COLOR II

A

RANDOMIZED CLINICAL TRIAL

COMPARING

LAPAROSCOPIC AND OPEN SURGERY

FOR

RECTAL CANCER

Version #4: November 2008

INDEX

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2.1 COORDINATING CENTER

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2.2 RANDOMIZATION

Randomization for all centers will be done through the internet:

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3 SUMMARY PROTOCOL

3.1 INTRODUCTION & BACKGROUND

Laparoscopic resection of colorectal malignancies is still controversial, mainly due to initial reports on port-site metastases that caused major concern. Although retrospective studies with large numbers of patients now suggest that the incidence of port-site metastases is comparable to the incidence of wound metastases in open surgery, the pathogenesis of these recurrences remains unclear. Experimental studies and one randomized clinical trial (Lacy) indicate that laparoscopic surgery might even result in lower recurrence rates. In this trial comparing laparoscopic versus open colectomy for colonic cancer, an improved 3-year survival following laparoscopic resection was found.
Benefits of laparoscopic surgery in general are less postoperative pain, a shorter recovery period and earlier return to work and daily activities. These benefits are likely to apply to laparoscopic colorectal surgery as well.
With ever advancing technique in laparoscopic surgery, the possibilities for longer and more complex operations are expanding. Along with this trend laparoscopic surgeons are performing more demanding surgical procedures, such as Total Mesorectal Excision (TME) for rectal cancer. We believe that the development of laparoscopic TME procedures should be performed within a trial setting, because long-term results are not established. Within a trial, the technique can be standardized and quality control is assured.

3.2 STUDY DESIGN

The COLOR II trial is a randomized, international, multi center study comparing the outcomes of laparoscopic and conventional resection of rectal carcinoma with curative intent. Clinical and operative data will be collected centrally in the coordinating center in Halifax, Nova Scotia, Canada. Quality of life and costs will be assessed on a national basis.
Prior to the start of the COLOR II trial, a feasibility study will be performed. The objective of this feasibility study is to control quality of laparoscopic TME procedures. Per center, five consecutive TME's are performed, and either recorded or observed by an expert in laparoscopic TME. All resected specimens are pathologically analyzed. Furthermore, each participating center should at least send one unedited video of a laparoscopic TME to the monitoring committee for approval.

3.3 ENDPOINTS

Primary endpoint of the phase III trial is locoregional recurrence rate 3 years postoperatively. Secondary endpoints are disease free and overall survival at three, five and seven years, rate of distant metastases, port-site and wound-site recurrences, macroscopic evaluation of the resected specimen, 8-week mortality and morbidity, quality of life and costs.

3.4 STATISTICS & RANDOMIZATION

Using log rank statistics with a power of 80 % and a type I error of 5%, 1275 patients are needed to detect a difference between both treatment arms of 5% in locoregional recurrence rate 3 years postoperatively, assuming a 10% recurrence rate in the open group. Randomization will be 2:1, laparoscopic versus open resection respectively. Analyses will be on "intention to treat" basis. Randomization is stratified for each participating center, planned procedure, radiotherapy and sex.

3.5 MAIN SELECTION CRITERIA

Patients with a single rectal cancer at less than 15 cm from the anus at rigid rectoscopy, eligible for surgery with curative intent, can be included. Not included are patients who have local excision of a rectal cancer. Also not eligible are patients with concomitant metastases or other malignancies, with malignancies in their medical history or with signs of acute obstruction.

3.6 FOLLOW-UP

Patients will be examined at least once a year for seven years. Every year, up to 7 years after surgery, anamnesis and physical examination are performed. In case of recurrent disease, follow up should be until 3 years from the time of diagnosis of recurrence.

4 INTRODUCTION

4.1 EPIDEMIOLOGY

Colorectal cancer is the third most frequent malignancy in males, after prostate and lung cancer, and the second most frequent malignancy in females, after breast cancer. Every year, colorectal cancer afflicts 221000 new patients and causes 111000 deaths in the European Union. Death rates of colorectal cancer in Western European countries vary from 17 to 19 per 100,000 population.
In the Netherlands yearly 8.600 patients are newly diagnosed with colorectal cancer and 25 % of these tumors is located in the rectum.
About 75 % of all rectal cancer patients can be treated by surgery with curative intent, of which 10% is cured by local excision. In about 25% of patients, extensive surgery is not an option because of poor performance or advanced stage cancer.

4.2 SURGERY FOR COLORECTAL CANCER

Adequate resection of colorectal cancers is the only curative treatment. The tumor-bearing bowel is excised with its accompanying mesentery containing the vascular supply and the lymph draining vessels. Survival after resection of colorectal malignancies depends on stage of disease, radicality of resection and adjuvant therapy, surgical technique being critical both in respect of cure and local recurrence. Conventional surgery for colorectal cancer requires extensive laparotomy. Preferred margins for resection of the bowel vary, depending on the site of the tumor, from 2 to 5 cm. Sufficient resection of lymphatic tissue adjacent to the tumor is considered essential by most colorectal surgeons.
The limited workspace in the lower pelvis and the bony structures surrounding it, make it difficult to operate on the rectum and impede complete resection of rectal cancer. Until the late seventies blunt dissection of the rectum along the presacral fascia was performed, which was distally directed cone-wise to allow for a low anastomosis. Lateral excision was often incomplete in this procedure with high rates of local recurrences as a consequence, up to 45 %, were reported. A new procedure, Total Mesorectal Excision (TME) was introduced by Heald in 1982.
Sharp dissection along anatomical planes results in a more complete resection, especially on the lateral sides. Local recurrence rates dropped significantly because of this. In addition, the presacral nerves and vessels are better preserved, resulting in better outcome considering bladder and sexual function postoperatively.
The low recurrence rates reported by surgeons who specialize in TME are now reproduced by Kapiteijn et al. in a multi-center randomized controlled trial [1]. In this trial the TME technique was standardized and extensive training in the technique was offered, allowing for very reliable results.
Currently open TME must thus be regarded the pillar of cure for rectal cancer and the gold standard against which any modification of the technique must be judged.

4.3 LAPAROSCOPIC SURGERY FOR COLORECTAL CANCER

Recently, Lacy et al published the first long-term results of a randomized trial comparing laparoscopic colectomy versus open colectomy for the treatment of colonic cancer. This study demonstrated improved 3-year cancer related survival following laparoscopic surgery compared to open surgery (91% vs 74% respectively). The observed benefit could mainly be attributed to lower tumor recurrence and a longer overall survival of patients with stage III colonic cancer [2]. The authors concluded that laparoscopic colectomy is preferred to open colectomy in patients with colonic cancer. Results of this study have to be interpreted with great care because it represents a single institution experience with a relative small number of patients. Results of large multi-center trials will have to be awaited. Interim analysis of these randomized trails have not shown significant differences of recurrence rate so far, as none of the trials have ceased including new patients for this reason.
Laparoscopic colorectal surgery was first reported in 1991 by Jacobs et al [3]. In spite of the technical complexity and initial high financial costs of laparoscopic colorectal surgery, feasibility to use laparoscopic techniques for almost the entire spectrum of colorectal surgery has been established [4-10]. In a registry, supported by the American Society of Colon & Rectal Surgeons and the American College of Surgeons, of 453 laparoscopic resections for colorectal cancer, subjective violation of cancer principles occurred in only 1 percent of patients [11].
However, first reports on abdominal wall metastases after laparoscopic resection of colorectal cancers have caused major concern [12]. Comparison of the incidences of abdominal wall metastases after open and laparoscopic colectomy is not possible because true incidence rates are unknown. Incidences of abdominal wall metastases vary from 0.69 % to 16.6 % [13-16] following open resection for colorectal cancer and from 0.6 % to 21 % [11, 12, 17, 18] following laparoscopic resection of colorectal cancer. Review of laparoscopic resections for colorectal cancer has shown the majority of reported abdominal wall metastases to occur in patients with loco-regionally advanced disease or diffuse peritoneal carcinomatosis [8, 19]. Recent reports on laparoscopic colon resection for malignancies do not show an increased incidence of abdominal wall

