

**COLOR III: A MULTICENTRE RANDOMISED CLINICAL TRIAL  
COMPARING TRANSANAL TME VERSUS LAPAROSCOPIC TME FOR  
MID AND LOW RECTAL CANCER**

SHORT STUDY TITLE: COLOR III trial

COLOR III study group



*Figure based upon COLOR study by W. Kandinsky: c.1913*

**RESEARCH REFERENCE NUMBERS**

**Clinical trials.gov Number:**

(after institutional review board approval, trial will be registered at Clinicaltrials.gov)

**SIGNATURE PAGE**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor’s SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**

Signature:  
.....

Date:  
...../...../.....

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Position:  
Board of directors

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Prof. H J Bonjer

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## TRIAL SYNOPSIS

Trial Title	COLOR III: A multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer	
Internal ref. no. (or short title)	COLOR III	
Clinical Phase	Phase 3	
Trial Design	Multicentre, randomised clinical trial, superiority design 2 (TaTME) : 1 (laparoscopic TME) randomisation	
Trial Participants	Patients with mid or low rectal cancer	
Main Inclusion criteria	Mid or low rectal cancer, distance 0-10cm from anal verge (MRI defined) Histological biopsy showing adenocarcinoma Stage I-III (MRI and CT abdomen), curative intent (including downstaged after neoadjuvant therapy) Centrally reviewed preoperative MRI	
Main Exclusion criteria	T4 tumour and T3 with MRF involvement on MRI (after neoadjuvant therapy) Ingrowth in anal sphincter complex or m. levator requiring abdominoperineal resection Previous rectal surgery	
Intervention	Rectal resection by transanal TME with laparoscopic surgery	
Control arm	Rectal resection by laparoscopic TME	
Quality assurance	All surgeons will be trained and will have peer reviewed established procedure competence. All surgical procedural videos are kept within patient record information database electronically. All MRI and pathology data will be centrally reviewed.	
Translational research	Tissue from the primary tumour will be used for translational research on prognostic and predictive factors.	
	Objectives	Outcome Measures
Primary	Involved circumferential resection margin (CRM) rate	Pathology CRM <1mm percentage
Secondary	<ul style="list-style-type: none"> <li>• Quality of specimen</li> <li>• Morbidity and mortality</li> <li>• Residual mesorectum</li> <li>• Local recurrence</li> <li>• Disease-free and overall survival</li> <li>• Sphincter saving procedure</li> <li>• Functional outcome</li> <li>• Health related Quality of Life</li> </ul>	<ul style="list-style-type: none"> <li>• Quality assessment by 'Quirke'</li> <li>• Clavien Dindo, 30 &amp; 90 days</li> <li>• Postoperative MRI 3 year</li> <li>• MRI, pathology</li> <li>• Follow-up regimen</li> <li>• Colostomy percentage 1 year</li> <li>• LARS score</li> <li>• EORTC QLQ-29 and 30, EQ 5-D</li> </ul>
Planned Sample Size	1098 patients in total; 732 in the TaTME arm and 366 in the laparoscopic TME arm to demonstrate a reduction of CRM involvement from 7% in the control group to 3% in the TaTME group. (Power 80% with a two-sided level of significance of 5%)	
Planned Trial Period for inclusion	Four years (20+ centres, multinational)	
Total duration of trial – report primary outcome	Nine years - four years	

## **TRIAL SUMMARY**

### **Introduction and background**

The quality of rectal cancer surgery has improved during the last decades with the total mesorectal excision (TME) technique, adaptation of laparoscopic surgery and extralevatory approach for abdominoperineal resection (APR). Nevertheless, surgery for mid and low rectal cancer is associated with relative high rates of incomplete mesorectal excisions and relative high rates of circumferential resection margin (CRM) involvement resulting in significant number of local recurrences. Moreover, patients with mid and low rectal cancer suffer from high rates of morbidity, permanent colostomies and significant impairment of quality of life.

The transanal TME (TaTME) has been developed with use of laparoscopic single port platforms to improve the quality of the TME procedure in mid and low rectal cancer. In TaTME, the tumour is distally approached through the anus with laparoscopic instruments. This potentially facilitates a better quality dissection of the distal mesorectum with adequate visual determination of the distal resection margin and intact specimen. Potentially better specimen results in lower local recurrence rate. The new TaTME technique also facilitates difficult resections in the lower pelvis and has been shown to result in relative low morbidity.

Published cohort studies have shown that the TaTME procedure is safe and is associated with low CRM involvement, better specimen quality and less morbidity in experienced centres compared with laparoscopic TME. Before adaptation of the TaTME as standard surgical therapy for mid and low rectal cancer, a well-designed study is essential to demonstrate its efficacy and safety in a multicentre randomised setting. The primary concern is oncological safety in terms of CRM involvement and local recurrence rate. Secondary concerns are safety in terms of morbidity and functional outcome.

### **Study design**

The COLOR III trial is an international multicentre randomised study comparing short- and long term outcomes of TaTME and laparoscopic TME for rectal cancer. The study will include a quality assessment phase before randomisation to ensure required competency level and uniformity of the new TaTME technique and the laparoscopic TME. During the trial the clinical data will be reviewed centrally to ensure uniform quality.

### **Endpoints**

The primary endpoint of the COLOR III trial is quality of resection defined by involvement of CRM. Secondary endpoints include morbidity and mortality, residual mesorectum on postoperative MRI, local recurrence, disease-free and overall survival, percentage of sphincter saving procedures, functional outcome and quality of life.

### **Statistics and randomisation**

In laparoscopic TME the percentage of involved CRM is estimated 7%. To detect a reduction to 3% with a two-sided level of significance of 5% and a power of 80% a total of 1098 patients is needed, 732 patients in the TaTME arm and 366 patients in the laparoscopic TME arm. Randomisation will be in a 2:1 ratio in favour of the TaTME procedure. It will be stratified for T-stage, preoperative radiotherapy, height of the tumour, gender and BMI. All analyses will be performed on intention-to-treat basis.

### **Main selection criteria**

Patients with a histologically proved single mid or low rectum carcinoma (0-10cm from anal verge) on MRI, eligible for TME surgery with a curative intent, are included. Main exclusion criteria are T4 tumours, T3 tumours with a suspected involved mesorectal fascia (MRF) after neoadjuvant therapy, patients with concomitant metastases or other malignancies, with malignancies in their medical history or with signs of acute mechanical obstruction by the tumour.

### **Follow-up**

Follow-up is based on national guidelines with extra MRI imaging and functional outcome questionnaires. Patients will visit outpatient clinic at least yearly for a follow-up period of five years. At the outpatient clinic the physician will carry out anamnesis and perform physical examination to check for distant metastasis and/or local recurrence. In case of the development of recurrence disease, follow-up should be pursued up to 3 years after diagnosis of recurrence.

### **Hypothesis**

The hypothesis is that TaTME will result in a better mesorectum specimen quality with a lower rate of involved CRM and therefore lower rate of local recurrence. Furthermore, because of direct endoscopic visualisation we expect less morbidity due to less conversion rates and better anastomotic techniques. Moreover, the TaTME procedure will potentially enable more sphincter saving procedures. These expected results will have positive effect on functional outcome and health related quality of life.

**FUNDING AND SUPPORT IN KIND**

<b>FUNDER(S)</b> (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	<b>FINANCIAL AND NON FINANCIAL SUPPORT GIVEN</b>

## KEY TRIAL CONTACTS

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COLOR III study group	All included centers; Follows



