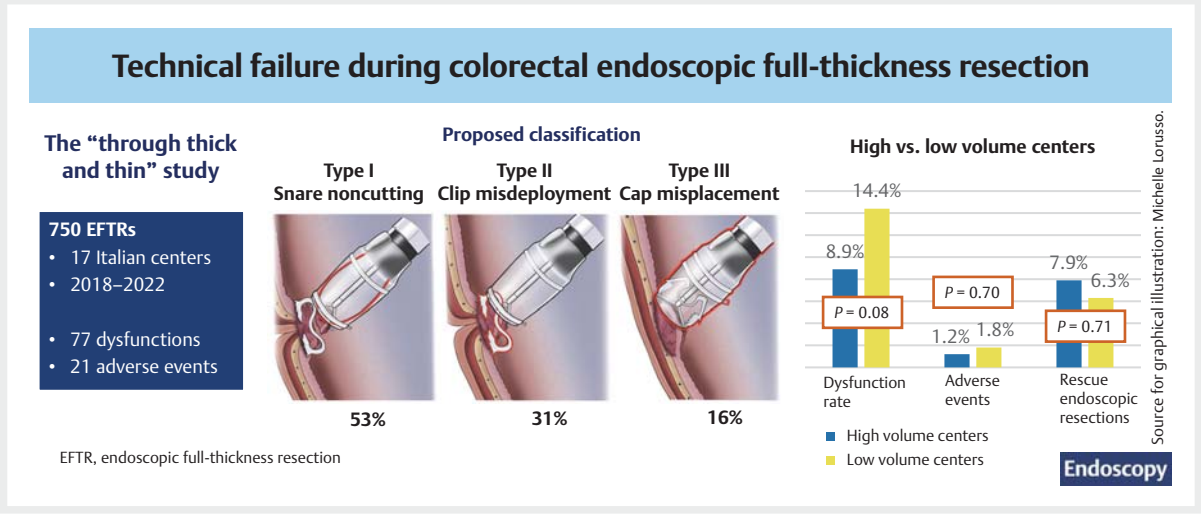
Technical failure during colorectal endoscopic full-thickness resection: the "through thick and thin" study

GRAPHICAL ABSTRACT



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ABSTRACT

Background Endoscopic full-thickness resection (EFTR) is an effective and safe technique for nonlifting colorectal lesions. Technical issues or failures with the full-thickness resection device (FTRD) system are reported, but there are no detailed data. The aim of our study was to quantify and classify FTRD technical failures.

Methods We performed a retrospective study involving 17 Italian centers with experience in advanced resection techniques and the required devices. Each center shared and classified all prospectively collected consecutive failures during colorectal EFTR using the FTRD from 2018 to 2022. The primary outcome was the technical failure rate and their classification; secondary outcomes included subsequent management, clinical success, and complications.

Results Included lesions were mainly recurrent (52 %), with a mean (SD) dimension of 18.4 (7.5) mm. Among 750 EFTRs, failures occurred in 77 patients (35 women; mean [SD] age 69.4 [8.9] years). A classification was proposed: type I, snare noncutting (53 %); type II, clip misdeployment (31 %); and type III, cap misplacement (16 %). Among endoscopic treatments completed, rescue endoscopic mucosal resection was performed in 57 patients (74 %), allowing en bloc and R0 resection in 71 % and 64 %, respectively. The overall adverse event rate was 27.3 %. Pooled estimates for the rates of failure, complications, and rescue endoscopic therapy were similar for low and high volume centers (P = 0.08, P = 0.70, and P = 0.71, respectively).