metastases [20, 21]. In a recent review of current literature the incidence of port site metastasis is 1% or less[22]. Experience of the surgeon and standardization of the technique seem to play an important role [23-25].
The pathogenesis of abdominal wall metastases remains unresolved. Inadvertent grasping of the tumor and extraction of the tumor through narrow incisions of the abdominal wall are likely to play an important role. Precise localization of the tumor and protection of either the abdominal wall or the specimen during extraction are therefore used by most experienced surgeons. Whether the increased intra abdominal pressure or the use of CO_2 gas to establish the pneumoperitoneum compromise cancer free survival remains uncertain. Some experimental studies have shown that gasless laparoscopy results in less tumor growth [26].
Laparoscopic surgery appears to be associated with less operative trauma and blood loss than open surgery. These factors are considered beneficial for survival [27, 28]. Experimental studies have shown that tumor take and growth are significantly less after laparoscopic surgery [29, 30]. Clinical studies on interleukin-6 response to open and laparoscopic colectomy showed significant lower levels of interleukin-6 after laparoscopic procedures, indicating a lower degree of surgical trauma and less attenuation of immunity [22, 31].
The motives to approach colorectal disease laparoscopically are similar to those of laparoscopic cholecystectomy. Compared to open cholecystectomy, laparoscopic cholecystectomy is associated postoperatively with less pain, reduced respiratory impairment, earlier return of gastro-intestinal function, earlier mobilization, shorter hospital stay, earlier return to daily activities and work, improved cosmetic results and less incisional hernias [32, 33]. These same advantages are likely to apply to laparoscopic colorectal surgery.

4.4 LAPAROSCOPIC SURGERY FOR RECTAL CANCER

With ever improving technical assets associated with laparoscopic surgery, the possibilities for longer and more complex operations are expanding. Along with this trend, laparoscopic surgeons are exploring new endoscopic surgical procedures. TME for rectal cancer is one of the more recent procedures to be performed laparoscopically. The limited workspace in the lower pelvis lends itself well for a laparoscopic approach and technical advances make laparoscopic resection possible. Reports on laparoscopic TME are still rare because the technique is developed only recently and performed by a select number of surgeons. Few highly skilled laparoscopic surgeons have engaged laparoscopic TME so far [34-36].
The outcome after resection of rectal cancer is mainly dependent on the extent of resection according to TME principles. Few case reports and short non-randomized series are published so far. In these series extent of resection upon pathological examination of the resected specimen was comparable to open resection [35, 37]. To our knowledge, only one randomized controlled trial, the CLASICC trial, has also addressed open versus laparoscopic resection for rectal cancer. However, results of the CLASICC trial have not been published.
We believe the laparoscopic approach to rectal cancer should not be performed outside a trial setting, because long term results on local recurrence are unknown. Within a trial setting, the technique can be standardized and quality control is performed. Postponing such a trial could result in incorporating laparoscopic TME into clinical practice before its exact role is established in comparison to conventional techniques. A similar process has occurred in the introduction of laparoscopic cholecystectomy [38], where randomized controlled trials became available after incorporation of the technique into general practice.
Laparoscopic surgery for colon cancer was performed around the world, including Western Europe without any proof of this minimally invasive technique being associated with equal or better survival than conventional surgery. Such practice was not desirable and the COLOR trial, a randomized clinical trial comparing both techniques, was instigated. For resection of the colon, operating on patients with benign disease could first optimize the technique. However, TME can only be developed by operating on patients with malignancies of the rectum, because performing a TME for benign disease is rare.
Therefore we consider it important to start a trial at this moment, as standardization of the technique in an early phase is required. Introduction of laparoscopic TME in surgical practice, without prove that it will provide at least similar results as open TME, is undesirable.

4.5 ADJUVANT THERAPY

Extensive studies have been performed throughout the years to investigate the efficiency of many different regimes in controlling local recurrence. With the rise of the TME procedure, with its low recurrence rate, it is now reinvestigated what adjuvant therapy is best in optimizing local recurrence rates and long-term survival. Survival benefits for most regimes have to be proven again and benefits of adjuvant therapy have to be weighed against additive morbidity. In a recent publication, Kapiteijn et al showed that significantly less local recurrences occur after short preoperative radiation with 5*5 Gy in patients with rectal cancer (overall recurrence rate 8.2 vs. 2.4 respectively)[1]. Although no survival benefit was found, this might be caused by the relatively short follow-up of 2 years. The operative procedure was extensively standardized and

optimized in this study.
Post-operative chemotherapy is not standard treatment in rectal cancer. Chemotherapy is predominantly applied in randomized clinical trials.

4.6 OBJECTIVE

The objective of this study is to randomize patients with rectal cancer for either open or laparoscopic surgery to assess the role of laparoscopic TME in the treatment of rectal cancer. The most important endpoint in this study is locoregional recurrence rate 3 years postoperatively. A multi-center, international trial, with participation of centers in Western Europe has been designed, according to the COLOR I trial.

5 STUDY DESIGN

This trial is a randomized, international, multi-center study comparing laparoscopic and conventional resection for rectal cancer. Patients will be accrued by the participating hospitals of the COLOR II study group. The COLOR II study group is an international group of surgeons with interest and expertise in laparoscopic and colorectal surgery. Since 1997 the COLOR I study group has performed and almost completed a large international randomized controlled trial comparing laparoscopic to open surgery for colon cancer. Many centers of the COLOR I study group will join the COLOR II study group.
The design involves allocation of all suitable consecutive patients with rectal carcinoma to either of the two procedures at a randomization ratio of 2:1, in favor of the laparoscopic procedure. Excluded are patients with a carcinoma treated by local resection and palliative resections. The trial will be stratified according to participating center, resection type, preoperative radiotherapy and sex.

6 ENDPOINTS

6.1 PRIMARY ENDPOINT

- locoregional recurrence rate 3 years postoperatively

6.2 SECONDARY ENDPOINTS

6.2.1 Clinical

- survival free of cancer recurrence at three, five and seven years
- overall survival at three, five and seven years
- distance of the tumor to the endopelvic fascia and the distal resection margin
- port-site and wound-site recurrences
- distant metastases rate
- 8-week or in-hospital operative mortality and morbidity
- macroscopic evaluation of the resected specimen

6.2.2 Quality of life

- duration of in-hospital stay postoperatively
- duration of absence of work
- postoperative health related quality of life (quality adjusted life years), including standardized questionnaires on sexual and bladder function

6.2.3 Costs (national)

- in hospital direct and indirect costs
- out-of-hospital postoperative costs

7 ETHICS

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 randomization into the study. Patients remain free to withdraw at will at any time from the study without giving reasons.
To guarantee optimal treatment for patients in both treatment arms, interim analyses will be performed to compare survival and recurrence in both treatment arms. If differences of survival or recurrence rates are significant, accrual of patients will be stopped.
To assess the feasibility of laparoscopic rectal cancer resection, a phase II trial will precede the accrual of patients in this trial.

