- The MATILDA study -

Multicenter, randomised controlled trial comparing endoscopic **M**ucosal resection (EMR) **A**nd endoscopic submucosal dissec**TI**on (ESD) for resection of **L**arge **D**istal non-pedunculated colorectal **A**denomas'

Version 1.6

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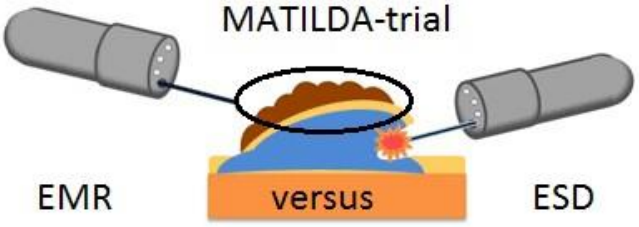

PROTOCOL TITLE

'Multicenter, randomised controlled trial comparing endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for the resection of large distal non-pedunculated colorectal adenomas'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee
APC	Argon Plasma Coagulation
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects
CRC	Colorectal Cancer
CRP	C-reactive Protein
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EMR	Endoscopic Mucosal Resection
ESD	Endoscopic Submucosal Dissection
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
hESD	Hybrid Endoscopic Submucosal Dissection
IB	Investigator's Brochure
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
pEMR	Piecemeal Endoscopic Mucosal Resection
QoL	Quality of Life
(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
VAS	Visual Analoge Scale
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Colorectal cancer (CRC) is the third most prevalent cancer in the Netherlands, with 13.000 new cases per year. Endoscopic resection of polyps in the colon is the cornerstone of effective CRC prevention, because it allows the removal of precursor lesions that may progress to cancer. Two modalities are available for the endoscopic resection of large non-pedunculated distal adenomas, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Although both techniques are standard of care in the Netherlands, a direct randomized comparison between ESD and EMR is lacking. Therefore, the choice for either of both therapies remains operator-dependent instead of evidence-based.

Objective: the aim of this study is to compare both procedures with regard to recurrence rates and complete (R0) resection rate, and to put this into perspective against the costs and complication rates of both strategies and the burden perceived by patients on both short and long term-term.

Hypothesis: We hypothesize that ESD is initially more time consuming and associated with higher costs, but is cost-effective and associated with a lower patients' burden on the long term due to a higher number of R0-resections and lower recurrence rates with less need for repeated procedures.

Study design: Multicenter randomized controlled trial

Study population: Patients 18 years of age or older with a non-pedunculated polyp larger than 20 mm in the rectum, sigmoid, or descending colon suspected to be an adenoma by means of endoscopic assessment, found during screening, surveillance or diagnostic colonoscopy.

Intervention: In the EMR-arm, endoscopic resection will be performed using the EMR technique, whereas patients randomized to the ESD-arm will undergo resection using the ESD technique.

Endpoints: Primary endpoints is recurrence rate at follow-up colonoscopy at 6 months, Secondary endpoints: 1. radical (R0-) resection rate 2. Perceived burden and quality of life, 3. cost effectiveness at 36 months, 4. surgical referral rate at 36 months, 5. complication rate, 6. recurrence rate at 36 months. The cost-effectiveness of ESD against EMR will be performed with the costs per recurrence free patient and the cost per quality adjusted life year (QALY) as outcome measures

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The two endoscopic resection techniques investigated in this study are standard care in the Netherlands and thus will not contain any additional risks for participating patients. Certain procedures that are optional but recommended in standard care will be performed in all participating patients, including (1) application of argon plasma coagulation or tipping with the snare using forced coagulation after pEMR, (2) marking of the opposite colonic wall of the resection site in case the adenoma is located in the sigmoid or descending colon, (3) biopsies of the scar at follow-up colonoscopies. Follow-up colonoscopy is standard care after resection of an adenoma, and will be performed 6 and 36 months after resection as recommended by the current Dutch guideline for colonoscopy surveillance. The questionnaires to evaluate patients' burden and quality of life are grouped as much possible to limit the frequency of questionnaires. Taken together, neither an unacceptable risk nor a direct benefit is expected for patients participating in this study. This study will increase the knowledge on the preferred endoscopic method that is currently unknown. This is important as the detection rate of these adenomas is expected to further increase with the introduction of the Dutch CRC screening program. The study will therefore support an optimal use of health resources in the future.

1. INTRODUCTION AND RATIONALE

Colorectal cancer (CRC) is the third most prevalent cancer in the Netherlands, with 13.000 new cases per year.[1] The majority of colorectal cancers arise from pre-malignant precursors along the adenoma-carcinoma sequence.[2] Resection of these lesions has shown to lower the mortality rate due to CRC with 60%.[3, 4] The Dutch CRC screening program is expected to detect relevant colorectal lesions in 51.6% of patients, of which 43.4% concerns advanced adenomas.[5]

Currently, two modalities are available for the endoscopic resection of large distal non-pedunculated colorectal adenomas in the Netherlands, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The EMR technique starts with injection of fluid into the submucosal space underneath the lesion, which results in separation of the overlying mucosal lesion from the underlying muscle layer. The lesion is subsequently strangled with a snare and resected by applying high-frequency current (figure 1a).[6] The ESD technique consists of lifting of the lesion with injection of fluid into the submucosal space and circumferential incision of the target area, followed by dissection of the submucosa underneath the specimen just above and parallel to the underlying muscle layer (figure 1b).[7] EMR is the most used technique and widely available in Western countries, however, maintains some important limitations. In large lesions, EMR can often only be performed in a piecemeal fashion (pEMR) due to the limited size of the snare, difficulty to position the endoscope, and often extension of the polyp over one or multiple folds.[8, 9] Piecemeal resection lowers the reliability of assessing the dysplasia free resection margins (R0 resection) at histology. This is also reflected by the relative high recurrence rate at follow-up colonoscopy after EMR ranging between 12-16%.[10, 11] For this reason ESD was developed in Japan. ESD results in a high en-bloc resection rate even in large lesions, a high R0 resection rate and a low recurrence rate between 1-2%. However, ESD is technically difficult to perform and associated with a higher perforation rate and a longer procedure time.[12-16]

Several retrospective studies compared EMR and ESD[17-24]. A recent meta-analysis pooled the results yielding a total of 2299 lesions.[25] The rates of en bloc resection and radical resection were much higher, and the rate of recurrence was much lower in the ESD group (91.7%, 80.3% and 0.9% respectively) than in the EMR group (46.7%, 42.3% and 12.2% respectively). The length of the procedure for ESD was about 3-fold longer than that for EMR. Although the rate of delayed bleeding was equal after ESD and EMR, more perforations occurred with ESD (5.7% vs 1.4%). Most perforations could be treated conservatively. Importantly, several important limitations for the generalizability of these results must be mentioned. First of all, all studies were biased by baseline differences due to its lack of a randomized design with special regard to tumor location and polyp size. All

studies included lesions in the right colon and included both adenomas and carcinomas, and the size of the lesions treated with ESD was significantly larger than those treated with EMR. This is important, as left sided resections and a larger polyp size are both associated with increased risk for complications. Second, all studies were performed in Asia and the results cannot be simply extrapolated to Western countries due to major differences with regard to experience with ESD between both areas. This is because the prevalence of early gastric cancers is much higher in Asia, in which ESD is easier to perform and what makes it easier to acquire overall experience with ESD.[26, 27] Only a few, small, single center cohorts have been published on ESD for large colorectal non-pedunculated polyps performed in Western countries.[28-32] This all limits the applicability of these results in the decision for one of the resection techniques for large colorectal adenomas.