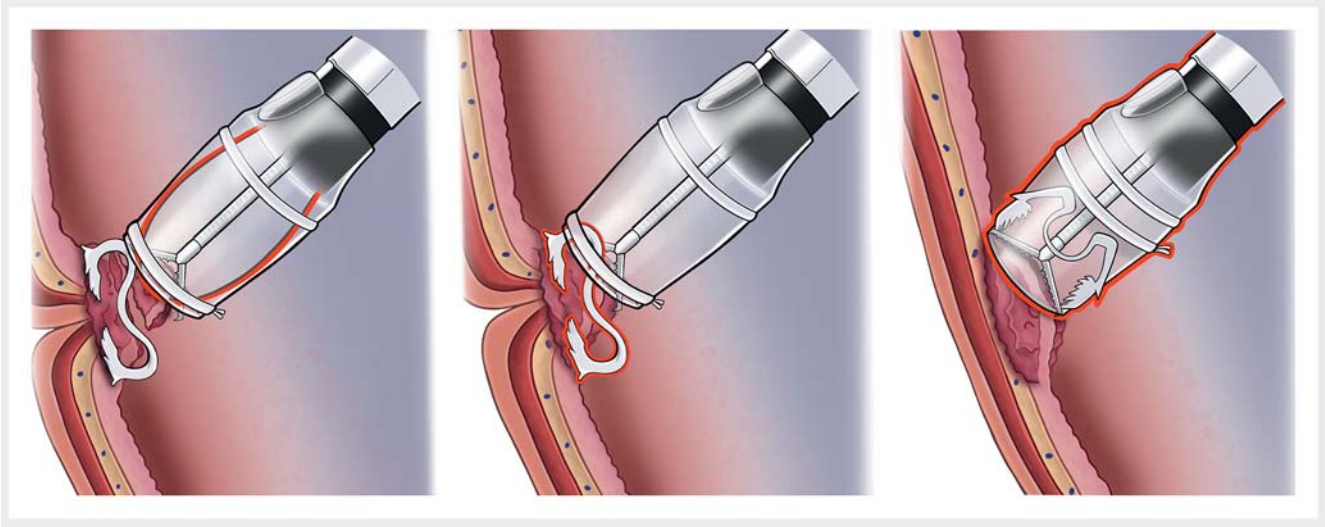
Conclusions Colorectal EFTR with the FTRD is a challenging technique with a non-negligible rate of technical failure and complications. Experience in rescue resection techniques and multidisciplinary management are mandatory in this setting.

Introduction

Endoscopic full-thickness resection (EFTR) is emerging as an effective and safe technique for difficult colorectal lesions [1, 2]. It may offer a valid alternative to surgery for "nonlifting" lesions that are not amenable to standard resection with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) because of fibrosis or invasion beyond the submucosal layer.

EFTR procedures are traditionally divided into exposed and nonexposed techniques. The exposed approach involves performing full-thickness resection first, with subsequent closure of the temporary peritoneal exposure. Exposed EFTRs are classified as tunneled or non-tunneled techniques and originate from ESD. In nonexposed EFTR, a secure serosa-to-serosa apposition is obtained before full-thickness resection of an isolated lesion [3]; this is commonly achieved using over-the-scope (OTS) clip deployment with the Ovesco full-thickness resection device (FTRD; Ovesco Endoscopy, Tübingen, Germany). The colonic FTRD obtained a CE mark for EFTR in the lower gastrointestinal tract in 2014. A later version of the device is also registered for the gastroduodenal tract, improving its safety profile even in particularly critical areas.

With increasing adoption of this system, there has been growing evidence supporting its effectiveness and safety [4–8]. The largest recently published meta-analysis reported a technical success rate of 87 % using the Ovesco FTRD only, and an R0 resection rate ranging from 78.8 % to 81.6 % [9, 10].



▶ **Fig. 1** Schematic showing the proposed classification of technical failure, assigned according to the reported frequency of each, as: **a** type I, snare noncutting; **b** type II, clip misdeployment; **c** type III, cap misplacement. Source: Michelle Lorusso.

Despite these satisfying results, EFTR remains a technically demanding procedure with some limitations and potential risks [11, 12]. The use of the FTRD for colorectal lesions has been linked in previous studies to the risk of clip misdeployment or snare dysfunction, leading to procedure failure or unpredictable adverse events (AEs). Technical failures have been reported differently among the published studies, with a lack of standardization and of a detailed cause–effect relationship with AEs.

The aim of the present study was to quantify and classify the technical failures occurring during colorectal EFTR with the FTRD system.

