

Long-term oncologic outcomes of endoscopic full-thickness resection after previous incomplete resection of low-risk T1 CRC

LOCAL - study

A national prospective cohort study

Correspondence

Drs. Barbara Bastiaansen, MD

Department of Gastroenterology and Hepatology

Amsterdam University Medical Centers, location AMC

Meibergdreef 9

1105 AZ Amsterdam

The Netherlands

Tel: +31 20 5661746

Fax: +31 20 691 7033

Email: b.a.bastiaansen@amsterdamumc.nl

MAIN STUDY SITE:

Amsterdam University Medical Centers, location AMC

Department of Gastroenterology and Hepatology

Principal Investigators: Prof. Dr. E. Dekker, MD, PhD (e.dekker@amsterdamumc.nl), Prof. Dr. P.

Fockens, MD, PhD (p.fockens@amsterdamumc.nl)

COLLABORATING INSTITUTIONS:

Alrijne Hospital, Leiderdorp, the Netherlands

Department of Gastroenterology and Hepatology

Dr. W.R. ten Hove, MD, PhD (wrtenhove@alrijne.nl)

Albert Schweitzer Hospital, Dordrecht, the Netherlands

Department of Gastroenterology and Hepatology

Dr. W. van de Vrie, MD, PhD (w.vandevrie@asz.nl)

Amphia Hospital, Breda, the Netherlands

Department of Gastroenterology and Hepatology

Dr. T.C.J. Seerden, MD, PhD (tseerden@amphia.nl)

Amsterdam University Medical Centers location AMC, Amsterdam, the Netherlands

Department of Pathology

Dr. A. Farina Sarasqueta, MD, PhD (a.farina@amsterdamumc.nl)

Amsterdam University Medical Centers location AMC, Amsterdam, the Netherlands

Department of Surgery

Dr. R. Hompes, MD, PhD (r.hompes@amsterdamumc.nl)

Antoni van Leeuwenhoek Hospital, the Netherlands

Department of Gastroenterology and Hepatology

Dr. T.D. de Wijkerslooth, MD, PhD (t.d.wijkerslooth@nki.nl)

Catharina Hospital, Eindhoven, the Netherlands

Department of Gastroenterology and Hepatology

Dr. R.M. Schreuder, MD, PhD (ramon.michel@catharinaziekenhuis.nl)

Dijklander Hospital, Hoorn, the Netherlands
Department of Gastroenterology and Hepatology
Drs. M.S. Vlug, MD (m.s.vlug@westfriesgasthuis.nl)

Deventer Hospital, Deventer, the Netherlands
Department of Gastroenterology and Hepatology
Dr. F. ter Borg, MD, PhD (frank2pad@icloud.com)

Flevoziekenhuis, Almere, the Netherlands
Department of Gastroenterology and Hepatology
Dr. M.M. Mundt, MD PhD (MMundt@Flevoziekenhuis.nl)

Gelderse Vallei, Ede, the Netherlands
Department of Gastroenterology and Hepatology
Drs. P.R. Bos, MD (BosP@zgv.nl)

Haaglanden Medical Center, the Hague, the Netherlands
Department of Gastroenterology and Hepatology
Dr. L.E. Perk, MD PhD (l.perk@haaglandenmc.nl)

Haga Hospital, the Hague, the Netherlands
Department of Gastroenterology and Hepatology
Dr. M.H.M.G. Houben, MD, PhD (m.houben@hagaziekenhuis.nl)

Isala Clinics, Zwolle, the Netherlands
Department of Gastroenterology and Hepatology
Drs. H. van der Sluis, MD (h.vandersluis@isala.nl)

IJsselland Hospital, Capelle aan den IJssel, the Netherlands
Department of Gastroenterology and Hepatology
Dr. F.C. Bekkering, MD, PhD (fcbekkering@ysl.nl)

Jeroen Bosch Hospital, Den Bosch, the Netherlands
Department of Gastroenterology and Hepatology

LOCAL study

Dr. J.S. Terhaar sive Droste, MD, PhD (j.terhaar@ibz.nl)

Leiden University Medical Center, Leiden, the Netherlands

Department of Gastroenterology and Hepatology

Dr. J.J. Boonstra, MD, PhD (j.j.boonstra@lumc.nl)

Leiden University Medical Center, Leiden, the Netherlands

Department of Surgery

Dr. K.C.M.J. Peeters, MD, PhD (k.c.m.j.peeters@lumc.nl)

Maastricht University Medical Center, Maastricht, the Netherlands

Department of Gastroenterology and Hepatology

Drs. R.J.J. de Ridder, MD (r.de.ridder@mumc.nl)

Martini Hospital, Groningen, the Netherlands

Department of Gastroenterology and Hepatology

Drs. H.J. Wolters, MD (h.j.wolters@mzh.nl)

Maxima Medical Center, Veldhoven, the Netherlands

Department of Gastroenterology and Hepatology

Dr. J.W.A Straathof, MD, PhD (j.straathof@mmc.nl)

Meander Medical Center, Amersfoort, the Netherlands

Department of Gastroenterology and Hepatology

Dr. M.P. Schwartz, MD, PhD (mp.schwartz@meandermc.nl)

Nij Smellinghe, Drachten, the Netherlands

Department of Gastroenterology and Hepatology

Drs. F.J. Rando Muñoz, MD (F.RandoMunoz@nijsmellinghe.nl)

Noordwest Hospital Group, Alkmaar, the Netherlands

Department of Gastroenterology and Hepatology

Drs. B.W. van der Spek, MD (b.w.vander.spek@nwz.nl)

OLVG, Amsterdam, the Netherlands

LOCAL study

Department of Gastroenterology and Hepatology

Dr. S.T. Rietdijk, MD, PhD (s.t.rietdijk@olvg.nl)

Radboud University Medical Center, Nijmegen, the Netherlands

Department of Gastroenterology and Hepatology

Drs. G.J. Bulte, MD, PhD (geert.bulte@radboudumc.nl)

Reinier de Graaf Hospital, Delft, the Netherlands

Department of Gastroenterology and Hepatology

Drs. R. Quispel, MD (R.Quispel@rdgg.nl)

