Critical appraisal and potential improvement of rectal cancer treatment

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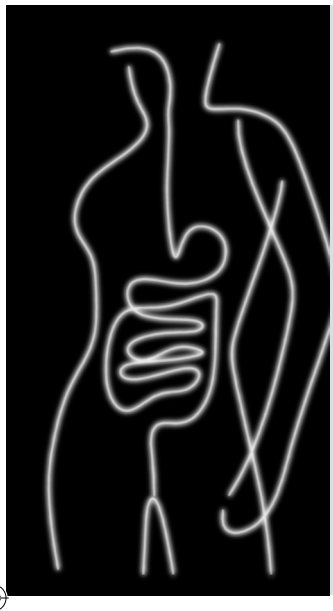
Wie wil starten moet eerst de basis aanleren,
pas daarop kunnen stevige fundamenten worden gebouwd.

Filip Verheyden en Tony Le Duc

Aan mijn ouders
Voor Laura, Sterre en Zoë

Contents



General Introduction

General Introduction

Rectal cancer

Colorectal cancer is the second most common cancer in the western world after breast and lung cancer and approximately one third of these tumours are located in the rectum or rectosigmoid.[1] Annually, over 2,600 patients are registered with a newly diagnosed rectal carcinoma in the Netherlands.[2-3] With the introduction of short-term preoperative radiotherapy and the introduction of total mesorectal excision (TME) as standard surgical technique for rectal carcinomas, the incidence of local recurrences has decreased from 11-30% to 6-16% in randomised controlled trials.[4-8]

However, therapeutic interventions of any kind are often associated with complications or long term toxicity. For example, surgery on its own for rectal cancer has a significant morbidity [9-12] and when combined with preoperative radiotherapy, it leads to additional complications such as more perineal wound infections and worse long-term functional outcome.[9,13-14]

Therefore, not only the improved local tumour control should play a role in the debate concerning rectal cancer treatment, but also the increased morbidity due to the newly applied treatment. An attempt should be made to introduce treatment protocols for rectal cancer patients which adequately balance the benefits and harms of the proposed therapeutic strategies. Ideally, they offer patients the most effective treatment at the reasonably lowest cost in terms of additional morbidity.

Protective loop ileostomies

The incidence of anastomotic leakage after rectal resection varies from 8-18 percent.[15-18] A loop ileostomy is often constructed to temporarily protect such an anastomosis.[19] It probably does not reduce the incidence of anastomotic leakage, but rather decreases the detrimental effects once leakage occurs.[20-24] Traditionally, stoma closure is not planned earlier than two to three months after construction although there is, as yet, no evidence that this period is really required for complete healing of the colonic anastomosis and for making the ileostomy easily accessible for closure.[25-27]

In the presence of an ileostomy, stoma-related morbidity and complications (e.g. leakage around the appliance, skin rash, high output and prolapse) frequently occur. Moreover, a loop ileostomy has in itself an adverse effect on the quality of life, which is further enhanced if stoma-related complications occur.[28-31] Especially with a liberal policy to use protective loop ileostomies, many of the created ileostomies will be superfluous. Therefore, earlier closure of an ileostomy (within 10 days after construction) might provide optimal protection of the anastomosis while reducing the stoma-related morbidity and the patient's discomfort.

Recurrent rectal cancer disease

Despite the improvements in rectal cancer treatment, locally recurrent disease remains inevitable in a (small) portion of patients. In these patients, it is often accompanied with

intractable pain and severely disabling other complications which are difficult to treat.[32-34] It has a tremendous impact on quality of life [35] and frequently induces an awful last period of patient's life. While data concerning primary rectal cancer treatment are widely available, data on treatment of recurrent rectal cancer disease are relatively sparse. Several treatment modalities have been described to treat these latter patients.[36-37] However, the only potentially curative option for these patients is complete surgical resection of the recurrent tumour mass.[38-41] This often requires major surgery (*i.e.* the need to perform a sacral resection and/or posterior exenteration)[42-44] and poses difficulties in closure of the enormous defect caused by extended resection for which *e.g.* an inferiorly based rectus abdominis myocutaneous flap[45] can be used.

Aim of the Thesis

The aim of this thesis is to critically appraise rectal cancer treatment and to evaluate potential improvements regarding rectal cancer treatment, especially strategies concerning protective loop ileostomies and specific treatment options in case of recurrent rectal cancer disease.

Outline of the Thesis

PART I

Influence of Total Mesorectal Excision with or without preoperative radiotherapy on local recurrence and survival, complications, and functional outcome

Compared to historical controls, rectal resection obtained with Total Mesorectal Excision (TME) proved to decrease local recurrence in rectal cancer patients. In Greater Amsterdam, the region of the Comprehensive Cancer Center Amsterdam (CCCA), TME was broadly introduced in 1996 and 1997. This introduction was facilitated by the CCCA. The influence of the introduction of TME on local recurrence and survival in rectal cancer patients is described in **Chapter 1.** In this population-based study two cohorts of rectal cancer patients (*i.e.* before and after the introduction of TME in Greater Amsterdam) are compared.

Before TME was introduced as the surgical standard, short-term preoperative radiotherapy improved local control and survival. When these two treatment modalities were combined in a large randomised clinical trial, short-term preoperative radiotherapy showed a limited benefit in reduction of local recurrence and so far there is no survival benefit. On the other hand, it should be realised that preoperative radiotherapy does increase postoperative morbidity. In **Chapter 2** a model is introduced to weigh the harms and benefits of short-term preoperative radiotherapy in the treatment of resectable rectal cancer based on data from the last four randomised clinical trials on this issue.

To properly balance the harms and benefits of short-term preoperative radiotherapy in rectal cancer patients, a clear classification is required what to consider major morbidity and, to a lesser extent, minor morbidity among these patients. A Delphi round was organised among 21 colorectal surgeons to reach a consensus regarding major and minor complications. In **Chapter 3** the consensus process is described and the results are reported.

After colorectal surgery patients often experience impaired functional outcome. This is reflected by increased bowel movements, urgency for defecation, incomplete evacuation, soiling or incontinence for flatus or stool. These complaints are often evaluated by means of self-assessment questionnaires. So far, there is no validated self-assessment questionnaire evaluating functional outcome after colorectal surgery. In **Chapter 4** the development and validation of the COloREctal Functional Outcome questionnaire (COREFO) is described. The reliability and validity of the COREFO questionnaire is prospectively evaluated and compared with a Dutch translation of the Hallböök questionnaire and a transformed Vaizey Scale in patients with and without impaired functional outcome after surgery.
To gain insight in the pathophysiological mechanism contributing to the impaired anorectal function, the motor response of the neo-rectum in patients after preoperative radiotherapy and total mesorectal excision is examined and compared to that of healthy volunteers. The results of the manometry and barostat studies are reported in **Chapter 5**.

PART II
Potential reduction of morbidity induced by loop ileostomies

A temporary loop ileostomy is often created to protect a low colonic anastomosis and to limit the consequences in case of anastomotic failure. However, ileostomy-related morbidity and complications (*e.g.* leakage around the appliance, skin rash, high output and prolapse) frequently occur and an ileostomy has also in itself an adverse effect on quality of life. In **Chapter 6** the stoma-related morbidity due to temporary loop-ileostomies is quantified, thus defining the potential advantages of early ileostomy closure. In **Chapter 7** a pilot study is described to investigate the feasibility of early closure of loop ileostomies (*i.e.* during the same hospital admission as the initial operation).

PART III
Surgical treatment for (recurrent) rectal cancer disease; techniques and results

Recurrence after rectal cancer treatment is inevitable in a (small) subgroup of patients, despite all preventive efforts such as preoperative radiotherapy and the introduction of Total Mesorectal Excision. Data on recurrent disease therapy are relatively sparse compared to all available information concerning primary rectal cancer treatment. In **Chapter 8**, the population-based results of recurrent rectal cancer treatment in Greater

Amsterdam after the broad introduction of Total Mesorectal Excision are described. This series involves all patients with recurrent rectal cancer initially treated with a microscopically radical resection diagnosed between 1998 and 2000 in any of the 20 hospitals in the region of the Comprehensive Cancer Centre Amsterdam. In **Chapter 9**, the results of surgical treatment in patients with locally recurrent rectal cancer at the Netherlands Cancer Institute are described. Long term survival can be achieved with salvage surgery for locally recurrent rectal cancer, if a radical re-resection is feasible. To obtain a radical re-resection, partial removal of the sacrum might be indicated. In **Chapter 10** indications and technique of sacral resection are reported as well as the experience in 26 patients at the Netherlands Cancer Institute with this procedure. A challenge and possible concern is the closure of the enormous defect after sacral resection and its related wound problems. In **Chapter 11** the technique of harvesting and transferring the Inferiorly Based Rectus Abdominis Myocutaneous (IBRAM) flap is described and the outcome in 37 patients treated at the Netherlands Cancer Institute is reported.

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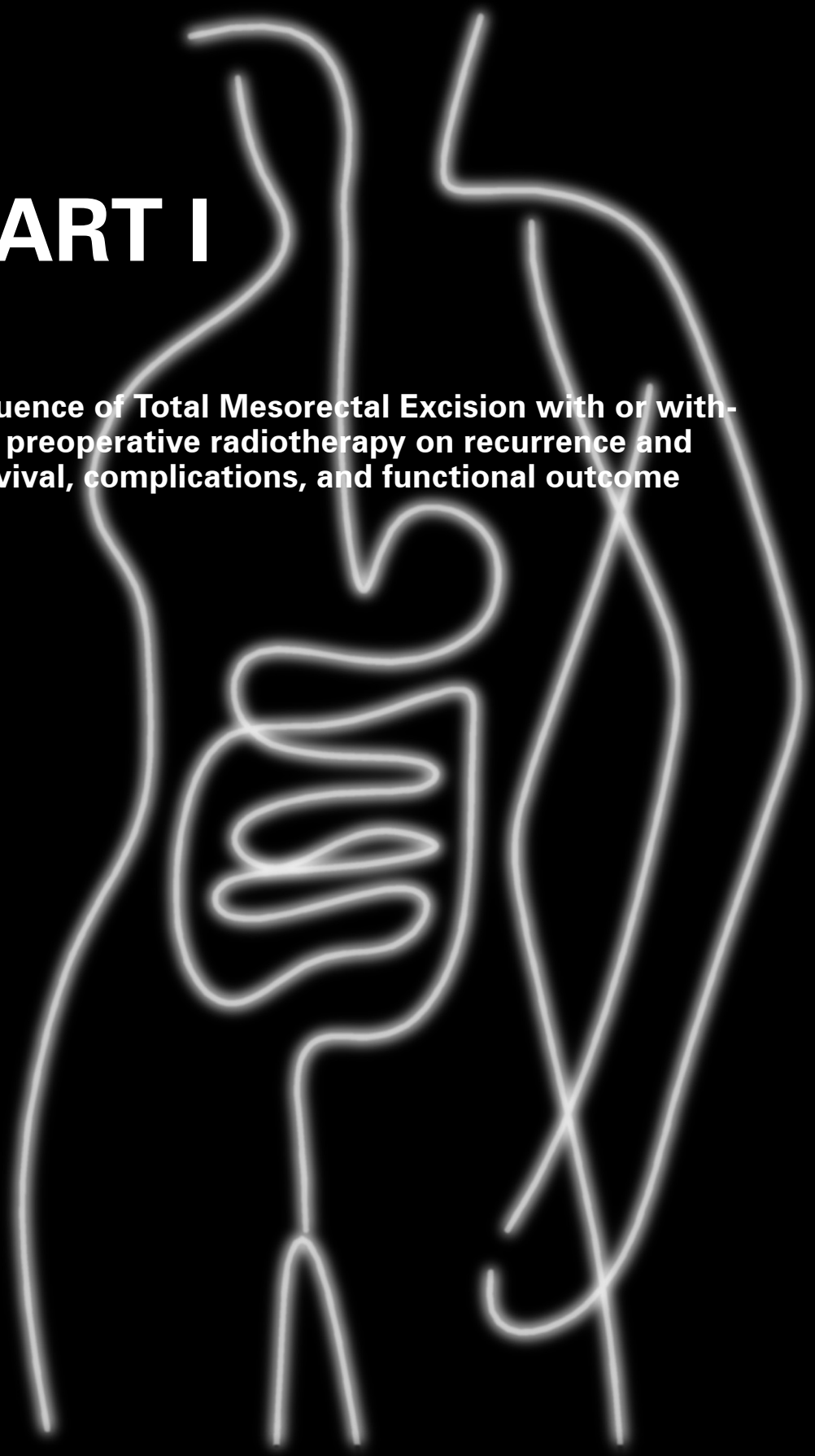
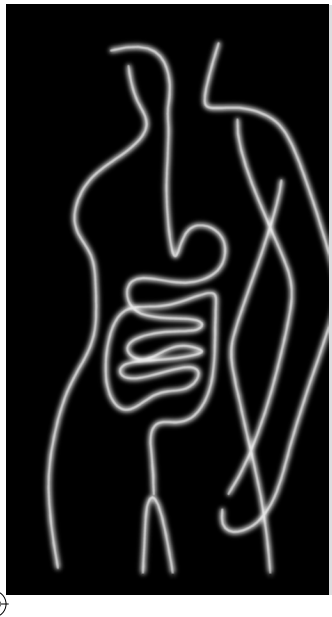
PART I

Influence of Total Mesorectal Excision with or without preoperative radiotherapy on recurrence and survival, complications, and functional outcome





CHAPTER 1

Journal of surgical oncology, in press

The influence of Total Mesorectal Excision on local recurrence and survival in rectal cancer patients; a population-based study in greater Amsterdam

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Abstract

Background and Objectives. To determine retrospectively in a population-based setting the influence of the introduction of Total Mesorectal Excision (TME) on local recurrence and survival in patients with rectal carcinoma.

Methods. All rectal carcinomas diagnosed during 1988-1991 (979 patients, conventional surgery with blunt dissection of the rectum) and 1998-2000 (890 patients, TME resection) were selected from the Amsterdam Cancer Registry. For all patients who underwent a macroscopically radical resection in the absence of distant dissemination, information on the occurrence of local recurrent disease and distant metastasis was collected.

Results. The cumulative five-year recurrence rate decreased significantly from 20% for patients diagnosed in 1988-1991 to 11% in 1998-2000. Stage (T-category, nodal status), period of diagnosis (conventional surgery versus TME resection), radiotherapy and chemotherapy were independent variables of local recurrence in multivariate analysis. Five-year relative survival for all rectal carcinoma cases increased from 52% (95%CI 48-55) for patients diagnosed in 1988-1991 to 59% (95%CI 55-63) in 1998-2000. In stage III, a significant increase of 18% was observed.

Conclusions. A significant decrease in local recurrence and a trend for an increase in survival were observed. The broad introduction of TME and the shift towards preoperative radiotherapy are the most plausible explanations for these observations.

Introduction

Colorectal cancer is the second most common cancer in the western world and approximately one third of these tumors are located in the rectum.[1] Annually, over 2,600 patients are registered with a newly diagnosed rectal carcinoma in the Netherlands.[2-3] In the past, surgical treatment of rectal cancer was associated with a high incidence of local recurrence, with rates of up to 30%.[4-5] With the introduction of total mesorectal excision (TME) as standard surgical technique for rectal carcinomas and the introduction of short-term preoperative radiotherapy, the incidence of local recurrences has decreased in controlled trials.[6-10]

In 1996 and 1997, the technique of TME was introduced in Greater Amsterdam, the region of the Comprehensive Cancer Centre Amsterdam (CCCA), facilitated by the CCCA. Introduction meetings and workshops were organized and surgeons in 13 out of 17 general hospitals were supervised by one of the four teacher-surgeons (with specialization in colorectal surgery) from the three oncological centers in Amsterdam in order to qualify as TME-surgeon. On average, teacher-surgeons supervised seven TME resections per hospital (range 1-16). Surgeons in the remaining four general hospitals were already qualified in TME-surgery. A documentation project was started to investigate the influence of TME-surgery on the incidence of local recurrences and survival. Moreover, the majority of the hospitals participated in the Dutch TME trial, a randomized study which investigated the value of short-term preoperative radiotherapy.[8]

The aim of the present study was to investigate in a population-based setting the influence of the introduction of TME on the local recurrence rate and survival in rectal cancer patients in Greater Amsterdam. For that reason, two cohorts of rectal cancer patients, before and after the introduction of TME were analyzed.

Materials and Methods

Cancer registry data

All primary rectal carcinomas (rectosigmoid excluded) diagnosed in patients with residence in Greater Amsterdam (that is the region of the CCCA) between January 1st 1988 and December 31st 1991 (four years period) and between January 1st 1998 and December 31st 2000 (three years period) were selected from the cancer registry of the CCCA, the Amsterdam Cancer Registry. The Amsterdam Cancer Registry is a regional, population-based cancer registry with complete regional coverage. Cases with preceding invasive cancers and cases with non-epithelial cancers, carcinoids and tumors without pathological confirmation were excluded. Cases diagnosed in a hospital outside the region of the CCCA but with residence in Greater Amsterdam, are routinely obtained from the national registry and included in the regional registry. The population of the region increased from 2.5 million on January 1st, 1988, to 2.8 million on December 31st 2000, approximately 17% of the total population of the Netherlands.

The information for the cancer registry is routinely extracted from detailed hospital and outpatient records by registration clerks. Apart from demographic data, data are collected on morphological classification, stage of the tumor and primary treatment of the patients. The TNM system for classification of malignant tumors is prospectively registered to classify all rectal carcinomas.
Stage grouping in this study was performed according to the 6th edition of the TNM-classification,[11] based on a combination of cTNM and pTNM. For all surgically treated patients pTNM was used, otherwise cTNM-data were used. Stages IIIA and IIIB were combined because of the small number of cases diagnosed in stage IIIA.

Vital status

The vital status of all registered patients with residence in Greater Amsterdam was updated by active follow-up in the hospitals, by linking files with deceased persons to the files of the cancer registry and by linkage to the electronic death register of the Central Office for Genealogy in September 2003 and February 2005, as described earlier.[12] Completeness of follow-up of the vital status is estimated to be over 99.5%.

Recurrence

A subset of cancer patients was defined by selecting cases from the cancer registry who underwent a macroscopically radical local resection in the absence of distant dissemination during the period 1988-1991 (conventional surgery with blunt dissection of the rectum) or 1998-2000 (TME). Of these cases a supplementary data set was extracted from the medical record by registration clerks. Patients with transanal resections, patients with polypectomies and patients with macroscopically residual disease after resection were excluded. Patients with residence in Greater Amsterdam but treated in hospitals outside Greater Amsterdam (approximately 1% of the cases) were also excluded, because of the unavailability of treatment-data. Data of the first period were collected in 1996 and 1997 and data of the second period in 2005. The data sets included the occurrence and the date of local recurrence or distant dissemination. Local recurrence was defined as cancer recurrence within the lower pelvis. Cases were generally followed for five years, but at least for three years after the date of surgery. All medical records could be retrieved from the hospitals. However, patients dying outside the hospital without information regarding recurrence were classified as 'unknown' (18 patients diagnosed in 1988-1991 and 7 patients diagnosed 1998-2000).

Statistical methods

Because the cause of death was not available for the majority of cases, we were unable to calculate disease specific survival. As an alternative, for the comparison of the survival of the two cohorts, we calculated relative survival using STATA 7.0 (Stata Corporation, College Station, TX, USA) according to statistics developed by Dickman et al.[13] This method corrects crude survival for expected mortality according to annual life tables of the Dutch general population.

A Cox regression analysis was also performed with STATA to calculate the hazard ratio (HR) and 95% confidence intervals (95%CI) of prognostic factors for the occurrence of recurrent disease.[14] For the comparison of the local recurrence rate (LRR) between hospitals a stage-standardized LRR was calculated for all individual hospitals. This stage-standardized LRR was based on the number of cases according to stage and the stage-specific LRR for all hospitals combined, and the stage-specific LRR in a specific hospital and the number of cases according to stage in that hospital. Exact 95%CIs based on the Poisson distribution of the observed number of recurrences and Kaplan-Meier survival curves were calculated using STATA.[15]

Results

A total of 979 patients (529 males, 450 females) were diagnosed with primary rectal carcinoma during 1988-1991, while 890 patients (505 males, 385 females) were diagnosed during 1998-2000. Patients diagnosed during 1988-1991 were slightly older than patients diagnosed during 1998-2000 (below the age of 65: 37% and 43%, respectively; between 65 and 74 years: 30% and 28%, respectively; 75 or older: 33% and 30%, respectively [chi^2 test: p=0.07]). The age-standardized incidence rate (European standardized rate) for both sexes combined slightly increased from 10.9 per 100,000 in 1988-1991 to 11.6 in 1998-2000. There were only small and insignificant differences in stage distribution in 1988-1991 compared to 1998-2000 (chi^2 test: p=0.63; Table 1). Cases diagnosed in stage I-III almost all were treated surgically. A macroscopically radical local resection (conventional surgery with blunt dissection of the rectum) in the absence of distant dissemination was performed in 669 out of 979 patients (68%) during 1988-1991. In 632 out of 890 patients (71%) a macroscopically radical local resection (TME) in the absence of distant dissemination was performed during 1998-2000.

In 1988-1991, radiotherapy was administered postoperatively in 53% of the patients with resectable stage II and III disease and preoperatively in 2%. In 1998-2000, 24% of resectable stage II and III patients were irradiated postoperatively and 46% preoperatively. The proportion of patients receiving chemotherapy increased from 4% in 1988-1991 to 9% in 1998-2000 and the proportion of stage IV-patients who underwent a metastectomy from the liver and/or lungs increased from 2% in 1988-1991 to 5% in 1998-2000 (results not shown).

Local recurrence

Out of 669 patients diagnosed in 1988-1991 who underwent a macroscopically radical local resection (conventional surgery with blunt dissection of the rectum) for rectal carcinoma, the tumor recurred locally within five years after diagnosis in 116 patients (17%), including 51 cases with distant metastasis (8%, Table 2). Out of 632 patients diagnosed in 1998-2001 who underwent a macroscopically radical local resection (TME) local recurrence occurred in 62 patients (10%), including 36 cases (6%) with distant

Table 1. Primary treatment of rectal carcinoma patients according to TNM-stage and period of diagnosis in Greater Amsterdam, the Netherlands

Stage/period of diagnosis	Number of cases (% of total)†	Primary treatment (%)¶					
		Surgery*	Surgery + radioth.*	Radioth.+ surgery*	Radioth.*	Chemoth.	Other
Stage I							
1988-1991	276 (28)	262 (95)	13 (5)	-	1 (0)	-	-
1998-2000	240 (27)	143 (60)	5 (2)	90 (38)	1 (0)	-	1 (0)
Stage II							
IIA							
1988-1991	176 (18)	108 (61)	62 (35)	4 (2)	2 (1)	-	-
1998-2000	184 (21)	73 (40)	26 (14)	80 (43)	2 (1)	-	3 (2)
IIB							
1988-1991	54 (6)	12 (22)	14 (26)	3 (6)	14 (26)	-	11 (20)
1998-2000	40 (5)	2 (5)	6 (15)	12 (30)	9 (23)	-	11 (28)
Stage III							
IIIA, IIIB							
1988-1991	158 (16)	60 (38)	95 (60)	3 (2)	-	-	-
1998-2000	152 (17)	37 (24)	44 (29)	66 (43)	4 (3)	-	1 (1)
IIIC							
1988-1991	83 (8)	19 (23)	60 (72)	-	1 (1)	-	3 (4)
1998-2000	73 (8)	15 (21)	23 (32)	34 (47)	1 (1)	-	-
Stage IV							
1988-1991	163 (17)	63 (39)	9 (6)	1 (1)	21 (13)	16 (10)	53 (33)
1998-2000	149 (17)	50 (34)	4 (3)	17 (11)	13 (9)	19 (13)	46 (31)
Stage unknown							
1988-1991	69 (7)	30 (43)	2 (3)	-	4 (6)	-	33 (48)
1998-2000	52 (6)	14 (27)	-	4 (8)	9 (17)	-	25 (48)

† percentage vertically; ¶ percentage horizontally * includes cases who also received chemotherapy and/or immunotherapy; surgery + radioth. = surgery with postoperative radiotherapy; radioth. + surgery = surgery with preoperative radiotherapy; radioth. = radiotherapy; chemoth. = chemotherapy; other: includes immunotherapy, palliative surgery (creation of ostomies) or no treatment

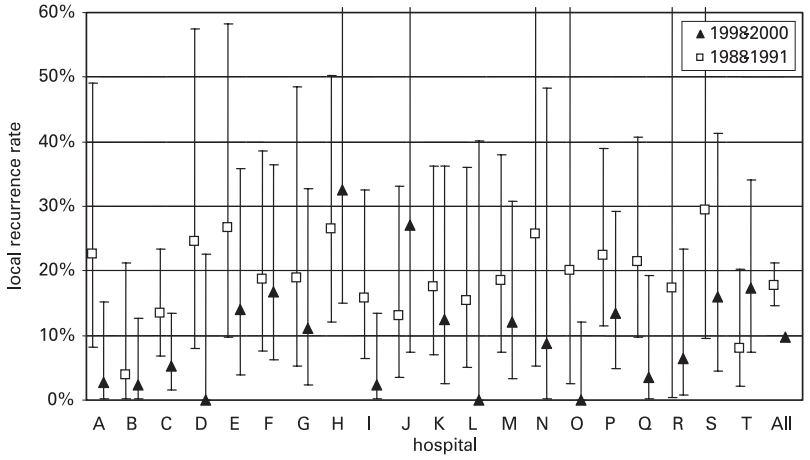
Table 2. Recurrence within five years after diagnosis in patients with rectal carcinoma initially treated with a macroscopically radical local resection in the absence of distant dissemination, according to period of diagnosis

	1988-1991		1998-2000	
Recurrence	N	%	n	%
None	428	64%	475	75%
Local only	65	10%	26	4%
Distant only	107	16%	88	14%
Local and distant				
- synchronous	31	5%	24	4%
- local prior to distant	16	2%	6	1%
- distant prior to local	4	1%	6	1%
Unknown	18	3%	7	1%
TOTAL	669		632	

metastasis. Using the actuarial method, the cumulative 5-year recurrence rate decreased from 20% to 11% for patients diagnosed in 1988-1991 and 1998-2000, respectively (log-rank test: p<0.0001).The crude local recurrence rate (LRR) within the first year decreased from 6% for patients diagnosed in 1988-1991 to 3% for patients diagnosed in 1998-2000. The LRR decreased from 9% to 6% in the second and third year and from 2% to 1% in the fourth and fifth year. Between 1988-1991 and 1998-2000 the LRR decreased in all stages, from 10% to 5% in stage I, from 14% to 11% in stage IIA, from 33% to 20% in stage IIB, from 22% to 12% in stage IIIA/IIIB and from 32% to 17% in stage IIIC.

Several factors were analyzed to identify prognostic factors for local recurrence. The results of the multivariable Cox regression analysis are shown in Table 3. The risk for local recurrence increased with increasing T-category (HR 5.4, 9.5 and 19.0 for T2, T3 and T4 in comparison to T1, respectively) and with increasing numbers of positive lymph nodes (HR 2.0 and 3.4 for N1 and N2 in comparison to N0). The risk for local recurrence was also increased if no lymph nodes were examined pathologically (NX; HR 2.6). The period in which a patient was treated (1988-1991 = conventional surgery with blunt dissection of the rectum, 1998-2000 = TME) was an independent prognostic value (HR 0.6, 95% CI 0.4-0.8, in favor of TME) and so was preoperative radiotherapy (HR 0.5, 95% CI 0.3-0.9). Postoperative radiotherapy increased the risk of local recurrence in the univariate analysis (HR 1.4, 95% CI 1.0-1.9), but in the multivariable analysis a decreased risk was observed (HR 0.6, 95% CI 0.4-1.0). Only a small number of patients received adjuvant chemotherapy (n=36 or 3%), but a statistically significant decreased risk of local recurrence was observed (HR 0.2, 95% CI 0.1-0.9).

As is depicted in figure 1, the LRR decreased between 1988-1991 and 1998-2000 in 17 out of a total of 20 hospitals, while an increase was observed in three hospitals (H, J and T).



O. Visser, Figure 1.

Figure 1. Local recurrence rate after surgery for rectal carcinoma in Greater Amsterdam according to hospital (A-T) and period of diagnosis (□ =1988-1991; ▲ =1998-2000). The results per hospital were standardized according to stage, using the stage distribution in 1998-2000 for all 20 hospitals combined as a reference (bars represent 95% confidence intervals).

Table 3. Multivariable Cox regression analysis for potential prognostic factors for the risk of local recurrence after intentionally curative resection for rectal carcinoma in Greater Amsterdam (cases with distant dissemination and/or macroscopic residual disease at time of initial treatment are excluded)

Factor	Cases	Hazard ratio[a]	95% CI
Sex			
Male	721	1	Reference
Female	580	1.2	0.9-1.6
Age			
0-64	564	1	Reference
65-74	383	1.1	0.8-0.5
75+	354	1.1	0.7-1.6
T-category			
T1	91	1	Reference
T2	439	5.4*	1.3-22
T3	672	9.5*	2.3-39
T4	80	19.0*	4.3-84
TX	19	9.0*	1.6-51
Nodal involvement			
N0	794	1	Reference
N1	297	2.0*	1.4-2.9
N2	147	3.4*	2.1-5.4
Unknown[b]	63	2.6*	1.3-4.9
Period of diagnosis			
1988-1991 (conventional surgery)	669	1	Reference
1998-2000 (total mesorectal excision)	632	0.6*	0.4-0.8
Radiotherapy			
No	662	1	Reference
Post-operative	336	0.6*	0.4-1.0
Pre-operative	303	0.6*	0.3-0.9
Chemotherapy			
No	1265	1	Reference
Yes	36	0.2*	0.1-0.9

[a] Hazard ratio < 1 = decrease in local recurrences; hazard ratio > 1 = increase in local recurrences
[b] No lymph nodes examined pathologically. * P<0.05. CI=confidence interval.

In one out of these three hospitals (H) the LRR in 1998-2000 was statistically significantly higher than the LRR for all hospitals combined. There was no association between (non-) participation in the teaching sessions and (absence of a) decrease in the LRR.

Distant dissemination

Distant dissemination within five years after diagnosis occurred in 158 patients after intentionally curative treatment in the period 1988-1991 (24%, table 2) and in 124 patients (20%) diagnosed in 1998-2000 (logistic regression corrected for gender, site, T-category and regional lymph node metastasis: OR 0.7, p=0.05). The decrease of the distant dissemination rate was observed within the first year after diagnosis (15% for patients diagnosed 1988-1991, compared to 9% for patients diagnosed 1998-2000) and an almost stable rate was observed in the subsequent years (9% for patients diagnosed in 1988-1991 and 10% in 1998-2000).

Table 4. Relative survival (%) of rectal carcinoma patients according to TNM-stage and period of diagnosis in Greater Amsterdam, the Netherlands

Stage/period of diagnosis	Number of cases	years after diagnosis (95% confidence interval)			
		1	3	5	10
Stage I					
1988-1991	276	98 (95-101)	97 (91-101)	93 (86-99)	77 (67-86)
1998-2000	240	97 (93-100)	96 (90-100)	95 (87-101)	
Stage II					
All					
1988-1991	230	86 (81-91)	67 (59-73)	57 (49-65)	47 (37-56)
1998-2000	224	90 (85-94)	77 (70-83)	68 (59-75)	
IIA					
1988-1991	176	94 (88-97)	81 (73-88)	70 (61-79)	58 (47-69)
1998-2000	184	94 (89-98)	82 (75-89)	72 (63-80)	
IIB					
1988-1991	54	62 (47-75)	18 (8-31)	10 (3-21)	6 (1-20)
1998-2000	40	71 (53-83)	48 (30-69)	47 (28-66)*	
Stage III					
All					
1988-1991	241	85 (79-89)	56 (49-63)	39 (32-46)	33 (26-41)
1998-2000	225	92 (87-95)	66 (58-73)	57 (49-65)*	
IIIA, IIIB					
1988-1991	158	87 (80-92)	60 (51-68)	45 (36-54)	43 (33-53)
1998-2000	152	93 (87-97)	72 (63-80)	67 (57-76)*	
IIIC					
1988-1991	83	80 (69-88)	49 (37-60)	29 (19-40)	16 (8-26)
1998-2000	73	88 (78-95)	53 (40-64)	37 (25-49)	
Stage IV					
1988-1991	163	33 (25-40)	4 (2-8)	1 (0-5)	2 (0-6)
1998-2000	149	43 (35-52)	15 (10-22)*	4 (1-9)	
Stage unknown					
1988-1991	69	58 (45-71)	44 (26-57)	30 (16-47)	13 (3-32)
1998-2000	52	55 (39-69)	30 (17-46)	25 (12-42)	
All stages combined					
1988-1991	979	79 (76-81)	61 (57-64)	52 (48-55)	42 (38-47)
1998-2000	890	83 (80-85)	66 (63-70)	59 (55-63)	

* significant difference in relative survival.

Survival for all patients

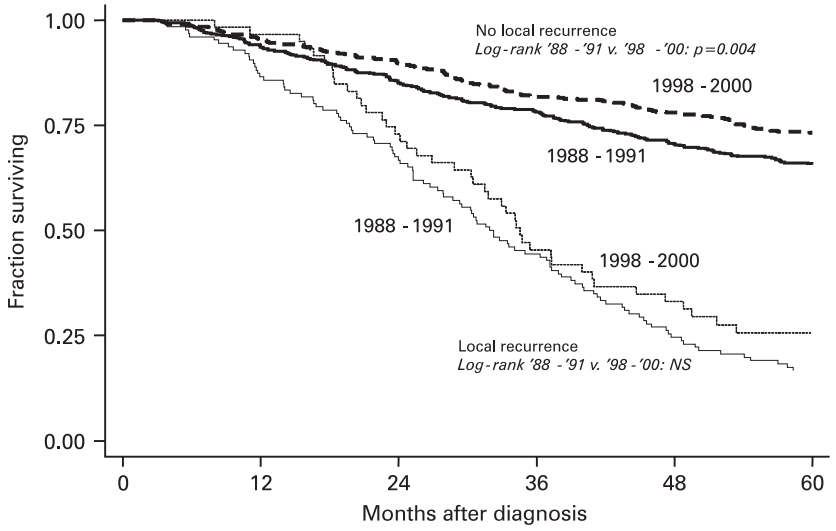
The crude one- and five-year survival for all stages combined of patients diagnosed in 1988-1991 was 75% and 41%, respectively. The crude survival increased to 80% (one year survival) and 49% (five year survival) for patients diagnosed in 1998-2000. The relative survival rate (RSR) according to TNM-stage and period of diagnosis is summarized in Table 4. The one-, three- and five-year RSR for all stages combined of patients diagnosed in 1988-1991 was 79%, 61% and 52%, respectively. The ten-year RSR was 42% (95%CI: 38-47%). The one-, three- and five-year RSR of patients diagnosed 1998-2001 was 83% (+4%), 66% (+5%) and 59% (+7%), respectively.

Between 1988-1991 and 1998-2000, an increase in the five-year RSR was observed numbering 2%, 11%, 18% and 3% in stage I, stage II, stage III and stage IV, respectively. The increase was statistically significant in stages IIB and III. Variation in survival was large within stage II and III for the various T- and N-categories. Five-year RSR of stage IIA was 70% for cases diagnosed in 1988-1991 and 72% in 1998-2000, while five-year RSR of stage IIB was 10% for cases diagnosed in 1988-1991 and increased to 47% in 1998-2000. Within stage III, the five-year RSR for stage IIIC was statistically significantly worse than the five-year RSR for stage IIIA/IIIB.

A statistically significant increase of the three-year RSR was observed for stage IV rectal carcinoma, from 4% for cases diagnosed in 1988-1991 to 15% in 1998-2000 (+11%). The five-year RSR was 1% in 1988-1991 and 4% in 1998-2000 (+3%).

Survival in relation to local recurrence and distant dissemination

The crude survival of patients subdivided according to local recurrence or no local recurrence is shown in Figure 2 (excluding cases dying within 3 months after diagnosis and cases with unknown local recurrence). Crude 5-year survival of patients with a local recurrence increased from 17% to 26% between 1988-1991 and 1998-2000 (log-rank test: not significant). The crude 5-year survival of patients who remained local recurrence-free increased from 63% to 71% (log-rank test: p=0.004), mainly because of an increased survival after distant dissemination. The median survival after distant dissemination increased from 8 months for patients diagnosed in 1988-1991 to 15 months for patients diagnosed in 1998-2000 (log-rank test: p=<0.001).



O. Visser, Figure 2.

Figure 2. Crude survival of rectal cancer patients after macroscopically radical local resection in the absence of distant dissemination in Greater Amsterdam, in the periods 1988-1991 and 1998-2000 (excluding cases dying within 3 months after diagnosis and cases with unknown local recurrence). Log-rank test adjusted for age, sex and stage; NS= not significant.

Discussion

In this study we evaluated the survival and treatment outcome of patients with rectal carcinoma between 1988-1991 and 1998-2000. In parallel with the broad introduction of TME, there was an increase in the use of radiotherapy as well as a clear shift towards preoperative radiotherapy during the second period. Although the influence on stage-distribution of short-term preoperative radiotherapy is negligible due to the absence of down staging [16], down staging may have occurred in cases treated with long-term preoperative radiotherapy. Although we did not collect information on the duration of preoperative radiotherapy, based on the interval between the date of initial diagnosis and date of surgery only a minority of the patients (mainly clinical T4-cases) received long-term preoperative radiotherapy. Down staging occurred in 43 out of 59 clinical T4-cases who received preoperative radiotherapy. However, the overall influence of down staging was probably negligible, since there was no clear difference in tumor distribution between the two periods (Table 1). Therefore, it is unlikely that observed differences in outcome between these periods are due to differences in stage distribution.

