

Prospective Registration of endoscopic Full Thickness Resection in the Netherlands

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1. INTRODUCTION AND RATIONALE

Colorectal adenomas and sessile serrated adenomas are the well-known precursor lesions of colorectal cancer. [1, 2] Colonoscopic polypectomy of these lesions reduces colorectal cancer incidence and mortality. [3, 4] The majority (>90%) of all colorectal polyps are small or pedunculated and are therefore easily removed during colonoscopy. Large sessile or non-polypoid polyps are less prevalent (5%) but have the tendency to reach an enormous size and harbor a great frequency of high-grade dysplasia and early invasive disease. [5, 6] Traditionally these large (≥ 20 mm) non-pedunculated colorectal polyps have been managed with surgical resection (SR). [7, 8] Over the last decade endoscopic resection (ER) techniques, such as piecemeal endoscopic mucosal resection (pEMR) of these polyps, has progressed significantly. An increasing body of evidence suggests that many lesions currently referred for surgery are amendable to endoscopic treatment in experienced hands. In these experienced hands over 90% all large non-pedunculated colorectal polyps can be removed by ER, avoiding surgery related costs, adverse events and mortality in these patients. [9-12]

However, pEMR is associated with a local recurrence rate up to 16%, requiring surveillance colonoscopies in these patients and the piecemeal removal of the lesion results in the retrieval of poorer quality histological samples and therefore it is often not possible to evaluate the completeness of resection, depth of invasion, lateral resection margins and other prognostic features in the case of malignant progression. [12-16] Additionally, there are limitations in the technical ability to completely resect certain colorectal lesions during colonoscopy. Risk factors for the technical inability of complete polypectomy are a lesion size larger than 40 mm, a flat morphology or lesions located at the ileocecal valve, appendiceal orifice, dentate line, involving a diverticulum or within an inflamed segment of colitis. [17] Another major complicating factor is the so called non-lifting sign, which can occur due to submucosal invasion or after a prior failed attempt of endoscopic removal or in case of local recurrence in the previous resection site due to submucosal scarring and fibrosis. [17-19]

In order to overcome some technical challenges of the endoscopic removal of complex colorectal lesions a novel endoscopic device is developed to perform endoscopic full-thickness resection (eFTR) in primary or secondary non-lifting lesions, colorectal lesions at difficult anatomic locations or invasive early carcinomas. This Full-Thickness resection device (FTRD by Ovesco Endoscopy, Tübingen, Germany) consists of a modified over-the-scope clip (OTSC) mounted on a long cap with a preloaded snare. This device has been investigated in preclinical trials and moreover a recent clinical case series demonstrated successful resection of 25 colorectal lesions. [20-25] However more clinical research is needed to further investigate the clinical applicability, technical success rates and safety of performing eFTR with the FTRD. Therefore we will perform a prospective registration of scheduled eFTR procedures with the FTRD in the Netherlands to further investigate the applicability, technical success rates and safety of this device.

2. OBJECTIVES

Primary objective:

We aim to study the applicability, safety and technical success of all scheduled eFTR procedures in the Netherlands.

Secondary objectives:

This study also aims to investigate the technical success of all scheduled eFTR procedures in the Netherlands by studying the number of endoscopic complete en bloc resections and the number of histologically confirmed R0 and full-thickness resection. The applicability and safety of all scheduled eFTR procedures will be studied when investigating the number of scheduled eFTR procedures that were not completely performed, procedural time, complication rates and the occurrence of local recurrence during surveillance colonoscopies.

3. STUDY DESIGN

This is a prospective registration of all eFTR procedures in the Netherlands. Therefore we will include all patients who are scheduled for an eFTR procedure with the FTRD device performed by one of the trained endoscopists in performing eFTR.

3.1 Study population

3.1.1 Population

We will prospectively include all patients who are scheduled to undergo an eFTR procedure with the FTRD performed by one of the trained endoscopists in the Netherlands.

