Endoscopic full-thickness resection of T1 colorectal cancers: a retrospective analysis from a multicenter Dutch eFTR registry

Zwager, L.W.; Bastiaansen, B.A.J.; Spek, B.W. van der; Heine, D.N.; Schreuder, R.M.; Perk, L.E.; ... ; Dutch eFTR Grp

Endoscopic full-thickness resection of T1 colorectal cancers: a retrospective analysis from a multicenter Dutch eFTR registry

Authors

Liselotte W. Zwager[*,1], Barbara A. J. Bastiaansen[*,1], Bas W. van der Spek[2], Dimitri N. Heine[2], Ramon M. Schreuder[3], Lars E. Perk[4], Bas L. A. M. Weusten[5], Jurjen J. Boonstra[6], Hedwig van der Sluis[7], Hugo J. Wolters[8], Frank C. Bekkering[9], Svend T. Rietdijk[10], Matthijs P. Schwartz[11], Wouter B. Nagengast[12], W. Rogier ten Hove[13], Jochim S. Terhaar sive Droste[14], Francisco J. Rando Munoz[15], Marije S. Vlug[16], Hanneke Beaumont[17], Martin H. M. G. Houben[18], Tom C. J. Seerden[19], Thomas R. de Wijkerslooth[20], Eric A. R. Gielisse[21], Yark Hazewinkel[22], Rogier de Ridder[23], Jan-Willem A. Straathof[24], Manon van der Vlugt[1], Lianne Koens[25], Paul Fockens[1], Evelien Dekker[1], on behalf of the Dutch eFTR Group

Institutions

1 Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, location AMC, Amsterdam Gastroenterology & Metabolism, University of Amsterdam, Amsterdam, the Netherlands
2 Department of Gastroenterology and Hepatology, Noordwest Hospital Group, Alkmaar, the Netherlands
3 Department of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, the Netherlands
4 Department of Gastroenterology and Hepatology, Haaglanden Medical Center, the Hague, the Netherlands
5 Department of Gastroenterology and Hepatology, St. Antonius Hospital, Nieuwegein, the Netherlands
6 Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, the Netherlands
7 Department of Gastroenterology and Hepatology, Isala Clinics, Zwolle, the Netherlands
8 Department of Gastroenterology and Hepatology, Martini Hospital, Groningen, the Netherlands
9 Department of Gastroenterology and Hepatology, IJsselland Hospital, Capelle aan den IJssel, the Netherlands
10 Department of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands
11 Department of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, the Netherlands
12 Department of Gastroenterology and Hepatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
13 Department of Gastroenterology and Hepatology, Alrijne Medical Group, Leiden, the Netherlands
14 Department of Gastroenterology and Hepatology, Jeroen Bosch Hospital, Den Bosch, the Netherlands
15 Department of Gastroenterology and Hepatology, Nij Smellinghe Hospital, Drachten, the Netherlands
16 Department of Gastroenterology and Hepatology, Dijklander Hospital, Hoorn, the Netherlands
17 Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, location VU, Amsterdam, the Netherlands
18 Department of Gastroenterology and Hepatology, Haga Teaching Hospital, the Hague, the Netherlands
19 Department of Gastroenterology and Hepatology, Amphia Hospital, Breda, the Netherlands
20 Department of Gastroenterology and Hepatology, Antoni van Leeuwenhoek Hospital (NKI /AVL), Amsterdam, the Netherlands
21 Department of Gastroenterology and Hepatology, Rode Kruis Hospital, Beverwijk, the Netherlands
22 Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, the Netherlands
23 Department of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, the Netherlands
24 Department of Gastroenterology and Hepatology, Maxima Medical Center, Eindhoven, the Netherlands
25 Department of Pathology, Amsterdam University Medical Centers, location AMC, University of Amsterdam, Amsterdam, The Netherlands

submitted 2.4.2021
accepted after revision 6.9.2021
published online 6.9.2021

Bibliography
Endoscopy 2022; 54: 475–485
DOI 10.1055/a-1637-9051
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Tables 1 s–4 s
Supplementary material is available under https://doi.org/10.1055/a-1637-9051

[*] Both authors contributed equally to this article

Corresponding author
Barbara Bastiaansen, MD, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, location AMC, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
b.a.bastiaansen@amsterdamumc.nl

ABSTRACT

Background Complete endoscopic resection and accurate histological evaluation for T1 colorectal cancer (CRC) are critical in determining subsequent treatment. Endoscopic full-thickness resection (eFTR) is a new treatment option for T1 CRC < 2 cm. We aimed to report clinical outcomes and short-term results.

Methods Consecutive eFTR procedures for T1 CRC, prospectively recorded in our national registry between November 2015 and April 2020, were retrospectively analyzed. Primary outcomes were technical success and R0 resection. Secondary outcomes were histological risk assessment, curative resection, adverse events, and short-term outcomes.

Results We included 330 procedures: 132 primary resections and 198 secondary scar resections after incomplete T1 CRC resection. Overall technical success, R0 resection, and curative resection rates were 87.0% (95% confidence interval [CI] 82.7%–90.3%), 85.6% (95%CI 81.2%–89.2%), and 60.3% (95%CI 54.7%–65.7%). Curative resection rate was 23.7% (95%CI 15.9%–33.6%) for primary resection of T1 CRC and 60.8% (95%CI 50.4%–70.4%) after excluding deep submucosal invasion as a risk factor. Risk stratification was possible in 99.3%. The severe adverse event rate was 2.2%. Additional oncological surgery was performed in 49/320 (15.3%), with residual cancer in 11/49 (22.4%). Endoscopic follow-up was available in 200/242 (82.6%), with a median of 4 months and residual cancer in 1 (0.5%) following an incomplete resection.

Conclusions eFTR is relatively safe and effective for resection of small T1 CRC, both as primary and secondary treatment. eFTR can expand endoscopic treatment options for T1 CRC and could help to reduce surgical overtreatment. Future studies should focus on long-term outcomes.

Introduction

Implementation of colorectal cancer (CRC) screening programs has led to a significant increase in the detection of T1 CRCs [1, 2]. The risk for lymphatic spread is relatively low in T1 CRC, and management must strike the right balance between cancer cure and minimizing treatment-associated morbidity, mortality, and cost [3, 4]. This ultimate quest has led to implementation of minimally invasive endoscopic treatment methods for T1 CRC supplanting radical surgery in low-risk cases according to international guidelines [5, 6].

For optimal treatment selection, complete endoscopic en bloc resection and precise histopathological risk evaluation for lymph node metastasis (LNM) remain critical [7, 8]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are effective methods of achieving en bloc resection but have their limitations. In EMR, sufficient control over lateral and deep resection margins is considered difficult, especially when deep submucosal invasion is present leading to incomplete lifting. In ESD, excellent control over resection margins can be achieved when superficial submucosal invasion is present, but deeper invasion can compromise radicality. Furthermore, colorectal ESD is considered one of the most technically challenging procedures in the endoscopic arsenal and is not widely used in daily practice [9].