Rode Kruis Hospital, Beverwijk, the Netherlands

Department of Gastroenterology and Hepatology

Drs. E. Gielisse, MD (egielisse@rkz.nl)

St. Antonius Hospital, Nieuwegein, the Netherlands

Department of Gastroenterology and Hepatology

Prof. dr. B.L.A.M. Weusten, MD, PhD (b.weusten@antoniusziekenhuis.nl)

University Medical Center Groningen, Groningen, the Netherlands

Department of Gastroenterology and Hepatology

Prof. dr. W.B. Nagengast, MD, PhD (w.b.nagengast@umcg.nl)

University Medical Center Utrecht, Utrecht, the Netherlands

Department of Gastroenterology and Hepatology

Dr. L.M.G. Moons, MD, PhD (l.m.g.moons@umcutrecht.nl)

University Medical Center Utrecht, Utrecht, the Netherlands

Department of Pathology

Dr. M.M. Lacle, MD, PhD (m.m.lacle@umcutrecht.nl)

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Coordinating investigator:	drs. B.A.J. Bastiaansen, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers location AMC, the Netherlands Room C2-207, telephone: +31 20 56 61746 Email: b.a.bastiaansen@amsterdamumc.nl Dr. L.M.G. Moons University Medical Center Utrecht, Utrecht, the Netherlands Department of Gastroenterology and Hepatology Email: l.m.g.moons@umcutrecht.nl drs. S.C. Albers, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers location AMC, the Netherlands Room C2-231, telephone: +31 610461558 Email: s.c.albers@amsterdamumc.nl
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Prof. dr. E. Dekker, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers location AMC, Amsterdam, the Netherlands Room C2-115, telephone: +31 20 56 66867 Email: e.dekker@amsterdamumc.nl Prof. dr. P. Fockens, Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers location AMC, Amsterdam, the Netherlands Email: p.fockens@amsterdamumc.nl

Participating Centers:

<Multicenter research: per site>

1. Albert Schweitzer Hospital, Dordrecht
2. Alrijne Hospital, Leiderdorp
3. Antoni van Leeuwenhoek Hospital, Amsterdam
4. Amphia, Breda
5. Catharina Hospital, Eindhoven
6. Deventer Hospital, Deventer
7. Dijklander Hospital, Hoorn
8. Flevoziekenhuis, Almere
9. Gelderse Vallei, Ede
10. Haaglanden Medical Center, the Hague
11. Haga Medical Center, the Hague
12. IJsselland Hospital, Capelle aan den IJssel
13. Isala Clinics, Zwolle
14. Jeroen Bosch Hospital, 's Hertogenbosch
15. Leids University Medical Center, Leiden
16. Maastricht University Medical Center, Maastricht
17. Martini Hospital, Groningen
18. Maxima Medical Center, Veldhoven
19. Meander Medical Center, Amersfoort
20. Nij Smellinghe, Drachten
21. Noordwest Hospital Group, Alkmaar
22. OLVG, Amsterdam
23. Radboud University Medical Center, Nijmegen
24. Reinier de Graaf Hospital, Delft
25. Rode Kruis Hospital, Beverwijk
26. St. Antonius, Nieuwegein
27. University Medical Center Groningen, Groningen
28. University Medical Center Utrecht, Utrecht

Sponsor	Amsterdam University Medical Centers, location AMC
Laboratory sites	Not applicable
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	Adverse Event
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CRC	Colorectal Cancer
DSMB	Data Safety Monitoring Board
eFTR	endoscopic Full-Thickness Resection
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic Submucosal Dissection
FTRD	Full-thickness Resection Device
GCP	Good Clinical Practice
IC	Informed Consent
LNM	Lymph Node Metastasis
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
R0	Tumor-free lateral and basal resection margins
R1	Positive resection margins
Rx	Indeterminate resection margins
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Endoscopic resection is an attractive treatment for early colorectal cancer (CRC) due to substantially lower morbidity and mortality rates as compared to radical surgery. Complete endoscopic polypectomy in one piece (*en bloc*) can be considered a curative treatment for T1 CRC without histological high-risk features for lymphatic spread. In contrast, incomplete excision with unclear resection margins (R1 resection) or with margins that are indeterminate (Rx resection) is considered a high-risk factor for residual disease and local recurrence. Therefore international guidelines recommend additional oncologic resection in case of R1/Rx resections, even in the absence of histological high-risk features. Recent introduction of minimally invasive local treatment options, as endoscopic full-thickness resection (eFTR), can serve as a valid alternative treatment option to perform a second attempt for radical *en bloc* resection of low-risk T1 CRC or to confirm local radicality of the previous resection. At present, completion treatment with eFTR after previous incomplete resection of low-risk T1 CRC has already been adopted in some practices in the Netherlands. However, oncologic safety of this strategy has not been established and long-term data are lacking. Besides, at present surveillance following completing eFTR varies widely in practice and require standardization.

Objective: This project aims to investigate the feasibility and oncological safety of eFTR as minimal invasive completion treatment after previous (potentially) incomplete endoscopic resection (Rx/R1) of low-risk T1 CRCs.

Study design: a nationwide, multicenter, prospective cohort study.

Study population: Patients scheduled to undergo additional scar resection by eFTR following a previous (potentially) incomplete resection (Rx/R1) of T1 CRC in the Netherlands.

Main study parameters/endpoints: Primary endpoint is to assess the 2- and 5-year local luminal tumor recurrence rate after eFTR completion treatment following previous (potentially) incomplete excised (Rx/R1) low-risk T1 CRC. Secondary study endpoints are to assess the feasibility of completion eFTR, defined as a macroscopic complete *en bloc* scar resection in > 80% of cases, the percentage of curative eFTR resections, defined as no residual cancer in the scar or in case of any residual cancer a histological R0 resection of T1 CRC without one or more high-risk features (poor differentiation, lymphatic or vascular invasion, tumor budding), the presence of scar tissue and complete scar excision at histopathology, the procedure-related adverse event rate and safety of eFTR compared to oncological surgical resection, the 2- and 5-year nodal and/or distant tumor recurrence rate and the 5-year disease-specific survival rate and overall survival rate.