Local recurrence

Development of local recurrence in patients undergoing rectal surgery has been reported at rates varying from 18% to 23% in population-based settings. [5,17-18] Results are generally more favorable in randomized clinical trials due to selection and referral bias and maybe even due to the dedication of the participants. In the latest four randomized clinical trials evaluating the value of preoperative radiotherapy the LRR ranged from 11% to 30% for patients treated by surgery alone and from 6% to 16% for patients treated with radiotherapy plus surgery. [10,19-21]

The cohort 1988-1991 represents day-to-day practice in the pre-TME period in Greater Amsterdam. In 1996 and 1997, TME was introduced in Greater Amsterdam facilitated by the CCCA and an important aspect of this introduction was the supervision of participating surgeons by teacher-surgeons in order to qualify as TME-surgeon. Therefore, period 1998-2000 represents day-to-day practice after introduction of TME. Following this broad introduction, a steep decrease in the (crude) LRR was observed from 17% to 10%. A decrease in LRR was seen in all but three of the 20 hospitals.

In the multivariate analysis, the period of diagnosis was a prognostic factor for local recurrence. The most important difference between the two periods is the surgical technique applied. Period 1998-2000 is practically synonymous with TME surgery and indicates that TME is probably superior to conventional surgery with blunt dissection of the rectum.

Another difference between the two study periods is the increased use of radiotherapy in combination with surgery. In the first period (1988-1991) 266 patients (27%) underwent radiotherapy in combination with surgery, compared to 411 patients (46%) in the second period (Table 1). There was a clear shift towards preoperative radiotherapy (1% in 1988-1991 versus 34% in 1998-2000 for all patients combined) and in the multivariate analysis,

apart from the apparent effect of stage and the period of diagnosis, preoperative as well as postoperative radiotherapy was a prognostic factor for local recurrence. One could argue that since preoperative radiotherapy was almost exclusively limited to the second time period, inclusion of both preoperative radiotherapy and time period in a multivariate analysis is questionable. However, only 46% of the patients who underwent a macroscopically radical local resection in the absence of distant dissemination in the second period received preoperative radiotherapy, while all patients underwent rectal resection with TME surgery. Therefore the majority of patients did not undergo preoperative radiotherapy, which makes the correlation between the use of preoperative radiotherapy and TME less pronounced. Next to that, it could be expected that in case of a strong correlation between TME and preoperative radiotherapy, one of these factors would no longer be a prognostic factor in a multivariate analysis, which is not the case (Table 3).

Almost all hospitals in Greater Amsterdam participated in the Dutch TME trial. [8] After the enrolment of patients in the TME trial was stopped in December 1999 it was decided not to continue with preoperative radiotherapy in Greater Amsterdam until long term results of the trial were available. This explains why, despite the clear shift towards preoperative radiotherapy, the number of patients treated with preoperative radiotherapy in the period 1998-2000 was still below 50%. After publication of the results of the Dutch TME trial, preoperative radiotherapy was included in the national guidelines of resectable rectal cancer in the Netherlands. In 2001, 72% of stage II and III patients were treated with preoperative radiotherapy [22] which further increased to 81% in 2003 (unpublished data). The full impact of preoperative radiotherapy on LRR will have to be substantiated in future research.

Distant dissemination

The observation of a significant decrease in the distant dissemination rate (from 14% to 9%) within the first year after diagnosis is remarkable. A change in local treatment strategies is unlikely to have contributed to this effect. Possibly, the increased use of adjuvant chemotherapy has contributed to the decrease in the distant dissemination rate, although only a small proportion of the surgical patients received chemotherapy (2% in 1988-1991 and 6% in 1998-2000). Improved staging procedures may be another explanation. Improved detection of distant dissemination at primary diagnosis would have caused an increase of stage IV disease and a decrease in the distant dissemination rate of stage I-III cases, especially in the first year after diagnosis ("stage migration"). However, stage migration was not observed (Table 1).

Survival

According to the EUROCARE-study on survival of cancer patients in Europe, which covers patients diagnosed in 1990-1994, survival of rectal cancer patients in the Netherlands (data for the Netherlands in the EUROCARE-study were mainly derived from Greater Amsterdam) is among the highest in Europe. [23] The EUROCARE-study reports equally high rates for France, Norway, Sweden and Switzerland and these rates have also been

reported for Western Australia. [24] Relatively low survival rates were observed in Eastern European countries, Denmark and the United Kingdom, but have also been reported for India and Cuba. [25-26] Between 1988-1991 and 1998-2000, an increase in the five-year relative survival rate (RSR) was observed from 52% to 59% (not statistically significant), mostly because of a statistically significant increase of the relative survival rate of stage III rectal carcinoma from 39% to 57%. Considering the relatively high survival in the Netherlands already in the early nineties, a further increase of 5% in the late nineties is remarkable. However, in the United States the reported rectal cancer survival rates from the SEER Program are higher than in Europe. [27] The reported five-year RSR from the SEER Program for 1990-1999 was as high as 62%, compared to 59% for cases diagnosed during 1998-2000 in our study. Stage-specific rates of 92%, 73%, 56% and 8% for stage I, II, III and IV, respectively, were reported from the SEER Program compared to 95%, 68%, 57% and 4% in our study (period 1998-2000). Although the slightly lower overall survival in our study compared to the SEER-data may be influenced by differences in staging procedures and (in)completeness of follow-up between the Netherlands and the United States, differences in treatment strategies may also have influenced the results. Differences in treatment (other than the introduction of TME and preoperative radiotherapy) and diagnostic practices may also have contributed to the increase in survival between 1988-1991 and 1998-2000, as observed in several stages.

Conclusions

A significant decrease in the local recurrence rate and a trend for increased relative survival rate were observed from the first to the second time period assessed in this study. The introduction of TME and a shift towards preoperative radiotherapy is the most plausible explanation for this observation. However, as with all time-trend analyses, it is always difficult to attribute a change in outcome to any one individual aspect of care. Nonetheless, the decrease in local recurrence rate observed in almost all hospitals in this population-based study not only underlines the benefit of a carefully guided regional introduction program, but also likely indicates that TME, although never investigated by means of a randomized clinical trial, is indeed superior to conventional surgery with blunt dissection of the rectum. [28-29]

Acknowledgements

The surgeons in the twenty participating hospitals (Academic Medical Centre, Free University Medical Centre, Sint Lucas Andreas Hospital, Netherlands Cancer Institute, BovenIJ Hospital, Onze Lieve Vrouwe Hospital, Slotervaart Hospital, Waterland Hospital, Amstelland Hospital, Zaans Medical Centre, Flevo Hospital, IJsselmeer Hospitals, Gooi-Noord Hospital, Hilversum Hospital, Kennemer Hospital, Red Cross Hospital, Spaarne Hospital, Gemini Hospital, Westfries Hospital, Medical Centre Alkmaar) are greatly acknowledged.

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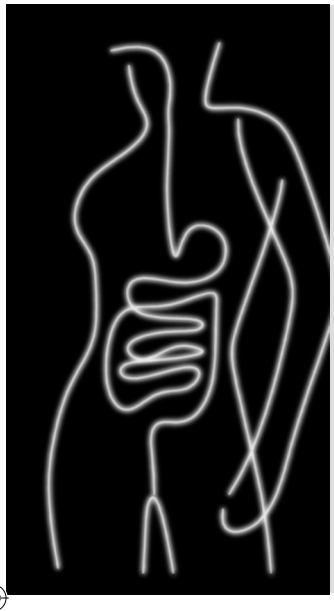

CHAPTER 2

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Harm and benefits of short-term preoperative radiotherapy in patients with resectable rectal carcinomas

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Abstract

Background and Objectives. To weigh the harms and benefits of short-term preoperative radiotherapy in the treatment of resectable rectal cancer.

Methods. The benefits (reduction of local recurrence) and harm (increase of short-term complications) of short-term preoperative radiotherapy are balanced using a model which classifies patients in one of five outcome combinations; 1 benefit without additional harm, 2 benefit with additional harm, 3 no benefit, no additional harm, 4 no benefit but additional harm, 5 mortality due to combined treatment.

The results of four randomised clinical trials (RCT) which study the addition of short-term preoperative radiotherapy in rectal cancer were classified according to this model.

Results. 5 – 13% of the patients have benefit without additional harm of preoperative radiotherapy, while 0 – 2% have benefit with additional harm; 74 – 87% has neither benefit nor additional harm and 6 - 11% have no benefit but additional harm. A small percentage of patients (1% - 6%) dies postoperatively as a result of the addition of radiotherapy.

Conclusions. This model provides a transparent appreciation of the harmful and beneficial effects of any treatment modality investigated by means of a randomised clinical trial. As for short-term preoperative radiotherapy in resectable rectal cancer is shown, a small percentage of patients benefits from such treatment. Most patients have neither benefit nor additional harm, while a small percentage suffers from additional harm while not receiving any benefit.

Introduction

Short-term preoperative radiotherapy for rectal cancer improved pelvic control and survival in multiple clinical trials. [1-4] In the Swedish Rectal Cancer Trial (SRCT), local recurrence rate was significantly lower in the radiotherapy group (9% versus 23%, Absolute Risk Reduction (ARR) 14%, 95% Confidence Interval of ARR (CI): 10 – 19%). There was also a significant five-year survival benefit in this trial (0.58 versus 0.48, ARR 0.10, 95% CI: 0.04 – 0.16). [5] In the Dutch TME trial, the local recurrence rate in patients treated with or without preoperative radiotherapy followed by TME was 6% versus 11% respectively (ARR 5%, 95% CI: 3 – 8%). Despite this reduction, no survival benefit has been observed in this trial after a median follow up of 4.8 years. [6]

The introduction of new operational techniques as Total Mesorectal Excision (TME) appeared to improve pelvic control.[7-11] Although this is based on data from study designs with historical controls and has never been substantiated in a randomised clinical trial (RCT), TME has been accepted as the standard for rectal resections.

Reports of randomised clinical trials tend to focus on possible benefits rather than on negative side-effects. Therapeutic interventions are often associated with complications or long term toxicity, with a damage to patients' quality of life. Surgery for rectal cancer has a significant morbidity. [12-15] Preoperative radiotherapy leads to more perineal wound infections and worse long-term functional outcome. [6,12,16] Such complications should be balanced against the reduction of local recurrence rates or improved survival as primary endpoints. In recent years, four meta-analyses and one systematic overview have been published evaluating the beneficial effect of preoperative radiotherapy.[1-4,17] These reports are often used to advocate short-term preoperative radiotherapy, but hardly address the increase in morbidity caused by preoperative radiotherapy. The increase in morbidity should also play a role in the debate concerning the use of preoperative radiotherapy. The percentage of patients who might benefit from preoperative radiotherapy is limited, due to the low incidence of local recurrence after TME surgery.

The aim of this study is to weigh the harm and benefits of short-term preoperative radiotherapy in the treatment of resectable rectal cancer, using an adapted model [18-19] and based on data from the latest four RCTs on this issue. [5,13-14,20]

Materials and Methods

Selection of randomised clinical trials

A literature search was conducted in MEDLINE/PUBMED to identify randomised clinical trials (RCT) comparing short-term (≤ 7 days) preoperative radiotherapy followed by surgery and surgery alone in patients with resectable rectal cancer. Only trials with preoperative radiotherapy at a biologically effective dose ≥ 30 Gy were included. [3,17] Four randomised clinical trials fulfilled these criteria; the Stockholm I trial [13,21], the Stockholm II trial [14,22],

the Swedish Rectal Cancer Trial (SRCT) [5] and the Dutch TME trial. [6,20] These RCTs also reported on morbidity, either in the initial article or in an additional paper [6,12,15]

Characteristics of the four selected randomised clinical trials

Stockholm I Trial [13,21]

From 1980 to 1987, 849 patients with a clinically resectable rectal adenocarcinoma were randomised between radiation therapy (25Gy over 5 to 7 days using a 2 portal technique) before surgery versus surgery alone (no TME). Surgery was considered curative if patients had undergone a complete local resection based on the assessment of the radicality as judged by the surgeon and pathologist. In 684 patients (81%) a "curative" resection was performed. The surgery was considered curative in 331 of the 424 patients (78%) treated with radiotherapy versus 348 of the 425 patients (82%) treated with surgery alone (difference not significant). Median follow-up time was 8.9 years.

Stockholm II Trial [14,22]

Between 1987 and 1993, 557 rectal cancer patients younger than 80 years of age were randomised between short-term preoperative radiotherapy (25Gy) using a four-portal technique followed by surgery and surgery alone (no TME). This technique was used to decrease the target volume compared with the Stockholm I trial, in order to avoid the increased postoperative mortality while maintaining the reduction in local recurrences. Surgery was defined as curative if all macroscopic tumour was removed, no distant metastasis were found and the pathologist reported tumour free margins of the specimen. The surgery was considered curative in 481 patients (86%), 230 (85%) in the group treated with radiotherapy and 251 (87%) in the surgery alone group. Median follow-up was 8.8 years.

Swedish Rectal Cancer Trial [5]

Between March 1987 and February 1990, 1168 patients younger than 80 years of age who had resectable rectal cancer were randomised between preoperative irradiation (5x5Gy using a three beam technique of four-beam "box" technique) followed by surgery within one week or surgery alone (no TME). Surgery was considered locally curative if both the surgeon and the histopathologist considered the margins of the resected tissue to be free of tumour, even if the bowel was perforated during surgery. Nine hundred and eight patients (78%) underwent a "curative" resection equally distributed over both groups. Median follow-up was 6.3 years.

Dutch TME Trial [6,20]

Between January 1996 and December 1999, a total of 1861 patients with a mobile adenocarcinoma of the rectum were randomised between either short-term (5x5Gy) preoperative radiotherapy plus TME or TME alone. Much effort was made to apply standardised radiotherapy, surgery (nation-wide introduction of TME-technique) and pathology. A macroscopically complete local resection was achieved in 1748 patients

(94%), 873 (94%) in the group treated with radiotherapy and 875 (93%) in the TME alone group. Median follow-up was 4.8 years.

Weighing complications against benefits [18-19]

Absolute Risk Increase (ARI)

The difference in complications between two treatment modalities is reflected by the Absolute Risk Increase (ARI). The complication rates can be divided into mortality and morbidity, resulting in $ARI_{mortality}$ and $ARI_{morbidity.}$ In general, surgery-related mortality is calculated over a period of 30 days or during hospital stay and is an indisputable parameter. Treatment-related morbidity is more subject to discussion due to the differences in severity of the complications. Calculations in the present analysis are based on all complications mentioned in the articles regardless of the severity of each complication. To prevent overestimation of morbidity, the number of patients with complications was used and not the total number of complications. Thus, if a patient had more than one complication, this was counted as one harmful event.

Absolute Risk Reduction (ARR)

The beneficial effect of short-term preoperative radiotherapy plus surgery over surgery alone can be expressed by the absolute risk reduction (ARR). This is defined as the difference in primary outcome over a specific time period between the two groups. In case of rectal cancer treatment, two different endpoints (benefits) can be used, namely reduction of local recurrences or improvement in survival.

Reduction of local recurrences is not directly influenced by postoperative mortality provided that this difference in mortality is limited thus implicating that the number of patients at risk for a local recurrence is equal in both groups. Therefore the $ARR_{local\ recurrence}$ is the difference in local recurrences between the two groups.

On the other hand, improvement in survival is directly influenced by postoperative mortality.

The $ARR_{survival}$ is the difference in deaths between the treatment arms including the toxic deaths. The $ARR_{survival}$ minus the $ARI_{mortality}$ could be defined as the disease related ARR.

Model to calculate five different outcome combinations

The ARI and ARR can be used to identify five groups of patients with different outcome combinations with respect to harm and benefit.[18-19] It is important to realise that the 'harm' in this model is the difference in complications between the two treatment modalities. The difference in survival or the difference in local recurrences between the two treatment arms is the 'benefit' in this model.

Group 1 **full benefit, no harm** (reduction of local recurrences or improved survival, no additional morbidity: **ARR x (1-$ARI_{morbidity}$)**)

Group 2 **benefit with harm** (reduction of local recurrences or improved survival, with additional morbidity: **ARR x $ARI_{morbidity}$**))

Group 3 **no benefit, no harm** (no reduction of local recurrences or improved survival, no additional morbidity: **(1-(ARR + $ARI_{mortality}$)) * (1-$ARI_{morbidity}$)**)

Group 4 **no benefit, but harm** (no reduction of local recurrences or improved survival, with additional morbidity: **(1-(ARR + $ARI_{mortality}$)) * $ARI_{morbidity}$)**)

Group 5 **full harm** (patients who die postoperatively due to the addition of short-term preoperative radiotherapy: **$ARI_{mortality}$**)

Results

Benefits based on selected RCTs and their consequent Absolute Risk Reduction (ARR) in local recurrence rate (Table 1) and long-term survival

Table 1. Local recurrence rates, Absolute Risk Reduction (ARR) and 95% Confidence Intervals based on the selected RCTs.

	Local recurrence rates		$ARR_{local\ recurrence}$	95% CI	Follow up
	RT + surgery	**Surgery alone**			
Stockholm I [21]	16% (55/337)	30% (105/347)	14%	8 – 20%	8.9 (5.2 – 12.0)
Stockholm II [22]	12% (28/230)	25% (63/251)	13%	6 – 20%	8.8
SRCT 5	9% (41/454)	23% (106/454)	14%	10 – 19%	6.3 (5.0 – 8.0)
Dutch TME [6]	6%*	11%*	5%	3 – 8%	4.8 (1.2 – 7.7)

Local recurrence rates are calculated using only patients after "curative" resection (numbers of patients with recurrence and entire group with curative resection are between parentheses), $ARR_{local\ recurrence}$ = absolute risk reduction in local recurrence = the difference in local recurrence rates between the two groups, 95% CI = 95% Confidence Interval of ARR, follow up = median follow up in years (range), RT = radiotherapy, SRCT = Swedish Rectal Cancer Trial, TME = Total Mesorectal Excision, * absolute numbers are not published yet and are therefore not mentioned.

Stockholm I Trial [21]

The incidence of pelvic recurrence at five years was 16% in the radiation-before-surgery group and 30% in the surgery-alone group (only patients after "curative" resection). There was no difference in five-year survival between the two groups (exact data not given).

Stockholm II Trial [22]

The incidence of pelvic recurrence at five years was 12% in the combined therapy group and 25% in the surgery alone group (only patients after a "curative" resection). The overall five-year survival in the combined therapy group was 0.39 and in the surgery alone group 0.36. This difference is not statistically significant.

Swedish Rectal Cancer Trial [5]

The rate of local recurrence at five years was 9% in the group that received radiotherapy before surgery and 23% in the group treated with surgery alone (only patients after a locally "curative" resection). The overall five-year survival rate was 0.58 in the combined therapy group and 0.48 in the surgery-alone group leading to an ARR for survival of 0.10 (95% CI: 0.04 – 0.16).

Dutch TME Trial [6,20]

After a median follow up of 4.8 years, the rate of local recurrence was 6% in the combined therapy group and 11% in the TME alone group (only patients who underwent a macroscopically complete local resection). The five-year overall survival was similar in both groups (0.64).

Mortality and morbidity of short-term preoperative radiotherapy and the consequent Absolute Risk Increase (ARI) (Table 2)

Table 2. Postoperative mortality and morbidity as described in the selected randomised clinical trials with consequent Absolute Risk Increase (ARI).

	Mortality		$ARI_{mortality}$	95% CI
	RT + surgery	Surgery alone		
Stockholm I [13]	8% (35/424)	2% (7/425)	6%	4 – 9%
Stockholm II [14]	2% (6/272)	1% (3/285)	1%	-1 – 3%
SRCT [15]	4% (22/573)	3% (15/574)	1%	-1 – 3%
Dutch TME [12]	4% (28/695)	3% (24/719)	1%	-1 – 3%
	Morbidity		$ARI_{morbidity}$	95% CI
	RT + surgery	Surgery alone		
Stockholm I [13]	26% (112/424)	19% (81/425)	7%	2 – 13%
Stockholm II [14]	41% (111/272)	28% (79/285)	13%	5 – 21%
SRCT [15]	43% (235/547)*	33% (182/549)*	10%	4 – 15%
Dutch TME [12]	48% (336/695)	41% (297/719)	7%	2 – 12%

Mortality = 30-day mortality (numbers of patients are between parentheses), $ARI_{mortality}$ = absolute risk $increase_{mortality}$ = the difference in postoperative mortality between the two groups, $ARI_{morbidity}$ = absolute risk $increase_{morbidity}$ = the difference in morbidity between the two groups, 95% CI= 95% Confidence Interval of ARI, Morbidity = all complications reported in the articles are taken into account, despite their differences in seriousness, * only patients after anterior resection and abdominoperineal resection, RT = radiotherapy, SRCT = Swedish Rectal Cancer Trial, TME = Total Mesorectal Excision.

Stockholm I Trial [13]

Postoperative mortality was 8% in the combined therapy group and 2% in the surgery alone group. This difference is statistically significant.

Morbidity was 26% in the combined therapy group and 19% in the surgery alone group. Morbidity included wound infection, wound dehiscence, anastomotic leakage, bowel obstruction, haemorrhage, thrombosis and others.

Stockholm II Trial [14]

The mortality rates in the Stockholm II trial were lower than in the Stockholm I trial. There was no significant difference (2 vs. 1%) between the two groups in this trial.

Morbidity in the combined therapy group was 41% and 28% in the surgery alone group. Morbidity mentioned were wound sepsis, septicaemia, anastomotic leakage, wound dehiscence, bowel obstruction and others.

Swedish Rectal Cancer Trial [15]

The difference in mortality was not significant; 4% in the combined group vs 3% in the surgery alone group.

Reported morbidity included wound infection, perineal wound infection, septicaemia, anastomotic dehiscence, wound rupture, postoperative ileus and miscellaneous and was significantly higher in the combined therapy group than in the surgery alone group (43% vs 33% respectively).

Dutch TME Trial [12]

The mortality between the two groups was not significantly different (4% after combined therapy versus 3% after TME alone).

Morbidity was 48% in the combined group versus 41% in the TME alone group and included infectious, general and surgical complications.

Classification of results in five different outcome combinations (Table 3 a + b)

Based on the ARIs and ARRs, the results are classified into the different outcome combinations. For every trial, the patients are grouped into one of the five outcome combinations, using the local recurrence rate as primary endpoint (Table 3a & Figure). To better understand the meaning of the groups, the data are translated to natural frequencies for a cohort of a thousand patients. For example, it can be seen that in the Stockholm I trial (Table 3a, row 1) 140 patients in groups 1 and 2 do not develop a local recurrence as a result of radiotherapy in a virtual cohort of a thousand patients. However, this is at the costs of 60 patients in group 5 who die perioperatively as a result of the addition of radiotherapy and 60 patients in group 4 who do not benefit from radiotherapy but suffer from morbidity. The large majority of patients (740 in group 3) has neither benefit nor additional harm from the combined therapy.

Although only the SRCT showed a significantly improved 5-year survival in the combined therapy group (0.58 vs. 0.48) [5], patients from the four trials were classified according to this model. (Table 3b)

Table 3a. Classification in five different outcome combinations with difference in local recurrence rates as primary endpoint for a cohort of 1000 patients.

	Group 1 *full benefit, no harm**	Group 2 *benefit with harm**	Group 3 *no benefit, no harm**	Group 4 *no benefit, but harm**	Group 5 *full harm#*
Stockholm I [13,21]	130	10	740	60	60
Stockholm II [14,22]	110	20	750	110	10
SRCT [5,15]	130	10	760	90	10
Dutch TME [6,12]	50	0	870	70	10

Benefit = reduction in local recurrence, * harm = additional morbidity compared to surgery alone group, # full harm = patients who die due to the combined therapy, SRCT = Swedish Rectal Cancer Trial, TME = Total Mesorectal Excision

Table 3b. Classification in five different outcome combinations with difference in 5-year survival as primary endpoint for a cohort of 1000 patients.

	Group 1 *full benefit, no harm**	Group 2 *benefit with harm**	Group 3 *no benefit, no harm**	Group 4 *no benefit, but harm**	Group 5 *full harm#*
Stockholm I [13,21]	60	0	820	60	60
Stockholm II [14,22]	30	10	830	120	10
$ SRCT [5,15]	100	10	790	90	10
Dutch TME [6,12]	10	0	910	70	10

Benefit = Improvement in five year survival, * harm = additional morbidity compared to surgery alone group, # full harm = patients who die due to the combined therapy, $ SCRT is the only trial with a significant difference in five year survival, SRCT = Swedish Rectal Cancer Trial, TME = Total Mesorectal Excision

Discussion

Benefits of short-term preoperative radiotherapy.

An attempt was made to classify the results of four randomised clinical trials comparing short-term preoperative radiotherapy (5x5Gy) followed by surgery versus surgery alone. This classification was based upon the reported harm and benefits, with the reduction of local recurrence as primary endpoint, because all trials showed a significant decrease in local recurrence percentages.[5,6, 12-14, 21-22] Although there is some overlap between the Stockholm II trial and the SRCT (60% of the Stockholm II trial patients are also enrolled in the SRCT) the decision was made to analyse them separately.

The presented model gives an impression of the distribution of patients over five groups (Table 3a) and provides a balanced understanding of the value of preoperative radiotherapy in the treatment of resectable rectal carcinomas.

Improvement in survival was used as an alternative endpoint (Table 3b) although only the SRCT trial showed significant improvement in survival. In this trial, as in the Stockholm I & II trials, the TME technique was not applied in contrast to the Dutch TME trial. The use of this technique, which is nowadays recognised as standard surgical treatment, might explain the absence of survival benefit in the Dutch TME trial. For that reason and the fact that four meta-analyses using the results of the other trials have been published previously [2-4,17], the decision was made not to perform a new meta-analysis again.

Complications of short-term preoperative radiotherapy.

When weighing the harms and benefits of short-term preoperative radiotherapy, it is important to define which complications should be incorporated in the model. Classification of morbidity into minor and major is required. The severity of complications should be weighed in relation to the primary endpoint (benefit) to classify the complications into minor and major. For example, a superficial wound infection is of less importance after rectal resection for cancer than permanent disabling incontinence.

Major complications have a substantial impact on patients' recovery and might be a reason for some of them to refrain from preoperative radiotherapy, if known in advance. Currently, there is no consensus which complications to consider major or minor in the treatment of rectal cancer. A clear consensus would be needed for a better appreciation of the benefits of radiotherapy. This could be established by means of a so-called Delphi round, which is currently performed.[23-24] Incorporation of these results, i.e. using only those complications, which are classified as major, would improve the fairness of this model. Due to the current absence of such a consensus, all reported postoperative complications in the four RCTs were incorporated in the present morbidity analysis (Table 2).

Ideally, a combination of short-term complications (i.e. radiotherapy and surgery related complications occurring within 6 weeks after surgery) and long-term complications (i.e. negative influence on functional outcome such as incontinence or urge, sexual dysfunction or voiding problems, persisting or occurring at least 6 weeks after surgery) should be taken into account. However, only two of the four RCTs supplied detailed, quantified information on the impact on long-term functional outcome. Moreover, this information was based only on a small subgroup of the original trial population.[16,25] Therefore, the impact of preoperative radiotherapy on long-term functional outcome was excluded in our analysis.

Remarks concerning the use of the presented model.

Double-calculations in morbidity should be avoided for correct application of this model. If a patient experiences more than one complication, these should be counted as one single event only, in order to prevent overestimation of the number of patients suffering from morbidity (resulting in an incorrect shift from group 1 to group 2 and, more importantly, from group 3 to group 4). The trials used in this analysis all reported the proportion of patients not having experienced postoperative complications. Therefore, it was possible to calculate the number of patients with and without complications and thus to avoid double-calculations in morbidity.

All above-mentioned problems are less relevant when using source data of the RCTs to present the results according to this model. When using source data, one can easily avoid double calculations and impute only major complications instead of all complications. Next to that, sub-groups of patients, for example based on preoperative characteristics, could be imputed to get a more detailed overview.

Applicability of the presented model.

It is important to realise that the presented model is not only applicable to short-term preoperative radiotherapy for rectal cancer but can be applied to any adjuvant or neo-adjuvant treatment modality investigated by means of a randomised clinical trial (e.g. the harms and benefits of radiotherapy in breast-conserving surgery or the harms and

benefits of chemotherapy in colon cancer). Therefore, authors are encouraged to use this model when presenting results of their randomised clinical trials. It will provide a clear appreciation of the harmful and beneficial effects of experimental treatments and thus will lead to an improved overall judgement.

Conclusions

In conclusion, despite the above mentioned drawbacks, interpretation of the results of four RCTs using this model provides a balanced insight in the harms and benefits of the combined treatment. It becomes clear, that the majority of patients (74-87%) treated with short-term preoperative radiotherapy for resectable rectal cancer has neither benefit (in terms of reduction of local recurrence) nor additional harm of this therapeutic intervention. The percentage of patients truly benefiting (group 1 and 2) is relatively small (5-14%) and sometimes (group 2) at the expense of serious complications (0-2%), while some of the patients that do not benefit (group 4) nonetheless experience complications (6-11%). Therefore, we should look for subsets of patients with relatively low benefit and relatively much additional harm, in whom we might omit short-term preoperative radiotherapy.

This is especially important in the light of the tendency to even increase the intensity of preoperative treatment of rectal cancer by adding chemotherapy.[26-27] This increased intensity will at best provide a very low gain since the local recurrence rate among patients treated with radiotherapy in the Dutch TME trial was as low as 5.8%.[6] Nonetheless, it will lead to additional morbidity due to the chemotherapy with a subsequent, undesirable shift of patients from group 3 (no benefit, no additional harm) to group 4 (no benefit, but with additional harm).

The use of source data as well as more extensive and detailed information concerning the incidence of major short-term complications and the impact on long-term functional outcome are required to make an appropriate and rational balance between harms and benefits of short-term preoperative radiotherapy. Authors of future randomised trials should be requested to report their data in more detail or to report their data according to this model.

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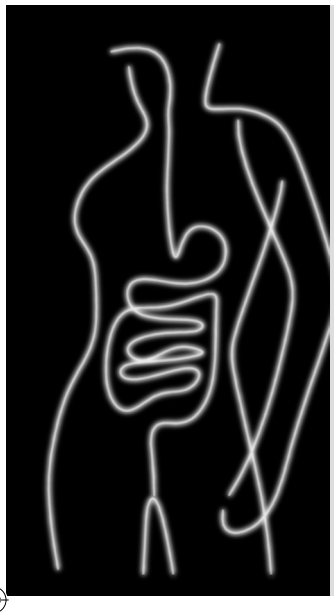

CHAPTER 3

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Categorisation of major and minor complications in the treatment of patients with resectable rectal cancer using short-term preoperative radiotherapy and total mesorectal excision; A Delphi round

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Abstract

Objectives. To properly balance the benefit (reduction of local recurrence) of short-term preoperative radiotherapy for resectable rectal cancer against its harm (complications), a consensus concerning the severity of complications is required.

Aim. To reach consensus regarding major and minor complications after short-term radiotherapy followed by total mesorectal excision in the treatment of rectal carcinoma, using the Delphi technique.

Methods. A Delphi round was performed in cooperation with 21 colo-rectal surgeons from the Netherlands, United Kingdom and Sweden. The key-question was: "Which of the predefined complications, caused or substantially aggravated by radiotherapy, are so important (major) that they might lead to the decision to abandon short-term preoperative radiotherapy (5x5Gy) when treating patients with resectable rectal cancer ($T_{1-3}N_{0-2}M_0$)?"

Results. After three rounds, consensus was reached for 37 of the 54 complications (68%) of which 13 were considered major and 24 considered minor. The following complications were considered to be major: mortality, anastomotic leakage managed by relaparotomy, anastomotic leakage resulting in persisting fistula, postoperative hemorrhage managed by relaparotomy, intra-abdominal abscess without healing tendency, sepsis, pulmonary embolism, myocardial infarction, compartment syndrome of the lower legs, long-term incontinence for solid stool, long-term problems with voiding, pelvic fracture with persisting pain, and neuropathy with persisting pain (legs). Three of 17 complications without consensus showed a tendency to be considered as major: perineal wound dehiscence managed by surgical treatment, small bowel obstruction leading to relaparotomy, long-term incontinence for liquid stool.

Conclusions. The 13 major and three 'accepted as major' complications can be used to properly balance the benefit and harm of short-term preoperative radiotherapy in resectable rectal cancer. This may eventually lead to improved treatment strategies for these patients.

Introduction

Short-term preoperative radiotherapy followed by total mesorectal excision (TME) is considered standard treatment for patients with resectable rectal cancer in a large part of western Europe. Reduction of local recurrences is the main benefit of this treatment, while so far it has not shown to improve survival.[1]

On the other hand, preoperative radiotherapy has some disadvantages. There is an increase in postoperative morbidity and it has, in combination with TME, a negative influence on functional outcome.[2] Many reports on short-term preoperative radiotherapy address these negative effects, but there is a lack of consensus about the severity of these side effects.[3-4] It is self-evident that a superficial wound infection is of less importance after rectal resection for cancer than for instance long-term disabling incontinence. However, to properly balance the benefits and harms of short-term preoperative radiotherapy a clear classification is required what to consider major morbidity and, to a lesser extent, minor morbidity among these patients.[5] Because such classification is not available, an honest and fair judgement is impossible, which indicates the need for a consensus concerning this matter.

To reach consensus, a panel of experts should reach agreement. There are several ways to interview multiple experts and to gather their opinions.[6] As of today, the Delphi round is often used because it is a solid way to gather the desired information.[7-10] It is a structured process that uses series of questionnaires to gather information and is relatively easy to organise. Experts are requested to give their opinion by regular mail or email. The questionnaire rounds are repeated until a group consensus is reached.

The aim of this study was to reach consensus regarding major and minor complications after short-term radiotherapy followed by total mesorectal excision in the treatment of resectable rectal cancer, using the Delphi technique.

Materials and Methods

The Delphi technique

The Delphi technique is named after the ancient Oracle at Delphi and has been established by the RAND Corporation in the 1950's. It is a structured process consisting of several rounds of interviews using questionnaires, in an attempt to reach 'group' consensus.[7-10] Anonymity is used to provide an equal chance for each of the participants to present and react to ideas unbiased by the identities of the other group members.[11-12] Reactions are given independently, so each opinion carries the same weight and is given equal importance in the analysis.[13]

The experts

Twenty-eight colo-rectal surgeons from the Netherlands (18), Belgium (3), United Kingdom (4) and Sweden (3) were invited to participate in this Delphi round of whom 21 agreed

on participation. This selection included surgeons working in university (10), training (6) and non-training (5) hospitals as well as junior and senior colo-rectal surgeons. The remaining seven did not participate because they do not use short-term preoperative radiotherapy (Belgian surgeons) or replied to be unable to participate.

The complications

A questionnaire with 49 complications (Table 1, 2 & 3, first column) was compiled based upon reported complications from the literature.[3-4,14-16] The degree of severity was taken into account for several complications, based on the management or the possible outcome of the complication (Table 1, 2 & 3, second column). The complications were also categorised into acute complications (*i.e.* occurring early postoperatively) and late complications (*i.e.* occurring during follow-up). The acute complications were divided into treatment related complications (*i.e.* anastomotic leakage, perineal wound infection, etc.) and general surgery-related complications (*i.e.* mortality, pneumonia, urinary tract infection, etc.). The late complications were divided into complications related to defecation, voiding, and sexual functioning. After the first round, five additional complications were included based on comments made by the participants. (Table 1 & 2, complications in **bold**)

Key-question

The key-question used in this questionnaire was: "Which of the following complications, caused or substantially aggravated by radiotherapy, are so important (major) that they might lead to the decision to abandon short-term preoperative radiotherapy (5x5Gy) when treating patients with resectable rectal cancer ($T_{1-3}N_{0-2}M_0$)?"

Table 1. Major complications

Complication/ symptom	Managed by or leading to	Round
Treatment related acute complications		
Anastomotic leakage	(relaparotomy with ileo- or colostomy and drainage)	III
Anastomotic leakage	(resulting in fistula)	III
Postoperative hemorrhage	(relaparotomy)	III
Intra-abdominal abscess	**(without healing tendency)**	III
General surgery-related acute complications		
Mortality		I
Sepsis/ multiple organ failure		I
Pulmonary embolism		II
Myocardial infarction		III
Compartment syndrome lower legs		III
Late complications		
Long-term incontinence for solid stool		II
Long-term problems with voiding	(self catheterisation)	III
Pelvic fracture	**(persisting pain)**	II
Neuropathy (legs)	**(persisting pain with muscle weakness)**	III

Round = round during which consensus was reached for the specific complication;
complications in bold are the additional complications mentioned by participants during the first round

Table 2. Minor complications

Complication/ symptom	Managed by or leading to	Round
Treatment related acute complications		
Deep pelvic pain due to RTX	(analgesics required)	III
Deep pelvic pain due to RTX	(adjustment of radiotherapy required)	III
Perineal wound dehiscence/ abscess	(non-surgical treatment, < 6 weeks)	II
Complication of colostomy after APR	(non-surgical treatment)	I
Intra-abdominal abscess	(percutaneous drainage)	II
Postoperative hemorrhage	(non-surgical treatment)	I
Small bowel obstruction	(non-surgical treatment)	I
Complication of protective ostomy	(non-surgical treatment)	II
Wound infection (abdominal)	(non-surgical treatment)	I
Wound infection (abdominal)	(surgical treatment)	III
Delay rectal resection due to preoperative radiotherapy		II
Increase in rectal cancer treatment costs		II
General surgery-related acute complications		
Pneumonia		II
Deep venous thrombosis		III
Intra-venous catheter sepsis		II
Urinary tract infection		I
Bladder retention		I
Late complications, related to defecation		
Use of pads		II
Long-term soiling at night		III
Long-term incontinence for flatus		I
Use of medication for thickening the stool		I
Late complications, related to sexual functioning		
Erectile dysfunction	(less erections)	III
Retrograde ejaculation		II
Decreased lubrication (in female)		II

Round = round during which consensus was reached for the specific complication; complications in bold are the additional complications mentioned by participants during the first round, RTX = radiotherapy, APR = Abdomino Perineal Resection

The procedure

The questionnaire with accompanying letter was mailed to an international group of 28 colo-rectal surgeons with a request to complete and return the questionnaire. Comments on statements or complications could be written down at the end of the questionnaire. After receiving the completed first round questionnaires, all answers were analysed and an abstract with complications for which consensus was reached, was written.

The remaining complications together with five additional complications (based on the additional comments of the experts) formed the second round questionnaire. On this questionnaire the level of agreement per question for the entire group was shown as well as the first round answers given by the individual participant, offering the opportunity to compare their answer with the group's opinion and to change their opinion if wanted. This second questionnaire together with the abstract was sent to the participants by

email and all participants were asked to complete the entire questionnaire, even if they did not want to adjust their previous answers.
The same procedure was performed after the second round. In the third round questionnaire, one additional question was added to evaluate what the experts considered the benefit of short-term preoperative radiotherapy.

