THE TRIASSIC STUDY

Multicentre, randomised controlled trial comparing **TR**ansanal minimal **I**nv**A**sive **S**urgery (TAMIS) and endoscopic **S**ubmucosal d**I**sse**C**tion (ESD) for resection of non-pedunculated rectal lesions

Version 1.3

15 June 2020

ZonMw

Leids Universitair Medisch Centrum

ijsselland ziekenhuis

PROTOCOL TITLE

'Multicentre, randomised controlled trial comparing **TR**ansanal minimal **I**nv**A**sive **S**urgery (TAMIS) and endoscopic **S**ubmucosal d**I**sse**C**tion (ESD) for resection of non-pedunculated rectal lesions'

Protocol ID	NL61603.058.18
Short title	TRIASSIC study
Version	1.3
Date	15-06-2020
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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
AE	Adverse Event
AR	Adverse Reaction
AVG	General Data Protection Regulation (In Dutch: Algemene Verordening Gegevensbescherming)
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
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
TAMIS	Transanal Minimally Invasive Surgery
TEM	Transanal Endoscopic Microsurgery
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 Analogue Scale
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Colorectal cancer (CRC) is the second most prevalent cancer in the Netherlands, with 15,000 new cases per year and 5000 colorectal cancer related deaths. The Dutch National Colorectal Cancer screening program began in 2014 and is expected to save 1400 lives per year in the short term through early diagnosis and treatment of cancer. In the longer term it is expected to save an additional 1000 lives per year through the prevention of cancer by removing advanced polyps. In the last few years two new highly promising innovative approaches have become available for minimally invasive en bloc resection of large non-pedunculated rectal lesions. One is a new surgical technique called transanal minimally invasive surgery (TAMIS) and the other is a new endoscopic technique called endoscopic submucosal dissection (ESD). Although both techniques are standard of care in the Netherlands, a direct randomised comparison between TAMIS and ESD 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 in both the short and long term.
Hypothesis: We hypothesize that ESD will be associated with longer procedure times but lower costs. For lesions that prove to be benign, we hypothesize that ESD will lead to a higher number of R0 resections and lower recurrence rates, particularly for lesions involving the dentate line, and less serious complications than TAMIS. For lesions that prove to be invasive we hypothesize that TAMIS will have a higher R0 resection rate but that this will not translate to a reduced need for additional surgery.
Study design: Multicentre randomised controlled trial
Study population: Patients 18 years of age or older with a large non-pedunculated polyp in the rectum found during screening, surveillance or diagnostic colonoscopy. In total 198 patients will be included.
Intervention: In the TAMIS-arm, resection will be performed using the TAMIS technique, whereas patients randomised to the ESD-arm will undergo resection using the ESD technique.
Endpoints: The primary endpoint 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 12 months, 4. Surgical referral rate at 12 months, 5. Complication rate, 6. Recurrence rate at 12 months.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The two 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) MRI of the rectum and (2) biopsies of the scar at follow-up rectoscopies. Endoscopic ultrasound of the lesion is still recommended. Follow-up rectoscopy is standard care after resection of an adenoma, and will be performed 6 and 12 months after resection. 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 current knowledge as to the preferred minimally invasive resection method, which 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 healthcare resources in the future.

1 INTRODUCTION AND RATIONALE

Colorectal cancer (CRC) is the second most prevalent cancer in the Netherlands, with 15.000 new cases per year of which 5,000 are in the rectum.[1] The majority of colorectal cancers arise from pre-malignant precursors along the adenoma-carcinoma sequence. Resection of these lesions has shown to lower the mortality rate due to CRC by 50%.[2] The Dutch CRC screening program is expected to detect relevant colorectal lesions in 51.6% of patients, of which 43.4% will have advanced adenomas and 8% invasive colorectal cancer.[3]

Along with clearly benign polyps and clearly invasive cancers, iFOBT-based screening detects many lesions in the act of progressing from one to the other. These present the gastroenterologist, the radiologist, the pathologist and the surgeon with both a diagnostic challenge and complex clinical decision making to avoid overtreatment and unnecessary mortality and morbidity on the one hand and under treatment on the other. This dilemma is most acute for rectal lesions where standard surgical resection techniques are associated with higher rates of mortality and serious morbidity such as a permanent stoma and sexual dysfunction, which can be avoided by organ sparing techniques.[4]

Ideally, preoperative staging would allow for accurate prediction of the presence of invasion and the chance of local lymph node metastases. With this knowledge efficient organ sparing techniques such as piecemeal endoscopic mucosal resection (pEMR) could be performed on all non-invasive lesions, en bloc organ sparing techniques such as Endoscopic Submucosal Dissection (ESD), Transanal Endoscopic Microsurgery (TEM) and Transanal Minimally Invasive Surgery (TAMIS) could be used for early invasive cancer, and standard surgical resection reserved for massively invasive cancer and those with a higher risk of lymph node involvement. Unfortunately, current preoperative staging is far from perfect. The magnitude of this problem is perhaps most clearly demonstrated by the TREND study[5], where 13% (27/202) of large rectal polyps preoperatively clinically staged as benign were subsequently found to be malignant at histology.

Currently staging is performed primarily by careful endoscopic evaluation of the lesion looking for endoscopic surface features of the lesion predictive of invasion. While reasonably sensitive when performed by experts, it is not highly specific so that only 50% of lesions predicted to be invasive by expert endoscopic evaluation prove to be invasive at pathology.[6] Biopsy of the lesion is frequently performed but is prone to sampling error and is often too superficial to accurately diagnose invasion. Cross sectional imaging with MRI has a good predictive value for differentiating more advanced tumour stages but performs poorly in distinguishing pT0 from pT1 and pT1 from pT2, tending towards an over staging of benign pT0 lesions as pT2 cancers. Endoscopic ultrasound is highly operator dependent but again tends to lead to over staging

due to an inability to differentiate submucosal fibrosis from invasive cancer.

The consequence of the poor performance of preoperative staging methods is that staging of early stage cancers is increasingly being performed by en bloc diagnostic resection. This approach has already been formalized for other early GI cancers such as oesophageal cancer[7] but not yet for colorectal cancer. For diagnostic resection, accurate pathological examination must be possible. Currently most colorectal lesions that are not overtly cancerous by endoscopic assessment are resected by piecemeal endoscopic mucosal resection (pEMR). pEMR is quick, cheap and safe and therefore highly efficient to perform. However, the pathologist cannot optimally assess the resulting multiple pieces of polyp or cancer and missing pieces go unnoticed. This can lead to diagnostic uncertainty so that even after histology T0 lesions cannot be differentiated from T1. This leads to both possible over staging with unnecessary surgical resection and under staging with under treatment. Surgical resection due to uncertain histology after pEMR for lesions staged as benign at endoscopic inspection has been reported to occur in 3.5% of cases.[8] Malignant recurrence at the site of pEMR resection of benign adenomas is seen in 1-2% of cases.[9,10] The likely explanation is that small areas of invasion were missed in the pEMR specimens.

Since the great majority of lesions endoscopically assessed to be benign are indeed benign the current approach outside Japan is to accept these limitations of pEMR especially outside the rectum. Outside the rectum en bloc local resection with ESD is more difficult with higher rates of complications and surgical resection is relatively straightforward. However, within the rectum the reverse applies. ESD is easier and safer in the rectum and standard surgical resection has higher rates of complications and may require removal of the anus and a permanent stoma, which patients are very keen to avoid. Within the rectum TEM and TAMIS are also possible alternative treatments. The safety and feasibility of en bloc resection in the rectum coupled with the current limitations of preoperative staging of polyps are leading to a shift away from pEMR in the rectum especially in lesions where early invasion cannot be completely excluded on endoscopic inspection.

There are currently several techniques available for local en bloc resection of large non-pedunculated rectal lesions in the Netherlands, including endoscopic submucosal dissection (ESD), surgical transanal resection, transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS).