Importantly, the majority of T1 CRC is misdiagnosed as benign before endoscopic resection, and the subsequent diagnosis of cancer is therefore unexpected. As result, inappropriate polypectomy techniques might be used, hampering precise histopathological assessment [10]. Uncertainty about completeness of endoscopic resection of T1 CRC frequently leads to treatment dilemmas in daily practice, especially in the absence of high-risk features for LNM, and guiding evidence is limited [11].

Endoscopic full-thickness resection (eFTR) is a new technique that allows colorectal transmural resection and has attracted attention as a potential valid diagnostic and therapeutic treatment option for T1 CRC. By including the muscularis propria, eFTR can provide an optimal specimen for risk stratification and radical resection, even for cases with deeper submucosal invasion. As secondary treatment, scar excision after previous incomplete resection (R1/Rx) of low-risk T1 CRC could offer an attractive strategy to confirm completeness of the previous resection or, in case of residual cancer, a second chance for radical resection.

Several clinical studies on colorectal eFTR have been published, showing encouraging results in terms of safety and efficacy for various indications, including our first feasibility study [12–18]. However, application of eFTR as a potential diagnostic and therapeutic treatment for T1 CRC is not well studied. Therefore, investigations to gather further insights into clinical applicability are warranted. The aim of this study was to determine the clinical and short-term oncological outcomes of eFTR procedures for T1 CRC.

Methods

Registry and study design

In 2015, the Dutch colorectal eFTR registry was founded at Amsterdam UMC as a secure online database [19]. All eFTR-certified endoscopists are invited to register their consecutive cases. In this registry, data relating to all attempted colorectal eFTR procedures are prospectively recorded. The feasibility results from the first 367 cases with various indications were

published previously [20]. Of these 367 previously published cases, 221 were T1 CRC cases and were included in the current study describing a more in-depth analysis of early CRC [20]. For the current study we retrospectively analyzed all consecutive T1 CRC procedures registered between November 2015 and April 2020. Informed consent was obtained.

As data were collected as part of standard medical care, the Institutional Review Board of Amsterdam UMC regarded the study as being beyond the legalization regarding Medical Research Involving Human Subjects Act and formal ethical approval was therefore not deemed necessary (W16_262#16.308). Our registry is listed in the Dutch Trial Register: NL5868 (http://www.trialregister.nl/).

Study subjects

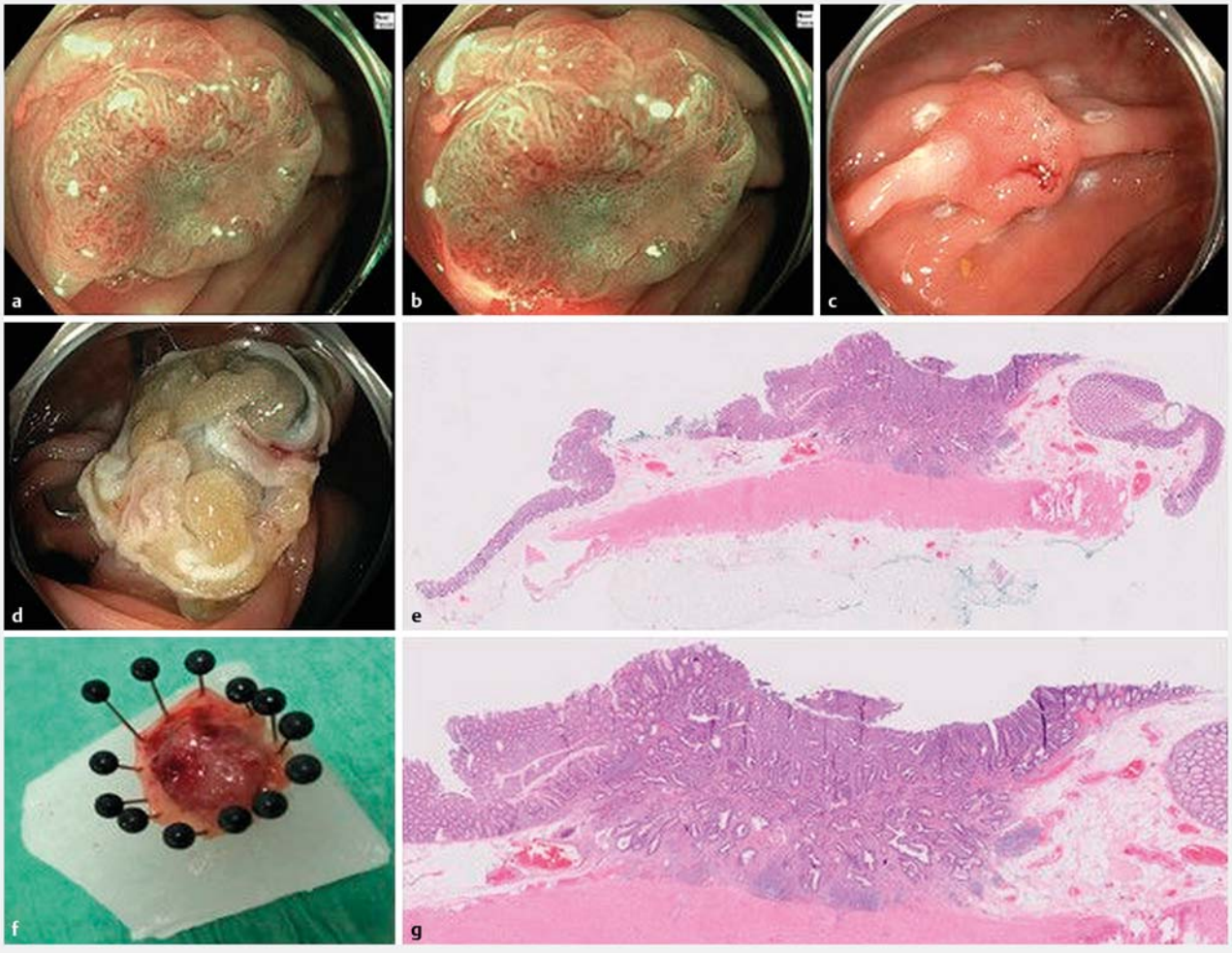
The study included eFTR procedures for one of the following indications.

1. Primary treatment for lesions with an optical diagnosis of T1 CRC.
2. Primary treatment for nonlifting lesions with histology-proven adenocarcinoma.
3. Secondary treatment after previous incomplete endoscopic resection of histology-proven low-risk adenocarcinoma (R1, Rx, or R0 with < 1 mm lateral and/or deep resection margins).

We excluded hybrid procedures (combination of eFTR and other endoscopic resection techniques).

eFTR procedure and management

Patients were treated using the full-thickness resection device (FTRD; Ovesco Endoscopy AG, Tübingen, Germany). For management details, we refer to our previous publication [20]. A representative case is described in ▶ **Fig. 1**.