Methods

This was a retrospective study, involving 17 Italian centers, that included all consecutive technical failures during colorectal EFTR using the FTRD from 2018 to 2022. All of the centers had experience in advanced resection techniques and ≥ 5 years of expertise in Ovesco devices. All cases in which it was impossible to reach the lesion with the device (e. g. because of severe diverticular diseases, stenosis, or curvature) were excluded.

The Ethics Committee of the center that proposed the research approved the data collection, which was subsequently shared with the other participating centers. The study conformed to the current EU regulation on the protection of personal data, Regulation (EU) 2016/679 of the European Parliament, and to the Declaration of Helsinki's ethical guidelines.

Device and endoscopic technique

Each participant confirmed the correct use of the FTRD according to the manufacturer's settings and guidelines [3]. The colonic FTRD consists of an applicator cap with a ready-to-use mounted FTRD clip, integrated snare, and thread. The cap carries a modified 14-mm OTS clip that can be mounted over a standard colonoscope, similarly to the OTS clip system. Compared with the conventional OTS clip system, the cap has greater depth (23 mm vs. 6 mm) to accommodate more tissue, and the clip design is slightly modified. The outer diameter of the device is 20 mm. A 13-mm monofilament snare is preloaded in the tip of the cap. The snare catheter runs along the outer surface of the colonoscope, constrained by a transparent plastic sheath to prevent entrapment of tissue between the scope and the snare. The complete positioning of the device on the colonoscope allows control of the system through a handwheel. The target lesion is pulled into the cap with a grasping or anchoring device before clip deployment. Turning the handwheel tensions the thread and the clip is released. The target tissue is cut above the clip using the integrated snare. Immediately after clip deployment, the tissue above the clip is resected with the snare.

All of the participants confirmed that a previous endoscopic evaluation of technical feasibility had been performed in terms of reaching the lesion and evaluating the polyp's size and location [13].

Definitions

All of the investigators participated in several online meetings to share video cases, discuss definitions, and obtain agreement on failure classification.

"Technical failure" was considered in terms of device dysfunction and defined as the inability to achieve en bloc resection after successful application of the OTS clip system. The inability to achieve complete enclosure of the lesion inside the cap or insufficient traction/suction into EFTR cap was classified as "cap misplacement"; the inability to release the clip was classified as "clip misdeployment"; the inability to achieve resection of the lesion after snare placement and electrical current application was defined as "snare noncutting." Classification into types I, II, or III was subsequently assigned according to

the reported frequency of each. A graphical representation is reported in the ▶ **Fig. 1**.

In addition, investigators were invited to state whether the dysfunction related to the device itself or was patient related, considering unexpected factors like angulation of the lesion site or heavily fibrotic tissue to resect. Clinical success was considered in terms of the rates of EFTR (histologically confirmed full-thickness resection) and R0 resection (complete removal of the tissue with tumor-free lateral and deep margins on histologic examination).

AEs were classified according to the AGREE classification [14] as follows. Grade I includes any deviation from the standard post-procedural course, without the need for pharmacologic treatment or endoscopic, radiologic, or surgical intervention. It also includes hospital admission of < 24 hours, without any intervention or the prescription of drugs such as antiemetics, antipyretics, analgesics, and electrolytes or diagnostic tests (radiology and laboratory tests). Grade II refers to AEs requiring pharmacologic treatment with drugs other than those allowed for grade I AEs (i. e. antibiotics, antithrombotics, etc.), or blood or blood product transfusion, or hospital admission for > 24 hours. Grade III AEs include events requiring endoscopic, radiologic, or surgical intervention (grade IIIa, endoscopic or radiologic intervention; grade IIIb, surgical intervention). Grade IV AEs include those requiring intensive care unit/critical care unit admission (grade IVa, single-organ dysfunction [including dialysis]; grade IVb, multiorgan dysfunction). Grade V refers to the death of the patient.

AEs were also divided into intraprocedural and post-procedural AEs depending on whether they occurred during the procedure or after the procedure had been completed, in subsequent hours of observation and in the following days, with all patients followed up for at least 3 months.

Each center was invited to report the training performed for full-thickness resection, experience in exposed FTRDs, colorectal ESD, and suturing devices, with participation in national EFTR registries or screening programs also evaluated. According to the median number of overall EFTRs performed in the study period, centers were divided into high volume (> 30 procedures/study period) or low volume (< 30 procedures).