TEM utilizes specialized equipment and endoscopic instruments for a magnified three-dimensional view of 220° of the rectum and access up to 24 cm from the anal verge, for precise dissection of select low, middle, and upper rectal tumours. The resectoscope allows access to more proximal rectal lesions than traditional transanal excision; however, as the distal rectum will form the seal with the resectoscope, tumours less than 5 cm from the anal verge are not well visualised. With better visualisation, TEM results in improved oncologic outcomes than

traditional transanal excision.[11] TEM uses a specialised rigid proctoscope (12 or 20 cm in length) with an adapted insufflator, a 30° TEM scope, and specialised angled instruments. Transanal Minimally Invasive Surgery (TAMIS)[12,13] (figure 1) provides the benefits of advanced videoscopic transanal excision at a fraction of the cost of TEM.[14] Compared to TEM, TAMIS requires no investment. The SILS ports are relatively inexpensive, and normal laparoscopic instruments, including graspers, thermal energy devices, and needle drivers, are used for resection.[14] The TAMIS port has a shorter shaft length, allowing an increased working angle and more distal dissection compared to the TEM port.[15] In addition, TAMIS may be less traumatic to the anal sphincter than traditional TEM.[16]

Endoscopic Submucosal Dissection (ESD) is performed by lifting the lesion by 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 2). ESD results in a high en-bloc resection rate even in large lesions, a high R0 resection rate and a low recurrence rate of around 2%.[17] However, ESD is technically difficult to perform and associated with high rates of perforation (5%)[18] and long procedure times. Fortunately the clinical consequences of perforation in the rectum are usually limited and can almost always be treated conservatively. ESD also appears to be cheaper than TEM[19] although no cost comparison with TAMIS has been published to date.

Currently colorectal ESD is centralized in expert centres in Western countries. A relatively long learning curve, long procedure times, uncertain indications, poor financial compensation, lack of formalized training and shortage of gastroenterologists due to the introduction of colorectal cancer screening programs have meant that colorectal ESD has been slow to be introduced in the West with a shortage of skilled operators and capacity. In contrast TAMIS has been shown to have a short learning curve, short procedure times, requires no specialist equipment, is financially well compensated and is being quickly introduced even in relatively small peripheral hospitals in the Netherlands.

While there have been no published reports of a comparison between ESD and TAMIS, several attempts have been made to compare ESD and other local surgical excision techniques, either TEM or direct transanal resection (TAR), in a non-randomised fashion. One large single centre study including 63 patients concluded that TEM and ESD were equivalent in terms of R0 resection and recurrence but recommended ESD as the treatment of choice due to the avoidance of anaesthesia.[20] Two systematic reviews have been performed to compare the ESD with surgical local resection approaches.[17,21] The most recent compared ESD to local excision including both TAR and TEM (but not TAMIS), and included data from four studies with a total of 307 patients.[21] The authors found equivalent rates for R0 resection and complications but significantly lower rates of recurrence (1.6% vs 15.2%) and shorter hospital stay for ESD. The second slightly older study compared 11 ESD and 10 TEM series between

1984 and 2010 including 2077 patients.[17] The authors show a significantly lower en bloc and R0 resection rate for ESD and a higher rate of further abdominal treatment necessary after ESD. The complication rates were equivalent for both procedures but ESD led to significantly fewer recurrences (2.6%) compared to TEM (5.2%).

These two systematic reviews come to opposite conclusions as to which is the treatment of choice. The older and bigger of the two includes data from the early years of performance of ESD largely performed in the Far East and is therefore not representative for current practice in the West. The study also only includes TEM as the surgical technique and not TAMIS. The more recent review includes relatively few patients for a meta-analysis and includes both TEM and TAR as the surgical technique, the latter of which has clearly been shown to be an inferior approach and is largely obsolete.[21] Finally, none of the studies randomised patients to one treatment or the other and therefore are likely to be greatly influenced by selection bias. As a result, in daily clinical practice the choice between ESD and TAMIS depends on the availability and nature of local expertise and is not evidence based.

For this reason, the aim of this study is to perform a multicentre, randomised controlled study comparing ESD to TAMIS for large (>20 mm) non-pedunculated rectal lesions in a Western population. We aim to test our hypothesis that ESD is initially more time-consuming but is more cost-effective in both the short and long term due to lower costs, a higher number of R0-resections and lower recurrence rates in lesions that prove to benign with equivalent rates of additional surgical resection for invasive lesions. Additionally we hope to be able to comment on a trend towards worse oncological outcome in patients undergoing additional resection for malignant lesions after TEM compared to pEMR. This counterintuitive trend was seen in the TREND study, possibly due to the breaching of oncological planes during the TEM procedure. The TREND study also found higher rates of conversion to transabdominal resection with TEM for benign lesions compared to pEMR perhaps due to the immediate availability of this option.