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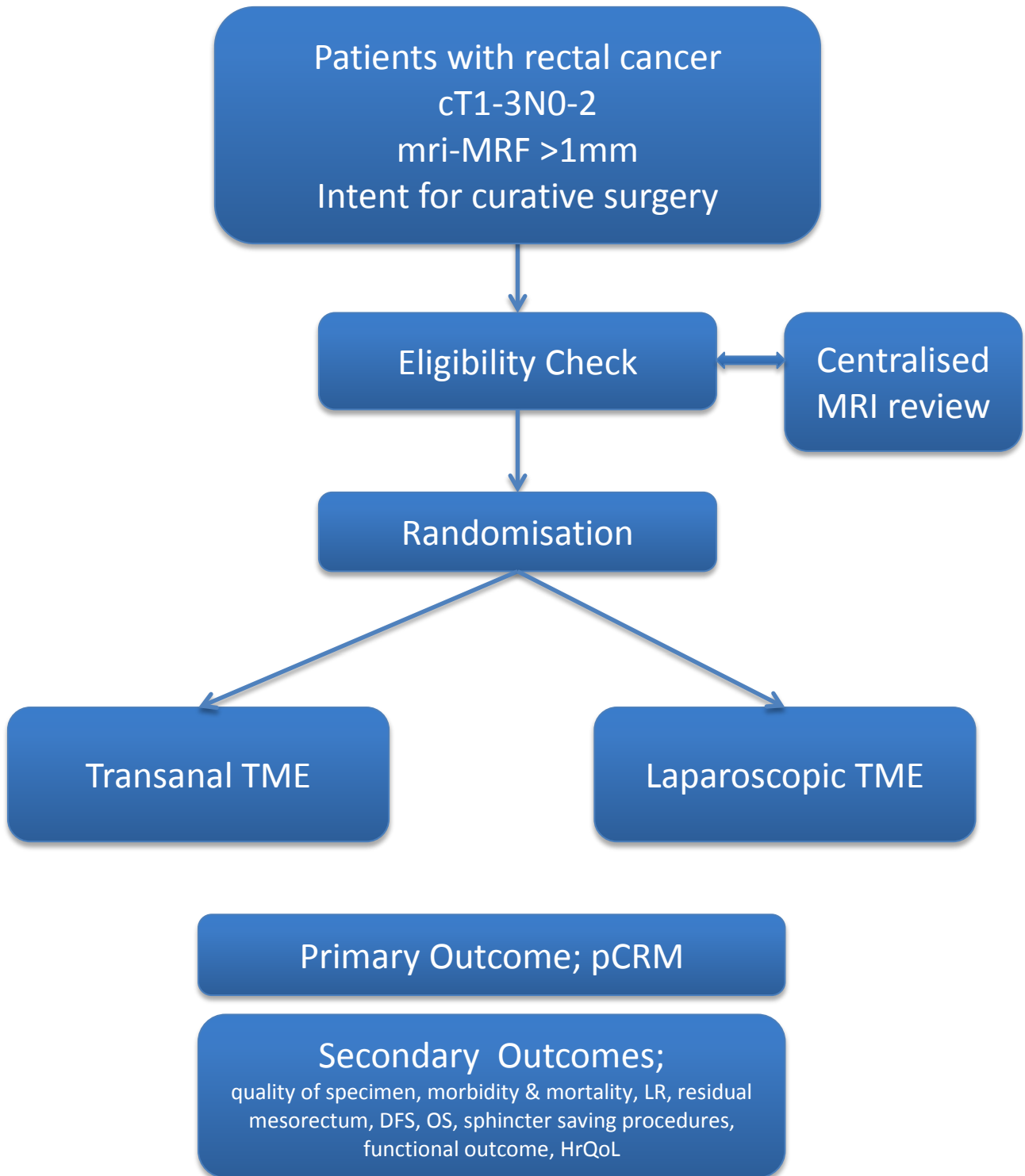
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## LIST OF ABBREVIATIONS

AE	Adverse Event
APR	Abdominoperineal Resecton
AR	Adverse Reaction
cCRM	Clinical Circumferential Resection Margin
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CTA	Clinical Trial Authorisation
DFS	Disease-free Survival
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EUCTD	European Clinical Trials Directive
GCP	Good Clinical Practice
HrQOL	Health related Quality Of Life
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LAR	Low Anterior Resection
MRI	Magnetic Resonance Imaging
NHS R&D	National Health Service Research & Development
OS	Overall Survival
PA	Pathology
pCRM	Pathological Circumferential Resection Margin
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SDV	Source Data Verification
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAMIS	Transanal Minimally Invasive Surgery
TaTME	Transanal Total Mesorectal Excision
TME	Total Mesorectal Excision
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

**TRIAL FLOWCHART**



## STUDY PROTOCOL

### 1 BACKGROUND

Worldwide, colorectal cancer (CRC) is the third most common malignancy in males after prostate and lung cancer, and the second most common malignancy in females after breast cancer. Each year, colorectal cancer afflicts approximately 728,000 new patients and causes about 320,000 deaths in developed countries. CRC is the second cause of cancer related death in western world with mortality rates of 15.1 and 9.7 per 100,000 patients, respectively. Approximately 34% of these tumours are located in the rectum.<sup>1,2</sup>

Special attention towards rectal cancer has been present due to higher recurrence rates, higher morbidity rates and poor functional outcome compared to colon cancer. The anatomy of the narrow pelvis with nerve plexus close to the mesorectal fascia (MRF) accounts for complex surgical dissection.<sup>3</sup>

The standard potential curative treatment for rectal cancer is surgery. The total mesorectal excision (TME) technique introduced in 1982 has been the standard technique to dissect in anatomical planes with the aim to obtain a complete mesorectal excision and intact specimen.<sup>4</sup> The introduction of laparoscopic surgery for rectal cancer has shown to enhance the postoperative recovery of patients compared with open abdominal surgery and is oncologically safe with similar disease-free and overall survival.<sup>5-10</sup>

#### Concerns in rectal cancer surgery; mid and low rectal cancer

Laparoscopic TME is considered a technically challenging procedure, with an estimated learning curve of 50 procedures.<sup>11</sup> Especially the mid and low rectal cancers defined as 5-10cm and 0-5cm from the anal verge (on MRI) are technically demanding due to the requirement of a complete mesorectal excision down to the pelvic floor. Patients with mid and low rectal cancer are faced with higher recurrence rates, high morbidity rates, high colostomy rates and poor functional outcome compared with high rectal cancer.<sup>5,6,8,12,13</sup>

The relative high recurrence rates are directly related to the quality of the mesorectal dissection. Good TME is challenging due to the limited space in the small pelvis especially in the lower part of the rectum. Because of the narrow anatomy of the small pelvis in men and bony landmarks, there is limited space to mobilise the rectum distal from the tumour on the levator plane. Quality of the surgery has been shown to affect recurrence rate and survival. The quality of the surgery can be assessed by evaluation of specimens after surgery including the circumferential resection margin (CRM) involvement.<sup>13-16</sup> Another quality indicator is the residual mesorectum found on postoperative MRI. A study performed by Bondeven et al. showed that incomplete resection of the mesorectum was detected on postoperative MRI in 36% of the patients treated with TME for rectal cancer.<sup>17</sup> An involved CRM and not intact mesorectum are the most important independent factors predicting local recurrence rates.<sup>18,19</sup>

A systematic review was performed by our study group including large randomised trials for laparoscopic and/or open surgery for rectal cancer and large national surveys. Only randomised trials reporting involvement of CRM and including 100 patients or more in one arm were included. We searched in Pubmed Medline and OVID Embase. Mesh terms we used were: "Colorectal neoplasms" [majr] OR ((colorectal OR rectal OR rectum OR rectosigmoid) AND (cancer\* OR carcinoma\* OR adenocarcinoma\* OR malignan\* OR tumour\* OR tumour\* OR neoplasm\*)) AND ((local[ti] OR transanal\*[ti] OR rectoscop\* OR endoscop\*[ti] OR limited[ti]) AND (surgery OR surgical\* OR resect\* OR excision OR treatment OR therapy) OR microsurgery[ti] OR microsurgical\* OR spts OR parks) AND (for systematic reviews) ("meta-analysis" [pt] OR "meta-anal\*" [tw] OR "metaanal\*" [tw] OR ("quantitativ\* review\*" [tw] OR "quantitative\* overview\*" [tw]) OR ("systematic\* review\*" [tw] OR "systematic\* overview\*" [tw]) OR ("methodologic\* review\*" [tw] OR "methodologic\* overview\*" [tw]) OR ("review" [pt] AND "medline" [tw])). In total 6 trials and 2 reports were included. The review

showed high percentages of involved CRM. Only one large randomised trial, the COREAN trial, reported a low rate of involved CRM of 2.9%. The other randomised trials incorporating a large number of patients, reported involved CRM in 7.7% to 16% of the patients operated for rectal carcinoma. Two national surveys including 30.000 and 2.500 patients showed involved CRM rates of 7.2% and 5.2% (Table 1 and Table 2). In conclusion: the average CRM rate after abdominal rectal resection including TME is approximately 7%. Moreover, it is reported that resection of low rectal tumours results in higher rates of involved CRM compared with higher tumours.<sup>5,6,8,12,13,16,20-23</sup>

**Table 1. Involved CRM after abdominal rectal resection (LAR + APR) - total rectum**

Study/national report	RCT/report	Year	Percentage involved CRM	Tumour height
CLASICC	RCT	2005	Lap. 16% Open 14%	Total rectum
Dutch TME	RCT	2007	Open 16%	0-15cm
MRC CR07	RCT	2009	Lap. + open 10%	0-15cm
NBOCAP	Report	2012/13	Lap. + open 7.2%	Total rectum
DSCA	Report	2014	Lap. + open 5.2%	Total rectum

**Table 2. Involved CRM after abdominal rectal resection (LAR + APR) - mid and low rectum**

Study/national report	Year	Percentage involved CRM	Tumour height
COREAN	2010	Lap. 2.9% Open 4.1%	0-9cm
COLOR II	2013	Lap. 9.4% Open 10.8%	0-10cm (subgroup)
Rullier et al.	2013	Lap. + open 7.7%	low-mid
Denost et al.	2014	Lap. 18%	0-6cm

Because involved CRM seems to be associated with a higher risk on local recurrence, reducing the number of involved CRMs potentially leads to a decrease of local recurrences.