Nature and extent of the burden and risks associated with participation, benefit and group

relatedness: Positive polypectomy margin status is associated with residual disease in the colon wall, but not with LNM. Current guidelines advise therefore secondary radical surgical resection for T1

CRCs with incomplete resection margins, even in the absence of other unfavourable histological factors. A segmental resection serves to clear the patient of the risk of residual tumor but carries significant inherent morbidity and mortality. The fact that the majority of patients (> 80%) has no evidence of residual disease on histological evaluation of their surgical specimens suggests a substantial overtreatment, especially for those without histological high-risk features for lymphatic spread. eFTR is a relatively new technique that allows complete *en bloc* resection of the previous resection site/scar to determine the local completeness of the previous resection, potentially avoiding unnecessary surgical risks.

At present completion treatment with eFTR after previous (potentially) incomplete resection (Rx/R1) of low-risk T1 CRC has been already adopted in some practices in the Netherlands. However, the oncologic safety of this strategy has not been established and long-term data are lacking. Besides, at present no standard surveillance protocol exists following completion eFTR and surveillance varies widely in practice.

1. INTRODUCTION AND RATIONALE

The implementation of colorectal cancer (CRC) screening programs worldwide has led to a significant increase in the early detection of CRCs. (1-5) “Polyp cancers” or T1 CRCs are defined as tumors with invasion through the muscularis mucosa that extend into the submucosal space without invading the muscularis propria. These lesions have a limited risk for lymph node metastasis (LNM), varying between 1-16% depending on histopathological risk features. (6-9) Therefore, endoscopic resection can be a potential curative and attractive treatment option compared to surgical resection because of its low morbidity and mortality rates and substantially lower costs. (10-13)

After endoscopic treatment of T1 CRCs, the decision between endoscopic surveillance alone or to proceed with additional oncologic surgical resection depends on the presence of histopathological risk factors for local recurrence and LNM. (14) Previous studies have shown that the risk of local recurrence and LNM is very low in the absence of the following high-risk features: poor differentiation, lymphatic or vascular invasion, deep submucosal invasion ($\geq 1000 \mu\text{m}$), high-grade tumor budding (grade 2 or 3) and a positive resection margin (R1/Rx resection). (6, 7, 9, 15-17) If one of these high-risk features is present, patients are currently counselled for subsequent oncological surgical resection according to current guidelines.(18, 19)

Positive polypectomy margin status (i.e. a positive resection margin $< 0.1 \text{ mm}$ (R1) or an uncertain or indeterminate resection margin (Rx)) is a strong risk factor for residual disease in the colon wall and local recurrence. (6, 20-22) Current guidelines therefore advise additional oncological surgical resection in patients with average surgical risk, even in the absence of unfavourable histological factors for LNM. (17, 23) However, even in the presence of high-risk factors for LNM, residual disease is noted in less than 20% of patients undergoing surgery and therefore an additional surgical resection can be considered potential overtreatment, especially in patients without increased risk for LNM. (6, 20, 21)

In clinical practice, decision-making regarding the risk-benefit balance between the morbidity and mortality of surgery and the risk of residual cancer in the bowel wall when additional surgery is omitted remains a considerable challenge. The underlying evidence for current guidelines is often poor and knowledge regarding the long-term outcomes of patients surveyed endoscopically is lacking. (6, 14, 24)

Despite the apparent overtreatment for patients who undergo additional surgery after endoscopic resection of low-risk T1 CRC, a number of patients are at risk for having residual cancer with associated possibility for lymphatic spread when no additional treatment is performed. Among the small group of patients in whom no additional surgery was performed and who developed recurrent cancer, 41.7% died as result. (14)

At the time of endoscopic resection, the endoscopist is often unaware that the polyp is malignant. As a result, inappropriate polypectomy techniques might be used, such as piecemeal endoscopic mucosal resection (pEMR) or regular polypectomy without submucosal lifting which hampers histologic assessment leading to uncertainty about the completeness of excision. Previous studies show that piecemeal resection is an independent risk factor for incomplete resection and the risk for residual cancer is reported up to 30%, when the completeness of excision cannot be confirmed at histopathology (either close or involved tumor resection margins) (14, 25) Besides, previous piecemeal resection or snare polypectomy can hamper adequate histological assessment of other histological risk factors. Therefore, one could argue if a R1/Rx resection status should be seen as a potential risk factor for LNM, since certain high-risk factors can be missed. To achieve definite histopathological confirmation about completeness of excision, or in case of remaining cancer within the bowel wall, a second attempt at radical *en bloc* resection and additional endoscopic *en bloc* resection of the previous resection scar might be an attractive strategy.

Until recently, no safe endoscopic *en bloc* re-resection technique was available for the re-resection of scar tissue or non-lifting, previous resected lesions. The introduction of Endoscopic full-thickness resection (eFTR) has changed the therapeutic endoscopic field for colorectal lesion not amenable to conventional resection techniques. The full-thickness resection device (FTRD, Ovesco Endoscopy, Tübingen, Germany) has been approved in Europe (Conformité Européenne mark) for colorectal resection since September 2014. Several clinical studies have shown that eFTR is feasible, efficacious and safe in the treatment of non-lifting lesions, submucosal tumors and early carcinomas. (26-29) The full-thickness resection device (FTRD) is a pre-assembled over-the-scope device designed for one-step transmural colonic resection. The device consists of a modified over-the-scope clip (OTSC) mounted on a long cap with a preloaded monofilament snare. Colon tissue can be pulled into the cap in order to create a full-thickness duplication of the colonic wall. Once the OTSC is deployed, the created pseudo-polyp can be resected using the pre-loaded snare, while the OTSC secures the integrity of the colonic wall. This eFTR-technique allows a transmural local excision of the scar and therefore can potentially serve as a valid option for curative completion treatment after incomplete excision of T1 CRC, avoiding unnecessary surgical risks. Scar excision helps to exclude residual cancer

at the resection site or enables a second attempt for radical *en bloc* resection in case of residual cancer found within the scar. (30-35)