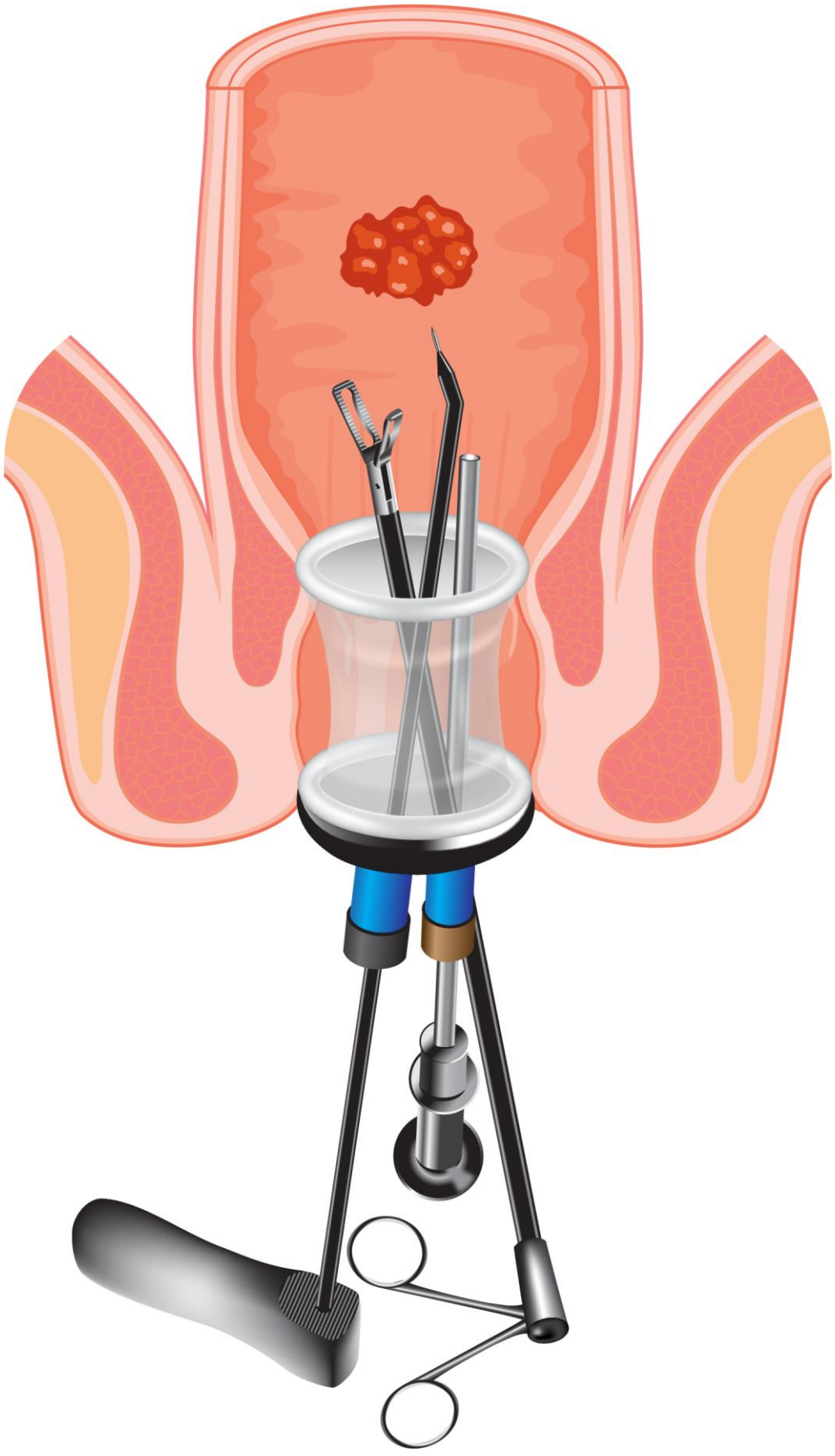

Figure 1. 1a) TAMIS technique

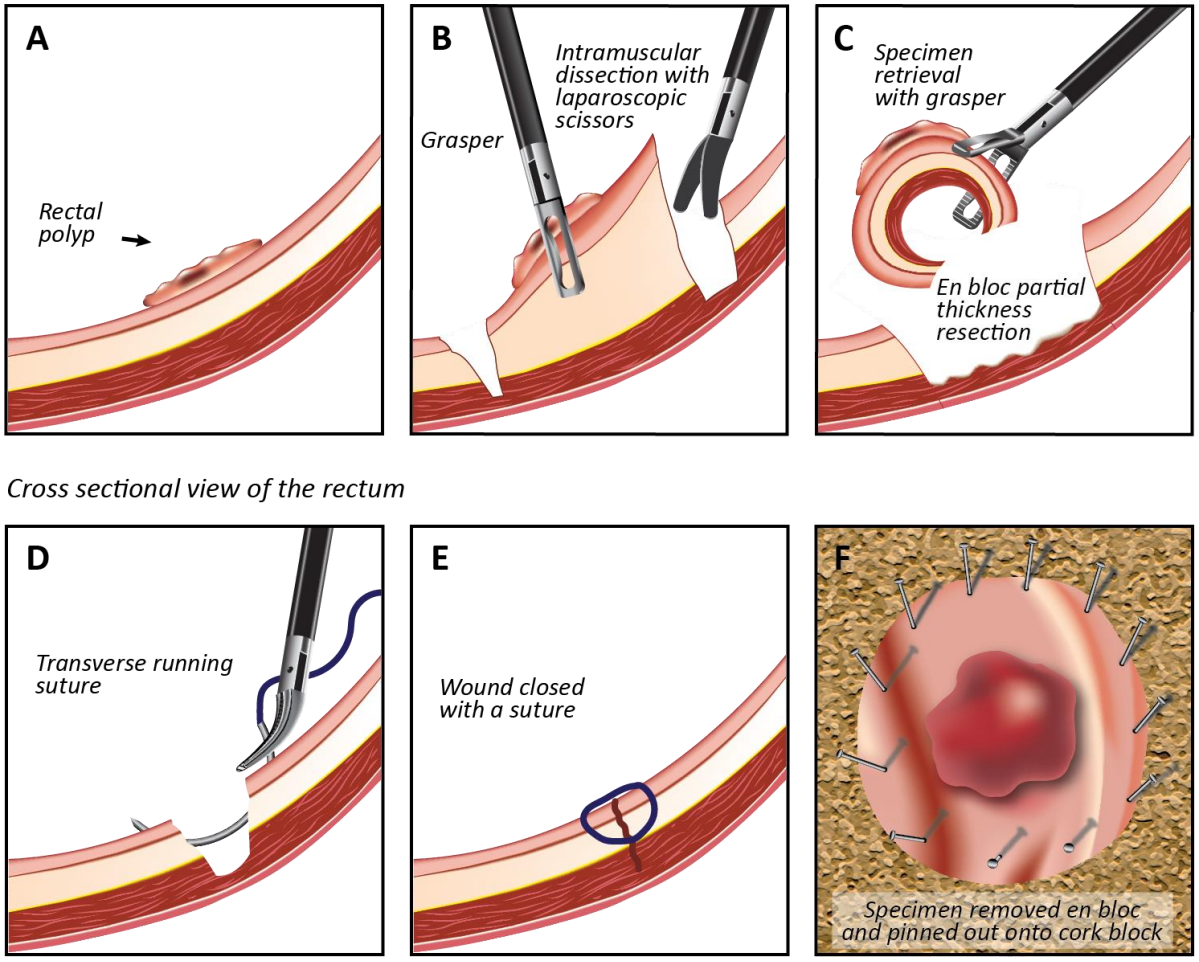

Figure 1.1b) TAMIS technique

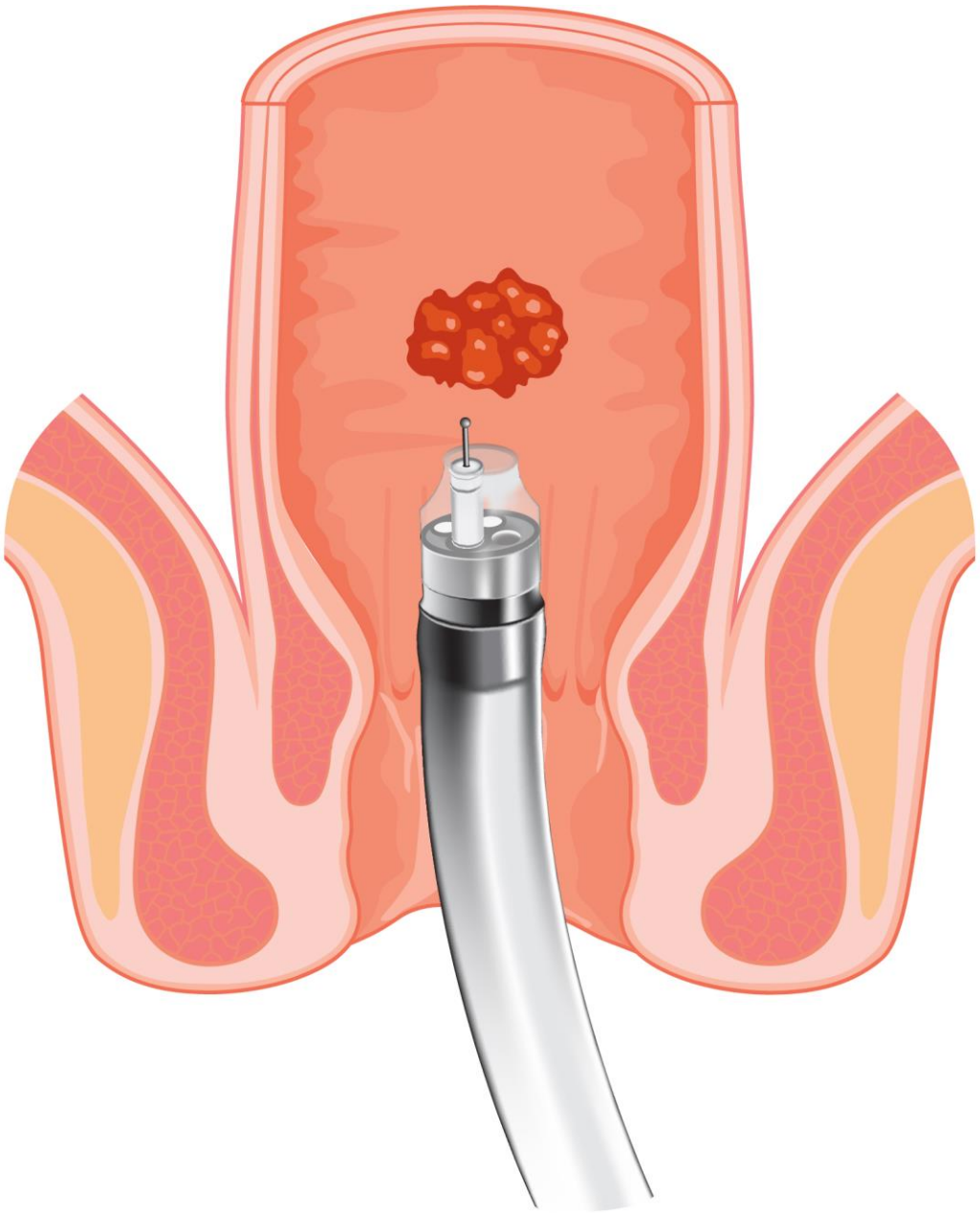

Figure 2. 2a) ESD technique

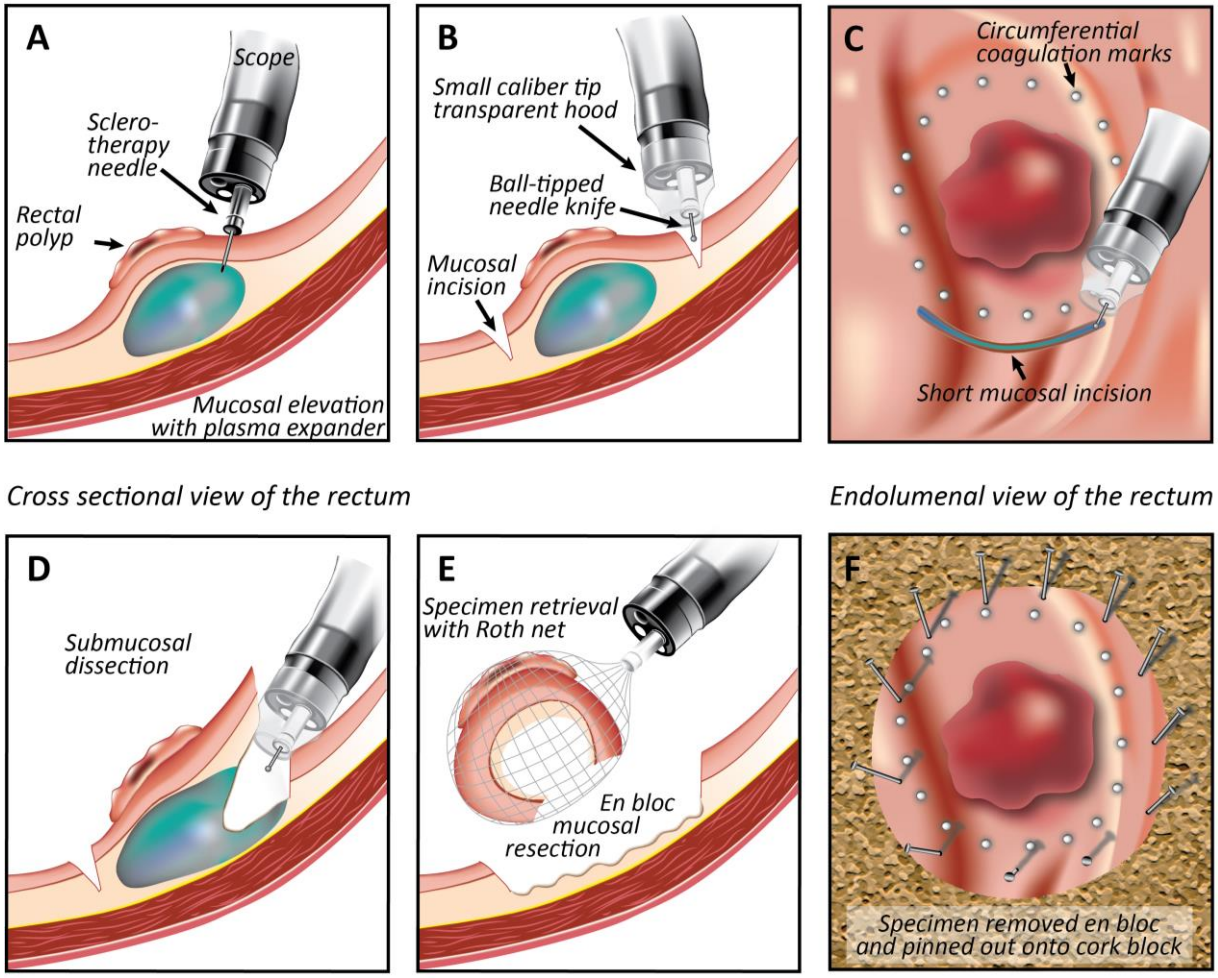

Figure 2. 2b) ESD technique

2 OBJECTIVES

All objectives will be a comparison between the two study arms.

Primary Objective:

- To compare the cumulative recurrence rate at follow-up rectoscopy after 6 and 12 months, either as visible residual disease confirmed at histology as neoplastic after removal or, if no visible residual disease is present, from biopsies of the scar

Secondary Objectives:

- To compare the en bloc resection rate, defined as macroscopic removal of the lesion in a single piece.
- To compare the radical (R0-) resection rate, defined as dysplasia free vertical and lateral resection margins at histology for benign lesions
- To compare the radical (R0-) resection rate, defined as dysplasia free vertical and lateral resection margins at histology for invasive lesions.
- To compare the perceived burden and quality of life among patients
- To compare the cost effectiveness at 12 months
- To compare the need for additional trans abdominal surgery (open or laparoscopic) for either complications of the initial procedure or due to unfavourable pathology at 12 months
- To compare the complication rate
- To compare the long-term recurrence rate at follow-up rectoscopy at 12 months either as visible and subsequently resected recurrent/residual disease or, if not present, from biopsies of the scar.

3 STUDY DESIGN

Design

The study will consist of a multicentre, randomised controlled comparison of TAMIS and ESD for the resection of rectal non-pedunculated adenomas larger than 20 mm. All patients identified with such a lesion suitable for local resection will be rescheduled for a new procedure to locally resect the lesion (standard care). Prior consultation will take place to explain the risks and benefits of resection (standard care) and to discuss informed consent (study care). Reasons for non-participation and/or exclusion will be recorded. Patients will be randomised to either