Colorectal surgery: optimisation of functional results and management of complications

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You cannot stop the waves, but you can learn to surf
Swami Satchidinanda

Voor Arend & Anna Sophie
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General introduction

COLORECTAL SURGERY

Over the past decades, the incidence of colorectal cancer has been increasing in western society. In the Netherlands, colorectal carcinoma is the third most common cancer after breast and lung cancer with annually over 9,000 patients registered with a newly developed colorectal carcinoma, with approximately one third located in the rectum.\(^1\)\(^,\)\(^2\) Surgical resection of the primary tumour with its regional lymph nodes is a pivotal part of potentially curative therapy.

Increasing incidences are also seen for benign colorectal diseases, such as inflammatory bowel disease\(^3\) and diverticulitis.\(^4\) Over 5,700 Dutch patients are annually diagnosed with inflammatory bowel disease. A large proportion of patients diagnosed with inflammatory bowel disease will need one or more partial bowel resections within 15 years after onset of the disease.\(^5\)

Therefore, the surgeon plays an important role in the multidisciplinary treatment of both colorectal cancer and benign colorectal disease. This encompasses not only the technical procedure, but also the recognition and management of complications in order to improve functional results and to critically appraise treatment protocols.

FUNCTIONAL OUTCOME AFTER RECTAL SURGERY

Nerve sparing techniques resulting from a better understanding of pelvic anatomy have improved functional outcome of surgery for both benign and malignant diseases of the rectum.\(^6\) Despite advances in neoadjuvant therapy, surgery remains the cornerstone of treatment for rectal cancer. Since the introduction of the abdominoperineal resection by Sir Earnest Miles at the beginning of the last century,\(^7\) the era has changed towards sphincter saving surgery. Understanding of the mesorectal tumour spread resulted in the total mesorectal excision (TME) technique, thereby reducing the local recurrence rate from 20 - 30% as described by historic studies to 10%.\(^8\) This change in philosophy plus the acceptance of 1 - 2 cm distal resection margins, and the technical development of stapling devices, made it possible to perform a low anastomosis with good oncological results, while preserving sphincter function.
A further reduction in local recurrence rates has been established by combining TME with preoperative radiotherapy, as described in a recent Cochrane systematic review that analysed 19 randomised trials. After publication of the results of the Dutch TME trial, short course radiotherapy followed by TME, with sphincter saving surgery if possible, became the standard treatment for rectal cancer (except for T1N0) in the Netherlands. Most recently, chemoradiotherapy resulting in downstaging of the primary tumour is increasingly used, thereby further improving local control in high risk patients. This downstaging also potentially increases the sphincter preservation rate in patients with tumours close to the dentate line if combined with intersphincteric resection techniques.

These developments all have their consequences for functional outcome. Performing a coloanal anastomosis has the possible disadvantage of developing the much referred ‘anterior resection syndrome’, a set of symptoms comprising a high defaecation frequency, faecal urgency and soiling. Several factors have been described as possible influential causes of this impaired functional outcome after rectal resection: impaired sphincter function, loss of neorectal sensation, decreased neorectal compliance, impaired neorectal capacity and increased neorectal irritability. Most patients encounter this diminished anorectal function particularly in the first postoperative year. However, in about 30% of patients these dysfunctional symptoms may persist and become the main issue of their postoperative quality of life. Surgery alone can cause a significant impairment of pelvic organ function, but recent trials have shown an additionally diminished function due to preoperative radiotherapy.

Therefore, one should not only aim at a better local control and survival, but also focus at improvement of anorectal, sexual and urinary function, thus improving quality of life.