In clinical practice, eFTR is currently used as a standard tool to perform a second attempt for radical resection of T1 CRCs with previous incomplete resection margins (26, 28, 36). In a multicenter study of 229 T1 CRCs, no local tumor recurrence was found at first endoscopic follow-up of 3 months after eFTR. (Zwager, L. prospective eFTR study, manuscript in preparation) Further, a recent meta-analysis of additional local excision after incomplete polypectomy of low-risk T1 rectal cancer supports these findings. Only 1% of patients developed a local recurrence after a median follow-up of 47 months (range 11-109). (37) This suggests a low rate of local tumor recurrence after eFTR. However, supporting evidence for long-term oncologic safety is lacking and currently there is no standard surveillance protocol for this subgroup. To regulate surveillance for this group of patients in the Netherlands, the Dutch T1 working group recently designed a strict follow-up schedule (“richtsnoer T1 CRC”) for the surveillance of T1 CRCs after re-resection of incomplete resection margins (manuscript in preparation). This strict follow up schedule has the intention to detect local recurrence and/or distant metastases at an early stage to allow potential curative salvage treatment. Furthermore, with this strict surveillance schedule we hope to be able to determine the most appropriate surveillance schedule for these patients in the future. Therefore, prospective studies are needed to clarify the role of additional eFTR in the treatment of T1 CRCs, the long-term outcomes in current clinical practice and to determine the most appropriate surveillance schedule after this additional treatment. In this prospective observational multicenter study we aim to investigate the local luminal tumor recurrence 2 and 5 years after eFTR for T1 CRCs with incomplete resection margins in current clinical practice in the Netherlands.

OBJECTIVES

2.1 Primary Objective:

Primary objective:

To assess the 2- and 5- year local luminal tumor recurrence rate after scar resection by eFTR following a previous (potentially) incomplete resection (Rx/R1) of low-risk T1 CRC.

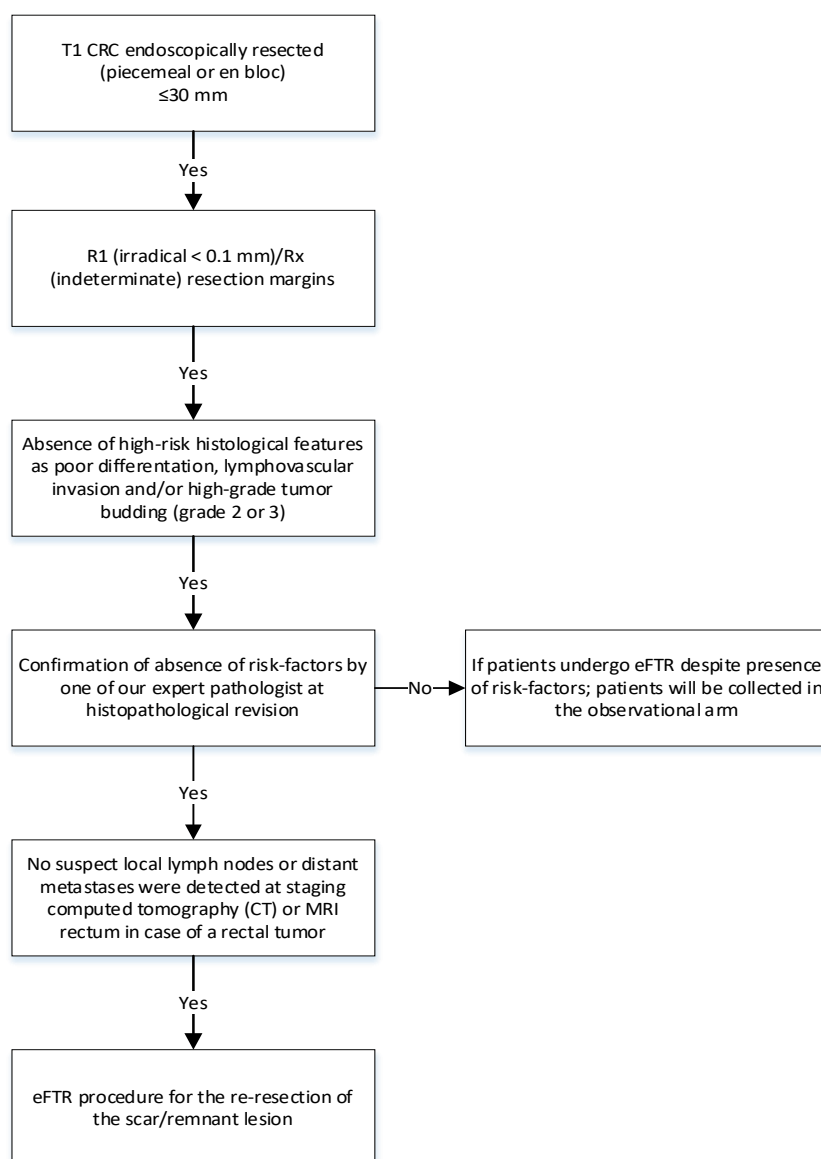
Secondary objective(s):

1. To assess the feasibility of completion eFTR, defined as a macroscopic complete *en bloc* scar excision in >80% of cases
2. To assess the percentage of curative eFTR resections, defined as no residual cancer in the scar or in case any residual cancer a R0 resection for T1 CRC without high-risk features (poor differentiation, lymphovascular invasion and/or high-grade tumor budding (grade 2 or 3))
3. To assess the presence of scar tissue and/or complete scar excision at histopathology
4. To assess the procedure-related adverse event rate and safety of eFTR compared to oncologic surgery in a historical patient-cohort for T1 CRC
5. To assess the 2- and 5- year locoregional nodal and/or distant tumor recurrence rate
6. To assess the 5-year disease-specific survival rate and overall survival rate
7. To assess the 2- and 5-year luminal, nodal and distant tumor recurrence rate in patients not meeting our inclusion criteria, but who did undergo eFTR completion treatment followed by strict surveillance and are included in our observational arm

3. STUDY DESIGN

This project aims to investigate the feasibility and oncological safety of eFTR as minimal invasive completion treatment following previous (potentially) incomplete endoscopic resection (Rx/R1) of low-risk T1 CRC. Patients living in the Netherlands referred for an eFTR procedure for the re-resection of a T1 CRC with positive resection margins < 0.1 mm (R1) or indeterminate margins (Rx) and without the presence of high-risk features for LNM are eligible for participation in this prospective cohort study. Patients will be followed by protocolized surveillance during 5 years.

