Adverse events of endoscopic full-thickness resection: results from the German and Dutch nationwide colorectal FTRD registry

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Background and Aims: Endoscopic full-thickness resection (eFTR) is emerging as a minimally invasive alternative to surgery for complex colorectal lesions. Previous studies have demonstrated favorable safety results; however, large studies representing a generalizable estimation of adverse events (AEs) are lacking. Our aim was to provide further insight in AEs after eFTR.

Methods: Data from all registered eFTR procedures in the German and Dutch colorectal full-thickness resection device registries between July 2015 and March 2021 were collected. Safety outcomes included immediate and late AEs.

Results: Of 1892 procedures, the overall AE rate was 11.3% (213/1892). No AE-related mortality occurred. Perforations occurred in 2.5% (47/1892) of all AEs, 57.4% (27/47) of immediate AEs, and 42.6% (20/47) of delayed AEs. Successful endoscopic closure was achieved in 29.8% of cases (13 immediate and 1 delayed), and antibiotic treatment was sufficient in 4.3% (2 delayed). The appendicitis rate for appendiceal lesions was 9.9% (13/131), and 46.2% (6/13) could be treated conservatively. The severe AE rate requiring surgery was 2.2% (42/1892), including delayed perforations in .9% (17/1892) and immediate perforations in .7% (13/1892). Delayed perforations occurred between days 1 and 10 (median, 2) after eFTR, and 58.8% (10/17) were located on the left side. Other severe AEs were appendicitis (.4%, 7/1892), luminal stenosis (.1%, 2/1892), delayed bleeding (.1%, 1/1892), pain after eFTR close to the dentate line (.1%, 1/1892), and grasper entrapment in the clip (.1%, 1/1892).

Conclusions: Colorectal eFTR is a safe procedure with a low risk for severe AEs in everyday practice and without AE-related mortality. These results further support the position of eFTR as an established minimally invasive technique for complex colorectal lesions. (Gastrointest Endosc 2023;97:780-9.)

(footnotes appear on last page of article)

Endoscopic full-thickness resection (eFTR) is an emerging en-bloc resection technique for complex colorectal lesions that has become part of the endoscopic armamentarium in daily clinical practice. Conventional advanced endoscopic techniques like EMR and endoscopic submucosal dissection (ESD) are limited to the submucosal layer and require some degree of submucosal lifting for safe and complete resection. eFTR can overcome limitations because of submucosal scarring and subsequent nonlifting by enabling a transmural resection without fecal spill, which offers a minimally invasive alternative to surgery.[1-3] The main indications are nonlifting lesions, lesions at difficult anatomic locations such as the appendicular orifice, or diverticula and subepithelial tumors. In addition, more-recent studies provided further insight in eFTR for early colorectal cancer.[1-14]

The full-thickness resection device (FTRD; Ovesco Endoscopy AG, Tübingen, Germany) is an over-the-scope system that allows for a single-step procedure. Over the past years, several retrospective and prospective studies have investigated its efficacy and safety,[1-14] demonstrating favorable safety. However, experience reported in the literature remains limited, and large studies representing a generalizable estimation of the risk of adverse events (AEs) with detailed description are lacking. eFTR is now considered an established technique and is used widely, which indicates the need to evaluate AEs in a large cohort of patients.

The aim of this study was to evaluate the overall rate of AEs after eFTR in the German and Dutch colorectal eFTR registries. Because both registries include multiple academic and nonacademic centers (Supplementary Table 1, available online at www.giejournal.org), this study can be expected to provide a representative overview and insight in eFTR-related AEs.

METHODS

Study design

The German eFTR Registry was initiated after the European launch of the FTRD in 2014. In 2015, the Dutch eFTR Registry was founded at Amsterdam UMC. Both nationwide registries aimed to assess the efficacy and safety of the FTRD in daily practice. All centers using the FTRD were invited to register their consecutive cases in an online national database. For this study, all included cases from both national FTRD registries from July 2015 through March 2021 were selected for analysis. The following variables of all registered cases were collected: patient and lesion characteristics, previous endoscopic resection attempt, indication for eFTR, history of appendectomy for appendiceal lesions, procedural or technical issues, and type of AEs and their management.

For patients with severe AEs (SAEs; ie, requiring surgical treatment), missing or additional information was requested at local hospitals such as intensive care unit stay, unscheduled admission with length of hospital stay, and mortality within 90 days. Furthermore, for cases with SAEs, potential predefined risk factors such as body mass index, American Society of Anesthesiologists score, medication use (ie, immunosuppressants, anticoagulant or antiplatelet therapy, antibiotics, statins, stool softeners), smoking history, hypertension, diabetes, and cerebrovascular disease were collected.

To identify potential clinical and endoscopic risk factors for SAEs and AEs, bleeding, or delayed perforations, variables such as age, gender, indication for eFTR, lesion location, previous resection attempt, and technical or procedural issues of all patients were used. Technical issues were defined as snare dysfunction or clip dysfunction. Procedural issues were defined as lesion not reached, inability to incorporate tissue in the cap, wrong sequence of steps, grasper issues, or perforation because of FTRD introduction. Dutch centers were subdivided into low-volume centers (<20 cases, n = 6), middle-volume centers (20-40 cases, n = 7), and high-volume centers (>40 cases, n = 7). No patient identification details were used, and only pseudonymized data were shared for analysis.

Because data were collected as part of standard medical care, the Institutional Review Board of the Amsterdam UMC regarded the study beyond the legalization regarding Medical Research Involving Human Subjects Act, and formal ethical approval was not deemed necessary. The Dutch eFTR Registry is listed in the Dutch Trial Register (NL5868; http://www.trialregister.nl/).