one or other treatment modality. Stratified weighted randomisation will be performed to ensure similar numbers of lesions involving the dentate line and similar numbers of lesions <4cm in diameter and ≥4cm in diameter are randomised to each treatment arm. Due to the nature of the treatment, neither patients nor the doctors participating in this study will be blinded. All patients will undergo MRI of the rectum (recommended standard care, fixed study care) and have a follow-up rectoscopy after 6 months (standard care) with biopsies of the scar (recommended standard care, fixed study care). In case of recurrence, an attempt at endoscopic resection will be performed. All patients will be then scheduled for a further follow-up rectoscopy at 12 months (figure 3). Endoscopic ultrasound investigation is recommended (standard care).

Setting

Colorectal ESD is technically highly demanding. In the 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.[22-24] Based on this literature, a minimum of 25 colorectal ESD-procedures is considered to be required to achieve expert experience. To ensure that our results are not 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 randomised to the ESD arm. Previous oesophageal and stomach ESD experience alone will not be enough to ensure colorectal ESD expertise, as colorectal ESD is known to be technically more demanding than upper gastro-intestinal ESD due to the more challenging anatomical characteristics of the colon (thin wall and existence of peristalsis, folds, flexures, and faecal fluid).[25] Patients randomised to the ESD arm will therefore be referred to ESD expert centres (UMC Utrecht, Erasmus MC, LUMC), or other medical centres, which obtain this threshold during the study period. ESD in lesions in the rectum not involving the dentate line is easier and safer than in the rest of the colon.

TAMIS, due to its use of standard laparoscopic equipment, has a relatively steep learning

curve.[26] To ensure that our results are not biased by the TAMIS learning curve, this study will only allow surgeons that have performed > 25 TAMIS procedures in the past 3 years to treat patients randomised to the TAMIS arm.