Statistics

All data were analysed using SPSS Statistical Software (SPSS Inc., Chicago, IL, USA). After every round, the level of agreement was evaluated based on the percentage of similar answers to each question. The required level of agreement (in order to classify a specific complication as "major" or "minor") was set to >95% in the first round, >90% in the second round and >85% in the third and last round. Complications with level of agreement between 75% and 85% in favour of "major" after three rounds were analyzed separately. Based on their tendency to be classified as "major", these complications are accepted as "major" complication.

Results

Consensus

Consensus, based on the preclassified criteria, was reached for 37 of the 54 (68%) tested complications. Thirteen complications (24%) were considered to be major (Table 1), 24 complications (44%) were considered to be minor (Table 2) and for 17 complications (32%) consensus was not be reached within three rounds (Table 3). The complications "perineal wound dehiscence leading to surgical treatment", "small bowel obstruction leading to relaparotomy" and "long-term incontinence for liquid stool" tended to be considered as major complication.

Benefit of preoperative radiotherapy according to the participants

All participants mentioned reduction in local recurrence as the main benefit of preoperative radiotherapy and referred to the results of the Dutch TME trial as basis for their opinion.[1] Improved survival was never mentioned as the primary benefit of preoperative radiotherapy.

Discussion

To properly weigh the benefits and harms of short-term preoperative radiotherapy in the treatment of resectable rectal cancer, it is necessary to know the value of its benefit and the severity of its harm. In this study, an attempt has been made to quantify the harm of complications during a Delphi round in cooperation with several experts in this field.

Table 3. Complications without consensus according to preclassified criteria

Complication/ symptom	Managed by or leading to	% agreement in favour of major (round I/II/III)
Treatment related complications		
Deep pelvic pain due to RTX	(interruption of radiotherapy required)	47/42/50
Perineal wound dehiscence/ abscess	(non-surgical treatment >6 weeks)	52/55/47
Perineal wound dehiscence/ abscess	**(surgical treatment)**	**59/79/75**
Complication of colostomy after APR	(surgical treatment)	37/47/56
Intra-abdominal abscess	(relaparotomy)	52/65/65
Small bowel obstruction	**(relaparotomy)**	**62/75/77**
Complications of protective ostomy	(surgical treatment)	45/44/47
Late complications, related to defecation		
Defecation frequency	(> 5 times per day)	52/65/65
Nocturnal defecation	(> once per night)	43/40/39
Tenesmus		44/42/39
Urge	(inability to postpone defecation > 15 minutes)	48/55/41
Inability to discriminate between flatus and stool		29/30/23
Soiling during the day		24/20/29
Long-term incontinence for liquid stool		62/75/77
Late complications, related to sexual functioning		
Erectile dysfunction	(impotence erigendi)	55/55/41
Erectile dysfunction	(impotence ejaculandi)	52/45/24
Pain during sexual intercourse (female)		60/60/53

complications in bold tend to be considered as major complications, RTX = radiotherapy, APR = Abdomino Perineal Resection

Consensus was reached for 37 of the 54 complications (68%) based on the preclassified criteria of which 13 were considered to be major. Three complications tended to be considered as major as well, although they did not fulfil the strictly defined criteria. These 13 'major' complications and the three 'accepted as major' complications should be taken into account when balancing the benefits and harms of short-term preoperative radiotherapy. According to the experts, these 16 complications might lead to the decision to abandon short-term preoperative radiotherapy in the treatment of patients with resectable rectal cancer if these complications would occur significantly more often after preoperative radiotherapy followed by TME compared to TME alone. Alternatively, this information might be helpful to define specific subgroups of patients who will or will not benefit from preoperative radiotherapy.

Recently, we adapted and proposed a model to weigh the harms and benefits of experimental treatments investigated by means of randomised clinical trials.[5] This model uses the absolute risk increase (ARI) and absolute risk reduction (ARR) to provide a more transparent understanding of the value of an additional treatment. In case of short-term preoperative radiotherapy for resectable rectal cancer, the harm relates to the difference in complications observed between the group of patients treated with radiotherapy and surgery versus the group of patients treated by surgery alone. The benefit relates to the

difference in local recurrences between these groups. The model classifies patients in one of five outcome combinations: 1 patients who benefit (reduction of local recurrence) without harm (no additional complications), 2 patients who benefit with harm, 3 patients who do not benefit without harm, 4 patients who do not benefit with harm, 5 patients who die due to the additional therapy. In this classification the severity of complications play a significant role and we argued that at least major complications should be incorporated in the analysis. Incorporation of the 16 major complications in this model leads to a more balanced insight into the harms and benefits of radiotherapy and might lead to better patient selection for neo-adjuvant radiotherapy.[5] Therefore major complications should be quantified when reporting the results of randomised clinical trials. So far most publications in this field reported all complications regardless of their severity and did not explicitly divide them into major and minor.[3-4, 14-16]

The benefit of short-term preoperative radiotherapy is a reduction of the risk of a local recurrence, which was also affirmed by the participating experts. The true value of this benefit is the avoidance of the devastating effect of a local recurrence.[17] In our opinion, the key-question in the debate concerning preoperative radiotherapy is: what is acceptable in terms of major complications when aiming for this benefit? To a certain extent patients and doctors will accept major complications if a local recurrence is avoided. However, will major complications also be acceptable if there is no benefit for the majority of treated patients? And is a local recurrence as devastating as generally depicted? There is hardly any evidence in the literature concerning the severity of a local recurrence.[17-21] Moreover, not only treatment of rectal cancer has improved but also treatment of local recurrence[22-25] including pain management[26] and even euthanasia[27], offer patients a more dignified last period of their life in case of a recurrence. There is definitely a turning-point on which the harms outweigh the benefits, but we lack empirical information about the way patients value postoperative complications when informed of the minimal effects of preoperative radiotherapy.

There are two remarks concerning this Delphi round which have to be made.

First, clinical practice should preferably be based on Evidence-Based Practice (EBP), but there are circumstances where it does not provide answers. Consensus methods like Delphi round or Nominal Group Technique are valid constructs which have been supported through exercises in the fields of social science.[28] Therefore, they are suitable methods to reach consensus in the absence of EBP. These methods are also reliable if they fulfil two requirements: individuals make independent judgements and individual judgements are expressed through mathematical rating of items.[28] The Delphi round performed is in our opinion the appropriate method to reach consensus and fulfils all mentioned requirements.

Second, as a Delphi round is conducted with experts, the question is raised whether other experts would identify the same issues.[29] Therefore, definition of experts is the most potentially confounding effect on Delphi outcome.[28] In this study, only colorectal surgeons were invited to participate, because they treat the majority of complications. Selection of other experts might change the outcome of the categorisation into major

and minor complications. Therefore, the established consensus is not synonymous with invariably correct[28] and cautious interpretation of the results is required.

Conclusions

In the present paper, a classification of complications into two categories, major and minor, was obtained through a Delphi round. In future studies, it can be a valuable tool to more accurately describe the benefit or harm of short-term preoperative radiotherapy in the treatment of resectable rectal cancer. Presentation of results using the harm versus benefit model in combination with the major complications would facilitate the decision making and might lead to better patients selection for short-term preoperative radiotherapy.

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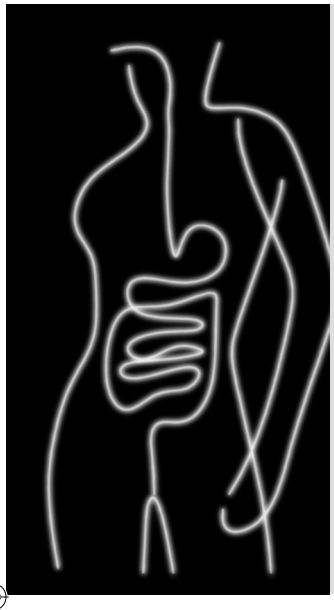

CHAPTER 4

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Development and validation of a COloREctal Functional Outcome questionnaire

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Abstract

Background and Objectives. After colorectal surgery patients often experience impaired functional outcome. Faecal incontinence grading systems and self-assessment questionnaires are frequently used to assess these complaints. The available faecal incontinence grading systems have been validated, but have a limited focus, while more comprehensive questionnaires, which have been developed have not been validated.
Aim. To investigate the reliability and validity of a newly developed, COloREctal Functional Outcome (COREFO) questionnaire and of Dutch translations of the Hallböök questionnaire and an adapted version of the Vaizey questionnaire.
Methods. Two hundred and fifty seven patients with and without impaired functional outcome after (colorectal) surgery received a booklet containing the 3 questionnaires in random order by mail. One hundred seventy nine (70%) completed them, and 160 patients (90%) completed a retest within on average 18 days.
Results. Reliability and validity were adequate for the COREFO and Hallböök questionnaire, with slight differences in the psychometric analyses in favour of the COREFO questionnaire. Significantly more patients found the COREFO questionnaire to reflect their problems best. The reliability of the Vaizey questionnaire was not sufficient.
Conclusions. The newly developed COREFO questionnaire and the previously unvalidated Hallböök questionnaire are both suitable instruments to evaluate functional outcome after colorectal surgery. The psychometric analyses showed a slight difference in favour of the COREFO questionnaire and significantly more patients preferred the COREFO questionnaire to the other questionnaires. Therefore, we prefer to use the COREFO questionnaire in future research.

Introduction

After colorectal surgery, for example rectal resection or proctocolectomy, patients often experience impaired functional outcome.[1-3] This is reflected by increased bowel movements, urgency, incomplete evacuation, soiling or incontinence for flatus or stool and can have substantial impact on the people's lives, causing embarrassment and shame.[4]
Faecal incontinence grading systems have become widely used tools to assess the degree of complaints. Some have been validated and are used regularly for research purposes.[5-8] One of the latest, and perhaps the best, faecal incontinence grading system has been published by Vaizey et al. [8] However, faecal incontinence grading systems have some disadvantages. They contain only a limited number of questions (varying from 5 to 7 questions) focussing mainly on incontinence. Other important issues related to impaired functional outcome are lacking (e.g. number of bowel movements, difference in complaints between day and night, impact on social and sexual activities). Second, if they are based on patients' answers to questions from an interviewer, there is a reasonable chance of getting socially desirable or biased answers, due to the embarrassing nature of the problem.
Therefore, we prefer self-assessment questionnaires to evaluate the degree of complaints. The questionnaires are completed independently by the patients in private, in an attempt to avoid socially desirable answers. Several self-assessment questionnaires measure impaired functional outcome after colorectal surgery.[9-12] They consist of larger numbers of questions (varying from 13 to 28 questions) covering many relevant aspects of impaired functional outcome. Despite the frequent use of these questionnaires for research purposes, none have been validated.

Of the available questionnaires, the Hallböök questionnaire [9] is probably the best available questionnaire, because it is comprehensive and contains most of the relevant items. However, it still lacks relevant items (e.g. it does not distinguish between day and night, it does not cover the adjustment of activities to the availability of a toilet). Therefore, we chose not just to validate the already existing Hallböök questionnaire, but also to newly develop the COloREctal Functional Outcome questionnaire (COREFO).
The Vaizey scale is in our opinion the most properly validated, faecal incontinence grading system and has gained wide acceptance. The original Vaizey scale was transformed into a self-assessment questionnaire, thus providing the opportunity for patients to complete it by themselves.
The purpose of the present paper is to investigate the reliability and validity [13] of the newly developed COREFO questionnaire and of Dutch translations of the Hallböök questionnaire [9] and a transformed Vaizey Scale [8] in patients with and without impaired functional outcome after surgery.

Materials and methods

Patients

Four groups of patients were selected; patients with an ileo-anal anastomosis, with a colo-anal anastomosis, patients after a right-sided hemicolectomy and after a laparoscopic cholecystectomy. Patients with an ileo-anal or colo-anal anastomosis form a group of patients with impaired functional outcome and are referred to as patients with complaints. Patients after right-sided hemicolectomy or after laparoscopic cholecystectomy form a group of patients with minimally or without impaired functional outcome, and are referred to as patients without complaints.

Patients with an ileo-anal anastomosis

These patients all had ulcerative colitis or familiar adenomatosis polyposis coli and underwent proctocolectomy after failure of medical treatment. Functional outcome is impaired due to the removal of the entire colon and rectum.

Patients with a colo-anal anastomosis

They underwent rectal resection, all of them due to cancer. The impaired functional outcome is caused by the loss of the native rectal function. However, the functional outcome is expected to be less impaired than in patients with an ileo-anal anastomosis.

Patients after right-sided hemicolectomy

The functional outcome in these patients is expected to be only minimally impaired, if impaired at all, since at least half of the colon and the entire rectum are left in situ. They were mainly operated on because of malignant disease and were expected to have roughly the same age as patients with a colo-anal anastomosis.

Patients after laparoscopic cholecystectomy

These patients had been operated on because of benign disease. They are not expected to have impaired functional outcome and are expected to have roughly the same age as patients with an ileo-anal anastomosis.

Measurement instruments

The COREFO questionnaire

The COREFO questionnaire was developed based on information from published articles [8-12,14-15], input from four colorectal surgeons, and input from patients experiencing impaired functional outcome. Ten patients were interviewed during a visit to our out-patient clinic and asked to indicate all stool-related complaints.

This information resulted in a questionnaire (appendix) with 27 questions. The questions concern a two week period. All questions can be answered by choosing from 5 response options; *No, never, Yes, less than once a week, Yes, 1-2 days per week Yes, 3-5 days per week & Yes, 6-7 days per week.*

Hallböök questionnaire [9]

Permission was granted from the author to use the questionnaire in a comparative study. The questionnaire (appendix) was literally translated into Dutch and the lay-out was similar to the English version. The response options (with wide range of response options, depending on the type of question) were also identical to those in the English version. All questions concern a two-week period

Faecal Incontinence Scale of Vaizey [8]

Permission was granted from the author to use the faecal incontinence scale in a comparative study. Originally, the faecal incontinence scale (Vaizey scale) is not a self-assessment questionnaire. It is based on answers given by a patient during an office visit. Vaizey and colleagues have also used diary cards (filled in by patients at home) to evaluate the validity of their faecal incontinence grading system.

We transformed the Vaizey scale into a self-assessment questionnaire, referred to as Vaizey questionnaire. The questions on the diary cards were literally translated into Dutch, and constitute, with one additional question, the Vaizey questionnaire. This additional question is needed to cover the same aspects as are involved in the Vaizey scale. (question 6, appendix)

The response options used for the Vaizey questionnaire were kept similar to the options used for the original faecal incontinence scale; *Never; Rarely; Sometimes; Weekly; Daily.* The questions concern a four week period.

Pilot-testing

The COREFO questionnaire, and the Dutch versions of the Hallböök questionnaire and Vaizey questionnaire were pilot-tested among 12 healthy volunteers to check grammar, orthography and indistinctness.[16] This led to minimal changes (mainly orthographic) to all three questionnaires, resulting in a better understanding of the questionnaires.

Procedure

The period between operation and distribution of the questionnaires had to be at least 6 months, to guarantee a stable situation after surgery as needed for the test-retest analysis.

A booklet containing the three questionnaires in random order, and a debriefing form was sent to all patients by mail. In the cover letter (signed on behalf of their treating surgeon), the aim of the study was explained and the patients were requested to complete and return the questionnaires, using an enclosed (stamped) envelope. The questionnaires were entitled A, B and C as not to disclose their origin. On the debriefing form, patients were asked to state which questionnaire reflected their complaints best and to state any comment or remark concerning the questionnaires.

If the questionnaires were not returned within 4 weeks, a set of questionnaires with a cover letter was sent again. If patients did not respond after the second letter, they were contacted by telephone to encourage them to complete the questionnaires.

Upon receiving the completed questionnaires, one questionnaire (the first of the original set) was sent as a retest, as was already announced in the first invitation letter. Patients were requested to complete and return this questionnaire. If the retest was not returned within two weeks, a reminder was sent to the patient followed by a phone call if necessary.

Statistical Analyses

Descriptive statistics were used to describe patient characteristics, to compare numbers of missing values across questionnaires and to compare patients' preferences for questionnaires. We investigated (1) the scale structure, (2) the reliability of scale scores and (3) the validity of scale scores. All analyses described below were carried out multiple times: for the entire group of patients, separately for groups of patients with and without complaints and separately for groups of patients with different complaints.

1. Scale structure

The analysis of the internal structure of a questionnaire is aimed at composing scales of multiple items that measure the same attribute. To establish these multi-item scales, principal components analysis was used on each of the questionnaires resulting in several scales per questionnaire. Next to that, a total score for each questionnaire was calculated consisting of all questions in the questionnaire

2. Reliability of scale scores

The reliability of the scale scores concerns the question whether the scales of the questionnaires yield consistent and reproducible results. The reliability of the scale scores was assessed in two ways: internal reliability and test-retest reliability.

Internal reliability. Internal reliability (or consistency, or homogeneity) means that all items of a multi-item scale should measure the same attribute. Internal reliability was expressed by Cronbach's alpha coefficient[17], which was calculated for the entire group and for patients with and without complaints. Cronbach's alphas above 0.70 are generally considered sufficient.[18]

Test-retest reliability. Test-retest reliability concerns the stability of the questionnaires, which should yield consistent scores if used repeatedly on the same patient, while the patient's condition has not changed. Test-retest reliability was investigated by calculating intraclass correlation coefficients between the repeated measurements over time and values above .70 are generally accepted to be adequate.[13]

3. Validity of scale scores

The validity of scales concerns the question whether the scales measure the attribute that they are supposed to measure. Two types of validity were evaluated: construct validity and criterion validity.

Construct validity. Construct validity was evaluated by calculating the correlations between all scales of all questionnaires. These correlations indicate whether scales with

the same attribute truly measure the same content. Correlations between scales from different questionnaires measuring the same attribute ("convergent validity") should be higher than correlations between scales measuring different attributes ("discriminant validity"), even if the latter scales come from the same questionnaire. This method of investigating construct validity is often called multitrait-multimethod analysis, which assesses convergent validity and discriminant validity. Construct validity was considered sufficient if convergent validity exceeded discriminant validity.

Criterion validity. Criterion validity concerns the question whether the measurement instrument discriminates between groups of respondents that are known to differ with respect to the attributes that are measured [19]. Here we compared scale scores of groups of patients with different degrees of impaired functional outcome. Analysis of variance (ANOVA) was used to test statistical significance of group differences (at 1 percent level of significance) and standardised mean differences were calculated to evaluate the size of the group differences. Effect sizes of 0.20, 0.50 and 0.80 are considered small, medium and large, respectively and give an impression of the discriminatory properties of the different scales and questionnaires. [20]

Results

Descriptives

Patient and questionnaire collection characteristics

Two hundred and fifty seven patients received the questionnaires, of whom 179 (70%) completed and returned them; 47 patients with an ileo-anal anastomosis, 49 patients with a colo-anal anastomosis, 37 patients after right-sided hemicolectomy, and 46 patients after laparoscopic cholecystectomy.

The median age for the entire group was 54 years (range 22-95), for the group with an ileo-anal anastomosis 41 years (25-68), with a colo-anal anastomosis 66 years (32-94), after right-sided hemicolectomy 65 years (22-95), and after laparoscopic cholecystectomy 48 years (28-81).

One hundred and sixty (90%) patients completed the retest with a median time between test and retest of 18 days (range 4-88 days). The COREFO questionnaire was completed as retest by 58 (36%) patients, the Hallböök and Vaizey questionnaire by 51 (32%) patients each.

Missing values analysis

There was a median of 1 (range 0-3) missing value per question (total 27 questions) in the initial COREFO questionnaire for the entire group (n=179). In the COREFO retest questionnaires (n=58) there was a median of 0 (range 0-1) missing values per question.

In the initial Hallböök questionnaires (n=179) a median of 3 (range1-18) missing values per question (total 31 questions) was found, primarily with questions that relate to the frequency of defecation. There was no clear reason for the missing values, based on the

debriefing form, as only five patients (3%) indicated these questions to be difficult. Only few missing values (median 1, range 0-4) were seen in the Hallböök retest questionnaires (n=51).
There were considerably more missing values in the Vaizey questionnaire (n=179): 0-26 (median 7.5) missing values per question. Twenty seven patients (15%) found the first two questions confusing, and eleven patients (6%) found these questions difficult. These patients indicated problems with understanding the structure of the questionnaire.
In the Vaizey retest questionnaires (n=51) there was a median of 5 (range 0-15) missing values per question.

Patients' preference for a questionnaire

Significantly more patients with complaints (n=96) found the COREFO questionnaire to reflect their problems best; 45 patients (46%) preferred COREFO, 23 patients (24%) preferred Hallböök, 8 patients (8%) preferred Vaizey, while 20 patients (20.3%) had no preference (chi-square test, p=.008, COREFO vs Hallböök).
When evaluating the four groups of patients combined, (i.e. patients with and without complaints), the COREFO questionnaire was also preferred over the other two questionnaires. (data not shown) The preference of the patients was not influenced by the order in which the questionnaires were completed.

Scale structure

Principal components analyses, as well as substantive considerations, suggested five multi-item scales for the COREFO questionnaire: Incontinence (9 questions), Social impact (9 questions), Frequency (2 questions), Stool related aspects (3 questions) and Need for medication (3 questions). (appendix) Question 19 (Have you used medicines to make your stools thinner?) was excluded from analysis because patients with impaired functional outcome mainly suffer from incontinence, not from obstipation.
Principal components analyses suggested four multi-items scales for the Hallböök questionnaire: Incontinence (8 questions), Social impact (10 questions), Frequency (8 questions) and Abdominal pain (4 questions). (appendix) Questions 3 and 4 of the Hallböök questionnaire requested patients to mention any use of medication. Obviously, these questions are not independent, since patients completed either question 3 or question 4. Therefore, they were combined after careful examination for duplicate answers.
For the Vaizey questionnaire, two multi-items scales, Incontinence (3 questions) and Social impact (4 questions), were suggested by principal components analysis. (appendix)
However, the total score is considered as one scale for incontinence in subsequent analyses, because it was originally designed as an incontinence score. Nonetheless, the results for the Vaizey score are presented to give an impression of the Vaizey questionnaire.

Table 1. Internal Reliability (Cronbach's alpha) and Test-retest Reliability (Intraclass Correlation Coefficient) of the questionnaires.

Scales	No. of Items	Entire group	without complaints	with complaints	Test-Retest
		α (95%CI)*	α (95%CI)*	α (95%CI)*	ICC(95%CI)*
COREFO-Score					
Patients per group		179	83	96	58
Incontinence	9	.81 (.77-.85)	.54 (.36-.67)	.83 (.77-.88)	.86 (.78-.92)
Social impact	9	.84 (.81-.88)	.74 (.64-.81)	.84 (.79-.89)	.94 (.91-.97)
Frequency	2	.76 (.68-.82)	.18 (-.28-.47)	.73 (.60-.83)	.93 (.89-.96)
Stool related aspects	3	.54 (.41-.65)	.55 (.35-.70)	.49 (.27-.64)	.79 (.66-.87)
Need for medication	3	.61 (.50-.70)	.67 (.52-.78)	.54 (.36-.68)	.86 (.78-.92)
Total score	26	.90 (.87-.92)	.79 (.71-.85)	.88 (.84-.91)	.93 (.87-.96)
Hallböök					
Patients per group		179	83	96	51
Incontinence	8	.77 (.71-.82)	.56 (.40-.70)	.78 (.71-.85)	.87 (.78-.92)
Social impact	10	.73 (.67-.79)	.69 (.58-.79)	.74 (.65-.81)	.91 (.84-.95)
Frequency	8	.52 (.39-.63)	.23 (-.09-.49)	.41 (.20-.58)	.42 (.07-.66)
Abdominal pain	4	.81 (.76-.85)	.79 (.67-.84)	.83 (.76-.88)	.79 (.66-.87)
Total score	30	.85 (.82-.89)	.74 (.64-.82)	.86 (.80-.89)	.83 (.71-.90)
Vaizey					
Patients per group		179	83	96	50
(Incontinence)	3	.54 (.39-.65)	.36 (.05-.58)	.57 (.39-.71)	.46 (.18-.67)
(Social impact)	4	.16 (-.07-.35)	-.14 (-.63-.22)	.16 (-.16-.41)	.66 (.46-.80)
Total score	7	.60 (.49-.69)	.46 (.23-.64)	.59 (.44-.71)	.67 (.44-.81)

No. of items = number of questions per scale; without complaints = group of patients after right-sided hemicolectomy or laparoscopic cholecystectomy; With complaints = group of patients with colo-anal or ileo-anal anastomosis; α = Cronbach's alpha; * 95%CI = 95% confidence interval; ICC = Intraclass Correlation Coefficient.

Reliability of scales score

Internal reliability

In the group of patients with complaints, three of five COREFO questionnaire scales, and the total score exceeded the .70 criterion for internal reliability, indicating that the items forming these scales all measure the same attribute on an adequate manner. (Table 1) In the group of patients without complaints, one scale and the total score met the desired score. This indicates that the questionnaire is less suitable to be used in people without complaints, which is not remarkable since it was not designed for this population.

Three of the five scales of the Hallböök questionnaire and the total score met the .70 criterion in the group of patients with complaints. The frequency scale did not exceed the .70 criterion, indicating that the questions forming this scale not all measure the aspects of frequency. In the groups of patients without complaints, two scales and the total score met this criterion. As is true for the COREFO questionnaire, the Hallböök questionnaire is less suitable to be used in patients without complaints.

The Vaizey scales and the Vaizey total score did not meet the .70 criterion, indicating that the items forming these scales do not measure the same attribute on an adequate

manner. This makes it less suitable to evaluate functional outcome after colorectal surgery.

Test-retest reliability

Test-retest reliability for all scales of the COREFO and of the Hallböök questionnaire exceeded .70, except for the frequency scale of the Hallböök questionnaire. (Table 1) This indicates that all but one scale of these questionnaires are able to yield consistent results on different occasions when conditions remain stable. The intraclass correlation for the Vaizey questionnaire did not reach .70. This questionnaire is thus unable to yield consistent results when used repeatedly.

Validity of the scale scores

Construct validity

The results of the multitrait-multimethod analysis for patients with complaints are shown in Table 2a (correlations within the same questionnaire) and Table 2b (correlations between the different questionnaires). The results for the other groups (entire group,

Table 2a. Discriminant validity within the same questionnaire of patients with impaired functional outcome.

		COREFO					
	Scale	Incontinence	Social impact	Frequency	Stool related aspects	Medication	Total
COREFO	Incontinence	1.000					
	Social impact	.507	1.000				
	Frequency	.234	.205	1.000			
	Stool related aspects	.218	.397	.370	1.000		
	Medication	.264	.305	.440	.319	1.000	
	Total	.797	.848	.442	.531	.567	1.000
		Hallböök					
	Scale	Incontinence	Social impact	Frequency	Abdominal pain	Total	
Hallböök	Incontinence	1.000					
	Social impact	.469	1.000				
	Frequency	.404	.376	1.000			
	Abdominal pain	.155	.284	.193	1.000		
	Total	.836	.785	.614	.785	1.000	
		Vaizey					
	Scale	Incontinence	Social impact	Total			
Vaizey	(Incontinence)	1.000					
	(Social impact)	.428	1.000				
	Total score	.840	.850	1.000			

COREFO = COREFO questionnaire; Hallböök = Hallböök questionnaire; Vaizey = Vaizey questionnaire; Total score = Total score of individual questionnaire; correlations = discriminant validity within one questionnaire

Table 2b. Scale convergent and discriminant validity between questionnaires of patients with impaired functional outcome.

		COREFO					
	Scale	Incontinence	Social impact	Frequency	Stool related aspects	Medication	Total
Hallböök	Incontinence	**.839**	.560	.228	.194	.216	.737
	Social impact	.436	**.805**	.087	.294	.245	.684
	Frequency	.340	.530	**.526**	.390	.252	.563
	Abdominal pain	.134	.246	.038	.247	-.062	.202
	Total score	.731	.773	.275	.359	.241	**.824**
		COREFO					
	Scale	Incontinence	Social impact	Frequency	Stool related aspects	Medication	Total
Vaizey	(Incontinence)	.640	.405	.135	.194	.152	.551
	(Social impact)	.507	.515	.379	.270	.375	.625
	Total score	**.741**	.569	.291	.383	.363	**.759**
		Hallböök					
	Scale	Incontinence	Social impact	Frequency	Abdominal pain	Total	
Vaizey	(Incontinence)	.620	.448	.284	.293	.636	
	(Social impact)	.571	.425	.337	.081	.553	
	Total score	**.735**	.513	.372	.196	**.708**	

COREFO = COREFO questionnaire; Hallböök = Hallböök questionnaire; Vaizey = Vaizey questionnaire; Total score = Total score of individual questionnaire; bold correlations = convergent validity, other correlations = discriminant validity.

patients with ileo-anal anastomosis, with colo-anal anastomosis, after hemicolectomy or cholecystectomy) are highly comparable, with only minimal differences compared to reported data in Table 2 a&b. (data not shown)

The COREFO and Hallböök questionnaire have 3 scales with similar content: Incontinence, Social impact and Frequency. The convergent validity correlations of the 'incontinence' and 'social impact' scales are higher than the discriminant validity correlations. This indicates that these scales measure the same content (i.e. incontinence and social impact)

The Hallböök 'frequency' scale does not discriminate between the scales 'frequency' and 'social impact' of the COREFO, as expressed by similar correlations. (.530 and .526) This might indicate that the Hallböök frequency scale measures not only the frequency but also aspects of social impact. However, since the Vaizey questionnaire does not have a frequency scale and thus comparison with a third scale is impossible, the actually measured attribute of the Hallböök frequency scale remains uncertain.

The 'total scale' of the Vaizey questionnaire and the 'incontinence' scales of COREFO and Hallböök questionnaire have similar contents. The convergent validity correlations between these scales are higher than the discriminant validity correlations for these questionnaires and therefore these 'incontinence' scales all three truly measure incontinence.

Table 3. Known-groups comparison of the three questionnaires.

		without complaints			with complaints				
	Scales	No.	Mean	SD	No.	Mean	SD	ES	(p)
COREFO	Incontinence	83	5.6	7.5	96	17.9	18.7	0.78	(<.001)
	Social impact	83	9.2	11.0	96	22.7	20.4	0.75	(<.001)
	Frequency	83	6.2	8.8	96	29.8	17.3	1.29	(<.001)
	Stool aspects	83	7.7	12.9	96	19.1	17.8	0.68	(<.001)
	Medication	83	6.1	15.6	96	23.8	27.4	0.73	(<.001)
	Total score	83	7.2	7.0	96	21.3	14.6	1.04	(<.001)
Hallböök	Incontinence	82	13.6	12.4	96	29.1	22.0	0.78	(<.001)
	Social impact	82	9.5	9.4	96	18.0	14.7	0.65	(<.001)
	Frequency	82	19.8	8.7	96	29.5	10.2	0.90	(<.001)
	Abdominal pain	82	17.4	20.5	96	23.8	23.4	0.28	(.06)
	Total score	82	14.1	8.0	96	25.0	12.4	0.92	(<.001)
Vaizey	(Incontinence)	70	7.9	14.2	87	16.3	20.9	0.45	(.004)
	(Social impact)	78	39.6	14.5	90	52.1	20.5	0.65	(<.001)
	Total score	66	23.2	11.8	83	34.1	17.6	0.67	(<.001)

Without complaints = group of patients after right-sided hemicolectomy or laparoscopic cholecystectomy; With complaints = group of patients with colo-anal or ileo-anal anastomosis; No. = number of patients per scale (variation for the Vaizey questionnaire due to missing values); Mean = mean score per answer-category after linear transformation to a score from 0-100, higher scores represent a higher level of symptomatology; SD = Standard Deviation; ES = Effect Size, effect sizes of 0.2, 0.5 and 0.8 are considered small, medium and large respectively; p=p-value, relates to one-way analysis of variance (ANOVA); COREFO = COREFO questionnaire; Hallböök = Hallböök questionnaire; Vaizey = Vaizey questionnaire

Figure a & b. Effect size per scale of the three questionnaires.

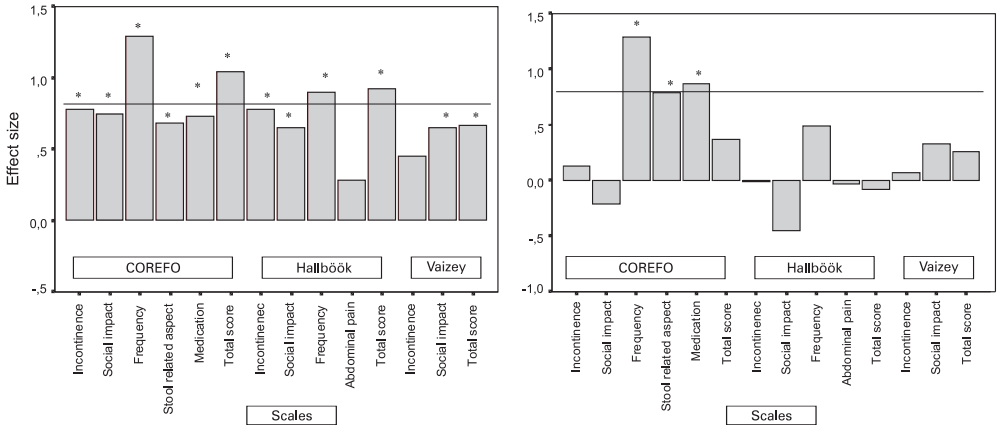

Figure a. Effect sizes of the mean scale difference between patients with and without complaints based on known-groups comparison, * = p<0.001, line indicates effect size > 0.8 which is generally considered a large effect.

Figure b. Effect sizes of the mean scale difference between patients with a colo-anal and ileo-anal anastomosis based on known-groups comparison, * = p<0.001, line indicates effect size > 0.8 which is generally considered a large effect.

	Scales	colo-anal			ileo-anal				
		No.	Mean	SD	No.	Mean	SD	ES	(p)
COREFO	Incontinence	49	16.7	18.2	47	19.2	19	0.13	(.515)
	Social impact	49	24.9	21.9	47	20.5	18.6	-0.21	(.298)
	Frequency	49	18.9	12.8	47	41.2	13.8	1.29	(<.001)
	Stool aspects	49	12.2	14.7	47	26.2	18.1	0.79	(<.001)
	Medication	49	12.1	14.7	47	36.0	32.1	0.87	(<.001)
	Total score	49	18.7	13.9	47	24.1	15.0	0.37	(.068)
Hallböök	Incontinence	49	29.2	22.7	47	29.0	21.4	-0.01	(.963)
	Social impact	49	21.3	15.9	47	14.7	12.7	-0.45	(.028)
	Frequency	49	27.0	11.8	47	32.0	7.5	0.49	(.016)
	Abdominal pain	49	24.4	25.6	47	23.1	21.3	-0.03	(.784)
	Total score	49	25.5	13.4	47	24.6	11.4	-0.08	(.711)
Vaizey	(Incontinence)	45	15.5	23.6	42	17.0	18.2	0.07	(.730)
	(Social impact)	45	48.7	18.6	45	55.6	22.0	0.33	(.114)
	Total score	39	31.6	17.6	44	36.3	17.6	0.26	(.233)

Criterion validity

The mean scale scores of all three questionnaires are shown in Table 3 and the related effect sizes are graphically presented in the Figure a&b. All scales of the COREFO questionnaire showed statistically significant differences between patients with and without complaints, thus were able to distinguish between these patients. Three scales ('frequency', 'stool related aspects', and 'medication') showed also statistically significant differences between patients with an ileo-anal anastomosis (theoretically more impaired) and patients with a colo-anal anastomosis (theoretically less impaired). In other words, these scales of the COREFO are also able to detect smaller differences.

The scales of the Hallböök questionnaire, except the scale 'abdominal pain', showed statistically significant differences between patients with and without complaints and thus can distinguish between these patients. No statistically significant differences were found between patients with an ileo-anal or colo-anal anastomosis. In contrast to the COREFO questionnaire, the Hallböök questionnaire is not able to detect smaller differences.

The total score of Vaizey showed a statistically significant difference between patients with and without complaints, but could not distinguish between patients with an ileo-anal or colo-anal anastomosis. Large differences can, therefore, be detected using the Vaizey questionnaire, but smaller differences are not distinguished.

Discussion

Reliability, as tested by internal reliability and test-retest reliability, and validity were adequate for the majority of the multi-item scales of the COREFO and Hallböök questionnaires when

tested among patients with complaints, indicating that both questionnaires are suitable to be used to evaluate functional outcome after colorectal surgery.
However, these results need careful interpretation concerning reliability and validity of the COREFO and Hallböök questionnaires.
First of all, the internal reliability as well as the test-retest reliability of the Hallböök frequency scale did not exceed the .70 criterion indicating that the questions within this scale not all measure the same attribute (frequency) and they do not yield reproducible results. Moreover, the convergent validity of the Hallböök frequency scale compared with the COREFO scales, was not adequate. This indicates that the frequency scale of Hallböök is less suitable to evaluate defecation frequency after colorectal surgery. This might be due to the different type of questions evaluating frequency. The COREFO questionnaire has two questions about frequency, while the Hallböök questionnaire has 5 questions evaluating different aspects of frequency.

Second, the internal reliability of the 'stool related aspects' and 'need for medication' scales of the COREFO questionnaire did not exceed the .70 criterion. This also indicates that the questions within these scales not all measure the same attribute.
Third, the criterion validity of the COREFO questionnaire is slightly better than that of the Hallböök questionnaire, since three scales (frequency, stool related aspects and need for medication) are also able to distinguish between patients with relatively small differences in complaints (patients with a colo-anal vs patients with an ileo-anal anastomosis). None of the other scales of any of the three questionnaire can detect these smaller differences.

The original faecal incontinence grading scale of Vaizey has been designed and validated, but not as a self-assessment questionnaire.[8] It was transformed into a questionnaire to be used in this study. This adapted Vaizey questionnaire was considered as one scale for incontinence, because the faecal incontinence score was originally designed to evaluate incontinence. The reliability of the Vaizey questionnaire was not adequate when tested as a self-assessment questionnaire, indicating that the questions of this questionnaire do not measure the same attribute, nor yield reproducible results. Construct validity and criterion validity on the other hand were considered sufficient.
Based on the insufficient reliability, the Vaizey questionnaire is not considered suitable to be used as a self-assessment questionnaire to evaluate functional outcome after colo-rectal surgery. This disappointing behaviour might, at least partly, be caused by the transformation of the faecal incontinence grading scale into a self-assessment questionnaire. Nonetheless, the Vaizey incontinence scale remains an important tool in assessing faecal incontinence, but only when used as intended and not as a self-assessment questionnaire.

