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:	NCT02736942

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:

..../...../.....

Name (please print):

VU University Medical Centre

Position:

Board of directors

Chief Investigator:

Signature: Date:

..../...../.....

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Prof. H J Bonjer

Statistician:

Signature:

.....

Name: (please print):

E S M De Lange-de Klerk.....

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, non-inferiority 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) Intention for primary anastomosis	
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 resection (excl. local excision), prostatectomy	
Intervention	Rectal resection by transanal TME with laparoscopic surgery	
Control arm	Rectal resection by laparoscopic TME	
Quality assurance	The technical performance of TaTME will be standardised, including mandatory surgical steps and quality. An operation manual and notes will be written based on the standardisation to monitor compliance. Before entering the trial, all centres will have peer reviewed established procedure competence by assessment of unedited videos of three consecutive cases (2 TaTME + 1 laparoscopic TME). All surgical procedural videos are kept within patient record information database electronically. The videos will be evaluated using CAT. This competency assessment tool (CAT) is developed to evaluate the performance of TaTME. All MRI and pathology data will be centrally reviewed.	
Translational research	Blood and tissue from the primary tumour will be collected in specific centres and used for translational research on prognostic and predictive factors.	
	Outcome	Measurement
Primary	Local recurrence at 3 years	Event of local recurrence at 3 year follow-up
Secondary	• Quality of specimen • Involved Circumferential Resection Margin (CRM) • Morbidity and mortality • Residual mesorectum • Disease-free and overall survival • Sphincter saving procedure • Functional outcome • Health related Quality of Life	• Quality assessment by 'Quirke' • Clavien Dindo, 30 & 90 days • Postoperative MRI 3 year • MRI, pathology • Follow-up regimen • Colostomy percentage 1 year • LARS score • EORTC QLQ-29 and 30, EQ 5-D

Planned Sample Size	1104 patients in total; 735 in the TaTME arm and 369 in the laparoscopic TME arm to demonstrate a non-inferior effect on local recurrence of 4% after 3 years between the control group and the TaTME group. (Power 80% with a one-sided level of significance of 2.5%, dropout of 5%)
Planned Trial Period for inclusion	Four years (20+ centres, multinational)
Total duration of trial – report primary outcome	Inclusion period; three years Primary outcome at six years 5 year follow up at eight years
Interim analysis	Planned at 50% of the inclusion with regards to the sample size and conversions

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 conversions, permanent colostomies, and incomplete mesorectal excisions and relative high rates of circumferential resection margin (CRM) involvement resulting in significant number of local recurrences.

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. In TaTME, the tumour is distally approached through the anus with laparoscopic instruments. Latest systematic review of cohort studies showed that the TaTME technique is feasible and facilitates difficult resections in the lower pelvis. A low conversion rate and more sphincter saving procedures are reported. Moreover the current data from cohort studies have shown that the TaTME procedure is safe and is associated with less conversions and less morbidity in experienced centres compared with laparoscopic TME.

Before adaptation of the TaTME as standard surgical therapy for mid an 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 local recurrence rate. Secondary concerns are conversion rate, permanent colostomy rate and safety in terms of pathology, 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 design is non-inferiority compared to conventional laparoscopic surgery. 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 aim is to show non inferiority of TaTME compared to standard laparoscopic TME for mid and low rectal cancer local recurrence after 3 years of follow-up as primary endpoint. Secondary endpoints include morbidity and mortality, residual mesorectum on postoperative MRI, pathology, disease-free and overall survival, percentage of sphincter saving procedures, functional outcome and quality of life.

Statistics and randomisation

This trial is designed as a non-inferiority trial. The expected percentage of patients with a local recurrence after laparoscopic TME surgery is 5% after 3 years. TaTME is believed to be inferior to laparoscopic TME when there is a difference in local recurrence rate of more than 4% after 3 years in favour of conventional TME. Therefore, sample size is calculated based on non-inferiority with a difference of 4%with a one-sided level of significance of 2,5%,a power of 80% and a 5% drop-out rate. A total of 1104 patients is needed, 735 patients in the TaTME arm and 369 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 curative TME surgery with a intention for anastomosis, 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 international guidelines including imaging of the pelvis after three years with extra 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 be non-inferior in mesorectum specimen quality and involved CRM and therefore will result in comparable rate of local recurrence. After TaTME which allows 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