Outcomes

Primary study outcome was to describe the overall AE rate of all colorectal eFTR procedures in both national registries and to present a detailed description of all SAEs. Secondary outcomes were identification of potential clinical and endoscopic risk factors for AEs, SAEs, delayed perforations, and bleeding. For delayed perforations, a detailed description of predefined risk factors was provided.

eFTR procedure and management

Colorectal eFTR in both registries was performed using the FTRD (Fig. 1), after informed consent was obtained from patients. Technical details have been described previously.[3,13] All endoscopists were FTRD-certified after a mandatory 1-day course in theoretical background and hands-on training in ex vivo porcine models. Prophylactic antibiotics were not routinely administered but left to the discretion of the endoscopist.

Definition of AEs

The following definitions were used for ranking the severity of AEs. Mild AEs were those *not* requiring blood transfusion, repeat endoscopy, and angiographic and/or surgical intervention. Moderate AEs required blood transfusion, repeat endoscopy, and/or angiographic intervention. SAEs were defined as requiring surgical intervention and/or leading to death.

Statistical analysis

Continuous variables are reported as mean with standard deviation; non-normally distributed variables are reported as median and interquartile range (IQR); categorical variables are shown as counts with percentages. For comparison between countries, continuous variables were tested using the t test, and categorical variables were analyzed using the χ^2 test or 2-sided Fisher exact test.

To assess associations between potential clinical and endoscopic risk factors and each outcome variable (AEs, SAEs, delayed perforation, and bleeding), univariate logistic regression was performed. In this univariate analysis, we considered 1 AE per case. Odds ratio (OR) and 95% confidence interval (CI) were provided for each model. Multivariable logistic regression was built to assess the effect of potential confounding factors. Potential clinical and endoscopic risk factors with $P \leq .1$ in the univariable analysis were included in the multivariable analysis.

All statistical tests were 2-sided, and $P < .05$ was considered to be statistically significant. Analyses were performed in R statistical software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

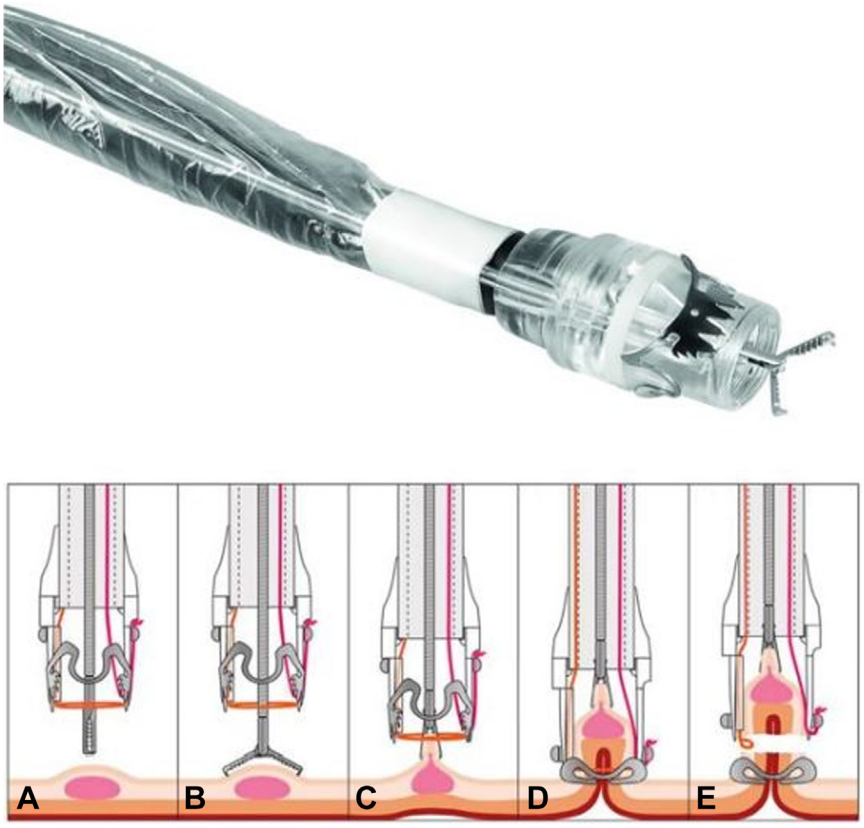

Figure 1. Full-thickness resection device from Ovesco Endoscopy AG (Tübingen, Germany) and schematic illustration of the procedure. **A**, The lesion is identified. **B** and **C**, The lesion is grasped and pulled into the cap. **D**, The over-the-scope clip is deployed. **E**, The lesion is resected above the clip with the integrated snare. (Image is used with permission from Ovesco Endoscopy AG.)

RESULTS

Patients and procedures

In total, 1892 consecutively registered eFTR cases between July 2015 and March 2021 were analyzed. These comprised 1178 German cases (65 centers) and 714 Dutch cases (20 centers). Baseline characteristics for both countries are presented in Table 1. Mean patient age was 68.3 ± 10.8 years, and 61.6% of cases (1165/1892) were men. Indications for eFTR were difficult polyp (n = 998), early carcinoma (n = 695), subepithelial tumor (n = 107), diagnostic (n = 16), or other (n = 76), with significant differences for all indications between both registries. Technical and procedural issues were reported in 6.4% of cases (122/1892) and 7.7% of cases (145/1892), respectively, without a significant difference between both registries.

Overall AEs

In total, 213 AEs occurred in 206 patients with an overall AE rate of 11.3% (213/1892). Two AEs occurred in 5 patients and 3 AEs in 1 patient. Table 2 shows an overview of all AEs. No AE-related mortality was observed. SAEs occurred in 2.2% (42/1892), moderate AEs in 3.5% (67/1892), and mild AEs in 5.5% (104/1892).