Many clinical trials compare functional outcome after colo-rectal surgery using self-assessment questionnaires [12,14,21-29] However, none of these questionnaires have been validated. Therefore it is impossible to compare results obtained in different trials with

each other. The validation of the COREFO and Hallböök questionnaire offer the opportunity to use validated questionnaires. Results obtained from different clinical trials, even when gathered by different research groups or in different countries, can be compared if these results are analysed according to the above mentioned scale structures. To offer researchers outside the Netherlands the opportunity to use the validated COREFO questionnaire, it was translated into the English language using a two-stage process[16]. A native English speaker, who is also fluent in Dutch, performed the forward translation. A native Dutch speaker, who was blinded to the original questionnaire, did the backward translation. Thereafter, the forward-backward translation was compared to the original questionnaire. Existing differences were discussed until agreement upon the adequate translation was reached.

Conclusions

The newly developed COREFO questionnaire and the previously unvalidated Hallböök questionnaire are reliable, valid and suitable instruments to evaluate functional outcome after colorectal surgery by means of a self-assessment questionnaire. This in contrast to the adapted Vaizey questionnaire, which is not reliable and therefore not suitable as a self-assessment questionnaire.
Although the Hallböök questionnaire has been used in clinical trials, these previously published results were not analysed according to the scale-structure established in the current study. Comparison of these previous results with future results will therefore be impossible.
Furthermore, there is a slight difference, based on the psychometric analyses, in favour of the COREFO questionnaire and significantly more patients considered the COREFO questionnaire to reflect their problems best. Therefore, we suggest the use of the validated COREFO questionnaire in future research.

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Appendix

Questions, answer-categories and scales of the COREFO questionnaire, scales of the Hallböök and Vaizey Questionnaire.

COREFO

- **Incontinence**
  - Question 7 Have you unintentionally passed wind?
  - Question 8 Have you unintentionally passed **liquid** stools during the day?
  - Question 9 Have you unintentionally passed **liquid** stools during the night?
  - Question 10 Have you unintentionally passed **solid** stools during the day?
  - Question 11 Have you unintentionally passed **solid** stools during the night?
  - Question 12 Have you had a smear of faeces in your underwear during the day?
  - Question 13 Have you had a smear of faeces in your underwear, pyjamas or night-gown at the end of the night?
  - Question 14 Was it difficult to distinguish between passing wind and a bowel movement?
  - Question 23 Have you used something to protect your underwear, such as sanitary towels, panty liners or nappies?

- **Social impact**
  - Question 3 In case you needed to go urgently, did you have trouble stopping your bowel movement for longer than fifteen minutes?
  - Question 4 Have you had a false alarm? (= A need to go without a bowel movement)?
  - Question 15 When you went to the toilet, did your bowel movement require more than 15 minutes?
  - Question 16 Did you have the idea that your bowels were not empty after your bowel movement?
  - Question 17 After you had a bowel movement, did you have to return to the toilet within one hour for a bowel movement?
  - Question 24 Did you adjust your activities to the availability of a toilet?
  - Question 25 Were you limited in your daily activities (e.g. work or house work) due to problems with your bowel movements?
  - Question 26 Were you limited in your social activities (e.g. family visits, visits to the theatre, or eating out) due to problems with your bowel movements?
  - Question 27 Were you limited in your sexual activities (with or without sexual intercourse) due to problems with your bowel movements?

- **Frequency**
  - Question 1 How many bowel movements have you had during the day?
  - Question 2 How many bowel movements have you had during the night?

- **Stool related aspects**
  - Question 5 Have you had pain during your bowel movements?
  - Question 6 Have you experienced blood loss during your bowel movements?
  - Question 22 Have you had irritated skin around your anus?

- **Need for medication**
  - Question 18 Have you used medicines to thicken your stools?
  - Question 20 Have you eaten certain foods **on purpose** to make your stools thicker or thinner?
  - Question 21 Have you **purposely** avoided certain foods to prevent your stools becoming loose or hard?
- **Total score**
  - Question 1 to 27, after exclusion of question 19 (Have you used medicines to make your stools thinner?)

Hallböök

- **Incontinence**
  - Question 17 Can you break wind without soiling your underclothes?
  - Question 18 How long can you withstand the urge to pass a motion if there is no toilet available?
  - Question 19 How often do you break wind involuntarily?
  - Question 20 How often do you soil your underclothes (soiling from the bowel)?
  - Question 21 How often do you have leakage if the motion is loose?
  - Question 22 How often do you have leakage if the motion is not loose?
  - Question 23 How often do you wear any kind of protection against leakage (i.e. diaper or pad) *during the day?*
  - Question 24 How often do you wear any kind of protection against leakage (i.e. diaper or pad) *at night?*

- **Social impact**
  - Question 2 What is the usual consistency of the motion?
  - Question 4 Do you take any medication for the bowels (combined with question 3)
  - Question 5 How often do you experience difficulty in emptying the bowels?
  - Question 6 How often do you need to use fingers to help empty the bowels?
  - Question 7 How much time do you usually need to empty the bowels?
  - Question 8 How much time do you usually need to strain before passing a motion?
  - Question 11 How often do you have a feeling of incomplete emptying?
  - Question 25 Does bowel function adversely affects your general well being?
  - Question 26 Does the bowel function adversely affect your social activities / social life?
  - Question 27 Would you prefer a stoma (bag on the tummy) if this helped you with your bowel problems?

- **Frequency**
  - Question 1 How many times do you usually pass a motion during the day/ at night?
    What is the highest/lowest number of time you have passed a motion during 24 hours?
    Did you pass a motion less than once a day?
  - Question 9 How often do you need to return to the toilet within one hour to empty the bowels?
  - Question 10 How many times do you have to return to the toilet before you feel as though your bowels are fully emptied?
  - Question 16 How often do you have any warning before passing a motion?

- **Abdominal pain**
  - Question 12 How often do you have pain in the tummy?
  - Question 13 How often do you have tummy pain that is relieved by passing a motion?
  - Question 14 How often does your tummy swell up?
  - Question 15 How often do you have swelling of the tummy that is relieved by passing a motion?

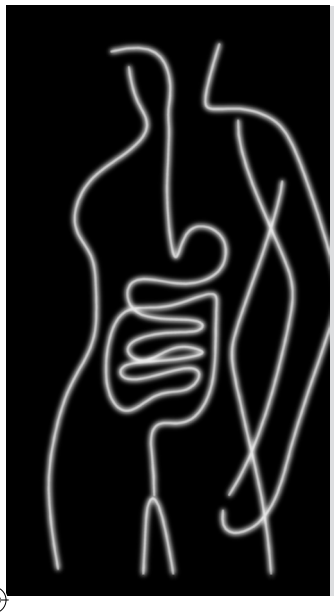
- **Total score**
  Question 1 to 27 (questions 3 and 4 combined to one question)

Vaizey

- **Incontinence**
  - Question 1 Did you leak gas, without being aware of it at first?
  - Question 2 Did you leak liquid, without being aware of it at first?
  - Question 3 Did you leak solid, without being aware of it at first?

- **Social impact**
  - Question 4 Did you wear a pad or use a plug of tissue paper?
  - Question 5 Did you take Imodium (loperamide), codeine or other medicine?
  - Question 6 Did your loss of stool or fear of loss of stool stop you from doing anything?
  - Question 7 Were you able to postpone defecation for 15 minutes?

- **Total score**



Chapter 5

Submitted for publication

Neo-rectal irritability after short-term preoperative radiotherapy and surgical resection for rectal cancer

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Abstract

Background and Objectives. Preoperative radiotherapy followed by rectal resection with total mesorectal excision (TME) and colo-anal anastomosis severely compromises anorectal function which has been attributed to a decrease in neo-rectal capacity and neo-rectal compliance. However, it is still unknown to what extent altered motility of the neo-rectum is involved.

Aim. To compare the motor response to (prolonged) filling of the (neo-)rectum in patients after preoperative radiotherapy and rectal resection with that in healthy volunteers (HV).

Methods. Neorectal function was studied in ten patients (median age 61 years, 7 males) 5 months after short-term preoperative radiotherapy (5x5 Gy) and rectal resection with TME for rectal cancer and compared to that of ten volunteers (median age 41 years, 7 males). (Neo-)rectal sensitivity was assessed using a step-wise isovolumetric and isobaric distension protocol. (Neo-)rectal motility was determined during prolonged distension at the threshold of urge to defaecate.

Results. The neo-rectal volume of patients at the threshold of urge to defaecate (113 ± 33 ml) was significantly lower compared to that of HV (272 ± 87 ml, $p<0.05$). The pressure threshold however did not differ between patients (21 ± 5 mmHg) and HV (23 ± 9 mmHg). In HV, no rectal contractions were observed during prolonged rectal distension. In contrast, in all 10 patients prolonged isovolumetric and isobaric distension induced 3 (range 0-5) rectal contractions/ 10 min, which was associated with an increase in sensation in half of the patients.

Conclusions. Patients who underwent preoperative radiotherapy and rectal resection with TME, but not HV, developed contractions of the neo-rectum in response to prolonged distension. We suggest that this neo-rectal "irritability" represents a new pathophysiological mechanism contributing to the urgency for defaecation after this multimodality treatment.

Introduction

Short-term preoperative radiotherapy (5x5Gy) followed by rectal resection with total mesorectal excision (TME) is currently considered the treatment of choice for patients with a resectable rectal carcinoma.[1-2] During surgery, a neo-rectum is created using the sigmoid colon or descending colon. After this multimodality treatment, anorectal function is often compromised as reflected by an increase in frequency and urgency of defaecation and by incontinence.[3-4] Recent publications show that up to 60% of patients experience some degree of incontinence.[5-6] Suggested explanations for the impaired functional outcome include decreased internal and external anal sphincter function due to direct injury of the nervous supply,[7-13] the low level of anastomosis,[14-16] impaired neo-rectal capacity and decreased compliance,[7,9-10,17] and the loss of rectal sensation.[18-20]

Faecal continence results from the complex interplay between the rectum, the anal sphincter complex, the musculature of the pelvic floor and the nerves innervating these structures. In addition to sphincter pressure generated by the anal sphincter, the importance of the rectum as a reservoir in warranting continence is increasingly appreciated. Arrival of faecal contents in the rectum will not only generate the sensations of urge, but will also trigger an adaptive relaxation of the musculature, thus creating a reservoir. This relaxation together with anal sphincter contraction are important factors in the ability to defer defaecation.[21-23] Abnormalities in rectal reservoir capacity, either due to impairment of this relaxation or decreased compliance (fibrosis due to previous radiation therapy or inflammation) are considered to play an important role in the pathogenesis of faecal incontinence and urgency. In line with this, previous studies have shown an increase in urgency, tenesmus and defaecation frequency due to a decreased neo-rectal reservoir capacity and a decreased neo-rectal compliance in patients who underwent TME surgery.[24-25] Reactive rectal contractions were observed at the onset of distension of a barostat balloon and in the neo-rectum these contractions were followed by one or more extra contractions during distension periods of two minutes, suggesting neo-rectal irritability.[25-26]

In the present study, we want to further explore this observation and hypothesise that the neo-rectum lacks the capacity to adapt to distension. Rectal filling with faecal content would lead to prolonged distension of the neo-rectum inducing neo-rectal contractions, subsequently contributing to the feeling of urgency. To test this hypothesis, the motor response to prolonged filling of the neo-rectum in patients after short-term radiotherapy followed by rectal resection with TME was compared with the motor response to prolonged filling of the rectum in healthy volunteers.

Materials and Methods

Subjects

Ten patients (7 males) with a median age of 61 years (range 33-76 years) treated for a rectal carcinoma located in the lower 2/3 of the rectum were evaluated. Treatment consisted of short-term preoperative radiotherapy (5x5Gy) followed by rectal resection with TME and colo-anal anastomosis (side-to-end in 6 patients, or J-pouch in 4 patients). None of the patients received chemotherapy and/or postoperative radiotherapy. Five months (range 4-6 months) after surgery, patients were invited to undergo an anorectal function study. Protective loop ileostomies were closed at least 4 weeks before measurements to ensure bowel function.

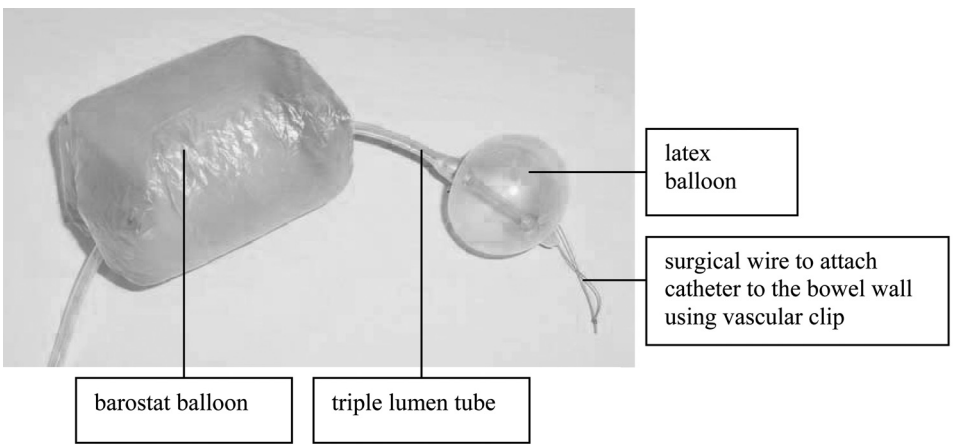
In addition, ten healthy volunteers (HV, 7 males) with a median age of 41 years (19-70 years) served as controls. None of the volunteers had defaecation problems as tested by the COREFO questionnaire,[27] nor a history of abdominal surgery and/or previous radio- or chemotherapy possibly compromising bowel function.

Rectal barostat and anorectal manometry

A non-compliant polyethylene bag (figure 1) was hermetically fixed to one of two specially designed triple-lumen polyvinyl tubes and connected to the barostat. The maximum capacity of this bag was 450 ml and had a length of 10 cm when used for the patients. The maximum capacity of the bag was 600 ml and had a length of 15 cm when used in the healthy volunteers. This balloon was connected to an electronic barostat (Synetics Medical, Stockholm, Sweden) to measure rectal compliance and rectal sensory motor function. [28] The barostat balloons were inflated up to 10 mmHg, prior to and following completion of the experiment to rule out any leakage of air.

A compliant latex balloon (figure 1) was hermetically fixed onto the catheter 5 cm above the barostat balloon to allow distension of the bowel proximally of the (neo)-rectum.

Figure 1. Barostat catheter with barostat balloon and latex balloon.



This balloon was inflated up to 150 ml of air prior to and following the completion of the experiment to rule out any leakage of air.

Sphincter pressure was measured by anorectal manometry using a multi-lumen, waterperfused sleeve catheter assembly containing a 4.5 cm long sleeve and 4 radially distributed side holes (Dentsleeve Pty Ltd, Parkside, Australia). Each sidehole was perfused with degassed water at a rate of 0.3 ml/min and intraluminal pressures were sensored by external transducers, connected to a polygraph (Synetics Medical, Stockholm, Sweden).

Anorectal manometry and rectal barostat were performed simultaneously. The results were monitored and analyzed with commercially available software (Polygram for Windows, version 1.11, Synetics Medical).

Study protocol (figure 2)

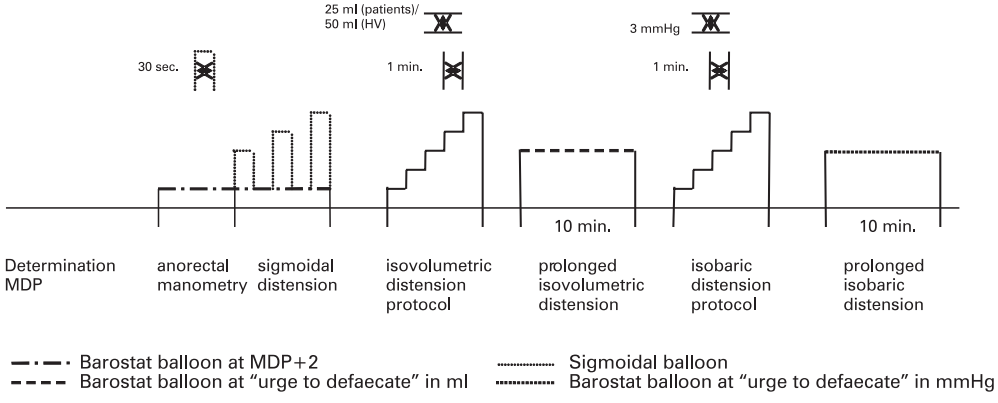
Positioning of the catheters

Participants received a water-enema to clean the bowel and to avoid interference of stool during the measurements. Thereafter, the catheter with the latex balloon and barostat balloon attached was endoscopically inserted and placed in the right position with the lower edge of the barostat balloon just above the anal verge. The tip of the catheter was attached to the bowel wall using a disposable vascular clip to maintain its position. The endoscope was removed, while the catheter was left behind in the (neo-)rectum. The barostat balloon was inflated with up to 150 ml of air to allow adequate unfolding.

The anorectal manometry catheter was inserted ventrally of the barostat catheter in the anal canal. All measurements were performed with the subjects in left lateral position.

After insertion of the two catheters, a recovery period of 15 minutes was introduced after which the minimal distending pressure (MDP) of the barostat balloon was determined. MDP is defined as the minimum pressure at which the intrabag volume is > 30 ml.

Figure 2. Schematic representation of the study protocol.



HV = Healthy Volunteer, MDP = minimal distension pressure.

Anorectal manometry

Anorectal manometry was performed with the barostat balloon set to MDP + 2 mmHg. The mean value of the resting pressure was measured for 2 minutes. Thereafter, the subjects were instructed to maximally squeeze on three occasions.

Sigmoidal distension

To evaluate the response of the (neo-)rectum to sigmoidal distension, the barostat balloon was set to MDP + 2 mmHg and the latex balloon was distended during 30 seconds in different volume steps (50, 75, 100, 125, 150 ml or until discomfort was reported).
The (neo)rectal-anal inhibitory reflex (RAIR) was assessed during sigmoidal distension. RAIR was defined as a reduction of the internal anal sphincter pressure from baseline of at least 10 mmHg of 5 seconds duration. [29]

Step-wise isovolumetric distension protoco. [30]

The isovolumetric distensions were performed with volume steps of 25 ml in patients and 50 ml in HV. Each distension lasted one minute after which the volume was further increased until discomfort or pain was reported by the participant. Sensations were scored 30 seconds after each distension step using a six-point scale with verbal descriptors (0 = no sensation, 1 = first sensation, 2 = first sense of urge, 3 = normal urge to defaecate, 4 = severe urge to defecate, 5 = discomfort/ pain).[28] Sensations were logged onto the data file at each score point. If the participant reported discomfort or pain, the barostat balloon was instantly deflated.

Prolonged isovolumetric distension

To evaluate the motor response of the (neo-)rectum to rectal filling, a prolonged isovolumetric distension (10 min) was performed with the volume fixed at the level of urge to defaecate (sensation 3) as scored during the preceding step-wise isovolumetric distension protocol. During the period of prolonged distension, sensations were scored every minute or when the participant indicated an increase or decrease in sensation.

Step-wise isobaric distension protocol [30]

The step-wise isobaric distension protocol was performed with fixed pressure steps of 3 mmHg above MDP. Each distension lasted one minute and sensation was scored 30 seconds after each distension. The barostat balloon was deflated if the participant indicated discomfort or pain.

Prolonged isobaric distension

A prolonged isobaric distension (10 min) was also performed to obtain information about the motor response of the (neo-)rectum to rectal filling. The pressure was fixed at the level of urge to defaecate (sensation 3) as scored during the preceding step-wise isobaric distension protocol. Sensations were scored every minute or when the participant indicated an increase or decrease in sensation.

Data analysis

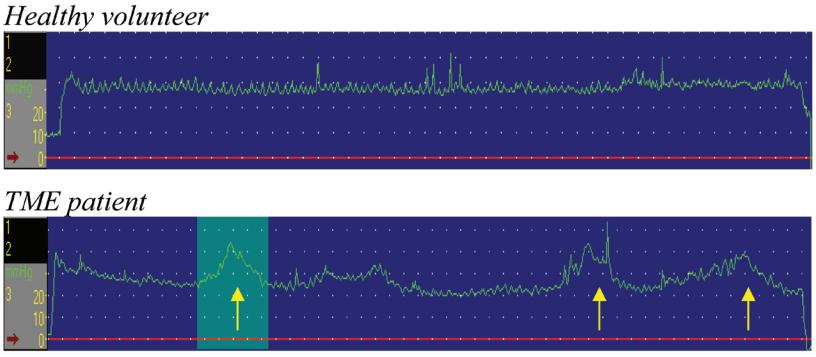
All data are given as mean ± standard deviation (SD) unless stated otherwise. Continuous data were compared using Student's t-test, while a non-parametric test (Mann-Whitney) was used in case of ordinal data. Differences were considered significant at the 5% level.

The reported values for the maximum squeeze pressure are the mean of three efforts.

The response during sigmoidal distension is presented as the absolute volume decrease (in ml) in the barostat balloon and as the percentage volume decrease of the barostat balloon. The barostat volume, measured just prior to each sigmoidal distension was used as baseline volume and was subsequently set as 100%.

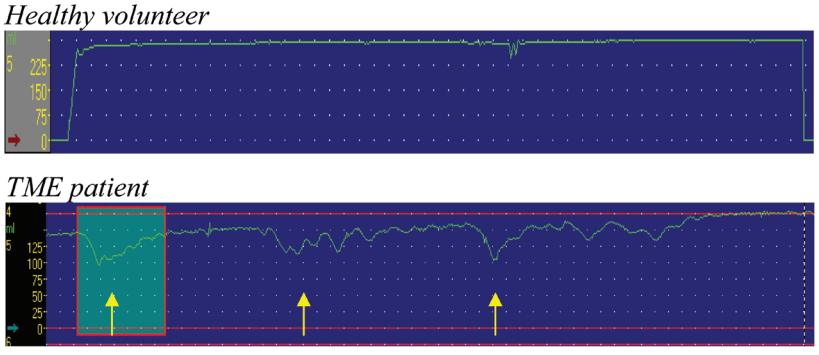
A temporary increase of > 10 mmHg in the barostat balloon during prolonged isovolumetric distension was considered a contraction (figure 3). A temporary decrease of > 15% of the barostat balloon volume during prolonged isobaric distension was considered a contraction (figure 4). (Neo-)rectal capacity was determined at the end of the isobaric distension protocol.

Figure 3. Representative tracing showing rectal pressure during isovolumetric distension. Contractions (indicated by arrow) were observed in TME patients (below) but not in healthy volunteers (above)



Barostat pressure (in mmHg) during isovolumetric distension, contraction is defined as a temporary increase of > 10 mmHg.

Figure 4. Representative tracing showing rectal volume during isobaric distension. Contractions (indicated by arrow) were observed in TME patients (below) but not in healthy volunteers (above)



Barostat volume (in ml) during isobaric distension, contraction is defined as a temporary decrease of > 15% of the baseline volume.

The compliance was calculated using a non-linear mixed-effect model for fitting the pressure volume curves of each individual.[31-32] The pressure volume curves were constructed using the mean volume of the last 30 seconds (when equilibration of the volume was reached) at each of the consecutive pressure steps during the step-wise isobaric distension protocol. In a first analysis all curves were fitted individually to a 4 parameter logistic curve, using non-linear regression analysis. This provided the mean values of the parameters C (compliance), V_0 (volume at time point zero), and V_m (maximum volume) for each individual as well as their standard errors. The SD of the within patient measurement error was assumed to be equal for all individuals.
In a second analysis the individual parameters C, V_0 and V_m were assumed to be derived from a 3-dimensional normal distribution, leading to a non-linear mixed effect regression analysis. No assumptions were made about the correlations between the three parameters. Group means and SDs for C, V_0 and V_m were derived from this analysis.
Statistical evaluations were performed using commercially available software (SPSS 11.0; SPSS Inc., Chicago, IL, USA).

Results

Sphincter function

There was a significant difference in resting pressure between patients (40 mmHg, SD 15) and HV (71 mmHg, SD 25; $p<0.05$). Although the maximum squeeze pressure was lower in patients (107 mmHg, SD 47) than in HV (153 mmHg, SD 66; $p=0.15$), this difference was not statistically significant.

Sigmoid distension-induced (neo-)rectal contractions

Distension proximal of the (neo-)rectum resulted in a volume decrease of the rectal barostat balloon in all subjects except in one patient. Volume decrease occurred immediately after minimal distension (50-75 ml) of the sigmoidal balloon. The percentage volume decrease (figure 5) after sigmoidal distension was larger in patients than in HV, but did not reach statistical significance. Similarly, distension of the sigmoid induced a transient relaxation of the anal sphincter in all but 2 HV. In contrast, in only one of the 10 patients we observed a reduction in anal sphincter pressure in response to sigmoid distension. The mean resting pressure in this patient was 53 mmHg, compared to 41 mmHg (range 29 – 60 mmHg) in the rest of the patients.

(Neo-)rectal sensitivity

Volume controlled distension

Thresholds for 'first sensation' and 'urge to defaecate' during the step-wise isovolumetric distension protocol were smaller in patients than in HV. (Figure 6) In all ten HV, 'discomfort' was reached during this protocol at a mean volume of 360 ± 97 ml. In 9 of 10 patients, the threshold of discomfort was not reached. In these patients, maximum

Figure 5. Effect of sigmoidal distension on rectal volume in healthy volunteers and patients.

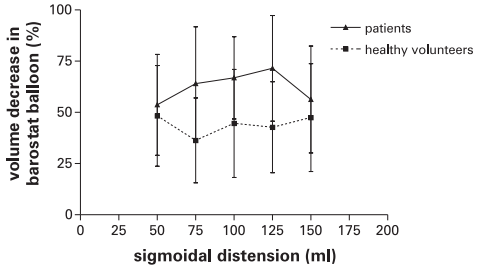
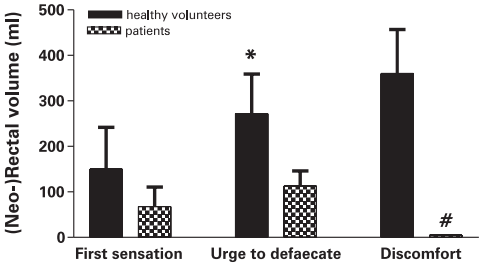
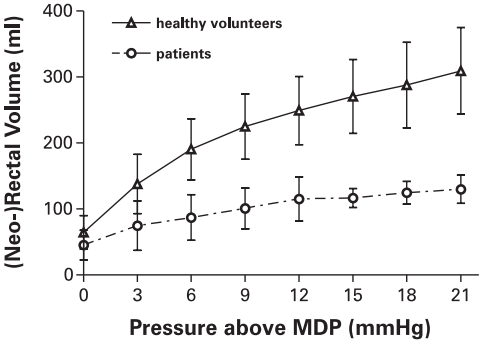


Figure 6. Thresholds of first sensation, urge to defaecate and discomfort during step-wise isovolumetric distension.



* significant difference between healthy volunteers and patients ($p<0.05$, Student's t-test), # maximum safety pressure (55 mmHg) was reached before threshold for discomfort was reached in 8 of 9 patients.

Figure 7. Volume-pressure curves obtained during step-wise isobaric distension protocol. MDP= minimal distension pressure



(safety) pressure (55mmHg) was reached before the sensation of discomfort could be reported.

Pressure controlled distension

Thresholds for 'first sensation', 'urge to defaecate' and 'discomfort' during isobaric distension were not different between patients and HV (Table 1.) All subjects, HV and patients, reached the threshold for 'discomfort'. Rectal capacity was significantly higher in HV (308 ± 77 ml) than the neo-rectal capacity in patients (154 ± 37 ml; $p<0.05$). Compliance of the rectum in HV (26 ± 8 ml/mmHg) was significantly higher than compliance of the neo-rectum in patients (13 ± 7 ml/mmHg;$p=0.003$). The compliance curves are shown in Figure 7.

(Neo-)rectal irritability

In HV, the mean threshold for urge was 272 ± 87 ml during isovolumetric distension and 21 ± 5 mmHg during isobaric distension. No rectal contractions were observed during either prolonged isovolumetric distension (figure 3) or prolonged isobaric distension (figure 4) at the threshold of urge to defaecate.

The mean threshold for urge in patients was 113 ± 33 ml during isovolumetric distension and 23 ± 9 mmHg during isobaric distension. In patients, prolonged isovolumetric distension (figure 3) at the threshold of urge to defaecate induced a median of 3 contractions (range 0-5) per patient with a mean increase in pressure of 19 ± 5 mmHg per contraction. During prolonged isobaric distension (figure 4) at the threshold of urge to defecate a median of 3 contractions (range 0-5) per patient were seen with a mean volume decrease of 28 ± 18 % of the barostat balloon. In one patient, no contraction was seen during prolonged isovolumetric distension and in one patient, no contraction was seen during prolonged isobaric distension. The contractions

Table 1. Thresholds of 'first sensation', 'urge to defaecate' and discomfort' during step-wise isobaric distension in healthy volunteers and patients.

	Healthy volunteers pressure (mmHg)	Patients pressure (mmHg)
First sensation	12 ± 3	16 ± 3
Urge to defaecate	21 ± 5	23 ± 9
Discomfort	29 ± 6	32 ± 12

Results between healthy volunteers and patients are not significantly different.

seen during prolonged distension (either isovolumetric or isobaric) occurred during the entire period of distension and were not limited to the first few minutes after the start of distension.

In five of ten patients, the onset of a neo-rectal contraction during either prolonged isovolumetric or prolonged isobaric distension resulted in a simultaneous increase of sensation of one level in sensation score. All sensations returned to the level prior to the neo-rectal contraction.

Discussion

Ano-neorectal function is often compromised after radiotherapy and rectal resection with TME, resulting in urgency for defaecation and faecal incontinence.[3-4] In the present study, we show that, in contrast to HV, patients who underwent TME develop neo-rectal contractions in response to prolonged distension (10 minutes) suggesting increased neo-rectal irritability. This motor pattern in combination with the decreased neo-rectal capacity, decreased neo-rectal compliance and decreased anal resting pressure[7-13], most likely explains the occurrence of urgency in these patients.

Under physiological circumstances, the rectum acts as a reservoir and accommodates to rectal filling, contributing to our capacity to postpone defecation. This motor pattern is most likely triggered by mechanoreceptors in the rectal wall. In the guinea-pig rectum, a high density of slowly adapting, low threshold mechanoreceptors with specialized intraganglionic laminar endings (rIGLEs) have been demonstrated.[34] This specialised class of mechanoreceptors probably detects both rectal distension and contraction and is likely to be involved in activation of recto-spinal pathways for defaecation. Lynn et al.[34] recently demonstrated that these mechanoreceptors adapted to maintained distension suggesting a role in the accommodation to rectal filling. In our study, prolonged distension at the threshold of urge to defaecate failed to induce rectal motor activity in healthy subjects. Similarly, Kwan et al.[33] did not observe deviating rectal motor activity during prolonged rectal distension in healthy volunteers. In contrast to HV, prolonged distension of the neo-rectum in patients at the threshold of urge to defaecate triggered contractile activity, as illustrated by an increase of more than 10 mmHg in the barostat

balloon during isovolumetric distension and a reduction of more than 15% of baseline volume of the barostat balloon during isobaric distension. These contractions were seen during the entire period of distension and were not limited to the first few minutes after distension. In half of the patients, a contraction was even associated with an increase in sensation. A similar response has been reported by Corsetti et al.[39] during a barostat procedure in healthy subjects with the barostat balloon placed in the descending colon. Colonic contractions were observed in response to prolonged colonic distensions (30 min), which increased in frequency after the administration of neostigmine. These contractions were associated with an increase in sensation reported by the majority of the volunteers (7 out of 10). We hypothesise that the contractions occurring in the neo-rectum during prolonged distension in our study are similar to the colonic contractions described by Corsetti et al.[39] Comparable contractions to distension have also been shown in the guinea-pig distal colon: maintained circumferential stretch resulted in an ongoing discharge of synchronised ascending excitatory and descending inhibitory neuronal pathways to the circular muscle, leading to propulsion of a bolus.[35-38] In this respect, it is important to emphasize that the rIGLEs are absent in the guinea-pig colon.[34] Therefore, as the neorectum is reconstructed from sigmoid / colon descendens, the different motor response to distension in patients after TME may be explained by the absence of rIGLEs and the lack of this adaptive mechanism. Based on these findings, we hypothesise that filling of the neo-rectum with faecal material induces neo-rectal contractions, probably as an intrinsic property of the colon, contributing to the occurrence of urgency in patients after rectal resection. In addition, as can be seen from the results of the isovolumetric distension protocol, the volumes triggering the different sensations are smaller in patients than in healthy volunteers as a result of decreased compliance. Therefore, sensations are reached sooner in patients further leading to increased stool frequency.

The rectum in HV as well as the neo-rectum in patients contracted in response to sigmoidal distension, representing the peristaltic reflex. This reflex consists of a smooth muscle contraction oral to and relaxation anal to the site of the stimulus and has been first described by Bayliss and Starling.[40-41] Since there is no significant difference in response to sigmoidal distension between patients and HV, the peristaltic reflex seems to be undisturbed after rectal resection and does not appear to be involved in abnormal anorectal function.

Clinical implications

As the neuromuscular properties of the sigmoid and colon, especially the capacity to adapt to filling, is very different from that of the rectum, it seems unlikely that the neo-rectum will be suitable to functionally replace the rectum or function as a reservoir. In the present study, we provide evidence that the exaggerated motor response of the neo-rectum may play an important role in the impaired anorectal function of patients who underwent a rectum resection. Based on this observations, two major therapeutic strategies could be proposed to improve the clinical outcome after such an operation. First, formation of a J-pouch coloanal anastomosis[42-43] could theoretically lead to a

reduction in urgency. During pouch formation, the circular muscle layer is dissected and the propulsive direction of the distal part of the colon forming the pouch is reversed in relation to the propulsive direction of the proximal part of the colon forming the pouch, which also might reduce contractile activity. In addition, a larger neo-rectal capacity is created compared to a straight or side-to-end coloanal anastomosis, which may also contribute to impaired urgency and/or defaecation frequency. [17, 44-46] These supposed effects on neo-rectal neuromuscular function clearly needs to be substantiated in randomised clinical trials.

Secondly, medication reducing gastro-intestinal motility could be used to reduce the occurrence of urgency. For example, the 5-HT3 receptor antagonist granisetron has been shown to inhibit postprandial contractions in patients after low anterior resection.[47] Therefore, one might speculate that 5-HT3 receptor antagonists like granisetron might also inhibit neo-rectal irritability and thus reduce urgency in these patients.

Conclusions

In patients after short-term radiotherapy and rectal resection with TME a normal amount of stool in the neo-rectum will not only lead to more pronounced sensations due to the smaller neo-rectal capacity, but will also lead to neo-rectal contractions instead of neo-rectal accommodation. We suggest that this neo-rectal irritability represents a new pathophysiological mechanism which contributes to urge to defaecate.

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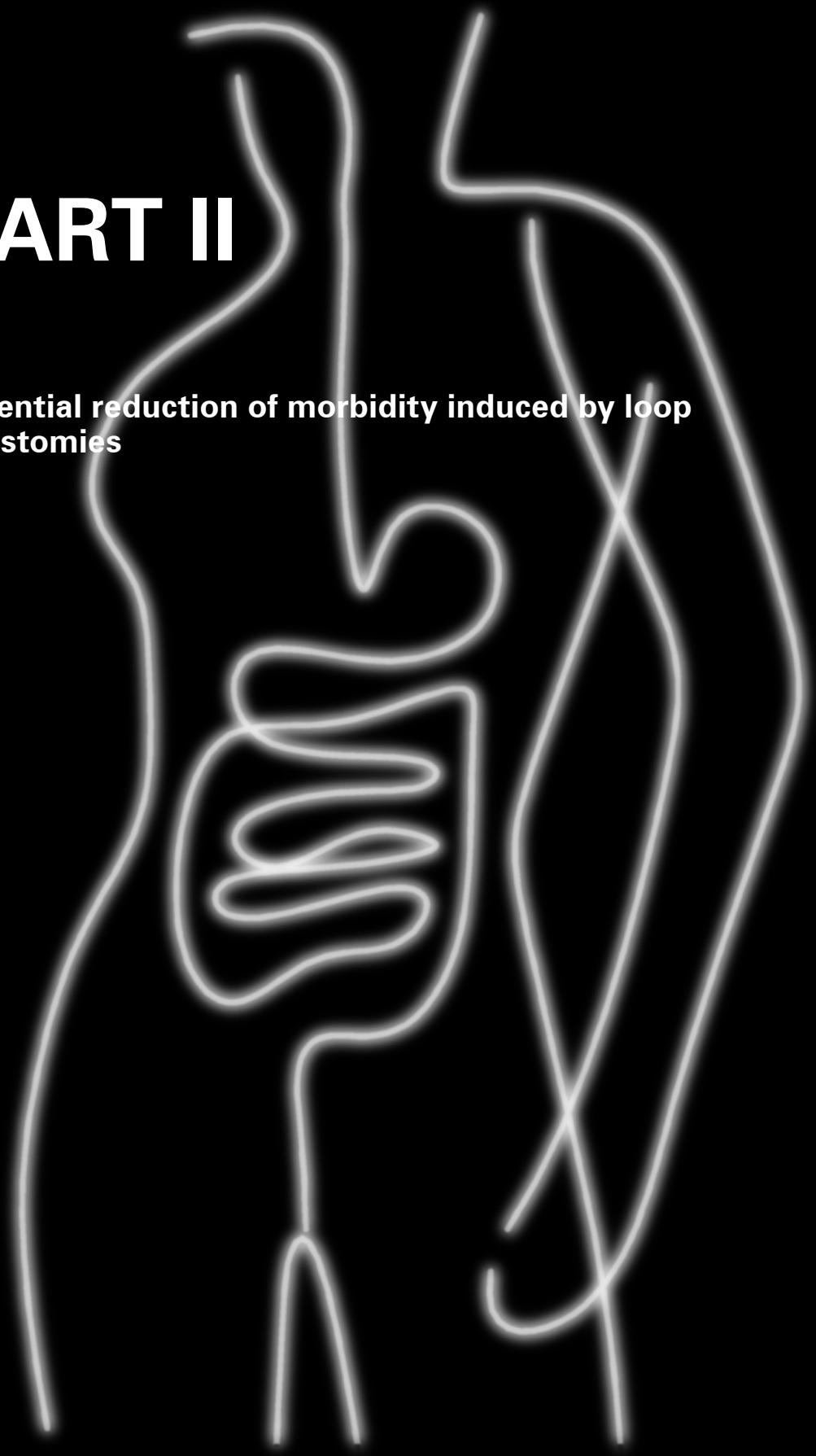
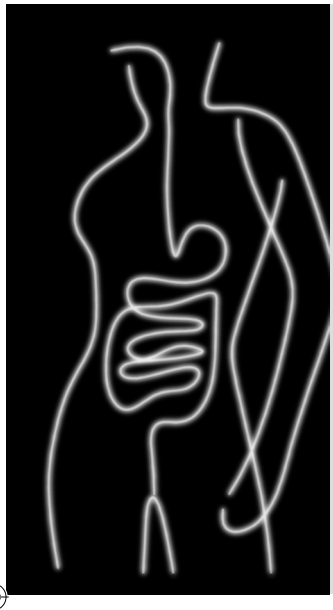
PART II

Potential reduction of morbidity induced by loop ileostomies





CHAPTER 6

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Morbidity of temporary loop ileostomies

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Abstract

Background and Objectives. A temporary loop ileostomy is constructed to protect a distal colonic anastomosis. Closure is usually performed not earlier than 8-12 weeks after the primary operation. During this period stoma-related complications occur and enhance the adverse effect on quality of life.