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

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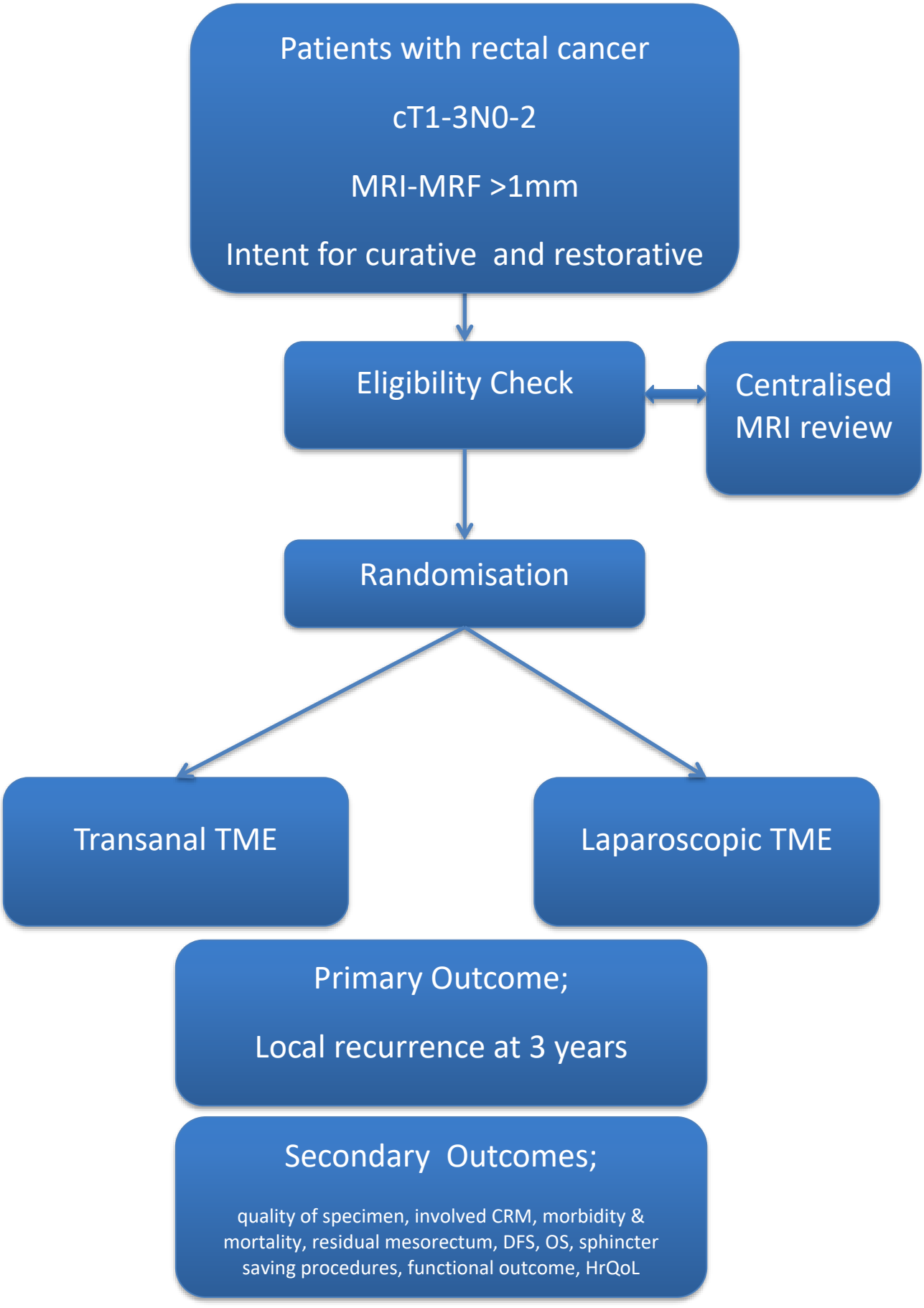
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LIST OF ABBREVIATIONS

AE	Adverse Event
APR	Abdominoperineal Resection
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 AND RATIONALE

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.[1,2]

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

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.[4] 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.[5-10]

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.[11] 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 high morbidity rates, high conversion rate, high colostomy rates and poor functional outcome compared with high rectal cancer.[5,6,8,12,13] In addition higher recurrence rates are reported for low rectal cancer compared to high rectal cancer.