▶ **Fig. 1** Endoscopic full-thickness resection for an optically suspect T1 colorectal cancer. **a, b** Narrow-band imaging of the target lesion in the ascending colon, with central depression. **c** Endoscopic image of the lesion, marked with the full-thickness resection device marking probe. **d** Full-thickness resection site with the over-the-scope clip in place. **e, g** Histopathology revealing a moderately differentiated adenocarcinoma with deep submucosal invasion (sm 3) invading close to, but not into, the muscularis propria, no lymphovascular invasion or high grade tumor budding. Lateral and deep resection margins clear. **f** The resected specimen pinned onto paraffin.

Study outcomes

Primary outcomes were: 1) technical success, defined as number of macroscopic complete en bloc resections; 2) R0 resection, defined as tumor-free lateral and deep resection margins at histopathology. A macroscopically complete scar resection without histological evidence for residual lesion or cancer was considered as R0.

Secondary outcomes were: 1) possibility of histopathological discrimination between high-risk and low-risk CRC; 2) curative resection rate, defined as an R0 resection without high-risk features in cases of residual cancer; 3) procedure-related adverse events; 4) evidence of luminal recurrence at first follow-up endoscopy; and 5) evidence of residual cancer (luminal or nodal disease) at histopathology of surgical specimen.

High-risk T1 CRC was defined as submucosal invasive cancer with presence of at least one of the following risk factors: poor differentiation, lymphovascular invasion (LVI), deep submucosal invasion (sm2–3), tumor budding grade 2/3, or incomplete resection (tumor-positive deep or lateral resection margins [R1] or indeterminate margins [Rx]). If one of these risk factors was not assessable, lesions were classified as high-risk. In the Dutch guideline, tumor budding is not included as a risk factor, and therefore not routinely assessed and reported [21]; therefore, we included budding as a high-risk factor only when reported.

In addition, we compared high- and low-risk lesions without including sm2–3 invasion as a high-risk factor, based on supportive evidence that sm2–3 is associated with low risk for LNM in the absence of other histological risk factors [22, 23].

Adverse events and follow-up

All procedure-related adverse events that resulted in prolonged admission or re-admission and/or an intervention (i.e. blood transfusion, endoscopy, or surgery) were recorded. Severity of adverse events was graded according to the system of the American Society for Gastrointestinal Endoscopy [24].

Follow-up colonoscopies for scar surveillance with high-definition white-light and/or (digital) chromoendoscopy were scheduled at 3–6 months. Biopsies of the scar were not routinely taken. Patients referred for additional surgery were excluded from scar surveillance.

Statistical analysis

Descriptive statistics were used and reported as mean with standard deviation for continuous and normally distributed variables, as median with interquartile range (IQR) for non-normally distributed continuous variables, and as counts and percentages for categorical variables. Categorical variables were tested using chi-squared or two-sided Fisher's exact tests. A P value of <0.05 was considered statistically significant. As the study was considered exploratory, no correction for multiple testing was done. Statistical analysis was performed using Statistical Package for Social Sciences 26 (SPSS, IBM Corp., Armonk, New York, USA).

▶ **Table 1** Baseline characteristics of patients and procedures.

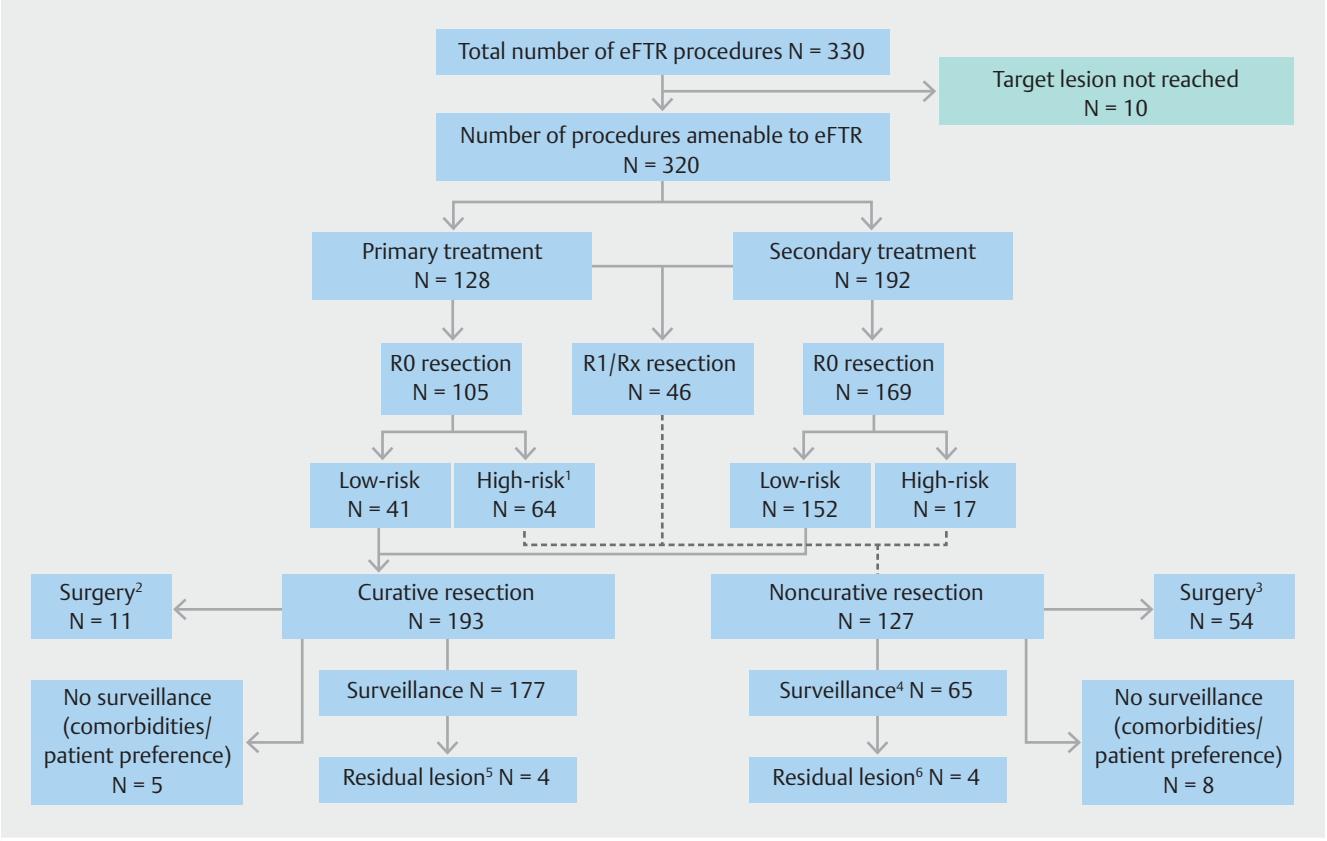
Patients, n	**324**
Male, n (%)	211 (65.1)
Age, median (IQR)	70.0 (62–75)
ASA score, median (IQR)	2 (2–2)
eFTR procedures, n	330
Indication, n (%)	
▪ Primary treatment	132 (40.0)
– Optically suspect T1 CRC	118 (35.8)
– Nonlifting proven adenocarcinoma	14 (4.2)
▪ Secondary treatment after:	198 (60.0)
– R1 resection	67 (20.3)
– Rx resection	103 (31.2)
– R0 < 1 mm resection	28 (8.5)
Lesion size, median diameter (IQR), mm*	
▪ Primary treatment	15 (12–16)
▪ Secondary treatment	10 (7–15)
Lesion location, n (%)	
▪ Proximal (cecum – splenic flexure)	100 (30.3)
– Cecum	17 (5.2)
– Appendix	1 (0.3)
– Ascending colon	38 (11.5)
– Hepatic flexure	14 (4.2)
– Transverse colon	23 (7.0)
– Splenic flexure	7 (2.1)
▪ Distal (descending colon – rectum)	230 (69.7)
– Descending colon	16 (4.8)
– Sigmoid	142 (43.0)
– Rectum	72 (21.8)