Currently, EMR is widely performed in Western countries, whereas colorectal ESD is centralized in ESD expert centers where most experience exists with distal lesions. Due to lack of high quality Western studies and a direct randomized comparison, the debate on the preferred endoscopic technique in Western countries is still ongoing. As a result, in daily clinical practice the choice for either one of the resection methods remains operator dependent.

For this reason, the aim of this study is to perform a randomized comparison between ESD and EMR in large (>20 mm) distal non-pedunculated adenomas in a Western population. We aim to test our hypothesis that ESD is initially more time-consuming and associated with higher costs, but is cost-effective on the long term due to a higher number of R0-resections and lower recurrence rates with less need for repeated procedures. Moreover, we hypothesize repeated procedures will not only be a burden itself among patients, but will also result in an increased perceived risk of colorectal cancer compared to patients in which no recurrence is found.

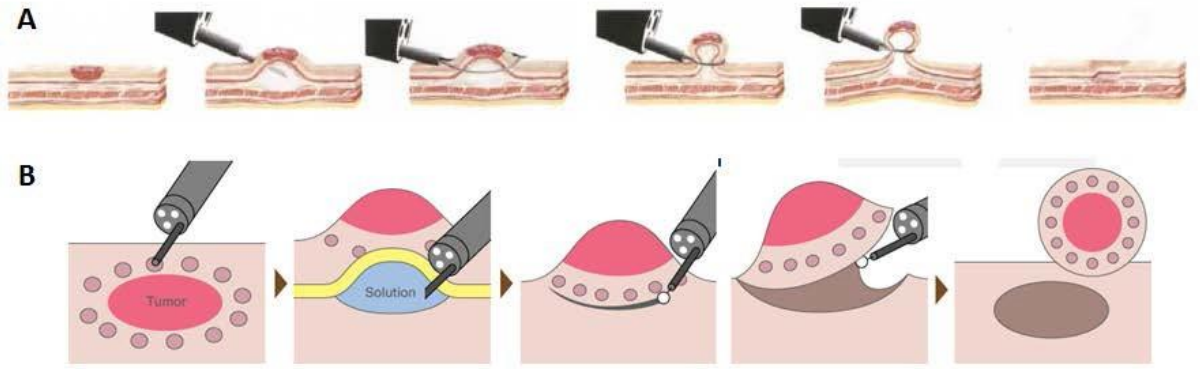


Figure 1. 1a) EMR technique, 1b) ESD technique

2. OBJECTIVES

All objectives will be a comparison between both study arms.

Primary Objective:

- to compare the recurrence rate at follow-up colonoscopy after 6 months, observed from resected residual disease or, if not present, from biopsies of the scar

Secondary Objectives:

- to compare the radical (R0-)resection rate, defined as dysplasia free vertical and lateral resection margins at histology
- To compare the perceived burden and quality of life among patients
- To compare the cost effectiveness at 36 months
- To compare the surgical referral rate defined as the number of patients that are referred for surgical management at 36 months
- To compare the complication rate
- To compare the long-term recurrence rate at follow-up colonoscopy after 36 months, observed from resected residual disease or, if not present, from biopsies of the scar

3. STUDY DESIGN

Design

Multicenter, randomized comparison for the endoscopic resection of distal non-pedunculated adenomas larger than 20 mm between EMR and ESD. All patients identified with such a lesion suitable for endoscopic resection will be rescheduled for a new colonoscopy (standard care). Prior consultation will take place to explain the risks and benefits of endoscopic resection (standard care) and to discuss informed consent (study care). Reasons for non-participation and/or exclusion will be recorded. Patient will be randomized for either of both arms. Due to the nature of the treatment, neither patients nor endoscopists participating in this study will be blinded. All patients will have a follow-up colonoscopy after 6 months (standard care) with biopsies of the scar (recommended standard care, fixed study care). In case of recurrence, a second endoscopic resection attempt will be performed and a follow-up colonoscopy will be planned after 6 months to re-evaluate recurrence (standard care) (figure 2). Patients with a technical failure to resect the polyp or persistent recurrence after three procedures have an indication for surgery (standard care). In cases of no recurrence at the 6 months follow-up colonoscopy, patients are scheduled for a follow-up colonoscopy at 36 months (figure 2). All colonoscopy intervals are based on the current guidelines for surveillance colonoscopy.[33]

Setting

The operational difficulty of colon ESD is very high. In literature, there is clear evidence of a learning curve in colorectal ESD, with the en bloc resection rate increasing and the perforation rate decreasing with increasing experience.[30, 34-36] Based on this literature, a minimum of 25 colorectal ESD-procedures is considered to be required to achieve expert experience. To prevent that our results will be biased by this ESD learning curve, this study will only allow endoscopists that have performed > 25 colorectal ESD procedures in the past 3 years to treat patients randomized to the ESD arm. Previous esophageal and stomach ESD experience alone will not be enough to ensure colorectal ESD expertise, as colorectal ESD is known to be technically more difficult than upper gastro-intestinal ESD due to the unsuitable anatomical characteristics of the colon (thin wall and existence of peristalsis, folds, flexions, and fecal fluid).[36] Patients randomized to the ESD arm will therefore be referred to ESD expert centers (UMC Utrecht, Erasmus MC, LUMC), or other medical centers which obtain this threshold during the study period. Patients randomized to the EMR arm will be treated by endoscopists which have extensive experience with EMR, defined as >500 prior EMR's. All local investigators of the participating centers fulfill this criterion.

Duration

Inclusion period	maximum	24 months*
Follow-up period	36 months	
Total	**maximum**	**60 months**

* If inclusion speed is disappointing, the number of participating centres will be extended from 15 to 20 centres, in order to ensure a maximum inclusion period of 24 months.