**COLORECTAL SURGERY; MANAGEMENT OF ANASTOMOTIC DEHISCENCE**

Coloanal surgery is known for its potentially complicated course. Large multicentre trials describe overall complication rates after (colo)rectal resections of 32 to 50 percent. The incidence of anastomotic leakage after colorectal resections varies from 1 to 25 percent, partly depending on the method of evaluation. In general, leakage rates are higher for more distal resections. Anastomotic leakage not only leads to an increased morbidity and mortality, but is also associated with a worse oncological outcome. Early recognition and treatment might reduce morbidity and mortality. Anastomotic leakage often evolves subclinically, which makes early recognition difficult. The necessity of diagnostic imaging can cause an additional delay in diagnosis, while its diagnostic value is questionable.

Therefore, thorough clinical observation in the early postoperative period and the awareness of the limited role of diagnostic imaging might be helpful in early diagnosis, and early treatment.

**RECTAL CANCER; CRITICAL APPRAISAL OF CURRENT TREATMENT**

Local recurrence rate is the most relevant endpoint for interventional studies on neo-adjuvant treatment in rectal cancer, as survival is not or only marginally improved. Although large randomised trials did not show impact of preoperative radiotherapy on anastomotic leakage and postoperative mortality, some single institutional experiences actually did suggest the opposite.

Despite the absolute risk reduction of approximately 5% by routine use of short course preoperative radiotherapy, locally recurrent disease remains inevitable in a small subgroup of patients. Most studies report local recurrence rate as a homogenous endpoint. Less is known about clinical presentation and treatment modalities of locally recurrent rectal cancer after surgery alone or after surgery combined with (chemo)radiotherapy for the primary tumour. Symptomatic local recurrence, especially in case of intractable pain, is the most relevant clinical entity that should be kept to a minimum given its impact on quality of life. The ultimate effect of (chemo)radiotherapy on this specific subgroup of patients with locally recurrent rectal cancer has not yet been extensively studied. In subgroup analysis it seems that short course preoperative radiotherapy is only of additional value in selected cases and only when a radical resection is foreseen, emphasising the importance of an adequate excision of the mesorectum. This has shifted the focus on better selection of patients for surgery alone on the one hand and more intensified preoperative treatment for downsizing on the other hand.

This application of neoadjuvant short course radiotherapy for rectal cancer potentially limits the treatment options for future recurrent disease. Therefore, the benefit of neoadjuvant radiotherapy in terms of local control should not only be balanced against its negative side effects, but also against its impact on symptoms and treatment possibilities of locally recurrent rectal cancer.
Aim of the thesis

The aim of this thesis is to critically appraise rectal cancer treatment, to evaluate functional outcome and to provide strategies in the management of complications after colorectal surgery.

Outline of the thesis

PART I
FUNCTIONAL OUTCOME AFTER RECTAL SURGERY

Many studies focussed on analysing the cause of the previously described ‘anterior resection syndrome’. In 1986 Lazorthes and Parc attributed the defaecatory disorders mainly to the loss of rectal reservoir, and described the colonic-J-pouch as a possible solution.26,27

The colonic J-pouch is constructed to closely mimic the native rectum by the creation of a double barrelled configuration as a reservoir, thus enlarging neorectal compliance and capacity. Furthermore, by transection of the circular muscular fibres, the hypercontractility of the neorectum is potentially diminished.

Theoretically, these factors can contribute to an improved postoperative function in colonic J-pouch patients. Several randomised studies have demonstrated the superiority of the colonic J-pouch in comparison with the end-to-end anastomosis. 28 The side-to-end anastomosis, however, could be a compelling alternative to the colonic J-pouch as it is technically easier to construct.29 Chapter 1 describes the results of a multicentre randomised controlled trial, comparing the colonic J-pouch with the side-to-end anastomosis.

Further research was conducted to gain insight in the pathophysiological mechanisms contributing to the impaired functional results after rectal resection. The motor response of the neorectum in patients after preoperative radiotherapy and total mesorectal excision is examined and compared to that of healthy volunteers; these results are reported in Chapter 2.