Outcomes and patient population

The primary outcome was to assess the device dysfunction rate, overall and according to the proposed classification. Secondary outcomes included the management of dysfunction, clinical success, the rate and grading of AEs, and the correlation between a center's experience in EFTR and the occurrence of the aforementioned outcomes.

The study included consecutive colorectal nonexposed EFTR procedures using the Ovesco FTRD with failure due to device dysfunction. Exclusion criteria were: EFTR performed by an exposed technique, procedures with devices other than the Ovesco FTRD, cases confirmed as failure due to inability to reach the lesion, and inability of the patient to give informed consent for data collection.

Statistical analysis

Data were reported as mean (SD) for quantitative variables, and absolute and relative frequencies for categorical variables, when necessary 95 %CIs were properly calculated. An a priori sample size determination was not feasible owing to the explorative nature of the present data collection.

Heterogeneity between subgroups (high vs. low volume centers) was also estimated. This measure indicates whether data from all centers can be pooled into one measure, or have a variance that prevents them being pooled overall ($P < 0.05$ in the latter case), indirectly indicating whether differences exist between the subgroups.

Two-sided P values < 0.05 were considered to be significant. Analyses were conducted using STATA 17 (StataCorp. 2017, release 15; StataCorp LLC, College Station, Texas, USA) with the "metaprop" function.