Bleeding occurred in 6.2% (117/1892), of which 31 occurred during the procedure (immediate) and 86 after the performed eFTR (delayed). Delayed bleeding occurred at median post-eFTR day 1 (IQR, 1-6). Of all immediate bleeding, 25.8% of patients (8/31) did not require additional treatment, and 74.2% (23/31) were treated during the same session. Treatment methods for immediate bleeding were hemostatic clips (n = 8), coagulation (n = 8), injection (n = 5), hemostatic powder (n = 1), and unspecified (n = 1). In 1 patient treated with hemostatic powder, a second endoscopy was needed, and in all others hemostasis was achieved. For delayed bleeding, repeat endoscopy was performed in 72.1% of cases (62/86): 48 (77.4%) German cases and 14 (22.6%) Dutch cases. Of these, 61 cases were treated successfully, although in 18 cases no intervention was required. In 1 patient a repeat endoscopy was performed after 5 days for a second bleeding episode, and 1 patient needed emergency surgery (see further details below). Two patients received a blood transfusion.

Perforations occurred in 2.5% (47/1892). This included 27 immediate perforations (27/1892, 1.4%) where a transmural defect was seen immediately during the procedure. Of these 27 immediate perforations, 24 were caused by technical or procedural issues (wrong sequence of steps in 7, perforation because of FTRD introduction in 4, clip release dysfunction in 12, and inability to incorporate

TABLE 1. Baseline characteristics of all cases

Characteristics	Total	German registry	Dutch registry	*P* value
No. of procedures	1892	1178	714	
Male sex	1165 (61.6)	713 (60.5)	452 (63.3)	.242
Mean age, y (standard deviation)	68.3 (10.8)	67.8 (11.8)	69.0 (8.9)	.024
Indication for eFTR				
T1 colorectal cancer	695 (36.7)	217 (18.4)	478 (66.9)	.001
Difficult polyp	998 (52.7)	790 (67.1)	208 (29.1)	.001
Subepithelial tumor	107 (5.7)	80 (6.8)	27 (3.8)	.006
Diagnostic eFTR	16 (.8)	16 (1.4)	0 (0)	.001
Other	76 (4.0)	75 (6.4)	1 (.1)	.001
Hybrid cases	74 (3.9)	38 (3.2)	36 (5.0)	.019
Previous endoscopic resection attempt	1035 (54.7)	637 (54.1)	398 (55.7)	.446
Technical issues*	122 (6.4)	75 (6.4)	47 (6.6)	.847
Procedural issues*	145 (7.7)	91 (7.7)	54 (7.6)	.929
Lesion location				
Right side (cecum to transverse colon)	936 (49.5)	642 (54.5)	294 (41.2)	.001
Cecum	209 (11.0)	153 (13.0)	56 (7.8)	.001
Appendix	131 (6.9)	90 (7.6)	41 (5.7)	.135
Ascending colon	390 (20.6)	250 (21.2)	140 (19.6)	.446
Transverse colon	207 (10.9)	150 (12.7)	57 (8.0)	.001
Left side (descending colon to rectum)	956 (50.0)	536 (45.5)	420 (58.8)	.001
Descending colon	116 (6.1)	66 (5.6)	50 (7.0)	.279
Sigmoid	410 (21.7)	192 (16.3)	218 (30.5)	.001
Rectum	429 (22.7)	277 (23.5)	152 (21.3)	.282

Values are n (%) unless otherwise defined.
eFTR, Endoscopic full-thickness resection.
*In the German registry a total of 154 technical and procedural issues were reported. Because of different definitions used in this article, 12 additional cases were graded as technical and procedural issues.

tissue into the cap in 1). Two other immediate perforations occurred during EMR in hybrid procedures, and the other perforation occurred during balloon dilatation of a stenosed sigmoid before device introduction. Delayed perforations were observed in 20 cases (20/1892, 1.1%) after a median of 3 days (IQR, 2-6).

Perforations were endoscopically closed in 29.8% of cases (14/47), including 13 of 27 immediate perforations and 1 of 20 delayed perforations. Of these 14 cases, the defect was closed with an over-the-scope clip (OTSC) in 12 and with hemostatic clips in 2. In 1 immediate perforation, endoscopic closure failed and was followed by surgery. Conservative treatment with antibiotics was sufficient in 4.3% (2/47, both delayed). These cases were graded as mild in .8% (16/1892) and moderate in .1% (1/1892). Surgical repair was performed in 64.0% (30/47) of perforations and graded as severe in 1.6% (30/1892). These are described in further detail below.

In total, 131 lesions involved the appendiceal orifice. The overall rate of appendicitis was 9.9% (13/131) diagnosed after a median time of 3 days (IQR, 2-4). Information regarding appendectomy status was missing in most German cases. In the Dutch registry, the secondary appendicitis rate for cases without a prior appendectomy was 21.2% (7/33), and 71.4% (5/7) were treated with surgery. Conservative treatment with antibiotics was successful in 46.2% (6/13) of all patients with appendicitis with a median admission time of 9 days (IQR, 3-11). In the other 53.8% of cases (7/13), emergency surgery was performed, as described below.

A luminal stenosis was observed in .5% (9/1892). In 6 of 9 patients, the stenosis was seen during the procedure and reported. In 4 patients, no additional treatment was necessary, and in 2 patients, additional surgery was performed. In the other 3 cases, a symptomatic stenosis was diagnosed after the procedure. One case (ascending colon) presented with a functional stenosis and needed clip removal, another case (sigmoid) required a dilatation, and 1 patient (cecum) presented with obstruction complaints treated conservatively with laxatives.

Postpolypectomy syndrome was observed in .8% (15/1892). All subsided with conservative therapy, of which 7 patients received antibiotics. Diverticulitis was observed in 2 patients (.1%), both managed with antibiotics.