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. Substantial morbidity is directly related to surgical procedure and collateral damage to nerves or pelvic floor. 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.[13-16] 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.[17] An involved CRM and not intact mesorectum are the most important independent factors predicting local recurrence rates.[18,19]

Morbidity and conversions in laparoscopic TME

Rectal cancer surgery is associated with high morbidity rates. Potential factors are less optimal anastomotic techniques resulting in leakages 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.[5,8,24] Several large RCTs and two national surveys reported abdominoperineal resection(APR) rates of 22% to 32%.[5,8,21,22] Although an end colostomy does not necessarily affect quality of life compared to sphincter saving procedures in low rectal cancer, the APRs is associated with relative high morbidity, mostly presacral abscess and infection of the perineal wound[39].

Margins and specimen quality after laparoscopic TME

A systematic review was performed by our study group including large randomised trials for laparoscopic and/or open surgery for rectal cancer. Only randomised trials reporting involvement of CRM, local recurrence rate after 3 years 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 5 trials 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. This involved CRM correlates with local recurrence after 3 – 5 years. Roughly 50% of the patients with an involved CRM, developed a local recurrence. 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.[5,6,8,12,13,16,20-23]

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

Study/national report	RCT/ report	Year	Percentage involved CRM	Percentage local recurrence	Tumour height
CLASICC	RCT	2005	Lap. 16% Open 14%	Lap. 7.8 Open 7.0 3Y	Total rectum, only AR
Dutch TME	RCT	2007	Open 16%	5.6% 5Y after RT	0-15cm
MRC CR07	RCT	2009	Lap. + open 10%	4.4% 3Y after RT	0-15cm
DSCA	Report	2014	Lap. + open 5.2%		Total rectum

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. Pathology remains however a surrogate endpoint for local recurrence, the most important outcome after treatment for stage 1 to stage 3 rectal cancer.

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

Study/national report	Year	Percentage involved CRM	Percentage local recurrence	Tumour height
COREAN	2010	Lap. 2.9% Open 4.1%	Lap. 1.2% 3Y Open 2,4%	0-9cm
COLOR II	2013	Lap. 9.4% Open 10.8%	Mid 6.5 3Y Low 4.4	0-10cm (subgroup)

Transanal laparoscopic surgery for rectal cancer

To overcome the problem of irradical resection, the transanal approach was introduced by Lacy et al. in 2010.[25] 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 with better imaging of tumour and level of anastomosis, less conversions to open surgery, good anastomotic technique avoiding cross stapling and good specimen quality.

Latest systematic review showed that the oncological quality including percentage of involved CRM, quality specimen and resection margins for TaTME is comparable to that of open and laparoscopic TME 38. Though possibility for publication bias is present we believe that the potential benefits of TaTME are more sphincter saving procedures and less conversion to APR or open technique with a comparable oncological outcome. 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 high perioperative morbidity in first operated patient and might also result in 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 proctored environment to avoid potential dangers the TaTME technique in the learning curve such as damage of urethra and prostate and rectal side wall damage. We believe that due to this learning curve the morbidity as shown in literature at the moment will decrease and eventually add to the benefit of TaTME. However, due to TaTME resection for very distal located rectal carcinomas can be performed with the creation of a coloanal anastomosis, which is to be evaluated the effect on morbidity and quality of life.

From 2010 to date, 34 non-randomised series have been published regarding hybrid TaTME (series including TaTME cohorts 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, but comparable to conventional surgery when recent cohort studies are analysed.

Author	Year publication	Operative time (min)	Conversion (%)	major morbidity %	minor morbidity %	CRM rate %
Sylla	2010	270	0	0	0	0
Dumont	2012	360	0	0	25	0
Zorron	2012	355	0	50	0	0
Lacy	2013	143	0	33,33	0	0
Lacy	2013	234,7	0	20	0	0
Sylla	2013	274,6	0	60	0	0
Velthuis	2013	175	NR	40	20	0
Rouanet	2013	304	6,7	33,33	13,33	13,3
Zhang	2013	300	0	0	0	0
Fernandez-I	2014	215	0	24,32	8,11	0
Velthuis	2014	NR	NR	NR	NR	4
Atallah	2014	243	NR	75	25	5
Chouillard	2014	265	6,3	0	18,75	0
Meng	2014	365	0	0	0	0
Zorron	2014	311	22	11,11	11,11	11
Veltcamp H	2015	204	5	26,25	12,5	2,5
Tuech	2015	270	5,4	19,64	5,36	5,4
Muratore	2015	241	0	15,38	11,54	0
Elmore	2015	236	0	0	33,33	0
Knol	2015	235	0	20	0	0
Serra-Aracil	2015	240	0	18,75	25	0
Lacy	2015	166	0	36,43	10	6,4
Perdawood	2015	300	0	28	24	4
McLemore	2015	359	0	100	100	NR
Buchs	2015	315,3	15	25	10	5,9
Chen	2015	182,1	2	20	6	4
Prochazka	2015	280	0	23,53	11,76	11,76
Kneist	2015	339	NR	12,5	12,5	8,33
Burke	2016	267	2,2	28	18	4
Rasulov	2016	320	4	27	0	5
Marks	2016	NR	0	25	0	0
Foo	2016	247,5	10	20	0	0
Buchs	2016	368,6	7,5	27,5	12,5	5