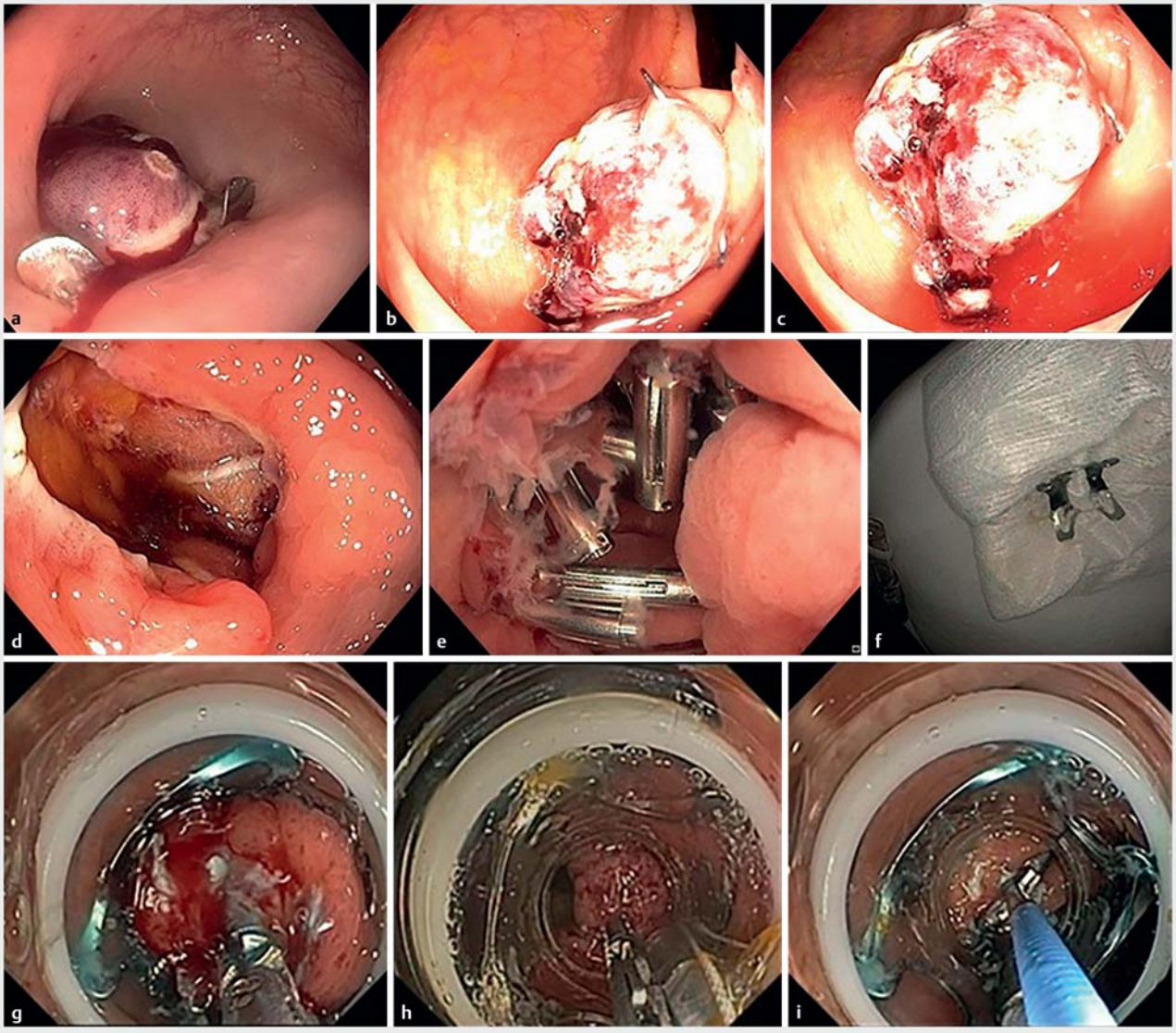
Results

During the study period, a total of 750 patients underwent colorectal full-thickness resection. Dysfunction occurred in 77 patients (10.3 %). The most frequent type of failure was snare noncutting (type I) in 41 patients (53.2 %). Clip misdeployment (type II) occurred in 24 patients (31.2 %), with cap misplacement (type III) reported in 12 patients (15.6 %). Endoscopic images of included population are shown in ▶ **Fig. 2**. The dysfunction events were judged by endoscopists to be strictly device related in 44 patients (57.1 %) and to be patient related in the remaining cases. Among the former group, there were 22 events reported as type I, 19 as type II, and three as type III. Baseline data for patient and lesion characteristics, and procedure details are reported in ▶ **Table 1**.

R0 resection was obtained in 49 cases (63.6 %). Other post-procedural outcomes are reported in ▶ **Table 2**. There were 61 lesions (79.2 %) where endoscopic resection was completed by conservative rescue endoscopic resection. The remaining 10 cases did not require further intervention despite the intraprocedural failure, mostly represented by clip misdeployment. Four patients (5.1 %) underwent elective surgical treatment because of failure of the endoscopic resection.

A total of 21 AEs were reported after technical failure and were mainly classified as grade I (n = 13; 16.9 %); four cases (5.2 %) of intraprocedural perforation were managed during the procedure and were classified as grade II. The remaining AEs included: one intraprocedural perforation observed at a different site to the location of the EFTR probably due to snare cutting damage that required endoscopic reintervention (full-thickness suture with a dedicated device), and a late post-procedure pericolic hematoma after intraprocedural OTS clip placement that required radiologic drainage (both grade IIIa; 2.6 %); two perforations were treated by urgent surgical intervention (grade IIIb; 2.6 %).

Of the 21 AEs, 18 were intraprocedural (23.4 %), including bleeding and perforation (both 10.4 %), along with two cases of substenosis of the lumen secondary to OTS clip closure. The post-procedural complication rate was 3.9 % and included two



▶ **Fig. 2** Endoscopic images of: **a–c** type I failure showing snare noncutting; **d–f** type II failure with clip misdeployment leading to: **d,e** perforation and; **f** clip release at the end of the procedure; **g–i** type III failure with lesions not completely pulled into the cap, corresponding to cap misplacement.

perforations and one pericolic hematoma occurring 1 week after the procedure. The AEs are summarized in ▶ **Table 3**.

The training and experience of the centers are summarized in **Table 1 s**, see online-only Supplementary material. As can be seen in ▶ **Fig. 3**, heterogeneity between the low and high volume centers was not significant ($P = 0.08$) and similar results were obtained for the overall AEs rate, being 1.8 % (95 %CI 0.2 %–4.5 %) in high volume centers and 1.2 % (95 %CI 0.1 %–5.3 %) in low volume centers ($P = 0.70$), and for the rescue resection rate, being 7.9 % (95 %CI 3.6 %–13.5 %) in high volume centers and 6.3 % (95 %CI 1.8 %–12.4 %) in low volume centers ($P = 0.71$).