Aim. To evaluate the length of time between ileostomy construction and closure, to quantify the stoma-related morbidity and to examine the potential advantages of early ileostomy closure.

Methods. Sixty-nine patients with a temporary, protective loop ileostomy (constructed between January 1996 and December 2000), were retrospectively analysed. The analysis was done by reviewing the medical records and the registration of the stoma care nurse.

Results. Sixty ileostomies (87%) were closed after a median period of 24 weeks (range 2-124). Stoma-related complications occurred in 29 (42%) of the 69 patients and eleven patients (18%) had complications after ileostomy closure.

Conclusions. The length of time between ileostomy construction and closure is substantially longer than initially planned. Earlier ileostomy closure (preferably even during the initial admission) could reduce the frequently occurring stoma-related morbidity and thus improve quality of life.

Introduction

In colorectal surgery, a loop ileostomy or loop colostomy is often constructed to protect temporarily a distal colonic anastomosis. [1] Compared to a loop colostomy, a loop ileostomy probably induces less morbidity. Moreover, it is easier to construct and to close.[2-4] Therefore, the loop ileostomy is favoured by most surgeons.[5-9] A loop ileostomy probably does not reduce the incidence of anastomotic leakage, but rather decreases the detrimental effects once leakage occurs. [10-14] In general, closure is not planned earlier than 8-12 weeks after construction. [15-17] Because ileostomy closure does not have a high, medical priority in an era of stringent financial budgeting, this operation is often postponed. [5] In the presence of an ileostomy, stoma-related complications (e.g. leakage around the appliance, skin rash, high output and prolapse) frequently occur. Moreover, a loop ileostomy has in itself an adverse effect on the quality of life, which is further enhanced if stoma-related complications occur. [18-21]

The aim of this study was to evaluate the length of time between ileostomy construction and closure, to quantify the stoma-related morbidity and to examine the potential advantages of early ileostomy closure.

Materials and Methods

The records of 69 consecutive patients with a temporary loop ileostomy operated on between January 1996 and December 2000 at the Academic Medical Center in Amsterdam, were retrospectively analysed. Only protective loop ileostomies were included in this analysis, while ileostomies as treatment for anastomotic leakage or inflammatory bowel disease were excluded. All ileostomies were constructed with the intention to be closed within 8-12 weeks after the primary operation. Before closure, contrast enema examination, often combined with endoscopy, was carried out to ensure adequate healing of the anastomosis.

Data were collected regarding the indications for surgery, technical details of the operation, stoma-related morbidity, date of presentation of stoma-related complication, date of ileostomy closure, surgical details concerning ileostomy closure, morbidity and mortality.

Almost all patients were seen by the stoma care nurse on a regular basis, who prospectively registered stoma-related complications, both in the hospital and in the outpatient department. Contacts by phone were not registered. This registration was also analysed and combined with the data obtained from the medical records.

Results

Sixty-nine patients (32 female, 37 male) with a median age of 57 years (range 28-83) were included in the study. Indications for surgery, procedures performed and type of anastomoses are listed in Table 1. The ileostomies were always created to protect a distal anastomosis. One patient, with preexistent renal insufficiency, died 57 days postoperatively due to sepsis, secondary to perforated diverticular disease, and multiple organ failure.

Table 1. Indications for surgery, procedures performed and type of anastomoses in 69 patients with temporary loop ileostomies.

Indications		Procedures		Types of anastomoses	
• Carcinoma	36	• Rectal resection	37	• Colo-anal	35
• Diverticular Disease	12	• Sigmoid resection	11	• Colo-rectal	21
• Ulcerative Colitis	12	• Proctocolectomy	11	• Ileo-anal	11
• Adenoma (rectal)	3	• Posterior exenteration	5	• Colo-sigmoidal	2
• Hartmann's reversal	3	• Hartmann's reversal	3		
• Other	3	• Left hemicolectomy	2		

Thirty-two stoma-related complications were seen in 29 of the 69 patients (42%) during the time-period in which the ileostomy was present. (Table 2.) Stoma-related complications presented after a median of 29 days (range 7-197) (Figure) and occurred more frequently (albeit not significantly) after proctocolectomy (64%) than after rectal or colonic resection (38%, p=0.113, chi-square test).

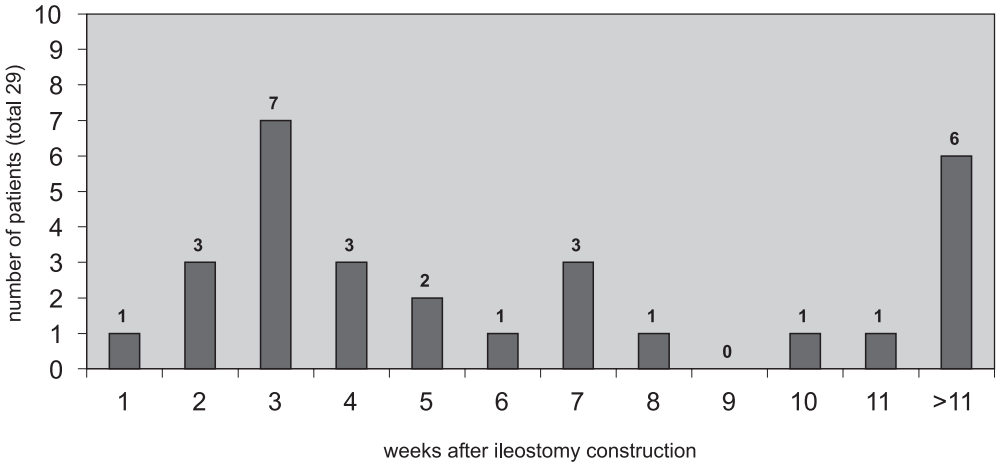
Table 2. Stoma-related complications.

Excessive leakage around the appliance	17
High-output stoma	3
Small bowel obstruction	2
Skin rash	5
Prolapse	4
Pain located at ileostomy	1

In one patient, early ileostomy closure was performed two weeks after the initial procedure, because of a prolapse causing obstruction. Three patients were readmitted due to stoma-related complications (excessive leakage around appliance, high-output stoma, small bowel obstruction). None of these patients needed operative treatment for these problems.

The stoma-related complications in the remaining 25 patients all resolved after non-operative treatment. The majority of these complications were effectively treated by the stoma-care nurse, like changing the appliance in case of excessive leakage or skin rash. Patients experiencing stoma-related complications visited the stoma-care nurse more

Figure. Onset of stoma-related complications in weeks after ileostomy construction.



frequently (median 3 times, range 1-11) than patients without complications (median 2 times, range 0-6, p=0.061, chi-square test).

At the end of follow-up, 60 ileostomies (87%) had been closed after a median period of 24 weeks (range 2-124). Six ileostomies (9%) had been closed within the planned 12 weeks after construction.
There were several reasons for not closing the ileostomy; one patient died shortly after the initial operation due to sepsis and multiple organ failure, one patient did not want the ileostomy to be closed, two patients developed persisting distal anastomotic fistulas, one patient with haemophilia-A treated with factor VIII developed a factor VIII-inhibition and was considered inoperable, two patients developed malignant disease (progression of known liver metastases, newly diagnosed cholangiocarcinoma) and in two patients the reason remained unknown (one patient was lost to follow up).

The reasons for delayed closure (closure more than 12 weeks after construction) were not specified in 38 of 54 patients (70%). Of the other 16 patients, two patients had to wait a long period due to the low urgency of the operation, before closure was performed. Fourteen patients (26%) had a plausible medical reason for delayed closure (i.e. anastomotic fistula, postoperative radiotherapy, recurrent or progressive malignant disease, prolonged recovery after initial operation or anastomotic leakage)

The median admission time for ileostomy closure was 7 days (range 4-51) and the median operation time was 59 minutes (range 35-110). There was no post-operative mortality. Eleven patients (18%) experienced 15 complications after ileostomy closure. (Table 3.) Four of these patients required operative treatment for small bowel obstruction (1), wound infection (1), wound infection with anastomotic fistula (1) or peritonitis secondary

Table 3. Complications of ileostomy closure in 11 of the 60 patients (18%).

Peritonitis	1
Wound infection	4
Anastomotic fistula of the distal colonic anastomosis	1
Small bowel obstruction	5
Incisional hernia (not at previous ileostomy site)	1
Prolapse (after re-creation of loop ileostomy)	1
Other	2

to colitis (1). In this last patient, an ileostomy was created again, which was closed one year thereafter with an uncomplicated postoperative course.

The median follow-up after ileostomy closure was 72 weeks (range 1-219). During this period, incisional hernia at the site of the previous stoma was seen in five patients (7%).

Discussion

In this retrospective series, most of the temporary loop ileostomies (87%) were closed, which is in line with other reports.[16,18,20,22] However, after construction of the ileostomy, many patients (42%) experienced stoma-related complications. In the literature this percentage ranges from 9 to 74%. [5,9,17,20,23-25] These complications enhance the adverse effect of an ileostomy per se on the quality of life. The relatively high percentage of complications in the present series might be due to the fact that we also used the information from the stoma care nurse. Many complications were only treated by the stoma care nurse and were not mentioned to the treating surgeon by the patient. As reported previously, many stoma-related complications are not registered by the treating physician.[5] These relatively mild complications (from a medical point of view) impair quality of life substantially.[21]

The percentage of patients who suffered from complications (18%) due to the ileostomy closure is in line with previous reports.[5,9,16-17,22] During follow up, five incisional hernias (8%) at the site of the previous stoma were seen. However, this number is probably underestimated. Several patients are only seen once or twice after ileostomy closure and are discharged before incisional hernias develop.

A major concern is the long period of time (median 24 weeks) during which the ileostomy is present. All ileostomies were intended to be closed within 8-12 weeks.[16,20,22] Although biased by the retrospective nature of this study, no specific medical reason for this delay was found in the majority of the patients. The delay in closure might be related to the low medical urgency of the procedure combined with the sparse medical resources available.

A high percentage of patients (42%) experienced stoma-related complications during this period, enhancing the adverse effect of ileostomies per se on the quality of life. Stoma-related complications presented during the whole period the stoma was in place. Therefore, many of the encountered complications could have been avoided if the ileostomy had been closed earlier after its construction, for example during the same hospital admission.[26] An uncomplicated recovery after the initial operation and the absence of anastomotic leakage as radiologically tested by water soluble contrast enema examination, are of course crucial prerequisites for this early closure. Therefore, early closure will only be feasible in selected cases.

Nevertheless, the length of time between ileostomy construction and closure can be substantially reduced by closure within the regular period of 8-12 weeks or maybe even more if closure within 10 days after the initial operation is possible. This probably reduces stoma-related complications and improves quality of life.

Conclusions

The great majority of temporary loop ileostomies (87%) were closed in this retrospective series, albeit after a median period of 24 weeks. This period is considered unnecessarily long and many stoma-related complications occurred during this period. Therefore, ileostomy closure at an earlier stage will reduce stoma-related complications and improve quality of life in these patients.

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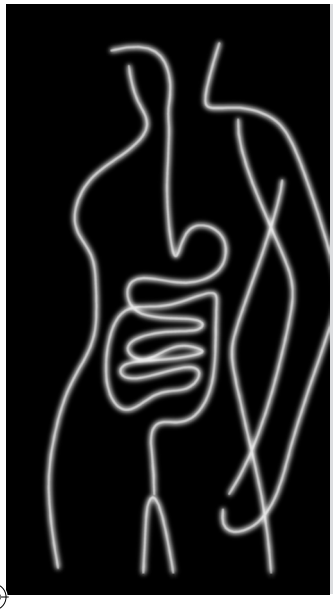

CHAPTER 71

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Feasibility of early closure of loop ileostomies: a pilot study

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Abstract

Background and Objectives. A loop ileostomy is constructed to protect a distal anastomosis and closure is usually performed not earlier than after two to three months. Earlier closure might reduce stoma-related morbidity, improve quality of life and still effectively protect the distal anastomosis.

Aim. To investigate the feasibility of early closure of loop ileostomies, i.e. during the same hospital admission as the initial operation.

Methods. Twenty-seven consecutive patients with a protective loop ileostomy were included. If patient's recovery was uneventful, water-soluble contrast enema examination was performed, preferably after seven to eight days. If no radiologic signs of leakage were detected, the ileostomy was closed during the same hospital admission.

Results. Twenty-seven patients (8 female, 19 male) were analyzed (mean age 60 years). Eighteen patients had early ileostomy closure on average 11 days (range 7-21 days) after the initial procedure. In nine patients the procedure was postponed because of leakage of the anastomosis (n = 3), delayed recovery (n = 1), small bowel obstruction (n = 1), gastroparesis (n = 1), logistic reasons (n = 2) or irradical cancer resection followed by radiotherapy (n = 1). There was no mortality and four mild complications occurred after early closure: superficial wound infection (n = 2), intravenous-catheter sepsis (n = 1), small bowel obstruction (n = 1).

Conclusions. Closure of a loop ileostomy early after the initial operation was feasible in 18 out of 27 patients and was associated with low morbidity and no mortality.

Introduction

In colorectal surgery, a temporary loop ileostomy or loop colostomy is often constructed to protect a distal anastomosis.[1] The loop ileostomy is favored by most surgeons because it is easy to construct and to close.[2-5] In general, stoma closure is not planned earlier than two to three months after construction although there is, as yet, no evidence that this period is really required for complete healing of the colonic anastomosis.[6-8] However, during this two to three month period, stoma-related complications, such as skin rash, prolapse, parastomal herniation and electrolyte disturbances, occur in about 30 percent of the patients increasing the stoma-related costs.[9-10] An ileostomy, accompanied by discomfort for the patient, has an adverse effect on the quality of life especially if related complications occur.[9,11-14]

A loop ileostomy should effectively protect the colonic anastomosis or at least decrease the detrimental effects once leakage occurs.[15-19] Leakage rates after rectal resection vary from 8 to 18 percent.[20-23] Especially with a liberal policy to use loop ileostomies, many of these ileostomies will be superfluous. Early closure in these patients might reduce the stoma-related morbidity and the patient's discomfort.

Since anastomotic leakage mostly presents within a period of five to seven days, [24] it is probably justified to state that, if there are neither clinical nor radiologic signs of anastomotic leakage after one week, the colonic anastomosis has sufficiently healed. Therefore, early closure of the ileostomy could be considered if the patient is physically fit to be operated on again.

The aim of this pilot study was to investigate the feasibility to close protective loop ileostomies during the same hospital admission, shortly after the initial operation.

Materials and Methods

Twenty-seven consecutive patients with a loop ileostomy after colorectal or coloanal anastomosis were prospectively studied. The study was approved by the hospitals' ethics committees. Written informed consent was obtained from all patients.

If the patient's recovery was uneventful, a water-soluble contrast enema examination [25] was performed seven or eight days after the initial operation. A soft, flexible catheter was carefully inserted without inflating the balloon and water-soluble contrast was instilled. If there were no radiologic signs of contrast leakage, patients were scheduled for ileostomy closure. All patients received prophylactic antimicrobial agents (i.v. cefuroxim & clindamycin) just prior to the second operation.

Closure of the ileostomy was performed under general anesthesia as a local procedure, i.e. the laparotomy wound was not reopened. A one-layer running suture (polydioxanone suture (PDS®) 3.0, Ethicon, Hamburg, Germany) was used to close the small bowel defect after excision of the stoma-edge or, if a limited small bowel resection was indicated (e.g.

in case of damage to the bowel loop), an end-to-end anastomosis was performed using the same material. Stapling devices were not used. The skin was only partially closed.

Results

Twenty-seven patients (8 female, 19 male) entered the study (mean age 60 years, range 31-86 years). Twenty-two underwent a rectal resection with total mesorectal excision for tumors located in the middle one third and distal one third of the rectum, followed by coloanal anastomoses. Fourteen of these patients (63.6 percent) underwent preoperative radiotherapy. Four patients underwent a recto-sigmoid resection and one had a traumatic perforation of the rectum (7 cm from the anal verge) which was primarily closed. Anastomoses were performed using the double stapling technique. In all patients a loop ileostomy was constructed to protect the anastomosis.

In twenty-one patients a water-soluble contrast enema examination was performed shortly after the initial operation. These examinations revealed anastomotic leakage in one patient and sufficiently healed anastomoses in twenty patients. (Table 1.) The contrast enema examination was not performed in six patients for several reasons; two patients had an anastomotic leakage already diagnosed by CT-scan, one patient had a gastroparesis, one patient a small bowel obstruction and in one patient, with a microscopically irradical resection, radiotherapy was given priority over early ileostomy closure. The sixth patient, a 70-year old man had a delayed recovery caused by a combination of respiratory insufficiency, wound infection, urinary tract infection and insufficient oral intake. None of these six patients were believed to be eligible for early closure, thus contrast enema examination was without consequences and therefore not performed.

In 18 of the 27 patients (67 percent) early closure of the loop ileostomy was feasible. Early ileostomy closure was performed after a median of 11 days (range 7-21 days) after its construction. The median operation time was 90 minutes (range 34-120 minutes) and in 14 patients (78 percent) a limited resection of the small bowel with end-to-end anastomosis was performed.

Table 1. Contrast Enema Examination Characteristics.

Total number of loop ileostomies	27
Number of contrast enema examinations performed early after initial operation	21 (78%)
Anastomotic leakage *	1
No leakage	20

* leakages as identified only on contrast enema examination.

There were various reasons to postpone ileostomy closure. (Table 2.) Closure was of course postponed in the six patients who didn't undergo contrast enema examination as well as in the one patient with radiologically proven anastomotic leakage. In two patients ileostomy closure was postponed because of logistic problems. These problems were caused by the inability to schedule a second operation within a few days after the initial operation.

Table 2. Ileostomy Closure Characteristics.

Total number of loop ileostomies	27
Number of early closure of loop ileostomies	**18 (67%)**
Reasons for postponing ileostomy closure	**9 (33%)**
Anastomotic leakage *	3
Gastroparesis	1
Delayed recovery †	1
Small bowel obstruction	1
Logistic reasons or ‡	2
Postoperative radiotherapy §	1

* All anastomotic leakages together, irrespective of the diagnostic test performed, † patient had a delayed recovery caused by a combination of respiratory insufficiency , wound infection, urinary tract infection and insufficient oral intake, ‡ logistic impossibility to schedule a second operation within a few days, § postoperative radiotherapy was given priority over early ileostomy closure since the performed rectal cancer resection was microscopically irradical.

The median admission time for the initial operation together with closure of the ileostomy during the same hospital admission was 22 days (range 13-38 days). Three patients were discharged from the hospital for a weekend before ileostomy closure. These days were excluded from the total admission time. The median hospital stay after ileostomy closure was six days (range 3-20 days).

None of the 27 patients died in the postoperative period. Ten patients (37 percent) had a total of 13 complications after the initial operation. In one patient, the primary postoperative period was complicated by sepsis based on leakage of the distal anastomosis which required operative pelvic drainage. Two patients had an abdominal abscess for which a percutaneous drain was placed. One patient developed a benign anastomotic stenosis which was dilated during ileostomy closure nine months after the initial operation. One patient had a small-bowel obstruction, one a wound infection, and one a gastroparesis which all resolved spontaneously. One patient suffered from hematemesis because of esophagitis, which was successfully treated with intravenous proton pump inhibitors. Three patients had a urinary-tract infection and one had a pneumonia, all successfully treated with antimicrobial agents. One patient had temporary neuropraxis of the peroneal nerve.

After early ileostomy closure, 4 of the 18 patients (22 percent) had complications. Two patients had a superficial wound infection and one patient had a small bowel obstruction which all responded well to conservative treatment. One patient developed a central venous catheter sepsis which was successfully treated with removal of the catheter

and i.v. antibiotics. This was the only patient who received total parental nutrition after surgery. There were no clinical signs of severe malnourishment among patients, as reflected by loss of more than 10 percent of body weight in the period prior to surgery. There were no cardiac or respiratory complications following the second operation.

The median follow-up for all 27 patients was 29 weeks (range 5-225 weeks). During this period, no anastomotic leakage was identified in any of the patients with early ileostomy closure.
In five of the nine patients with postponed ileostomy closure, the ileostomies were closed several months after the initial operation with a median operation time of 49 minutes (range 45-52 minutes, $P = .233$ early *vs.* postponed closure). The median admission time for these five patients was seven days (range 4-7 days). In the remaining four patients the ileostomy was not closed yet because of ongoing recovery after anastomotic leakage (n = 3) and on patient's request (n = 1).

Two patients were readmitted after two and four weeks respectively. The first one because of gastroenteritis which was treated conservatively. The second suffered from temporary abdominal cramps without any signs of peritonitis or sepsis. Plain abdominal X-ray and laboratory tests didn't reveal any abnormalities and this patient was discharged after one day of clinical observation.

Discussion

In this pilot study it was feasible to perform early closure of a loop ileostomy in the majority of patients (18/27) without major complications.

The median period between the initial operation and the closure of the ileostomy was 11 days and the median hospital admission time was 22 days. Ideally, this should be reduced.
Especially in the beginning logistic problems occurred which resulted in a relatively long period between the two operations and even postponing ileostomy closure in two patients, although they were eligible according to the contrast enema examination. This partly explains the long hospital admission time. The desired reduction was achieved by performing the contrast examination specifically on the seventh day and ileostomy closure the day after. Presently, ileostomy closure is planned at the moment of scheduling the initial operation, but is only performed if the patient is physically fit and has a sufficiently healed anastomosis as tested by a contrast enema examination.
Furthermore, in this pilot study we were cautious and discharged patients only if we were absolutely satisfied with the patient's physical status. Therefore, patients were probably hospitalized several days too long. Now that the feasibility and safety of early

closure have been demonstrated, it might be possible to shorten hospital stay after the second operation.

Loop ileostomies are generally not closed earlier than two to three months after primary surgery. Stoma-related complications are common during this period, having an adverse effect on the quality of life.[6,8-9,11-14] Clinically significant anastomotic leakage results in a considerable morbidity and impaired functional outcome.[15,18,26-28] Poon *et al*.[15] reported anastomotic leakages in patients with and without a loop ileostomy in 3.2 percent and 12.6 percent respectively. Karanjia *et al*.[27] reported anastomotic leakages in 0.8 percent and 8 percent respectively. Based on these data, the number of patients needed to treat with a loop ileostomy to decrease the detrimental effects of one distal anastomotic leakage ranges between 11 and 14 patients. This would imply, that a loop ileostomy has to be created in 11 to 14 patients to possibly prevent a clinically relevant anastomotic leakage in one patient. [15] Therefore the majority of patients will have an unnecessary ileostomy for several months. In a large number of patients, discomfort and stoma-related morbidity are introduced to prevent clinically relevant anastomotic leakages in only a small minority.
Early closure may combine optimal temporary protection of the colonic anastomosis with reduction of patient's discomfort and stoma-related morbidity. Therefore, the concept of early closure of loop ileostomies seems an attractive strategy and could improve quality of life.

Although there are only limited data available concerning the temporal process of anastomotic healing in the colon, uncomplicated healing can probably be judged reliably after a period of one week. This is supported by studies in baboons, in which measurement of bursting pressures of colonic anastomoses showed a rapid increase in tensile strength after the fifth day and by the seventh day the strength greatly exceeded the initial strength.[29] Furthermore, anastomotic failure has been reported to present mostly within five to seven days. [24]
If leakage is not clinically manifest, subclinical anastomotic leakage can be detected by contrast enema examination.[30] However, it is unclear whether contrast enema is reliable in the early postoperative stage. There is a discrepancy between clinically relevant and radiologically apparent leakage, the number of radiological leakages being substantially higher.[31-34] Haynes *et al.*[33] reported radiological leakages in 20.5 percent of patients 7 to 16 days after operation, whereas clinical leaks were noted in only 11.9 percent of the patients. Shorthouse *et al*.[32] reported an overall incidence of clinically relevant leaks of 12.5 percent after rectal resection, but radiological examination doubled the leak rate to 24.1 percent after a median postoperative interval of 12 days. In our study, two patients (7.4 percent) had clinically relevant anastomotic leakages. Contrast enema examination revealed one additional leakage early after the initial operation. In four patients contrast enema examination was not performed. In two of these four patients leakage had already been demonstrated by CT-scan. However, we believe that the anastomotic leakage rate, in the present study, early after the construction of the anastomoses is acceptable and in

line with other reports. In our view, closure of the loop ileostomy should be postponed in case of radiological contrast leakage, although the leakage might not be of any clinical relevance.

Shortly after the initial operation in this study, three clinically relevant distal anastomotic leakages were encountered. In these three patients closure was postponed. In the absence of clinical and radiological signs of leakage, early ileostomy closure did not lead to secondary distal leakage in any of the 18 patients. This suggests that in the absence of clinically apparent leakage, a contrast enema examination is a reliable indicator of the quality of the distal anastomotic healing process one week after the initial operation. However, these data must be interpreted with caution because of the limited number of patients.

Conclusion

In this pilot study, early closure of a loop ileostomy was feasible and appeared to be safe for the majority of patients after colorectal or coloanal anastomosis. More data are needed to substantiate these preliminary results.

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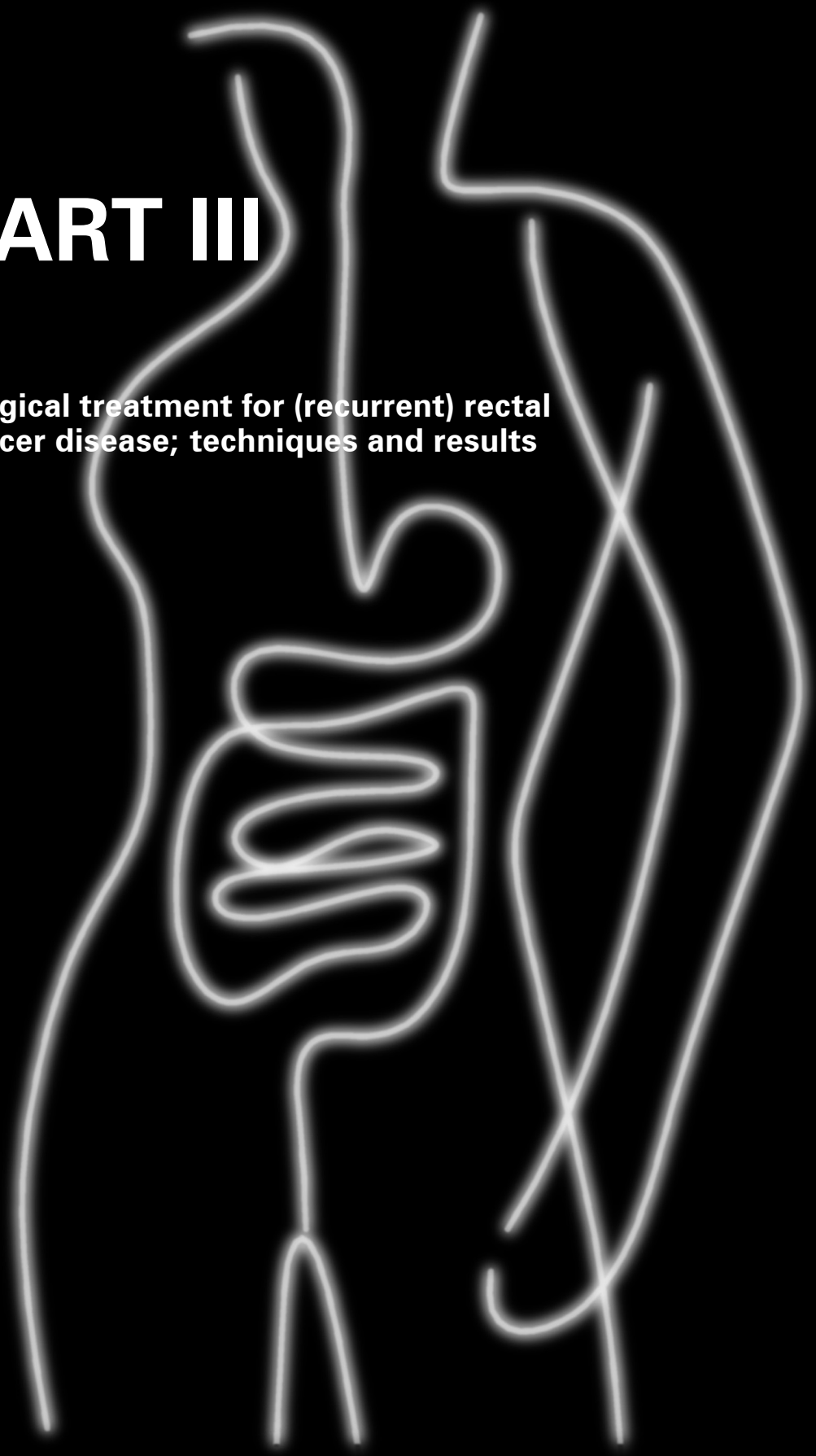
PART III

Surgical treatment for (recurrent) rectal cancer disease; techniques and results



CHAPTER 8

Submitted for publication

Management and survival of patients with recurrent rectal cancer after total mesorectal excision; a population based study in greater Amsterdam

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Abstract

Background and Objectives. To analyse retrospectively in a population-based study the management and survival of patients with recurrent rectal cancer initially treated with a macroscopically radical resection obtained with total mesorectal excision (TME).

Methods. All rectal carcinomas diagnosed during 1998-2000 and initially treated with a macroscopically radical resection (632 patients) were selected from the Amsterdam Cancer Registry. For patients with recurrent disease, information on treatment of the recurrence was collected from the medical records.

Results. Local recurrence with or without clinically apparent distant dissemination occurred in 62 patients (10%). Thirty-two patients had an isolated local recurrence. Ten of these 32 patients (31%) underwent radical re-resection and experienced the highest survival (three quarters survived for at least three years). Eight patients (25%) underwent non-radical surgery (median survival 24 months), seven patients (22%) were treated with radio- and/or chemotherapy without surgery (median survival 15 months) and seven patients (22%) only received best supportive care (median survival 5 months).

Distant dissemination occurred in 124 patients (20%) of whom 30 patients also had a local recurrence. The majority (54%) of these patients were treated with radio- and/or chemotherapy without surgery (median survival 15 months). Twenty-seven percent of these patients only received best supportive care (median survival 6 months), while 16% underwent surgery for their recurrence. Survival was best in the latter group (median survival 32 months)

Conclusions. Although treatment options and survival are limited in case of recurrent rectal cancer after radical local resection obtained with TME, patients can benefit from additional treatment, especially if a radical resection is feasible.

Introduction

Colorectal cancer is the second most common cancer in the western world and approximately one third of these tumours is located in the rectum or rectosigmoid.[1] Annually, over 3,000 patients are registered with a newly diagnosed rectal or rectosigmoid carcinoma in the Netherlands.[2-3] In these patients, locally recurrent disease is a major concern and is often accompanied with intractable pain and severely disabling complications which are difficult to treat.[4-6] It has a tremendous impact on quality of life [7] and frequently induces an awful last period of patient's life. Therefore, the focus in rectal cancer research has been on the prevention of locally recurrent disease, which resulted in the introduction of preoperative radiotherapy and total mesorectal excision (TME).[8-12]

There are many reports on the treatment of recurrent rectal cancer.[4,6,13-16] However, these reports present mainly results from randomised clinical trials or specialised institutes, which are known to be biased.[17] There are only a few population-based reports on the treatment of locally recurrent rectal cancer disease,[13,18] although they are probably the best reflection of daily practice.

In 1996, TME was introduced in Greater Amsterdam, the region of the Comprehensive Cancer Centre Amsterdam (CCCA). Its introduction was facilitated by the CCCA. Surgeons were supervised by teacher-surgeons in order to qualify as TME-surgeon and a documentation project was started to investigate the influence of TME-surgery on the incidence of local recurrences and survival.[19] From 1998 on, all patients in Greater Amsterdam are treated with TME in case of rectal resection.

The aim of the present study was to analyse retrospectively in a population-based setting the management and survival of patients with recurrent rectal cancer, initially treated with macroscopically radical local resection obtained with total mesorectal excision (TME).

Materials and Methods

Cancer registry data

All primary rectal carcinomas (rectosigmoid excluded) diagnosed in patients with residence in Greater Amsterdam, the region of the Comprehensive Cancer Centre Amsterdam (CCCA), between January 1st 1998 and December 31st 2000 and who underwent a macroscopically radical resection obtained with total mesorectal excision (TME) in the absence of distant dissemination, were selected from the Amsterdam Cancer Registry of the CCCA. The Amsterdam Cancer Registry is a regional, population-based cancer registry with complete regional coverage. Non-epithelial cancers, carcinoids and cases with preceding invasive cancers were excluded. The population of the region amounted to 2.8 million inhabitants on December 31st, 2000, approximately 17% of the total population of the Netherlands.

The information for the cancer registry is routinely extracted from detailed hospital and outpatient clinic records by registration clerks. Apart from demographic data, data are collected on morphological classification, stage of the tumour and primary treatment of the patients. The TNM system for classification of malignant tumours is prospectively registered to classify all rectal carcinomas. Stage grouping in this study was performed according to the 6th edition of the TNM-classification[20], based on the available information after surgery (pTNM).

Of the selected cases a supplementary data set was extracted from the medical records. This data set included the occurrence and the date of local recurrence or distant dissemination. Local recurrence was defined as cancer recurrence within the lower pelvis. Additional treatment of recurrence, the presence of microscopic or macroscopic residual disease after salvage surgery for recurrent disease, the date of salvage surgery and the cause of death were also collected. Cases were generally followed for five, but at least three years after the date of initial surgery.

Vital status

The vital status was updated by active follow-up in the hospitals, by linking files with deceased persons to the cancer registry and by linkage to the electronic death registry of the Central Office for Genealogy in September 2003 and February 2005, as described earlier.[21] Completeness of follow-up of the vital status is estimated to be over 99.5%.

Statistical methods

P-values of 0.05 or below were considered statistically significant. All statistical analyses were performed using a two-sided 5 percent level of significance.

Survival probabilities were estimated using the Kaplan-Meier method.[22] Multivariate analyses using the Cox proportional-hazard method were performed to calculate the hazard ratio (HR) for death after recurrent disease. [23] Cox regression and Kaplan-Meier survival curves were calculated with STATA (Stata Corporation, College Station, TX, USA).

Results

Initial treatment and incidence of local recurrence

A total of 632 patients diagnosed with primary rectal carcinoma in the absence of clinically manifest distant dissemination between 1998 and 2000 underwent a macroscopically radical local resection obtained with TME. Characteristics of the initial treatment of the primary tumour in these patients are given in Table 1. Local recurrence within five years after diagnosis occurred in 62 patients (10%), including 30 cases with distant dissemination (6%). Of these 30 patients, 24 patients had synchronous local and distant recurrence, while six patients developed distant dissemination after the local recurrence.

Table 1. Initially applied radiotherapy in surgically treated, primary rectal carcinoma patients according to pTNM-stage in Greater Amsterdam, the Netherlands, 1998-2000 (RT=radiotherapy)

Stage of disease	Number of cases (% of total)	Radiotherapy, number of patients (%)		
		No RT	Postoperative RT	Preoperative RT
I	209 (33)	115 (55)	1 (0)	93 (45)
IIA	180 (28)	72 (40)	26 (14)	82 (46)
IIB	20 (3)	2 (10)	6 (30)	12 (60)
IIIA	32 (5)	8 (25)	11 (34)	13 (41)
IIIB	113 (18)	26 (23)	32 (28)	55 (49)
IIIC	72 (11)	13 (18)	23 (32)	36 (50)
unknown	6 (1)	2 (33)	-	4 (67)
Total	632	238 (38)	99 (16)	295 (47)

Treatment of local recurrence

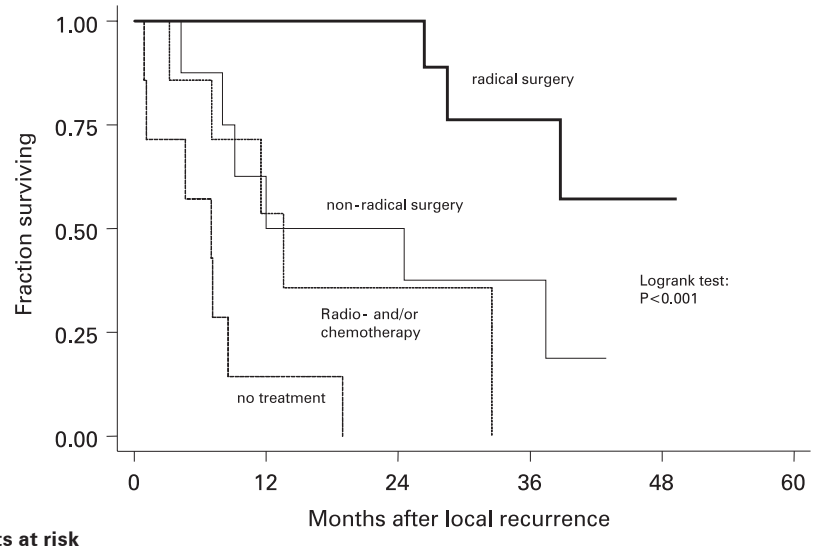
There were 32 out of 62 patients (52%) without signs of distant dissemination at the time of diagnosis of recurrent disease. Median survival after recurrence in the absence of distant dissemination was 25 months. Ten of these 32 patients underwent a microscopically radical resection of their recurrence (Table 2). As is depicted in Figure 1, radical surgery resulted in a significantly better survival than non-radical surgery, radio- and/or chemotherapy without surgery or best supportive care (log-rank test radical surgery versus other treatments: $p<0.001$). About three quarters of the patients who underwent a radical resection survived for at least three years. Median survival after non-radical surgery (8 patients) was 24 months, 7 months after radio- and/or chemotherapy without surgery (7 patients) and was 5 months in case of best supportive care only (7 patients).

