effect of the combined rescue procedures. One event of appendicitis was observed in a hybrid dissection (EMR+EFTR) of a polyp in the appendiceal orifice, successfully treated with antibiotics. Mean hospitalization time was 1.4 days.

Endoscopic follow up

Endoscopic follow up was available in all the patients except for the case which was treated surgically (Table 4). All patients were followed-up for at least 12 months, with a mean follow up of 15.4 months (range 12-24 months). Endoscopic follow up showed no recurrent or residual adenoma, confirmed both macroscopically and microscopically. The over-the-scope clip was not observed during the initial endoscopic follow up at 6 or 12 months for all cases.

Discussion

Hybrid procedures seem to be safe and effective as rescue interventions during EMR and ESD for complex colorectal lesions with a non-lifting sign and/or difficult position. When a polyp is not amenable to EMR, ESD or EFTR alone, combined removal techniques such as EMR+EFTR and ESD+EFTR could prove an effective approach, avoiding further surgical treatment [10,11]. To the best of our knowledge, this is the first series to date in Greece, and one of the limited series worldwide, to provide results regarding the effectiveness and safety of piecemeal EMR and ESD combined with EFTR, along with follow-up data. To minimize the risk of incomplete resection and complications, especially for lesions located in the ascending colon with significant wall motility, the combined approaches should be available at every advanced polypectomy referral center [19-22].

Provided that the endoscope could be advanced to the site of the lesion, technical success was 100%. Complex colorectal polyps include lesions with a non-lifting sign secondary to fibrosis, or lesions located at difficult areas in the colon, such as the appendiceal orifice and diverticular regions. The non-lifting sign is usually encountered in recurrent adenomas after previous EMR attempts and T1 carcinomas, because of a desmoplastic reaction and infiltration. Fibrosis penetrating into the submucosal space below the surface of a polyp hinders the lifting of the polyp with the injected solution, and precludes removal with conventional snare-based techniques, including EMR. Although submucosal dissection can deal with the fibrosis, and effectively destroys the connecting fibers in the submucosa, the ESD technique is technically challenging and more time-consuming compared with EMR. Additionally, the learning curve for challenging ESD cases such as fibrotic polyps is demanding, and requires dedication to the technique, including training in referral centers [19,21]. The diffusion of the ESD technique in the West has been increasing over the last 2 decades, and only a limited number of endoscopists have already become familiar with advanced ESD [23]. The complication rate in demanding ESD procedures rises to 20% when they are performed in the right-sided colon [22]. In addition, colonic ESD outside the rectum is not yet well established in the Western world, and is associated with low rates of complete resection (<70%) [20]. From this perspective, ESD for complex and fibrotic colonic polyps is considered doubtful and possibly ineffective. Therefore, hybrid salvage techniques using a combination of ESD and EFTR should be offered as rescue therapy after an ineffective ESD. In our series, even though fibrosis and the non-lifting sign constituted the major indication for a combined approach (10/14), the choice

Table 3 Procedural data

Number of patients (n=14)	
Procedure time (min), mean (range)	53.8 (35-120)
Technical success, n (%)	14 (100)
Macroscopic complete resection, n (%)	14 (100)
Histology, n (%)	
Rx*	11 (78.6)
R0	3 (21.4)
T1 carcinoma**	6 (42.9)
Minor adverse events, n (%)	
Post-procedural pain	4 (28.5)
Moderate adverse event n (%)	
Appendicitis***	1 (7.1)
Days of hospitalization, mean (range)	1.4 (1-3)
Surgery, n (%)	1 (7.1)

*R0 resection cannot be proven because of piecemeal resection (EMR + EFTR)

**Further endoscopic management in all except 1 case. No recurrence or residual adenoma detected during follow up. Further surgery in 1 case without residual tissue – negative lymph node infiltration (0/18)

***Successful antibiotic management

EMR, endoscopic mucosal resection; EFTR, endoscopic full-thickness resection

Table 4 Endoscopic follow up

Number of patients (n=13)*	
Follow up, months after resection, mean (range)	15.4 (12-24)
No recurrent or residual adenoma**, n (%)	13 (100)

*Endoscopic follow up not available in 1 patient (surgery)

**Macroscopically and histologically, with evaluation of at least 4 biopsies

between using EMR or ESD as the initial dissection method depended on the department's expertise. When the ordinary procedures, either EMR alone or ESD alone, failed to dissect the polyp, the combination with the FTRD was selected.