8 FEASIBILITY STUDY

The objective of the feasibility study is to control quality of laparoscopic TME procedures per center. Five consecutive laparoscopic TME's are performed, and either images are recorded or the procedure is observed by an expert in laparoscopic TME surgery. The protocol committee assigns laparoscopic TME experts per country. At least one recording of a laparoscopic TME has to be submitted to the monitoring committee for approval. The specimens of the 5 consecutive laparoscopic TME's will be examined both macroscopically and microscopically by the pathologist of the involved center as described below.

9 ELIGIBILITY

9.1 INCLUSION CRITERIA

- solitary rectal cancer observed at colonoscopy or on barium enema X-ray
- no evidence for distant metastases
- distal border of the tumor within 15 cm of the anal verge at rigid rectoscopy
- suitable for elective surgical resection
- informed consent according to local requirements

9.2 EXCLUSION CRITERIA (PRE-RANDOMIZATION)

- T1 tumor treated by local excision
- T4 tumors, staged prior to pre-operative chemo/radiotherapy
- T3 tumors with margins less than (<) 2mm to endopelvic fascia, by CT scan or MRI
- malignancy other than adenocarcinoma at cytological/histological examination
- patients under 18 yrs of age
- signs of acute intestinal obstruction
- more than one colorectal tumor
- Familial Adenomatosis Polyposis Coli (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), active Crohn's disease or active colitis ulcerosa
- scheduled need for other synchronous colon surgery
- preoperative indication of invasion of adjacent organs (immobile at palpation or CT/MRI showing invasion into surrounding structures)
- preoperative evidence of metastases (at least chest X-ray and ultrasonography of liver required to rule out metastases)
- other malignancies in medical history, except adequately treated basocellular carcinoma of the skin or in situ carcinoma of the cervix uteri
- absolute contra-indications to general anesthesia or prolonged pneumoperitoneum, such as severe cardiovascular or respiratory disease (ASA class > III)
- pregnancy

9.3 EXCLUSION CRITERIA (POST-RANDOMIZATION)

- no adenocarcinoma
- local invasion of uterus and/or vagina at operation

9.4 PATIENTS REFUSING PARTICIPATION

Patients, who meet all inclusion criteria but do not wish to participate, should be registered. Date, hospital patient identification number, gender, location of tumor, type of operation, ASA class, TNM stage, Dukes stage and a short reason for refusal should be noted.

Possible reasons:
- objects to laparoscopic operation
- objects to conventional operation
- objects to participate in medical studies

9.5 NON INCLUDED & EXCLUDED PATIENTS

All patients suspected of having rectal cancer, who are considered for operation, should be registered. Thus patients who do not meet the inclusion criteria, as well as patients excluded after randomization, should be registered concerning date, hospital patient identification number, gender, location of tumor, type of operations, ASA class, TNM stage and Dukes stage. In addition to this registration, a short reason for non-

inclusion or exclusion should be noted.

For example:
- metastases
- inoperability
- no adenocarcinoma in resected specimen
- laparoscopic surgery contraindicated (include reason)

10 RANDOMIZATION

Once eligibility has been established and patient details have been logged, the patient will be allocated to either laparoscopic or conventional operation. Randomization will be performed by computer at time of randomization. Randomization will be balanced and stratified by participating center, resection type, radiotherapy and sex. When patients are not subjected to the treatment modality as randomized, data will be analyzed on an “intention to treat basis” (once randomized, patients will not be excluded or changed groups because of conversion or type of resection).

Randomization for all centers will be done through internet:

www.color2.org (click “investigators”)

11 PERI-OPERATIVE CARE & EXAMINATIONS

11.1 PRE-OPERATIVE WORK-UP

Colonoscopy or lateral barium enema radiography of the complete colon is performed to exclude concomitant tumors. The entire colon should be imagined either pre-operatively, or within 3 months after surgery. Biopsies are mandatory. Lateral barium enema radiography or rigid rectoscopy should be performed to assess the localization of the cancer in the rectum. CT or MRI of the pelvis is performed to show its relation to surrounding structures. The radiologist should report the estimated distance between the tumor margin and the endopelvic fascia. Endorectal sonography is optional. Pre-operative work-up should include imaging of chest and liver. CT scan of both thorax and abdomen is the preferred preoperative screening to assess metastatic disease.

11.2 PRE-OPERATIVE CARE

Bowel preparation, antibiotic prophylactics and deep venous thrombosis prophylactics will be according to local standards and should be standardized by each center for all of their patients. Preoperative care should be the same in each treatment arm throughout the trial.

11.3 INTRA-OPERATIVE CARE

Anesthetic care should be standardized by each center for all of their patients in each treatment arm throughout the trial. New anesthesiology protocols can be introduced during the study, when these protocols apply to both arms.

11.4 POST-OPERATIVE CARE

Analgesic care and allowance of restoration of diet will be according to local standards, but this should be standardized for all patients in each treatment arm throughout the trial.

12 SURGICAL PROCEDURE

12.1 LAPAROSCOPIC TECHNIQUE [34]

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 mobilized 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.

12.2 CONVERSION

Conversion is defined as a change in operative approach to achieve the final goal and will be at the discretion of the individual surgeon for concerns of patient safety, technical difficulties, inability to complete the planned operation for sphincter sparing or associated conditions requiring treatment. Utilizing the extraction site for transverse stapler insertion to accomplish the distal anastomosis will not be considered a conversion. Identification of any grossly visible positive margins or extension into adjacent organs will mandate conversion to an open procedure. Completion of the pelvic dissection through open surgery will be considered conversion. Conversion is defined as a fascial incision longer than 10 cm, utilized to achieve anything other than specimen extraction. (Largest handport size is 8 cm)

13 HISTOPATHOLOGY.

All resected specimens are analyzed by the pathologist. Macroscopical assessment of the quality of mesorectal dissection will be scored in 3 grades.

- Complete: intact mesorectum with only minor irregularities of the mesorectal surface. No defect is deeper than 5 mm. No coning towards the distal margin of the specimen. Smooth circumferential resection margin on slicing.
- Partial incomplete: the majority of the mesorectum has been removed. Moderate coning of the specimen towards the distal margin. At no site is the muscularis propria visible with the exeption of the area of the insertion of the levator muscles. Moderate irregularity of the circumferential resection margin.
- Incomplete: mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin, coning.

The unopened resected specimen is received fresh, opened anteriorly except in the area of the tumor where the full circumference of the bowel should be left intact and pinned under gentle tension to a cork board for fixation in formalin. After fixation, the peritoneal reflection is identified and the relative position of the tumor 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. Tumors completely covered by peritoneum are handled in the routine manner for colonic specimens, whereas those with a retroperitoneal component are subjected to close scrutiny for circumferential margin involvement by tumor. The site of the tumor is sliced as thinly as possible including up to 2 cm above and below, and laid out on a flat surface for macroscopic inspection.

The extent of tumor involvement of the perirectal tissue is assessed with particular attention being paid to the circumferential resection margin. The maximum extent of tumor spread from the outer limit of the muscularis propria is measured using a ruler. This should be to the edge of tumor's greatest distance of penetration from the muscular wall, be it direct, discontinuous, and vascular or lymph node involvement. 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 tumor. On average four blocks will suffice for the majority of tumors. The circumferential resection margin of the block should be marked with India ink to demarcate it on histology and rule out false positive tumor involvement of a tissue margin caused by poor embedding practice.