Discussion

Performing colorectal EFTR is now recognized as a safe and effective technique for advanced resection of complex lesions; large international registries support this evidence and its use is increasing. The use of nonexposed resection devices is further encouraged by their ease of handling and simple procedural steps. The present study confirmed that colorectal EFTR is a challenging procedure, with unpredictable technical failures occurring because of device dysfunction and a wide spectrum of consequences. We observed a failure rate of 10.3 % among eligible patients, with type I (snare dysfunction) the most frequently observed; however, when considering all of the failures reported, they were related to the device itself in only half of cases, so this could require more attention be given to patient selection

▶ **Table 1** Baseline characteristics of the 77 included patients, their lesions, and the procedures they underwent.

	Patients with eFTR
Patient characteristics, n (%)	
Sex, male	42 (54.5 %)
Age, mean (SD), years	69.4 (8.9)
Lesion characteristics, n (%)	
Colorectal site	
▪ Cecum	9 (11.7 %)
▪ Appendiceal orifice	5 (6.5 %)
▪ Ascending colon/right flexure	22 (28.6 %)
▪ Transverse colon	9 (11.7 %)
▪ Descending and sigmoid colon	16 (20.8 %)
▪ Rectum	16 (20.8 %)
Size, mean (SD), mm	18.4 (7.5)
Morphology according to Paris Classification [13]	
▪ Polypoid lesions	9 (11.7 %)
▪ Non-polypoid lesions	68 (88.3 %)
Recurrent lesion	40 (51.9 %)
▪ After EMR	38 (49.4 %)
▪ After ESD	2 (2.6 %)
Histology	
▪ Adenocarcinoma	17 (22.1 %)
▪ Adenoma	53 (68.8 %)
▪ Neuroendocrine tumor	2 (2.6 %)
▪ Fibrotic tissue	5 (6.5 %)
Procedure characteristics, n (%)	
Use of the PrOVE cap	27 (35.1 %)
Trimming performed	5 (6.5 %)
Rescue endoscopic resection	61 (79.2 %)
▪ EMR	57 (74.0 %)
▪ ESD	4 (5.2 %)
Surgical treatment	6 (7.8 %)
▪ Elective surgery	4 (5.1 %)
▪ Urgent surgery for adverse events	2 (2.6 %)
Positioning of another OTS clip	8 (10.4 %)
Treatment with suturing device	1 (1.3 %)
En bloc resection	55 (71.4 %)
Injury to extraluminal structures	
▪ Anal trauma	5 (6.5 %)

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; OTS, over the scope.

▶ **Table 2** Summary of post-procedure outcomes.

Outcome	n (%)
Histologically confirmed full-thickness resection	47 (61.0 %)
R0 resection	49 (63.6 %)
Over-the-scope clip retained for > 12 weeks	12 (15.6 %)
RemOVE system used	1 (1.3 %)

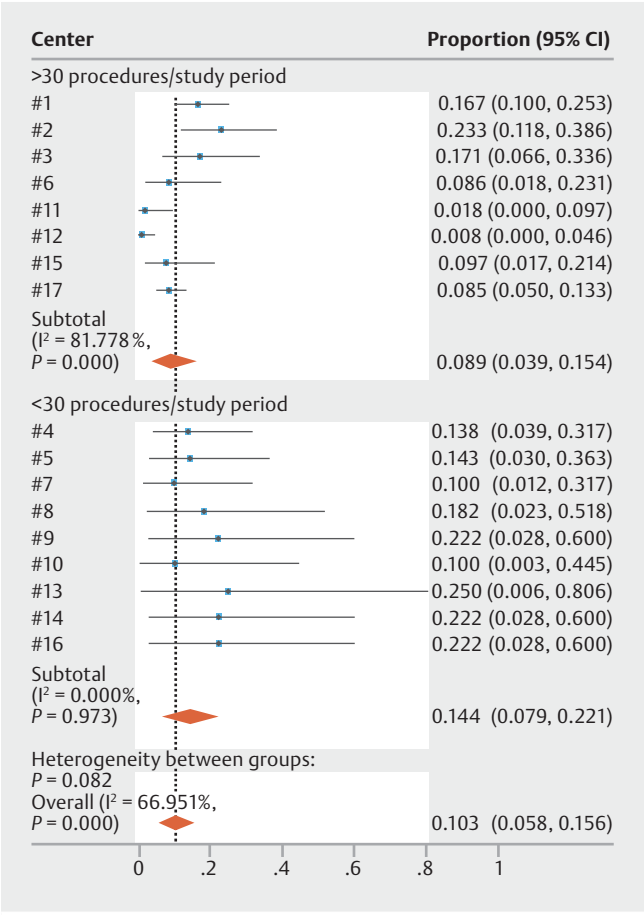
▶ **Table 3** Summary of adverse events.