TABLE 2. Overview of all 1892 cases with AEs

AEs	Overall	Mild	Moderate	Severe
Overall AEs	213 (11.3)	104 (5.5)	67 (3.5)	42 (2.2)
All bleeding	117 (6.2)	54 (2.9)	62 (3.3)	1 (.1)
Direct bleeding	31 (1.6)	30 (1.6)	1 (.1)	—
Delayed bleeding	86 (4.5)	24 (1.3)	61 (3.2)	1 (.1)
All perforations	47 (2.5)	16 (.8)	1 (.1)	30 (1.6)
Direct perforation	27 (1.4)	14 (.7)	—	13 (.7)
Delayed perforation	20 (1.1)	2 (.1)	1 (.1)	17 (.9)
Appendicitis	13 (.7)	6 (.3)	—	7 (.4)
Postpolypectomy syndrome	15 (.8)	13 (.7)	2 (.1)	—
Diverticulitis	2 (.1)	2 (.1)	—	—
Infection/inflammation	5 (.3)	5 (.3)	—	—
Stenosis	9 (.5)	5 (.3)	2 (.1)	2 (.1)
Other*	5 (.3)	3 (.2)	—	2 (.1)

Values are n (%).
AE, Adverse event; —, not available.
*Other mild AEs were a pressure ulcer (n = 1), collapse with head injury (n = 1), and bladder retention (n = 1). Two other AE cases graded as severe requiring surgery included severe pain after endoscopic full-thickness resection close to the dentate line (n = 1) and grasper entrapment in clip (n = 1).

Infectious adverse events occurred in 5 patients (.3%). Of these 5, 3 developed fever with unknown cause, 1 had a urinary infection, and 1 developed a cecal-pole abscess. Other reported miscellaneous AEs were a pressure ulcer (n = 1) located in the rectum, collapse with a head injury (n = 1), and bladder retention (n = 1), all graded as mild. Finally, 2 cases needed surgical intervention for miscellaneous AEs as described below.

Severe AEs

Additional information regarding SAEs was achieved in 90.7% of cases (39/43). Perforations with need for immediate surgical repair occurred in 1.6% (30/1892), of which .9% (17/1892) were delayed and .7% (13/1892) were immediate perforations. All 13 immediate perforations were caused by technical or procedural issues (ie, perforation because of FTRD introduction in 4, wrong sequence of steps in 4, and clip dysfunction in 5). All 4 perforations caused by FTRD introduction were located in the sigmoid, in 1 diverticulosis was reported as the potential cause, and in the others no cause was reported.

Seventeen delayed perforations occurred between days 1 and 10 post-eFTR with a median of 2 days (Table 3). In 10 cases a segmental colonic resection was performed, with colostomy formation in 3. Five perforations were treated by surgical suturing, and 1 required a temporary loop colostomy. In 2 cases the type of surgery was not reported. Patients were admitted for a median of 10 days (IQR, 8-16), and 7 patients needed intensive care unit admission for a median of 2 days (IQR, 1-7). In 64.7% (11/17) of delayed perforations, a previous endoscopic resection attempt was performed. In total, 58.8% of perforations (10/17) were located in the left-sided colon, and no patient received postprocedural stool softeners.

Of all delayed perforations, we identified predefined risk factors in 76.5% (13/17). Four patients (30.8%) used immunosuppressive therapy. Of these 4, 1 had active Crohn's disease during eFTR. In a second case, a clip release dysfunction occurred, and the perforation was directly closed with an OTSC. However, this closure failed and resulted in fecal peritonitis. The other 2 patients had poor health status in addition to immunosuppressive treatment. In 23.1% of patients (3/13), a technical issue occurred (snare dysfunction in 2 and clip dysfunction in 1). Six of 13 patients had at least 1 risk factor.

Secondary appendicitis with additional surgery occurred in .4% of cases (7/1892). In 6 cases this included a laparoscopic appendectomy and in 3 cases an ileocecal resection. The median hospitalization duration was 5 days (IQR, 4-7).

Stenosis requiring surgery occurred in .1% of patients (2/1894). In 1 rectal case (10 cm of the anal verge), a luminal stricture was seen without additional treatment. The patient presented the next day with an acute ileus, and the clip was removed during transanal surgery. In the other case (sigmoid), a stenosis was observed immediately after eFTR and the patient was referred for sigmoid resection.

Delayed bleeding requiring surgery was observed in 1 patient with anticoagulant use (.1%) 14 days after eFTR. First, a repeat endoscopy was performed with an active bleeding at the resection site (sigmoid) that was successfully treated with a fibrinogen injection. That same day, an arterial bleed was found during repeat endoscopy and treated unsuccessfully with 2 OTSCs and hemospray (Cook Medical, Winston-Salem, NC, USA). The patient was referred for emergency surgery (kind of surgery unknown).

In the 2 final patients who needed emergency surgery, 1 (.1%) had severe pain after eFTR close to the dentate line, and in the other patient (.1%) the grasper was entrapped

