

Diverting ileostomy/colostomy versus no  
diversion  
after low anterior resection for rectal cancer

A prospective randomised multicenter trial

Study Protocol

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## 1. Background

Colorectal cancer is listed as the third most frequently occurring cancer after lung and prostate cancer in men and as second after breast cancer in women.

### 1.1. Surgery

The basic principle in colorectal cancer treatment is wide „en bloc“ resection of the tumour bearing bowel segment with its mesentery containing the vascular supply and lymph draining structures. Also in rectal cancer adherence to this principle calls for a wide surgical excision, but both the bony structures of the pelvis and the difficult exposure in the narrow male pelvis in particular, limits the extent of the procedure. The conventional procedure mostly implied partially blunt dissection of the rectum along the presacral fascia, more distally directed „cone-wise“ towards the rectal wall to allow for a low anastomosis. This procedure did not take into account the lateral extension for which the disease has a propensity and often resulted in incomplete removal of mesorectal tissue and persistent cancer at the lateral margins. (1-4). This phenomenon is reflected in the high rate of local recurrences in some studies.

### 1.2. Recurrence

Pelvic recurrence following surgery for rectal cancer cause severe disabling symptoms, are difficult to treat and usually have a fatal outcome (5). About 20 % of patients with recurrent disease have a local recurrence only. Most of them become overt within two years of surgery.

For patients with TNM-stage II or III rectal cancer, the risk of distant metastases ranges from 17 % to 56 %. the liver is the most common site of distant metastases. Patients with rectal cancer and transmural invasion or lymph node metastases are at risk for local recurrence and systemic metastases. Adjuvant therapies of pelvic irradiation and chemotherapy can have an additional role in these subsets of patients

### *1.3. Total Mesorectal Excision*

Surgeons who have specialised in rectal surgery have better results in terms of improved local control and less morbidity. They claim excellent local control (local recurrence rates 5 - 8 %) due to routine total excision of the mesorectum. Heald (6) and Enker (1) advocate the concept of circumferential or total mesorectal excision (TME). Moriya et al (7) routinely perform an extended lateral pelvic lymph node dissection (D3 lymphadenectomy). In an study by Havenga et al.(31) three series of patients who underwent a standardized surgery ( i.e. total mesorectal excision or D3-lymphadenectomy) were compared with two series of patients who underwent conventional surgery. All patients underwent a R0-resection and had a stage II or III rectal tumour. Five year overall survival was 62 to 75 percent in the standardized groups and 42 to 44 percent in the conventional surgery groups. Local recurrence rates ranged from 4 to 9 percent in the standardized surgery groups and 32 to 35 percent in the conventional surgery groups. This study strongly suggests that standardized surgery gives superior survival and local control when compared to conventional surgery.

The main principle of the TME technique, as advocated by Helad, is to achieve cure by means of total mesorectal excision. This is accomplished by precise sharp dissection within the true pelvis around the integral mesentery under direct vision, enveloping the entire rectum, with preservation of the hypogastric plexus. Thus a „perfect tumour package“ is created. Further dissection continues caudally over the surface of the piriformis muscle to the pelvic floor, freeing the rectum until the levator muscles are visible over some 270 degrees. Anterior dissection should proceed in front of Denovilliers fascia. In men, this fascia merges with the prostatic capsule distally where it is incised. If a TME is adequately performed, the distal mural margins can be reduced to 1 cm or even less, allowing the sphincters to be saved without any impact on local control of the tumour (2,6). After performing a TME, over 80 % of male patients should remain potent and retain normal ejaculation. Spontaneous voiding should not be affected in males or females. On the other hand, operating time increases to some 3 - 4 ½ hours with the possibility of added morbidity.

Data from randomized trials indicate that a pouch reconstruction leads to better results than an end-end anastomosis (8). Therefore it is discouraged to perform an end-end-anastomosis.

#### *1.4. Protecting Stoma*

Recent years have seen a dramatic decrease in the frequency of abdominoperineal resection of rectal cancers in favour of sphincter-preserving procedures. Although it is generally agreed that patient satisfaction and quality of life are superior following sphincter-preserving surgery, significant morbidity and mortality do occur, with anastomotic dehiscence being the primary concern. The incidence of anastomotic leakage following anterior resection varies from 2 to 25 percent depending on the level of anastomosis (9), surgical expertise (10) and the method of reconstruction (11). In the presence of generalised abdominal sepsis mortality rates of around 50 % are reported (12,13) and those surviving the immediate consequences of anastomotic failure can expect a poor functional result because of stenosis and reduced compliance of the neorectum (14).