IQR, interquartile range; ASA, American Society of Anesthesiologists; eFTR, endoscopic full-thickness resection; CRC, colorectal cancer.
* Lesion size estimated by the endoscopist. Scars not estimated in size or defined as 0 mm were excluded from analysis.

Results

Baseline characteristics

In total, 330 procedures in 324 patients (median age 70 years [IQR 62–75]; 65.1 % male) from 4 academic and 16 nonacademic hospitals were included in the study. Indications were: 1) primary treatment (n = 132), including optically suspect T1 CRC (n = 118) and nonlifting lesions with histology-proven adenocarcinoma (n = 14); 2) secondary treatment (n = 198) after previous R1 (n = 67), Rx (n = 103), or R0 < 1 mm (n = 28) resection. Median estimated lesion size was 15 mm (IQR 12–16) for primary resection and 10 mm (IQR 7–15) for secondary resec-



▶ **Fig. 2** Flowchart of patient outcomes.
[1]A lesion was defined as high risk if one of the following risk factors were present or not assessable: poor differentiation, lymphovascular invasion, sm2–3, tumor budding grade 2 or 3 (if assessed), or a T2 colorectal cancer (CRC).
[2]Surgical resection after curative resection was performed because of a post-procedural complication (n = 6), a synchronous CRC (n = 3), preference for a surgical resection (n = 1), and recurrence of a previously treated CRC (n = 1).
[3]Surgical resection after a noncurative resection was performed for oncological resection (n = 49), post-procedural complication (n = 1), synchronous CRC (n = 1), another polyp that could not be resected endoscopically (n = 1), patient participation in the TESAR trial and receipt of adjuvant chemoradiotherapy (n = 1), and presence of mucin fields (n = 1).
[4]Surveillance after a noncurative procedure was performed for the following reasons: sm2–3 invasion as only risk factor (n = 36), comorbidities and/or patient preference (n = 22), or unknown (n = 7).
[5]Residual lesion after curative resection showed adenoma with low grade dysplasia (n = 3) and a hyperplastic polyp (n = 1).
[6]Residual lesion after a noncurative resection showed adenocarcinoma (n = 1), adenoma with high grade dysplasia (n = 1), and a hyperplastic polyp (n = 2). eFTR, endoscopic full-thickness resection.

tion. Scars not estimated in size or those defined as 0 mm were excluded from the analysis. See ▶ **Table 1** and ▶ **Fig. 2** for patient characteristics and outcomes.

Technical success and R0 resection

Overall technical success was achieved in 287/330 procedures (87.0 %; 95 % confidence interval [CI] 82.7 %–90.3 %). In 10/330 procedures (3.0 %), the target lesion either could not be reached or retracted into the cap. In the remaining 320 procedures amenable to eFTR, histological R0 resection was achieved in 274 (85.6 %; 95 %CI 81.2 %–89.2 %). R0 resection was 80.0 % for lesions >20 mm and 85.9 % for lesions ≤20 mm (P = 0.60). Median diameter of the specimen at histopathology was 24 mm (IQR 20–29) (▶ **Table 2**).

Primary resections (n = 132) achieved technical success in 118/132 (89.4 %; 95 %CI 82.5 %–93.9 %) and R0 resection in 105/128 (82 %; 95 %CI 74.0 %–88.0 %) of eFTR-amenable cases. R0 resection was 95/116 (81.9 %; 95 %CI 73.4 %–88.2 %) for primary suspect T1 CRC and 10/12 (83.3 %; 95 %CI 50.9 %–97.1 %) for nonlifting lesions with adenocarcinoma at histopathology. In the secondary treatment group (n = 198), technical success was reached in 169/198 (85.4 %; 95 %CI 79.5 %–89.8 %) and R0 resection was achieved in 169/192 (88.0 %; 95 %CI 82.4 %–92.1 %) of eFTR-amenable cases. When categorizing all secondary resections in previous R1, Rx, or R0 < 1 mm resections, R0 resection was reached in 54/65 (83.1 %; 95 %CI 71.3 %–90.9 %), 90/100 (90.0 %; 95 %CI 82.0 %–94.8 %), and 25/27 (92.6 %; 95 %CI 74.2 %–98.7 %), respectively.

Curative resection and risk stratification

Overall, curative resection (histological R0 without high-risk features in cases of residual cancer) was reached in 193/320

▶ **Table 2** Technical success and R0 resection.

	Overall	Primary treatment	*Suspect T1 CRC*	*Primary treatment nonlifting lesions*	Secondary treatment	*Re-resection R1*	*Re-resection RX*	*Re-resection R0 < 1 mm*
eFTR procedures[1], n	330	132	118	14	198	67	103	28
▪ Technical success, n (%)	287 (87.0)	118 (89.4)	106 (89.8)	12 (85.7)	169 (85.4)	58 (86.6)	87 (84.5)	24 (85.7)
Procedures amenable to eFTR[2], n	320	128	116	12	192	65	100	27
R0 resection, n (%)								
▪ Per-protocol	274/320 (85.6)	105/128 (82.0)	95/116 (81.9)	10/12 (83.3)	169/192 (88.0)	54/65 (83.1)	90/100 (90.0)	25/27 (92.6)
▪ Intention-to-treat	274/330 (83.0)	105/132 (79.5)	95/118 (80.5)	10/14 (71.4)	169/198 (85.4)	54/67 (80.6)	90/103 (87.4)	25/28 (89.3)
Full-thickness, n (%)								
▪ Per-protocol	258/320 (80.6)	105/128 (82.0)	94/116 (81.0)	11/12 (91.7)	153/192 (79.7)	50/65 (76.9)	81/100 (81.0)	22/27 (81.5)
▪ Intention-to-treat	258/330 (78.2)	105/132 (79.5)	94/118 (79.7)	11/14 (78.6)	153/198 (77.3)	50/67 (74.6)	81/103 (78.6)	22/28 (78.6)
Diameter of resected specimen, median (IQR)[3], mm	24 (20–29)	27 (23–31)	27 (23–32)	27 (23–30)	22 (18–26)	20 (20–25)	22 (18–26)	20 (16–25)
Histology, n (%)								
▪ T1 CRC	112 (35.0)	97 (75.8)	87 (75.0)	10 (83.3)	15 (7.8)	11 (16.9)	4 (4.0)	0 (0)
▪ T2 CRC	23 (7.2)	12 (9.4)	10 (8.6)	2 (16.7)	11 (5.7)	8 (12.3)	3 (3.0)	0 (0)
▪ Scar tissue	151 (47.2)	2 (1.6)[4]	2 (1.7)	0 (0)	149 (77.6)	41 (63.1)	82 (82.0)	26 (96.3)
▪ Adenoma with LGD	15 (4.7)	8 (6.3)	8 (6.9)	0 (0)	7 (3.6)	2 (3.1)	5 (5.0)	0 (0)
▪ Adenoma with HGD	10 (3.1)	6 (4.7)	6 (5.2)	0 (0)	4 (2.1)	0 (0)	4 (4.0)	0 (0)
▪ Sessile serrated lesion	4 (1.3)	2 (1.6)	2 (1.7)	0 (0)	2 (1.0)	0 (0)	1 (1.0)	1 (3.7)
▪ Other[5]	4 (1.3)	1 (0.8)	1 (0.9)	0 (0)	3 (1.6)	2 (3.1)	1 (1.0)	0 (0)
▪ No specimen obtained[6]	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (1.5)	0 (0)	0 (0)