Another problem in rectal cancer surgery are high morbidity rates as result of poor anastomotic techniques and high conversion rates because of the limited workspace and visualisation in the narrow pelvis. Despite the increasing uptake of laparoscopic TME in the treatment of rectal cancer, conversion rates to open procedures are reported up to 34%. Conversion is frequently needed in male, obese patients or in case of bulky or distally located tumours.<sup>5,8,24</sup>

Several large RCTs and two national surveys reported abdominoperineal resection( APR) rates of 22% to 32%.<sup>5,8,21,22</sup> APRs show a high morbidity, mostly presacral abscess and infection of the perineal wound. Furthermore, because of the high percentage of APR in low rectal tumours, low rectal cancer surgery results in a high colostomy rate and could lead to a reduced quality of life. Unfortunately, in extra low rectal tumours sphincter saving resection is not always possible because of the limited workspace and visualisation.

### Transanal laparoscopic surgery for rectal cancer

To overcome the problem of irradical resection, the transanal approach was introduced by Lacy et al. in 2010.<sup>25</sup> Transanal total mesorectal excision (TaTME) may offer advantages over laparoscopic and open approaches because the direct endoscopic visualisation facilitates exact dissection of the distal resection margin, and presacral and perirectal planes. This procedure can be particularly advantageous in case of the narrow male pelvis and distally located tumours. Potential benefits of TaTME are better quality of resection resulting in better quality of specimen with lower involved

CRM rate and less residual mesorectum, less morbidity, more sphincter saving procedures, less conversion to APR or open technique. On the long term the TaTME possibly results in better functional outcomes and quality of life.

A significant problem is the learning curve of surgeons and team when implementing a new surgical technique. This possibly creates a bias within a trial. To overcome this problem training workshops have been facilitated and attended. The procedure ideally should be trained within a protected and procured environment to avoid potential dangers the TaTME technique in the learning curve such as damage of urethra and prostate and rectal side wall damage.

From 2010 to date, several non-randomised series have been published regarding hybrid TaTME (series including 20 or more patients are listed in Table 2). These series suggest that TaTME is feasible and safe regarding short-term outcomes with high-quality specimen and lymph node retrieval in selected patients. Our group recently analysed the results of our pilot study in which 80 patients underwent TaTME. In 2.5% of the patients incomplete resection was found. In 0% of the patients a colostomy was created. Our results and the other series show that the rates of incomplete resection and permanent colostomies have decreased after TaTME compared with the laparoscopic TME. Furthermore, our results showed that TaTME is safe regarding short-term morbidity and mortality. At the present time there is only one randomised trial published addressing perineal versus laparoscopic TME for rectal cancer. It included 100 patients with rectal cancer within 6cm from the anal verge suitable for sphincter preservation. The rate of involved CRM was 4% in the group of patients who had a perineal resection and 18% in the group that underwent laparoscopic abdominal resection (P = 0.025).<sup>23,26-33</sup>

**Table 3. Involved CRM after TaTME**

Group	Patients	T-stage	% involved CRM	Remarks
Lacy et al.	140	cT1-T4	6.4%	
Veltcamp				
Helbach et al.	80	cT2-T3	2.5%	
Tuech et al.	56	cT1-T4	5.4%	
Denost et al.	50	cT1-T4	4%	Perineal open TaTME
Rouanet et al.	30	cT2-T4	13%	Only patients with unfavourable anatomical and/or tumour characteristics
Muratore et al.	26	cT1-T3	0%	
Atallah et al.	20	cT2-T4	5%	

**Conclusion**

TaTME will probably result in a better mesorectum specimen quality with a lower rate of involved CRM and therefore lower rate of local recurrence. Furthermore, because of direct endoscopic visualisation we expect less morbidity due to less conversion rates and better anastomotic techniques. Moreover, the TaTME procedure will potentially enable more sphincter saving procedures. These expected results will have positive effect on functional outcome and health related quality of life.

Before adaptation of TaTME as standard surgical therapy for mid and low rectal cancer, a well-designed study is essential to demonstrate its efficacy and safety in a multicentre randomised setting: COLOR III trial. Furthermore, a major challenge in surgical cancer clinical trials is lack of consistency in surgical quality. This study aims at addressing this limitation by applying a robust surgical quality assurance protocol prior to the start and throughout the clinical trial to ensure consistency and validity.

## **2 RATIONALE**

To improve oncological and functional outcomes of patients with rectal cancer new surgical techniques are being developed. The adoption of the TME technique has resulted in better oncological outcome in the last decades. The addition of neoadjuvant therapy has further improved oncological outcome. The minimal invasive laparoscopic resection of rectal cancer has shown to be safe and to result in improved short-term outcomes and reduced morbidity.

Nevertheless, the laparoscopic resection of mid and low rectal cancer remains challenging due to the anatomy of the narrow pelvis and is associated with a relative high risk of resections with tumour involved CRM resulting in increased risk of recurrence.

In attempt to improve the quality of the TME procedure in low rectal cancer and further improve oncological results the TaTME has been developed, in which the rectum is dissected transanally according to TME principles. First series have been described since 2010 and although randomised evidence is still lacking this new technique has shown to be feasible and safe. The rectum including the total mesorectum is mobilised transanally in a reversed way with minimally invasive surgery including high quality imaging techniques.

The TaTME technique for mid and low rectal cancer has shown to have potential benefits: better specimen quality with less CRM involvement, less morbidity as result of avoiding extraction wounds in the majority of patients and more sphincter saving rectal resections without compromising oncological outcomes.

We propose to evaluate the TaTME technique compared with conventional laparoscopic rectal resection for patients with mid and low rectal cancer in an international randomised trial: the COLOR III trial.



### **3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS**

#### **3.1 Objective**

The objective of this trial to assess the role of TaTME in the treatment of patients with mid and low rectal cancer.

#### **3.2 Primary endpoint/outcome**

The primary endpoint is the percentage of patients with involvement of CRM (<1mm).

(defined as tumour cells present within 1mm from the lateral surface of the mesorectum)

(primary endpoint will be centrally reviewed by pathologists)

#### **3.3 Secondary endpoints/outcomes**

Pathological

- Quality of specimen (as proposed and published by Quirke et al.)<sup>14</sup>
- Distal resection margin (defined as distance in cm from distal border of the tumour to distal resection surface)
- Translational research will be performed on predictive/prognostic biomarkers and imaging methods.

Clinical

- Length of hospital stay postoperatively (calculated as time from surgery to discharge in days)
- Morbidity within 28 days after surgery and within 90 days (graded by Clavien-Dindo Classification)

Definitions complications:

- Anastomotic leak<sup>34</sup>: defect of the intestinal wall integrity at the colorectal or coloanal anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments. A pelvic abscess close to the anastomosis is also considered as anastomotic leakage.

Grades:

A. Anastomotic leakage requiring no active therapeutic intervention

B. Anastomotic leakage requiring active therapeutic intervention but manageable without relaparotomy

C. Anastomotic leakage requiring re-laparotomy

- Collection: abdominal CT-scan demonstrating the presence of a collection without gas
- Ileus<sup>35</sup>: state of absence or reduced peristalsis that can be attributed to a 'normal', prolonged, or a pathological response of the gastrointestinal tract. This failure of peristalsis results in accumulation of gastrointestinal secretions, leading to abdominal distension and vomiting.
- Mortality within 28 days after surgery and within 90 days
- Local recurrence at three and five years (defined as cancer recurrence within the pelvic and perineal area)

- Disease-free survival at three and five years (calculated as time from surgery to last follow-up or date of recurrence)
- Overall survival at three and five years (calculated as time from surgery to last follow-up or death)

#### Quality of life

- Percentage of sphincter saving procedures (defined as colostomy percentage at 1 year postoperatively)
- Postoperative health related quality of life (quality adjusted life years) and functional outcome (measured with EORTC QLQ-CR29 and C30, EQ5D and LARS score). A difference of more than 10% in the EORTC list is considered significant.

See 'Chapter 12 Follow-up' for follow-up moments.

#### Costs (national) (sidestudy)

- In-hospital direct and indirect costs (measured with EQ5D and cost incremental analysis)
- Out-of-hospital postoperative costs (measured with EQ5D and cost incremental analysis)

## 4 TRIAL DESIGN

The study concerns an international, randomised, multicentre trial comparing traditional and transanal laparoscopic TME as the surgical treatment for rectal cancer. Patients will be accrued by all participating hospitals participating in the COLOR III study group (list of participating hospitals can be obtained through [rectalcancersurgery.eu](http://rectalcancersurgery.eu) → 'COLOR III Trial'). All centers will follow a quality assurance program of the procedure itself and the data before data will be entered in the COLOR III trial. The COLOR III study group is an international group of surgeons with interest and expertise in minimally invasive colorectal surgery.