The specimen is now turned over, so the mucosal aspect faces downwards and the retroperitoneal/ mesenteric faces upwards. The C node is identified and sampled and the whole of the specimen, from the proximal margin, (i.e. that nearest the surgical ligature of the inferior mesenteric artery, down to the previously excised tumor segment) is sliced serially down to the external aspect of the muscularis propria. Similarly, the segment of the rectum below the tumor is also serially sliced. Whilst incising the mesentery and the mesorectum, lymph nodes and tumor deposits should be identified and sampled. Metastases and lymph nodes adjacent to the circumferential margin should be sampled "en-bloc" with the resection margin, which again should be identified by painting with India ink.

Lymph nodes further than 1 cm from the circumferential resection margin or present in the mesentery of the sigmoid colon may be sampled in a routine fashion. If the tumor is close to the distal resection margin (i.e. < 2 cm away or in a bulky or poorly differentiated tumor < 5 cm away) then of course this margin should also be sampled.

Accurate measurement of the minimum distance between tumor and circumferential resection margin should

be performed by microscopy on the haematoxylin and eosin stained slide using the Vernier scale on the microscope stage. Shrinkage of tissue occurs during processing but this does not materially affect the accuracy of this measurement. Assessment by microscopy is preferred as a florid peri-tumoral inflammatory reaction or fibrosis will lead to an overestimate of macroscopic tumor spread. Macroscopic measurements are accurate enough for the distance from the muscular wall to the edge of the tumor as this measurement is only used for the comparison of local recurrence rates between surgeons.

13.1 TUMOR DEPOSITS

Sometimes tumor deposits are present without the structure of a lymph node. To avoid that the patient is incorrectly classified as node negative, please pay attention to the WHO definition: "a tumor nodule > 3 mm across in the connective tissue in the lymph drainage area of a primary tumor without histological evidence of residual lymph node in the nodule is classified in the N category as a regional lymph node metastasis. However a tumor nodule of <3mm is classified in the T category, i.e. discontinuous extension".

13.2 NUMBER OF LYMPH NODES

The exact number of lymph nodes and the lymph nodes along the vascular trunk are not always mentioned in the pathology report. To be able to compare the number of examined and the number of positive lymph nodes between the laparoscopically and open operated group, these two numbers should always be mentioned.

13.3 CIRCUMFERENTIAL MARGIN

A circumferential margin of < 2 mm is considered as positive. Since the margin of 2 mm is crucial, it should always be mentioned that this margin is less than 2 mm (positive) or more than 2 mm (negative). Sometimes we read "circumferential margin is 2 mm". In the database we can distinguish between "true" positive circumferential margins and 0 to 2-mm circumferential margins. When a positive lymph node is closer to the circumferential margin than the tumor itself, the margin between the positive node and the margin should be registered. The < 2 mm circumferential margin is crucial for the classification in R0 or R1. Therefore the exact margin should be expressed in two digits instead of one, since differentiation between 0.21 cm (R0) or 0.20 cm (R0) or >0.19 cm (R1) is crucial.

13.4 R-CLASSIFICATION

TNM and pTNM describe the anatomical extent of cancer in general without considering treatment. The residual tumor (R) classification deals with tumor status after treatment. It reflects the effects of treatment, influences further therapeutic procedures and is a strong predictor of prognosis. This R classification must be differentiated from the completely different Japanese R classification, which classifies tumor resections according to the extent of lymph node dissection. The Japanese Joint Committee for TNM classification decided in 1993 to use the symbol D to classify the extent of lymph node dissection in place of R in the coming editions of their General Rules (Japanese Research Society for Gastric Cancer 1993) to avoid confusion with the Residual Tumor Classification of TNM.
In the R classification, not only is local-regional residual tumor to be taken into consideration, but also distant residual tumor in the form of remaining distant metastases. R0 corresponds to complete remission or resection for cure. It is appropriate for cases in which residual tumor cannot be detected by any diagnostic means. R0 classification, therefore, does not exclude non-detectable residual tumor that may give rise to tumor recurrence or metastasis during follow-up. R0, in fact, corresponds to no detectable residual tumor and is not identical to cure.
The R classification can be used following surgical treatment alone, after radiotherapy alone, after chemotherapy alone or following multimodal therapy. After non-surgical treatment, the presence or absence of residual tumor is determined using clinical methods. Following surgical treatment, the R classification is possible through close cooperation between the surgeon and pathologist in a two-step process.
In the R0 group there may be M0 cases as well as M1 cases. In the latter, not only the primary tumor, and its lymphatic drainage but also the distant metastasis must be removed completely. Within the M1 group, there are statistically significant differences in relation to the R classification.
In tumor resection specimens with formal lymphadenectomy the "marginal" lymph node is the one near the resection line that is most distant from the primary tumor. Involvement of such "marginal" or "apical" nodes does not influence the R classification.
Difficulties arise in case of removal of the tumor in two or more parts and not "en bloc". Without an exact and reliable topographical orientation the pathologist cannot make a definitive assessment of the resection line. In these cases the classification Rx (presence of residual tumor cannot be assessed) is appropriate.
Positive cytology on lavage of the peritoneal cavity performed during staging laparoscopy or immediately after opening the abdomen (beginning of laparotomy) corresponds to M1, and is classified R1, even if there is no other evidence of residual tumor. This is based on the worse prognosis of such cases in comparison to those with negative cytology.

14 POST-OPERATIVE TREATMENT

14.1 PRE-OPERATIVE

Pre-operative adjuvant radio and/or chemotherapy may be part of the treatment of rectal carcinoma. Different schedules of preoperative radio- and/or chemotherapy may be used in trial patients, according to local standards and surgeons preference. Protocols for pre-operative adjuvant therapy should be equal in both treatment arms. Radiation protocols should be made known to the main coordinating center. Any changes in these protocols during the study period should be reported to and approved by the protocol committee.

14.2 POST-OPERATIVE CHEMOTHERAPY

Post-operative chemotherapy is not standard treatment in rectal cancer. Chemotherapy is predominantly applied in randomized clinical trials. It can be part of treatment, as long as patients in each treatment group are treated according to the same protocol. Protocols should be made known to the main coordinating center. Any changes in these protocols during the study period should be reported to and approved by the protocol committee.

14.3 POST-OPERATIVE RADIOTHERAPY

If post-operative radiotherapy is applied, patients in both treatment arms should be treated according to the same protocol. Radiation protocols should be made known to the main coordinating center. Any changes in these protocols should be reported to and approved by the protocol committee.

15 FOLLOW-UP

15.1 FOLLOW-UP VISITS

For the COLOR II trial, clinical examination is performed every year for 7 years. More frequent follow-up visits and other investigations will not be obligatory but on indication or to the preference of the surgeon. At three years after surgery, a CT scan or MRI of the pelvis is performed to exclude local recurrences. Imaging of chest and liver is performed to assess distant metastases. For the sake of interim analysis, recurrences or deaths should be reported by fax to the coordinating center within 2 weeks of detection. Follow-up of patients with recurrent disease should continue at least 3 years after diagnosis of recurrence or until death.

15.2 FOLLOW-UP FORMS

The follow-up part of the case record forms contains one normal follow-up form to complete each year. Minor complaints or complications can be noted in these forms. Complaints that are more serious or complications necessitating hospital intake, but not related to cancer should be noted in the form for events not related to cancer. In case of recurrences, the recurrence form and the recurrence follow-up form should be completed.