CRC, colorectal cancer; eFTR, endoscopic full-thickness resection; IQR, interquartile range; LGD, low grade dysplasia; HGD, high grade dysplasia.
[1] All initiated eFTR procedures.
[2] All cases in which eFTR was performed (lesions reached and over-the-scope clip deployed).
[3] Size measured at histopathology.
[4] Only normal tissue was found after eFTR because the lesion was not resected completely.
[5] One resected specimen was metastasis of gastric cancer (n = 1), one inflammatory disease (n = 1), one showed presence of mucin fields (n = 1), and one had malignant strictures (n = 1).
[6] No resection specimen was obtained because snare resection could not be performed safely after clip deployment, due to technical difficulty.

procedures (60.3%; 95%CI 54.7%–65.7%). The curative rate was 41/128 (32.0%; 95%CI 24.2%–40.9%) for primary treatment and 152/192 (79.2%; 95%CI 72.6%–84.5%) after secondary treatment (▶ **Table 3**).

Histopathology showed adenocarcinoma in 135 procedures overall, in 109/128 primary resections, and in 26/192 secondary resections. Histological discrimination between high-risk and low-risk lesions was feasible in 134/135 procedures (99.3%; 95%CI 95.3%–99.9%). Prevalence of each histological risk feature is provided in **Table 1 s** (see the online-only Supplementary material).

After primary resection, histology showed adenocarcinoma in 109/128 lesions (85.2%), with T1 CRC in 97/109 (89.0%) and T2 CRC in 12/109 (11.0%). Of all 97 T1 CRCs, 27 (27.8%) had only low-risk features, and curative resection was reached in 23 (23.7%; 95%CI 15.9%–33.6%) (▶ **Table 3**, ▶ **Table 4**). After

▶ **Table 3** Curative resection rate.

	n/N	%	95 %CI
Overall curative resection rate PP[1]	193/320	60.3	54.7–65.7
▪ Overall curative resection rate ITT	193/330	58.5	52.9–63.8
▪ Only lesions with T1 CRC at histology	23/112	20.5	13.7–29.4
▪ When excluding sm2–3 as risk factor[2]	67/112	59.8	50.1–68.8
Curative resection for primary treatment PP	41/128	32.0	24.2–40.9
▪ Curative resection for primary treatment ITT	41/132	31.1	23.5–39.8
▪ Primary treatment (only T1 CRC at histology)	23/97	23.7	15.9–33.6
▪ Primary treatment (excluding sm2–3 as risk factor)	59/97	60.8	50.4–70.4
Curative resection for secondary treatment PP	152/192	79.2	72.5–84.5
▪ Curative resection for secondary treatment ITT	152/198	76.8	70.1–82.3
▪ Secondary treatment (only T1 CRC at histology)	0/15	0	0–5.3
▪ Secondary treatment (excluding sm2–3 as risk factor)	8/15	53.3	27.4–77.7

CI, confidence interval; PP, per protocol; ITT, intention-to-treat; CRC, colorectal cancer; sm2–3: deep submucosal invasion.
[1] A curative resection is defined as a histological R0 resection and, in case of residual cancer, without high-risk features for lymph node metastasis (LNM).
[2] Deep submucosal invasion (sm2-3) excluded as a risk factor for LNM.

excluding sm2–3 invasion as a risk factor, a potential curative resection would be reached in 59/97 cases (60.8 %; 95 %CI 50.4 %–70.4 %). In the subgroup of 116 lesions with optical suspicion of T1 CRC, noninvasive histology was found in 18 (15.5 %).

After secondary treatment, scar tissue was found in 149/192 (77.6 %), T1 CRC in 15/192 (7.8 %), and T2 CRC in 11/192 (5.7 %). None of the residual T1 CRC resections (0/15) was curative by strict definition. However, after excluding sm2–3 invasion as a risk factor, curative resection would be achieved in 8/15 (53.3 %; 95 %CI 27.4 %–77.7 %) (▶ **Table 3**, ▶ **Table 4**).

Safety

Overall, adverse events occurred in 26/320 procedures (8.1 %), including 7 severe events (2.2 %), which were perforations (2 immediate, 5 delayed) (**Table 2 s**). The two immediate perforations were caused by incorrect deployment of the clip before resection; both patients required surgery. All five delayed perforations occurred within 1–8 days post-eFTR and were treated surgically. One case concerned a lesion that was resected in the transverse colon in a patient with poor nutritional status (body mass index 14). In the other four patients, lesions were located in the sigmoid; one patient used immunosuppressive therapy for inflammatory bowel disease. None of these four patients received post-procedural stool softeners. In total, four perforations were treated by surgical suturing and three by oncological sigmoid resection, with no residual cancer apparent on histopathology.

Moderate adverse events were observed in 6/320 procedures (1.9 %). All six were delayed bleeding requiring re-admission and/or repeat endoscopy. A mild adverse event occurred in 13/320 (4.1 %). Four of these events (4/320, 1.3 %) were perforations, two of which were immediately clipped successfully. The other two perforations occurred at Day 2 and Day 3, respectively, and both were located in the sigmoid and treated conservatively with antibiotics.

Surgery and follow-up

Additional surgery was performed in 65/320 patients (20.3 %) (▶ **Table 5**). In 49 patients (15.3 %), surgery involved an oncological resection for presence of one or more high-risk features (n = 13), R1/Rx resection after eFTR (n = 10), combination of both (n = 7), or T2 CRC (n = 19). Histology was available for 47 oncological resections (47/49, 95.9 %). Residual luminal cancer was found in four patients, two of whom had concomitant LNM. In another seven, LNM was found without residual luminal cancer. In all 11 residual cancer cases, previous histology showed either LVI and/or an incomplete resection, and none had sm2/3 invasion as the only risk factor (**Table 3 s**).