The introduction of total mesorectal excision (TME), has been a major advance in the surgical strategy for rectal cancer resulting in a reduction in local recurrence without adjuvant therapy (13,15,16).

In radically operated patients the local recurrence rate with TME after 5 and 10 years is reported to be less than 10 % and the 5-year survival rate is 80 %.

In rectal cancer surgery following the principles of TME, the distal rectum is divided 1 – 2 cm above the dentate line for low and mid rectal cancers, aiming at a free distal resection margin of at least 2 cm of rectal wall. In high rectal tumors the mesorectum is divided 5 cm below the tumor leaving a variable length of rectum (PME). Such a resection potentially endangers the blood supply to the residual distal rectum and leaves a large pelvic space for accumulation of clot and fluid with concomitant risk of pelvic infection. This may contribute to a high frequency of anastomotic problems with consequent septic complications.

The prevention of septic complications caused by anastomotic leaks after rectal surgery is a major goal of the dedicated colorectal surgeon. There are several studies (17-19) suggesting to fashion a protective stoma in patients after TME, with adjuvant/neoadjuvant treatment, obese patients and after technical demanding procedures. A stoma may not prevent an anastomotic disruption, however it might mitigate the consequences of an anastomotic leak.

It is generally accepted that anastomatic complications occur more frequently after colonic resection with anastomoses below the peritoneal reflection than for intraperitoneal anastomoses (20). However in the literature there has been little definition concerning the precise criteria for the use of a proximal stoma after elective rectal resections. Furthermore,

common experience has shown that some surgeons use a proximal vent frequently whereas others rarely do so.

The role of a temporary diverting stoma in patients undergoing low anterior resection remains controversial (21-23). Opponents consider the risk of leakage to be sufficiently low that patients do not routinely require diversion (22).

Controversy continues as to whether all low anastomoses should have a temporary stoma (13) or whether a selective approach is optimal (25). Selective or non-routine use of a fecal diversion is supported by the knowledge that stoma reversal can cause morbidity and even mortality (26,27). Stoma reversal also implies a second hospital stay and several temporary stomas become permanent. To date there are, however, only two small randomised studies that have examined the rate of a temporary fecal diversion and neither of them showed any clear benefit of using a diverting stoma (28,29).

In a non randomised study no advantage was found for stoma patients regarding anastomotic complications or pelvic sepsis. Hospital stay was significantly prolonged in the stoma group (30).

## **2. Study Objectives**

### *2.1. Primary Objective*

- To determine if a protective diverting ileostomy/colostomy improves short term outcome in patients with operable rectal cancer treated by mesorectal excision and colonic J-pouch-rectal/anal anastomosis.

### *2.2. Secondary Objectives*

- To compare the surgical complication rates
- To compare the mortality rate and length of hospital stay
- To compare the subjective Quality of Life between both treatment groups

### **3. Selection Criteria**

#### *3.1. Inclusion Criteria*

- Age from 19 to 85 years
- Patients with operable rectal cancer, with or without pre- or planned postoperative radiochemotherapy
- Distal border of the tumor is within 16 cm from the anal verge as demonstrated by rigid rectoscopy
- WHO status  $\leq 2$
- Signed written informed consent of the patient

#### *3.2. Exclusion Criteria*

- Patients with previous rectal surgery
- Emergency cases
- Planned laparoscopic resections
- Metastatic disease
- Synchronous colon cancer

#### *3.3. Premature Withdrawal*

All patients are allowed to withdraw from the protocol at any time and for whatever reason without affecting their right to appropriate treatment.

Since intraoperative findings may change the intended operative strategy, patients must be withdrawn from the study if one the following applies:

- No Mesorectal Excision is performed
- No colonic pouch performed for anastomoses below 5 cm from the anal verge
- An intraoperatively performed underwater air test is suspicious for impaired anastomotic integrity

Patients should be followed up until the reason for withdrawal is clarified and will be documented in the CRF.

## **4. Study Participants**

### *4.1. Principal Investigator*

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## 5. Study Design

Two arm, randomised, open-label multicenter study in patients with operable rectal cancer. Patients will be randomized stratified by gender (male, female), anastomotic height (TME/PME) and preoperative radiotherapy (yes/no) to be operated either by

**Group A:** Mesorectal Excision and colo-anal/rectal anastomosis with a diverting ileostomy/colostomy

**Group B:** Mesorectal Excision and colo-anal/rectal anastomosis without protective stoma

### 5.1. Expected Study Duration

A total of 222 patients with operable rectal cancer will be enrolled in this study, 111 to receive a Mesorectal Excision with diverting ileostomy/colostomy, 111 patients without diverting ileostomy/colostomy. Based on an expected recruitment rate of approximately 30 patients per year per center, the recruitment of the 222 patients will take approximately 3 years.