Table 2. Secondary treatment of local recurrence (in the absence of distant dissemination) according to treatment with radiotherapy and stage at initial diagnosis (after a macroscopically radical resection obtained with total mesorectal excision).

Secondary treatment	Stage and treatment with radiotherapy at initial diagnosis									Total
	stage I			stage II			stage III			
	no RT	post RT	pre RT	no RT	post RT	pre RT	no RT	post RT	pre RT	
Radical surgery*	3	-	1	3	-	1	1	-	1	10
(+/- radiotherapy and/or chemotherapy)										(31%)
Non-radical surgery*	-	-	-	2	1	2	-	3	-	8
(+/- radiotherapy and/ or chemotherapy)										(25%)
Radiotherapy and/or chemotherapy without surgery	2	-	-	1	1	-	1	2	-	7
										(22%)
Best supportive care	1	-	-	-	1	3	1	-	1	7
										(22%)
Total	6	-	1	6	3	6	3	5	2	32

* radical surgery was defined as surgery without microscopically residual isease; all other surgery cases were classified as non-radical, no RT= no radiotherapy; post RT=postoperative radiotherapy; pre RT=preoperative radiotherapy

Figure 1. Crude survival after isolated local recurrence in rectal cancer patients initially treated with a macroscopically radical local resection obtained with total mesorectal excision in Greater Amsterdam according to treatment for recurrence.
Radical surgery is defined as surgery without macroscopically or microscopically residual disease. Non-radical surgery is defined as surgery with macroscopically or microscopically residual disease.



Number of patients at risk						
Radical surgery	10	10	9	4	2	1
Non-radical surgery	8	5	4	3	-	-
Radio- & chemotherapy	7	3	3	-	-	-
Best supportive care	7	1	-	-	-	-

In 30 patients (48%), distant dissemination was present at the time of diagnosis of local recurrent disease. Median survival after local recurrence in the presence of distant dissemination was 10 months. None of these patients underwent curative surgery, two patients underwent non-radical surgical resection, 14 patients were treated with radio- and/or chemotherapy without surgery (median survival 14 months) and 14 patients received best supportive care only (median survival 9 months).

Prognostic factors for survival after recurrence

Several factors were analysed to identify prognostic factors for improved survival after local recurrence. The results of the multivariate analysis are shown in Table 3. Surgery for recurrent disease (radical and non-radical) was a prognostic factor for improved survival, while radiotherapy applied during the initial treatment did not influence survival after local recurrence (Figure 2).

Distant dissemination

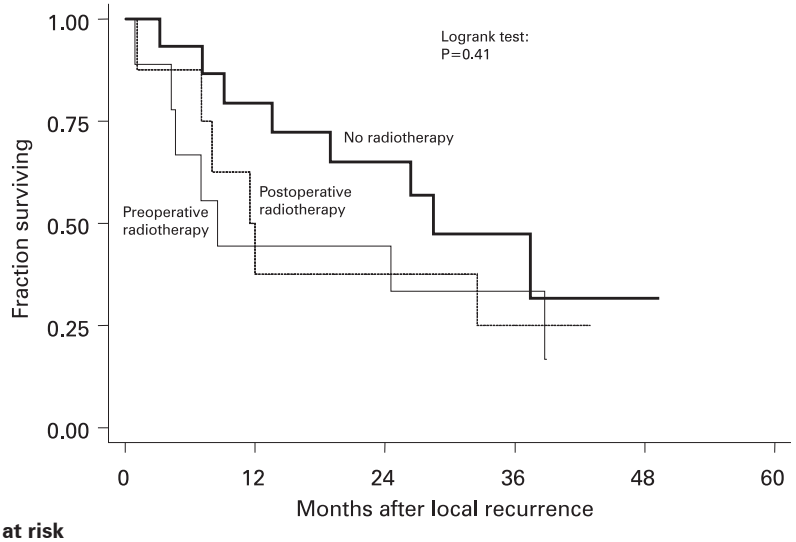
Distant dissemination within five years after diagnosis occurred in 124 patients (20%). The majority of patients (54%) with distant dissemination were treated with radio- and/or chemotherapy (Table 4). The median survival after distant dissemination was 15 months.
Twenty patients (16%) underwent surgery for their recurrence, including liver resections in eight patients, lung resections in five patients, and other surgical procedures in seven

Table 3. Multivariate analysis of potentially prognostic factors for improved survival after treatment of patients with a locally recurrent rectal carcinoma in Greater Amsterdam (cases with distant dissemination and/or macroscopic residual disease at time of initial treatment are excluded)

Parameter	Number of cases	Hazard Ratio* (95% Confidence Interval)
Sex		
Male (reference) vs. female	33/29	1.9 (0.9-3.7)
Radiotherapy at initial treatment		
No radiotherapy	23	1.0
Preoperative radiotherapy	23	1.2 (0.6-2.5)
Postoperative radiotherapy	16	0.9 (0.4-1.8)
Distant dissemination at time of local recurrence		
Absent (reference) vs. present	32/30	0.8 (0.4-1.6)
Surgical treatment of locally recurrent disease		
No surgery	42	1.0
Radical surgery	10	0.1 (0.0-0.3)
Non-radical surgery	10	0.5 (0.2-1.3)

* Hazard Ratio > 1= worse prognosis, Hazard Ratio <1= better prognosis.

Figure 2. Crude survival after isolated local recurrence in rectal cancer patients initially treated with a macroscopically radical local resection obtained with total mesorectal excision in Greater Amsterdam according to radiotherapeutic treatment of the primary tumour.



Number of patients at risk						
No radiotherapy	15	11	8	3	2	1
Preoperative radiotherapy	9	5	5	2	-	-
Postoperative radiotherapy	8	4	3	1	-	-

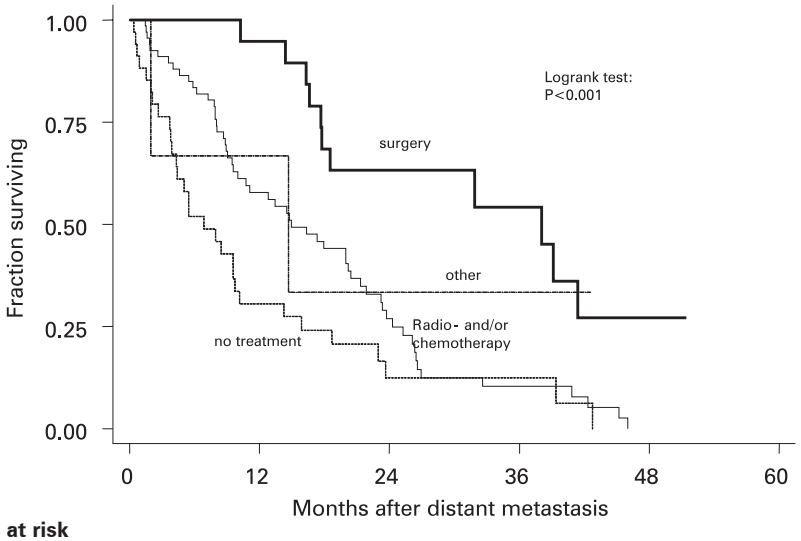
patients. Median survival after surgery was 32 months, while median survival after radiotherapy and/or chemotherapy without surgery was 15 months and 6 months if best supportive care was applied (Figure 3). Patients with distant dissemination who were treated surgically experienced the highest survival (log-rank test surgery versus other treatments: $p<0.001$).

Table 4. Treatment of distant dissemination in patients initially treated with a macroscopically radical local resection obtained with total mesorectal excision in the absence of distant metastasis.

Treatment	No local recurrence		Local recurrence*		Total	
	n	%	n	%	n	%
Surgery* (+/- radiotherapy and/or chemotherapy)	18	19%	2	7%	20	16%
Radiotherapy and/or chemotherapy	54	57%	13	43%	67	54%
Other	1	1%	2	7%	3	2%
Best supportive care	21	22%	13	43%	34	27%
Total	94		30		124	

* synchronous with distant metastasis or prior to distant metastasis

Figure 3. Crude survival after distant dissemination in rectal cancer patients initially treated with a macroscopically radical local resection obtained with total mesorectal excision in Greater Amsterdam according to treatment for distant dissemination.



Number of patients at risk

Surgery	20	18	11	6	2	-
Radio- and/or chemoth.	67	34	13	4	-	-
Best supportive care	34	10	3	2	-	-
Other	3	2	1	1	-	-

Discussion

This is the first population-based study concerning recurrent rectal cancer treatment after the introduction of TME. All patients in this study were initially diagnosed between 1998 and 2000 in Greater Amsterdam and treated by macroscopically radical local resection obtained with TME. A local recurrence occurred in 62 of the 632 patients (10%), while distant dissemination was found in 124 patients (20%).

Treatment of patients with isolated recurrent disease

Of the 32 patients with an isolated local recurrence, 31% were treated by a radical resection. These patients experienced a significantly better survival compared to patients who underwent a non-radical resection for their recurrence. As has been shown previously, radical resection of locally recurrent disease can achieve long-term survival[4,13-15,24] and should therefore be aimed at, even if extended resection (e.g. abdominosacral resection or exenteration)[16,25-26] or flap-reconstruction [27] is required.

Survival in patients treated with non-radical surgery and patients treated with radiotherapy and/or chemotherapy without surgery was comparable, but was significantly worse in patients not treated with either surgery, radiotherapy or chemotherapy. Although no information concerning the extent of recurrent disease was available in this study, treatment has probably been more aggressive in case of limited disease and, therefore, selection bias may have played an important role in the outcome of the various treatment modalities.

Treatment of patients with distant dissemination

The median survival after distant dissemination was 15 months for patients diagnosed in 1998-2000. In a previous study, we have described that patients diagnosed in 1988-1991 in Greater Amsterdam only survived 9 months after distant dissemination (log-rank test: p=0.004).[19] The majority of patients diagnosed in 1998-2000 (54%) with distant dissemination were treated with radiotherapy and/or chemotherapy without surgery, while 16% were treated with surgical resection and 27% received only best supportive care. Survival was significantly better in the group of patients treated with surgery compared to other groups. This is probably due to the limited spread of disease in these patients (selection bias). As no treatment data were available for the patients diagnosed in 1988-1991 in Greater Amsterdam, it is unclear which treatment modality has contributed to the increase in the median survival.

Conclusions

In this population-based study, treatment options and survival were limited in patients with recurrent rectal cancer after macroscopically radical local resection obtained with Total Mesorectal Excision. Approximately one third of the patients only received best supportive care with a subsequent poor survival. On the other hand, in one third of the patients with an isolated local recurrence, radical resection was feasible with a favourable survival. We conclude, that a locally recurrent rectal cancer without distant dissemination does not automatically lead to a hopeless situation.[28] However, survival after local recurrence in combination with distant dissemination remains extremely poor.

Acknowledgements

The surgeons in the twenty participating hospitals (Academic Medical Centre, Free University Medical Centre, Sint Lucas Andreas Hospital, Netherlands Cancer Institute, BovenIJ Hospital, Onze Lieve Vrouwe Hospital, Slotervaart Hospital, Waterland Hospital, Amstelland Hospital, Zaans Medical Centre, Flevo Hospital, IJsselmeer Hospitals, Gooi-Noord Hospital, Hilversum Hospital, Kennemer Hospital, Red Cross Hospital, Spaarne Hospital, Gemini Hospital, Westfries Hospital, Medical Centre Alkmaar) are greatly acknowledged.

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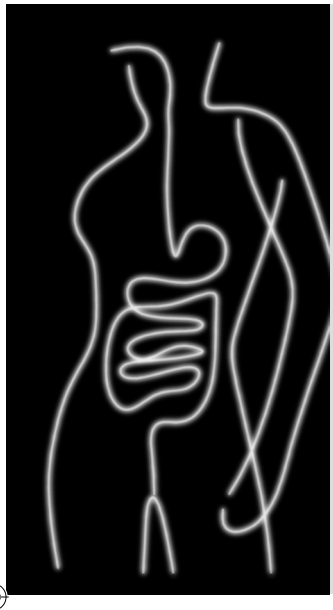

CHAPTER 9

European Journal of Surgical Oncology 2004; **30(8)**: 857-63

Surgical treatment of locally recurrent rectal cancer

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Abstract

Background and Objectives. The aim of our study was to analyse data of patients treated by salvage surgery for locally recurrent rectal cancer, with emphasis on the question whether salvage surgery is still worthwhile when adjuvant radiotherapy is no longer a treatment option.

Methods. 40 patients (19 male/ 21 female) treated by surgery with curative intent for locally recurrent rectal carcinoma were analysed. Local recurrence was defined as cancer recurrence within the lower pelvis. Salvage surgery included abdominoperineal resection, abdominosacral resection, exenteration (posterior or total) and local resection. Clinical and pathological factors were analysed to identify prognostic factors for survival.

Results. The median overall survival was 25 months (95% CI: 13-37 months) and 5-year survival was 28% (95% CI: 12-45%). The absence of symptoms at the time of recurrence, central localisation and the absence of microscopic involvement of surgical margins, but not additional radiotherapy, were found to be significant independent prognostic factors for better survival after salvage surgery.

Conclusion. Salvage surgery, alone or in combination with radiotherapy, can achieve radical resection of locally recurrent rectal cancer and can result in long-term survival.

Introduction

Annually, over 2000 patients are registered with a newly diagnosed rectal carcinoma in the Netherlands. [1] In the past, rectal cancer was associated with a high incidence of local recurrence, with rates of up to 30%. [2-3] Although the introduction of Total Mesorectal Excision (TME) [4] and preoperative radiotherapy [5-8] have reduced the number of local recurrences, these recurrences still occur in over 10% of cases and remain a major concern. [9]

In the Netherlands, treatment of rectal carcinoma has changed substantially. In 1994, according to population-based data of the Comprehensive Cancer Centre Amsterdam (CCCA), seven of 135 patients with a stage II or III (resectable) rectal carcinoma were treated with preoperative radiotherapy and 68 patients with postoperative radiotherapy. In 2001, 133 of 184 patients were treated with preoperative radiotherapy and 13 with postoperative radiotherapy. A further increase of the number of patients treated with preoperative radiotherapy is expected because of the results of the Dutch TME study, resulting in its inclusion in the national treatment guidelines of resectable rectal carcinoma in the Netherlands.

Therefore, most patients with newly diagnosed local recurrences have already had radiotherapy before the primary operation. Radiotherapeutic options will therefore be reduced in future cases of recurrence. Although little evidence exists to the effect of radiotherapy on survival, most clinicians will include some form of radiotherapy in their treatment strategy for recurrent rectal cancer.

In the Netherlands Cancer Institute, patients with a potentially resectable recurrence are treated by salvage surgery in combination with external beam radiotherapy. In patients who have been irradiated as part of their primary treatment, only resection is performed. The aim of our study was to analyse the data of patients treated by this strategy and to evaluate factors related to survival after salvage surgery with emphasis on the question whether salvage surgery is still worthwhile when adjuvant radiotherapy is no longer a treatment option.

Materials and Methods

The registry of the Netherlands Cancer Institute was searched for patients with locally recurrent rectal carcinoma who had undergone surgery with curative intent between 1985 and 2000. Local recurrence was defined as cancer recurrence within the lower pelvis (defined as below the sacral promontory). Curative intent was defined as an attempt at complete resection with tumour negative surgical margins, irrespective whether this goal was reached or not. Only patients who had initially undergone rectal resection (with or without additional chemo- and/or radiotherapy) were included, thus excluding patients after transanal excision.

40 patients (19 male/ 21 female) with a median age of 63 years (range 39-77) were identified. Nineteen patients were operated between 1985 and 1994, while the remaining 21 patients were operated between 1995 and 2000. Of these patients the charts, operation reports and pathology reports were reviewed. Primary tumour and treatment details (type and dates of radiotherapy, surgery and chemotherapy), hospital of initial treatment (Netherlands Cancer Institute or elsewhere) and initial TNM stage were registered.

The following data were collected concerning the detection of the local recurrence: date of recurrence, symptoms at time of presentation and diagnostic work-up. Type and date of treatment prior to and after the salvage surgery as well as type and date of operation, blood loss, operation time and administered units of packed cells were recorded. Time of admission at the ICU, ventilation time after surgery, perioperative complications and date of discharge were also gathered. Microscopic involvement of surgical margins and localisation of recurrence (central, i.e. tumour growth originating from the anastomosis or from the bowel wall versus peripheral, i.e. tumour growth from any other location in the small pelvis) were noted based on pathology reports.

Surgical procedures were classified as follows: low anterior resection (LAR), abdomino-perineal resection (APR), Hartmann resection, proctocolectomy, posterior exenteration (rectal resection with radical hysterectomy and total or posterior vaginectomy), total exenteration (removal of all pelvic viscera with the formation of a permanent colostomy and urinary diversion), abdominosacral resection (APR or exenteration with sacral resection) or local resection (resection not classified by any other mentioned before). [10] All abdominosacral resections were performed under the level of S2. [11,12] Information concerning follow-up included: date of progression, site of progression (local and/or distant metastases), symptoms related to local re-recurrence or distant metastases, date of last follow-up or death and cause of death (tumour related or not) if applicable.

Statistical methods

Event-free survival was calculated as the time from salvage operation to the date of an event. An event is defined as local re-recurrence or progression, distant metastasis or death. Patients without disease progression that did not die were censored at the date of last follow up.

Survival time was calculated as the time from salvage operation to the date of death (irrespective of cause) or date of last follow-up. Patients who were alive at the end of follow-up period were censored.

Survival probabilities were estimated using the Kaplan-Meier method. [13] Logrank tests and multivariate analyses using the Cox proportional-hazard method were performed to identify potential factors associated with survival after salvage surgery. [14] All statistical analyses were performed using a two-sided 5 percent level of significance. Statistical analyses were performed using SPSS Statistical Software (SPSS Inc., Chicago, IL, USA).

Results

Initial treatment

Five patients received treatment for their primary tumour at the Netherlands Cancer Institute, the other 35 patients were primarily treated elsewhere and referred to our institute for treatment of their recurrence. As initial surgical treatment, 26 patients had undergone low anterior resections, 11 abdominoperineal resections, one patient a Hartmann resection, one patient a proctocolectomy and one patient a posterior exenteration. One patient had undergone radiotherapy before and 16 patients after resection of the primary tumour.

Presentation of Local recurrence

The local recurrence was observed at a median period of 17.3 months after primary surgery (range 5-188.1)(Table 1). 25 patients had complaints, while the recurrence was found in 15 patients solely on basis of routine follow-up investigations.

In two patients, distant metastases (liver and lung) were found during preoperative work-up. They were included as they were subsequently operated for their metastases with curative intent.

Five patients were treated elsewhere for their recurrence by surgery and radiotherapy, but were referred for treatment of a second local recurrence.

Table 1. Inter-operative interval and symptoms at time of local recurrence detection .

Median disease-free interval (months)*	
All patients	17.3 (range 5-188.1)
TNM Stage I**	22.3 (range 6.1-188.1)
TNM Stage II**	26.7 (range 8.3-44.48)
TNM Stage III**	14.5 (range 5-39.5)
Cause leading to detection of local recurrence	
Routine screening (including CEA-elevation screening)***	15 patients
Symptoms	25 patients
Pain	12
Rectal blood loss	4
Pain and rectal blood loss	2
Small bowel obstruction	5
Tumour in wound of previous operation	2
Median inter-operative interval (months)****	
All patients	24.7 (range 6.2-192.8)
TNM Stage I**	24.5 (range 6.6-192.8)
TNM Stage II**	31.5 (range 19.6-94.2)
TNM Stage III**	17.8 (range 6.2-40.2)

* disease-free period = period between primary surgery and detection of local recurrence. ** TNM stage at the time of primary surgery.*** CEA-elevation is not regarded as a symptom, since it doesn't lead to the detection of a recurrence based on patients' complaints.**** inter-operative period = period between primary surgery and salvage surgery.

Table 2. Salvage surgery characteristics.

Type of surgery	
Abdominoperineal resection (APR)	13
Abdominosacral resection (ASR)	8
Exenteration (posterior/total)	9 (2/7)
Local resection	10
Median duration of surgery [hours]	6 (range 1-12)
Median operative blood loss [L]	4 (range 0-17)
Median units of administered packed cells	6 (range 0-24)
Need for artificial ventilation	9 patients
Median ventilation time after surgery in 9 patients [hours]	20 (range 2-40)

Treatment of local recurrences

Median time between the initial rectal cancer resection and salvage surgery was 24.7 months (range 6.2-192.8) (Table 1).

All but three patients stayed at the Intensive Care Unit after salvage surgery for a median of 3 days (range 1-18 days). Other salvage surgery characteristics are shown in Table 2. Surgical margins were microscopicaly free in 16 patients, while margins were involved in 19 cases, and uncertainty remained in five. In the analysis these latter five were included in the involved margins group.

In 13 patients salvage surgery was combined with radiotherapy. Three patients received preoperative radiotherapy, nine postoperative radiotherapy and one patient both before and after salvage surgery. Five patients did not receive radiotherapy during the entire treatment of the primary and recurrent tumour.

Complications

29 patients experienced 35 complications after salvage surgery and 13 of them needed reoperation (Table 3). Two patients died in the hospital, one due to multiple organ failure with respiratory insufficiency after major blood loss (17L) and the other due to

Table 3. Postoperative morbidity and admission time.

Complications	
Pelvic abscess/ fistula	8
Wound infection/ dehiscence	4/3
Urinary dehiscence	6
Sepsis/ multiple organ failure	1
Colostomy/ urostomy necrosis	1/1
Small bowel obstruction/perforation	1/1
Cardiovascular	2
Pulmonary	4
Renal insufficiency	1
Micturation problems	2
Number of re-operations for complications	13
Median hospitalisation time [days]*	29 (range 4-91)

* hospitalisation time = time between admission to and discharge from the hospital.

a pelvic abscess, which caused major septic bleeding. The latter patient died during reoperation.

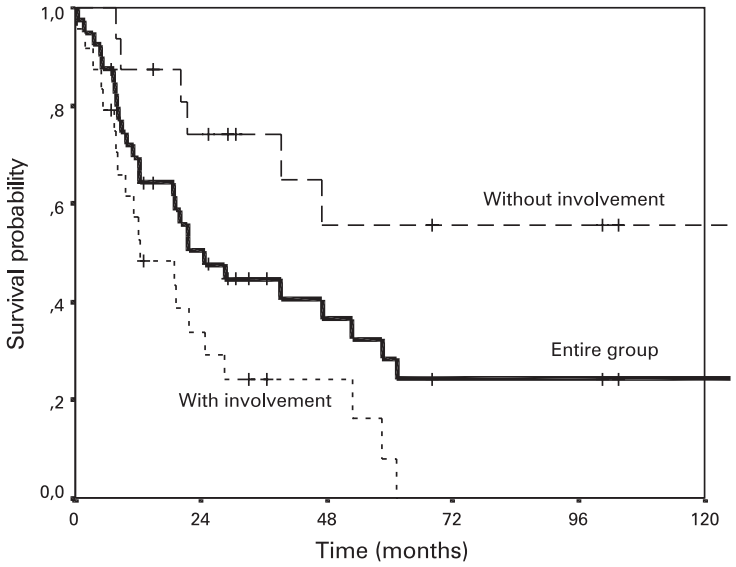
Follow up

At the time of analysis, the median actuarial follow up was 100 months (range 4-200). 12 patients had complete three-year follow up and seven had complete five-year follow up. In 27 patients new tumour recurrences developed, after a median interval of 9.5 months (range 1-41). Local re-recurrence alone was seen in 18 patients, distant metastases in sevenpatients and a combination of both in two patients. 13 patients with progressive disease received additional treatment for their re-recurrence. 26 patients died during follow-up of whom 2 the cause of death was not cancer related (renal insufficiency and cardiac arrest). The majority of patients (20/26) who died experienced symptoms caused by the tumour in the lower pelvis.

Survival

The median time to progression was 18 months (95% confidence interval: 8-28 months), the 5-year disease free survival 26% (95% confidence interval: 11-41%). The median overall survival and 5-year survival were 25 months (CI:13-37 months) and 28% (95% confidence interval: 12-45%) respectively (Figure). There were seven long-term survivors (survival > 5 years); all but one were event-free after 5 years.

Figure. Kaplan-Meier survival curves showing patients with and without microscopic involvement of surgical margins after resection of locally recurrent rectal carcinoma with curative intent (p=.006) and Kaplan-Meier survival curve of entire group (bold).



Number of patients at risk

Entire group	40	18	9	5	5	3
Without involvement	16	11	6	5	5	3
With involvement	24	7	3	0	0	0

Prognostic factors

Clinical and pathological factors were analysed to identify prognostic factors for survival. The results of univariate analysis are shown in Table 4. Factors found to be significant in this analysis were also significant in the multivariate analysis with a hazard ratio of 3.3 (95% confidence interval (CI) 1.3-8.1) for the absence of symptoms, 3.1 (95% CI: 1.1-8.3) for the absence of microscopic involvement of margins (Figure) and 3.3 (95% CI: 1.0-10.9) for a central localisation. Radiotherapy did not significantly influence survival (hazard ratio 0.5, 95% CI: 0.3-1.8).

Table 4. Uni-variate analysis of potentially prognostic factors (Cox proportional hazards analysis).

Variable	Number	Hazard Ratio *(95% Confidence Interval)
Gender		
Male vs. female	19/21	0.6 (0.3-1.3)
Tumour stage primary tumour		
Stage I	10	1
Stage II	13	0.8 (0.3-2.3)
Stage III	17	0.8 (0.3-2.0)
Time to recurrence		
< 2 years vs. > 2 years	25/15	1.6 (0.7-3.5)
Symptoms		
Absent vs. Present	15/25	2.4 (1.0-5.6)
Radiotherapy at time of salvage surgery		
yes vs. no	13/27	0.5 (0.3-1.8)
Microscopic involvement of surgical margins		
Absent vs. Present	16/24	4.6 (1.8-11.7)
Recurrence localisation		
Central vs. Peripheral	13/17	5.0 (1.6-15.1)

* Hazard Ratio < 1= worse prognosis, Hazard Ratio >1= better prognosis.

Discussion

Locally recurrent rectal cancer remains a major concern despite the introduction of TME [4] and short-term preoperative radiotherapy. [5-8] Local recurrence is often accompanied with intractable pain and complications which are difficult to treat. Therefore, it has a tremendous impact on quality of life [9] and might provide an awful last period of patient's life.

Other series have shown that complete resection of the recurrent disease is the best and actually only serious option for these patients. [12,15-24] Our present series is in line with these reports showing a median survival of 25 months and an overall 5-year survival of 28%, with seven long-term survivors. Although postoperative morbidity and mortality were considerable, it seems to be offset by the survival benefit obtained by this aggressive strategy.

Preoperative imaging

The absence of microscopic involvement of the surgical margins was one of three independent prognostic factors for improved survival after salvage surgery. Adequate preoperative work up, indicating whether or not a radical surgical approach might be successful, is a prerequisite in the treatment of locally recurrent rectal cancer. [3,18] Nowadays, MRI and PET are valuable tools for the selection of patients with a possible benefit of salvage surgery. It gives an impression about the degree of tumour involvement of the surrounding tissues and provides useful information regarding the presence or absence of metastases.

Extent of surgery

If the decision is made to operate upon these patients, an aggressive attempt has to be made to obtain a microscopically radical resection. [3,18] This implies in many cases extended operations. [25] A posterior or total exenteration may be indicated in case of an anteriorly located recurrence, while an abdominosacral resection may be indicated when dealing with a posteriorly located recurrence. Abdominosacral resection below the level of S2 is technically feasible and can be performed safely. [11,12,26]

Combination with other treatment modalities

The disappointing high number of patients with again locally recurrent disease after salvage surgery indicates that the above mentioned aggressive surgical intervention should probably be intensified with other treatment modalities. There are now small series of patients treated by external beam reirradiation (alone or combined with chemotherapy), [27,28] by intraoperative radiotherapy (IORT) [23,29-31] and by postoperative brachytherapy. [32] Improvements in survival have been claimed by IORT compared to surgery alone but are based on historical controls. There is no evidence based on randomised trials to support these claims. In our opinion, IORT merits further evaluation, preferably in a randomised trial.

Influence of preoperative radiotherapy

In contrast to the period described in this study, presently almost all patients will have undergone radiotherapy as part of their initial treatment. In this series the fate of patients was completely dominated by the completeness of their resection, without clear influence of additional radiotherapy. Our results support the assumption that radical resection will remain the mainstay of treatment of local recurrent rectal cancer, even if it can not be supported by additional radiotherapy.

Conclusions

Of course, these data present at best only level 3 evidence. [33] However, there is currently no better evidence available. In our opinion, surgical treatment with curative intent should always be considered in case of a locally recurrent rectal carcinoma. Salvage surgery (with or without salvage radiotherapy) can achieve long-term survival which underpins the value of trying especially in the light of the devastating effect of a non-treated recurrence.

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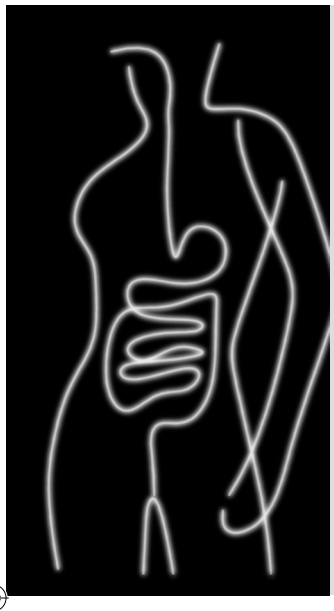

CHAPTER 10

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Sacral resection in cancer surgery; Surgical technique and experience in 26 procedures

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Introduction

Many surgeons consider a tumor irresectable once it infiltrates the sacrum. This reluctance to remove parts of the sacrum in radical cancer surgery is based on a number of fears. Many fear uncontrollable blood loss if the so-called presacral venous plexus is opened during operation. There is fear for extensive neurological damage and for instability of the pelvic ring.[1-2] Lastly it is feared that tumors that extend into the sacrum have such poor prognosis that extensive radical resection will not translate into a worthwhile gain in survival and that the quality of life during that time will be extremely poor.
In this paper we report on the practice of sacral resections in the Netherlands Cancer Institute. In the first part we describe some aspects of indications and surgical technique while we report in the second part on our experience in 26 procedures, with focus on per-operative events, post-operative recovery and lasting functional effects.

Surgical techniques

Functional considerations

The sacrum forms the dorsal part of the pelvic ring. The merged transverse processi of the first two sacral vertebrae are attached to the iliac os at the sacro-iliac joint. As long as this joint is preserved stability of the pelvic ring remains intact, although there is uncertainty about the contribution of the sacrospinal ligaments. Probably it is sufficient if the corpus of the first sacral vertebra and the lateral wings of the first two are preserved. If more is removed complicated osteosynthetic reconstructions are needed to guarantee stability.[2]
The sacral nerve roots have important functions and the innervation to the pelvis is rather complex.[1,3-7] However, S-1 mainly contributes to the ischiadic nerve and provides motoric and sensory functions to the leg. S2-5 together regulate sphincter and sexual function, with some predominance of S-2 for control of the bladder function, S-3 for anal function and S-4 for sexual function. S2-5 provide sensitivity for the saddle area. Whether these functions are important depends on the presence of the target organs. For instance loss of the S-3 roots has no consequence after abdominoperineal rectum resection. Loss of sexual functions has often already occurred in earlier surgery in many of these cases.
Based on these considerations of mechanical stability and neurological functions we are very reluctant to resect above the S-2 level.

Pre-operative imaging

As this paper concentrates on surgical technique of sacral resections we will not give detailed selection criteria for all different tumor situations, in which sacral resection may be considered. For preparation of the operation we find MRI most useful, especially the sagital projections (fig 1). In cases of recurrent (rectal) cancer after previous surgery and radiation, PET can be useful to determine what part of the CT or MRI image is tumor

recurrence and what is just scar tissue. Based on these images the level of transection of the sacrum can usually be predicted and consequences discussed with the patient before he/she agrees with the planned operation.

Operative approach of sacral resection S1-S2-S3

The first stage of the operation is carried out through a midline laparotomy extended well into the upper abdomen. The small bowel and ascending colon are mobilized and packed away in the upper abdomen. Of course the abdomen is carefully reviewed for metastases that might turn the patient incurable. We usually start with the anterior plain of dissection. Dependent on the actual tumor situation this plain follows Bill Heald's holy plain behind the rectum, the plain in front of the fascia of Denonvillier in front of the rectum, the plain in front of uterus and vagina, or the plain in front of the bladder, in case of a combined sacral resection with total exenteration. Depending on the anterior plain, the rectum and the ureters are transected. After the anterior dissection has reached the pelvic floor, the posterior dissection is undertaken.

Preventing major blood loss

Many surgeons have a deeply ingrained fear of the so-called presacral venous plexus. In our opinion this is a misnomer as no major veins are present in front of the corpus of the sacrum. The main veins are those that drain blood from the epidural plexus through the sacral foramina to the laterally placed internal iliac veins. These are big veins down to S-2, but usually do not exceed 1 mm diameter from S-3 downwards. Major bleeding usually occurs at this point of the posterior dissection, if uncontrolled traction is placed on the specimen to gain vision into the presacral space and a fixed thin walled sacral vein tears out of the internal iliac vein.

To prevent this we have developed the following approach. The posterior dissection is carried out over the aortic bifurcation, the common iliac arteries, and caudal to these the iliac veins. From here the sacral promontory is reached. Laterally the split of internal and external iliac artery and vein is cleared. From here, the presacral plain is dissected medial to the sacral foramina, down to the planned level of sacral transection, or as far down as the actual tumor situation allows. After this the obturator fossa is cleared of its fatty and lymph node content, preserving the obturator nerve. Between the obturator fossa and the pre-sacral plain a spur of tissue remains that contains the anterior branches of the internal iliac artery and vein. Over this spur a vascular Endo GIA bite is placed, providing a double row of staples and transecting in between. By doing so, the tension on the posterior sacral veins is released and the risk of heavy bleeding diminishes. The relation between the internal iliac vein and the sacral veins can now be seen. No attempt is made in this stage to ligate and cut the sacral veins. In stead, a monofilament suture ligature is placed over the internal iliac vein stem, to prevent back bleeding in the second stage of the operation.

Marking the level of sacral transection

Determining the right level of transection of the sacrum is often difficult, especially in cases of recurrent cancer attached or infiltrating the sacrum from anterior. Careful dissection of the anterior aspect of the sacrum will have to show how far down one dares to go, trying to strike a balance between descending too low and thus entering the tumor and descending not enough with the risk of unnecessary loss of function. Once the level of transection is determined, we find it helpful to put a Steinman pin in at that level and hammer it through the sacrum, deep enough for the point to stick out at the posterior side (fig 2). The right depth should be measured on MRI, to avoid the pin from penetrating the skin.

Omental transposition

For whatever indication, removal of the sacrum always leaves a large tissue defect (fig 3). As most of these patients also have been heavily irradiated, wound-healing problems are more rule than exception. Whenever possible, we therefore use an omental transposition to fill up the defect. After complete mobilization from transverse colon and major curvature of the stomach, the omentum based on the right gastro-epiploic vessels, will in most patients easily reach the perineum. The flap is temporarily positioned on top of the specimen.

The transabdominal part of the operation is now completed. If a colostomy and/or urinary deviation has to be made, this is done. The abdomen is closed.

Positioning for the dorsal approach

We do all sacral resections in the so-called Salam position, popularized by neurosurgeons for hernia nuclei pulposi operations. The major advantages are that it provides a very stable position, with the abdomen free, and it gives an unobstructed venous return. As the sacral region is well above the heart, this means that the epidural venous plexus is empty, which greatly reduces blood loss.

Laminectomy and preservation of sacral nerve roots

A midline incision is made from S1 to as far down as needed to meet the anterior plain of dissection. This is done first, to allow the surgeon's hand to be entered on the anterior side of the specimen, which is very helpful for three-dimensional orientation during the rest of the operation. Skin, subcutis and muscle are cleared from the posterior aspect of the sacrum, as far lateral as the sacro-iliac joints. The point of the Steinman pin shows the level of transection. A laminectomy is performed proximal to the tip of the pin. If the dural sack reaches as far down as the chosen transection level it is ligated with a permanent, nonabsorbable suture to prevent spinal fluid leakage. The sacral nerve roots are now in view and decisions have to be made on their preservation or transection. The roots to be preserved and the corresponding foramina, which the roots take from the sacral vertebral channel to the anterior side, are identified. Starting in the foramen, the bone of the lateral wing of the sacrum is nibbled away in the direction of the caudal

margin of the sacro-iliac joint, taking care to spare the underlying nerve root. After this has been done on both sides, only the corpus vertebrae is left. Using an osteotome the corpus vertebrae is cut at the level of the Steinman pin. This severs the last bony attachment and immediately provides mobility for the specimen. Guided by the interior hand, the strong sacrospinal ligaments between the lateral sacral margin and the ischial processus are cut, after which the complete specimen can be removed. Blood loss at this stage of the operation is usually surprisingly limited.