Although diminished bowel function has been described extensively, sexual and urinary dysfunctions are frequent and distressing complications of rectal cancer treatment.30 Pelvic organ function might be impaired by radiotherapy, but surgery alone can also affect function due to damage of the pelvic nerve system.31,32 Chapter 3 evaluates incidence of sexual and urinary functional disorders and their influence on quality of life after rectal resection in the short and the long term.

PART II
COLORECTAL SURGERY; MANAGEMENT OF ANASTOMOTIC DEHISCENCE

Anastomotic leakage is the most feared complication after colorectal surgery and has been described extensively. Several studies identified risk factors, assessed methods to reduce leakage and advocated the more liberal construction of a diverting ostomy in case of low anastomoses to reduce symptomatic leakages.33 In the postoperative course it is important to recognise anastomotic leakage in an early stage in order to prevent further deterioration of the clinical course and thus increased morbidity and mortality. The delay in diagnosis from the occurrence of clinical symptoms associated with anastomotic leakage and treatment of anastomotic leakage has been evaluated in Chapter 4, with assessment of factors that contributed to this delay.

A large proportion of patients are subjected to diagnostic imaging (CT-scan/barium enema) to aid the diagnosis of anastomotic leakage. Chapter 5 evaluates the additional value of the imaging modalities by assessing the predictive value and the delay in diagnosis after additional tests.

PART III
RECTAL CANCER; CRITICAL APPRAISAL OF CURRENT TREATMENT

Promising results from randomised trials with improvement in local control by preoperative radiotherapy followed by total mesorectal excision had an important impact on (inter)national treatment protocols.

However, higher rates of early postoperative adverse events have been reported after preoperative radiotherapy in comparison with surgery alone, mainly consisting of perineal wound infections after abdominoperineal resections35 and toxicity from rectal cancer radiation.9 In contrast to results from large prospective studies, individual experiences from non-specialised low-volume hospitals suggested an increased risk of anastomotic leakage after preoperative radiotherapy.34-36 Chapter 6 describes morbidity and mortality of total mesorectal excision with special emphasis on anastomotic leakage after the introduction of short course preoperative radiotherapy in an unselected cohort of patients. Chapter 7 critically appraises the role of routinely adding radiotherapy to adequate TME surgery for primary rectal cancer, by a systema-
tic review of current literature from the point of view of the different clinical entities of locally recurrent rectal cancer.

REFERENCES


Part I

Functional outcome after rectal surgery
Chapter 1

J-pouch versus side-to-end coloanal anastomosis after preoperative radiotherapy and total mesorectal excision for rectal cancer: a multicentre randomised trial

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A. Vincent
W.F. van Tets
M.A.G. Sprangers
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ABSTRACT

Aim: Comparison of the functional and surgical outcome of the J-pouch with the side-to-end coloanal anastomosis after preoperative radiotherapy and total mesorectal excision in rectal cancer patients.

Methods: In a multicentre study patients with a carcinoma of the lower two third of the rectum were randomised to either a J-pouch or side-to-end reconstruction. Primary outcome was function of the neorectum one year after surgery. A functional outcome questionnaire (COREFO), and two quality of life questionnaires (EORTC-QLQ-CR38 and SF-36) were to be completed by all participants preoperatively, and 4 and 12 months postoperatively. Independent data managers recorded surgical outcome. A group size of 30 patients in each group was calculated based on a 15 point difference of the COREFO scale.

Results: In total 107 patients were randomised, 55 in the J-pouch and 52 in the side-to-end group. The COREFO incontinence scale at 4 months and the total functional outcome at 4 and 12 months showed better results for the J-pouch group in comparison with the side-to-end group. The remaining COREFO scales (frequency, social impact, stool related aspects and bowel medication), surgical outcome (complications, reoperations, length of hospital stay, re-admissions and mortality), and quality of life did not show significant differences between treatment groups.

Conclusion: Overall results of a colonic J-pouch and a side-to-end anastomosis are comparable, although functional results are slightly better by constructing a J-pouch. The side-to-end anastomosis is technically less demanding and therefore a justified alternative in sphincter saving surgery.