Another 73 patients (73/320, 22.8 %) were not scheduled for oncological surgery despite histological presence of one or more high-risk factor(s), T2 CRC (n = 4), and/or incomplete resection; reasons were: sm2–3 invasion as only risk factor (36/73, 49.3 %), comorbidities and/or patient preference (30/73, 41.1 %), or unknown (7/73, 9.6 %).

No follow-up was planned in 13 patients because of severe comorbidity. Endoscopic follow-up was available for 200/242 procedures (82.6 %). Median time to follow-up was 4 months (IQR 3–7). In 42/242 (17.4 %), surveillance was still pending or not recorded.

Residual lesion was found in 8/200 patients (4.0 %), 2 of whom were referred for surgery. One concerned a previous incomplete eFTR (R1) with "at least sm3 invasion." Initial surveillance was chosen for comorbidity reasons. Colonoscopy after 12 months showed residual adenocarcinoma. Final surgical histopathology showed pT3N1M0. In the other patient, scar biopsies 4 months after previous R0 resection for T1 CRC showed

▶ **Table 4** Risk stratification for all procedures with a T1 colorectal cancer at histology.

	Primary treatment (n = 97)	Secondary treatment (n = 15)
Including sm2–3 as risk factor[1], n (%)		
▪ Low-risk	27 (27.8)	3 (20.0)
– R0	23 (85.2)	0 (0)
– R1 or Rx	4 (14.8)	3 (100)
▪ High-risk	69 (71.1)	12 (80.0)
– R0	55 (79.7)	10 (83.3)
– R1 or Rx	14 (20.3)	2 (16.7)
▪ Missing or Rx[2]	1 (1.0)	0 (0)
Excluding sm2–3 as risk factor[3], n (%)		
▪ Low-risk	73 (75.3)	13 (86.7)
– R0	59 (80.8)	8 (61.5)
– R1 or Rx	14 (19.2)	5 (38.5)
▪ High-risk	23 (23.7)	2 (13.3)
– R0	19 (82.6)	2 (100)
– R1 or Rx	4 (17.4)	0 (0)
▪ Missing or Rx[2]	1 (1.0)	0 (0)

sm2–3, deep submucosal invasion.
[1] A lesion was defined as high-risk if one of the following risk factors was present: poor differentiation, lymphovascular invasion, sm2–3, and tumor budding grade 2 or 3.
[2] All risk factors were indeterminate (n = 1).
[3] A lesion was defined as high-risk if one of the following risk factors was present: poor differentiation, lymphovascular invasion, and tumor budding grade 2 or 3.

high grade dysplasia. Surgical histopathology showed high grade dysplasia and tumor-negative nodes. In one patient, a second eFTR was performed because the target lesion was missed initially. Final histology showed an R0 resection with low grade dysplasia. None of the other five residual lesions contained adenocarcinoma at histopathology and were treated endoscopically (**Table 4 s**).

Discussion

This multicenter study investigated outcomes and short-term oncological results of 330 prospectively recorded eFTR procedures for T1 CRC from the Dutch eFTR registry. eFTR was shown to be an effective and relatively safe treatment method, with an overall technical success rate of 87.0 %, R0 resection rate of 85.6 %, and severe adverse event rate of 2.2 %. Accurate histopathological risk assessment was possible in almost all cases, and a curative resection was achieved in 6 out of 10.

Available literature regarding eFTR for T1 CRC is scarce. Most previously reported studies included mainly benign lesions and only a limited number of T1 CRC without detailed histological results [12–18]. Only one retrospective study reported the outcomes of 156 eFTR procedures for T1 CRC, with an overall R0 resection rate of 71.8 % [25]. The higher R0 rate in the current study could be partly explained by different case selection. First, for primary treatment, we mainly included lesions with optical suspicion of T1 CRC, with R0 resection rate of 81.9 %. In contrast, Kuellmer et al. retrospectively included 73 nonlifting lesions that were initially classified as benign but diagnosed as adenocarcinoma at histopathology, suggesting inclusion of possibly more complex lesions, reflected in a significantly lower R0 rate of 60.9 % [25]. Additionally, the difference in R0 resection rate can be explained by the difference in average lesion size. The median size in the Kuellmer et al. study was 20 mm compared with 15 mm in the current study. In contrast to previous studies, our study did not find a significant drop in R0 resection for lesions > 20 mm [12, 25], possibly because of the small number of lesions > 20 mm included in our study. Considering that the average size of the resected specimen was 24 mm, we believe the maximum size for T1 CRC should not exceed 20 mm.

Until recently, oncological surgery constituted the reference standard for early CRC. Over the past decade, endoscopic resection techniques such as EMR and ESD have expanded the therapeutic possibilities for T1 CRC without the need for lymph node dissection. However, EMR is generally not recommended for malignant lesions owing to its insufficient control over resection margins [5, 26]. For ESD, R0 rates of 85.6 % have been reported from expert Asian centers, but the R0 rate drops to 71.3 % if performed in Western countries [27]. It is important to consider, however, that these studies included predominantly benign lesions, and that data on R0 and curative resection for malignant lesions is often lacking. Deeper submucosal invasion hinders adequate lifting, which can complicate safe and complete resection. Furthermore, submucosal dissection can impede the possibility of radical resection in sm2–3 cases, as demonstrated by a recent study showing a significant drop in R0 resection between superficial and deep submucosal invasive cases (97.4 % vs. 64.7 %) [27, 28]. We believe eFTR has potentially strong advantages over ESD. First, eFTR is regarded as being less hazardous and time-consuming. Second, a transmural resection can achieve the necessary radical margins for cases with deeper submucosal invasion, delivering an optimal specimen for assessment [5, 27].

Accurate histopathological evaluation is fundamental for further decision making and imperative for a patient-centered multidisciplinary discussion, considering factors such as age, comorbidity, and patient preference. In this study, discrimination between high-and low-risk lesions was possible in 99.3 %. Kuellmer et al. showed comparable results (99.4 %) [25]. The potential for a safe “excisional biopsy” with optimal histopathology is unique and can be seen as a critical step forward to avoid unnecessary surgery [29].

Several studies have shown that deep submucosal invasion, in the absence of other histological risk factors, is a weak predictor for LNM, with risks around 1.2 %–1.6 % [22, 23]. This limited risk needs to be balanced against mortality (1.7 %) and local recurrence rates (1 %–2 %) of oncological surgery [4, 30]. However, obtaining a radical resection for sm2–3 cancers

▶ **Table 5** Indications for additional surgery after endoscopic full-thickness resection.