EFTR with the FTRD is restricted by the physical dimension of the cap (length 23 mm, inner diameter 13 mm), with the lesion size being the major limitation [24]. The polyp size amenable to *en bloc* EFTR with the FTRD has been reported to be a maximum of 20-25 mm, depending on the tumor characteristics and the rigidity of the colonic wall. To overcome this limitation and perform an EFTR effectively for larger fibrotic polyps, a combination of EMR and EFTR has been proposed in the literature [11-14]. The main drawback of this technique is the weaker histological confirmation of margin-free resection (R0), due to the piecemeal manner of polyp removal with EMR and finally with EFTR (Rx resection, indistinguishable borders of the resection). On the other hand, the major advantage of hybrid EMR+EFTR is that it is associated with an easier learning curve. The procedure is much more common in the West, available for training in many referral centers. Compared to ESD, there are also lower complication rates, approximately 10-12%, including 5% major adverse events [14,25].

Polyps in our study were mostly located in the right colon (50%), where the bowel wall is thinner and more susceptible to perforation and major bleeding during advanced endoscopic procedures, especially during ESD [19,20,22]. Moreover, 2 lesions were removed from the appendiceal orifice. EFTR applied to appendiceal lesions is associated with appendicitis at rates up to 17% [26], but this could be eliminated by both pre- and post- procedure antibiotic use as a prophylactic treatment. In our series, appendicitis was encountered in 1 of 2 patients treated with EMR+EFTR for an appendiceal orifice polyp. Hence, we cannot suggest that the technique is absolutely safe, because of the small sample size. However, the patient had a favorable outcome and was treated conservatively. Meier *et al* [14] reported a higher appendicitis rate up to 33% after hybrid salvage resection. In any case, the usage of hybrid EMR+EFTR for appendiceal polyps has to be examined with caution and the decision should be taken according to the patient's willingness after a detailed informed consent. Technically, in our cohort the advancement of the colonoscope to the right colon was feasible in all but 2 patients who had severe chronic diverticulitis and fixation of the sigmoid colon. Inserting a colonoscope with an FTRD cap attached through a sigmoid colon that is tortuous and rigid because of diverticular disease is extremely challenging, and might cause a large perforation that is difficult to deal with. In these cases, passage of the FTRD device was impossible and the cases were not included in the analysis. Mean procedural time, measured from first insertion of the endoscope to the final extubation, was 53.8 min, which is faster when compared to colonic ESD in the western world for fibrotic colonic polyps [19,20,27].

The results of the present study are in accordance with previous published studies on hybrid EFTR in the colorectum [10-14]. Mean lesion size (33.9 mm), tumor location predominantly in the right-sided colon (50 %), mean procedural time (53.8 min) and macroscopic complete resection (100%) were comparable with the 2 larger relevant studies [12,14]. On the other hand, we report for the first time cases that were treated not only with hybrid EMR+EFTR, but also with an ESD+EFTR technique. Specifically, our study included 3 such lesions, which could not be fully resected with ESD alone, because of an unstable scope position and severe fibrosis that made effective lifting of the submucosal layer impossible. EFTR with FTRD facilitated the accomplishment of difficult dissections, which otherwise would have been referred for surgical resection. All the ESD+EFTR resected specimens were removed *en bloc*, with histological confirmation of R0 resection. Precise and cautious ESD is mandatory, when the endoscopist has to deal with a fibrotic and scarred polyp. When a difficult position makes the maneuverability of the scope unpredictable during the dissection, the risk of a complication arises and a salvage hybrid removal should be considered. Flat morphology (Paris classification 0-IIa, 0-IIa+c, 0-IIa+Is) and LST classification as G-type/Mixed seemed to be correlated with severely scarred and fibrotic polyps, though only as a trend and without a statistically significant interrelation.