INTRODUCTION

Rectal cancer treatment has changed dramatically over the past decades. Understanding of the mesorectal tumour spread resulted in the total mesorectal excision (TME) technique, thereby reducing the local recurrence rate from 20 - 30% as described by historic studies to approximately 10%. A further reduction of local recurrence rates has been established by combining TME with preoperative radiotherapy in a dose of 5x5 Gy, as described in a recent Cochrane systematic review that analysed 19 randomised trials.1 These developments with the acceptance of 1 - 2 cm distal resection margins, and the technical development of stapling devices, made it possible to perform a low anastomosis with good oncological results, while preserving sphincter function.

Performing a coloanal anastomosis and thus avoiding a permanent colostomy has the possible disadvantage of developing the much referred ‘anterior resection syndrome’, a set of symptoms comprising a high defaecation frequency, feacal urgency and soiling.2 Most patients encounter this diminished anorectal function particularly in the first postoperative year. However, in about 30% of patients these dysfunctional symptoms may persist and become the main issue of their postoperative quality of life.3

Improvement of functional results by the technically more demanding J-pouch has been demonstrated in comparison with the straight coloanal anastomosis. Primarily within the first postoperative year the J-pouch has advantages over the end-to-end anastomosis due to a lower frequency and a lower prevalence of feacal urgency,4-6 and has therefore been recommended as the procedure of choice. Few studies have been conducted to compare the J-pouch with the side-to-end anastomosis, whereas the side-to-end anastomosis is a technically less demanding procedure and therefore a compelling alternative.

The objective of the present study was to compare functional and surgical results of the J-pouch with the side-to-end anastomosis and their impact on quality of life.
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PATIENTS AND METHODS

Design

The design of the study was a multicentre randomised trial. Patients were allotted either to a J-pouch or side-to-end reconstruction after total mesorectal excision for cancer of the distal rectum.

Patients

The protocol was approved by the Medical Ethical Committee of the Academic Medical Centre of the University of Amsterdam, and subsequently in the six other participating Dutch centres. All patients were registered after written informed consent. An independent trial office verified if in- and exclusion criteria were met before randomisation. The inclusion criteria comprised histologically proven rectal cancer located in the middle or distal part of the rectum (≤ 10cm from the anal verge), and a WHO performance status ≤ 2. Exclusion criteria were: cT1 or cT4 tumours, distant metastases, medical history of a colonic resection, anorectal surgery or chemo-radiotherapy, pre-existing faecal incontinence grade III or IV according to Parks,7 and a life expectancy of less than one year.

At the start of the trial, patients were randomised one day before surgery. Automated randomisation was performed via the ALEA system using institute and gender as stratification factors.4 Due to the unexpectedly frequent preoperative detection of metastatic disease and/or irresectable tumours the protocol was modified after 1.5 years. The amended protocol stated that the trial office was to be contacted during the operation after successful rectal resection and the patient was randomised after reconfirming the in- and exclusion criteria. The study protocol described the operation technique and the pre- and postoperative management in detail. Participants and assessors were not blinded to group assignment.

Surgical procedure

All patients received preoperative radiotherapy by a standardised protocol of 5x5 Gy. Within 5 days after radiotherapy patients were planned for surgery. To standardise the surgical procedure, supervision was provided by an experienced surgeon for the first colonic J-pouch procedures. The size of the colonic J-pouch was instructed to be 4 - 6 cm, as larger pouches can cause severe evacuation problems. The size of the side limb of the side-to-end anastomosis was instructed to be 3 - 4 cm. All anastomoses were performed with a circular stapler. A temporary loop ileostomy was performed in all patients. None of the patients received postoperative chemotherapy.