Reconstructing the pelvic floor

The omentum is spread out to form a safe barrier between bowel and the new pelvic floor, also covering the proximal sacrum. A nonabsorbable mesh graft is placed over the omentum to prevent a massive central herniation. Subcutis and skin are closed over a drain. If necessary, a transpelvic rectus abdominis musculocutaneous flap is used to close the defect.[8]

Operative approach of sacral resection S4-S5

Transection of the lower sacrum is usually possible from the anterior side. The operation follows the above sketched procedure. The patient is however not turned, but instead the caudal dissection is carried out from the perineum. From the perineal side, soft tissues are dissected off the sacrum as high as needed. The sacrum is then transected with an osteotome and the specimen is removed.

Results of 26 procedures

Materials and methods

The registry of the Netherlands Cancer Institute was searched for patients who had undergone sacral resection for isolated, pelvic malignancy with sacral involvement between January 1995 and July 2003. Twenty four patients (10 male/ 14 female) with a median age of 56 years (range 16-68) were identified. Of these patients the charts, operation reports and pathology reports were reviewed.

The following data were collected concerning the sacral resections: indication for sacral resection, type and date of operation, blood loss, operating time, administered units of packed cells, time of admission at the ICU, microscopic radicality, perioperative complications and date of discharge. Surgical procedures combined with sacral resection were classified as follows: abdominoperineal resection (APR), posterior exenteration (rectal resection with radical hysterectomy and total or posterior vaginectomy), total exenteration (removal of all pelvic viscera with the formation of a permanent colostomy and urinary diversion) or local soft tissue resection (resection not classified by any other mentioned before).

Information concerning follow-up included: late morbidity (especially neurological function of the lower limbs, signs of pelvic instability, bladder function problems), date of progression, date of last follow-up or death and cause of death (tumour related or not) if applicable.

Survival time was calculated as time from sacral resection to date of all-cause death or date of last follow-up. Patients who were alive at the end of follow-up were censored. Survival probabilities were estimated using the Kaplan-Meier method.[9]

Results

The indications for operation are shown in Table 1. A total of 26 sacral resections were performed, as a single procedure or in combination with other procedures. (Table 2) In two patients a second sacral resection at a higher level was done because of recurrence after the initial sacral resection. The median operating time was 6 hours (range 2.5–10.0) with a median blood loss of 3,600 ml (range 420-11,500) and administration of a median of 4 units of packed cells (range 0-20). In one patient, blood loss could only be controlled by gauze packing, which were removed during relaparotomy one day later. A transpelvic rectus abdominis musculocutaneous flap was used in 13 procedures (50%) and an omental transposition in 17 procedures (65%). All patients, except one, stayed at the Intensive Care Unit (ICU)/ Medium Care Unit (MCU) after sacral resection for a median of 3 days (range 1-7). A microscopically radical resection was accomplished in 15 procedures (58%).

Table 1. Indications for sacral resection.

Rectal cancer, primary	6
Rectal cancer, recurrent	14
Anal cancer, recurrent	3
Other	3

Other = Osteosarcoma, chordoma and recurrent squamous cell carcinoma of the buttock.

Table 2. Surgery characteristics. (26 procedures in 24 patients)

Type of surgery	
Sacral resection only	5
Sacral resection and abdominoperineal resection	6
Sacral resection and exenteration (posterior/total)	13 (7/6)
Sacral resection and local soft tissue resection	2
Level of sacral resection	
Corpus S1	1
Between S1 and S2	1
Corpus S2	6
Corpus S3	6
Between S3 and S4	4
Corpus S4	8

Corpus = resection through corpus vertebrae, Between = resection between corpora vertebrae

Figure 1. Sagital projection of recurrent rectal carcinoma on MRI, prior to and after sacral resection.

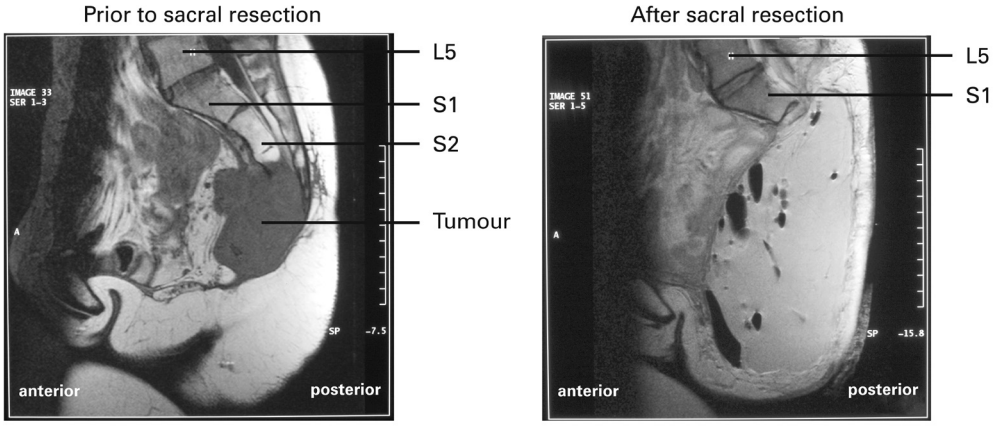
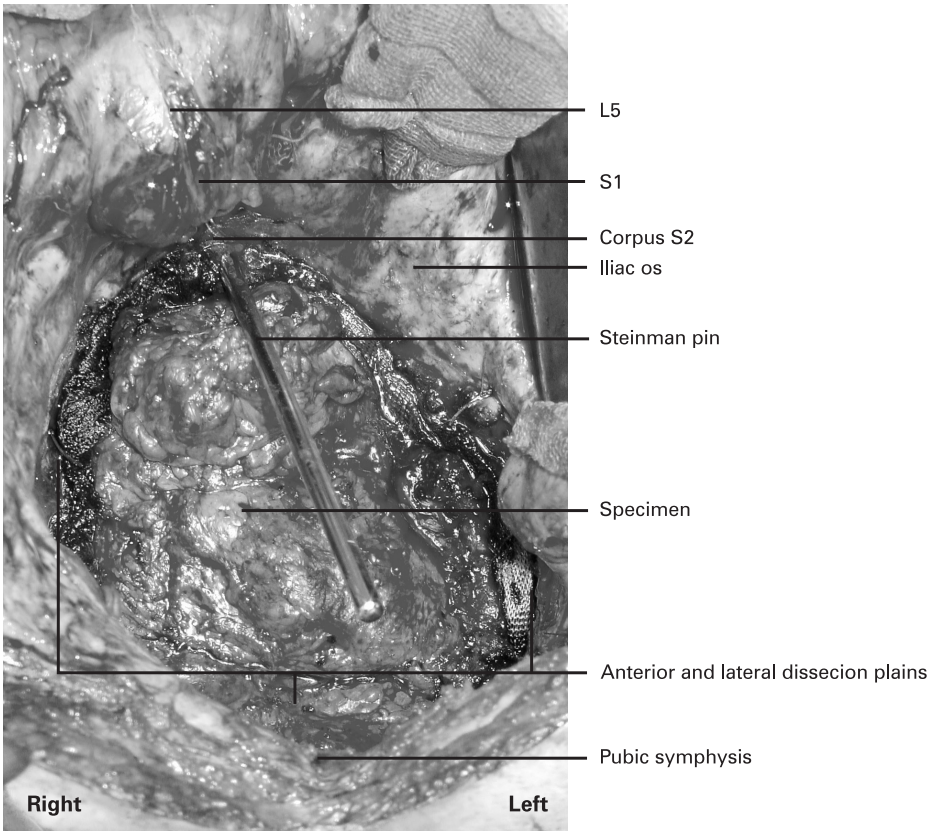


Figure 2. Steinman pen placed in corpus vertebrae S2, abdominal view.



One patient died postoperatively due to infections unresponsive to medical treatment. After six procedures no complications were seen, while after the remaining 20 operations, 10 non-operation related and 27 operation related complications occurred. (Table 3) Five patients underwent a relaparotomy for several reasons (Table 3).

Figure 3. Large tissue defect after sacral resection, dorsal view.

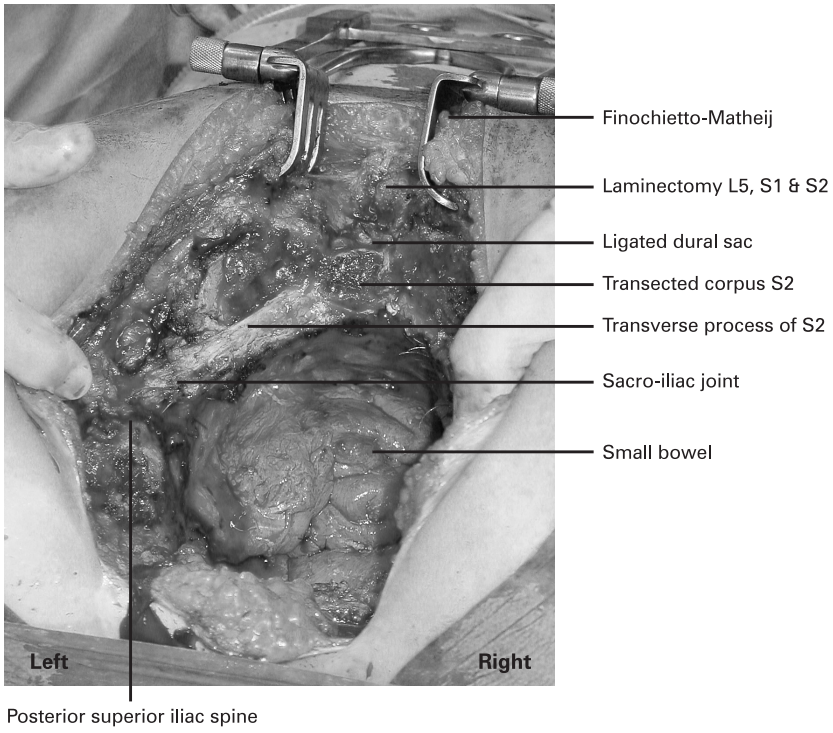


Table 3. Operation-related major complications (n=27) and reasons for relaparotomy (n=5).

Bladder dysfunction	9
Abdominal wound infection	2
Abdominal wound dehiscence	1
Perineal wound infection	5
Perineal wound dehiscence	3
Pelvic blood loss (relaparotomy)	3 (2)
Small bowel obstruction (relaparotomy)	1 (1)
Small bowel perforation (relaparotomy)	1 (1)
Temporary neuropathy of the lower limbs	1
Necrosis of urostomy (relaparotomy)	1 (1)
TOTAL COMPLICATIONS (RELAPAROTOMY)	27 (5)

Numbers between brackets indicate numbers of patients requiring relaparotomy to treat complication

The median hospital stay after the sacral resection was 20 days (range 5-202). Three patients were re-admitted after discharge. One patient had a perineal wound infection, one patient had a urosepsis, and one patient had anemia, constipation and fever e causa ignota. All complications resolved after (non-operative) treatment.

The median time between operation and date of last follow up was 14 months (range 1.1-78.3). The estimated two and five year survival were 82% (confidence interval: 62-100%)

and 51% (confidence interval: 15-88%) respectively. Locally recurrent disease developed in nine patients of whom one patient also had distant metastasis. Four patients have died due to malignant disease (4, 22, 39 and 47 months after sacral resection). At last follow up, 19 patients were still alive and 16 had no evidence of disease.
No patients reported motoric or sensory loss of function to their lower limbs, nor were there any reports of pelvic instability. Eight patients reported ongoing bladder function problems which were managed by intermittent self catheterisation.

Discussion

Sacral resections [10-16] are major operations for which different techniques have been described.[17-22] In this paper, we reported the practice of sacral resections in the Netherlands Cancer Institute with a detailed description of the surgical technique, related morbidity, mortality and long term outcome.
In contrast to Wanebo[20], we perform the sacral resection in one operative session with a combination of the abdominal and dorsal approaches. However, the median duration of the operation is considerably less than reported in the two day procedure (12 hours for the abdominal phase and 8 hours for the sacral phase vs 6 hours for both phases in this series). Temple and Ketcham[17] use the combined abdominal and perineal approach in the lithotomy position, but resections higher than S2 are not possible with this approach.
To determine the level of resection during the dorso-caudal phase of the operation, we hammer a Steinman pen through the sacrum when the transection level is reached. Others use a Kirshner wire for orientation purposes or choose the level of sacral transection on the position of the hand which is placed anteriorly of the sacrum during the dorsal approach.[21]
One of the major concerns is to keep blood loss within controllable limits and in all but one patient, we succeeded to do so. We want to emphasize that the often feared presacral plexus does not exist in reality. The main source of blood loss are the large veins connecting the internal iliac veins through the sacral foraminato the epidural venous plexus. These veins are laterally placed, not in front of the sacral corpora.
The dorsal approach in Salam position has been an eye-opener for us. Placing the sacral region high above the right atrium results in a subzero pressure in the epidural plexus, meaning empty vessels that won't bleed when opened. Cross-clamping the aorta is therefore not needed, as has been recommended when performing the sacral resection in supine position.[17]
A challenge and possible concern is closure of the enormous defect after sacral resection and its related wound problems. Omental transposition has been used by virtually all authors describing their results. A musculocutaneous flap (rectus abdominis flap, gracilis flap or gluteal flap) has frequently been applied and subcutaneous rotational flaps have also been described.[19] We prefer the use of the rectus abdominis flap which in our experience has been extremely reliable. The rectus abdominis muscle has not been

irradiated during previous treatment, thus providing healthy tissue in a severely damaged area. Wanebo et al.[20] had a considerable number of wound infections (28/53 patients = 52%) after sacral resection. Therefore, they changed their policy. They nowadays pack the wound and plan reconstruction after 48 to 72 hours. However, a third operation is needed, since they use a two day procedure for the actual sacral resection.

Neurological damage in our series was mainly limited to bladder dysfunction, while the neurological function of the lower limbs was remarkably well preserved. However, neurological evaluation of the lower limbs was not a standard procedure and therefore the symptoms might be underestimated. Since many patients have a colostomy, bowel dysfunctions are often not relevant. Sexual problems were not evaluated in this series, but are expected to be present in the majority, if not all patients.

Survival after sacral resections was evaluated in this series and gave encouraging results. However, due to the small size and the heterogeneity of the population, it remains difficult to interpret these results. They are however in line with findings in other series.[10-16]

In our opinion, the described technique is valuable treatment in selected patients. It is accompanied by acceptable perioperative morbidity and mortality, good functional preservation of lower limbs and pelvis and some long-term survivors. Therefore, sacral resection should be considered in patients with sacral involvement of non-metastatic, malignant disease.

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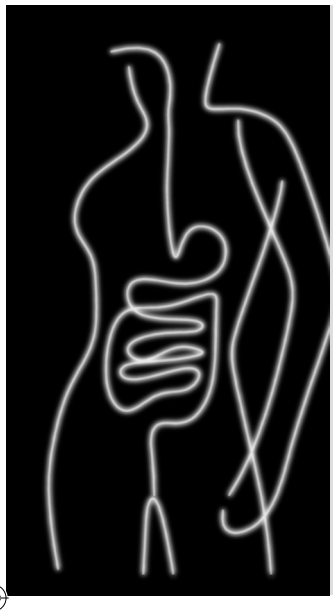

CHAPTER 11

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Inferiorly Based Rectus Abdominis Myocutaneous flaps in surgical oncology; Indications, technique and experience in 37 patients

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Introduction

Oncologic resections often result in major tissue defects. After closure of these wounds under tension, complicated wound healing is more rule than exception, especially if the area has previously been irradiated.[1] For years now it has been recognized that transfer of well vascularized unirradiated tissue in a post-irradiation surgical defect, greatly improves the chances on primary healing and also improves functional outcome.[2-3] The understanding of the principles of blood supply of muscles by anatomically identifiable blood vessels and the overlying skin by perforator vessels from the muscle, has led to the development of a number of myocutaneous transposition flaps that have revolutionized reconstructive surgery.[4] The Inferiorly Based Rectus Abdominis Myocutaneous (IBRAM) flap for perineal wounds was first described in 1984.[5] Based on the epigastric artery and vein it will reach any defect up to 25 cm from the groin, including perineum, sacrum, groin, and upper leg.

Despite its well established usefulness, only few oncologic surgeons have made the effort to learn this technique. Instead, they rely on plastic surgeons to help them close defects after resisted efforts at conservative wound care, leaving patients with an often very prolonged post-operative recovery and reduced function due to excessive scarring.

In the Netherlands Cancer Institute the Inferiorly Based Rectus Abdominis Myocutaneous (IBRAM) flap is used as primary closure technique for large defects in perineum and groin after surgical resection with or without prior irradiation. We describe in this paper the technique of harvesting and transferring this flap and report on the outcome in 37 patients.

Surgical Anatomy

The epigastric artery and vein, originating from the external iliac vessels just proximal to the inguinal ligament, provide the dominant blood supply for the rectus abdominis muscles. Based on these vessels the entire rectus muscle up to the costal margin can be safely mobilized. This muscle can support a large cutaneous island, based on perforating vessels from the muscle to the subcutaneous vascular network.[6] Around the umbilicus the perforator vessels are most densely placed and biggest in diameter.[7] A skin island is, for that reason, most reliable if harvested from the peri-umbilical area. The subcutaneous vascular network has a dermatomal structure, in line with the nerves. The perforator vessels at the level of the umbilicus can safely support a skin/subcutis flap reaching along the dermatoma for 15 cm or more. The useful range of this skin island is easily 25 cm from the groin, covering perineum or contralateral groin, without any tension.

Surgical technique

Harvesting is very easy once a midline laparotomy has been performed. Before dissection the pulsations in the epigastric artery should be checked. The skin island is lined out on the abdominal skin according to the size of the defect to be covered. To be

sure that at least one perforator vessel is included it is wise to make the skin island at least 6 cm in diameter and to include the direct para-umbilical skin. Small islands can be harvested vertically along the midline laparotomy in the upper abdomen. Larger islands are better harvested in an transverse way along the dermatoma based at the umbilicus (fig 1). The incision along the island is taken through skin, subcutis and anterior rectus sheet. Temporary sutures are placed through the skin and the external rectus sheet, to prevent damage to the fragile perforator vessel by reducing traction from the skin. The rectus muscle in now divided proximal to the skin flap. The posterior rectal sheet is left intact. The muscle with its skin island is mobilized from the posterior rectus sheet, from cranial to caudal, dividing anterior and posterior rectus sheets at the linea alba. Caudal to the skin island the muscle is also dissected from the anterior rectus sheet. Caudal to the linea semicircularis, where the posterior rectus sheet is absent, care has to be taken to preserve the epigastric vessels, which enter the rectus muscle from the lateral side. The muscle with its skin island is now fully mobile (fig 2.) and can reach the perineum or the contralateral groin without tension.

The inferior insertion of the muscle on the pubic bone is preferably left intact, as this prevents any undue tension on the vessels. If needed the insertion can be cut, providing a few centimeters more mobility. After exenterative surgery or abdominoperineal resections the flap is simply pulled through the open pelvis lateral to the somewhat mobilized bladder. (fig 3.) Care is taken not to rotate the flap, endangering the circulation. The anterior rectus sheet can be used to provide stability to the reconstruction, fixing it with a few sutures to bone or fascia. The skin is sutured to the wound edges. (fig 4.) After posterior exenteration in women it is often useful to use the anterior part of the flap to reconstruct the posterior vaginal wall.[8] (fig 5.)

If the IBRAM flap is used to reconstruct the contralateral groin (fig 6.) a choice has to be made to place the flap through a tunnel below the inguinal ligament or through a subcutaneous tunnel. In the first solution a weak spot is created below the inguinal ligament increasing the risk on femoral herniation, in the second solution the linea alba can not be closed completely, increasing the risk on midline herniation.

Results of 37 procedures

Materials and Methods

The registry of the Netherlands Cancer Institute was searched for patients who had undergone closure of a large perineal or inguinal wound using an inferiorly based rectus abdominis myocutaneous flap between April 1997 and July 2003. Thirty seven patients (15 male/ 22 female) with a median age of 58 years (range 28-85) were identified. Of these patients the charts, operation reports and pathology reports were reviewed.

The following data were collected concerning the operations: prior treatment (focus on prior radiotherapy), indication for operation, type and date of operation, perioperative complications and date of discharge. Surgical procedures were classified as follows:

Figure 1. Skin island from the right side to be harvested in an transverse way along the dermatoma (in a patient with a midline laparotomy).

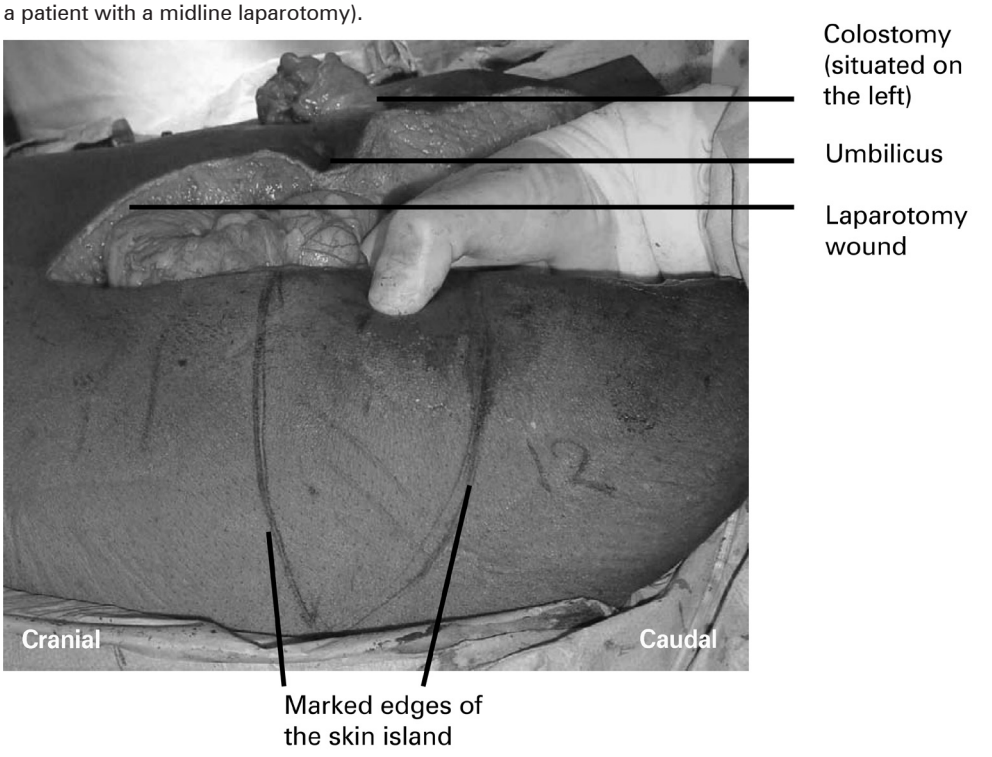
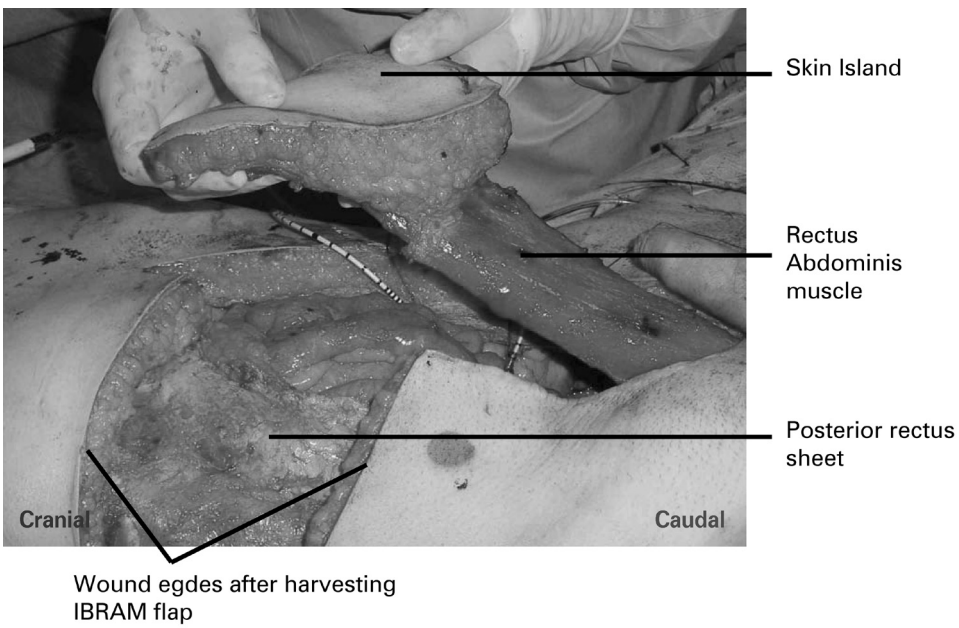
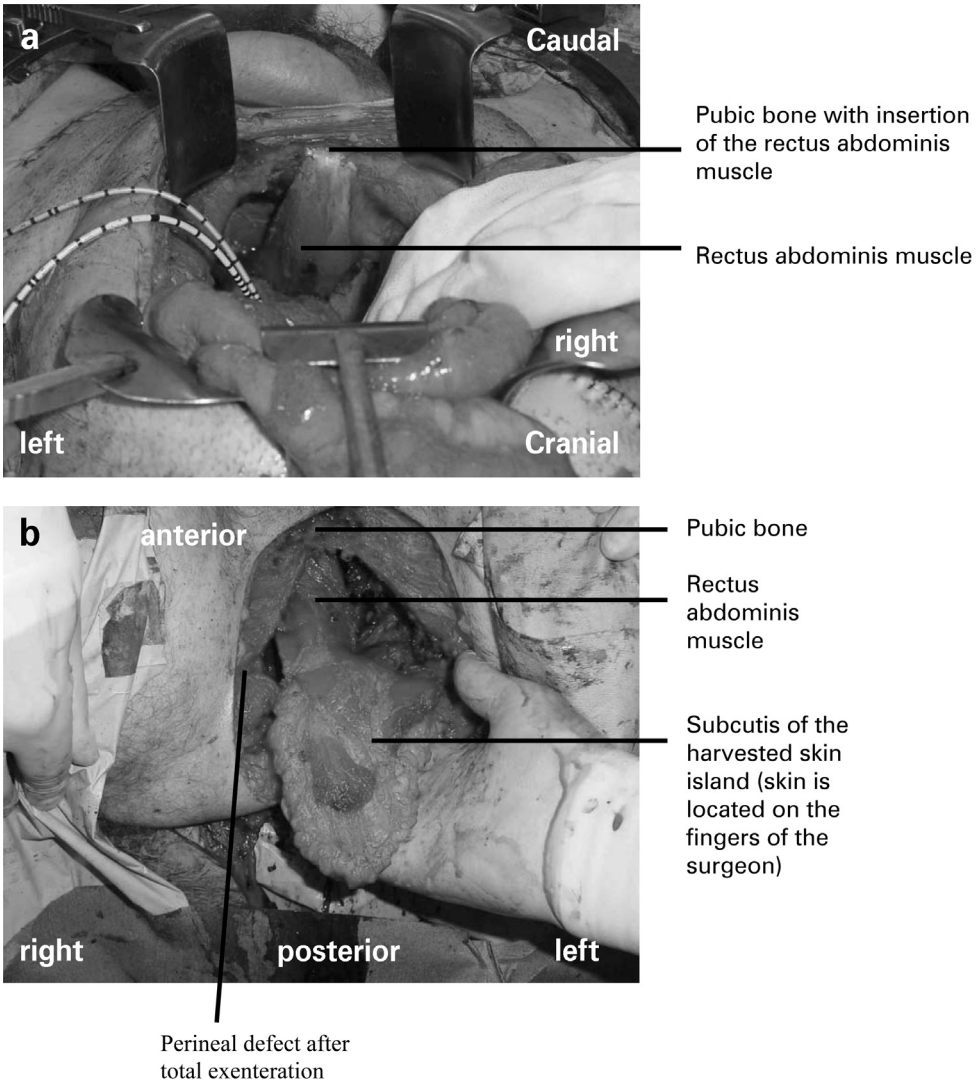


Figure 2. IBRAM with its mobile skin island harvested from the right side.



abdominoperineal resection (APR), posterior exenteration (rectal resection with radical hysterectomy and total or posterior vaginectomy), total exenteration (removal of all pelvic viscera with the formation of a permanent colostomy and urinary diversion), abdominosacral resection (APR or exenteration combined with sacral resection), local soft tissue resection (resection not classified by any other mentioned before), inguinal lymph node dissection or secondary closure of a wound using an IBRAM flap.
Information concerning follow-up included late morbidity (especially incisional hernia) and date of last follow-up or death.

Figure 3. IBRAM-flap pulled through pelvis, abdominal (a) and perineal (b) view.



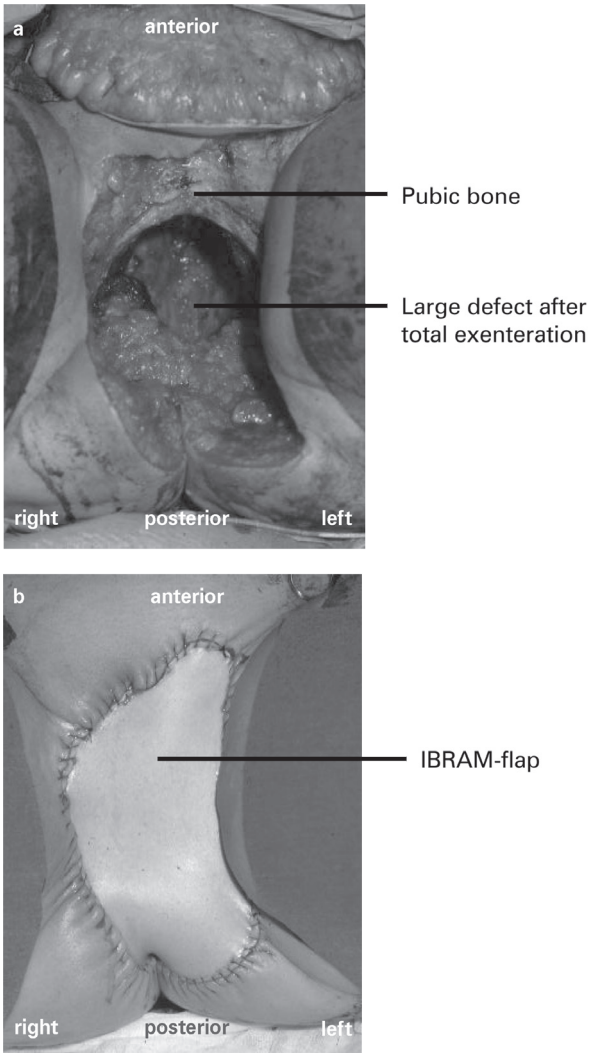


Figure 4. Perineal wound prior to (a) and after closure (b) using an IBRAM-flap, direct postoperatively (perineal view).

Results

The indications for operation and types of surgical procedures performed are shown in Table 1. All but five patients were previously treated with radiotherapy. The IBRAM flaps were harvested from the right side in 24 patients, from the left side in 12 patients and in one patient IBRAM flaps were used from both sides. The median operating time was 5 hours (range 2–10) with a median blood loss of 2,300 ml (range <150-11,500).

Nineteen patients (51%) did not experience any complications.

Eleven patients (30%) experienced IBRAM flap-related complications of whom one needed surgical exploration, due to ongoing bleeding at the recipient site of the IBRAM flap. The remaining 10 patients all had minor complications which resolved after non-operative treatment (one perineal wound infection, two abdominal wound infections, two partial perineal wound dehiscences, one partial abdominal wound dehiscence and

Figure 5. IBRAM flap used to reconstruct the posterior vaginal wall, situation several months after operation (perineal view).

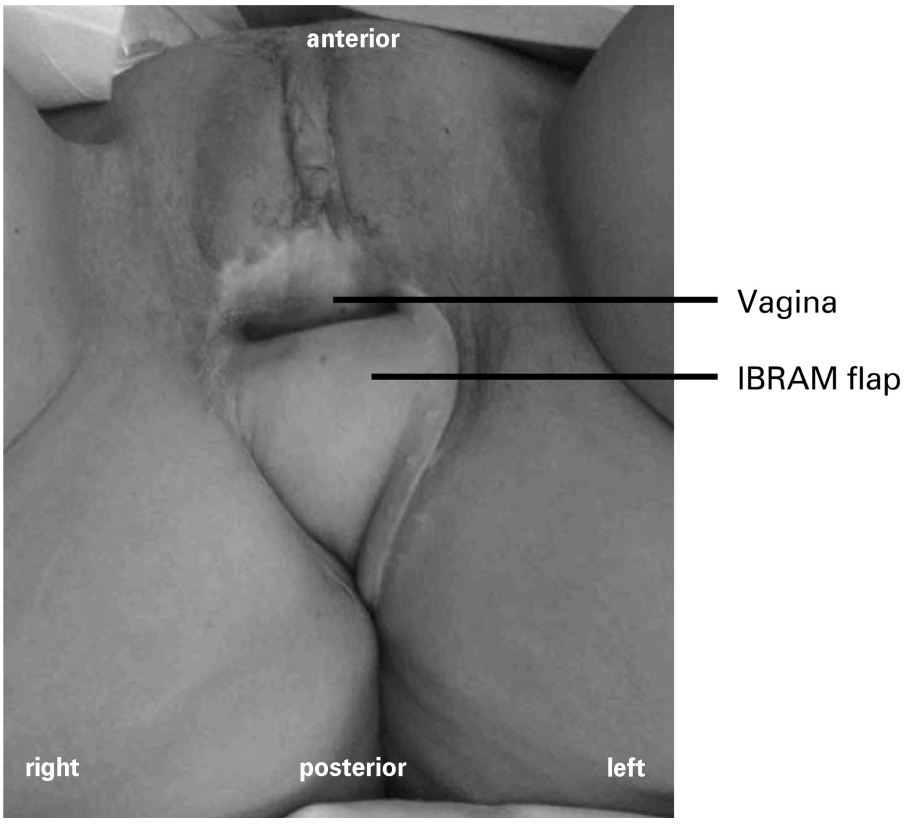


Figure 6. IBRAM flap used to close contralateral inguinal wound, early after operation.

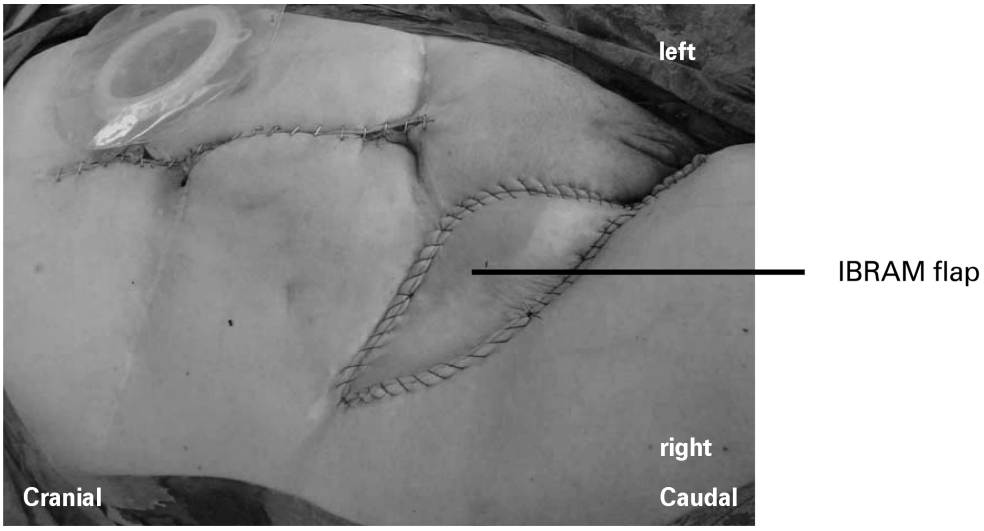


Table 1. Indications for operation and types of surgical procedures in 37 patients, in whom an Inferiorly Based Rectus Abdominis Myocutaneous flap was applied.

Indication for surgery	
Rectal carcinoma (primary/recurrent)	16 (6/10)
Anal carcinoma (recurrent)	9
Other malignancies (gynecologic/urologic/other)	8 (1/3/4)
Persisting wound problems requiring secondary closure (perineal/inguinal)	4 (2/2)
Type of surgical procedure	
Abdominal perineal resection	7
Exenteration (posterior/ total)	3 (2/1)
Abdominal sacral resection	13
Local soft tissue resection	4
Inguinal lymph node dissection 6	
Secondary wound closure (perineal/ inguinal)	4 (2/2)

seroma formation around recipient site of the IBRAM flap in four cases). Perineal and inguinal wound healing occurred in all patients after reconstruction with an IBRAM flap, and no flaps were lost.

Eleven patients (30%) experienced none-IBRAM flap-related complications. One patient died postoperatively, not related in anyway to the IBRAM flap. Two patients needed relaparotomy; one patient due to small bowel obstruction and one patient due to necrosis of the urostomy.

Four patients (11%) experienced IBRAM flap-related as well as none-related complications.

The median hospital stay after the operation was 17 days (range 6-54) and the median time between operation and date of last follow-up was 19 months (range 1-72). During follow-up, incisional hernia at the IBRAM flap donor site was seen in four patients of whom two required operative correction.

Discussion

Two decades ago the Inferiorly Based Rectus Abdominis Myocuteaneous flap has been introduced for reconstruction of large defects located at the groin or perineum.[4-5] This form of reconstruction has a low morbidity rate and the IBRAM flap is known for its viability, offering a reliable solution in an often irradiated, and therefore, troublesome area.[9-13] Harvesting the IBRAM flap is relatively easy, especially when a midline laparotomy is used for the initial procedure. Whether to harvest a vertical flap or transverse flap mainly depends on the desired size of the skin island and some technical differences. The abdominal wall can almost always be primarily closed after harvesting a transverse flap, while prosthetic material is often needed after a vertical flap.[14] The transverse flap can be larger and healing of the wound is better as the scar follows skin lines. So in

large perineal defects, especially if reconstruction of the vagina is performed, it has our preference. The extreme reliability of the flaps is reflected by the fact that no flaps were lost in these 37 patients. Therefore, it is surprising that in the oncologic surgical practice, this reliable reconstructive technique is so seldomly used. Presumably this is caused by the fact that many oncologic surgeons are unfamiliar with this technique and find it troublesome to organize the cooperation of a plastic surgeon on an on-call basis. In our series, all flaps were harvested by the oncologic surgical team without the assistance of a plastic surgeon. The major advantage is that the ability to perform this operation by the oncologic surgical team themselves, lowers the threshold to apply this technique, diminishing the morbidity of failed wound healing and the necessity of secondary, more difficult reconstructive efforts.