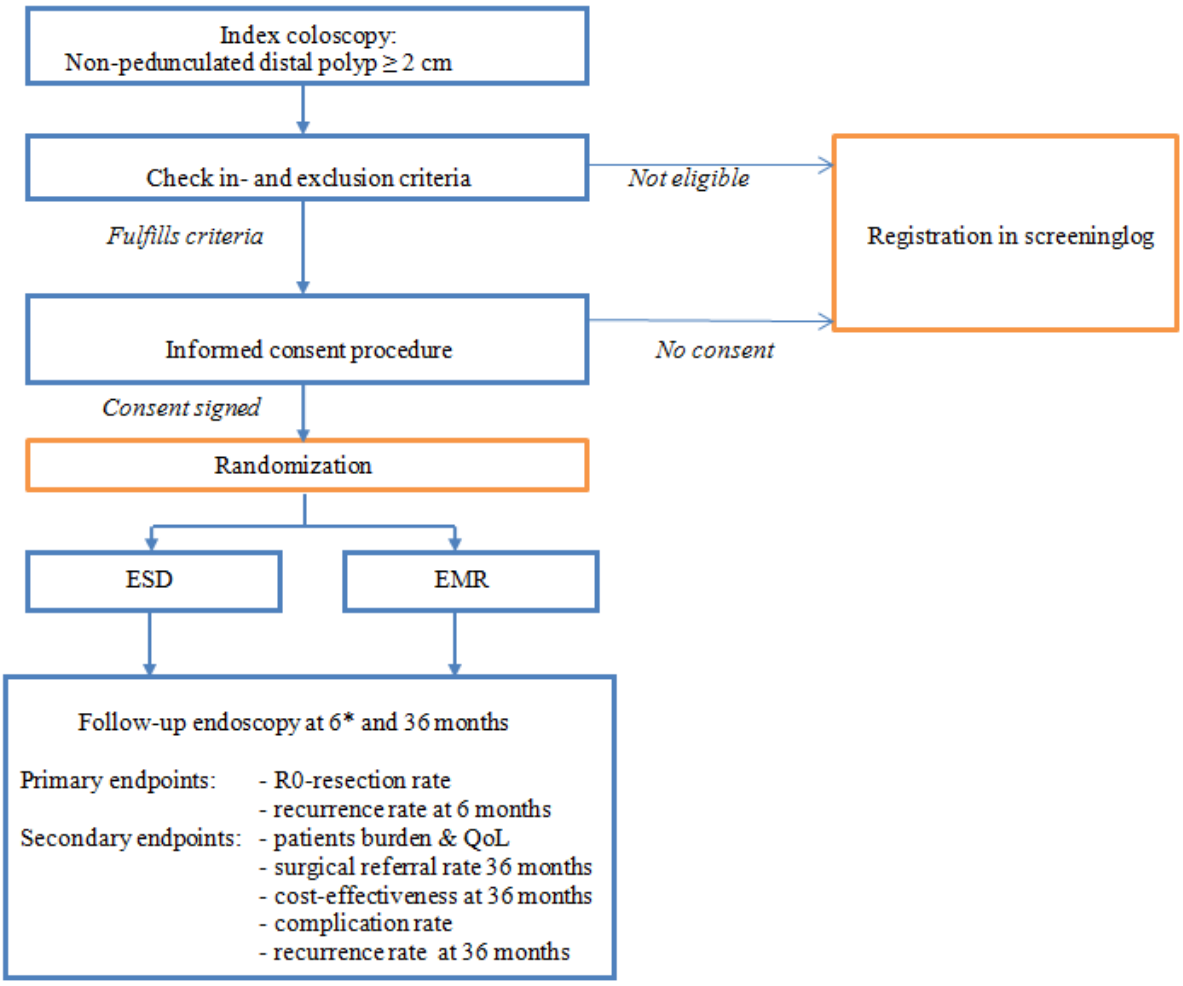


Figure 2. Flow-chart of the study design

4. STUDY POPULATION

4.1 Population

All patients 18 years of age or older with a lateral spreading polyp larger than 20 mm in the rectum, sigmoid, or descending colon suspected to be an adenoma by means of endoscopic assessment, found during screening, surveillance or diagnostic colonoscopy can participate in this study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- non-pedunculated polyp larger than 20 mm in the rectum, sigmoid or descending colon found during colonoscopy
- indication for endoscopic treatment
- ≥18 years old
- Written informed consent

4.3 Exclusion criteria

Exclusion criteria are:

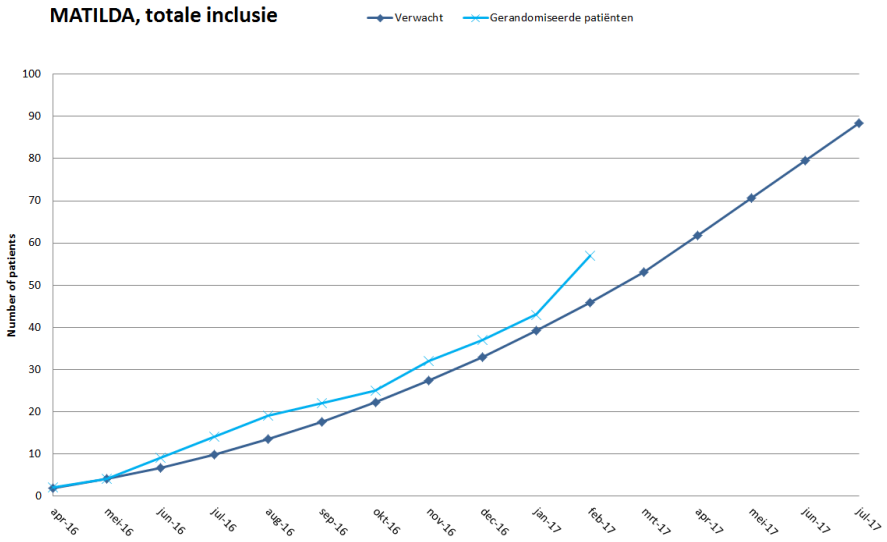
- suspicion of malignancy, as determined by endoscopic findings (invasive Kudo pit pattern[10], Hiroshima type C[37]) or proven malignancy at histology
- prior endoscopic resection attempt
- presence of synchronous distal advanced carcinoma that requires surgical resection
- the risk exceeds the benefit of endoscopic treatment, such as patient's with an extremely poor general condition or a very short life expectancy
- the inability to provide informed consent

4.4 Sample size calculation

The sample size is calculated for the primary outcome parameters recurrence rate at 6 months. Sample size for recurrence rate is calculated based on the assumption that the recurrence rate is 2% in the ESD group [25 30] and 12% in the EMR group[8 10 11]. With a power of 80% and an α of 0.05, the total number of patients needed is 198. To correct for patients lost-to-follow-up (7%), a total of 212 patients need to be included. To anticipate on screen-failures (16% unexpected T1 CRCs; based on recent results of the TREND-trial, Barendse et al, see appendix 1), 254 patients (212/0.84, round up towards even number) will be included; 127 patients in each arm.

We anticipated on an inclusion period of 2 years. Inclusion has started April 2016 and is better than expected (see figure on the next page). From April 2016 onwards, 16 centers have opened for inclusion. It can therefore be expected that the number of inclusions per month will further increase the next months. Therefore, we believe increasing our sample

size will not result in a troublesome delay of the study. If inclusion speed is nevertheless disappointing, the number of participating centres will be extended from 16 to 17 centers.