Data collection procedure

Preoperative questionnaires were given to the participating patients after completion of radiotherapy at hospital admission; the questionnaires at four and twelve months were received by post. All questionnaires were collected by qualified independent datamanagers from the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam. Operation reports, pathological reports and events during the postoperative course were registered. All collected data were put into two databases in order to prevent input mistakes by independent datamanagers in the NKI-AVL. In this institute an independent specialised statistician (AV) analysed the data.

Outcomes

The primary endpoint was the function of the neorectum as assessed at 12 months by the validated COlo RECTal Functional Outcome (COREFO) questionnaire’s summary score.9 This questionnaire comprises 26 questions that are combined into a total score (26 items) with 5 scales: frequency (2 items), incontinence (9 items), social impact (9 items), stool related aspects (3 items), and need for medication (3 items). The scores were linearly transformed into a score ranging from 0 - 100, with higher scores indicating more bowel function problems.

Secondary endpoint was the function of the neorectum as assessed by the same functional outcome COREFO score, at 4 months postoperatively. Furthermore, the surgical results as registered by operation reports, pathological reports and events during the postoperative course were secondary endpoints. Quality of life at 4 and 12 months as assessed by the EORTC-QLQ-CR38 and the SF-36 questionnaires were also secondary endpoints of the study. The EORTC-QLQ-CR38 is a validated colorectal cancer specific quality of life questionnaire that has been validated in Dutch patients.10,11 The questionnaire comprises 2 functional scales (body image and sexual function) and 7 symptom scales (defaecation problems, gastrointestinal symptoms, stoma-related problems, micturition problems, chemotherapeutic side effects, male and female sexual problems). The SF-36 is a validated general health survey12 that has had reliability and validity proven in the Netherlands.13 It yields an 8-scale profile of functional health and well-being scores. The EORTC-QLQ-CR38 as well as the SF-36 contain a score ranging from 0 - 100 with higher scores indicating better quality of life.
Statistical considerations

Sample size

With regard to the primary endpoint (i.e. the COREFO’s total functional outcome score at 12 months) the study was planned to have an 80% power to detect a difference of 15 points between the two treatment groups (at the 0.05 significance level) with 30 patients in each group assuming a standard deviation of 20.

Statistical analysis

Patients were assessed according to the intention-to-treat principle. Patients were considered eligible for functional assessment if their stoma was reversed and completed their 4 and 12 month questionnaire assessments within respectively 2 - 7 and 9 - 18 months post-randomisation. Clinical outcomes were compared between treatment groups using Fisher exact and Mann-Whitney-Wilcoxon tests. The within-patient differences were compared between treatment groups using the Mann-Whitney-Wilcoxon tests. Missing data were not imputed due to the significant number of patient attrition over time due to ineligibility. An ANCOVA was applied with covariates treatment group, gender, pelvic sepsis and tumour stage to test for their influence on functional outcome (the change-from-baseline COREFO primary endpoints). All tests were considered significant at the 0.05 level.

RESULTS

Patient population

Between April 2002 and January 2007 a total of 127 patients were registered for participation in the trial, of which 107 patients were randomised. The reasons for not randomising were patient refusal (n=3), exclusion criteria (n=16) and unknown (n=1). Exclusion criteria were: liver metastasis (n=1), long course preoperative radiotherapy (n=2), no preoperative radiotherapy (n=1), tumour located in upper third of the rectum (n=3), necessity of abdominoperineal resection (n=4), anal surgery in...
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history (n=1), endoscopic resection of a T1 tumour (n=1), simultaneous aorta replacement (n=1), simultaneous esophageal tumour (n=1) and the impossibility to construct a J-pouch anastomosis (n=1). The reason for not randomising was not reported in one patient. Patient and tumour characteristics are presented in Table 1, and with the exception of tumour stage, are well balanced between treatment groups. Tumour stage was more advanced in the side-to-end group (p=0.03).