Figure 1: study design



3.1 Population (base)

Eligible patients scheduled to undergo additional scar resection by eFTR following a previous incomplete resection of T1 CRC in the Netherlands.

3.2 Inclusion criteria

Patients meeting all of the following criteria will be invited for participation in the study:

- Recent polypectomy/(p)EMR/ESD of T1 CRC without the following histological high-risk features*:
 - Poor differentiation
 - Lymphovascular invasion
 - Tumor budding grade 2/3
- This recent polypectomy/(p)EMR/ESD for T1 CRC resulted in positive resection margins < 0.1mm (R1) or indeterminate resection margins (Rx)
- The resection scar after polypectomy/EMR/ESD is clearly recognized at endoscopy, either by a tattoo or by detecting a scar in the colonic segment where no other polypectomies were performed
- The diameter of the original lesion was ≤ 30 mm
- The diameter of the scar and/or residual lesion ≤ 15 mm
- The interval between index polypectomy/EMR and additional eFTR is at most 12 weeks
- Staging computed tomography (CT) of thorax and abdomen is performed and no local lymph node or distant metastases are detected. In case of rectal location an additional magnetic resonance imaging (MRI) of the pelvis is performed and no local suspicious lymph node(s) detected. If the target lesion is visible on MRI, rectal location is defined as location distal from the sigmoid take off. If not visible on MRI, rectal location is defined as < 15 cm from anal verge on endoscopy.
- Written informed consent is provided

*Before inclusion in this study, eligible histology needs to be centrally revised by an expert gastrointestinal pathologist (either Dr. M. Lacle University Medical Center Utrecht or Dr. A. Farina Sarasqueta Amsterdam UMC). In case of any doubt on the presence of high-risk features, both expert pathologist will have a case discussion in order to make a statement on either the presence of these risk features or the indetermination of those.

3.3 Exclusion criteria

Patients meeting any of the following criteria will be excluded from participation in this study:

- If lymphovascular invasion and/or tumor budding grade 2/3 cannot be assessed after prior polypectomy/(p)EMR, patients are **NOT** eligible for inclusion
- The patient is known with at least one of the following conditions:
 - o Active inflammatory bowel disease (IBD) in the colon
 - o Synchronous advanced CRC (defined as CRC in the 5 years before detection of T1 CRC, or elsewhere in the colorectum at the time of detection of T1 CRC)
- Index lesion located < 5 cm of the anal verge or with involvement of the valvula Bauhini or appendiceal orifice
- Age < 18 years
- Pregnancy

3.4 Observational arm

Patients who will undergo a completion eFTR after incomplete excised T1 CRC (after multidisciplinary team discussion) despite being non eligible for study participation, will be prospectively followed in our study database (after informed consent). Furthermore, outcome data of all non-eligible patients (eg because of the presence of high-risk features or the interdetermination of those) will be collected in case no eFTR is performed.

3.5 Sample size calculation

Up-to-date, no literature is available with regard to local luminal recurrence rates after endoscopic incomplete resection of T1 CRC (R1/Rx resections) for low-risk T1 CRC (thus without high-risk features for LNM). However, a local recurrence rate of 1% (1/102) during almost four years of follow-up is observed after minimally invasive transanal surgery. (37) This estimate is uncertain and the upper limit of its 95% one-sided confidence limit may extend to 4.6%. With already being frequently used in daily practice and considering that the follow-up duration in the current study will be five years (instead of four), we opt to qualify eFTR as unsafe if the upper 95% one-sided confidence limit of its related local recurrence rate after five years extends beyond 6.6%.

A single sample size of 137 patients will have at least 86% power to detect this non-inferiority limit of 6.6% using a one-sided exact test with a significance level of 0.05 for maximum actually observed local recurrence rates of 2% over five years (twice the possibly underestimated local recurrence rate over four years of 1% for minimally invasive surgical treatment).

To correct for potential drop-out patients in whom the primary outcome cannot be assessed the sample size will be adjusted to 153 (potential drop-out rate of 10%). These drop-out cases are patients with indication for additional surgery when histopathology review reveals high-risk features

(i.e. poor differentiation grade, lymphovascular invasion and/or high-grade tumor budding) for LNM or eFTR is technically impossible.

If during 5 years of follow up, more than 5 local luminal recurrences are observed -which implies that the upper limit of the confidence interval will exceed the non-inferiority limit- our study fails to establish oncological safety for completion endoscopic full-thickness resection after previous incomplete resection of low-risk T1 CRC.

4. TREATMENT OF SUBJECTS

4.1 Baseline examinations

At baseline, patients had undergone a polypectomy/EMR/ESD procedure for a T1 CRC with positive resection margins < 0.1mm (R1) or indeterminate resection margins (Rx).

To ensure that only patients with low-risk T1 CRC, i.e. without histological high-risk factors for LNM, will be included, all original specimens will be centrally revised by one of two expert gastrointestinal pathologists (dr. M. Lacle (UMC Utrecht) and dr. A. Farina Sarasqueta (Amsterdam UMC)). In principle, additional immunohistochemical staining will only be used by our expert pathologists when H&E slides show suspicion for LVI that needs further evaluation. The expert pathologist will review the slide within 5 working days. Afterwards, all slides will return to the original laboratories. In case of doubt on the presence of one or more histological high-risk features, the other expert pathologist will be consulted in order to make a statement on either the presence of these risk features or the indetermination of those. In case no consensus can be reached, a third expert pathologist will be consulted.

Furthermore, a staging CT thorax-abdomen or X-thorax and CT abdomen is performed. In case of a rectal lesion an additional magnetic resonance imaging (MRI) of the pelvis is performed. If the target lesion is visible on MRI, rectal location is defined as location distal from the sigmoid take off. If not visible on MRI, rectal location is defined as < 15 cm from anal verge on endoscopy. In addition, Carcinoembryonic Antigen (CEA) will be assessed.

4.2 eFTR procedure

4.2.1 Management of anti-coagulant use of the patient

Anticoagulant use in the study will be managed according to local protocols or the national NVMDL guideline 2016 “Beleid antitrombotische therapie rondom endoscopische procedures” during endoscopic procedures.