Graph 1: Inclusion MATILDA trial

5. TREATMENT OF SUBJECTS

5.1 Investigational treatments

5.1.1 Procedure definition of EMR-arm (standard care)

Dose and type of sedation given is at the discretion of the endoscopist and will be registered in the CRF. All colonoscopies will be performed with a high-resolution magnifying video-endoscope. A colloidal solution (such as succinylated gelatine) and dye will be used as the injection fluid, mixture with 1:100.000 adrenaline is optional. The purpose of this injection is to elevate the lesion away from the muscle layer, and to accentuate the plane of excision so that a wide and deep excision is achieved. Marking of the periphery of the polyp with coagulation is allowed to optimize the attempt of an en-bloc or R0-resection. A snare is then passed through the channel and opened around the lesion. The snare is snugged around the lesion and pulled. Cautery is applied to resect the lesion. Only when en-bloc resection is not feasible, the endoscopist is allowed to perform the resection in a piecemeal fashion (pEMR) in as less pieces as possible. The number of pieces will be registered in the CRF. In case of pEMR, adjunct therapy with either tipping with the snare using forced coagulation (ERBE VIO 300; 25W) or treatment with argon plasma coagulation (ERBE VIO 300; 60W, 2.0 L/min) will be performed. This will be applied in short bursts to coagulate the entire edge of the polypectomy site. Any remaining tissue in the polypectomy site will also be coagulated. In case of en-bloc EMR, adjunct therapy with coagulation will only be performed when remnant tissue is suspected and must be mentioned in the CRF. In case the adenoma is located in the sigmoid or descending colon, the opposite colonic wall of the resection site will be marked with India ink to ensure that the scar can be found during follow-up.

In case intraprocedural perforation occurs, this will be treated using clips. In case of a minor bleeding from a small vessel, contact coagulation with the tip of a knife or coagulation with hemostatic forceps will be used for hemostasis. In cases of a severe bleeding from a large vessel or artery, hemostatic forceps will be used for hemostasis. If a pulsating large vessel is exposed within the resection wound, clipping can optionally be used to prevent delayed bleeding. All of this is considered standard care, however, should be mentioned in the CRF. If overnight admission is required, this must be registered in the CRF including motivation.

Definitions of complications that are not considered standard care are mentioned in paragraph 6.1.2, and are defined according to the Dutch Complication registration of the Dutch society of gastrointestinal diseases (NVMDL)[40].

5.1.2 Procedure definition of ESD-arm (standard care)

Dose and type of sedation given is at the discretion of the endoscopist and will be registered in the CRF. All colonoscopies will be performed with a high-resolution magnifying video-endoscope. A 0.9% saline solution or succinylated gelatine together with dye will be used as the injection fluid. The purpose of this injection is to elevate the lesion away from the muscle layer, and to accentuate the plane of excision so that a wide and deep excision is achieved. A circumferential incision will be made using a ESD knife. The type of the knife must be mentioned in the CRF. The incision must be placed on a distance of 2-5 mm around the border of the polyp. This is because thermal damage otherwise makes it difficult to evaluate the histological resection margins after resection. A complete or partial circumferential incision is performed first and then further dissection is performed after the lesion is adequately situated. The endoscopist is allowed to perform the resection using the hybrid ESD (hESD) technique. This hESD technique consists of a circular incision around the lesion, with partial preparation in the submucosal layer that is sufficient to capture it with a snare in a single piece. Adjunct therapy with either tipping with the snare using forced coagulation (ERBE VIO 300; 25W) or treatment with argon plasma coagulation (ERBE VIO 300; 60W, 2.0 L/min) will only be performed when remnant tissue in suspected and must be mentioned in the CRF. In case the adenoma is located in the sigmoid or descending colon, the opposite colonic wall of the resection site will be marked with India ink to ensure that the scar can be found during follow-up.

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Definitions of complications that are not considered standard care are mentioned in paragraph 6.1.2, and are defined according to the Dutch Complication registration of the Dutch society of gastrointestinal diseases (NVMDL)[36].

After both procedures patients will be discharged the same day, unless the endoscopist has a reason not to do so. This must be registrered in the eCRF.

5.2 Use of co-medication (if applicable)

If patients use antithrombotic drugs, the Dutch guideline on the ‘Endoscopic interventions in patients with anticoagulation and platelet aggregation inhibition’ will be followed.[41] In

summary, patients are divided into high- and low-risk groups according to the predicted risk of thromboembolism. In high risk patients, withdrawal of coumarine derivates is required 3-5 days before the planned endoscopic resection. Bridging of antithrombotic drugs will be performed in consultation with the prescribing doctor. In low-risk patients, coumarine derivates are withdrawn for 3-5 days without bridging. In both low and high risk patients, the INR is measured on the day of the procedure and the name of the drugs, including the bridging drugs, will be registered in the CRF. After the procedure, all patients will restart their home medication.

5.3 Escape medication (if applicable)

Not applicable

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

- Recurrence rate at follow-up colonoscopy after 6 months, observed from resected residual disease or, if not present, from biopsies of the scar

6.1.2 Secondary study parameters/endpoints

- Radical (R0-)resection rate, defined as dysplasia free vertical and lateral resection margins at histology
- To compare the perceived burden and quality of life among patients (see study procedures for questionnaires that will be used)
- Overall complication rate*
- Surgical referral rate defined as the number of patients that are referred for surgical management at 36 months
- Long-term recurrence rate at follow-up colonoscopy after 36 months, observed from resected residual disease or, if not present, from biopsies of the scar
- Cost effectiveness at 36 months. Costs will be calculated for:
    - bowel preparation
    - used instruments & materials
    - time needed to perform the procedure
    - admission to the ward
    - length of hospital stay
    - costs of repeated treatment or (prolonged) hospital stay for complications
    - costs of repeated treatment or (prolonged) hospital stay for recurrence
    - costs made by the surgeon in cases of surgical referral

  All costs will be calculated with real prices at analysis date. Mean total costs will be calculated for both treatment strategies to achieve a complete resection of the lesion. The exact method of cost-effectiveness calculation is described in chapter 8 of the study protocol.

* Complications are defined as follows:
    - Intraprocedural perforation (yes/no), defined as the condition in which the abdominal cavity is visible from the colorectal lumen during the procedure because of mural tissue defects, that requires (1) (prolonged) admission or (2) surgery

- Intraprocedural bleeding (yes/no), defined as bleeding that occurs during the procedure that is not controlled by electrocoagulation and/or necessitated hemoclipping, and that requires (1) transfusion or (2) termination of the endoscopic resection
- Postprocedural bleeding (yes/no), defined as bleeding within 30 days after the procedure resulting in (1) new presentation at the hospital, (2) hospital admission, or (3) repeated colonoscopy to obtain hemostasis
- Postprocedural perforation (yes/no), defined as perforation within 30 days after the procedure that is detected after completing of the procedure during which perforation did not occur, diagnosed by abdominal pain with focal guarding and a rise in C-reactive protein and/or fever (T > 38.5 C) in combination with free air in the peritoneal cavity at abdominal CT
- Postprocedural serositis (yes/no), defined as abdominal pain with focal guarding and a rise in C-reactive protein and/or fever (T > 38.5 C) within 30 days after the procedure, but without signs of perforation (free air at abdominal CT) and in the absence of another infection focus (urinary, pulmonary etcetera).