16 RECURRENT DISEASE

Recurrences should be reported by fax to the coordinating center within 2 weeks after detection.

16.1 DEFINITIONS OF RECURRENT DISEASE

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

- locoregional macroscopic tumor assessed by colono- or proctoscopy or barium enema
- positive histology or cytology of adenocarcinoma, compatible with the primary tumor in any location
- liver metastases on ultrasound, CT-scan or MRI
- lung metastases on chest radiography, CT-scan or MRI
- bone metastases on radiography or bone scintigraphy
- death with cancer

16.2 DEFENITIONS OF LOCOREGIONAL RECURRENCE

- rectal exam positive for rectal cancer
- positive MRI or CT
- positive cytology or histology of adenocarcinoma

16.3 TREATMENT OF RECURRENT DISEASE

Treatment of recurrent disease should be according to local standards as long as patients in each treatment group are treated according to the same protocol. Protocols should be known to the main coordinating center. Any changes in these protocols during the study period should be reported to and approved by the protocol committee. Treatment should be noted in the recurrence follow-up form.

16.4 FOLLOW-UP OF RECURRENT DISEASE

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

17 DATA COLLECTION

All medical, quality of life and cost data will be collected by the main coordinating center, Erasmus MC Rotterdam, The Netherlands. 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 center. All patient data are coded and identified by means of a randomization number. The local investigator will have a decoding list with randomization numbers and hospital patient identification numbers of his patients in the investigator site file (see appendix).
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 open 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 (see appendix).
All patients who are considered for operative treatment of rectal carcinoma should be registered, including those who refuse randomization and those who do not meet inclusion criteria. Brief details of the reasons why patients are not randomized or excluded should be given. The number of patients operated in each center for rectal cancer will be registered.

17.1 DATA COLLECTED AT RANDOMIZATION

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

- eligibility criteria fulfilled?
- randomizing physician / surgeon
- hospital (+fax number)
- kind of operation planned
- sex of patient
- date of birth
- clinical TNM stage

17.2 DATA COLLECTED DURING PRE-OPERATIVE PERIOD

- ASA class
- length and weight
- number of previous abdominal operations
- date of diagnosis
- location of tumor
- proposed type of resection
- previous radiotherapy of the pelvis
- preoperative radiotherapy

17.3 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
- location and length of incision
- type and method of performing anastomosis
- blood loss (ml)
- “skin to skin” time
- intra operative complications
- wound protection / specimen protection used
- steps of operation accomplished laparoscopically
- reasons for conversion to conventional procedure

17.4 DATA COLLECTED DURING POST-OPERATIVE PERIOD

The post-operative period is defined as the period starting when the patient is leaving the operating theatre and ending 8 weeks after that. The day of operation is day 0.

- post-operative day with fluid intake > 1000 ml resumed
- post-operative day with passage of first stool
- day of discharge from hospital
- complications including death and cause of death and number of re-interventions and reasons of further abdominal surgery
- reason and duration of possible readmission in hospital within 8 weeks after surgery
- analgesic requirement during the first three days

17.5 DATA COLLECTED AT PATHOLOGIC ANATOMICAL EXAMINATION

- macroscopic description
- histology
- extent of local invasion
- circumferential margin
- distal margin
- peritoneal spread
- metastatic spread
- synchronous colon pathology
- pTNM (see appendix)

17.6 DATA COLLECTED DURING FOLLOW-UP PERIOD

Once a year the following data will be collected:

- date of visit
- adjuvant therapy
- details on recurrence, including date and method of diagnosis, site of recurrence and treatment consequences
- details on possible complications
- date of death and cause of death

18 SUB-STUDIES

18.1 QUALITY OF LIFE

Quality of life will be assessed by, at least:

- EuroQOL 5-D, scored no more than 5 days pre-operatively and on 4 weeks, 6 months, 12 months and 24 months postoperatively
- EORTC QLQ-CR38, scored no more than 5 days pre-operatively and on 4 weeks, 6 months, 12 months and 24 months postoperatively
- EORTC QLQ-C30, scored no more than 5 days pre-operatively and on 4 weeks, 6 months, 12 months and 24 months postoperatively
- Subset of EORTC QLQ-P25 on sexual and bladder function, scored no more than 5 days pre-operatively and on 4 weeks, 6 months, 12 months and 24 months and postoperatively

In addition, the following questionnaires **may** be used and **are** used as part of a national Dutch study:

- VAS for pain and nausea, scored no more than 5 days pre-operatively and on days 1, 3 and 7 days postoperatively
- Health and care questionnaires, scored no more than 5 days pre-operatively and every week for 8 weeks postoperatively

18.2 COSTS

Direct and indirect medical cost driving medical events will be assessed for the entire trial population based on data from the case record forms from the operation and the follow up period and also based on data from the Quality of Life substudy. The method has been described earlier (ref: Björholt I, Janson M, Jönsson B, Haglind E. Principles for the Design of the Economic Evaluation of COLOR II: an International Clinical trial in Surgery Comparing Laparoscopic and Open surgery in Rectal Cancer. Int J Technol Assess Health Care 2006;22(1):130-5.) Thereafter medical costs will be applied on a national basis for national health economy analyses.

18.3 OTHER SUBSTUDIES

Lateral substudies can be performed when measured variables are not part of primary or secondary endpoints of the COLOR II. The board of governors nust be informed and must confirm that there is no conflict of interest with the COLOR II trial.

19 STATISTICAL CONSIDERATIONS

19.1 SAMPLE SIZE AND STATISTICAL ANALYSIS

Locoregional cancer recurrence rate of operated patients with cancer stages <IV after 3 years is currently about 10 %. The primary objective of the study is to show that laparoscopic surgery does not lead to an increased locoregional recurrence rate. Equivalence of both treatments is considered to be shown if the resulting two-sided 95% confidence limits of the difference in 3-yrs locoregional recurrence rates excludes a difference greater then 5%. At a randomization ratio of 2:1, and assuming a recurrence rate of 10% in each group, 850 laparoscopic patients and 425 open patients are required to have a power of 80% for this study.

All analyses will be carried out on an “intention to treat” basis: patients, whose randomized laparoscopic operation was converted to an open resection, will be analyzed in the laparoscopic group.
Eight weeks operative mortality, pathological resection margins and complication rates will be compared using the Chi-square test. Locoregional recurrence rate, disease free survival and overall survival will be compared between the two procedures using log-rank statistic, adjusted for center. Exploratory analysis of the prognostic effects of various baseline data will be done using multivariate Cox-regression. Analysis of the primary endpoint will be performed 1.5 - 2 years after inclusion of all patients.

19.2 INTERIM ANALYSES

When an obvious difference in recurrence rate or survival between the two treatment groups appears during the inclusion phase of the trial, it is considered unethical to continue accrual of patients.
Formal interim analyses will be carried out after each 20 recurrences and each 20 in-hospital mortalities. For this purpose, recurrences and in-hospital mortalities have to be reported to the coordinating center within 2 weeks after detection.

20 ORGANIZATION

20.1 PROTOCOL AND WRITING COMMITTEE

The protocol committee is responsible for organization of the trial. The writing committee will be responsible for publication and presentation of all data. Publications will be coordinated by the Erasmus Medical Center.