The first COLOR study started in 1997 and completed a large RCT in 2003 comparing laparoscopic to open surgery for colon cancer.<sup>36,37</sup> Hereafter, many centres of this study group joined the COLOR II study group. The COLOR II study group recently completed a major RCT comparing laparoscopic to open TME in the treatment of rectal cancer.

The design involves allocation of all appropriate consecutive patients with mid or low rectum carcinoma to either of the two procedures at a randomisation ratio of 2:1 in favour of the TaTME procedure. Once eligibility has been established and patient details have been noted, the patient will be allocated to either transanal or laparoscopic TME. Assignment to one of the two treatment groups will not be blinded. Randomisation will be performed by computer and will be balanced by T-stage, preoperative radiotherapy, height of the tumour, BMI and gender. Data will be analysed on 'intention to treat' basis in case patients are not subjected to the randomised treatment modality. Randomisation will be done through internet: [rectalcancersurgery.eu](http://rectalcancersurgery.eu) (click 'COLOR III Trial → Professionals').

Included surgical procedures to obtain TME are 1. low anterior resection (LAR) with colorectal anastomosis 2. LAR with coloanal anastomosis 3. Intersphincteric APR

Excluded surgical procedures are extralevator abdominoperineal excision (ELAP) (i.e. patients with tumour in growth in the anal sphincter complex or levator ani).

Exclusion criteria are T4 tumours, T3 tumours with a suspected involved CRM after neoadjuvant therapy, patients with concomitant metastases or other malignancies, with malignancies in their medical history or with signs of acute mechanical obstruction by the tumour.

The trial will be stratified according to T-stage, preoperative radiotherapy, height of the tumour, BMI and gender.

### **Surgical Quality Assurance in COLOR III Trial**

To ensure both surgical quality and centre capability to adhere to the study protocol, including the recruitment process and data collection, a Quality Assurance Protocol has been developed and will be applied before entering into the trial.

To evaluate surgical quality a Quality Assurance Manual and a Competency Assessment Tool (CAT) for technical and oncological quality for laparoscopic and transanal TME within the scope of COLOR III have been developed. These will be used for surgeon selection into the trial and to measure adherence to agreed surgical quality standards during the trial. A Delphi methodology has been applied with a peer-nominated international group of expert colorectal consultants in the TaTME technique in order to develop a technical manual and operation logbook. A TaTME CAT was developed based on the results of the Delphi methodology. This tool has been validated in order to ensure acceptable reliability and validity standards prior to its implementation in the pre- and main trial phases.

When entering the COLOR III trial as a center the surgeon will be trained by a dedicated training program including cadaver training, proctor supervised training and quality assessment of the procedure by the developed CAT supervised by an independent board of trainers. Next, the centre's

capability to (i) recruit and randomise patients, (ii) comply with the treatment protocol and (iii) collect required data will be assessed. During this process patients will be randomised. Once recruitment and randomising 3 patients following the study protocol with good procedure quality has been performed the data will be entered in the COLOR III study. A pre-trial checklist will be used to measure the compliance.

If a centre is unsuccessful in completing the Trial Quality Assurance Procedure, the evidence will be reviewed by the COLOR III Trial Steering Committee and more evidence will be required for the component that is unsatisfactory. Within the scope of Surgical Quality Assurance, surgeons will be required to gain more experience with the support from COLOR III expert group and re-assessed.

The data collected during this Trial Quality Assurance Phase will not contribute to the main trial.

Before the trial entry, each surgeon will be required to submit 2 unedited videos for both laparoscopic and transanal TME. Two reviewers will assess the videos independently using the Competency Assessment Tool as the pre-trial entry procedure. During the main trial period, each surgeon will be required to submit 1 unedited video for every 3 cases for both laparoscopic and transanal TME. The videos will be assessed using the Competency Assessment Tool to monitor the adherence to agreed standards.

#### (I) Standardisation process

##### 1. Operation manual

- Aim: to reach a consensus on essential, optional and prohibited steps of the operation.
- Methods: Hierarchical Task Analysis (HTA) of TaTME via observation of procedures, interviews and Delphi process. HTA of laparoscopic TME has been developed in a previous study.
- Use: technical protocol, operation note and basis for assessment.

##### 2. Technical competency assessment tool

- Aim: to develop a video-based valid tool for objective assessment of technical competency (safety, efficiency, oncological quality).
- Method: interviews and Delphi to structure the tool and to examine its acceptability and reliability.
- Use: to ensure technical competency before entering RCT and for adherence to trial protocol.

#### (II) Pre-randomisation centre assessment

The COLOR III allows entry into the trial when the centre is ready.

##### 1. Centre compliance

- Aim: to ensure capability to comply with data collection and recruitment.
- Method: centre follows trial protocol for data collection and randomisation of 5 patients. A checklist will be used to measure the compliance.
- Outcome: ability to recruit and collect required data

##### 2. Technical competency

- Aim: to ensure surgeon has reached the required competency level for TaTME and laparoscopic TME.
- Method:
  - Audit of cases performed prior to the trial
  - Independent assessment of 2 unedited videos by 2 assessors who are blind to surgeon identity.
- Outcome recommendations
  - To progress to trial
  - OR to do more cases before entering the trial

Data from the pre-randomisation assessment process will not contribute towards the results of the main trial.

#### (III) Surgical quality assurance during RCT

- Aim: to ensure adherence to trial surgical quality protocol

- Method:
  - Risk adjusted CUSUM to examine trends in outcomes
  - Assessment of photographs / unedited videos using competency assessment tool for both laparoscopic and TaTME (one every 3 cases).
  - Analysis of major adverse events using modified Healthcare Failure and Mode Effects Analysis (HFMEA) and frameworks for assessing system safety.
- Use: This data will be utilised as control measures and explanatory variables for endpoints in the trial.

## **5 ELIGIBILITY CRITERIA**

### **5.1 Inclusion criteria**

- Solitary mid (5.1-10cm from anal verge on MRI) or low (0-5cm from anal verge on MRI) rectal cancer observed at colonoscopy and histologically proven through biopsy
- Distal border of the tumour within 10cm from the anal verge on MRI-scan
- Tumour with threatened margins downstaged after neoadjuvant therapy to free margins
- No evidence for distal metastases on imaging of thorax and abdomen
- Suitable for elective surgical resection
- Informed consent according to local requirements

### **5.2 Exclusion criteria**

- T3 tumours with margins less than 1mm to the MRF, determined by MRI-scan (as staged after preoperative chemo- and/or radiotherapy)
- T4 tumours, as staged after preoperative chemo- and/or radiotherapy
- Tumours with in growth more than 1/3 of anal sphincter complex or levator ani
- Malignancy other than adenocarcinoma at histological examination
- Patients under 18 years of age
- Pregnancy
- Previous rectal surgery (excluding local excision, EMR or polypectomy)
- Signs of acute intestinal obstruction
- Multiple colorectal tumours
- Familial Adenomatosis Polyposis Coli (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), active Crohn's disease or active ulcerative colitis
- Planned synchronous abdominal organ resections
- Preoperative suspicion of invasion of adjacent organs through MRI-scan
- Preoperative evidence for distant metastases through imaging of the thorax and abdomen
- Other malignancies in medical history, except adequately treated basocellular carcinoma of the skin or in situ carcinoma of the cervix uteri
- Absolute contraindications to general anaesthesia or prolonged pneumoperitoneum, as severe cardiovascular or respiratory disease (ASA class > III)

## **6 PERIOPERATIVE CARE AND EXAMINATIONS**

### **6.1 Perioperative treatment strategies**

Most international guidelines, including the current Dutch guideline for rectal cancer (2014), state that all patients diagnosed with rectal cancer should be discussed within a multidisciplinary oncological meeting preoperatively. Neoadjuvant radio- and/or chemotherapy should be considered in selected patients, according to local standards in multidisciplinary consultation. Changes in these protocols during the study period should be reported to and approved by the Protocol Committee.

### **6.2 Preoperative work-up**

To exclude multiple tumours, a complete colonoscopy or CT-colonography is performed preoperatively, or within 3 months after surgery if primary colonoscopy/ CT-colonography was impossible due to a stenosing tumour. Biopsies of tumours are mandatory. Recto- or colonoscopy is performed to obtain histology and to optionally mark the distal border of the tumour prior to surgery. MRI-scan of the pelvis is conducted to assess its height from anal verge, its relation to surrounding structures and to estimate lymph node status (see Appendix I: MRI protocol and staging definitions). The radiologist should report the estimated distance between the tumour margin and the MRF. Imaging of the thorax and abdomen is performed to screen for metastatic disease.