6.1.3 Other study parameters

- Age
- Gender
- ASA score (I-IV)
- Location of the polyp (descending colon, sigmoid, rectum-sigmoid, rectum)
- Size of the polyp by endoscopic assessment
- Surface features (granular, non-granular, mixed)
- Performing endoscopist
- Use of antithrombotics drugs (yes/no), if yes: continuation during procedure or date of restart
- Type of bowel preparation (complete or incomplete)
- Type and dose of sedative medication
- Tipping with the snare with forced coagulation or treatment with argon plasma coagulation used
- Piecemeal resection used, if yes: number of pieces
- Type and brand of ESD knife used (ESD-group)
- Length of the procedure (in minutes), defined as the total time needed for resection of the polyp, measured from the minute the injection fluid is injected until the endoscopist finishes final inspection of the resection wound.
- Hospital admission (yes/no) and duration of admission

- Repeated treatment (both groups)
- Histopathological details (histological type and resection margins in mm (horizontal and vertical). See paragraph 6.3.

6.2 Randomisation, blinding and treatment allocation

Randomization will be stratified by the size of the polyp (<40 mm vs ≥ 40 mm) and localisation (sigmoid vs descendens vs rectum) using random block sizes of five per block. Patient data are entered into a GCP-approved computerized database (http://castoredc.com/nl/) by datamanagers of IKNL-trialbureau after inclusion and exclusion criteria are checked and informed consent is obtained. This program will randomize patients to undergo either ESD or EMR. Results of this randomization will be directly copied to the study coordinator and IKNL-trialbureau by Castor EDC (automatic mail delivery).

6.3 Study procedures

A summary of the study procedures is provided in the table and described in this paragraph.

Table 1. Summary of the study procedures

	Before randomization	Baseline (prior to treatment)	Treatment (ESD/EMR)	30 days after ESD/EMR	Follow-up 4 days (Q)	Follow-up 4 weeks	Follow-up 6 months	Follow-up 12 months*	Follow-up 13 months (Q)	Follow-up 18 months**	Follow-up 24 months***	Follow-up 36 months
Informed consent	X											
Baseline eCRF - Patient characteristics - Polyp characteristics (incl stratification factors)		X										
Randomization		X										
Treatment eCRF - Complications - Histopathology			X									
30 day posttreatment eCRF				X								
Follow-up colonoscopy 6 months							X					
Follow-up colonoscopy 12 months *								X*				
Follow-up colonoscopy 18 months **										X**		
Follow-up colonoscopy 24 months ***											X***	
Follow-up colonoscopy 36 months												X

MATILDA-study

QoL questionnaires												
Colorectal cancer risk		X			X	X	X					X
Decision Evaluation Scale applied to CRC screening					X		X					
EUROQOL (short version)		X			X	X	X		X			X
COREFO		X				X						X

The 6 and 36 months colonoscopy will be performed in **all** patients according to the Dutch Guideline for colonoscopy Surveillance

* A 12 month endoscopy will only be performed when recurrence is found at the 6 month colonoscopy (as recommended by Dutch Guideline for colonoscopy Surveillance).

** A 18 month endoscopy will only be performed when recurrence is found at the 6 **and** 12 month colonoscopy.

*** A 24 month endoscopy will only be performed when recurrence is found at the 6 **and** 12 **and** 18 month colonoscopy.

Q = only follow-up for questionairres

Recruitment phase (both groups):

- Initial recruitment of patients will be performed by the local coordinating investigator of the participating center. In case of a study patient, inclusion and exclusion criteria are checked. In case of exclusion, reasons for exclusion will be communicated to the project leader, so that it can be recorded in the screening log (see figure 2).
- The local coordinating investigator will provide oral and written information on the study to the patient. Patients will have as much time as they like to think about participation and will have the chance to ask any questions on the study. Thereafter the informed consent form is signed. In case of non-participation, this will be communicated to the project leader, so that it can be recorded in the screening log (see figure 2).
- The local coordinating investigator will enter the stratification factors in Castor EDC. This program will randomize patients to undergo ESD or EMR. Results of this randomization will be directly copied to the study coordinator and IKNL trialbureau by Castor EDC (automatic mail delivery).

Treatment phase (per group):

1. EMR-group:
   - The patient is rescheduled for a new colonoscopy in the participating center
   - The patient will be prepared for the procedure according to the local protocol
   - EMR is conducted according to the procedure definition (see 5.1.1)
   - Length of the procedure (in minutes) is recorded
   - In case the adenoma is located in the sigmoid or descending colon, the opposite colonic wall of the resection site will be marked with India ink to ensure that the scar can be found during follow-up
2. ESD-group:
   - The patient is rescheduled for a new colonoscopy in one of the expert centers
   - The patient will be prepared for the procedure according to the local protocol
   - ESD is conducted according to the procedure definition (see 5.1.2)
   - Length of the procedure (in minutes) is recorded
   - In case the adenoma is located in the sigmoid or descending colon, the opposite colonic wall of the resection site will be marked with India ink to ensure that the scar can be found during follow-up

Handling of the resected specimen groups):

- Appropriate handling of the resected specimens by the endoscopist is critical for the accurate histological diagnosis and will be done as follows (identical to standard care). The resected specimen will be pinned on a paraffin, rubber or cork sheet so that the mucous membrane surrounding the lesion is evenly flattened and the mucous membrane surface can be observed (figure 2). As a specimen rapidly autolysis after resection, it must be fixed as quick as possible. To prevent drying of the specimen, it will be soaked in a formalin solution. Thereafter, the endoscopist is required to appropriately display the specimen so that the difference between the specimen and the clinical images is minimized and the tumor margin of the specimen can be judged. The endoscopists will provide documentation (an explanatory text) to the pathologist so that the basic information on preoperative diagnosis, the site and morphology of the lesion, and the tumor size can be accurately conveyed.
- Appropriate handling of the resected specimens by the pathologist will be done as follows (identical to standard care). The received specimen is fixed with a 4% buffered formaldehyde solution for 24 hours at room temperature. After fixation, the procedure is as follows:

i) The specimen is photographed, measured and the macroscopic appearance is described including the lesion, mucosal defects, other abnormalities and the resection margins
ii) The specimen is inked. A different ink color is used for the resection plane and the edges of defects
iii) A tangent that touches the focus closest to the horizontal tumor margin is assumed, as shown in figure 3
iv) The first cut is carried out in the direction perpendicular to the tangent. The specimen is sectioned into slices at intervals of 2 mm parallel to the first cut (figure 3)
v) All slices are embedded in cassettes for histological diagnosis. In case of long slices (> 2cm), the slice is cut in half and both halves are embedded after ink is applied at the cut edge.