4.2.2 Endoscopists, procedures and periprocedural management

All participating endoscopists are trained in ex vivo porcine models to perform eFTR procedures and are certified to perform eFTR procedures in the Netherlands. All endoscopists have extensive colonoscopy (≥ 1000 procedures) experience.

All patients will receive standard bowel preparation, which includes oral intake of a split-dose PEG-solution and bisacodyl in accordance with the standard bowel preparation protocol of the

participating center. Procedures will be performed under deep sedation with propofol administered by a certified anesthesiology nurse or under conscious sedation by a combination of intravenous midazolam and fentanyl at the discretion of the endoscopist. During the procedure no standard prophylactic antibiotic therapy is advised, unless this is standard local policy in a participating center or in case there is a specific indication at discretion of the endoscopist. (25) The time interval between the index polypectomy/EMR and the performed eFTR procedure has a maximum duration of 12 weeks. Before the start of the eFTR procedure the target lesion will be identified with a standard colonoscope using both HD white light endoscopy (WLE) and narrow band imaging (NBI), blue laser imaging (BLI) or other digital chromoendoscopy. Endoscopists preferably take a minimum of three photos of the target lesion. The lateral margins of the target lesions can be marked by the use of coagulation with the marking probe (Ovesco Endoscopy, Tübingen, Germany) at the discretion of the endoscopist. Hereafter the colonoscope will be extracted from the patient and the FTRD will be mounted onto the colonoscope. The colonoscope with the mounted FTRD will be reintroduced and advanced to the target lesion. Then the lesion will be resected as showed in Figure 1, whereafter the colonoscope will be withdrawn with the resection specimen in the cap. After collection of the specimen the FTRD will be removed and the colonoscope will be re-introduced to inspect the resection site. After the procedure, patients will be discharged to the discretion of the local endoscopist/protocol. A normal diet will usually be started at postoperative day one.

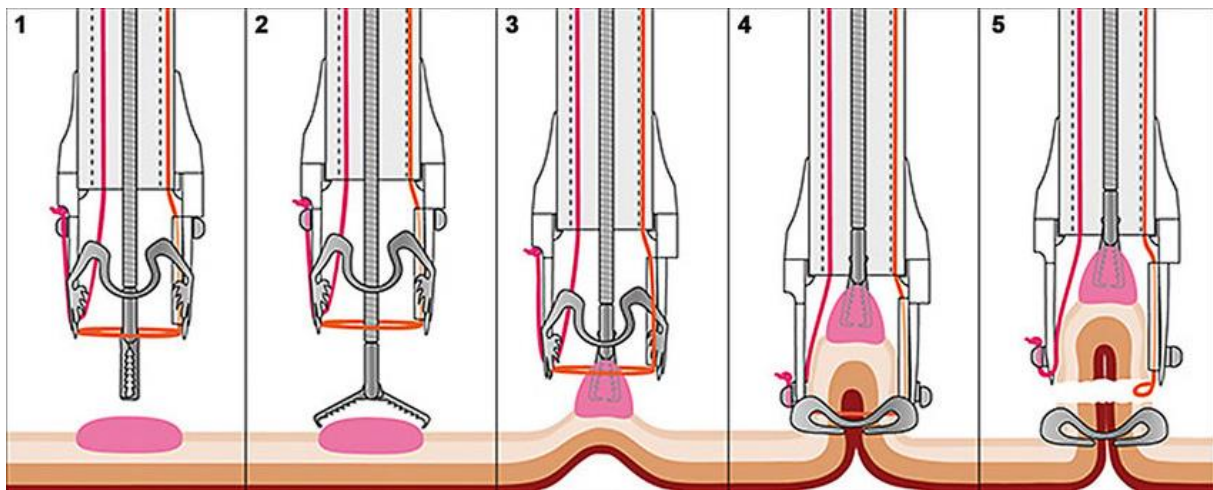


Figure 1. Schematic illustration of the resection procedure (www.ovesco.com).

4.2.3 Histopathology handling

The resection specimen is stretched and pinned down on paraffin before immersed into formalin. Histopathological analysis is performed by a gastrointestinal pathologist according to daily clinical practice. In case of presence of residual adenocarcinoma confirmation of a histological R0 resection

and all histological features will be assessed (differentiation grade, depth of invasion, lymphovascular invasion and tumor budding (grade 2 or 3)).

In case of presence of normal colonic wall/scar tissue, the pathologist will assess the presence of reactive changes compatible with presence of scar tissue in the specimen. Definite histopathological confirmation of resection of the complete scar is known to be difficult to assess for pathologists and might not always be technically possible. In case the pathologist is not able to histologically confirm a complete scar resection, further treatment will be based on the macroscopic completeness of scar excision and patients will be followed according to protocol.

In addition, central review of all resected eFTR specimen to confirm the presence of scar tissue and to further evaluate completeness of scar excision will be performed at once after all patients are included in the study. The central review will be performed by two independent expert gastrointestinal pathologists (Dr. M. Lacle University Medical Center Utrecht and Dr. A. Farina Sarasqueta Amsterdam UMC). In cases without consensus, meetings will be organized to discuss discrepancies to reach consensus. In case no consensus can be reached, a third expert pathologist (Dr. L. Koens (Amsterdam UMC)) will be consulted.

H&E slides of all resected eFTR specimens will be collected from the different laboratories and digitalized at the Amsterdam UMC for review. After digitalizing the slides will return to the laboratories to ensure the completeness of pathology archives and optimal patient care.

In case of residual cancer, histological high-risk features for LNM could be found after central revision. These patients will be at higher risk for local recurrences and therefore excluded from our primary analysis. In case of unexpected findings, the treating physician will be informed to discuss further treatment options with the patients after colorectal MDT discussion. Outcomes of these cases will be recorded in the study database.

4.3 Follow-up

In case the scar contains residual cancer with high-risk features and/or incomplete eFTR (Rx/R1 resection), the case should be discussed in a colorectal MDT for further treatment options depending on histological and endoscopic findings. The same accounts for cases in which completion eFTR of the scar was technically impossible. The outcomes, subsequent treatment and further follow-up procedures of these cases will be recorded in the study database.