In our opinion, an IBRAM flap should be broadly applied for reconstruction of large perineal or inguinal defects in oncologic surgery. This can be done with acceptable morbidity and excellent reliability of the harvested IBRAM flap, as has been shown in this large series.

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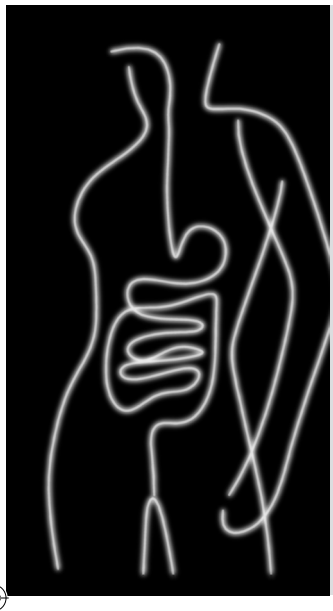


Summary

Summary

PART I

Influence of Total Mesorectal Excision with or without preoperative radiotherapy on local recurrence and survival, complications, and functional outcome.

In **Chapter 1** the influence of the introduction of Total Mesorectal Excision (TME) on local recurrence and survival is retrospectively analyzed in a population-based setting by comparing two cohorts of rectal cancer patients *i.e.* before and after the broad introduction of TME. All patients with a rectal carcinoma in Greater Amsterdam diagnosed during 1988-1991 (979 patients treated with conventional surgery with blunt dissection of the rectum) and 1998-2000 (890 patients, TME resection) were selected from the Amsterdam Cancer Registry. Information on the occurrence of local recurrence and distant dissemination was collected in those patients who underwent a macroscopically radical resection. The cumulative five-year recurrence rate decreased significantly from 20% for patients diagnosed in 1988-1991 to 11% in 1998-2000. In the multivariate analysis, stage (T-category, lymph node status), period of diagnosis (conventional versus TME resection), radiotherapy and chemotherapy were independent prognostic factors for a decreased local recurrence rate. The five-year relative survival for all rectal carcinoma patients increased (not significantly) from 52% (95% CI 48-55) for patients diagnosed in 1988-1991 to 59% (95% CI 55-63) in 1998-2000. The broad introduction of TME in combination with the shift towards preoperative radiotherapy is the most plausible explanation for this observation. It indicates that TME, although never investigated by means of a randomised clinical trial, is indeed superior to conventional surgery with blunt dissection of the rectum.

In **Chapter 2** a model is presented to weigh the harms (increase of short-term complications) and benefits (reduction of local recurrence) of short-term preoperative radiotherapy in the treatment of patients with rectal cancer. Based on the results of the latest four randomised clinical trials, patients are classified in one of five outcome combinations; 1 benefit without additional harm, 2 benefit with additional harm, 3 no benefit, no additional harm, 4 no benefit but additional harm, 5 mortality due to combined treatment. It is shown that the majority of patients (74 – 87%) have neither benefit nor additional harm, while a small percentage (6 – 11%) experience additional harm but lack any benefit. A small percentage of patients (5 - 13%) have benefit without additional harm and thus experience optimal treatment results.

One of the drawbacks of the results presented in chapter 2, next to the inability to use source data, is the lack of consensus regarding the severity of complications. Therefore, a Delphi round was organised in cooperation with 21 colorectal surgeons from the Netherlands, the United Kingdom and Sweden. The Delphi round procedure is explained in **Chapter 3.** The key-question was: "Which of the predefined complications, caused or substantially aggravated by radiotherapy, are so important (major) that they might lead to the decision to abandon short-term preoperative radiotherapy (5x5Gy) when

treating patients with resectable rectal cancer ($T_{1-3}N_{0-2}M_0$)?" Consensus was reached for 13 major complications (mortality, anastomotic leakage managed by relaparotomy, anastomotic leakage resulting in persisting fistula, postoperative haemorrhage managed by relaparotomy, intra-abdominal abscess without healing tendency, sepsis, pulmonary embolism, myocardial infarction, compartment syndrome of the lower legs, long-term incontinence for solid stool, long-term problems with voiding, pelvic fracture with persisting pain, and neuropathy with persisting pain (legs); moreover consensus was reached for three so-called 'accepted as major' complications (perineal wound dehiscence managed by surgical treatment, small bowel obstruction leading to relaparotomy, long-term incontinence for liquid stool). These 16 complications in combination with the previously mentioned model (chapter 2) can be used in future research to properly balance the benefit and harm of short-term preoperative radiotherapy.

The COloREctal Functional Outcome questionnaire (COREFO) is a self-assessment questionnaire evaluating functional outcome after colorectal surgery and consists of 27 questions. Its development is based on information from published articles, input from four colorectal surgeons and ten patients experiencing impaired functional outcome. The COREFO questionnaire, together with Dutch translations of the Hallböök questionnaire and an adapted version of the Vaizey questionnaire, was tested among 257 patients with and without impaired functional outcome **(Chapter 4)**. The reliability and validity were adequate for the COREFO and Hallböök questionnaires, but not for the Vaizey questionnaire. The psychometric analyses showed a slight difference in favour of the COREFO questionnaire and significantly more patients preferred the COREFO questionnaire to the other questionnaires. It was concluded that both the COREFO and the Hallböök questionnaire are suitable instruments to evaluate functional outcome after colorectal surgery.

Ten healthy volunteers (HV) and ten patients 5 months after short-term preoperative radiotherapy (5x5 Gy) and rectal resection with Total Mesorectal Excision were evaluated by manometry and barostat studies in **Chapter 5**. (Neo-)rectal sensitivity was assessed by using a step-wise isovolumetric and isobaric distension protocol. (Neo-)rectal motility was determined during prolonged distension at the threshold of urge to defecate. The neo-rectal volume of patients at the threshold of urge to defecate (113 $\pm$ 33 ml) was significantly lower compared to the rectal volume of HV (272 $\pm$ 87 ml). The pressure threshold, however, did not differ between patients (21 $\pm$ 5 mmHg) and HV (24 $\pm$ 9 mmHg). In HV, no rectal contractions were observed during prolonged rectal distension. In contrast, in all ten patients prolonged isovolumetric and isobaric distension induced 3 (range 0-5) rectal contractions/ 10 min. It is suggested that this neo-rectal "irritability" represents a new pathophysiological mechanism contributing to the impaired anorectal function after preoperative radiotherapy and rectal resection with TME.

PART II Potential reduction of morbidity induced by loop ileostomies.

In **Chapter 6** the period of time between ileostomy construction and closure is evaluated in 69 patients with a temporary, protective loop ileostomy. It appeared that 60 ileostomies (87%) were closed after a median period of 24 weeks, which is substantially longer than initially planned (8 to 12 weeks). During this period, stoma-related complications occurred in 29 patients and in 25 of these patients the complication occurred more than 2 weeks after ileostomy construction. Earlier ileostomy closure could possibly reduce this frequently occurring stoma-related morbidity. Therefore, early ileostomy closure (*i.e.* during the same hospital admission as the initial operation) was investigated by means of a feasibility study **(Chapter 7)**. Twenty-seven patients were included in this study. Criteria for early closure included uncomplicated postoperative recovery and the absence of radiologic signs of anastomotic leakage, based on water-soluble contrast enema examination. Eighteen of the 27 patients underwent early ileostomy closure on average 11 days after the initial procedure. Reasons to postpone ileostomy closure included anastomotic leakage, delayed recovery or logistic reasons. There was no mortality and four mild complications occurred after early ileostomy closure. It was concluded that closure of a protective loop ileostomy early after the initial operation is feasible.

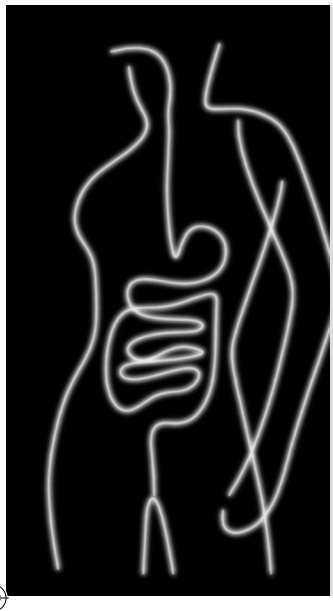
PART III
Surgical treatment for (recurrent) rectal cancer disease; techniques and results.

Treatment of recurrent rectal cancer remains a challenge. Between 1998-2000 a total of 632 rectal cancer patients were treated with a macroscopically radical resection in Greater Amsterdam. A population-based study among these patients was conducted to analyze treatment methods in case of recurrent rectal cancer disease (**Chapter 8**). Local recurrence occurred in 62 patients (10%) including 30 cases (6%) who had also developed distant dissemination. Ten of the 32 patients without distant dissemination underwent radical re-resection and experienced the highest survival (three quarters survived for at least three years). Results were significantly worse if radical re-resection was not possible. Patients treated with non-radical surgery (n = 8) had a median survival of 24 months, patients treated with radio- and/or chemotherapy without surgery (n = 7) had a median survival of 15 months and patients who received best supportive care (n = 7) had a median survival of 5 months.
Distant dissemination occurred in 124 patients (20%) of whom 30 patients (5%) also had a local recurrence. The majority of patients (54%) were treated with radio- and/or chemotherapy without surgery (median survival 15 months). Twenty patients underwent surgery for their recurrence and experienced the best survival (median survival 32 months). These results show that, although treatment options and survival are limited in case of recurrent rectal cancer, patients can benefit from treatment of their recurrence, especially if a radical re-resection is feasible.

In **Chapter 9** a study is described in 40 patients with recurrent rectal cancer treated by salvage surgery at the Netherlands Cancer Institute. Salvage surgery included abdominoperineal resection, abdominosacral resection, exenteration (posterior or total) and local resection. The median overall survival was 25 months (95% CI: 13-37 months) and 5-year survival was 28% (95% CI: 12-45%). In a multivariate analysis, the absence of symptoms at the time of recurrence, central localization and the absence of microscopic involvement of surgical margins (*i.e.* the possibility to perform a so-called R_0-resection), but not additional radiotherapy, were found to be significant independent prognostic factors for better survival after salvage surgery. Salvage surgery in case of a local recurrence can result in long-term survival, especially if microscopic radicality is achieved.

As has been shown in previous studies as well as in chapter 8 and 9, radical re-resection of a locally recurrent rectal cancer can lead to long term survival. In many cases, extended operations are needed to obtain radical re-resection. In **Chapter 10** the technique of sacral resection and the results in 26 patients treated in the Netherlands Cancer Institute are reported. The median operating time in this series was 6 hours (range 2.5-10 hours) with a median blood loss of 3600 ml (range 420-11,500 ml). A microscopically radical resection was accomplished in 15 patients (58%). One patient died postoperatively; six patients did not experience complications postoperatively. The median hospital stay after sacral resection was 20 days (range 5-202). The estimated two and five year survival were 82% (95% CI: 62-100%) and 51% (95% CI: 15-88%) respectively. The described therapy can be valuable when aiming for a radical re-resection of recurrent rectal cancer disease. It is accompanied with acceptable perioperative morbidity and mortality, good preservation of the function of lower limbs and pelvis and sometimes results in long-term survival.

A possible concern after sacral resection is closure of the enormous perineal defect. In the Netherlands Cancer Institute the Inferiorly Based Rectus Abdominis Myocutaneous (IBRAM) flap is used as primary closure technique for large defects in perineum and groin after surgical resection with or without prior irradiation. The technique of harvesting and transferring this flap as well as the results in a series of 37 patients is reported in **Chapter 11**. Eleven patients (30%) experienced IBRAM flap-related complications of whom one needed surgical exploration, while the remaining 10 patients all had minor complications which resolved after non-operative treatment. None of the IBRAM-flaps were lost which reflects the reliability of the flap, which can be used with acceptably low morbidity.



Samenvatting

Samenvatting

DEEL I

De invloed van de Totale Mesorectale Excisie met of zonder preoperatieve radiotherapie op het locale recidief en de overleving, de complicaties en stoelgang gerelateerde klachten

In **Hoofdstuk 1** wordt gekeken naar de invloed van de Totale Mesorectale Excisie (TME) bij patiënten met een rectumcarcinoom op het locale recidief en de overleving. In een retrospectief onderzoek op populatie-niveau worden 2 groepen patiënten met een rectumcarcinoom met elkaar vergeleken, een groep patiënten die behandeld zijn voor de introductie van de TME en een groep patiënten die behandeld is na de introductie van de TME. Alle patiënten met een rectumcarcinoom woonachtig in Noord Holland die behandeld zijn tussen 1988-1991 (979 patiënten allen geopereerd middels een conventionele operatie met een stompe dissectie van het rectum) en tussen 1998-2000 (890 patiënten, allen geopereerd middels een TME) werden geselecteerd uit de kankerregistratie van het Integraal Kanker Centrum Amsterdam (IKCA). Van de patiënten die een macroscopisch radicale rectumresectie hadden ondergaan, werd informatie over het optreden van een lokaal recidief en afstandmetastasen verzameld. Het percentage lokale recidieven daalde significant van 20% bij patiënten die geopereerd waren tussen 1988-1991 naar 11% bij patiënten die behandeld waren tussen 1998-2000. Uit de multivariate analyse kwam naar voren dat tumor stadium (T-stadium en lymfklier status), periode van diagnose (1988-1991 versus 1998-2000, met andere woorden niet of wel behandeld middels TME), radiotherapie en chemotherapie onafhankelijke prognostische factoren waren die samenhingen met een afname in het percentage lokale recidieven. De 5 jaars overleving voor alle patiënten met een rectumcarcinoom steeg van 52% (95% betrouwbaarheidsinterval (BI) 48-55) voor patiënten behandeld tussen 1988-1991 naar 59% (95 BI 55-63) voor patiënten behandeld tussen 1998-2000 (verschil is niet significant verschillend). De introductie van TME in combinatie met het vaker toepassen van preoperatieve radiotherapie lijkt de meest valide verklaring voor de geobserveerde verschillen. Hoewel de invloed van TME op het lokale recidief nooit onderzocht is in een gerandomiseerd onderzoek, laten deze resultaten zien dat TME inderdaad beter is dan de conventionele operatietechniek die eerder werd toegepast.

In **Hoofdstuk 2** wordt een model gepresenteerd waarmee bij patiënten met een rectumcarcinoom de nadelen van kortdurende preoperatieve radiotherapie (dat is een toename van korte termijn complicaties) worden afgewogen tegen de voordelen (dat is een reductie in het aantal lokale recidieven). Gebaseerd op de resultaten van de laatste vier gerandomiseerde onderzoeken naar de waarde van preoperatieve radiotherapie, worden patiënten ingedeeld in een van de vijf volgende categorieën; 1 patiënten met voordeel van preoperatieve radiotherapie zonder toename in complicaties, 2 patiënten

met voordeel van preoperatieve radiotherapie met een toename in complicaties, 3 patiënten zonder voordeel en zonder nadeel van preoperatieve radiotherapie, 4 patiënten zonder voordeel van preoperatieve radiotherapie maar met een toename in complicaties, 5 patiënten die overlijden ten gevolge van de preoperatieve radiotherapie. Uit het onderzoek komt naar voren dat de meerderheid van patiënten (74 – 87%) geen voordeel of nadeel ondervindt van preoperatieve radiotherapie terwijl een klein deel van de patiënten (6 – 11%) geen voordeel, maar wel nadeel van preoperatieve radiotherapie ondervindt. Een klein deel van de patiënten (5 – 13%) heeft voordeel van preoperatieve radiotherapie zonder dat er sprake is van een nadelig effect. Deze groep profiteert dus optimaal van de toegepaste behandeling in de vorm van preoperatieve radiotherapie.

Naast het feit dat geen gebruik gemaakt kon worden van de bron gegevens bij de berekeningen voor de resultaten in hoofdstuk 2, was het ontbreken van consensus aangaande de ernst van ervaren complicaties een belangrijk nadeel. Daarom werd een Delphi ronde georganiseerd met medewerking van 21 colorectale chirurgen uit Nederland, Engeland en Zweden. In **Hoofdstuk 3** wordt de procedure van een Delphi ronde nader uitgelegd en worden de behaalde resultaten gepresenteerd. De centrale vraag tijdens de Delphi ronde was: "welke van de genoemde complicaties, vindt u dermate ernstig (majeur) dat u zou besluiten af te zien van kortdurende preoperatieve radiotherapie (5x5Gy) bij de behandeling van patiënten met een resectabel rectumcarcinoom ($T_{1-3}N_{0-2}M_0$) indien u zou weten dat deze zou optreden/ verergeren ten gevolge van de radiotherapie?". Consensus werd bereikt voor 13 majeure complicaties (overlijden, naadlekkage behandeld middels relaparotomie, naadlekkage resulterend in persisterende fisteling, postoperatieve nabloeding waarvoor relaparotomie, intra-abdominaal abces zonder genezingstendens, sepsis, longembolie, myocardinfarct, compartiment syndroom van de onderbenen, incontinentie voor vaste ontlasting op de langere termijn, mictieproblemen op de langere termijn, heupfractuur met persisterende pijnklachten en neuropathie aan de benen met persisterende pijnklachten). Daarnaast werd er ook consensus bereikt voor drie "grote" complicaties (perineale wondproblemen waarvoor chirurgische behandeling noodzakelijk is, dunne darm obstructie waarvoor relaparotomie nodig is en incontinentie voor dunne ontlasting op de langere termijn). Deze 16 complicaties in combinatie met het model gepresenteerd in hoofdstuk 2 kunnen gebruikt worden om in de toekomst op genuanceerde wijze de voor- en nadelen van kortdurende preoperatieve radiotherapie tegen elkaar af te wegen.

De "ColoREctal Functional Outcome questionnaire (COREFO)" is een vragenlijst die stoelgang gerelateerde klachten bij patiënten na colorectale chirurgie evalueert en bestaat uit 27 vragen. De ontwikkeling van deze vragenlijst is gebaseerd op gegevens uit eerder gepubliceerde artikelen, expertise van vier colorectale chirurgen en informatie van 10 patiënten met stoelgang gerelateerde klachten na colorectale chirurgie. In een groep van 257 patiënten met en zonder stoelgang gerelateerde problemen werd de COREFO vragenlijst, samen een Nederlandse vertaling van de Hallböök vragenlijst en een aangepaste versie van de Vaizey vragenlijst, getest op betrouwbaarheid en validiteit **(Hoofdstuk 4)**. Zowel voor de COREFO als voor de Hallböök vragenlijst waren

de betrouwbaarheid en validiteit adequaat. Dit bleek niet het geval voor de Vaizey vragenlijst. De psychometrische analyses lieten een klein verschil zien tussen de COREFO en de Hallböök vragenlijst, ten faveure van de COREFO. Daarnaast gaven significant meer patiënten de voorkeur aan de COREFO vragenlijst ten opzichte van de twee andere vragenlijsten. Geconcludeerd werd dat zowel de COREFO als de Hallböök vragenlijst beide geschikte vragenlijsten zijn om stoelgang gerelateerde klachten na colorectale chirurgie te evalueren.

Bij tien patiënten met een rectumcarcinoom die behandeld zijn middels kortdurende radiotherapie gevolgd door een rectumresectie volgens het Totale Mesorectale Excisie-principe werd een manometrie en barostat onderzoek verricht vijf maanden na de operatie. Hetzelfde onderzoek werd verricht bij tien gezonde vrijwilligers en in **Hoofdstuk 5** worden de resultaten van beide groepen met elkaar vergeleken. Om de (neo-)rectale sensitiviteit te bepalen werd gebruik gemaakt van een stapsgewijs isovolumetrisch en isobarisch distensie protocol. De (neo-)rectale motiliteit werd bestudeerd tijdens verlengde distensie op het niveau waarop de proefpersoon aangaf het gevoel van aandrang te hebben. Het neo-rectale volume (113 ± 33 ml) waarbij patiënten aangaven het gevoel van aandrang te hebben was significant kleiner in vergelijking met gezonde vrijwilligers (272 ± 87 ml). Het druk niveau dat een aandrang gevoel induceerde was daarentegen niet verschillend tussen patiënten (21 ± 5 mmHg) en gezonde vrijwilligers (24 ± 9 mmHg). Tijdens de verlengde distensie werden bij gezonde vrijwilligers geen contracties in het rectum waargenomen. Bij patiënten daarentegen werden zowel tijdens de verlengde isovolumetrische als isobarische distensie contracties geobjectiveerd in het neo-rectum. Dit suggereert dat deze neo-rectale "irritabiliteit" een nieuw pathofysiologisch mechanisme vertegenwoordigd welke bijdraagt aan stoelgang gerelateerde klachten na preoperatieve radiotherapie en rectum resectie (TME)

DEEL II

Potentiële reductie van ileostoma-gerelateerde morbiditeit

In **Hoofdstuk 6** worden 69 patiënten met een tijdelijk, beschermend ileostoma geanalyseerd. Bij 60 patiënten (87%) werd het tijdelijke ileostoma opgeheven na een mediane periode van 24 weken, wat substantieel langer is dan aanvankelijk gepland was (8 tot 12 weken). Gedurende de periode dat het ileostoma aanwezig was, deden zich bij 29 patiënten stoma-gerelateerde complicaties voor. Bij 25 patiënten traden deze complicaties meer dan twee weken na het aanleggen van het ileostoma op. Het vroegtijdig opheffen van een ileostoma, dat wil zeggen binnen 10 dagen na het aanleggen, zou derhalve kunnen leiden tot een afname van stoma-gerelateerde complicaties. In **hoofdstuk 7** worden de resultaten van een haalbaarheids onderzoek naar het vroegtijdig opheffen van een dubbelloops ileostoma beschreven. Zevenentwintig patiënten werden in dit onderzoek geïncludeerd. Criteria voor het vroegtijdig opheffen van een beschermend ileostoma waren een ongecompliceerd postoperatief herstel en de afwezigheid van radiologische tekenen van een naadlekkage, gebaseerd op contrast onderzoek met waterig contrast op

dag 7 na het aanleggen van het ileostoma. Bij 18 van de 27 patiënten werd het ileostoma vroegtijdig opgeheven. De redenen om het ileostoma niet op heffen waren aanwijzingen voor naadlekkage, geprotaheerd beloop na de eerste operatie en logistieke problemen ten aanzien van de operatieplanning. Geen van de patiënten overleed na het vroegtijdig opheffen van het ileostoma en bij vier patiënten werden milde complicaties gezien. Geconcludeerd werd dat vroegtijdig opheffen van een beschermend, dubbelloops ileostoma haalbaar is.

DEEL III

Chirurgische behandeling van het (recidieverend) rectumcarcinoom; technieken en resultaten

De behandeling van het recidief rectumcarcinoom blijft een uitdaging. In de periode 1998-2000 werden in de regio van het Intergaal Kanker Centrum Amsterdam (IKA) in totaal 632 patiënten met een rectumcarcinoom behandeld middels een macroscopisch radicale resectie. Uit deze groep van patiënten werden alle patiënten geselecteerd met een recidief carcinoom. In **hoofdstuk 8** wordt de behandeling van deze patiënten op populatie-niveau geanalyseerd. Een lokaal recidief deed zich voor bij 62 patiënten (10%) waarbij bij 30 patiënten (6%) ook sprake bleek te zijn van afstandsmetastasen. Bij tien van de 32 patiënten met een geïsoleerd recidief bleek het mogelijk de tumor geheel te verwijderen bij een nieuwe operatie. De overleving in deze groep was aanzienlijk beter in vergelijking met de andere patiënten. Drie kwart van deze patiënten was na 3 jaar nog in leven. De overleving bleek significant slechter wanneer de tumor bij een nieuwe operatie niet geheel verwijderd kon worden (8 patiënten, mediane overleving 24 maanden). Patiënten die niet geopereerd werden maar behandeld werden met radio- en/of chemotherapie (7 patiënten) hadden een mediane overleving van 15 maanden, terwijl patiënten die niet behandeld konden worden met radio- of chemotherapie, of een operatie hadden een mediane overleving van 5 maanden.

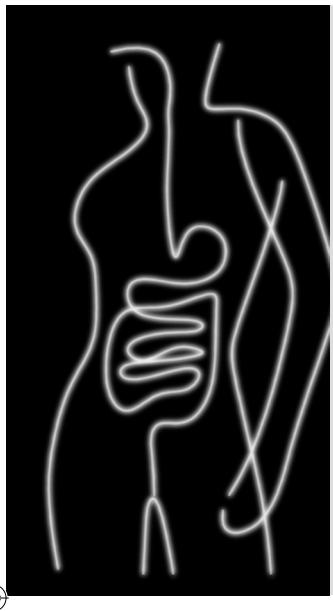
Bij 124 patiënten (20%) werden afstandsmetastasen gevonden waarbij bij 30 patiënten (5%) ook sprake was van een lokaal recidief. De meerderheid van deze patiënten (54%) werd behandeld met radio- en/of chemotherapie. De mediane overleving in deze groep was 15 maanden. Twintig patiënten werden geopereerd in verband met afstandsmetastasen en hadden de beste mediane overleving van de gehele groep (32 maanden). Deze resultaten laten zien dat, hoewel behandelopties bij een recidief rectumcarcinoom over het algemeen gelimiteerd zijn, een deel van de patiënten baat kan hebben bij behandeling van hun recidief, zeker wanneer een radicale re-resectie mogelijk is.

In **Hoofdstuk 9** worden 40 patiënten met een lokaal recidief van een rectumcarcinoom beschreven die geopereerd zijn voor hun recidief in het Nederlands Kanker Instituut. De uitgevoerde operaties betroffen abdominoperineale resecties, abdominosacrale resecties, exenteraties (zowel posterieur als totale exenteraties) en ruime lokale resecties. De mediane overleving was 25 maanden (95% betrouwbaarheids interval (BI): 13-37 maanden) en de 5-jaars overleving was 28% (95% BI: 12-45%). Bij multivariate analyse

bleek dat de afwezigheid van klachten ten tijde van de presentatie van het recidief, centrale lokalisatie van het recidief en radicale resectie van het recidief onafhankelijke prognostische factoren waren voor een betere overleving. Een hernieuwde operatie bij patiënten met een recidief rectumcarcinoom kan derhalve resulteren in lange overleving, zeker wanneer een radicale resectie van het recidief mogelijk is.

Om een radicale re-resectie te verkrijgen kunnen zeer uitgebreide operaties noodzakelijk zijn. In **Hoofdstuk 10** wordt de techniek van een sacrumresectie getoond. Tevens worden de behandelresultaten van 26 patiënten beschreven die een sacrumresectie hebben ondergaan in het Nederlands Kanker Instituut. De gemiddelde operatieduur was 6 uur (spreiding 2.5-10 uur) en het gemiddelde bloedverlies bedroeg 3600 ml (spreiding 420-11500 ml). Een radicale resectie van de tumor bleek mogelijk bij 15 patiënten (58%). Een patiënt overleed na de operatie terwijl bij 6 patiënten zich postoperatief geen complicaties voor deden. De mediane verblijfsduur na de operatie in het ziekenhuis was 20 dagen (spreiding 5-202 dagen). De twee en vijf jaars overleving bedroegen respectievelijk 82% (95% BI: 62-100%) en 51% (95% BI: 15-88%). De beschreven techniek kan waardevol zijn bij een poging om een radicale re-resectie te verkrijgen bij patiënten met een recidief tumor met doorgroei in het sacrum. De techniek gaat gepaard met een acceptabele postoperatieve morbiditeit en mortaliteit, behoud van functie van de onderste extremiteiten en het bekken en kan resulteren in lange overleving postoperatief.

Een mogelijk probleem na een sacrumresectie is het sluiten van het enorme perineale defect. In het Nederlands Kanker Instituut wordt de distaal gesteelde huidspierlap van de musculus rectus abdominis gebruikt om grote perineale en inguinale defecten te sluiten na chirurgische resectie, al dan niet voorafgegaan door radiotherapie. De techniek van het oogsten en verplaatsen van de huidspierflap wordt in **Hoofdstuk 11** beschreven. In totaal zijn 37 patiënten behandeld met deze huidspierflap. Bij 11 patiënten (30%) deden zich complicaties voor die gerelateerd waren aan het gebruik van de huidspierflap, bij een patiënt bleek chirurgische interventie noodzakelijk. Alle 37 distaal gesteelde huidspierflappen van de musculus rectus abdominis groeiden postoperatief in. Dit reflecteert de betrouwbaarheid van deze huidspierflap, die gepaard gaat met een lage morbiditeit.



Future Perspectives

Future Perspectives

As always, answering questions leads to new questions. And so happened during the writing of this thesis. Many ideas for future research projects arose, some seem to be feasible others seem to be unreasonable or at least not realistic on a short notice.
In this part of the thesis some reflections are expressed concerning research goals in the (near) future.

Part I
Influence of Total Mesorectal Excision with or without preoperative radiotherapy on local recurrence and survival, complications, and functional outcome.

Preoperative radiotherapy in rectal cancer patients; aiming for better patient selection

As has been shown in Chapter 1, introduction of TME did decrease local recurrence rate after rectal cancer. A further decrease in local recurrence is seen with the addition of short-term preoperative radiotherapy, which so far did not improve survival. However, the additional benefit of short-term preoperative radiotherapy is limited (Chapter 2) with an increase in treatment-related morbidity. It is attractive to apply the model presented in Chapter 2 together with the major complications from the Delphi round (Chapter 3) on the raw data from the Dutch TME trial.[1] It would lead to a better selection of patients benefiting optimally from radiotherapy, while on the other hand a group of rectal cancer patients is identified in whom radiotherapy could possibly be omitted.

Functional outcome after radiotherapy and rectal resection; are there options to improve it?

Impaired functional outcome after preoperative radiotherapy and rectal resection is a common problem. Attempts should be made to minimize the negative effect of this multimodality treatment. As has been shown in Chapter 5 rectal capacity is decreased after rectal resection and, in contrast to healthy volunteers, contractions are observed in the neo-rectum. Increasing rectal capacity and limiting neo-rectal contractions might improve functional outcome.
A J-pouch colo-anal anastomosis has a larger volume compared to a side-to-end colo-anal anastomosis and might reduce neo-rectal contraction since the circular muscles are transsected during the creation of the pouch. Currently a randomized clinical trial (POCASTER) comparing a side-to-end anastomosis with a J-pouch anastomosis is performed to answer this question. To evaluate the functional outcome, the recently developed COREFO questionnaire (Chapter 4) will be used.

Another option to reduce the neo-rectal irritability might be the use of loperamide or a selective 5-HT3 receptor antagonist like ondansetron in patients experiencing impaired functional outcome. Loperamide has a direct influence on the bowel and reduces

peristalsis, decreases urge for defecation and increases sphincter tone.[2-3] Ondansetron has an influence on peristalsis, prolongs the so called "mouth to anus time", decreases urgency for defecation and reduces defecation frequency.[4-5] A double-blind, placebo controlled cross-over trial is the most appropriate way to investigate the influence of loperamide or ondansetron in patients with impaired functional outcome after radiotherapy and rectal resection. The effect of loperamide or ondansetron could be evaluated by rectal barostat measurement and by using the COREFO questionnaire.

Exploring the histological differences between rectum and colon

In the guinea-pig rectum, a high density of slowly adapting, low threshold mechano-receptors with specialized intraganglionic laminar endings (rIGLEs) have been demonstrated which are not found more proximally in the guinea-pig colon.[6] These rIGLE's are a specialised class of mechanoreceptor which probably allows the rectum to act as a temporary low-pressure reservoir. If these rIGLEs also exist in humans, it might explain our observation that no contractions were seen during prolonged distension of the rectum of healthy volunteers (Chapter 5). The contractions seen in patients might be due to the absence of rIGLEs in the sigmoid colon which is used to create a neo-rectum and this could explain the inability to accommodate in response to distension. It seems interesting to investigate whether rIGLEs also exist in humans by means of pathological examination of the human colon and rectum.

Part II

Potential reduction of morbidity as induced by loop ileostomies

Early protective loop ileostomy closure (*i.e.* during the same hospital admission as the initial operation) is feasible (Chapter 7). Early closure might reduce stoma-related morbidity (Chapter 6) and thus might subsequently improve quality of life. However, ideally this should be investigated by means of a randomised clinical trial comparing early versus late closure of protective loop ileostomies.

Part III

Surgical treatment for (recurrent) rectal cancer disease; techniques and results

Although survival in case of recurrent rectal cancer is limited, some patients can benefit from surgical treatment if a microscopically radical re-resection is feasible (Chapter 9). This requires in some cases extended surgery (*i.e.* exenteration (posterior or total), abdominsacral resection) as is described in Chapter 10. These procedures are rarely performed and the required expertise is probably limited among individual colorectal surgeons. Moreover, regional guidelines regarding the treatment of recurrent rectal cancer are hardly available. It seems attractive to install a multidisciplinary advisory committee in Greater Amsterdam (the region of the Comprehensive Cancer Center Amsterdam), that can be asked to review patients with recurrent rectal cancer disease.

This committee (consisting of experts in medical oncology, radiation oncology and surgical oncology) could be invited to give a treatment advice for individual patients with residency in Greater Amsterdam and could direct patients to specialised centers for extended procedures (*e.g.* intraoperative radiotherapy or sacral resection). The formation of such a committee has some potential advantages. First, it might improve recurrent rectal cancer treatment in Greater Amsterdam, of which the data collection should preferably be performed prospectively for all patients with recurrent rectal cancer disease. Second, it offers the opportunity to perform more structural research among this relatively small group of patients. There are limited data on the severity of symptoms due to a local recurrence or the influence of recurrent disease on the quality of life. Creating a population-based database in parallel with the formation of a committee of experts could result in a database with many opportunities. The initiation of a research project to evaluate quality of life among patients with recurrent rectal cancer disease in Greater Amsterdam is highly desirable.

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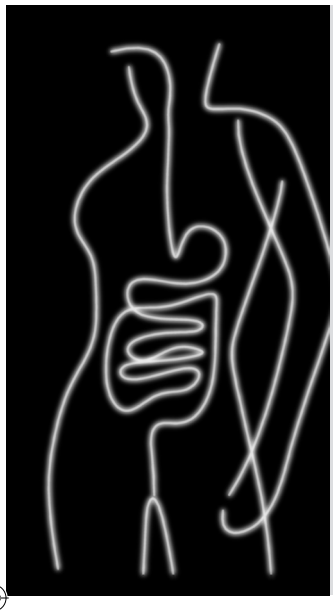

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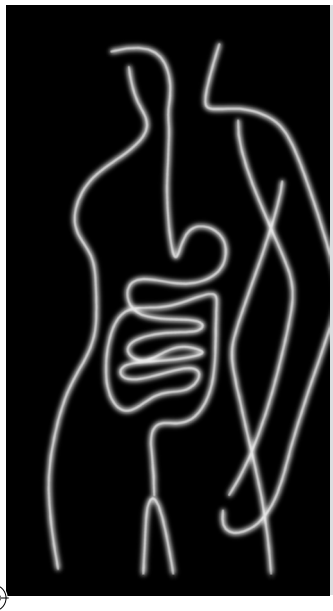

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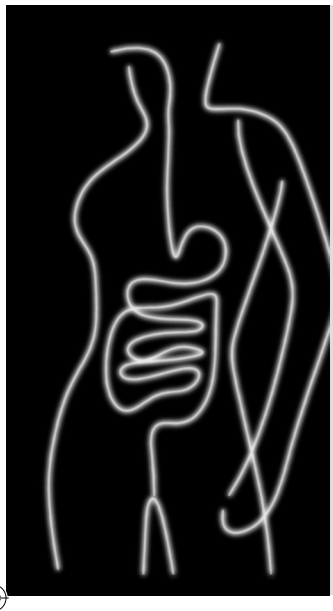

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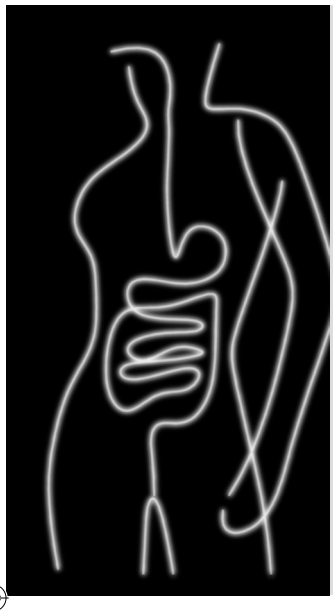

Curriculum vitae

Curriculum vitae

Roel Bakx werd geboren op 3 oktober 1973 in Utrecht. In 1986 ging hij naar de middelbare school, het Strabrecht College in Geldrop alwaar hij in 1992 zijn VWO-diploma haalde.
Datzelfde jaar startte hij met de studie Geneeskunde aan de Vrije Universiteit in Amsterdam. Tijdens zijn studie verrichtte hij in 1996 gedurende 6 maanden onderzoek op de afdeling "Molecular Pharmacology and Therapeutics" van het Memorial Sloan Kettering Cancer Institute in New York. Dit onderzoek vond plaats onder leiding van Prof. Dr. J.R. Bertino.
Na het behalen van zijn artsexamen in 2000, was hij 3 maanden werkzaam als arts-assistent chirurgie in het Albert Schweitzer Ziekenhuis te Dordrecht, locatie Amstelwijck (dr. O. Varin) en daarna 11 maanden als arts-assistent chirurgie in het Sint Lucas Andreas Ziekenhuis te Amsterdam (Dr. R.M.J.M. Butzelaar & Dr. E.Ph. Steller).
Vanaf juni 2001 werd zijn loopbaan voortgezet als arts-onderzoeker op de afdeling chirurgie van het Academisch Medisch Centrum in Amsterdam onder leiding van Prof. Dr. J.J.B. van Lanschot en heeft geresulteerd in deze dissertatie. Vanaf 1 juli 2004 is hij in opleiding tot chirurg afwisselend in de Gelre Ziekenhuizen in Apeldoorn (opleider dr. W.H. Bouma) en in het Academisch Medisch Centrum in Amsterdam (opleider Prof. Dr. J.J.B. van Lanschot).
Roel Bakx is getrouwd met Laura Oprel en heeft de twee meest fantastische dochters die een man zich wensen kan: Sterre en Zoë!