Histological diagnosis

Histological diagnosis of tumors is carried out in accordance with the WHO classification of tumors and Vienna classification by the pathologist of the center in which the resection is performed.[47] The histological type and resection tumor margins in mm (horizontal and vertical) of the lesion will be judged. Incomplete (R1) resection is defined as tumour infiltration of the margins and/or if infiltration cannot be determined because of coagulation artefacts, as in piecemeal resection. In the case of adenocarcinoma, it concerns a late exclusion (see randomization procedure).

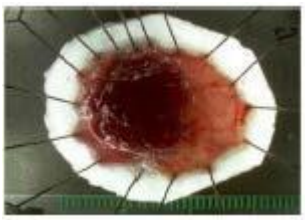


Figure 3a: fixed polypectomy specimen

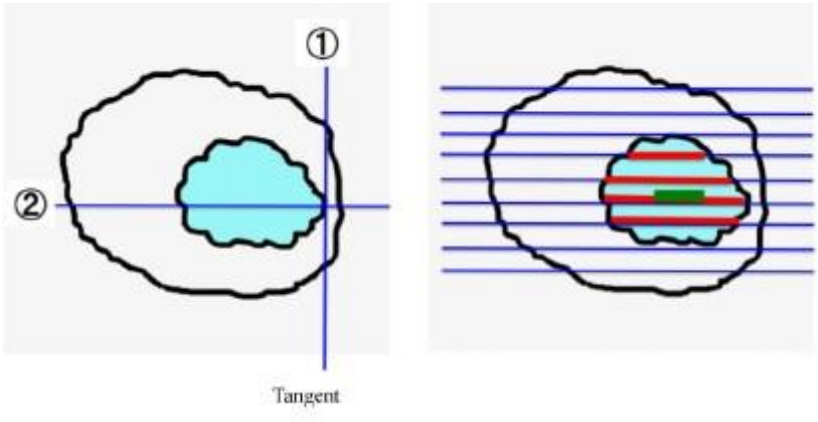


Figure 3b: Cut-out of a resected specimen

Postprocedural 30 days (both groups):

- Evaluation in the context of post-procedural clinical care will be performed as standard (standard care)
- Procedure-related complications within 30 days as defined in paragraph 6.1.2 will be filled out in the eCRF.

Follow-up at 6 months (both groups):

- A follow-up colonoscopy is performed 6 months after the procedure for all patients as recommended by the Dutch guideline for colonoscopy surveillance.[38] The scar is checked for residual disease. In case of macroscopic residual disease this is resected (standard care). If not**,** biopsies of the scar will be taken (recommended standard care, fixed study care).
- Evaluation in the context of the findings at follow-up colonoscopy will be performed as standard (standard care).
- If no recurrence is found at the 6 months colonoscopy, the next colonoscopy will be planned at 36 months (in accordance with the Dutch guideline for colonoscopy surveillance). If recurrence is found at the 6 months colonoscopy, a second follow-up colonoscopy will planned again after 6 months (T=12 months) to check the scar. This is repeated until no recurrence is found with a maximum of three attempts of endoscopic resection before referral to the surgeon (in accordance with the Dutch guideline for colonoscopy surveillance and common practice).[33]

Follow-up at 36 months (both groups):

- A follow-up colonoscopy is performed 36 months after the procedure for all patients as recommended by the Dutch guideline for colonoscopy surveillance.[38] The scar is checked for residual disease. In case of macroscopic residual disease this is resected (standard

care). If not**,** biopsies of the scar will be taken (recommended standard care, fixed study care).

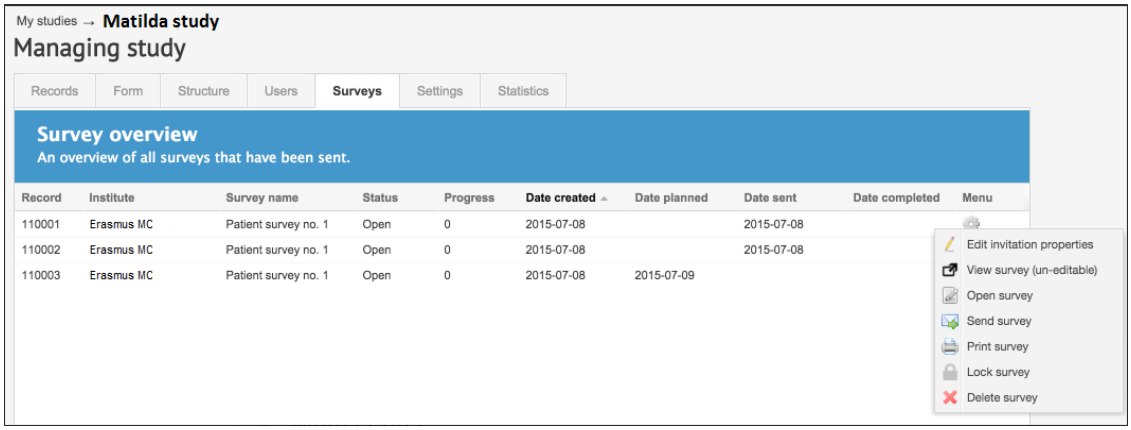
Perceived burden and quality of life assessment

Perceived burden and quality of life among patients will be assessed using questionnaires. These questionnaires will be send digital to the participating patients.

- Colorectal Cancer Risk[49]: uses a Likert scale to evaluate the patients perception of CRC risk (risk perception), confidence in participating in screening (self-efficacy) and response to screening (response efficacy). A higher number equals higher risk perception and efficacy. Measurement will be performed at baseline, 4 days and 4 weeks after EMR/ESD, and after the 6 and 36 months follow-up endoscopy.
- Decision Evaluation Scale applied to CRC screening[50]: uses a 5-point Likert scale to evaluate the patients experience of the colonoscopy procedure. A higher score equals stronger agreement with the item. Measurement will be performed 4 days after EMR/ESD and after the 6 months follow-up endoscopy.
- EUROQOL[51]: is a standardized instrument for use as a measure of health outcome. This questionnaire will be used to questionnaire is used to generate health status scoring profiles over time. Measurement will be performed at baseline, 4 days and 4 weeks after EMR/ESD, after the 6 months follow-up endoscopy, after 13 months, and after the 36 months follow-up endoscopy. This questionnaire will be used to generate health status scoring profiles over time, which will subsequently be translated in QALYs by applying time trade-off based health utility algorithms.
- COREFO[52]: will be used to measure disease-specific health related quality of life. Measurement will be performed at baseline, 4 weeks after EMR/ESD and after the 3 6 months follow-up endoscopy.

A summary of the time schedule of the quality of life measurements can be found in Table 1.

All questionnaires will be collected with the use of online surveys by IKNL-trialbureau, using the Survey function of Castor EDC (http://castoredc.com/nl/). These survey's will automatically be linked to the eCRF in Castor EDC. Castor EDC enables to specify a sending pattern for the survey. With the send pattern we will be able to schedule the sending of the survey invitations. Datamanagers of IKNL-trialbureau can track the progress of the surveys and will send a reminder when participants don't respond.
Patients who prefer to complete the forms on paper will receive the questionnaires by mail. The home address or e-mail address can be completed on the informed consent form.