20.2 DATA MONITORING

A trial monitor will be appointed to monitor trial progress on site, as frequently as seen fit. During these visits, case record forms and related records will be checked for completeness and consistency.

20.3 QUALITY CONTROL

To ensure quality control, a TME can only be performed if one member of the operating team has experience with at least 5 procedures. To assess the feasibility of laparoscopic rectal cancer resection, a phase II trial will precede the accrual of patients in this trial.
An instructional video on the laparoscopic TME technique will be distributed. If experience is lacking, special training sessions to individual surgeons on the technique of TME and autonomic nerve sparing will be organized during on-site instructional operations by experienced surgeons in the field. Surgeons with expertise in the TME procedure should initially assist surgeons with extensive laparoscopic experience to train and standardize the laparoscopic procedure.
Specimen examination by pathologists will be according to rules described in the protocol.

20.4 PRESENTATION & PUBLICATION

All presentations or publications will be in the name of the 'COLOR II Study Group'. Local accrual rates of each participating hospital will be listed in every publication or presentation. The sponsor has no influence over implementation of the research and content of the publications.
Data assessed nationally, on quality of life, costs and validation of endosonography can be published or presented by smaller groups of authors without international consent. Publication or presentation of these data can only be possible when it becomes clear that patients were included in COLOR II. If a center violates these rules, exclusion from COLOR II and exclusion from authorship will be the consequence. Publication of data will not take place until accrual of patients has been stopped.

21 LITERATURE

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APPENDICES

21.1 APPENDIX I: EXAMPLE OF WRITTEN INFORMATION FOR THE PATIENT

To whom it may concern,

The disorder with which you have been diagnosed requires removal of the affected part of the large bowel and rectum. The traditional approach towards this problem is to open the abdomen using a relatively large incision. A new method to operate on the rectum is through a laparoscopic operation. A laparoscopic operation differs from traditional surgery regarding the size of the incisions used. For a laparoscopic operation, several small incisions are made to allow placement of small diameter tubes to introduce a camera and instruments in the abdomen. The camera, after introduction into the abdomen, produces an image of the inside of the abdomen on a TV screen. These images guide the surgeon in performing the operation.

Since 1991, laparoscopic bowel surgery is done with an increasing frequency. Several studies have shown that laparoscopic removal of parts of the large bowel is possible in a safe and effective manner. The advantage of laparoscopic surgery for colonic cancer surgery is a faster postoperative recovery of the patient, which is probably mainly caused by the small size of the incisions. This has also been noticed after laparoscopic removal of the gallbladder. This study wants to investigate if the laparoscopic technique to remove lesions of the rectum is associated with reduced operative trauma (as a result of the smaller incisions) and therefore will result in improved postoperative recovery and possibly better cure of the disease. However, it is unclear if the laparoscopic removal of malignant tumors of the rectum is better for the patient than the traditional “open” operation in the long term. The purpose of this international study is to answer that question. If you agree to participate in this trial, the type of operation you will undergo (open or laparoscopic) will be determined by chance. An independent institution will take care of this. It is very important to stress the fact that the operative procedure being done is the same in the open and the laparoscopic operation. The length of the removed large bowel segment will be the same for either technique.

When you have decided to enroll the study, you are allowed to withdraw from the study at any time for any reason, in which case you are not obliged to explain your decision.

If you participate in this study, you will be asked to fill out a few short questionnaires before and after the operation. The pre- and postoperative care is similar to the care when you would not participate in this study.

The use of data related to your disorder and the treatment will be handled strictly confidentially and on anonymous basis. The results of this study will be published in international scientific journals.

In case you have any questions regarding this study or the consequences of participation, please feel free to consult your doctor.

Yours truly,

21.2 APPENDIX II: EXAMPLE OF INFORMED CONSENT FORM

INFORMED CONSENT **COLOR II** TRIAL

Mr. / Mrs. (name) : . . . . . .

Date of birth : . . . . . .

Address : . . . . . .

City / Country : . . . . . .

Patient code : . . . . . .

Randomization no. : . . . . . .

declares to be fully informed, both in writing and orally, on the COLOR II trial. The purpose of the trial has been explained to me and I hereby declare to participate voluntarily in this trial. I retain the right however, to stop participation at any given moment.

City : . . . . . Date : . . . . . .

Signature patient : . . . . . .

Name doctor : . . . . . .

Signature doctor : . . . . . .

21.3 APPENDIX III: TNM CLASSIFICATION OF COLORECTAL CANCER

T: Primary tumor
- Tx Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion or invasion of lamina propria
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through muscularis propria into subserosa or into non peritonealized pericolic or pericolirectal tissue
- T4 Tumor directly invades other organs or structures and/or perforates visceral peritoneum

N: Regional Lymph Nodes
- Nx Regional lymph nodes cannot be assessed
- N0 No regional lymph metastases
- N1 Metastases in 1-3 pericolic or perirectal lymph nodes
- N2 Metastases in 4 or more pericolic or perirectal lymph nodes

M: Distant metastasis
- Mx Metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis present

21.4 APPENDIX IV: STAGE GROUPING

Stage	**Primary Tumor**	**Regional lymph nodes**	**Distant metastases**	**Dukes' stage**
0	Tis	NO	M0	
I	T1 T2	NO NO	M0 M0	A
II	T3 T4	NO NO	M0 M0	B
III	Any T Any T	N1 N2/	M0 M0	C
IV	Any T	Any N	M1	D

21.5 APPENDIX V: INVESTIGATOR SITE FILE

The investigator site file is made for each participating center. In this file all forms, lists and data concerning the COLOR II trial are stored. The contents of this file are listed below.

1. Registration form not included / excluded patients
   All patients suspected of having a malignant rectal tumor, who do not meet the inclusion criteria or are excluded postoperatively, should be registered in this form.

2. Decoding list of patients
   List of patients with randomization numbers and their corresponding hospital patient identification numbers. As only randomization numbers should be mentioned in the case record forms, this list is used to find patient files from trial patients if needed.

3. Decoding list of surgeons COLOR II trial
   List of surgeons who operate on trial patients with their corresponding codes. Names of surgeons should not be mentioned in the case record forms.

4. Signed informed consent forms.
   Copies cannot be sent to the coordinating center, because of privacy reasons.

5. Ethical committee approval & correspondence

6. Protocol & amendments

7. Copies of completed case record forms and follow up forms
   Original completed forms should be sent to the coordinating center.