### **6.3 Preoperative care**

Each centre should standardise preoperative care concerning:

- bowel preparation:

1. day before surgery: Moviprep and enema
2. day of surgery: enema

- deep venous thrombosis prophylaxis (low dose heparin and thrombo-prophylactic stockings during admittance)

- antibiotic prophylaxis

- enhanced recovery program

Preoperative care should be equal in both treatment arms throughout the duration of the trial.

### **6.4 Intraoperative care**

Anaesthesia should be standardised by each participating centre for all patients in both treatment arms throughout the trial. The recommendation is not to use epidural anaesthesia.

Changes in anaesthetic protocols should apply to both treatment arms.

**7 INVESTIGATIONAL PRODUCT**

Not applicable.



**8 NON-INVESTIGATIONAL PRODUCT**

Not applicable.

## **9 SURGICAL PROCEDURE**

### **9.1 TaTME (intervention arm)**

TaTME starts with either the transabdominal or transanal phase. In the abdominal phase the sigmoid and the splenic flexure are mobilised from medial to lateral by multiport laparoscopy or through single port surgery with the single port located in the future ileostomy side. The inferior mesenteric artery is ligated after identification of the left ureter. After mobilisation of the descending colon, sigmoid and the proximal rectum the transanal phase is initiated.

The chosen transanal TME technique depends on the height of the tumour. In case of distal tumours (0-5cm from anal verge) an intersphincteric dissection is performed with the use of a retractor system. The transanal dissection is continued as proximal as possible in open fashion. Thereafter, the rectal stump is closed with purse-string suture to prevent spillage of bacteria and tumour cells. After closure of the rectal stump, the cavity is rinsed with a povidone-iodine solution and a transanal port is introduced. In case of distally located tumours a SILS port is used. It can be sutured to the perineal skin which allows traction to the port to create a greater working space. Furthermore, suturing the port prevents loss of pneumorectum in case of intersphincteric dissections.

In case of more proximally located tumours (5.1-15cm from anal verge), the rectal stump is either closed endoscopically or open with a purse-string suture with a minimal distal distance of 3 centimetres. In case of both distal and mid rectum carcinomas a pneumorectum is created with carbon dioxide at a pressure of 14 mmHg and a relatively low flow of 5 litre per minute to minimise rectal contractions.

The avascular dorsal plane is developed to proximal as far as possible by sharp dissection with a diathermic hook. Hereafter, the dissection is continued ventrally while sparing the urethra through partial blunt dissection. The lateral sides are dissected after progression of dorsal and ventral dissection to minimise the risk of damage to nerves or vascular structures. After full rectal dissection through TME principles the peritoneum is opened and the specimen is pushed to intra-abdominal to visualise and take care of remaining adhesions. Hereafter, the specimen is exteriorised transanally under direct visualisation through a camera in the abdominal port.

To restore continuity the sigmoid is divided from the specimen and the stapler head is introduced. The distal border of the sigmoid is sutured around the stapler head and the sigmoid and stapler are pulled back intra-abdominal. The remaining distal part of the rectum is also closed around the stapler pin with a purse string suture and an end-to-end anastomosis is created between the sigmoid and remaining rectum.

In most cases, the surgical procedure is completed by the construction of a diversion ileostomy.

In case of no creation of an anastomosis, the sigmoid is transected endoscopically. The specimen is then removed transanally and an end colostomy is created.

### **9.2 Laparoscopic TME (control arm)**

Complete laparoscopic dissection of the mesorectum is mandatory to qualify the procedure as a "laparoscopic TME". The level of transection of the inferior mesenteric artery is up to the surgeon's preference. Both right and left hypogastric nerves should be preserved. The splenic flexure should be mobilised when undue tension at the anastomoses is likely. Other aspects of the surgical procedure such as type of anastomoses, use of diverting ileostomy and drainage of surgical field are up to the discretion of the surgeon.

Included surgical procedures to obtain TME are 1. low anterior resection (LAR) with colorectal anastomosis 2. LAR with coloanal anastomosis 3. Intersphincteric APR

Excluded surgical procedures are extralevator abdominoperineal excision (ELAP) (i.e. patients with tumour in growth in the anal sphincter complex or levator ani).

### **9.3 Conversion**

In TaTME conversion (to either laparoscopic or open TME) is defined as interruption of transanal TME due to technical difficulties or complications during transanal dissection, requiring completion of the majority of the TME using an abdominal approach. In laparoscopic TME conversion is defined when completion of the dissection of the mesorectum is performed through a traditional open abdominal or transanal approach. Conversion is determined by the surgeon in case of concerns about patient safety, technical difficulties, inability to complete the TME procedure adequately or associated conditions that require treatment.

### **9.4 Quality Assurance**

The end product of the Delphi methodology will comprise a technical manual and operation logbook, and a competency assessment tool, which will be used for pre-trial entry and to monitor and measure adherence to agreed standards during the trial. A video and photographic methodology will be validated for use during the main COLOR III.

## 10 (HISTO)PATHOLOGY

All resected specimens are handled by one designated specialised pathologist per participating centre. Additionally, central review of the pathology will be performed (Dr. N.C.T. van Grieken, dept. of Pathology, VUmc Amsterdam) and will include tumour typing, grading and assessment of histological prognostic factors. Participating pathologists will be requested to submit when possible, tumour and normal tissue for studies related to the research questions of the trial. All studies will be performed on tissue that has already been obtained from patients for diagnostic purposes. No tissue will be collected with the sole purpose of research. Written informed consent will be obtained from patients prior to tissue collection.

The following protocol should be followed:

### 10.1 Macroscopic assessment of resected specimen

1. The fresh, unopened specimen is sent to the pathologist.
2. Photographs are made of the anterior and posterior side of the fresh specimen.
3. The proximal and distal resection margin are sampled. In case of a suspect margin involvement, sample(s) should be taken perpendicular to the margin.
4. Macroscopic assessment of the quality of the mesorectum will be scored in 3 grades as described by Quirke and will be performed separately for the part proximal and distal from the peritoneal reflexion:
  - *Complete*: Intact mesorectum with only minor irregularities of smooth mesorectal surface. No defect is deeper than 5 mm, and there is no coning toward the distal margin of the specimen. There is a smooth CRM at slicing.
  - *Nearly complete*: Moderate bulk to the mesorectum, but irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site is the muscularis propria visible, except for the insertion of the levator muscles.
  - *Incomplete*: Low bulk mesorectum with defects down onto the muscularis propria and/or a very irregular CRM.
5. Macroscopic assessment of involvement of the CRMs is performed.
6. The CRMs is inked and the specimen is opened anteriorly, except for the area with the tumour to leave the full circumference intact.
7. Under gentle tension the specimen is pinned to a cork board for fixation for 48 hours in formalin, if possible a gauze is inserted into the lumen before fixation .
8. After fixation, the peritoneal reflection is identified and the relative position of the tumour noted i.e. below, partially covered by peritoneum or totally covered by peritoneum. Areas covered by peritoneum are inspected for serosal penetration and if apparent are sampled separately. Tumours completely covered by peritoneum are handled in the routine manner for colorectal specimens, whereas those with a retroperitoneal component are subjected to close scrutiny for circumferential margin involvement by tumour.
9. The site of the tumour is sliced as thinly as possible (3-5mm slices) including up to 2cm above and below the tumour, and laid out on a flat surface for macroscopic inspection.
10. All slices will be numbered starting from the most proximal slice, thereafter all slices are photographed.
11. All slices are again assessed for the extent of tumour involvement of the perirectal tissue and the CRM is measured using a ruler.
12. Area or areas of involvement can usually be seen with the naked eye and any suspicious area or areas should be sampled for histology. One block should be sufficient, but up to six might need to be taken in cases with extensive spread before it is possible to be certain that all the margins are free of tumour. On average, four blocks will suffice for the majority of tumours. The locations

from where the blocks are taken need to be marked on the photographs of the slices mentioned in 9.

13. Whilst incising the mesentery and the mesorectum, all lymph nodes and tumour deposits should be identified and sampled. Metastases and lymph nodes adjacent to the circumferential margin are sampled "en-bloc" with the inked resection margin.
14. Definitive measurement of the minimum distance in mm (noted with 1 decimal) between tumour and CRM is performed microscopically on the H&E sections. Shrinkage of tissue occurs during processing but this does not materially affect the accuracy of this measurement. Microscopic assessment is most accurate as a florid peri-tumoural inflammatory reaction or fibrosis will lead to an overestimate of macroscopic tumour spread.

## **10.2 Microscopic assessment of resected specimen**

### **Tumour deposits**

Tumour deposits without signs of residual lymph node tissue are classified according to the 5<sup>th</sup> edition of the TNM classification: "a solitary tumour deposit with a diameter of > 3mm without histological evidence of residual lymph node in the nodule is classified in the N category as a regional lymph node metastasis. A tumour nodule of < 3mm is classified in the T category, i.e. discontinuous extension".