TABLE 3. Overview of delayed perforations requiring surgery

Patient no.	Gender	Age (y)	Lesion size (mm)	Previous endoscopic resection attempt	Indication for eFTR	Location	Technical/ procedural issues	Occurrence after eFTR (days)	No. of admission days	Risk factors
1	Female	76	12	Yes, polypectomy/ EMR	Difficult polyp, incomplete resection/ recurrence	Cecum	Yes, snare malfunction	1	8	ASA III, hypertension, smoking
2	Female	66	10	Yes, polypectomy/ EMR	Secondary treatment T1 CRC	Transverse colon	No	8	24	BMI of 14, smoking
3	Female	87	18	Yes, polypectomy/ EMR	Difficult polyp, incomplete resection/ recurrence	Transverse colon	No	2	9 (*2 days ICU)	ASA III, hypertension, diabetes, statin use, immunosuppressive therapy
4	Female	70	9	Yes, polypectomy/ EMR	Secondary treatment T1 CRC	Sigmoid	No	2	11	Hypertension, statin use
5	Male	41	12	No	Primary treatment T1 CRC	Sigmoid	No	4	14	Immunosuppressive therapy
6	Male	75	10	Yes, polypectomy/ EMR	Secondary treatment T1 CRC	Sigmoid	No	1	8	None
7	Female	55		Yes, polypectomy/ EMR	Secondary treatment T1 CRC	Sigmoid	Yes, clip was released with much effort	2	7	BMI > 30, hypertension, smoking
8	Male	62	27	No	Difficult polyp, nonlifting sign	Cecum	No	10	19 (*11 days ICU)	ASA III, BMI > 30, hypertension, smoking, immunosuppressive therapy
9	Female	57	25	Yes, polypectomy/ EMR	Difficult polyp, incomplete resection/ recurrence	Ascending colon	No	2	10	BMI > 30
10	Female	65	25	Yes, polypectomy/ EMR	Difficult polyp, incomplete resection/ recurrence	Ascending colon	No	4	17	Hypertension
11	Female	73	32	No	Difficult polyp, nonlifting sign	Transverse colon	Yes, snare malfunction	1	12	BMI > 30, hypertension
12	Female	73	27	No	Difficult polyp, nonlifting sign	Sigmoid	Yes, clip dysfunction	1	7 (*5 days ICU)	ASA III, smoking, immunosuppressive therapy
13	Female	59	20	Yes, polypectomy/ EMR	Difficult polyp, incomplete resection/ recurrence	Sigmoid	No	4	6 (*1 days ICU)	None
14	Female	21		No	Diagnostic biopsy sampling	Sigmoid	No	4	Missing	None
15	Male	65	15	No	Difficult polyp, non-lifting sign	Sigmoid	No	1	10 (*1 day ICU)	ASA III, BMI > 30, diabetes, hypertension,
16	Male	71	10	Yes, polypectomy/ EMR	Secondary treatment T1 CRC	Sigmoid	No	9	28 (*ICU stay, number of days missing)	ASA III, BMI > 30, diabetes, cerebrovascular disease, hypertension
17	Female	55	10	Yes, polypectomy/ EMR	Secondary treatment T1 CRC	Rectum	No	7	9	None

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CRC*, colorectal cancer; *eFTR*, endoscopic full-thickness resection; *ICU*, intensive care unit.
*Number of days at intensive care unit.

in the clip. Overall, no surgery-related mortality occurred, and all patients fully recovered.

Potential endoscopic and clinical risk factors for AEs

In univariable analysis, female gender (OR, 1.35; 95% CI, 1.00-1.81; $P = .05$) and technical issues (OR, 2.53; 95% CI, 1.57-3.95; $P < .001$) were both associated with an AE. Multivariable analysis showed that both remained significant risk factors (Table 4). Lesion size (<15, 15-20, >20 mm) was not associated with AEs. For the outcomes of SAEs, delayed perforations, and bleeding see Supplementary Tables 2, 3, and 4, respectively (available online at www.giejournal.org). Importantly, for delayed perforations, we also identified female gender (OR, 2.95; 95% CI, 1.20-7.90; $P = .02$) and technical issues (OR, 3.99; 95% CI, 1.12-11.21; $P = .02$) as significant risk factors in the multivariable analysis. AEs were also analyzed according to case-volume in the Dutch centers (n = 714). The highest AE rate was found in the high-volume centers (11.6%, 55/476). In middle-volume centers and low-volume centers, the AE rates were 9.7% (17/175) and 6.3% (4/63), respectively. No significant difference was observed ($P = .407$).

DISCUSSION

Nonexposed colorectal eFTR is now considered an established endoscopic resection technique for complex colorectal lesions, and its use is emerging rapidly across the globe. Detailed understanding of procedure-related AEs and their consequences is therefore important. With the lack of data coming from prospective comparative studies, large prospective registries currently provide the best available evidence regarding eFTR-related AEs. This international multicenter collaboration between Germany and the Netherlands, both early FTRD adapting countries, provides an accurate description of AEs that could be generalizable to real-world practice. This study demonstrates that eFTR is safe with a low overall AE rate of 11.3% and no AE-related mortality.

The highest number of AEs reported in our study were from bleeding (6.2%). A potential effect of antiplatelet or anticoagulant use on bleeding rates could not be demonstrated because this information was not registered routinely. Most bleeding AEs were graded as moderate or minor. Repeat endoscopy was performed in a relatively high number of cases with delayed bleeding (72%). Interestingly, most of those (77%) originated from the German registry and may reflect different approaches in bleeding management. Although speculative, a possible explanation might be a more conservative policy for repeat endoscopy in a recurrent bleeding in the Netherlands as compared with Germany.[15] Most postpolypectomy bleeding cases settle spontaneously without intervention, as was shown in a previous study.[16] Accordingly, also in this study, hemostasis was already achieved spontaneously at the time of repeat endoscopy in 30%, and no additional treatment was necessary. This suggests that a wait-and-see policy is justifiable in hemodynamically stable patients without signs of ongoing bleeding or with a low level of hemoglobin at presentation.