Our study also examined the presence of recurrent/residual tissue in all cases with at least 2 endoscopic assessments, at 6 and 12 months post-resection. The majority of our complications were mild and there was no need for extended hospitalization. Histologic examination after hybrid EFTR revealed a T1

carcinoma in 42.9% (6/14) of the cases. In all patients, neither the initial macroscopic evaluation (with standard and virtual chromoendoscopy) nor the tissue examination were suspicious for an invasive adenocarcinoma. Histopathology showed low-risk features in the majority of T1 carcinomas (5/6) and high-risk features in only 1 case, in which the patient underwent oncologic surgical resection. Patients with low-risk T1 carcinomas were followed up endoscopically and radiologically with computed scans in most cases for at least 12 months, without further histological evidence of residual/recurrent adenoma/carcinoma. For T1 carcinomas resected with hybrid EMR+EFTR, careful preoperative assessment of the lesion with chromoendoscopy, biopsies and endoscopic ultrasound (for rectal lesions) is mandatory, given the intrinsic disadvantage that the technique involves removing the lesion in pieces [6,27]. The likelihood of cutting the carcinoma in the middle is high, even though the aim of the endoscopist is to resect in 1 piece, preferably with EFTR. In such unfortunate cases, the presence of an invasive adenocarcinoma will result in the patient being directly referred for additional surgical resection. On the other hand, the hybrid ESD+EFTR offers a complete resection in 1 piece without this risk.

Endoscopic follow up showed no recurrence or residual tissue in all lesions, confirmed during re-endoscopy at least 6 and 12 months later, with histological confirmation obtained from 4 biopsies taken at the resection site. Given that piecemeal EMR could result in endoscopic residual or recurrent tissue up to 20% in complex colorectal polyps, even in experienced hands [28-31], we infer that hybrid techniques constitute an effective and acceptable solution for difficult polyps exhibiting a non-lifting sign, not amenable to conventional resection with EMR or ESD alone. Persistence of the over-the-scope clip at the resection site was not observed in any of the 13 cases during endoscopic follow up. In such a case the presence of the clip could interfere with the detection and sampling of residual tissue.

Our study had several limitations. Firstly, a major drawback was the retrospective study design and the relatively small sample size. Additionally, this was an uncontrolled study evaluating outcomes of hybrid EFTR only. Furthermore, 2 experienced endoscopists participated in the study and the results cannot be easily generalized, despite the 2-center design of the study. On the other hand, our study presents the longest follow-up period in the literature [12-14] regarding hybrid EFTR procedures (mean follow up: 15.4 months), and for the first time includes patients treated with either EMR+EFTR or ESD+EFTR resections. Hybrid EFTR was used for right-sided sessile polyps and LST in the majority of our cases with a non-lifting sign in the center of the lesion, where the fibrosis was encountered, and EFTR resection was considered necessary as a salvage technique. Although the referral center in Athens typically opted for ESD in cases of fibrotic polyps, there were 3 cases with prior attempts at EMR, multiple biopsies and a difficult position within a diverticulum, which required a rescue hybrid ESD+EFTR approach to overcome the fibrosis and maneuverability difficulty.

To conclude, EMR+EFTR and ESD+EFTR are safe and effective for advanced colorectal adenomas not amenable to EMR, ESD or EFTR alone. Hybrid EFTR could serve as a salvage technique for large scarred colorectal polyps, T1 carcinomas and polyps in difficult positions, and therefore it should be considered as an additional option, instead of surgery. Larger studies are needed to further investigate the role of these hybrid resections in the management of complex colorectal polyps.

Summary Box

What is already known:

- Endoscopic full-thickness resection (EFTR) with a full-thickness resection device (FTRD) is used for colonic fibrotic polyps with a non-lifting sign up to 25 mm
- Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the standard treatment options for the removal of colonic polyps
- Complex polyps are defined as lesions exhibiting a non-lifting sign secondary to fibrosis, or those located in difficult parts of the colon, such as the appendiceal orifice and diverticular regions

What the new findings are:

- EMR+EFTR and ESD+EFTR are safe and effective for advanced colorectal adenomas not amenable to EMR, ESD or EFTR alone
- Hybrid EFTR could comprise a salvage technique for large scarred colorectal polyps, T1 carcinomas, and polyps in difficult positions
- Hybrid EFTR should be offered as an additional option, instead of surgery

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