Our group published the results of our pilot study in which 80 patients underwent TaTME. Non conversions were necessary (COLORII 16%), anastomotic leakage rate was 4% (COLORII 13%). In 2.5% of the patients incomplete resection was found with CRM rate of 2.5% (COLORII 10%). 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.

Conclusion

The new TaTME technique has potential advantages due to better visualisation and dissection in the lower pelvis. Less conversions and more sphincter saving procedures are reported in the cohort series. TaTME will probably resulting in a comparable mesorectum specimen quality and rate of involved CRM and therefore comparable rate of local recurrence. 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.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Objective

The objective of this trial to evaluate the safety and efficacy TaTME for patients with mid and low rectal cancer.

3.2 Primary endpoint/outcome

The primary endpoint is the percentage of patients with local recurrence after 3 years of follow-up.

3.3 Secondary endpoints/outcomes

Pathological

- Involvement of CRM (defined as tumour cells within 1mm from the lateral surface of the mesorectum, centrally reviewed by pathologists)
- Quality of specimen (as proposed and published by Quirke et al.)[14]
- 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)
- Percentage of sphincter saving procedures (defined as colostomy percentage at 1 year postoperatively)
- Mortality within 28 days after surgery and within 90 days
- Local recurrence at 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

- 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) (side study)

- 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 is an international, randomised, non-inferior, 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 → 'COLOR III Trial'). All centres 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.[36,37] 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 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 (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

Excluded surgical procedures are extralevator abdominoperineal excision (ELAP) (i.e. patients with tumour in growth (more than 1/3) 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.

In order to ensure a standardised surgical quality an Operation 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 tested for usability, reliability and validity prior to its implementation in the pre- and main trial phases.

Quality assurance before entering the trial

1. Centre Participating Criteria:
    - Patient volume: minimum of 30 patients treated with rectal cancer per annum
    - Number of surgeons: minimum of 2 colorectal surgeons, performing laparoscopic low anterior resection and the TaTME procedure independently.
    - Training program: the centre has received training through a dedicated training program including cadaver training, and proctor supervised training. Centres with expertise in TaTME can be involved in hands on training and proctoring.

2. Trial entry criteria for quality assurance:
   The participating centre will be required to recruit three consecutive cases, one laparoscopic low anterior and two TaTME to demonstrate its capability of collecting unedited operative videos. Baseline characteristics (e.g. gender, age, tumour height, neoadjuvant therapy) need to be provide in order to have adequate assessment. The surgical performance will be assessed by two independent reviewers using competency assessment tool (CAT). Surgeons who do not satisfy the entry criteria will be required to gain more experience with the support from COLOR III training programme and re-assessed.

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

   Since TaTME (and Laparoscopic TME) is already performed on a regular basis in the included hospitals, the surgical quality assurance prior to the COLOR III trial does not included randomisation nor the data is used in the COLOR III trial, collected surgical videos of patients before start of the COLOR III trial are accepted without specific COLOR III informed consent. This is only applicable for the three patients needed for the Surgical Quality Assurance, prior to the COLOR III trial. All other patients, included in the COLOR III trial will need to give informed consent before participation.

Quality assurance during the trial

1. The first three cases will be monitored extensively to assure that all the required data, complying with the COLOR III protocol including the treatment, is provided; clinical data including MRI and pathology will be reviewed centrally through the COLOR III secure digital case record form. A checklist will be used to measure the compliance. For each registered patient automatic generated reminders will be send to the local trial coordinators for providing requested information in order to limit potential delay in follow-up.