### 5.2. Study Procedures

#### 5.2.1 Preoperative management

All the patients will have following preoperative investigations:

- Clinical history and physical examination including digital rectal examination.
- Routine laboratory investigations e.g.
  - complete blood count
  - blood glucose level
  - liver function tests
  - kidney function tests
  - protein
- Full colonoscopy or gastrografen/barium enema
- Rigid rectoscopy with biopsy
- Transrectal ultra sound or MRI or CT to evaluate degree of invasion of the rectal wall and regional lymph nodes
- Abdominal ultrasound/CT scan

- Chest x-ray or CT scan
- CEA level
- EORTC Quality of life Questionnaire

Patients will be randomised immediately before surgery after all preoperative investigations have been performed and written informed consent has been given by the patient.

All patients will have preoperative mechanical bowel preparation and will receive adequate thrombosis prophylaxis. Prophylactic antibiotics will be given 30 - 60 minutes before surgery. A surgeon or stoma therapist will mark the site of the stoma before the operation in all patients.

### **5.2.2 Intraoperative management**

In both groups of patients:

- Appropriate anaesthesia will be given
- A median laparotomy will be done, followed by routine abdominal exploration to rule out distant metastases.
- Complete mobilisation of the left colonic flexure, high ligation of the inferior mesenteric vein and flush ligation of the inferior mesenteric artery at the aorta, preserving the hypogastric nerves will be performed. A total mesorectal excision to the pelvic floor will be performed for tumors of the mid and low rectum (TME). For patients with tumors of the upper third of the rectum (12-16 cm from the anal verge) a mesorectal excision 5 cm below the tumor is sufficient (PME). In patients with anastomoses below 8 cm from the anal verge a colonic J-pouch will be fashioned. After completion of the anastomosis the anastomotic integrity will be tested by underwater air insufflation.

If the surgical procedure is not performed as planned (see 3.3) or a primary leak of the anastomosis is demonstrated intraoperatively, the patient will be withdrawn from the study – whatever treatment group was assigned.

In patients with uneventful air testing and tension free anastomosis who have been randomized to group A, a loop ileostomy in the lower right abdominal quadrant or transverse colostomy is performed.

Drains are optional. OR-time, intraoperative blood loss, and units of bloods given will be recorded.

### **5.2.3 Postoperative management**

In patients with clinical signs of a leak a gastrografin enema will be performed immediately. In case of a leak further management will be at the discretion of the surgeon in charge. In all other patients a gastrografin enema will be performed before dismissal from the hospital to determine the radiologic (silent) leak rate. The management of patients with silent leaks will be at the discretion of the surgeon in charge.

Stoma closure in an uneventful course will be scheduled 8-10 weeks after the primary operation. Stoma closure may be delayed by a leak, postoperative chemotherapy or at the discretion of the surgeon. Patients will receive a QoL questionnaire (EORTC 30, 38) preoperatively and 6 weeks after the primary surgery if no diversion was performed or before ileostomy closure.

Hospital stay for the primary operation and for ostomy closure, morbidity, mortality, silent leak rate, clinical leak rate, reoperation rate, type of reoperation, permanent stoma rate will be recorded.

## **5.3. Endpoints**

### **5.3.1 Anastomotic Leakage**

The primary efficacy endpoint of the present study is the total anastomotic leakage rate as defined by one of the following:

Radiologic leak: Radiologic evidence of a leak in a gastrografin enema and/or CT without clinical signs of anastomotic leakage

Clinical leak: Radiologic evidence of a leak in a gastrografin enema and/or CT with one of the following clinical signs: elevated temperature (>38C), leucocytosis, peritonitis, putrid or fecal discharge over the drains or fistulas (rectovaginal)

### **5.3.2 Surgical Complications**

Surgical complications related to the primary operation, to the stoma before closure and to the second operation for stoma closure will be recorded.

Primary operation:

- postoperative bleeding requiring transfusion or reoperation,
- anastomotic leak,
- pelvic abscess,
- anastomotic fistula,
- peritonitis,
- bowel obstruction defined by prolonged postoperative parenteral nutrition (>7 days) or restart of parenteral nutrition or reoperation,
- reoperation with or without stoma
- permanent stoma rate
- Death

Complications before stoma closure:

- Stoma prolapse
- Parastomal hernia
- High output
- Stoma retraction
- Bowel obstruction
- Incomplete diversion
- Death from complications

Complications of stoma closure:

- Wound infection requiring antibiotics or opening of the wound
- Enterocutaneous fistula
- Bowel obstruction
- Reoperation
- Death

Medical complications

- Pneumonia

- Urinary retention
- thromboembolism

### 5.3.3 Mortality

Perioperative mortality is defined as death due to any cause during the hospital stay due to the primary operation or stoma closure.