3.1.2 Inclusion criteria

In order to be eligible to be included in this study a patient must meet all of the following criteria:

- Scheduled to undergo eFTR procedure with the FTRD performed by one of the trained endoscopists in performing FTRD procedures in the Netherlands
- Provided written informed consent

3.1.3 Exclusion criteria

There are no formal exclusion criteria since the indication for a full thickness resection of all patients was already set by a trained endoscopist in the Netherlands.

4. METHODS

4.1 Study parameters/endpoints

4.1.1 Main study parameter/endpoint

Our main study endpoint is the technical success rate of all scheduled eFTR procedures with the FTRD defined as the number of patients with a complete endoscopic en bloc resection in the Netherlands.

4.1.2 Secondary study parameters/endpoints

The following secondary study parameters are designed to further study the technical success, the applicability and the safety of all eFTR procedures in the Netherlands;

- The number of patients with histologically confirmed R0 resection defined as negative lateral and deep margins
- The number of patients with a histologically confirmed full thickness resection (m. propria present in the resection specimen)
- The number of eFTR procedures in which the procedure was not technical succesfull, due to the inability to reach the lesion, the inability to retract all the tissue in the FTRD and technical difficulties with the FTRD
- Number of intra procedural complications, defined as any perforation or a bleeding for which an additional intervention, defined as transfusion, admission, radiologic intervention or surgical treatment is required
- Number of patients with early (48 hours) and late (until 14 days) postprocedural complications for which additional treatment is necessary, defined as presentation at the emergency ward, transfusion, admission, repeat endoscopy, radiologic intervention or surgical treatment
- The occurrence of recurrence during follow-up colonoscopies
- Procedural time (total procedural time and time for the eFTR procedure)

4.2 Study procedures

4.2.1. Patient recruitment

All eligible patients according to the inclusion criteria described above will be asked to participate in the study. The recruitment for the study will be done by the local gastroenterologists, gastroenterology fellows or the research nurses in the participating centers.

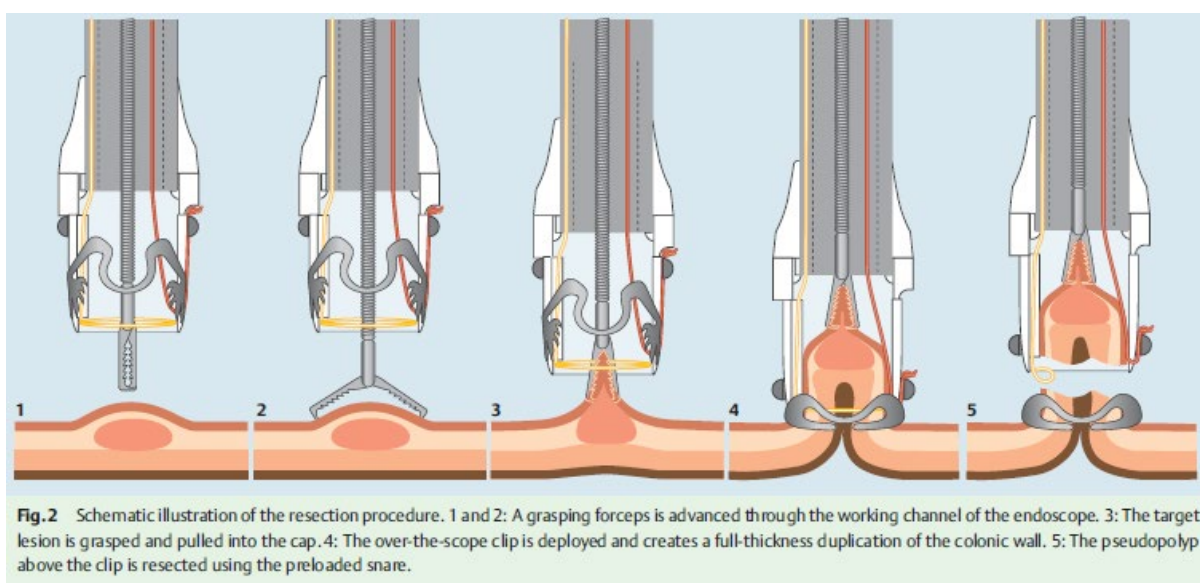
The eligible patient will be informed about the study aims and the prospective data collection associated to the eFTR procedure. After a reasonable period (approximately a week after the first telephone call) the patient is contacted again to find out if the patient is willing to participate in the trial. On the day of the colonoscopy the patients will sign the informed consent form in the presence the local gastroenterologists, gastroenterology fellows or the research nurses in the participating centers.