The Dutch T1 CRC working group recently designed a strict surveillance schedule for patients with high-risk T1 CRC who refrain from oncological resection for personal preference reasons or comorbidity (“Richtsnoer T1 CRC”, manuscript in preparation). This strict surveillance intends to detect a potential tumor recurrence at early stage to allow for curative salvage treatment. Furthermore, with this strict surveillance schedule we hope to determine the most appropriate surveillance schedule for these patients in the future. In this prospective cohort study, the follow-up schedule is in line with the upcoming Dutch “richtsnoer T1 CRC”.

4.4.1. Endoscopic follow-up

Endoscopic surveillance for lesions located in the colon will be performed by yearly eFTR scar checks at 12, 24, 36, 48 and 60 months. In patients with rectal T1 cancer endoscopic surveillance of the eFTR scar will be performed every 6 months during the first two years followed by yearly scar checks at 36, 48 and 60 months. According to the Dutch guideline, scar checks will be combined with a full colonoscopy at 12 months and 48 months for CRC surveillance. (23) The eFTR scar will be thoroughly inspected with HD WLE and (digital) chromoendoscopy. Endoscopists preferably take a minimum of three photos of the target lesion. Scar biopsies (3 biopsies) will be taken at every surveillance, also without signs of macroscopic recurrence. Endoscopic and histological findings compatible with granulation tissue or reactive changes can be left untreated. Recurrent/residual low-grade dysplastic adenoma or a sessile serrated lesion can be treated endoscopically with conventional treatment strategies. When endoscopic removal of the residual tissue is deemed impossible, when high-grade dysplasia or submucosal invasive cancer is found, a tattoo (SPOT) should be placed followed by case discussion in a colorectal MDT.

Local luminal tumor recurrence is defined as the presence of any adenocarcinoma at the site of the eFTR scar at follow-up colonoscopy. Further follow-up colonoscopies will be scheduled individually depending on histology and endoscopic findings and by the local protocol in the participating centers.

4.4.2. Radiological follow-up

For patients with a tumor located in the colon, a standard protocol CT thorax-abdomen will be performed yearly after the eFTR procedure at 12, 24, 36, 48 and 60 months to evaluate nodal and/or distant tumor recurrence. For rectal location, an MRI of the rectum will be performed every 6 months during the first 2 years after the eFTR procedure followed by yearly MRI scans at 36, 48 and 60 months. Results of our prospective eFTR registry showed the OTSC (clip) in situ after eFTR in only 10.9% after 4 months of follow-up. In the rare cases where the clip could possibly hamper scar

assessment or quality of radiologic follow-up, the OTSC can be removed with a dedicated cutting device. In case of suspected local, nodal and/or distant tumor recurrence the patient will be discussed in a multidisciplinary team meeting in the participating hospital to discuss further treatment options according to local clinical practice, which is based on the Dutch CRC guideline. (23)

4.4.2. Other follow-up

Surveillance with Carcinoembryonic Antigen (CEA) detection in serum will be performed every 6 months for 5 years after the performed eFTR procedure.

4.5 Observational arm

Patients who will undergo a completion eFTR after incomplete excised T1 CRC (after multidisciplinary team discussion) despite being non eligible for study participation, will be prospectively followed in our study database (after informed consent). Furthermore, outcome data of all non-eligible patients (eg because of the presence of high-risk features or the interdetermination of those) will be collected in case no eFTR is performed.

5. METHODS

5.1 Study parameters/endpoints

5.1.2 Main study parameter/endpoint

To assess the 2- and 5- year local luminal tumor recurrence rate after scar resection by eFTR following a previous (potentially) incomplete resection (Rx/R1) of low-risk T1 CRC.

5.1.3 Secondary study parameters/endpoints (if applicable)

1. To assess the feasibility of completion eFTR, defined as a macroscopic complete *en bloc* scar excision in >80% of cases.
2. To assess the percentage of curative eFTR resections, defined as no residual cancer in the scar or in case any residual cancer a R0 resection for T1 CRC without high-risk features (poor differentiation, lymphovascular invasion and/or high-grade tumor budding (grade 2 or 3)).
3. To assess the presence of scar tissue and/or complete scar excision at histopathology
4. To assess the procedure-related adverse event rate and safety of eFTR compared to oncologic surgery in a historical patient-cohort for T1 CRC
5. To assess the 2- and 5- year locoregional nodal and/or distant tumor recurrence rate
6. To assess the 5-year disease-specific survival rate and overall survival rate
7. To assess the 2- and 5-year luminal, nodal and distant tumor recurrence rate in patients not meeting our inclusion criteria, but who did undergo eFTR completion treatment followed by strict surveillance and are included in our observational arm

5.1.4 Other study parameters

Patient characteristics

- Age
- Gender
- Pregnancy
- Comorbidity according to the American Association of Anesthesiology (ASA classification)
- Anticoagulant or antiplatelet therapy
- CRC related history
 - Synchronous advanced CRC (defined as CRC in the 5 years before detection of T1 CRC, or elsewhere in the colorectum at the time of detection of T1 CRC)
- Active IBD
- Positive family history for CRC or polyposis

Endoscopic history

- Indication of the index colonoscopy
- Date
- Estimated size of lesion before the primary resection
- Tattoo
- Resection method to remove the lesion at the initial colonoscopy (polypectomy, EMR or ESD)
- Estimated size of lesion before the primary resection
- Optical suspicion of submucosal invasion
- *En bloc* or piecemeal resection
- Macroscopic *en bloc* resection
- Indication eFTR; positive margins < 0.1mm (R1) or intermediate margins (Rx)
- Histological features of the index lesion if assessable (differentiation grade, depth of invasion, lymphovascular invasion and grade of tumor budding)

Staging CT thorax-abdomen, or MRI of the rectum if applicable and/or CEA

- Date
- No evidence of locoregional and/or metastatic disease at CT thorax-abdomen, CT abdomen and/or X-thorax and MRI rectum if applicable
 - Other findings
- CEA level

eFTR procedural characteristics

- Date
- Institute of performing eFTR procedure
- Type of sedation
- Tumor location (rectum, sigmoid, descending colon, splenic flexure, transverse colon, hepatic flexure, ascending colon, cecum, ileocecal valve)
- Estimated diameter scar and/or residual lesion
- Scar recognized
- FTRD loaded
- PROVE cap used
- Marking of the lesion
- Lesion reached
- Endoscopic radical *en bloc* resection
- Technical success of the procedure