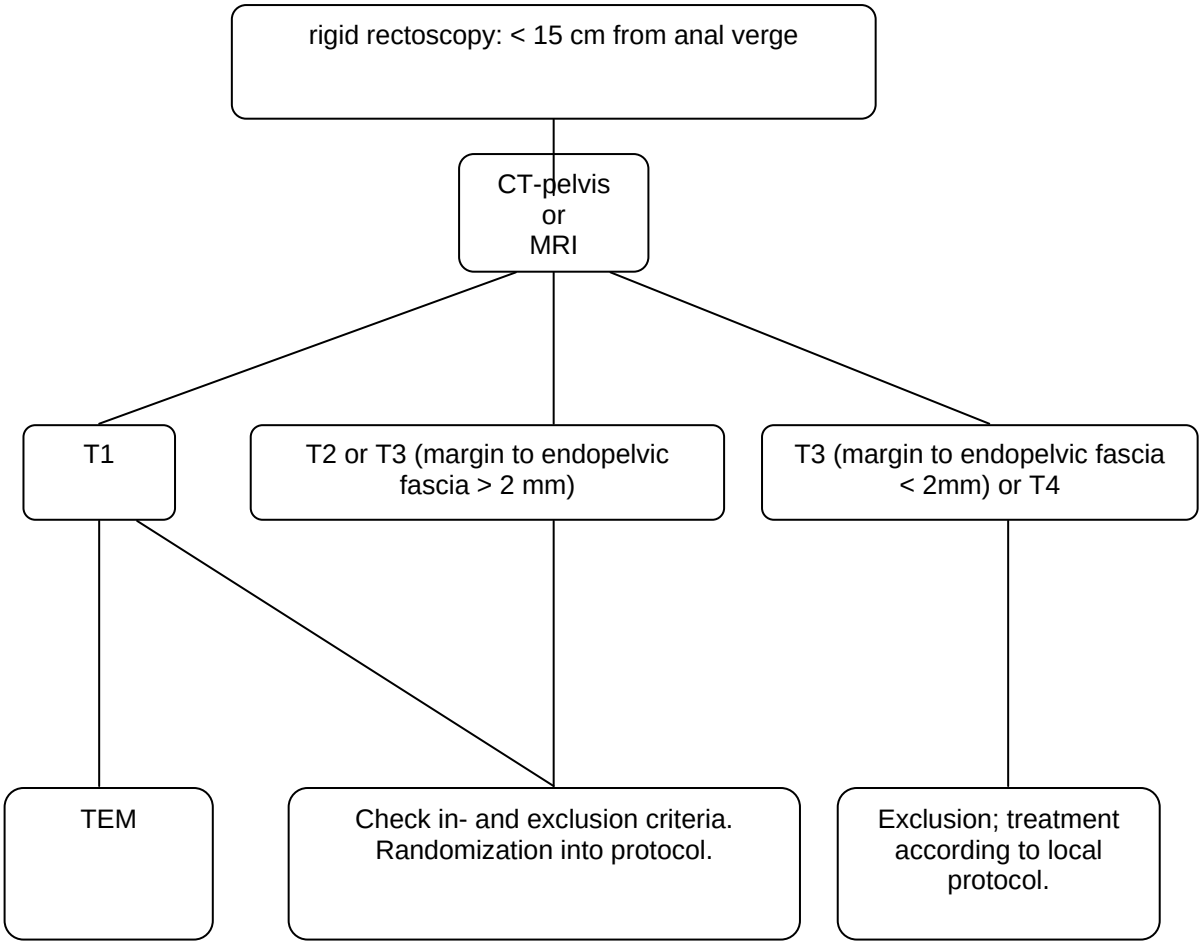
8. Monitor log & reports

21.6 APPENDIX VI: QUALITY OF LIFE SCHEDULE

QUESTIONNAIRE	**PREOP**	**POSTOP**				
	1 day	**1 day**	**Week 4**	**Month 6**	**Month 12**	**Month 24**
Euroqol-5D	X		X	X	X	X
EORTC QLQ-C30	X		X	X	X	X
EORTC QLQ-CR38	X		X	X	X	X
EORTC QLQ-PR25*	X		X	X	X	X

Table 1. Current questionnaires
** Only the first subset of questions (questions 31 to 37)*

21.7 APPENDIX VI: FLOW CHART OF RECTAL CANCER PATIENTS



21.8 APPENDIX VII: CASE RECORD FORMS

See next pages

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Canada B3H 2Y9
Tel: +1 (902) 473 7489
Fax: +1 (902) 473 4375

Date:
Procedure: **LAP / OPEN**
Rand nr:
Doctor:

IDENTIFICATION (no 1 - 6)

If appropriate, please encircle correct figure, more than one can be encircled per question

1. hospital :

2. randomization no. :

3. date of birth (dd/mm/yyyy) :

4. gender : 1 male
2 female

5. date of randomization (dd/mm/yyyy) :

6. randomized procedure : 1 laparoscopic
2 open

6A. clinical TNM stage: T _____ N _____ M _____

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Date:
Procedure: **LAP / OPEN**
Rand nr:
Doctor:

PREOPERATIVE PERIOD < 28 days prior to surgery (no 7 - 17)

If appropriate, please encircle correct figure, more than one can be encircled per question

7. date of admission (dd/mm/yyyy):
8. ASA class :
9. length : cm
10. weight : kg
11. no. of previous abd. operations :
12. date of diagnosis (dd/mm/yyyy) :

13. exact location of tumor : cm (distal border from anal verge)

    determined by : 1 rectoscopy
    2 colonoscopy
    3 MRI
    4 CT

14. proposed type of resection :

    1 Resection without TME (= Partial Mesorectal Excision)
    2 Resection with TME with preservation of the anus
    3 Resection with TME without preservation of the anus (APR)

15. previous radiotherapy of the pelvis : 0 no
    1 yes

16. preoperative radiotherapy : 0 no
    (if yes, please specify dose and duration) 1 yes …… X …… Gy

16a. preoperative chemotherapy : 0 no
    (if yes, please specify dose and duration) 1 yes ……

16b. Participation in Quality of Life substudy : 0 no
    1 yes

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Date:
Procedure: **LAP / OPEN**
Rand nr:
Doctor:

INTRAOPERATIVE PERIOD (no 18 - 39)

If appropriate, please encircle correct figure, more than one can be encircled per question

18. name(s) of surgeon(s) :

18a. experience (last year) : ☐ < 10 lap colorectal procedures
☐ 10 - 20 lap colorectal procedures
☐ > 20 lap colorectal procedures

19. date of surgery (dd/mm/yyyy) :

20. performed operative procedure : 1 resection without TME (= Partial ME)
2 resection with TME and preservation of the anus
3 resection with TME without preservation of the anus (APR)

21. please specify level of distal transaction : cm
(distance between distal transaction & dentate line)

22. ureter stent : 0 no
1 yes

23. presence of fibrosis considered to be due to radiation : 0 no
1 yes

24. macroscopic metastases : 0 no
1 liver
2 peritoneal
3 mesentery
4 other :

25. macr. invasion adj. organs : 0 no
(if yes, please mention which organ) 1 yes please specify:

26. Degree of pelvic autonomic nerve preservation:
1. Total preservation of autonomic nervous system. (hypogastric and pelvic preservation procedure)
2. Bilateral preservation of parasympathetic nerve system with complete removal of the sympathetic system. (bilateral pelvic preservation procedure)
3. Unilateral preservation of parasympathetic nerve system with complete removal of the sympathetic system. (unilateral pelvic preservation procedure)

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Date:
Procedure: **LAP / OPEN**
Rand nr:
Doctor:

---

27. if appropriate, reason for incomplete preservation:
    1. tumor invasion
    2. other :

28. length of incision : cm

29. location of incision :
    0 none
    1 transverse right
    2 transverse left
    3 Pfannenstiehl
    4 other:

30. anastomosis :
    0 no (stoma)
    1 handsewn
    2 circular stapler; size : mm
    3 other:

31. anastomosis configuration :

0	no (stoma)			
1	end to end	☐ ileostomy		☐ transverse colostomy
2	end to side	☐ ileostomy		☐ transverse colostomy
3	side to side	☐ ileostomy	☐ J-pouch	☐ transverse colostomy
4	side to end	☐ ileostomy	☐ J-pouch	☐ transverse colostomy

31a. Type of stapler used to transect the rectum

1	Roticulator	☐ blue	☐ green	……. firings
2	Curvature	☐ blue	☐ green	……. firings
3	Lineair stapler	☐ blue	☐ green	……. firings
4	Other	☐ blue	☐ green	……. firings