Adverse events	n (%)
Overall	21 (27.3 %)
Grade according to the AGREE classification	
▪ I	13 (16.9 %)
▪ II	4 (5.2 %)
▪ IIIa	2 (2.6 %)
▪ IIIb	2 (2.6 %)
▪ IV	0
▪ V	0
Intraprocedural events	18 (23.4 %)
▪ Bleeding	8 (10.4 %)
▪ Perforation	8 (10.4 %)
▪ Substenosis	2 (2.6 %)
Post-procedural events	3 (3.9 %)
▪ Perforation	2 (2.6 %)
▪ Pericolic hematoma	1 (1.3 %)

and lesion characteristics (recurrent fibrotic lesions [51.9 %] or advanced histology such as adenocarcinoma [21.9 %]).

In an Italian multicenter experience with EFTR published in 2019 [15], including 114 patients, with a technical success rate of 94.4 %, full-thickness resection was achieved in 91 % of patients, with lateral and deep R0 resection in 90 % and 92 %, respectively. AEs were reported in 11 % of the study population, while technical issues with snare malfunction were described in 12 cases (11 %) and incomplete clip deployment in five (4.5 %). Similar results were reported from a larger German registry that collected data from 1178 colorectal procedures from 2015 to 2019 [16]. Furthermore, reporting the Dutch experience, EFTR was shown to be an effective and relatively safe procedure for oncologic purposes, with an overall technical success rate of 87.0 %, R0 resection rate of 85.6 %, and severe AE rate of 2.2 % [17].

Technical issues can however arise, although it is still unclear the frequency of these and the consequences they may have for patients. Zwager et al. recently published the largest study describing AEs occurring during colorectal EFTR, based on the experience of the German and Dutch registries [18]. Among



▶ **Fig. 3** Heterogeneity between failure rate according to centers' experience (high versus low volume centers, defined as >30 or <30 procedures/study period).

1892 procedures, the overall AE rate was 11.3%, with female sex and technical issues being the main factors related to complications; however, no clear definition of technical issues was provided. Our study was the first to classify dysfunction based on the different procedural steps and to analyze the eventual link with complications. The classification was formulated on the assumption that the procedural steps were correctly observed. It should be noted though that the observed rate of AEs in our study was higher than that previously reported, but it was considered only in the subgroup of cases of technical failures and not in the entire population undergoing EFTR during the study period. We believe that this result is in line with the Dutch and German registries, which show that technical dysfunction increases the risk of AEs (mainly mild or moderate in severity) for patients, although two-thirds of dysfunctions were not followed by AEs.

Clinical success (i.e. the achievement of R0) was achieved in more than half of the study population. Despite the failures, most lesions (79.2%) were managed with rescue endoscopic resection, mainly EMR of complex lesions. This leads us to consider that the first-line treatment of relapsed or nonlifting colorectal lesions is debatable. A number of recent studies have compared resection with ESD and EFTR, with varying results according to the experiences in different countries.