2. In order to monitor the surgical quality, participating surgeons will be required to use the developed operation notes to document the procedure and explain any deviation from the standardised technique. Surgeons will be required to submit an unedited video of every operation performed for both laparoscopic TME and TaTME; the videos will be assessed using the Competency Assessment Tool to evaluate the learning curve within the trial.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

1) Solitary adenocarcinoma rectal cancer within 10 cm from anal verge defined by MRI
2) Stage 1-3 according to the AJCC classification including downstaged tumours based on adequate imaging of the thorax and abdomen
3) Intention for LAR with colorectal anastomosis or with coloanal anastomosis
4) Suitable for elective laparoscopic surgical resection
5) Informed consent according to local requirements

5.2 Exclusion criteria

1) T3 tumour with margins less than 1 mm to the mesorectal fascia or T4 tumour, determined by MRI-scan (staged after (chemo)radiotherapy if applicable)
2) Intention for APR
3) Malignancy other than adenocarcinoma at histological examination
4) Patients under 18 years of age
5) Pregnancy
6) Previous prostate or rectal surgery (excluding local excision)
8) Signs of acute intestinal obstruction
9) Multiple colorectal tumours
10) Familial Adenomatosis Polyposis Coli (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), active Crohn's disease or active ulcerative colitis
11) Planned synchronous abdominal organ resections
12) Other malignancies in medical history, except adequately treated basocellular carcinoma of the skin or in situ carcinoma of the cervix uteri
13) Absolute contraindication 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. (appendix I MRI Protocol) 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)

The main definition of a Transanal TME is the dissection of (at least) the distal third from the transanal approach; The first intersphincteric dissection can be performed in an open fashion whereas the distal mesorectal dissection is performed with a platform with insufflation and minimal invasive instruments and camera to obtain optimal view of the anatomy and dissection planes. Detailed protocol based upon a Delphi method is shown in the appendix III.
The abdominal part of the procedure is performed laparoscopically with standard procedure; The proximal TME plane is opened form the abdominal site although the extent of abdominal and the extent of the transanal dissection is up to decision the surgical team and depends on the individual case. The formation of a diverting ileostomy is up to the decision of decision the surgical team and depends on the individual case.

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
Excluded surgical procedures are abdominoperineal excision (APR) (i.e. patients with tumour in growth in the anal sphincter complex or levator ani more than 1/3).

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 (Appendix III)

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 evaluate 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 pathology protocol is included in appendix IV.

10.3 Translational research

From the Dutch 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. Within selected high volume centres blood samples will be collected and DNA is extracted for subsequent analysis of free circulating tumour DNA; Separate protocol)

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

According to the international guidelines (ASCO, NICE) patients participating in the COLOR III trial 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. A chest radiograph and a liver ultrasound or CT-thorax/abdomen are performed to assess development of distant metastases according to international guidelines. Follow-up of patients with recurrent disease should continue until at least 3 years after detection of recurrence or until death.

A CT or MRI of the pelvis must be performed three years postoperatively to assess possible local recurrence and/or residual mesorectum. In case of suspicion of recurrence on CT-abdomen a pelvic MRI is mandatory. In the NICE guidelines a minimum of two CTs of chest, abdomen and pelvis in the first 3 years is needed in the regular surveillance. The ASCO states that CT imaging of these regions is even needed annually in high risk patients. Since mid and low rectal cancer is associated with high recurrence rate and therefore patients should be marked as high risk patients compared to patients with a high rectal cancer and imaging of the pelvis after three years is considered standard of care.

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.

12.3 Questionnaires

To measure quality of life and functional outcomes, several questionnaires will be used. These questionnaires will be sent by email and access to an anonymized webtool (Castor) will granted, if the patient does not have an email account, the questionnaires will be send to the patients' home addresses, accompanied by a return envelope provided with postage stamps and the address of the hospital.

The following questionnaires will be used:

EQ 5D - 5L (Euroqol): This questionnaire is a simple, generic instrument for describing and valuing health related quality of life. It includes 5 items (mobility, personal care, daily activities, pain, and anxiety - depression) that are answered on a 3 - point scale ranging from no problems (level 1) to extreme problems (level 3).

Global quality of life (EORTC - QLQ - C30 - QL2): This sub questionnaire contains the 2 items of the global quality of life dimension of the EORTC - QLQ - C30 questionnaire.

Global quality of life (EORTC - QLQ - CR29): This questionnaire is developed to assess the quality of life
in colorectal patients.

LARS - score: Five questions (with at least one question representing each of the four known LARS symptom categories, namely incontinence, frequency, urgency and emptying difficulties) showing the highest prevalence and impact on QOL were identified.

Functional outcome and HRQoL after therapy will be measured using these validated questionnaires at admission and at 3, 6, 12, 24 and 36 months post - operatively.