### 5.3.4 Length of Hospital Stay

Length of stay in days for the primary operation and stoma closure.

### 5.3.5 Quality Of Life

The quality of life will be assessed through the EORTC QLQ-C30 in conjunction with the QLQ-CR38 quality of life instrument. It comprises a total of 38 questions which include four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and several multi-item scales that address a variety of symptoms which are often encountered in patients with colorectal cancer: radiotherapy side effects, chemotherapy side effects, general gastrointestinal symptoms, sexual dysfunction, defecation problems, stoma related problems, weight loss.

## 5.4. Flow Chart

	Group A and B				Group A	Group B
	Preoperative	Day 1 p.o.	Day 7 p.o.	Discharge	Stoma closure	10 weeks after discharge
Medical History	X					
ECG	X					
Chest x-ray	X					
Rigid rectoscopy	X					
TR ultrasound or MRI or pelvic CT	X					
Abdominal US or CT	X					
Gastrografin/barium enema	X			X		
Physical examination	X				X	X
Height	X					
Weight	X				X	X
WHO performance status	X					
QoL questionnaires (EORTC 30,38)	X				X	X
Hematology	X	X	X		X	
Kidney function parameters	X	X	X		X	
Clinical chemistry	X	X	X		X	
CEA	X	X	X		X	
Surgical and medical complications		X	X	X	X	X

## Statistical Considerations

### 5.5. *Analysis Populations*

The Intent-to-treat analysis population will be the primary analysis population and will include all randomized patients with a protocol-conform completion of the surgical procedure. All patients to be excluded from this population will be identified before the statistical analysis will be performed. A secondary worst-case analysis will be performed for the primary efficacy parameter interpreting all withdrawals due to an incomplete surgical procedure as anastomotic leaks.

### 5.6. *Interim Analysis*

Interim Analyses are planned after  $\frac{1}{4}$ ,  $\frac{1}{2}$  and  $\frac{3}{4}$  of the planned sample size is achieved and the primary efficacy endpoint is known in these patients. These analyses are planned to reject the null-hypothesis only with a Lan-DeMets Alpha Spending Function resembling a O'Brien & Fleming boundary for group sequential tests.

### 5.7. *Sample Size Estimation*

A maximum sample size of 210 patients is necessary to achieve 80% power with a two-sided significance level of 5%, an expected leakage rate of 5% with and 17% without diverting ileostomy and the planned interim analyses (see 5.6). Together with an expected drop-out rate of 5% before the end of the surgical procedure, a total of 222 patients (111 group A, 111 group B) have to be recruited.

### 5.8. *Statistical Methods*

The primary efficacy endpoint will be analysed using a chi-square statistic and comparing the resulting standardized normal statistics with the boundary as determined by the corresponding boundary (East Version 3.0). Secondary endpoints will be evaluated at a significance level of 5% only after the study has been terminated.

For nominal endpoints (e.g. complication rates, mortality), a Cochran-Mantel-Haenszel Test stratified by gender, tumor height and radiotherapy will be applied, two-sided 95% confidence intervals for the treatment effect will be calculated.

A logistic regression analysis investigating the influence of patient and procedure related factors (e.g. gender, tumor height, radiotherapy, study center, surgeons training level) on leakage and complication rates will be applied.

For length of hospital stay and other ordinal endpoints, a Mann-Whitney-Wilcoxon test for unpaired observations will be applied. Missing items in the EORTC Quality of Life scales will be imputed by the average of the corresponding items if at least half of the items from the scale have been answered. The absolute scales and changes from baseline will be compared between both treatment groups using a Mann-Whitney-Wilcoxon test for unpaired observations.

### 5.9. *Data Management*

Accurate and reliable data collection will be assured by the investigator. All data will be documented using an Internet-based electronic CRF, with automatic plausibility and completeness checks performed online. Access to study data is only possible using a personal username and password combination which the user is required to keep strictly confidential. Electronic communication between the server and the user's personal computer is encrypted without transmission of protected data (patient names, address, social security number etc.). A complete audit trail of all changes of study data will be available. Laboratory data will be verified using centre- and gender- dependent normal ranges. Descriptive and logical data checks are performed on the evolving database and the site personnel is informed on any improbable or conflicting entries which will be clarified and corrected by site personnel.

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## 7. Signatures

Principal Investigator

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Signature

Date

Statistician

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Signature

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Local Principal Investigator

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Signature

Date