### **Number of lymph nodes**

All lymph nodes should be examined. A minimum number of 10 lymph nodes is acquired for adequate assessment of N-stage. The total number of lymph nodes and the number of lymph node metastases are reported. Also, the number of tumour deposits are reported separately.

### **CRM**

The exact CRM in mm is reported. A circumferential margin of  $\leq 1$ mm is considered positive (R1). When a positive lymph node is closer to the circumferential margin than the tumour itself, the margin between the positive node and the margin must be registered.

### **Tumour regression grade**

Tumour regression is scored as follow:

- No regression
- Partial regression
- Complete response

Complete pathological response is only used after a standardized work-up of the specimen which includes blocking of the whole tumour area and cutting three levels of each block (at 250  $\mu$ m).

## **10.3 Translational research**

From all patients at least one block containing tumour tissue and one block containing normal tissue will be requested for biomarker side studies and will be processed anonymously. Informed consent for these side studies will be obtained.

### **General aim**

The general aim of translational research in the COLOR III study is to improve the clinical outcome of rectal cancer patients. Separate funding for this translational research project will be raised. We aim to validate molecular biomarkers to improve the clinical management of rectal carcinoma, thereby specifically addressing the following unmet clinical needs:

1. Identify the subgroup of rectal cancer patients at high risk to develop either local recurrence or metastatic disease (disease prognosis)
2. Develop minimal invasive diagnostics (e.g. blood sampling) for reading out tumour biology, to monitor disease recurrence (disease monitoring).

## **11 POSTOPERATIVE TREATMENT**

### **11.1 Postoperative care**

Analgesic care and allowance of restoration of diet will be according to an enhanced recovery program. It is required to be standardised for all patients in both treatment groups throughout the trial.

### **11.2 Postoperative chemotherapy**

Currently there is no indication for adjuvant chemotherapy in the treatment of rectal cancer in The Netherlands. Postoperative chemotherapy should be administered according to local standards.

### **11.3 Postoperative radiotherapy**

Currently there is no indication for adjuvant radiotherapy in the treatment of rectal cancer in The Netherlands. Postoperative radiotherapy should be administered according to local standards.

## 12 FOLLOW-UP

### 12.1 Follow-up visits

For the COLOR III trial, patients are asked to visit the outpatient clinic yearly for a period of 5 years. More frequent visits and additional examination are only on indication or to the preference of the attending surgeon. Three years postoperatively an MRI of the pelvis will be performed to assess possible local recurrence and/or residual mesorectum. A chest radiograph and a liver ultrasound or CT-thorax/abdomen are performed to assess development of distant metastases according to national guidelines. Follow-up of patients with recurrent disease should continue until at least 3 years after detection of recurrence or until death.

### 12.2 Follow-up forms

Every year, the follow-up forms should be filled in and should be sent to the coordinating centre. Minor complaints or complications have to be noted in these forms. More serious complaints or complications necessitating hospital intake (unrelated to cancer) should be recorded in the form for events not related to cancer. In case of recurrent disease, the recurrence form and the recurrence follow-up form should be completed.

	1 month	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Clinical evaluation		X	X	X	X	X	X	X	X	X
CEA		X	X	X	X	X	X	X	X	X
Colonoscopy					X				X	
CT-thorax/abdomen or CXR and ultrasound liver			X		X	X	X	X	X	X
MRI-pelvis								X		
Functional outcome and HrQoL	X	X	X		X		X	X		

## **13 RECURRENT DISEASE**

Recurrences should be reported through the internet to the coordinating centre within 2 weeks after detection.

### **13.1 Definitions of recurrent disease**

Evidence of recurrent disease is accepted when one of the following criteria is present:

- Local macroscopic tumour assessed by colono- or proctoscopy, (PET-)CT-scan or MRI of the pelvis
- Liver metastases on ultrasound, (PET-)CT-scan or MRI
- Lung metastases on chest radiography, (PET-)CT-scan or MRI
- Bone metastases on radiography, (PET-)CT-scan, MRI or bone scintigraphy
- Death with rectal cancer

### **13.2 Definitions of local recurrence**

- Cancer recurrence in the pelvic or perineal area
- Positive (PET-)CT-scan or MRI (high resolution with T2 weighted imaging)
- Positive histology or cytology of adenocarcinoma

### **13.3 Treatment of recurrent disease**

Treatment of recurrent disease should be according to local protocol and should be the equal in both treatment groups. Protocols have to be known to the main coordinating centre. Any changes in protocols throughout the trial period should be reported to and approved by the Protocol Committee. Treatment should be noted in the recurrence follow-up form.

### **13.4 Follow-up of recurrent disease**

Follow-up of patients with recurrent disease should continue at least until 3 years after diagnosis of recurrence or until death. Recurrences and potential treatment should be noted in the recurrence form and the recurrence follow-up form.



## 14 STATISTICS AND DATA ANALYSIS

### 14.1 Sample size calculation

The primary endpoint is the involvement of CRM. In laparoscopic TME the percentage of involved CRM is estimated 7%. For showing a reduction to 3% with a two-sided level of significance of 5% and a power of 80% a total of 1098 patients is needed, 732 patients in the TaTME arm and 366 patients in the laparoscopic TME arm.

In this sample size calculation, additional as treated analyses (estimated cross-over is 1% in both groups), exclusion of patients with complete remission after neoadjuvant therapy (estimated complete regression is 1% in both groups) and exclusion after conversion to APR (estimated conversion rate to APR is 5% in both groups) are taken into account.

Randomisation will be stratified for

- T3a and less / T3b and more
- Downstaged with chemoradiotherapy: yes / no / NA
- Preoperative radiotherapy: yes / no
- Height of the tumour: 0-2.0cm / 2.1-5.0cm / 5.1-10cm
- Gender: male / female
- BMI  $\leq$  30.0 / BMI  $>$  30.0

The randomisation will be executed in such a way that concealment of allocation for the indicating surgeon is guaranteed.

### 14.2 Statistical analysis plan

Baseline numerical data will be described in means, standard deviations or medians and interquartile ranges, baseline categorical data will be displayed in percentages. All comparative analyses will be conducted on an 'intention to treat' basis. Consequently, patients who are randomised to TaTME and converted to a laparoscopic or open TME, will be analysed in the TaTME group. Patients who are randomised to a laparoscopic resection and converted to TaTME or open TME, will be analysed in the laparoscopic group. Ninety days postoperative mortality, pathological resection margin and complication rates will be compared using the Chi-square test or an exact test if necessary. Local recurrence rate, disease-free and overall survival will be compared using the Log-rank test. Exploratory analysis of the prognostic effects of various baseline factors on disease-free survival will be carried out through multivariate Cox-regression. Apart from intention to treat analyses, per protocol analyses will be applied.

### 14.3 Subgroup analyses

Subgroup analyses will be performed regarding:

1. Height of the tumour:

- hypothesis is higher rate of involved CRM in the laparoscopic group in tumours 0-5cm from the anal verge compared with the TaTME group
- hypothesis is higher rate of local recurrence in the laparoscopic group in tumours 0-5cm from the anal verge compared with the TaTME group

2. Stage of disease:

- hypothesis is better disease-free and overall survival in patients with stage III disease compared with patients with stage I or stage II disease in the TaTME group as well as the laparoscopic group

## **15 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION**

### **15.1 Data collection tools and source document identification**

All medical, quality of life and cost data will be collected by the main coordinating centre. Data collection will be facilitated by case record forms for the perioperative period including data on pathology and follow-up. For privacy of patients, no hospital patient identification numbers will be revealed to the coordinating centre. All patient data are coded and identified by means of a randomisation number. This randomisation number does not include initials or date of birth from the patient. ~~and therefore will be not reducible.~~ The local investigator will have a decoding list with randomisation numbers and hospital patient identification numbers of his patients in the investigator site file.

At each trial operation, the code(s) of the performing surgeon(s) should be noted in the case record form. For this purpose, surgeons performing laparoscopic or transanal rectal resections in the trial must be coded and a list of these surgeons with their corresponding codes should be kept in the investigator site file. All patients who are considered for operative treatment of rectum carcinoma should be registered, including those who refuse randomisation and those who do not meet inclusion criteria. Brief details of the reasons why patients are not randomised or excluded should be given. The number of patients operated in each centre for rectal cancer will be registered.