6.4 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.

6.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

6.5 Replacement of individual subjects after withdrawal

If a patient is withdrawn before inclusion because of exclusion criteria, patients will be replaced and this will be registered in the screening log. If a patient withdraws during follow-up, this is considered a drop-out and no new patient will be enrolled.

6.6 Follow-up of subjects withdrawn from treatment

Follow-up of withdrawn patients will be performed by their regular physician.

6.7 Premature termination of the study

We do not expect that the study will be terminated prematurely due to ethically unacceptable events, as standard of care is guaranteed in both treatment arms. As mentioned in the study design, this study will only allow endoscopists with extensive experience to perform EMR and only endoscopists that have performed > 25 colorectal ESD procedures to treat patients randomized to the ESD arm. This will not only prevent that the study is biased by a learning curve, but will also prevent unacceptable high complication rates in the ESD arm.

In case of intraprocedural perforation or bleeding, this will be managed conservatively according to the procedure definition described in paragraph 5.1.1 and 5.2.1. Surgical rescue

can usually be avoided by this conservative treatment and by giving i.v. antibiotics.[43-45] Nevertheless, in case of incomplete closure of the perforation, which we expect to occur rarely based on our experience and previous literature (percentages are mentioned in next two paragraphs), surgery will be carried out as soon as possible to lower the risk of peritonitis.

Based on the literature, we expect the following complication rates to occur in our study:

- EMR: In EMR, perforation rates are reported to be 0.58 – 0.8%, delayed bleeding rates 1.15 – 1.7%, serositis 1-1.5%, and non-specific pain 2-4%.[8 10, 11]
- ESD: Only a few Western single center studies exist that evaluated complication rates of colorectal ESD. A study published in 2012 showed a perforation rate of 1.3% and the bleeding rate was 7.9%. All complications were managed conservatively and there was no need for surgical intervention. No procedure-related mortality was observed. A French study showed a perforation rate of 0% after experience with 25 colorectal ESDs.[30] In Asian studies, intraprocedural perforation rates are reported to be 5.9% and delayed bleeding rates 0.7-2.2%.[25] Delayed perforation are seldom reported (incidence of 0.1-0.4%).[43, 46-48] In a pilot evaluation of colorectal ESD in UMC Utrecht, complications rates are low. Thus far, no intraprocedural complications occurred that required surgery. Only one patient was referred for surgery because of a postprocedural perforation and no deaths occurred.

Based on the literature, we expect the following recurrence rates to occur in our study:

- EMR: In a meta-analysis of 25 studies on EMR R0 resection was achieved in 59% and recurrence rates of 12-14%.[8]
- ESD: Only a few Western single center studies exist that evaluated R0 resection of colorectal ESD. A study published in 2012 presented their experiences with ESD of rectal tumors (82 cases) and showed that R0-resection was achieved in 76-84.5% of the patients after experience with 25 ESDs. [34] A Swedish study analyzed the results of 29 ESD carried out in a single institution.[39] The percentage of en-bloc resections and R0 resections were 72% and 69%, respectively. A recent Polish study showed that en-bloc was achieved in 50/70 resection.[29] In this group, 96% cases were R0 resections. In Asian studies, the rates of en bloc resection, curative resection and the rate of recurrence were 91.7%, 80.3% and 0.9% respectively.[25]

7 SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the endoscopic resection. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Endoscopic resection related AEs are:

- Intraprocedural perforation, intraprocedural bleeding, postprocedural bleeding or postprocedural serositis that requires (prolonged) admission <10 days and/or maximum 4 (EH) blood transfusion and/or endoscopic or percutaneous (re-)intervention

This is defined according to the the Dutch Complication registration of the Dutch Society of Gastrointestinal Diseases (NVMDL) for non-severe complications. These AEs will be reported in line listings once a year.

7.2.2 Serious adverse events (SAEs)

Documentation and reporting of SAE's through the web portal *ToetsingOnline* to the METC will be limited to SAE's which are defined as severe by the Dutch Complication registration of the Dutch Society of Gastrointestinal Diseases (NVMDL), that occur within 30 days and that are related to the endoscopic resection procedure. These SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events. Endoscopic related SAE's are:

- *Intraprocedural perforation, intraprocedural bleeding, postprocedural bleeding or postprocedural serositis that requires:*

1) > 10 days (additional) admission and/or

2) > 4 (EH) blood transfusions and/or

3) angiographic or surgical intervention and/or

4) ICU admission

5) and/or death

- *Any other event with a possible or definite causal relation with the study intervention (endoscopic resection) as judged by the treating physician that requires:*

1) > 10 days (additional) admission and/or

2) > 4 (EH) blood transfusions and/or

3) angiographic or surgical intervention and/or

4) ICU admission

5) and/or death

These SAE's will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the local investigator has first knowledge of the serious adverse events. Local investigators will report SAE's to the project leader in the UMC Utrecht as soon as possible after having taken knowledge of a SAE. Related SAEs that result in death or are life threatening within a month should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse events. This is for a preliminary report with another 8 days for completion of the report. The local coordinating investigator will have the responsibility to report the SAE's to the project leader within the abovementioned time period. The project leader will have the responsibility to report his through the web portal *ToetsingOnline* within abovementioned time period.

7.3 Annual safety report

Annual safety report is not applicable (only applicable for research with a medicinal product). For the annual progress report see paragraph 10.4.

7.4 Follow-up of adverse events

All AE's will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the Protocol.

7.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable

8. STATISTICAL ANALYSIS

Normally distributed continuous variables will be expressed as mean (± SD) and not-normally distributed variables will be expressed as median (IQR and range). Categorical data will be presented with percentages. A p-value of < 0.05 will be considered significant.

8.1 Primary study parameter(s)

- Recurrence rate at 6 months will be compared using a Chi-square test.

8.2 Secondary study parameter(s)

- Radical (R0-)resection rate will be compared using a Chi-square test.
- Perceived burden and quality of life:
  - Colorectal Cancer Risk[49]: the Likert scale will be used to conduct paired and independent-sample t-tests. The perceived colorectal cancer risk will be compared using linear mixed model regression analyses and will include follow-up time, treatment group and the interaction between follow-up and treatment group, corrected for baseline measurements.
  - Decision Evaluation Scale applied to CRC screening[50]: the 5-point Likert scale will be used to compare the patients experience of the colonoscopy procedure after procedure between the ESD and EMR group using an independent-sample t-tests.
  - EUROQOL[51]: the healthcare scores will be compared using linear mixed model regression analyses and will include follow-up time, treatment group and the interaction between follow-up and treatment group, corrected for baseline measurements.
  - COREFO[52]: Symptoms after treatment will be compared with baseline measurements using McNemar's test.
- Cost and cost-effectiveness of both approaches will be calculated at 36 months. The cost-effectiveness of ESD against EMR will be performed with the costs per recurrence free patient and the cost per quality adjusted life year (QALY) as outcome measures. QALY will be calculated from the EUROQOL questionnaire by applying time trade-off based health utility algorithms. Incremental cost-effectiveness ratios will be calculated, reflecting the extra costs per additional recurrence free patient and the extra costs per additional QALY. We choose not to evaluate production losses (i.e. absence from work and lower efficiency while at work) in this study, as most of the patients will be above 65 years and thus retired.