Duration

Inclusion period maximum 36 months*

Follow-up period 12 months

Total maximum 48 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 36 months.

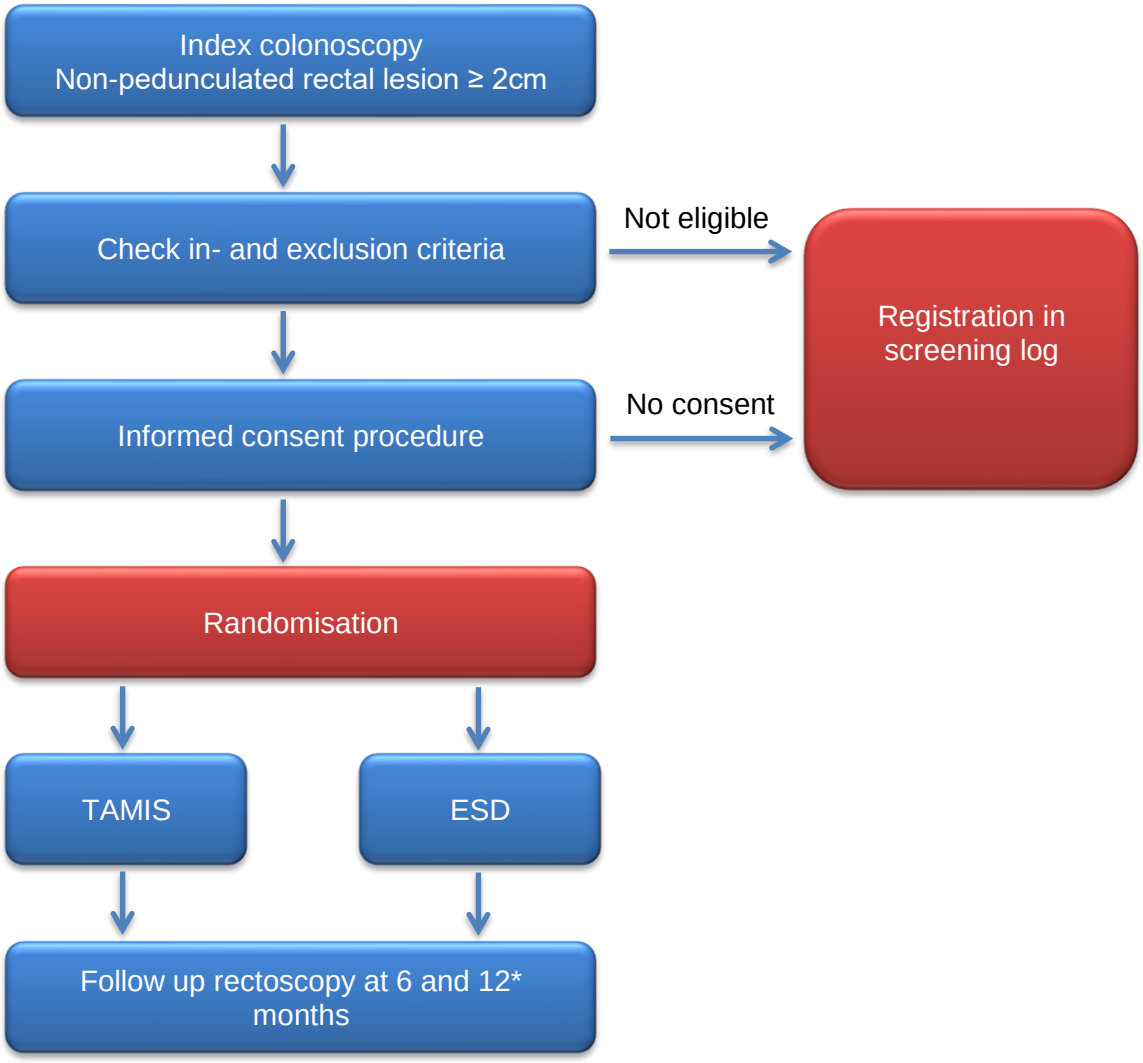

Figure 3. Flow-chart of the study design

* If recurrence is found at the 12-month colonoscopy this will be resected and a further surveillance colonoscopy planned 6 months later. In patients in whom no recurrence is found at the 6-month rectoscopy, the next surveillance rectoscopy will be 12 months after initial treatment.

4 STUDY POPULATION

4.1 Population

All patients 18 years of age or older with a non-pedunculated polyp in the rectum, with the presence of any endoscopic feature suggestive of early invasion 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 >2cm in the rectum where the bulk of the lesion is below 15cm from the anal verge found at colonoscopy
- ≥18 years old
- Written informed consent

4.3 Exclusion criteria

A subject is not eligible for inclusion in case of the presence of any of the following criteria:

- Features of advanced disease or deep-submucosal invasion at optical endoscopic evaluation.
- Features of advanced disease on cross-sectional imaging. Where there is discordance in the results, the optical endoscopic evaluation will be given the most weight and the case discussed by an expert panel of four study participants.
- Prior endoscopic resection attempt
- The risk exceeds the benefit of endoscopic treatment, such as patients 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 parameter cumulative recurrence rate at 12 months. Sample size for recurrence rate is calculated based on the assumption that the recurrence rate is 3% in the ESD group and 6% in the TAMIS group based on a systematic review of the literature specifically for studies performed in the West, that we have performed. If there is a true difference in favour of ESD of 3%, then 166 patients are required to be 80% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference in favour of the TAMIS of more than 6%.

(Software: PASS Version 15 – www.ncss.com). We have chosen a non-inferiority margin of 6% because we believe that this difference in risk of benign recurrence between the intervention group and usual care group is clinically acceptable. To correct for patients lost-to-follow-up (4%) and patients requiring additional surgical resection due to adverse histology (12%) a total of **198 patients** will be included; 99 patients in each arm.

Based on the extensive experience with colorectal screening programs in the US, the incidence of large rectal non-pedunculated polyps in the Netherlands is estimated to be between 250-500 new cases a year. We estimated participation of 15 centres is required to complete the inclusion period within 3 years.

To avoid unnecessary delay we will start this trial with 5 centres and will extend the number of centres during the course of the trial. In order to determine the number of centres that is interested in participating, we will organise a meeting in the LUMC Leiden. During this meeting potential local investigators will be able to give feedback on the protocol and to confirm their willingness to participate.

5 TREATMENT OF SUBJECTS

5.1 Investigational treatments

5.1.1 Procedure definition of TAMIS arm (standard care)

The dose and type of anaesthetic given will be at the discretion of the anaesthetist and will be registered in the CRF. The precise instruments and port used for TAMIS will be at the discretion of the surgeon and will be noted in the CRF.

The margins of the lesion may be marked with coagulation dots to facilitate the incision at the lesion margins at the discretion of the surgeon. The incision must be placed at a distance of at least 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. Pneumorectum is achieved using CO_2 for insufflation. Initial pressure settings should be between 12 and 20 mm Hg and can be increased if there is difficulty in maintaining distension for visualisation. An anal block with Bupivacaine or Ropivacaine bilaterally is recommended. If a lesion is very distal (i.e., at or just above the dentate line), the distal margin can be incised using standard transanal retractors and electrocautery. Before the start of the lateral portion of the dissection, the TAMIS port can be inserted to be used for the remainder of the dissection. A partial thickness resection of the lesion will be performed following the intramuscular plane of the muscularis propria using a diathermic hook. The wound will be closed, as required, with laparoscopic suture material in a transverse direction so as not to narrow the lumen of the rectum. All of this is considered standard care, however, it should be recorded 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 Surgical Colorectal Audit (DSCA) from the Dutch Institute of Clinical Auditing (DICA).