### **15.2 Data collected at randomisation**

At randomisation, the clinician will be asked to give the following information through the internet:

- Eligibility criteria fulfilled?
- Randomising physician/surgeon
- Hospital (+ fax number)
- Type of planned surgery
- Patient: gender
- Patient: date of birth
- Clinical TMN stage

### **15.3 Data collected during preoperative period**

- ASA classification
- Length and weight
- Previous abdominal operations
- Medical history
- Date of diagnosis
- Location of the tumour on MRI
- Tumour characteristics
- Proposed type of resection
- Previous radiotherapy of the pelvis
- Preoperative (chemo)radiotherapy

### **15.4 Data collected during operation**

- Code(s) of surgeon(s)
- Date of surgery
- Type and level of resection
- Use of ureter stent
- Presence of radiation damage
- Presence of liver or peritoneal metastases
- Invasion of adjacent organ(s)

- Degree of autonomic nerve preservation
- Type and method of performing anastomosis
- Blood loss in millilitres
- 'Skin to skin' operation time
- Intraoperative complications
- Wound protection / specimen protection used
- Reasons for conversion

#### **15.4 Data collected during postoperative period**

The postoperative period is defined as the period starting when the patient leaves the operating theatre and ending 90 days postoperatively. The day of operation is considered day 0.

- Postoperative day with fluid intake > 1000 mL resumed
- Postoperative day with passage of first stool or colostomy production in case of no diversion ileostomy
- Day of discharge from hospital
- Complications including death and cause of death and number of reinterventions and reasons of abdominal surgery
- Reason and duration of possible readmission in hospital within 90 days postoperatively
- Analgesic requirement during the first three days
- Duration of absence from work

#### **15.5 Data collected at pathologic anatomical examination**

- Macroscopic description
- Histology
- Extent of local invasion
- CRM
- Distal resection margin
- Peritoneal spread
- Metastatic spread
- Synchronous colon pathology
- pTNM
- Tumour regression grade

#### **15.6 Data collected during follow-up period**

Once a year the following data will be collected:

- Date of visit
- Adjuvant therapy
- Reversion of ileostomy
- Details on recurrence, including date and method of diagnosis, site of recurrence and treatment consequences
- Details on complications
- Date and cause of death

#### **15.7 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 and to the competent authority.

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

#### **15.8 Annual progress report**

The investigator will submit a summary of the progress of the trial to the accredited medical ethical committee 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/ serious adverse reactions, other problems, and amendments.

#### **15.9 End of study report**

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.

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority 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 and the Competent Authority.

#### **15.10 Monitoring, audit and inspection**

Governors will be appointed to monitor trial progress on site, as frequently as seen necessary. The medical ethical review board of the coordinating centre (VU University Medical Centre) will register the trial at the clinical research bureau (CRB).

#### **15.11 Authorship eligibility guidelines and any intended use of professional writers**

All presentations and publications will be in the name of the 'COLOR III Study Group'. The sponsor will have no influence on implementation of the research and content of publications.

Nationally assessed data, on for example quality of life and costs can be published or presented by subgroups of authors without international consent. Publication or presentation of these data can only be possible when the authors state that the corresponding patients were included in the COLOR III trial. If a centre violates these rules, exclusion from the COLOR III trial and exclusion from authorship will be the consequence. Publication of data will not take place until accrual of patients has been completed.

#### **15.12 Trial Management Committee**

The Protocol and Writing Committee is responsible for the organisation of the trial. The Protocol Committee is responsible for the publication and presentation of all data. Publications will be coordinated by the Coordinating Centre.

## **16 SAFETY REPORTING**

### **16.1 Section 10 WMO event**

In accordance to section 10, subsection 4, of the WMO, the investigator will inform the subjects and the reviewing accredited medical ethical committee 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 medical ethical committee, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

### **16.2 AEs and SAEs**

#### **16.2.1 Adverse events (AEs)**

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

#### **16.2.2 Serious adverse events (SAEs)**

A serious adverse event is any untoward medical occurrence or effect that :

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, disease, major safety finding from a newly completed animal study, etc.
- Any other important medical event that may not result in death, be life threatening, or require hospitalisation, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the subject or may require an intervention to prevent one of the outcomes listed above

Reporting procedure applies to all (S)AE's occurring from the time a subject gives consent until 30 days after surgery and to any SAE that occurs after the 30-day period, if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

A life threatening SAE, or SAE with death as a result, must be reported within 7 days after the local investigator has been informed. Other SAEs must be reported within 15 days . The study coordinator is responsible for reporting SAEs at CCMO module 'ToetsingOnline'.

For individual sites, the local investigator completes the SAE form providing as much detailed information as known and relevant to the event. The local investigator sends the complete SAE form by e-mail to the study coordinator within 24 hours of discovery of the event. Thus, the coordinating investigator will be notified by email or telephone within 24 hours after discovery of the event. Using the CCMO module 'ToetsingOnline', all SAEs will be reported to the CCMO and central medical ethical committee. By means of this website notifications will be sent to the relevant authorities. The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

The following SAE's do not require immediate reporting but will be reported once yearly in line-listings to the accredited medical ethical review board that approved the protocol:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- A hospitalisation which was planned before the subject consented for study participation and where admission did not take longer than anticipated
- Social and/or convenience admission to a hospital
- Disease recurrence in the follow-up year requiring hospitalisation

### **16.2.3 Follow-up of adverse events**

All AEs 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.

### **16.3 Data Safety Monitoring Board (DSMB)**

This study is considered a medium risk trial. To assure proper data safety monitoring and relevance a DSMB will be installed. The DSMB will guard the safety of the included patients, give advice on continuation of the study upon superiority of one of the types of treatment, and will guard the methodological quality of the study. Furthermore, to keep insight in SAE's, the trial coordinator will communicate all SAE's to the independent monitor and to the Trial Steering Committee (C L Deijen, S Velthuis, A Tsai, S Mavroveli, J B Tuynman, C Sietses, G B Hanna, A M Lacy, J H T M Van Waesberghe, N C T Van Grieken, H J Bonjer) of this study. The Trial Steering Committee will comment on the reports.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

# Charter DSMB COLOR III trial

CONTENT	
<b>1. Introduction</b>	
Name of trial ISRCTN and/or EUDRACT number	COLOR III trial
Study risk classification	Medium
Objectives of trial, including interventions being investigated	The COLOR III trial is an international multicentre randomised study comparing short- and long term outcomes of TaTME and laparoscopic TME for rectal cancer. The study will include a quality assessment phase before randomisation to ensure required competency level and uniformity of the new TaTME technique and the laparoscopic TME. During the trial the clinical data will be reviewed centrally to ensure uniform quality. The primary endpoint of the COLOR III trial is quality of resection defined by involvement of CRM. Secondary endpoints include morbidity and mortality, residual mesorectum on postoperative MRI, local recurrence rate, disease-free and overall survival, percentage of sphincter saving procedures, functional outcome and quality of life.
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent DSMB for the COLOR III trial, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues and relationships with other committees.
<b>2. Roles and responsibilities</b>	
A broad statement of the aims of the committee	To safeguard the interests of trial participants and assess the safety of the TaTME procedure during the trial.
Terms of reference	The DSMB should receive and review the safety data of this trial. The DSMB should inform the Chair of the Trial Steering Committee if, in their view:  The number of (serious) adverse events is skewed between the groups.  Interim review when 25% of the total of 1098 patients are included and at 50% inclusion. The DSMB will be supplied with all data to evaluate the number of (serious) adverse events in all groups at the above mentioned time points, the inclusion rate unexpected differences in endpoints between study arms and potential conflicts with new insights and/or developments within the field of rectal cancer.
Specific roles of DSMB	It is at the discretion of the DSMB to meet early in the course of the trial and to discuss the protocol with the interim analysis plan, and to have the opportunity to clarify any aspects with the principal investigators.
<b>3. Composition</b>	
Membership and size of the DSMB	DSMB members register their assent by confirming (1) that they agree to be on the DSMB and (2) that they agree with the contents of this Charter.  The members are independent of the trial and have no competing interest that could impact on the trial. Also see the competing interest form (Annex

## CONTENT

1).

The members of the DSMB for this trial are:

- (1) Prof. dr. C.J. Mulder (Chair; Gastroenterologist, VUmc)
- (2) Prof. dr. G.L. Beets (Gastrointestinal Surgeon, AvL Amsterdam)
- (3) Dr. P. van de Ven (Statistician, VUmc)

The Chair is expected to facilitate and summarise discussions.

The trial office team will provide input to the production of the DSMB report.

The trial PI may be asked, and will be available, to attend open sessions of the DSMB meeting. The other trial group members will not usually be expected to attend but can attend open sessions when necessary.

### 4. Relationships

Clarification of DSMB role

No payments or rewards will be awarded to the DSMB.

Competing interests

Competing interests of DSMB members – financial matters, involvement in other trials or intellectual investment – should be disclosed (Annex 1).

DSMB members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.

### 5. Organisation of DSMB meetings

Expected frequency of DSMB meetings

The DSMB will meet at least once in the first year after the start of patient inclusion. The DSMB will perform an interim analysis at two time points as mentioned before.

The meetings of the DSMB can be by conference call, as long as full discussion with all members can be guaranteed.

All sessions are in principle open, although the DSMB can decide otherwise.