	Overall	Primary treatment	Secondary treatment
Total, n	320	128	198
Indications for additional surgery, n (%)	65/320 (20.3)	41/128 (32.0)	24/198 (12.1)
Oncological surgery	49/320 (15.3)	34/128 (26.6)	15/198 (7.6)
R1/Rx resection without high-risk features	10/49 (20.4)	6/34 (17.6)	4/15 (26.7)
▪ *Residual cancer*[1]	2/10 (20.0)	0/6 (0)	2/4 (50.0)
One or more high-risk features	13/49 (26.5)	11/34 (32.4)	2/15 (13.3)
▪ sm2–3 as only present high-risk feature	4/13 (30.8)	4/11 (36.4)	0/0 (0)
▪ *Residual cancer*	0/4 (0)	0/4 (0)	0/0 (0)
▪ LVI (alone or in combination with others)	9/13 (69.2)	7/11 (63.6)	2/2 (100)
▪ *Residual cancer*	2/9 (22.2)	1/7 (14.3)	1/2 (50.0)
Combination of R1 /Rx and high-risk features	7/49 (14.3)	6/34 (17.6)	1/15 (6.7)
▪ *Residual cancer*	1/7 (14.3)	1/6 (16.7)	0/1 (0)
T2 CRC	19/49 (38.8)	11/34 (32.4)	8/15 (53.3)
▪ *Residual cancer*	6/19 (31.6)	3/11 (27.3)	3/8 (37.5)
Surgical management of adverse events	7/320 (2.2)	2/128 (1.6)	5/198 (2.5)
Oncological surgery	3/7 (42.9)	1/2(50.0)	2/5 (40.0)
▪ *Residual cancer*	0 (0)	0 (0)	0 (0)
Perforation closure	4/7 (57.1)	1/2 (50.0)	3/5 (60.0)
Other[2]	9/320 (2.8)	5/128 (3.9)	4/198 (2.0)

sm2–3, deep submucosal invasion; LVI, lymphovascular invasion; CRC, colorectal cancer.
[1] Residual cancer defined as presence of luminal and nodal adenocarcinoma.
[2] Surgical resection was performed for a synchronous CRC (n = 4), a polyp that could not be resected endoscopically (n = 1), preference for a surgical resection (n = 1), a patient who was participating in the TESAR trial and received adjuvant chemoradiotherapy (n = 1), recurrence of a previously treated CRC (n = 1), and presence of mucin fields (n = 1).

would only be justified if it leads to a potential curative resection in a relevant proportion of patients. In our study, the strict curative resection rate for T1 CRC primary resections was 23.7 %. If we exclude sm2–3 as a risk factor, the curative resection rate increases significantly to 60.8 %. As mentioned, these results are difficult to compare with the limited available curative resection rates for ESD in T1 CRC. A recent large multicenter study from Japan reported a strict curative resection rate of 24.8 % [31]. Further study is necessary to determine whether sm2–3 invasion can be disregarded as a risk factor. Meanwhile, patients should be well informed and treated with diligent follow-up, preferably in the context of a research protocol.

Our results showed that 15.5 % of resected lesions with optical suspicion of T1 CRC did not show malignant invasion at final histopathology. One could argue whether eFTR should be considered as overtreatment. However, for a clear distinction between submucosal invasive cancer and high grade dysplasia, pathologists need a well-orientated, high-quality specimen. As reported, endoscopic differentiation between high grade dysplasia or superficial invasive cancer is challenging [10]. The positive predictive value of diagnosing high grade dysplasia or sm1 in Japan NBI Expert Team (JNET) classification type 2B was only 46.3 % [32]. Additionally, in 9.4 % of primary resections, muscle invasion was present. These results highlight the challenges of optical diagnosis in daily practice, both our limitation in discriminating invasive from noninvasive lesions, as well as the inability to discriminate sm2–3 lesions from T2 CRC. However, even a noncurative excisional biopsy can help to estimate the metastatic risk before determining subsequent treatment. This may be particularly helpful for patients at higher surgical risk.

Incomplete endoscopic resection of T1 CRC (R1/Rx) is strongly associated with residual disease and local recurrence, varying between 6 % and 16 % [11, 33]. Therefore, guidelines advise additional oncological surgery, even in the absence of histological risk factors [5, 6]. However, even in the presence of high-risk factors for LNM, residual disease is noted in less than 20 % of patients [11, 33]. Therefore, local scar excision offers an attractive strategy to confirm completeness of the previous resection or a second attempt at radical resection. In this study, histopathology revealed only scar tissue in 77.6 % of secondary resections, confirming local radicality. We recognize that considering complete scar resection without histological evidence for residual lesion as R0 resection might overestimate

our results. However, as it is not straightforward for pathologist to confirm complete scar excision, we must rely on combined clinical and histological assessment. More studies addressing the long-term safety for completion of eFTR are warranted before this strategy can be incorporated safely into treatment algorithms.

None of the resected scars after previous R0 < 1 mm resection showed residual cancer. This indication was discarded during the course of the study, based on observations that histological confirmation of a clear resection margin suffices, regardless of distance [33]. Although most cases with confirmed residual cancer in the scar showed advanced histopathology, eFTR served as a diagnostic strategy to aid further decision making.

Severe adverse events occurred in 2.2 %, with two immediate and five delayed perforations (4/5 left-sided), all requiring immediate surgical repair. This severe adverse event rate is favorable compared with previous studies (3.8 %–4.4 %) [12, 25]. For colorectal ESD, perforation rates of 8.6 % have been reported, with the need for emergency surgery in 3.1 % [34]. Although this indicates the relative safety of eFTR, we hope future perforation rates may decrease further by use of laxatives for left-sided interventions.

Our study has several limitations. First, the study was based on a national registry and we must therefore rely on accurate data collection from all participating centers. Despite all efforts to minimize missing data, not all data or reasons for subsequent treatment were available. Second, only short-term follow-up data were available. Finally, tumor budding is not included as a high-risk factor in the Dutch guideline and is not routinely assessed or reported [21]. Therefore, tumor budding information was missing in 52.3 % of included cases and this could have led to an underestimation of the number of high-risk cases. However, tumor budding generally is believed to reflect the biological aggressiveness of the invasive front and several studies show its presence is often related to other histological risk factors [22, 35].

In conclusion, this large study provides further insight into the clinical applicability and performance of eFTR for T1 CRC in current practice. The relatively high overall R0 resection rates and advantage of delivering optimal histology for risk assessment can help to push the boundaries of traditional treatment paradigms and decrease the overuse of surgery. Further efficacy studies, focussing on long-term oncological results, are needed to establish the definitive role of eFTR in T1 CRC treatment.

Acknowledgment

We thank all participating endoscopists and centers of the eFTR Working Group for their efforts and contributions.

Clinical trial

Trial Registration: Netherlands National Trial Register | Registration number (trial ID): NL5868 | Type of study: Prospective multicenter study

Competing interests

Prof. dr. Fockens reports personal fees from Cook, Ethicon and Olympus, research support from Boston Scientific, outside the submitted work. Prof. dr. Dekker has endoscopic equipment on loan of FujiFilm, received a research grant from FujiFilm, received a honorarium for consultancy from FujiFilm, Olympus, Tillots, GI Supply and CPP-FAP and a speakers' fee from Olympus, Roche and GI Supply. Prof. dr. Weusten received research support from Pentax Medical Inc and Aqua Medical, outside the submitted work. Dr. Bastiaansen received a speakers' fee from Olympus, Tillotts Pharma AG and Ovesco Endoscopy AG. All other authors have nothing to disclose.