This study reveals an overall perforation rate of 2.5% and an overall emergency surgery rate for perforations of 1.6%. These results are in line with previous smaller eFTR studies.[1-14] This perforation rate is slightly higher compared with EMR (.9%-1.4%) and lower compared with colorectal ESD (4.2%-8.6%).[17,18] However, the rate of emergency surgery after perforation is higher for eFTR in comparison with EMR and is comparable with ESD.[17,18] In general, immediate eFTR perforations are larger and therefore more challenging to successfully close endoscopically as compared with (near) perforations that occur during EMR or ESD. To illustrate, a recent study demonstrated successful endoscopic closure for perforations after EMR in 97% as compared with the successful endoscopic closure rate of 48% in this study.[19]

Apart from lesion size restriction (up to 2 cm) for eFTR, another important difference of eFTR compared with EMR and ESD is the relatively larger proportion of delayed perforations (1.1%), which rarely occurs in EMR and ESD.[3,19,20] For endoscopists, delayed perforations are the most feared AEs because patients run the risk of fecal peritonitis with associated severe clinical illness and almost always require emergent surgery, often with (temporarily) stoma formation. Secure defect closure and adequate tissue repair is critical for a safe transmural resection in the colorectum. In analogy with surgical anastomoses, in which anastomotic failures are reported in 5% to 8%, impaired defect healing after eFTR may lead to delayed perforations and could be increased by known risk factors such as smoking, body mass index, and immunosuppressive therapy.[21-23] Most patients with delayed perforation (76%) had 1 or more potential risk factor.

The combined registries did not include sufficient information on all known potential risk factors to identify certain factors as significant predictors for delayed perforation. However, clinical and endoscopic risk factors could be analyzed and showed that technical issues (snare or clip dysfunction) were associated with delayed perforation. A potential explanation for the association between occurrence of a technical issue and delayed perforation could be the use of an additional snare after FTRD snare dysfunction. For example, if an additional snare is placed in close proximity of the OTSC, cauterization might cause thermal damage and tissue necrosis leading to a delayed perforation, which is less likely to occur when the integrated FTRD snare is used in which distance to the clip is set and well adjusted.

In this study, delayed perforations occurred slightly more often in the left-sided colon. We believe the relative stenosis that occurs because of partial wall excision in

TABLE 4. Clinical and endoscopic risk factors for AEs

Variables	Procedures without AEs (n = 1686)	Procedures with AEs (n = 206)*	Univariable odds ratio (95% confidence interval)	*P* value	Multivariable odds ratio (95% confidence interval)	*P* value
Female gender	634 (37.6)	93 (45.1)	1.37 (1.02-1.83)	.04	1.35 (1.00-1.81)	.05
Mean age, y	68.3	68.1	1.00 (.99-1.01)	.77		
No previous endoscopic resection attempt	752 (44.6)	105 (51.0)	.77 (.58-1.03)	.08	.78 (.58-1.05)	.10
Indication for eFTR						
T1 colorectal cancer	629 (37.3)	66 (32.0)	Reference		Reference	
Difficult polyp	877 (52.0)	121 (58.7)	1.31 (.96-1.81)	.09	1.27 (.93-1.75)	.14
Subepithelial lesion	97 (5.8)	10 (4.9)	.98 (.46-1.89)	.96	.90 (.42-1.75)	.77
Diagnostic eFTR	12 (.7)	4 (1.9)	3.18 (.87-9.42)	.05	2.51 (.67-7.64)	.13
Other	71 (4.2)	5 (2.4)	.67 (.23-1.57)	.41	.60 (.20-1.41)	.29
Proximal location	826 (49.0)	110 (53.4)	.84 (.63-1.12)	.23		
Technical issues	95 (5.6)	27 (13.1)	2.53 (1.58-3.93)	<.001	2.53 (1.57-3.95)	<.001
Procedural issues	127 (7.5)	18 (8.7)	1.18 (.68-192)	.54		

Values are n (%) unless otherwise defined.
AE, Adverse event; *eFTR*, endoscopic full-thickness resection.
*Only 1 AE per patient is included in the analysis.

combination with more solid stools and higher intraluminal pressure in the left-sided colon could contribute to tissue disintegration or rupture. Prescribing postprocedural laxatives might reduce the delayed perforation risk and is also used as a possible preventive measure to reduce anastomotic failures of colonic surgery.[3] None of the patients in our study with a left-sided perforation received postprocedural laxatives. However, laxative prescription is not registered routinely, hampering the evaluation of their potential preventive effect. Nevertheless, we currently recommend its routine use after left-sided eFTR for 14 days.

Another important AE is secondary appendicitis, occurring in 9.9% of procedures for appendiceal lesions. This is comparable with the 8.8% reported in the Wall-Resect study.[1] However, the rate of secondary appendicitis might be higher when only patients without previous appendectomy are considered. This was 21% in the Dutch registry, which is in line with 2 recent multicenter studies showing an appendicitis rate between 14% and 17%.[24,25] About half of these cases could be treated with antibiotics, however, with a median hospitalization of 9 days. The rate of surgical intervention for secondary appendicitis in our study was 54%, comparable with the 60% surgery rate for appendicitis in the study of Ichkhanian et al.[24] Most cases underwent appendectomy (median hospitalization of 5 days). Comparing these outcomes with primary surgery for appendiceal lesions, such as cecal wedge resection, is difficult because the latter mainly includes larger lesions. However, for primary surgery, morbidity rates of 20% are reported, and in 4% additional surgery was necessary because of positive resection margins.[26] Future comparative studies are eagerly awaited.

Significant clinical and endoscopic risk factors for AEs in our study were female gender and technical issues. Female gender has been identified as a risk factor for a perforation or postpolypectomy syndrome in some studies.[27] Although the theoretical background for this finding is unclear, a possible explanations might be that women have a longer and/or more mobile transverse colon.[27] Technical issues during eFTR seem a more intuitive risk factor for AEs, especially when additional snare cauterization is applied in too close proximity of the OTSC. Procedural issues were not a significant risk for AEs and may possibly be operator- or experience-dependent (eg, when the wrong sequence of procedural steps are followed). However, this remains a speculation. Further, we could not find a significant difference in AEs between high-, middle-, and low-volume Dutch centers. This may also confirm to the short learning curve of eFTR. In fact, we did observe a tendency to increased AE rates in high-volume centers, possibly because of the treatment of more complex patients, but this remains speculative. In contrast to a recent meta-analysis, lesion size was not associated with the AE rate in our study.[28] A potential explanation for this difference is the inclusion of various exposed and nonexposed full-thickness resection techniques in this meta-analysis, whereas we only included FTRD procedures. This could explain the higher rate of procedure-related AEs in larger lesions (>20 mm) in this meta-analysis. Accordingly, in this meta-analysis the overall AE rate was 15% for all included studies and 13% for FTRD studies only, which is in line with our results.[28]