- Intraprocedural complications associated with eFTR for which transfusion, hospitalization (unscheduled post procedural admission) and additional (endoscopic, surgical, radiologic) treatment is needed
- Unscheduled post procedural admission
- Duration unscheduled post procedural admission

Pathological assessment after eFTR

- Histopathological diagnosis
- In case of residual adenocarcinoma:
 - Histological features if assessable (differentiation grade, depth of invasion, lymphovascular invasion and grade of tumor budding)
 - Size of residual adenocarcinoma in mm
- R0 resection (tumor-free lateral and deep resection margins)
- Full-thickness resection (m. propria present in resected specimen)
- Diameter resection specimen in mm

Complications after eFTR

- Complications associated with eFTR for which transfusion, hospitalization (unscheduled post procedural admission) and additional (endoscopic, surgical, radiologic) treatment is needed
- Intraprocedural or postprocedural complication
- Type of complication
- Treatment after complication

In case of performed surgery after eFTR

- Indication surgery: histological high-risk features, incomplete resection, adverse events or unsuccessful performed eFTR.
- Type of surgical treatment
- Complications after surgery (until 30 days)

Pathology after performed surgery

- Tumor present
- Histopathological diagnosis
- In case of residual adenocarcinoma:
 - o Histological features if assessable (differentiation grade, depth of invasion, lymphatic and/or vascular invasion or tumor budding)

LOCAL study

- TNM classification version 8
- Tumor-free resection margin

Endoscopic follow-up during 5 years

- Date
- Institute of performing eFTR procedure
- Scar recognized
- OTSC clip presence at the resection site during follow-up
- Macroscopic residual or recurring tissue present at the resection site
- Estimated size of macroscopic residual/recurring tissue (mm)
- Macroscopic aspect of residual/recurring tissue
- Treatment of the residual tissue
- Type of residual/recurring tissue
- Macroscopic radical resection of additional treatment
- In case of no residual/recurring tissue, 3 biopsies of the scar will be taken
 - o Pathology of biopsies

Pathology after endoscopic follow-up

- Histopathological diagnosis of biopsies
- Histopathological diagnosis after additional treatment in case of residual/recurrent lesion
- In case of residual adenocarcinoma:
 - o Histological features if assessable (differentiation grade, depth of invasion, lymphatic and/ or vascular invasion or tumor budding)
 - o R0 resection (tumor-free lateral and deep margins)

Radiologic follow-up during 5 years

- Date
- Radiologic diagnosis of locoregional and/or metastatic disease and if present;
 - o Luminal
 - o Locoregional lymph nodes
 - o Metastatic disease

Other follow-up during 5 years

- Date
- CEA level

Revision of histopathology

- Presence of scar tissue and/ or complete scar excision
- In case of residual adenocarcinoma:
 - Histopathological diagnosis
 - Histological features if assessable (differentiation grade, depth of invasion, lymphovascular invasion and tumor budding)
 - R0 resection (tumor-free lateral and deep margins)
 - Full-thickness resection (m. propria present in resected specimen)

5.2 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Already collected data will not be deleted and may be used in analysis if appropriate.

6. STATISTICAL ANALYSIS

For our primary analysis all performed eFTR procedures in patients in whom the primary outcome (luminal local tumor recurrence rate after scar resection) can be assessed will be included. Thus patients in whom the procedure could not be performed for technical reasons or needing additional surgery due to the presence of high-risk features following completion eFTR will not be included for primary analysis.

For secondary analysis regarding feasibility of completion eFTR all included eligible patients will be analysed irrespective of the received completion eFTR or performed additional surgery.

Descriptive statistics will be used to describe patient, colonoscopy and eFTR characteristics. Variables will be reported as mean with standard deviation in case of continuous and normally distributed variables, as median with an interquartile range (IQR) in case of non-normally distributed continuous variables, and as percentages in case of count or categorical variables. We will use logistic regression with baseline variables to identify predictors for a successful completion eFTR.

The confidence interval of the 5 year disease-specific survival rate and overall survival rate will be calculated. Kaplan-Meier analysis will be used to estimate survival over time.

6.1 Primary study parameter(s)

Primary outcome measure as described in section 5.1.2

6.2 Secondary study parameter(s)

The secondary outcome measures as described in section 5.1.3

6.3 Interim analysis

No interim analysis is planned.

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (59th version, October 2008) and since this is a study in which we follow subjects in current clinical practice, patients neither are subjected to any other additional procedures nor will be imposed to any rules of behaviour; therefore, the investigators believe that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study.

7.2 Recruitment and consent

eFTR for the re-resection of Rx/R1 low risk T1 CRCs is currently offered to patients as an alternative to surgery in clinical practice. After case discussion in a colorectal MDT, recruitment for the study will be performed by gastroenterologists, gastroenterology fellows or research nurses in the participating centers. Eligible patients will be informed about the study aims, the prospective data collection, the eFTR procedure and follow up procedures and will receive an informed consent form. Patients will hand in the signed informed consent forms to the local gastroenterologists, gastroenterology fellows, research nurses or other member of the study team in the participating centers. Patients will be given as much time as needed to make an informed decision regarding participation. We also intend to include patients in retrospect. If baseline staging procedures were not performed, but surveillance procedures according to this study protocol showed no signs of local recurrences or LNM at time of inclusion patients are eligible for inclusion.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.1 Handling and storage of data and documents

Patients will be coded by a numeric code (pseudonymised) and only the local investigators and project leader will be the ones to have access to this code. The code lists will be stored digitally on the protected hard disc at the local center that included and treated the subject. The patient data will be recorded in an online secured database (Castor, CIWIT BV, Amsterdam). All study investigators at each study site will have access to the online database of their own site and will be able to insert data. The source data will be kept by the project leader for 15 years. Patient data will be retrieved from the endoscopy, surgical and pathology reports of the participating center by the local and/or coordinating investigators.

8.2 Public disclosure and publication policy

Following completion of the study, we intend to report the data from the entire study or from subsets of the study at a scientific meeting and publish in a scientific journal.

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