	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 or CT-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 local recurrence after 3 years. In laparoscopic TME the percentage of local recurrence is estimated 5%. A local recurrence increase of 4% is believed to be inferior. Based on this difference, sample size calculation has been done with a one-sided level of significance of 2,5% and a power of 80%.A total of 1104 patients is needed, 735 patients in the TaTME arm and 369 patients in the laparoscopic TME arm.
In this sample size calculation, additional post randomisation analyses (drop-out, cross-over total 5%), is 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 ≤ 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. 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 performing surgeon(s) are noted in the case record form. 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 date, 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 (T W A Koedam, 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	
1. Introduction	
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.
2. Roles and responsibilities	
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 50% of the total 1104 patients are included . 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.
3. Composition	
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.

CONTENT	
	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 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.

CONTENT	
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. 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.

CONTENT	
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 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

Appendix II: Definition anastomotic leakage

Appendix III: Quality Assurance

Appendix IV: Pathology

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):

Siemens	Siemens	GE	Philips
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

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

Appendix II Definition anastomotic leakage

- Anastomotic leak[34]: 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[35]: 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.

Appendix III Quality assurance

Surgical Quality Assurance

(i) Standardisation

A robust 4-round Delphi methodology has been applied with peer-nominated international group of expert consultants in TaTME.

Round I – Hierarchical Tasks Analysis (HTA) for TaTME

It is based on semi-structured interviews to identify key surgical steps and quality and ensure a saturation of variations is reached.

Round II-IV – Consensus Process

Questionnaires containing all variations of surgical stages and steps are written based on Round I and distributed to the same group of expert surgeons. They are asked to rate each step as either mandatory, optional or prohibited with a set level of agreement of 70% in multiple rounds. The development of operation manual and competency assessment tool will be based on the consensus result.

(ii) Operation Manual and Operation Note

A full operation manual including technical and oncological quality of TaTME will be developed based on the results of standardization. Operation note will be constructed accompanying the manual; it is designed for the purpose of clinical requirement for documentation and research requirement of measuring compliance to the standardized surgical quality. Any deviation from the agreed standard should be explained in the comment box provided.

(iii) Competency Assessment Tool (CAT)

A CAT form is composed of agreed surgical steps at X-axis and quality of performance at the Y-axis. Validation of CAT will ensure acceptability, reliability and clinical validity. The CAT tool will be used in the trial regulation process. Surgeons will be asked to submit unedited videos, which will be assessed by two independent assessors using the CAT tool to ensure the level of performance standard is reached at the trial entry and maintained during the trial period

(iv) Case difficulty and score adjustment

Further research has been designed to evaluate factors that determine the case difficulty and how they may affect performances and possibly the CAT score.

Trial Regulation

(i) Trial entry assessment

Centres that wish to enter the COLOR III trial will be required to recruit a minimum of 2 TaTME, and 1 Laparoscopic TME patient for surgical competency assessment. Each centre who wish to participate will be required to submit 3 unedited full length videos (1 laparoscopic and 2 transanal TME). In TaTME, both the abdominal and transanal components should be recorded and submitted.

Patient information concerning baseline characteristics (eg. gender, age, tumour height, neoadjuvant therapy) need to be provide in order to have adequate assessment. Two assessors approved by the expert panel will assess the videos independently using CAT. Surgeons who do not satisfy the entry criteria will be required to gain more experience with the support from COLOR III training programme and re-assessed.

Since TaTME (and Laparoscopic TME) is already performed on a regular basis in approached hospitals, and the surgical quality assurance does not included randomisation nor the data is used in the COLOR III trial, collected videos of patients before start of the COLOR III trial are accepted without specific COLOR III informed consent.

(ii) Trial monitoring

Surigcal Quality Assurance

For surgical competency assessment, only the pelvic/TME dissection will be assessed for the purpose and practicality of trial monitoring. Recording of pelvic dissections from both laparoscopic and transanal platform will be assessed. Each surgeon will be required to submit a video of every operations performed. The video assessments with CAT and together with operation notes will retrospectively be used to monitor adherence to the agreed surgical standards, but does not include monitoring during the trial on the quality of surgery. In the cases of unsuccessful surgical competency assessment, the level of case difficulty will be taken into account and evaluated by COLOR III group retrospectively.

In order to increase the compliance to the protocol follow-up, all patients will be registered in a central database, which will provide automatic mails to the local trial coordinators with information and request to provide their information.

Appendix IV Pathology

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 5th 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 ≤ 1mm 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 um).