5.1.2 Procedure definition of ESD arm (standard care)

The dose and type of sedation given will be at the discretion of the endoscopist and will be registered in the CRF. All endoscopies 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. The choice of ESD knife is at the discretion of the performing endoscopist. The type of ESD knife must be mentioned in the CRF. The margins of the lesion may be marked with coagulation dots to facilitate the incision at the lesion margins at the discretion of the endoscopist. The incision must be placed at a distance of at least 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. The endoscopist is allowed to perform the resection using the hybrid ESD (hESD) technique. The hESD technique consists of a circular incision around the lesion, with partial dissection of the submucosal layer sufficient to allow capture of the whole lesion 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 is suspected and must be mentioned in the CRF.
In the case of intraprocedural perforation, this will be treated using clips and desufflation of the peritoneal cavity if required, with an intravenous cannula. In the case of minor bleeding from a small vessel, contact coagulation with the tip of a knife or coagulation with haemostatic forceps will be used for haemostasis. In cases of a severe bleeding from a large vessel or artery, haemostatic forceps will be used for haemostasis. If a pulsating large vessel is exposed within the resection wound, clipping can be performed 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 Registration of Complications of Endoscopy (DRCE) from the Dutch Institute of Clinical Auditing (DICA).

5.2 Use of co-medication (if applicable)

If patients use antithrombotic drugs, the Dutch guideline on ‘Endoscopic interventions in patients with anticoagulation and platelet aggregation inhibition’ will be followed in the case of ESD and the Dutch Guideline ‘Perioperative use of anticoagulants’ from the Dutch Federation of Medical Specialists (https://richtlijnendatabase.nl) in the case of TAMIS.
In summary, patients are divided into high- and low-risk groups according to the predicted risk of thromboembolism. In high-risk patients, withdrawal of coumarin derivatives 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, coumarin derivatives 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

- Cumulative recurrence rate at follow-up rectoscopy after 6 and 12 months, histologically confirmed from resected visible 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 of the treatment 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 trans abdominal surgical management at 12 months
- Cost effectiveness at 12 months. Costs will be calculated from a hospital perspective, including costs of (repeat) surgery and hospital stay. The difference in costs will be compared to the difference in local recurrence and the difference in quality-adjusted life years (QALYs). For more details, see chapter 8 of this study protocol.

* Complications are defined as follows:

  - Intraprocedural peritoneal breach (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 cannot be controlled by standard local haemostasis techniques such as electrocoagulation or clips and that requires (1) transfusion or (2) termination of the TAMIS or ESD procedure.
  - 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 intervention to obtain haemostasis.
  - Postprocedural bowel perforation (yes/no), defined as a bowel perforation within 30 days after the procedure that is detected after completing of the procedure

during which a peritoneal breach 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 (distance of the anal edge of the lesion from the anal verge (mm))
- Size of the polyp by endoscopic assessment (length (mm) x width (mm))
- Surface features (granular, non-granular, mixed)
- Endoscopic ultrasound details.
- MRI of the rectum details.
- Performing endoscopist or surgeon.
- Use of antithrombotic 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
- En bloc resection performed, if no: number of pieces
- Type and brand of ESD implements used (ESD-group)
- Type and brand of TAMIS implements used (TAMIS-group)
- Length of the procedure (in minutes), defined as the total time from introduction of the endoscope or TAMIS port until removal of the endoscope or TAMIS port.
- 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

Randomisation will be stratified by the size of the polyp (<40 mm vs. ≥ 40 mm) and the involvement of the dentate line using random block sizes of five per block. Patient data are entered into a GCP-approved computerized database (http://castoredc.com/nl/) after inclusion

and exclusion criteria have been checked and informed consent has been obtained. This program will randomise patients to undergo either ESD or TAMIS. The results of this randomisation will be directly copied to the study coordinator and the Datacenter Department of Surgery (LUMC)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.

	Before randomization	Baseline (prior to treatment)	Treatment (ESD/TAMIS)	30 days after ESD/TAMIS	Follow-up 4 days (Q)	Follow-up 4 weeks	Follow-up 6 months	Follow-up 12 months	Follow-up 18 months*
Informed consent	X								
Baseline eCRF - Patient characteristics - Polyp characteristics		X							
Randomization		X							
Treatment eCRF Complications - Histopathology			X						
30 day post treatment				X					
Follow-up rectoscopy 6							X		
Follow-up rectoscopy 12								X	
Follow-up rectoscopy 18									X *
(EORTC) QLQ-CR29		X			X	X	X	X	
EQ-5D-5L		X				X	X	X	
COREFO		X			X	X	X	X	
(Shortened) iMCQ						X	X	X	
(Shortened) iPCQ						X	X	X	

Table 1. Summary of the study procedures

* An 18-month endoscopy will only be performed when recurrence is found at the 12-month colonoscopy.

6.3.1 Recruitment phase (both groups):

- The local coordinating investigator of the participating centre will perform initial recruitment of patients. 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 3).
- 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 3).
- The local coordinating investigator will enter the stratification factors in Castor EDC. This program will randomise patients to undergo ESD or TAMIS. The results of this randomisation will be directly copied to the study coordinator by Castor EDC (automatic mail delivery).

6.3.2 Treatment phase (per group):

1. TAMIS-group:
    - The patient is scheduled for a TAMIS procedure in one of the expert centres
    - The patient will be prepared for the procedure according to the local protocol
    - TAMIS is conducted according to the procedure definition (see 5.1.1)
    - Details of the procedure are recorded in the appropriate CRF.

2. ESD-group:
    - The patient is rescheduled for a new colonoscopy in one of the expert centres
    - 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)
    - Details of the procedure are recorded in the appropriate CRF.

6.3.3 Handling of the resected specimen

6.3.3.1 Handling by the endoscopist or surgeon.

Appropriate handling of the resected specimens 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 normal mucosa surrounding the lesion is evenly flattened and the mucosal surface can be observed (figure 4). The specimen must be fixed as quickly as possible as it autolyses rapidly after resection. The lesion will be soaked in a formalin solution to prevent drying of the specimen. Thereafter, the endoscopist or surgeon is required to appropriately display the specimen so that the difference between the specimen and the clinical images is minimized and the tumour margin of the specimen can be judged. The endoscopists and surgeons 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 tumour size can be accurately conveyed.

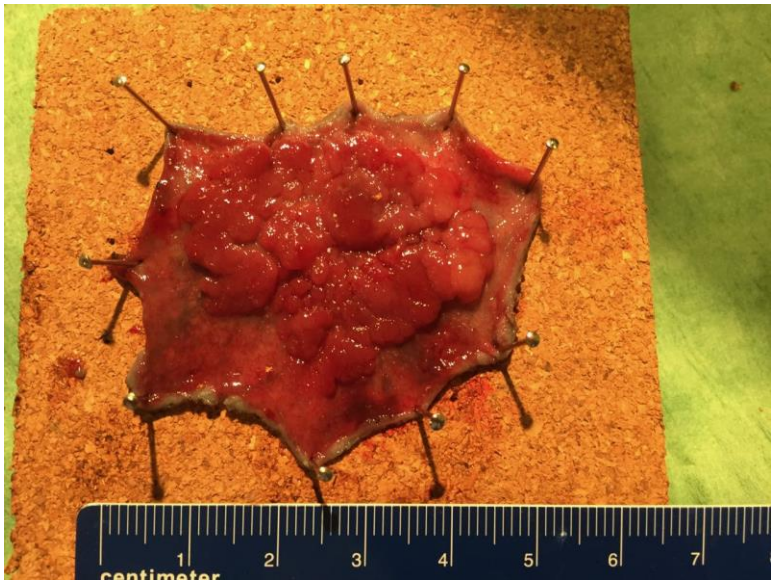

Figure 4: ESD specimen pinned out and photographed.