At present, this is the largest study available that describes AEs of colorectal eFTR. Its strength lies in combining data from 2 national FTRD registries, encompassing a wide

number of academic and nonacademic centers, that reflect everyday practice. However, some limitations need to be addressed because this study was based on retrospectively analyzed registry data. First, not all necessary data were available in both registries, despite our effort to collect additional information from all individual hospitals. As a result, specific potential risk factors for SAEs could not be included in our analysis. Second, it is possible that some AEs were missing because of reporting bias.

In conclusion, this large international registry-based study demonstrates that colorectal eFTR is a safe minimally invasive technique with relatively low AE rates and no AE-related mortality. The outcomes of this study contribute to a better understanding of eFTR-related AEs and patient information. Future comparative studies with both surgical and endoscopic alternatives are eagerly anticipated.

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Abbreviations: AE, adverse event; CI, confidence interval; eFTR, endoscopic full-thickness resection; ESD, endoscopic submucosal dissection; FTRD, full-thickness resection device; IQR, interquartile range; OR, odds ratio; OTSC, over-the-scope clip; SAE, severe adverse event.

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SUPPLEMENTARY TABLE 1. Participating centers

Participating centers	Academic or nonacademic	No. of cases
Germany		
Universitätsklinikum Freiburg im Breisgau	Academic	86
St Vinzenz Hospital Köln	Nonacademic	71
Diakoniekrankenhaus Halle a. d. Saale	Nonacademic	55
Klinikum Altenburger Land	Nonacademic	52
Klinikum Ludwigsburg	Nonacademic	49
Universitätsklinikum Ulm	Academic	48
Stadtkrankenhaus Delmenhorst	Nonacademic	42
Malteser Krankenhaus St. Anna Duisburg	Nonacademic	41
Universitätsmedizin Greifswald	Academic	40
Helios Klinikum Berlin Buch	Nonacademic	33
Kliniken des Landkreises Neumarkt i.d.OPf.	Nonacademic	33
Mathilden Hospital Herford	Nonacademic	31
Katholisches Klinikum Mainz	Nonacademic	31
Universitätsklinikum Marburg	Academic	29
Petrus Krankenhaus Wuppertal	Nonacademic	28
Klinikum Wolfsburg	Nonacademic	27
Elisabethkrankenhaus Essen	Nonacademic	26
Donau Isar Klinikum Deggendorf	Nonacademic	23
Christophorus-Kliniken Coesfeld	Nonacademic	21
Klinikum St. Marien Amberg	Nonacademic	20
Akademisches Lehrkrankenhaus Landshut Achdorf	Academic	20
Klinikum Passau	Nonacademic	18
Helios Klinikum Krefeld	Nonacademic	18
Klinikum Arnsberg Karolinen-Hospital	Nonacademic	18
St Bernhard-Hospital Kamp-Lintfort	Nonacademic	17
Klinikum Weiden	Nonacademic	17
Kliniken im Naturpark Altmühltal, Klinik Kösching	Nonacademic	16
St Anna Hospital Herne	Nonacademic	16
Krankenhaus der Barmherzigen Brüder Trier	Nonacademic	16
Marienhospital Düsseldorf	Nonacademic	15
Klinikum Dritter Orden München-Nymphenburg	Nonacademic	15
Evangelisches Krankenhaus Bethesda zu Duisburg	Nonacademic	14
Krankenhaus Barmherzige Brüder München	Nonacademic	14
Krankenhaus Porz am Rhein	Nonacademic	13
Klinikum St Georg Leipzig	Nonacademic	13
Asklepios Klinik Lich	Nonacademic	12
Johannes Hospital Dortmund	Nonacademic	11
Universitätsklinikum Schleswig-Holstein Campus Lübeck	Academic	11
Rems-Murr-Klinikum Winnenden	Nonacademic	11
Universitätsklinikum Mannheim	Academic	10
Städtisches Klinikum Braunschweig	Nonacademic	8
Städtisches Krankenhaus Heinsberg	Nonacademic	8
St Agnes hospital Bocholt	Nonacademic	7
Klinikum Darmstadt	Nonacademic	7

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Participating centers	Academic or nonacademic	No. of cases
Helios Dr Horst Schmidt Kliniken Wiesbaden	Nonacademic	7
AMEOS Klinikum am Bürgerpark Bremerhaven	Nonacademic	6
Stadtkrankenhaus Schwabach	Nonacademic	6
Sankt-Gertrauden Krankenhaus Berlin	Nonacademic	5
Stiftungsklinik Weißenhorn	Nonacademic	5
Helios-Klinikum Schleswig	Nonacademic	5
Klinikum Bremen-Ost	Nonacademic	4
Westküstenklinikum Brunsbüttel	Nonacademic	4
FEK - Friedrich-Ebert-Krankenhaus Neumünster	Nonacademic	4
Universitätsklinikum Augsburg	Academic	3
Klinikum Garmisch-Patenkirchen	Nonacademic	3
Klinikum Robert Koch Gehrden	Nonacademic	3
Universitätsklinikum Bergmannsheil Bochum	Academic	2
Malteser Krankenhaus Flensburg	Nonacademic	2
Theresienkrankenhaus Mannheim	Nonacademic	2
Krankenhaus Bad Reichenhall	Nonacademic	1
Klinikum Friedrichshafen	Nonacademic	1
Rotes Kreuz Krankenhaus Kassel	Nonacademic	1
Diakonissenkrankenhaus Mannheim	Nonacademic	1
Asklepiosklinik Langen, Offenbach	Nonacademic	1
Klinikum Stuttgart - Krankenhaus Bad Canstatt	Nonacademic	1
Netherlands		
Amsterdam UMC, location AMC	Academic	103
Leiden University Medical Center	Academic	50
Onze Lieve Vrouwen Gasthuis	Nonacademic	20
Antonius Hospital	Nonacademic	31
University Medical Center Groningen	Academic	23
Isala Clinics	Nonacademic	54
Catharina Hospital	Nonacademic	56
Meander Medical Center	Nonacademic	41
Jeroen Bosch Hospital	Nonacademic	26
Haaglanden Medical Center	Nonacademic	55
Amphia Hospital	Nonacademic	8
Amsterdam UMC, location VUMC	Academic	18
Noordwest Hospital Group	Nonacademic	116
Alrijne Hospital	Nonacademic	13
IJsselland Hospital	Nonacademic	27
Martini Hospital	Nonacademic	20
Nijsmellinge Hospital	Nonacademic	14
Dijklander Hospital	Nonacademic	29
Haga Hospital	Nonacademic	4
Antonie van Leeuwenhoek Hospital	Nonacademic	6