4.2.2. Description of the device

The FTRD (Ovesco Endoscopy, Tübingen, Germany) is a pre-assembled over-the-scope device consisting of a transparent cap with a modified 14-mm OTSC. The FTRD is mounted over a standard colonoscope. The transparent cap has an inner diameter of 13 mm and a length of 23 mm (measured from the tip of the endoscope). A monofilament 14-mm polypectomy snare is preloaded onto the tip of the cap. The snare is not advanced through the working channel but rather runs along the outer surface of the endoscope under a plastic sheath. This sheath is fixed onto the cap and pulled over the scope shaft after mounting the cap. The device had a Conformité Européenne (CE) mark and is commercially available in Europe. [20]

4.2.3. Resection technique of eFTR

The endoscope with the mounted FTRD is introduced into the colon and the target lesion is identified. A grasping forceps or a tissue anchor (Ovesco Endoscopy) is advanced through the working channel of the endoscope to grasp the lesion. The lesion is slowly pulled into the cap in order to capture a double full-thickness layer of the colonic wall. With the lateral margins of the lesions pulled into the cap, the OTSC is deployed. The pseudopolyp created by the OTSC is then resected using the pre-loaded snare while the OTSC secures integrity of the colonic wall. [20]



Schematic illustration of the resection procedure [20]

4.2.4. Endoscopists, Procedures and periprocedural management

All participating endoscopists are trained in an ex vivo porcine model to perform eFTR procedures and are therefore accredited to perform eFTR procedures in the Netherlands.

All patients will receive standard bowel preparation, which includes oral intake of a split-dose PEG-solution and Bisacodyl according to the standard bowel preparation protocol of the participating center. Procedures will be performed under non-conscious sedation with propofol administered by a (fellow) anesthesiologist or under conscious sedation by a combination of intravenous midazolam and fentanyl at the discretion of the endoscopist and the patient. During the procedure patients will receive prophylactic antibiotic therapy according to the local protocol in each participating center. The advised antibiotic treatment consists of one peri-procedural gift of metronidazole and cefalozin.

Prior to the eFTR procedure the target lesion will be identified with a standard colonoscope and the target lesions could be marked using coagulation with the attached marking probe (Ovesco Endoscopy, Tübingen, Germany) or by a mucosal biopsy at the discretion of the endoscopist. Thereafter 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 into the patient and advanced to the target lesion. Thereafter the lesion will be resected as described above, whereafter the colonoscope will be removed with the resection specimen in the cap. The FTRD will be removed from the colonoscope and the colonoscope will be re-introduced to inspect the resection site.

After the procedure patients will be hospitalized or discharged according to the local protocol in the participating centers and the discretion of the endoscopists. The advised regimen is to hospitalize patients for at least 24 hours on clear fluids to closely monitor for clinical signs of bleeding and perforation. A normal diet will usually be started at postoperative day 1.

4.2.5. Follow-up

Patients will be scheduled for a first colonoscopic follow-up 6 months after resection. Further follow-ups will be scheduled individually depending on histology and endoscopic findings and by the local protocol in the participating centers.

4.2.6. Data collection

Each participating gastroenterologist received personal codes to register the data into an online database provided by CastorEDC, Amsterdam, the Netherlands. No identifiable data will be registered in the online database, since every included patient will receive a study code.