6.3.3.2 Handling by the pathologist

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 should be photographed, measured and the macroscopic appearance described including the lesion, mucosal defects, other abnormalities and the resection margins
ii) The specimen should be inked. A different ink colour should be used for the resection plane and the edges of defects
iii) A tangent that touches the focus closest to the horizontal tumour 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 5)

v) All slices should be embedded in cassettes for histological diagnosis. In case of long slices (> 2cm), the slice should be cut in half and both halves embedded after ink is applied to the cut edge.

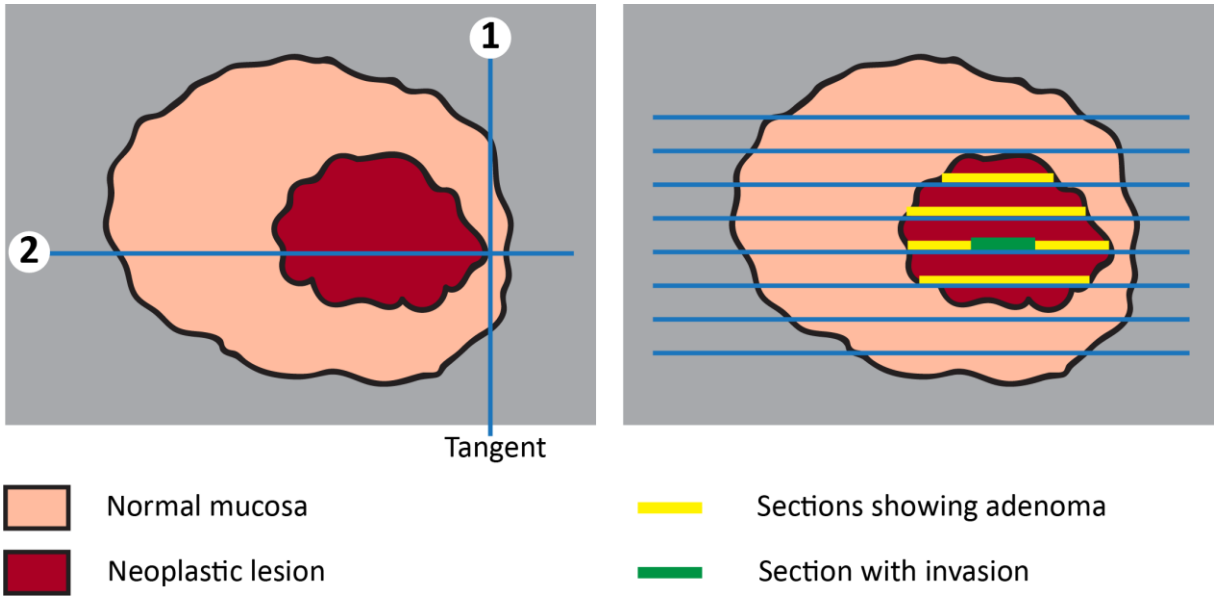

Figure 5: Plan for sectioning and paraffin embedding the specimen. A tangent (1) is drawn to the most threatened edge of the resected lesion. The first section (2) is made at right angles to this tangent and through the point where the tangent touches the lesion. Further sections are taken at regular intervals of 2mm from this section.

6.3.4 Histological diagnosis

The pathologist at the centre in which the resection is performed will carry out the histological diagnosis of tumours in accordance with the WHO classification of tumours and Vienna classification.[27] The histological type and resection tumour 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. In the case of adenocarcinoma, the width of the invasive component, minimal distance to the vertical and lateral resection margins, depth of submucosal invasion, (measured from the muscularis mucosae or a virtual line extrapolated from visible muscularis mucosae at the edge of the invasive area), the degree of differentiation, the presence of lymphatic or angio-invasion and the degree of budding will be assessed.

6.3.5 Follow up

6.3.5.1 Post procedural 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.

6.3.5.2 Follow-up at 6 months (both groups):

A follow-up rectoscopy will be performed 6 months after the procedure for all patients as recommended by the Dutch guideline for colonoscopy surveillance.[28] The scar will be checked for residual disease. In case of macroscopic residual disease this will be 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 rectoscopy will be performed as standard (standard care).

If no recurrence is found at the 6 months rectoscopy, the next rectoscopy will be planned at 12 months. If recurrence is found at the 6 months rectoscopy the recurrence will be treated by endoscopic resection and the next follow-up rectoscopy will planned again after 6 months (T=12 months) to check the scar. This will be repeated until no recurrence is found.

6.3.5.3 Follow-up at 12 months (both groups):

A follow-up rectoscopy will be performed 12 months after the procedure for all patients. The scar will be checked for residual disease. In case of macroscopic residual disease this will be resected (standard care). If not**,** biopsies of the scar will be taken (recommended standard care, fixed study care).

6.3.6 Perceived burden and quality of life assessment

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

- (EORTC) QLQ-CR29[29]: is a quality of life instrument specific for colorectal cancer and is recommended by the ICHOM for colorectal cancer. Measurement will be performed at baseline, 4 days and 4 weeks after TAMIS/ESD and after the 6 and 12 months follow-up endoscopy.
- EUROQOL EQ-5D-5L[30]: 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 TAMIS/ESD, and after the 6 and 12 months follow-up endoscopies. 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[31]: will be used to measure disease-specific health related quality of life. This has been specifically developed to measure ano-rectal symptoms and has been used in many previous studies of transanal surgery. Measurement will be performed at baseline, 4 days and 4 weeks after TAMIS/ESD and after the 6 and 12 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 using the Survey function of Castor EDC (http://castoredc.com/nl/). These surveys will automatically be linked to the eCRF in Castor EDC. Castor EDC will automatically send and collect the survey at time points specified by the user. Data managers of the Datacenter Department of Surgery (LUMC) can track the progress of the surveys and will send reminders when participants don't respond.
Patients who prefer to complete the forms on paper will receive the questionnaires by post. 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 dropout and no new patient will be enrolled.

6.6 Follow-up of subjects withdrawn from treatment

The follow-up of patients withdrawn from the study 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 that have performed >25 colorectal ESD procedures to treat patients randomised to the ESD arm and only allow surgeons that have

performed >25 TAMIS procedures to treat patients randomised to the TAMIS arm. This will not only prevent the study being biased by a learning curve, but will also prevent unacceptably high complication rates.
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 administration of intravenous antibiotics.[18] 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), rescue surgery will be carried out as clinically indicated.

To estimate the expected rates of complications in our study we have performed a review of the literature. It should be noted that for ESD the literature is dominated by the Far East where ESD has been practiced for longer and in far greater numbers. Where possible we have given more weight to the findings from Western studies which we feel will more accurately reflect the situation in the Netherlands.

TAMIS: There are several single centre studies of TAMIS that have published complication rates. The biggest and most recent of these had a complication rate of 11%. Haemorrhage (9%), urinary retention (4%), and scrotal or subcutaneous emphysema (3%) were the most common.[32] The authors noted peritoneal entry in 4% of cases but managed to close all cases successfully without sequelae. There was no procedure related mortality.
In a small series from the UK the complication rate was 11% consisting of urinary retention (7%) and postoperative bleeding (4%). There was no procedure related mortality.[33]
The second biggest series of 75 consecutive cases reported complications in 7% with 2 diverting ileostomies due to peritoneal entry and one case each of rectal stenosis, postoperative bleeding and recto-vaginal fistula. These last 3 were all managed non-operatively.[34]
A Norwegian series using TAMIS for 51 adenomas reported a 12% complication rate.[35]
A systematic review of all published reports of TAMIS from 2010 to 2013 reported complications in 7.4%.[15]

ESD: Only a few Western single centre studies have evaluated the complication rates of colorectal ESD. A study published in 2012 reported a perforation rate of 1.3% and a bleeding rate of 7.9%. All complications were managed conservatively and there was no need for surgical intervention. No procedure-related mortality was observed. A French study reported a perforation rate of 0% after experience with 25 colorectal ESDs.[22] In Asian studies,

intraprocedural perforation rates are reported to be 5.9% and delayed bleeding rates 0.7-2.2%.[36] Delayed perforations are seldom reported (incidence of 0.1- 0.4%).[37] In a pilot evaluation of rectal ESD in the LUMC Leiden, complications rates are low. So far, no periprocedural complications have occurred that have required surgery (n=45).