SUPPLEMENTARY TABLE 2. Clinical and endoscopic risk factors for severe AEs

Variables	Procedures without serious AEs (n = 1850)	Procedures with serious AEs (n = 42)	Univariable odds ratio (95% confidence interval)	*P* value	Multivariable odds ratio (95% confidence interval)	*P* value
Female gender	700 (37.8)	27 (64.3)	2.96 (1.58-5.73)	<.001	2.87 (1.52-5.60)	<.001
Mean age, y	68.3	66.1	.98 (.96-1.01)	.19		
No previous endoscopic resection attempt	838 (45.3)	19 (45.2)	1.00 (.54-1.87)	.99		
Indication						
T1 colorectal cancer	683 (36.9)	12 (28.6)	Reference			
Difficult polyp	971 (52.1)	27 (64.3)	1.58 (.81-3.26)	.19		
Subepithelial lesion	106 (5.7)	1 (2.4)	.54 (.03-2.77)	.55		
Diagnostic endoscopic full-thickness resection	15 (.8)	1 (2.4)	3.79 (.20-21.26)	.21		
Other	75 (4.1)	1 (2.4)	.76 (.04-3.93)	.79		
Proximal location	911 (49.2)	25 (59.5)	.66 (.35-1.22)	.19		
Technical issues	113 (6.1)	9 (21.4)	4.19 (1.85-8.62)	<.001	5.50 (2.36-11.82)	<.001
Procedural issues	136 (7.4)	9 (21.4)	3.44 (1.52-7.04)	<.001	3.97 (1.71-8.48)	<.001

Values are n (%) unless otherwise defined.
AE, Adverse event.

SUPPLEMENTARY TABLE 3. Clinical and endoscopic risk factors for delayed perforation

Variables	Procedures without delayed perforation (n = 1872)	Procedures with delayed perforation (n = 20)	Univariable odds ratio (95% confidence interval)	*P* value	Multivariable odds ratio (95% confidence interval)	*P* value
Female gender	714 (38.1)	13 (65.0)	3.01 (1.23-8.05)	.02	2.95 (1.20-7.90)	.02
Mean age, y	68.3	64.3	.97 (.94-1.01)	.09	.97 (.94-1.01)	.12
No previous endoscopic resection attempt	850 (45.4)	7 (35.0)	1.54 (.63-4.13)	.36		
Indication for endoscopic full-thickness resection			*		*	
Proximal location	929 (49.6)	7 (35.0)	1.83 (.75-4.89)	.20		
Technical issues	118 (6.3)	4 (20.0)	3.72 (1.05-10.32)	.02	3.99 (1.12-11.21)	.02
Procedural issues			*		*	

Values are n (%) unless otherwise defined.
*No events in 2 subgroups of this category; therefore, coefficient and corresponding confidence interval are not calculable.

SUPPLEMENTARY TABLE 4. Clinical and endoscopic risk factors for bleeding

Variables	Procedures without bleeding (n = 1779)	Procedures with bleeding (n = 113)*	Univariable odds ratio (95% confidence interval)	*P* value	Multivariable odds ratio (95% confidence interval)	*P* value
Female gender	686 (38.6)	41 (36.3)	.91 (.61-1.34)	.63		
Mean age, y	68.3	68.4	1.00 (.98-1.02)	.89		
No previous endoscopic resection attempt	801 (45.0)	56 (49.6)	.83 (.57-1.22)	.35		
Indication for eFTR						
T1 colorectal cancer	663 (37.3)	32 (28.3)	Reference			
Difficult polyp	932 (52.4)	66 (58.4)	1.47 (.96-2.29)	.08	1.47 (.96-2.30)	.08
Subepithelial lesion	98 (5.5)	9 (8.0)	1.90 (.83-3.95)	.10	1.88 (.82-3.92)	.11
Diagnostic eFTR	13 (.7)	3 (2.7)	4.78 (1.06-15.76)	.02	4.75 (1.05-15.75)	.02
Other	73 (4.1)	3 (2.7)	.85 (.20-2.45)	.79	.81 (.19-2.35)	.74
Proximal location	880 (49.5)	56 (49.6)	1.00 (.68-1.46)	.98		
Technical issues	133 (6.4)	9 (8.0)	1.28 (.59-2.46)	.50		
Procedural issues	143 (8.0)	2 (1.8)	.21 (.03-.66)	.03	.20 (.03-.65)	.03

Values are n (%) unless otherwise defined.
eFTR, Endoscopic full-thickness resection.
*Only 1 bleeding per patient is included in the analysis.