The following data will be collected during the data search and entered in the database:

Patient characteristics:

- Age
- Gender
- ASA score
- Anticoagulant use
- NSAID use

Clinical data:

Endoscopy history and lesion characteristics:

- Indication of the colonoscopy that identified the lesion treated with eFTR
- Number of colonoscopies to assess this lesion before eFTR
- (Number of) Attempts of removing the polyp endoscopically before eFTR
- Date of the eFTR procedure
- Estimated lesion size
- Lesion location (rectal, sigmoid, descending colon, splenic flexure, transverse colon, hepatic flexure, ascending colon, cecum, cecal valve)
- Lesion morphology (pedunculated, sessile, laterally spreading)
- Macroscopic appearance (Adenomatous, sessile serrated adenoma/polyp, hyperplastic, malignant?)

eFTR procedural characteristics:

- Indication of the eFTR procedure
- Date
- Performing endoscopist
- Used sedation
- Marked the lesion
- Reached the target lesion with eFTR
- Retracted the complete target lesion into the FTRD
- Performed eFTR
- Antibiotic prophylaxis given
- Complications associated with eFTR wherefore transfusion, hospitalization and additional (endoscopic, surgical, radiologic) treatment is needed
- Post-procedural admission
- Follow-up advice for further treatment given

Pathological data:

- Assessing the resection preparation:
 - o Diameter resection specimen
 - o Diameter resected lesion
 - o Type of pathology
 - o Type of dysplasia
 - o R0 resection
 - o Full-thickness resection

Follow-up colonoscopy

- Date
- Performing endoscopist
- OTSC present at the resection site
- Residual or recurring tissue present at the resection site
- Treatment of the residual or recurring tissue
- Complications associated with follow-up colonoscopy wherefore transfusion, hospitalization and additional (endoscopic, surgical, radiologic) treatment is needed
- Post-procedural admission
- Follow-up advice for further treatment given

5. STATISTICAL ANALYSIS

Normal distributed data will be described with the mean and the standard deviation, and data with a skewed distribution will be described using the median and the interquartile range. Student's t-test, Mann-Whitney U test and Kruskal-Wallis test are used to compare quantitative variables. This will be used to compare the distribution of continuous variables by outcome. Pearsons Chi Square or Fisher's exact test is used for categorical variables to test for association between categorical variables and outcome. Logistic regression will be performed to identify associated factors with performed surgical treatment for benign colorectal polyps. P-values are 2-sided and a $P < 0.05$ is considered as statistically significant.

6. ETHICAL CONSIDERATIONS

6.1 Regulation statement

The study protocol was presented to the Medical Ethics Review Committee of the Academic Medical Center. They decided that formal revision was not required, as in agreement with the Medical Research Involving Human Subjects Act (WMO), because patient data were retrieved during standard care and no additional interventions were performed for the sake of this study. Separate approval of the study in all participating centers was received and participating endoscopists provided written informed consent as they were regarded the study subjects. All contributing authors had access to the study data after the study period and reviewed and approved the final manuscript. The study was carried out in accordance with the declaration of Helsinki. [26]

6.2 Recruitment and consent

All eligible patients according to the inclusion criteria described above will be asked to participate in the study. The recruitment for the study will be done by the local gastroenterologists, gastroenterology fellows or the research nurses in the participating centers.

The eligible patient will be informed about the study aims and the prospective data collection associated to the eFTR procedure. After a reasonable period (approximately a week after the first telephone call) the patient is contacted again to find out if the patient is willing to participate in the trial. On the day of the colonoscopy the patients will sign the informed consent form in the presence of the local gastroenterologists, gastroenterology fellows or the research nurses in the participating centers.

6.3 Benefits and risks assessment

Since this is a prospective registry of all scheduled eFTR procedures in the Netherlands with only systematic data collection, no extra risks exist for the included patients.

7. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

7.1 Handling and storage of data and documents

The data of the subjects are coded in order of participation in an online database by CastorEDC (Amsterdam, the Netherlands). Qualified authorities can get insight in code and data, but only when accompanied by the investigators. Data will be stored 15 years after closure of the trial.

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