Based on the literature, we expect the following en bloc resection rates, R0 resection rates and recurrence rates to occur in our study:

TAMIS: The recurrence rate after TAMIS has been published in a number of single centre studies. The biggest and most recent showed an en bloc resection rate of 95%, an R0 resection rate of 93%. The local recurrence rate was 6% and the rate of metastasis 2%.[32]
A small UK series had a R0 resection rate for benign lesions of 70% and a recurrence rate of 6% although not all patients received follow up.[33]
In a series of 75 consecutive cases there was a 6% local recurrence rate. En bloc and R0 resection rates are not given.[34] It should be noted that recurrence rates and R0 resection rates for many series refer to both benign and malignant lesions together.
A Norwegian series of 51 patients in whom TAMIS was performed only for adenomas reported en bloc resection rate of 69% and an R0 resection rate of 47%.[35]
TAMIS and TEM are similar procedures and the results of the Dutch TREND study have just been published. Here the recurrence rate after TEM for benign rectal polyps was 11%.
A systematic review of all TAMIS procedures published between 2010 and 2013 did not report recurrence rates. Not all reports mentioned the en bloc or R0 resection rates but from those that did the authors conclude an en bloc resection rate of 96% and an R0 rate of 95.5% (positive margins in 4.5%).[15]

ESD: Only a few Western single centre studies exist that evaluated en bloc resection rates and R0 resection rates of colorectal ESD. A study published in 2012 presented their experiences with ESD of rectal tumours (82 cases) and showed that R0-resection was achieved in 76-84.5% of the patients after experience with 25 ESDs.[24] A Swedish study analysed the results of 29 ESD carried out in a single institution.[38] The percentage of en-bloc resections and R0 resections were 72% and 69%, respectively. A recent Polish study showed that en-bloc resection was achieved in 50/70 resections.[39] Within the en bloc resections 96% 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 resection procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

ESD related AEs are:
Intraprocedural perforation, intraprocedural bleeding, post procedural bleeding or post procedural serositis that requires (prolonged) admission <10 days and/or maximum 4 units of blood transfusion and/or endoscopic or percutaneous (re-)intervention.
This is defined according to the Dutch Registration of Complications of Endoscopy for non-severe complications.

TAMIS related AEs are:
Peritoneal entry, intraprocedural bleeding, post procedural bleeding or post procedural serositis that requires (prolonged) admission <10 days and/or maximum 4 units of blood transfusion and/or endoscopic or percutaneous (re-)intervention.
This is defined according to the Dutch Surgical Colorectal Audit for non-severe complications.

7.2.2 Serious adverse events (SAEs)

Documentation and reporting of SAE's to the METC will be limited to SAE's defined as severe by the Dutch Complication registration of the Dutch Society of Gastrointestinal Diseases (NVMDL) or Grade 3 according to the Clavien–Dindo classification of surgical complications[40], that occur within 30 days and that are related to the 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 project leader has first knowledge of the serious adverse event. Endoscopic related SAE's are:
Intraprocedural perforation, intraprocedural bleeding, postprocedural bleeding or postprocedural serositis that requires:

- 10 days (additional) admission and/or
- 4 (EH) blood transfusions and/or
- angiographic or surgical intervention and/or
- ICU admission
- and/or death

Any other event with a possible or definite causal relation with the study intervention (TAMIS or ESD) as judged by the treating physician that requires:

- 10 days (additional) admission and/or
- 4 (EH) blood transfusions and/or
- angiographic or surgical intervention and/or
- ICU admission
- and/or death

Local investigators will report SAE's to the project leader in the LUMC Leiden as soon as possible after becoming aware of a SAE. Related SAEs that result in death or are life threatening within a month should be reported not later than 7 days after the responsible investigator has first knowledge of the adverse event. 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 to the project leader within the abovementioned time period. The project leader will have the responsibility to report this 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

The statistician responsible for the trial will perform all statistical analyses. A non-inferiority study design will be used as outlined in the Sample Size calculation, section 4.4. Statistical analysis will be performed using SPSS software (IBM SPSS Statistics for Windows, version 20.0, Chicago). Data will be firstly summarized and extreme values will be verified to be correct. Statistical analyses will be performed both by intention-to-treat and by per protocol approach, as stated in the CONSORT recommendations for non-inferiority RCTs. To assess the non-inferiority of the ESD procedure, the difference between the cumulative recurrence rates at 12 months (primary outcome) in the intervention (ESD) and control (TAMIS) groups will be compared to the non-inferiority margin of 3% using a one-sided Mantel-Haenszel test (with alpha 0.025) to account for stratification factors.

For the other variables, we will first assess normality; continuous data will be presented as mean with standard deviation (SD) or as median (range) and categorical data as frequency (percentage). The secondary outcomes of the two groups will be compared using the student t-test or Mann-Whitney U test and Chi-square or Fisher's exact test as appropriate. Multivariate regression will be considered for adjustment for possible confounding if necessary. P-values and 95% confidence intervals (95% CI) will be reported. A p-value of <0.05 will be considered significant.

8.1 Economic evaluation

The Health Economic Expert responsible for the study will perform the Economic Evaluation. Costs will be calculated from a hospital perspective, including costs of (repeat) surgery and hospital stay. To perform a cost-price analysis for the TAMIS and ESD procedures, data will be gathered for time needed to perform the procedure, used materials and anaesthesia. Other healthcare will be valued and discounted according to the Dutch guidelines for economic evaluations[41,42]. A shortened version of the Medical Consumption Questionnaire (iMCP) and a shortened version of the Productivity Costs Questionnaire (iPCQ) will be used to evaluate the medical consumption and (loss in) productivity of the participants, used for the economic evaluation. [43,44]

The difference in costs will be compared to the difference in local recurrence (cost-effectiveness analysis, CEA) and to the difference in QALYs (cost-utility analysis, CUA). To estimate QALYs, generic quality of life will be measured using the EQ-5D-5L at baseline, 4 weeks, and 6 and 12 months (classification system and visual analogue scale). The value of quality of life (i.e. utility) will be calculated according to the Dutch tariff for the EQ-5D-5L[45]

(base-case analysis) and the power transformation for the visual analogue scale ($U = 1-(1-VAS/100)^{1.61}$). QALYs will be estimated as the area under the utility curves.
The differences in outcome and costs will be related to each other using net-benefit analysis, depending on the willingness to pay for outcome (NB = WTP×Outcome-Costs). Missing data will be taken into account using multiple imputation.

- Perceived burden and quality of life:
  - (EORTC) QLQ-CR29[29]:
  - (EUROQOL) EQ-5D-5L [30]: 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[31]: Symptoms after treatment will be compared with baseline measurements using McNemar's test.

8.2 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 analyse categorical variables.

8.3 Interim analysis (if applicable)

An interim analysis will be performed after 102 patients (50%) have completed the 6 months follow-up. In this short-term analysis R0-resection rate and recurrence rate between both treatment arms will be compared.

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/favourable 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 resection techniques investigated in this study are standard care in the Netherlands. In the case of benign histology follow-up rectoscopy will be performed 6 months after the procedure, which is standard care in the Netherlands. A further follow-up rectoscopy will be performed 12 months after the procedure which is optional in standard care and fixed care in this study. If macroscopic residual disease is found this will be immediately resected, which is standard care. If not, 3 biopsies of the scar and 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. With regard to the quality of life questionnaires, we have tried to keep the questionnaire length and density of sampling to a minimum 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. After considering these factors, 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 that is in accordance with article 7, subsection 9 of the WMO.
The sponsor (also) has an insurance that 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 an 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.

10.3 Amendments

Amendments are changes made to the research protocol 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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