A recent French multicenter retrospective study reported data extracted from the prospectively collected national databases of ESD cases and the FTRD register, including a total of 275 patients [19]. The en bloc and R0 rates were significantly higher for ESD on multivariate analysis after adjustment for lesion size; AEs were also higher in the ESD group. The authors suggested that ESD should be proposed as the best option for residual colorectal neoplasia whatever the size and location of the lesion, while considering use of the FTRD for lesions <20 mm or when ESD was unavailable. It must though be noted that ESD had an enormous spread within French endoscopy circles thanks to the uptake of traction techniques and intensive standardized training, which is currently not similarly widespread in Italy and the rest of Europe. Indeed, the randomized trial conducted in Italy in four referral centers over the same time period showed comparable R0 resection rates for ESD versus EFTR [20].

Some additional insights should be given to the costs of these devices. In Italy, there is currently no uniformly recognized reimbursement for EFTR procedures and, in all cases, we are dealing with the high cost of this device. Surely the future will involve a thorough economic and ecologic evaluation.

EMR also maintains a role in the treatment of recurrent and residual lesions, especially when combined with low cost ancillary techniques. Tate et al. first proposed a standardized approach with cold-forceps avulsion and adjuvant snare-tip soft coagulation (CAST) for nonlifting large laterally spreading colonic lesions [21,22], with AEs and recurrences comparable to standard EMR, without the need for additional expensive devices. More recently, the use of cold EMR snares combined with ablation using hybrid argon plasma coagulation has been suggested to overcome the intrinsic limits of submucosal fibrosis in an approach known as the "COld Snare with Ablation" (COSA) technique [23,24].

Interestingly, we showed that the occurrence of AEs, including intraprocedural and late complications, was quite low despite failures due to device dysfunction, which is in line with previous publications and demonstrates the safety of the device. The rate of surgical intervention, either immediately or post-procedurally, is low, which means that management has predominantly been conservative and performed by the endoscopist. AEs were mainly grade 1 according to the AGREE classification and no severe or fatal AEs (grade IV or V) were reported.

Any endoscopic technique has a learning curve: this consideration led us to assess whether high and low volume centers showed differences in the main outcomes, such as the failure rate, their ability to adopt an endoscopic salvage technique, and the complication rate. Although low volume centers showed a homogeneous trend toward higher dysfunction rates for all three outcomes, there were no significant differences. It may be argued that the cutoff chosen to define high vs. low volume centers may have been too low; however, this was in line with data published from the Dutch registry [17]. Furthermore, the learning curve in EFTR with a dedicated device is quite

rapid. In our experience, according to self-reported training, 7.6% of participants had no specific prior training and 35.3% had no hands-on training in models; we think this is an important point to emphasize in the context of national scientific societies that should verify and promote standardized training meetings throughout their national territory. An annual cutoff of procedures should be established, given that the low rate of AEs in our study population probably reflects centers with great experience in other resection methods [25]. Furthermore, performing colorectal EFTR could be the first training step, followed by upper digestive tract procedures, such as for submucosal gastric lesions or alternatively for complex duodenal lesions [26–28].

We acknowledge that the 17 centers that participated in our study were extremely heterogeneous in terms of experience, training, and joining the national register. Additionally, the sample size may not have been large enough to detect such a difference with a nominal *P* value of <0.05.

Our study has many other limitations. First, it involved retrospective cohort data collection and not a prospectively collected complete registry, so it was not possible to exclude some reporting bias. In addition, the sample was limited to cases where device dysfunction occurred and therefore we could not explore predictive or protective factors for device dysfunction.

In conclusion, we conducted the first multicenter study showing that unpredictable technical issues can complicate EFTR procedures and must be considered in all cases, despite the recognized safety profile [29]. Our proposal for a classification is to invite all endoscopists who perform this procedure to share a single language and merge data from national registries. In this way, it will be possible to obtain precise indications and recommendations for this procedure, limiting its risks and adverse consequences. We reported a failure rate of 10.3% among eligible patients, with type I (snare noncutting) being most frequently observed, which could bring more attention to patient selection. Technical failure was observed more often in low volume centers, but this may be considered part of the learning curve. Surgery was needed in <10% of patients and no severe AEs or deaths were reported. Experience in rescue resection techniques and multidisciplinary management are mandatory in this setting. These factors should be considered for future guidelines and recommendations on EFTR.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical Trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT05913453 | Type of study: Observational Cohort Retrospective Study

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