### 6. Trial documentation and procedures to ensure confidentiality and proper communication

Intended content of material to be available in open sessions

Accumulated information relating to the trial's safety data will be presented. Other outcome measures (e.g. efficacy) may be presented, at the discretion of the DSMB.

The DSMB members will not be blinded to the treatment allocation.

Who will see the accumulating data and interim analysis

The DSMB will discuss the results of the interim analysis with the Trial Steering Committee. DSMB members do not have the right to share confidential information with anyone outside the DSMB, other than the Trial Steering Committee.

External evidence

The PI and trial coordinator will identify and circulate external evidence that can influence the trial.

To whom the DSMB will communicate the decisions/ recommendations that are reached

The DSMB reports its recommendations in writing to the Trial Steering Committee. This will be copied to the trial coordinator in time for consideration at a TSC meeting.



## CONTENT

The DSMB members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DSMB members should destroy all interim reports.

### 7. Decision making

Decisions/recommendations open to the DSMB

Possible recommendations:

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of TaTME, futility, or external evidence

Decisions or recommendations within the DSMB

Every effort should be made for the DSMB to reach an unanimous decision. If the DSMB cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data.

It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made.

Effort should be made for all members to attend. The trial coordinator will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DSMB members cannot attend at all then the DSMB may still meet if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DSMB is considering recommending major action after such a meeting the DSMB Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DSMB.

If the report is circulated before the meeting, DSMB members who will not be able to attend the meeting may pass comments to the DSMB Chair for consideration during the discussions.

If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DSMB. If a member does not attend a third meeting, they should be replaced.

### 8. Reporting

Recommendations/decisions of the DSMB

The DSMB will report their recommendations/decisions in a letter to the Trial Steering Committee, within 4 weeks after the meeting. A copy of this letter will be lodged with the trial coordinator.

Disagreement between the DSMB and TSC

If the DSMB has serious problems or concerns with the Trial Steering Committee decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMB's concerns. Depending on the reason for the disagreement confidential data will have to be revealed to all those attending such a meeting. The meeting will be chaired by a senior member of the trials office staff or an external expert who is not directly involved with the trial.

### 9. After the trial

Publication of results

If requested by the DSMB, a meeting at the end of the trial will be held to allow the DSMB to discuss the final data with the principal trial investigators

**CONTENT**

and give advice about data interpretation

The DSMB will be given the opportunity to read and comment on any publications before submission, especially with respect to reporting of any DSMB recommendation regarding termination of a trial

The DSMB may discuss issues from their involvement in the trial when permission is agreed with the overseeing committee.

## **17 ETHICAL AND REGULATORY CONSIDERATIONS**

### **17.1 Regulation statement**

This trial will be conducted according to the principles of the declaration of Helsinki (Fortaleza October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other European guidelines, regulations and acts. Data management, monitoring and reporting of the study will be carried out in accordance with the ICH GCP guidelines.

The trial must be approved by the appropriate ethics committee of each participating institution prior to its entry into the study. Eligible patients should be informed in person by the treating surgeon and receive written information about the trial in their own language. Informed consent should be obtained from each patient according to the guidelines of the local ethical committee, prior to randomisation into the study. Patients remain free to withdraw at will at any time from the study without giving reasons.

### **17.2 Recruitment and consent**

The informed consent procedure should be performed by the treating physician or a representative that is aware of the details and complications of both treatments included in the trial. Therefore, it is the trial's preference that the consent is taken by the treating physician.

The information offered to the patient or representative contains:

- A statement that the trial involves research
- A full and fair explanation of the procedures to be followed
- A full explanation of the nature, expected duration, and purpose of the study
- A description of any reasonable foreseeable risks or discomfort to the patient
- A description of any benefits which may reasonably be expected
- A statement that patient data will be handled with care and confidentiality and the period of time the data is saved (15 years)
- A statement that patient bodily material is being stored for 15 years
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care.
- Patients are given a minimum of 72 hours to decide whether or not to participate in the study

### **17.3 Objection by minors or incapacitated subjects (if applicable)**

Minors and legally incompetent adults are excluded from the trial.

### **17.4 Benefits and risks assessment**

The potential benefit resulting from participation is improvement in oncological outcome and prevention from a permanent colostomy in the experimental arm. Patients in the experimental arm will be closely monitored with frequent follow-up visits. Because an extensive quality assurance program is integrated in the trial, the risk for surgical-related complications will be relatively low. Previous large cohort series have shown that the procedure is safe and has potential benefits. Nevertheless a Data Safety Monitoring Board will evaluate safety during the trial.

### **17.5 Compensation for injury**

The VU University Medical Centre 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.

1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million and five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

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**19 APPENDICES**

Appendix I: MRI protocol and staging definitions



**Hardware**

1.5 / 3.0 T

External Phased Array Coil (no endorectal coil)

**Patient Preparation**

Spasmolytics may be used in cases where significant bowel movement artefacts are visible on the planning images, especially 3T

No endorectal filling or enema

**Sequences and sequence angulation**

Imaging should be performed according the ESGAR recommendations: Magnetic resonance imaging for the clinical management of rectal cancer patients: recommendations from the 2012 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol (2013) 23:2522–2531

**2D T2-weighted sequences**

- sagittal and axial 2D T2-weighted sequence is mandatory for the assessment of tumour height, T-N-stage, MRF involvement and the presence of EMVI
- The use of a coronal 2D T2-weighted sequence is recommended
- axial and coronal T2-weighted sequence should be angulated perpendicular and parallel to the tumour axis for tumours in the middle part of the rectum
- For low rectal tumours, angulation depends on the extent of the tumour and may be performed perpendicular and parallel to either the tumour axis or the anal canal, or even both (4 series)
- Slice thickness: 3-4mm
- FOV: cranial border: upper side L5 / caudal border: beyond anal canal

Use of DWI is not obligatory for primary staging but is recommended for restaging (specifically for assessment of the T-stage) after CRT. B800-1000

No 3D T2-weighted and fatsuppressed sequences, T1-weighted sequence or contrast enhanced dynamic or steady state

**T2 sequence (examples):**

<u>Siemens</u>	<u>Siemens</u>	<u>GE</u>	<u>Philips</u>
TR > 6000 (8000-9000)	TR 4500	TR 4800	TR 5000-6000
TE 137	TE 128	TE 85	TE 135
Echotrain 61 (TSE)	Echotrain 25	Echotrain: 12	Echotrain
Acquisitions: 3	Acquisitions: 2-3	Acquisitions: 3	Acquisitions: 3
Slice thickness: 3-4mm	Slice thickness: 4	Slice thickness: 4	Slice thickness: 3
FOV: 240x 240	FOV: 240 x 240	FOV: 240 x 240	FOV: 240 x 240
Matrix 280 x 512	Matrix: 224 x 512	Matrix: 320 x 256	Matrix 320 x256meo
TR: shortest			
Matrix may vary per orientation			

### Standard operating procedures regarding image quality

All participating sites will be asked to send a dummy run with the T2-weighted and diffusion-weighted images to check the image quality and parameters. The dummy run may be performed on a healthy volunteer or a patient with rectal cancer.

The dummy run will be checked on quality. The results will be send to the participating site.

### MR staging

MR Images are judged on

- Position of tumour
  - o Distance to anal verge
  - o Length of internal sphincter complex
  - o Distance to the cranial border internal sphinctercomplex
  - o Extra low tumour: 0-2.0cm to anal verge
  - o Low tumour: 2.1-5.0cm to anal verge
  - o Mid tumour: 5.1-10.0cm to anal verge
  - o Location (anterior, right lateral, posterior, left lateral)
- Length of tumour
- Diameter of tumour
- T-status
  - o **T0**: no evidence of primary tumour
  - o **Tis**: carcinoma in situ: intraepithelial or invasion of lamina propria
  - o **T1**: tumour invades submucosa
  - o **T2**: tumour invades muscularis propria
  - o **T3a**: tumour invades beyond muscularis <1mm
  - o **T3b**: tumour invades beyond muscularis 1-5mm
  - o **T3c**: tumour invades beyond muscularis 5-15mm
  - o **T3d**: tumour invades beyond muscularis <15mm
  - o **T4a**: tumour invades directly into other organs or structures
  - o **T4b**: tumour perforates visceral peritoneum
- Distance to mesorectal fascia
  - o ≤ 1mm
  - o 1-2mm: mesorectal fascia at risk / threatened
- Extramural growth
  - o ≤ 5mm
  - o > 5mm
- EMVI: extramural vascular invasion
- N-status
  - o Malignant criteria:
    - Irregular borders
    - Round shape
    - Heterogenous signal intensity
  - o **N0**: no Lnn or Inn < 5mm without malignant criteria
  - o **N+**:
    - Lnn < 5mm with all malignant criteria
    - Lnn 5-9mm with ≥ 2 malignant criteria
    - Lnn ≥ 9mm (longest diameter)
  - o **N2**: at least 4 N+ Inn
- M- status if possible