32. blood loss : ml

33. skin to skin time : minutes

34. complication(s) : 0 none
1 bleeding
2 fixation of the tumor
3 gastrointestinal perforation
4 adhesions
5 hypercapnia
6 anastomosis related problems
7 injury to ureter
8 nerve injury
9 perforation tumor
10 other:

35. wound protection : 0 no
(if yes, please mention kind of) 1 yes please specify:

PLEASE FILL OUT NEXT QUESTIONS IN CASE OF A LAPAROSCOPIC PROCEDURE

36. laparoscopic operative steps : 1 inspection
2 mobilization of bowel
3 ligation of main vessels
4 oral transection of bowel
5 aboral transection of bowel
6 resection of bowel
7 anastomosis

38. conversion : 0 no
1 yes

39. if appropriate, reason for conversion :

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Date:
Procedure: **LAP / OPEN**
Rand nr:
Doctor:

POSTOPERATIVE PERIOD 1-28 days after surgery; day of operation = day 0 (no 40 - 47)

If appropriate, please encircle correct figure, more than one can be encircled per question

40. date of fluid intake > 1000 ml : (dd-mm-yyyy)
41. date of first passage of stool : (dd-mm-yyyy)
42. date of discharge from hospital : (dd-mm-yyyy)

43. if appropriate, date and nature of complication(s)

date (dd-mm-yyyy):

1 anastomotic leakage
2 cardiac complications:
3 respiratory complications:
4 abscess
5 ileus
6 other:

44. if appropriate, date and nature of re-intervention(s):

date (dd-mm-yyyy):
nature:

45. if appropriate, date and cause of death:

date (dd-mm-yyyy):
cause:

46. if appropriate, date, cause and duration of readmission:

date (dd-mm-yyyy):
cause:
readmission:

47. pain medication during first 3 days

Please mention what kind of medication, quantity (mg) and, where appropriate, speed of pump (mg/ml per hour)

Postoperative day 1

1 opiates :

2 non-opiates :

3 epidural :

Postoperative day 2

1 opiates :

2 non-opiates :

3 epidural :

Postoperative day 3

1 opiates :

2 non-opiates :

3 epidural :

COLOR II
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Date:
Procedure: **LAP / OPEN**
Rand nr:
Doctor:

Please add this information form for the pathologist to the resected specimen

COLOR II TRIAL

A randomized clinical trial comparing laparoscopic and open surgery for rectal cancer

Dear colleague,

The COLOR II trial is a randomized clinical trial comparing laparoscopic and open surgery for rectal cancer. The primary endpoint is locoregional recurrence three years post-operatively. In order to assess relevant oncological parameters, the pathological examination of the specimen is of utmost importance. Below you'll find the items which will be recorded for the COLOR II trial. You are kindly asked to document these items in your examination report.

Please provide the following data on pathology

- Completeness of resection

  Complete — Intact mesorectum with only minor irregularities of the mesorectal surface up to the dissection level. No defect is deeper than 5 mm. No coning towards the distal margin of the specimen. Smooth circumferential resection margin.

  Nearly Complete — Moderate bulk to the mesorectum, no visible muscularis propria, moderate coning, irregular circumferential resection margin.

  Incomplete — Little bulk to the mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin, coning.
- Size of tumor
- Distance of tumor from circumferential resection margin
- Distance of tumor from proximal resection margin
- Distance of tumor from distal resection margin
- If appropriate, position of tumor with respect to peritoneal deflection
- Type and differentiation of tumor
- Tumor tissue in surgical margins (i.e. radicality)
- Number of lymph nodes harvested
- Number of lymph nodes in proximal part of mesentery, that means all lymph nodes not along resected bowel (if none, please mention)
- If appropriate, nature of metastases
- If appropriate, synchronous colorectal pathology
- pTNM classification

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PATHOLOGY (no 48 - 60)

If appropriate, please encircle correct figure, more than one can be encircled per question

48. completeness of resection

    1. complete = intact mesorectum with only minor irregularities of the mesorectal surface up to the dissection level. No defect is deeper than 5 mm. No coning towards the distal margin of the specimen. Smooth circumferential resection margin on slicing.
    2. nearly complete = the majority of the mesorectum has been removed, no visible muscularis propria, moderate coning, irregular circumferential resection margin.
    3. incomplete = mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin, coning.

49. size of tumor : x cm
50. distance from circumferential resection margin : cm
51. distance from proximal resection margin : cm
52. distance from distal resection margin : cm
~~53. position of tumor with respect to peritoneal deflection : cm~~

54. type and differentiation of tumor :

55. tumor tissue in surgical margins : 0 no
    1 oral
    2 aboral
    3 circumferential
    4 other :

56. no. of lymph nodes harvested :
57. no. of lymph nodes in proximal part of mesentery :
    *(all lymph nodes **not** along resected bowel)*
58. if appropriate, nature of metastases :

59. if appropriate, nature of synchronous colorectal pathology:

60. pTNM classification : pT N M

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FOLLOW UP FORM FOR VISIT 1-7 YEAR(S) AFTER SURGERY

If appropriate, please encircle correct figure, more than one can be encircled per question

61. date of visit (dd/mm/yyyy) :

61A. Clinical TNM stage : T _____ N _____ M _____

62. recurrence : 0 no
(if yes, please fill out recurrence form) 1 yes

63. complications : 0 no
1 incisional hernia, please specify location
(which port or incision)
……
2 complaints of bowel function, other than ileus
3 stress urinary incontinence
4 sexual dysfunction
5 fecal incontinence
6 other :

63a. Bowel obstruction : 0 no
1 yes ☐ operative
☐ conservative

Cause of bowel obstructions : 1 benign
2 malignant
3 unknown

64. postoperative adjuvant therapy : 0 no
1 yes

65. re-admissions : 0 no
(if yes, please fill out event form) 1 yes

66. re-interventions : 0 no
(if yes please fill out event form) 1 yes

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RECURRENCE FORM

If appropriate, please encircle correct figure, more than one can be encircled per question

107. date of diagnosis of (re)recurrence (dd-mm-yyyy) :

108. number of recurrence (first, second, etc.) :

109. nature of recurrence : 1 locoregional
2 liver metastasis
3 lung metastasis
4 trocar wound recurrence
5 minilaparotomy wound recurrence
6 laparotomy wound recurrence
7 other :

110. date of cancer related death (dd-mm-yyyy) :

When completed, please fax this form to the coordinating center:
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Fax: +1 (902) 473 4375

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RECURRENCE FOLLOW UP FORM

In case of re-recurrence, please fill out a new recurrence form

111. treatment : *(if appropriate, please describe type of procedure)*

0 no

1 curative resection :

2 palliative resection :

3 other :

112. date of cancer related death (dd/mm/yyyy) :

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FORM FOR EVENTS

Please don't forget to mention randomization number in upper right corner

113. Date of event (dd-mm-yyyy) :

114. Sort event :

115. Date of death (dd-mm-yyyy) :

116. Cause of death :

117. Cause of bowel obstruction : 0 no bowel obstruction
1 herniation
2 strangulation
3 non malignant stenosis
4 other

118. Other complication(s) : 0 no
1 incisional hernia
2 complaints of bowel function (other than ileus)
3 other:

119. Date of re-operation (dd-mm-yyyy) :

120. Nature of re-operation :

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