Mean total costs will be calculated for both treatment strategies. For each patient, real medical costs will be calculated by multiplying volume of care (units of healthcare utilization reported in the case record form) with their corresponding unit prices. Data will be gathered in the eCRF for time needed to perform the procedure, admission to the ward, length of hospital stay, repeated treatment or (prolonged) hospital stay for complications, used anaesthesia, repeated treatment or (prolonged) hospital stay for recurrence and surgical referral. The Dutch costing guideline for health care research will be used to determine the relevant unit costs.[53] For the most important cost-items the unit price will be determined using the micro-costing method, which is based on a detailed inventory and measuring of all the resources used (including material that is needed to perform ESD and EMR).[54] All other unit prices will be determined using the proxy charges of real costs, based on Dutch consumer price indices and the Dutch Health Authority.[53,55] All costs will be expressed in 2018 euros.

- Surgical referral rate will be compared using a Chi-square test.
- Number and nature of complications in both groups will be recorded. Comparison of the number of complications will be done using a Chi-square test.
- Recurrence rate at 36 months will be compared using a Chi-square test.

8.3 Other study parameters

Analysis of the different parameters is performed by using the independent Student's T-test for analysis of normally distributed continuous data, the Mann-Whitney U test for nonparametric data and the Chi-square test or Fisher's exact test to analyze categorical variables.

8.4 Interim analysis (if applicable)

Not applicable

9 ETHICAL CONSIDERATIONS

9.1 Regulation statement

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. This clinical investigation shall comply with the practices set out in EN ISO14155:2011. This investigation shall not begin until an approval/favorable opinion has been received from a Medical Ethics Committee. The study will be conducted according to the rules on medical research involving human subjects (Medical Research (Human Subjects) Act), in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen (WMO).

9.2 Recruitment and consent

An Informed Consent letter shall be provided to each patient prior to being enrolled in the trial. After review, this shall be signed by the local coordinating investigator and the patient. Any new information arising in the course of the trial shall be provided to the patient and they shall be re-consented. Patients unable or refusing to provide informed consent will be treated according to current clinical practice.

9.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

9.4 Benefits and risks assessment, group relatedness

Please also see: “premature termination of the study”.

The two endoscopic resection techniques investigated in this study are standard care in the Netherlands. A follow-up colonoscopy is performed 6 and 36 months after the procedure, which is standard care in the Netherlands. In case of macroscopic residual disease this will be resected, which is standard care. If not, biopsies of the scar and surrounding area will be taken, which is optional in standard care and fixed care in this study. Colorectal biopsy is considered to be a low risk intervention. the effort required by the patient to answer a questionnaire. With regard to the quality of life questionnaires, we aimed to minimize questionnaire length and density of sampling to the highest necessary in order to balance the effort required by the patient to answer the questionnaires with the estimated goal of quality of life analysis for this study. Taken this together, neither an unacceptable risk nor a direct benefit is expected for patients participating in this study.

9.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.6 Incentives (if applicable)

None

10 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be collected and entered by the local investigators into a eCRF system (http://castoredc.com/nl/). Castor has been audited on GCP compliance by Profess Medical Consultancy and has obtained a GCP compliance certificate. With Castor, GCP-compliant data collection and data management is available for audit trail, electronic signing, reason for change, monitoring module, direct validation of data entered, authorisation per form, user and institute, adverse Event (AE) reports, and field comments. Patients will have a number, the key file will only be in possession of the study personnel and the key file will be stored on an account that is only accessible after entering a user name and password. The data will be stored coded for 15 years.

10.2 Monitoring and Quality Assurance

The conduct of the clinical study will be supervised through on-site monitoring as necessary. In this study we expect a minimal risk of minimal damage; therefore this study needs a minimum of monitoring in accordance with the NFU-criteria. The monitoring plan will be submitted separately.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC. Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

10.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

The results of this study will be submitted for publication according to the CCMO statement on publication policy.

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Appendix 1: Abstract TREND-study

Transanal endoscopic microsurgery versus endoscopic mucosal resection for large rectal adenomas (TREND-study).

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Inhoud

Non-randomised studies suggest that endoscopic mucosal resection (EMR) is equally effective in removing large rectal adenomas as transanal endoscopic microsurgery (TEM). EMR might be more cost-effective and safer. This trial compares the cost-effectiveness and cost-utility of TEM and EMR for large rectal adenomas. For this multicentre, randomised controlled non-inferiority trial, patients with rectal adenomas ≥3cm, without malignant features, at 17 Dutch and 1 Belgian hospital were included. Eligible patients were randomly assigned (1:1) to EMR or TEM, allowing endoscopic removal of residual adenoma at 3 months. Randomisation was stratified by whether patients had a primary adenoma or residual/recurrent disease after prior resection. Unexpected malignancies were excluded post randomisation. Primary outcomes were recurrence within 24 months and the number of recurrence-free days alive and out of hospital, analysed by intention to treat. The trial was designed to demonstrate non-inferiority of EMR with regards to recurrence rate with an upper limit of 10%. Secondary outcomes were complications, quality of life, anorectal function and costs. This trial is registered in the Dutch Trial Registry (NTR1422). Between Feb 3, 2009 and Sept 19, 2013, 209 patients were randomised to EMR (n=106) or TEM (n=103). In each group, 2 patients withdrew consent. There was 1 patient with prostate carcinoma instead of rectal adenoma in the EMR group, who was excluded. The remaining 204 patients (103 EMR, 101 TEM) were treated. Of those, 27 (13%) had unexpected cancer and were excluded. One additional patient withdrew consent. Of the remaining 176 (87 EMR, 89 TEM) patients, overall recurrence rates were 15% after EMR and 11% after TEM. However, EMR was statistically not non-inferior to TEM. The number of recurrence-free days alive and out of hospital was similar (EMR 609 ± 209, TEM 652 ± 188, p=0.16). Complications (mostly hemorrhage) occurred in 18% (EMR) vs. 26% (TEM) (p=0.23). Major complications occurred in 1% (EMR) vs. 8% (TEM) (p=0.064). Quality adjusted life years were equal in both groups. Although EMR patients scored more favourable on disease specific quality of life questionnaires, manometries were similar and continence improved after adenoma resection regardless of treatment. EMR was approximately €3000 cheaper and therefore more cost-effective.
Conclusions: Due to initially higher recurrence rates after both treatments while being slightly in favor of TEM, non-inferiority of EMR could not be demonstrated. With the number of severe complications and the higher costs not being in favor of TEM however, judgment on which treatment to recommend should be suspended.