References

[1] Reggiani-Bonetti L, Di Gregorio C, Pedroni M et al. Incidence trend of malignant polyps through the data of a specialized colorectal cancer registry: clinical features and effect of screening. Scand J Gastroenterol 2013; 48: 1294–1301

[2] Toes-Zoutendijk E, Kooyker AI, Elferink MA et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. Gut 2018; 67: 1745–1746

[3] Kim JB, Lee HS, Lee HJ et al. Long-term outcomes of endoscopic versus surgical resection of superficial submucosal colorectal cancer. Dig Dis Sci 2015; 60: 2785–2792

[4] Vermeer NCA, Backes Y, Snijders HS et al. National cohort study on postoperative risks after surgery for submucosal invasive colorectal cancer. BJS Open 2019; 3: 210–217

[5] Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2017; 49: 270–297

[6] Shaukat A, Kaltenbach T, Dominitz JA et al. Endoscopic recognition and management strategies for malignant colorectal polyps: recommendations of the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2020; 115: 1751–1767

[7] Beaton C, Twine CP, Williams GL et al. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorectal Dis 2013; 15: 788–797

[8] Ikematsu H, Yoda Y, Matsuda T et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology 2013; 144: 551–559

[9] Arezzo A, Passera R, Marchese N et al. Systematic review and meta-analysis of endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal lesions. United European Gastroenterol J 2016; 4: 18–29

[10] Vleugels JLA, Koens L, Dijkgraaf MGW et al. Suboptimal endoscopic cancer recognition in colorectal lesions in a national bowel screening programme. Gut 2020; 69: 977–980

[11] Butte JM, Tang P, Gonen M et al. Rate of residual disease after complete endoscopic resection of malignant colonic polyp. Dis Colon Rectum 2012; 55: 122–127

[12] Schmidt A, Beyna T, Schumacher B et al. Colonoscopic full-thickness resection using an over-the-scope device: a prospective multicentre study in various indications. Gut 2018; 67: 1280–1289

[13] Velegraki M, Trikola A, Vasiliadis K et al. Endoscopic full-thickness resection of colorectal lesions with the full-thickness resection device: clinical experience from two referral centers in Greece. Ann Gastroenterol 2019; 32: 482–488

[14] Aepli P, Criblez D, Baumeler S et al. Endoscopic full thickness resection (EFTR) of colorectal neoplasms with the Full Thickness Resection Device (FTRD): Clinical experience from two tertiary referral centers in Switzerland. United European Gastroenterol J 2018; 6: 463–470

[15] Valli PV, Mertens J, Bauerfeind P. Safe and successful resection of difficult GI lesions using a novel single-step full-thickness resection device (FTRD(). Surg Endosc 2018; 32: 289–299

[16] Andrisani G, Pizzicannella M, Martino M et al. Endoscopic full-thickness resection of superficial colorectal neoplasms using a new over-the-scope clip system: a single-centre study. Dig Liver Dis 2017; 49: 1009–1013

[17] Vitali F, Naegel A, Siebler J et al. Endoscopic full-thickness resection with an over-the-scope clip device (FTRD) in the colorectum: results from a university tertiary referral center. Endosc Int Open 2018; 6: E98–E103

[18] Meier B, Stritzke B, Kuellmer A et al. Efficacy and safety of endoscopic full-thickness resection in the colorectum: results from the German Colonic FTRD Registry. Am J Gastroenterol 2020; 115: 1998–2006

[19] Castor Electronic Data Capture. Amsterdam: 2019: https://www.castoredc.com Accessed: 2 April 2021

[20] Zwager LW, Bastiaansen BAJ, Bronzwaer MES et al. Endoscopic full-thickness resection (eFTR) of colorectal lesions: results from the Dutch colorectal eFTR registry. Endoscopy 2020: doi:10.1055/a-1176-1107

[21] Dutch Colorectal Cancer Guideline [In Dutch]. 2014: https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html Accessed: 2 April 2021

[22] Yasue C, Chino A, Takamatsu M et al. Pathological risk factors and predictive endoscopic factors for lymph node metastasis of T1 colorectal cancer: a single-center study of 846 lesions. J Gastroenterol 2019; 54: 708–717

[23] Nakadoi K, Tanaka S, Kanao H et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol 2012; 27: 1057–1062

[24] Cotton PB, Eisen GM, Aabakken L et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010; 71: 446–454

[25] Kuellmer A, Mueller J, Caca K et al. Endoscopic full-thickness resection for early colorectal cancer. Gastrointest Endosc 2019; 89: 1180–1189

[26] Hassan C, Repici A, Sharma P et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut 2016; 65: 806–820

[27] Fuccio L, Repici A, Hassan C et al. Why attempt en bloc resection of non-pedunculated colorectal adenomas? A systematic review of the prevalence of superficial submucosal invasive cancer after endoscopic submucosal dissection Gut 2018; 67: 1464–1474

[28] Watanabe D, Toyonaga T, Ooi M et al. Clinical outcomes of deep invasive submucosal colorectal cancer after ESD. Surg Endosc 2018; 32: 2123–2130

[29] Tanaka S, Asayama N, Shigita K et al. Towards safer and appropriate application of endoscopic submucosal dissection for T1 colorectal carcinoma as total excisional biopsy: future perspectives. Dig Endosc 2015; 27: 216–222

[30] Park EY, Baek DH, Lee MW et al. Long-term outcomes of T1 colorectal cancer after endoscopic resection. J Clin Med 2020; 9: 2451

[31] Nishimura T, Oka S, Tanaka S et al. Clinical significance of immunohistochemical lymphovascular evaluation to determine additional surgery after endoscopic submucosal dissection for colorectal T1 carcinoma. Int J Colorectal Dis 2020: doi:10.1007/s00384-020-03795-5

[32] Sumimoto K, Tanaka S, Shigita K et al. Diagnostic performance of Japan NBI Expert Team classification for differentiation among non-invasive, superficially invasive, and deeply invasive colorectal neoplasia. Gastrointest Endosc 2017; 86: 700–709

[33] Richards CH, Ventham NT, Mansouri D et al. An evidence-based treatment algorithm for colorectal polyp cancers: results from the Scottish Screen-detected Polyp Cancer Study (SSPoCS). Gut 2018; 67: 299–306

[34] Fuccio L, Hassan C, Ponchon T et al. Clinical outcomes after endoscopic submucosal dissection for colorectal neoplasia: a systematic review and meta-analysis. Gastrointest Endosc 2017; 86: 74–86

[35] Ohtsuki K, Koyama F, Tamura T et al. Prognostic value of immunohistochemical analysis of tumor budding in colorectal carcinoma. Anticancer Res 2008; 28: 1831–1836