According to the guidelines of the CONsolidated Standards Of Reporting Trials (CONSORT) statement the flow of participants from group assignment to final analysis is shown in Figure 1. Although 48 patients in the J-pouch group and 44 patients in the side-to-end group completed baseline assessments, only 30 and 22 patients (respectively) could be assessed for functional outcome due to the presence of stomas (Figure 1) and missing/late questionnaire completions (Table 2A). These patients were also evaluated for quality of life status (Table 3). Due to incomplete questionnaires, the primary endpoint (COREFO total score) could only be assessed in 24 and 17 patients, respectively (Table 2B). All patients were assessed for events in the postoperative course, apart from patients who underwent an abdominoperineal resection or did not undergo a resection (Figure 1).

### Table 2A

<table>
<thead>
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<th>Frequency</th>
<th>J-pouch n=48</th>
<th>Side-to-End n=44</th>
<th>4 months J-pouch n=22</th>
<th>4 months Side-to-End n=25</th>
<th>12 months J-pouch n=30</th>
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<td>(0 - 100)</td>
<td>(0 - 62)</td>
<td>(12 - 75)</td>
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<tr>
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<td>28</td>
<td>42</td>
<td>21</td>
<td>30</td>
</tr>
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<td>(20)</td>
<td>(20)</td>
<td>(16)</td>
<td>(18)</td>
<td>(13)</td>
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<td>1</td>
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</tr>
</tbody>
</table>

**Incontinence**

| Median    | 11           | 19              | 25                    | 36                       | 19                     | 37                        |
| (Range)   | (0 - 56)     | (0 - 64)        | (0 - 61)              | (6.5 - 83)               | (0 - 56)               | (6.3 - 78)                |
| Mean      | 16           | 21              | 21                    | 44                       | 20                     | 34                        |
| (St.Dev.) | (14)         | (15)            | (18)                  | (23)                     | (15)                   | (19)                      |
| Missing   | 1            | 1               | 0                     | 0                        | 1                      | 0                         |

**Stool Related Aspects**

| Median    | 19           | 28              | 25                    | 56                       | 14                     | 36                        |
| (Range)   | (0 - 94)     | (0 - 94)        | (2.8 - 72)            | (14 - 83)                | (0 - 64)               | (2.8 - 89)                |
| Mean      | 27           | 32              | 33                    | 48                       | 23                     | 36                        |
| (St.Dev.) | (24)         | (24)            | (23)                  | (23)                     | (20)                   | (21)                      |
| Missing   | 5            | 3               | 5                     | 1                        | 3                      | 1                         |

**Bowel Medication**

| Median    | 3            | 3               | 3                     | 1                        | 3                      | 1                         |
| (Range)   | (0 - 83)     | (0 - 92)        | (0 - 58)              | (0 - 67)                 | (0 - 50)               | (0 - 58)                  |
| Mean      | 28           | 34              | 18                    | 24                       | 11                     | 19                        |
| (St.Dev.) | (18)         | (20)            | (20)                  | (23)                     | (16)                   | (19)                      |
| Missing   | 0            | 1               | 0                     | 0                        | 0                      | 0                         |

**Total**

| Median    | 15           | 25              | 23                    | 42                       | 14                     | 34                        |
| (Range)   | (2.9 - 60)   | (1.9 - 66)      | (1.9 - 48)            | (13 - 67)                | (0.96 - 48)            | (6.7 - 75)                |
| Mean      | 20           | 26              | 25                    | 41                       | 19                     | 31                        |
| (St.Dev.) | (14)         | (19)            | (17)                  | (13)                     | (16)                   | (16)                      |
| Missing   | 5            | 5               | 5                     | 1                        | 5                      | 1                         |

### Table 2B

<table>
<thead>
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<th>Frequency</th>
<th>J-pouch n=22</th>
<th>Side-to-End n=25</th>
<th>4 months JP n=22</th>
<th>4 months STE n=25</th>
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<tr>
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<tr>
<td>(St.Dev.)</td>
<td>(25)</td>
<td>(24)</td>
<td>(26)</td>
<td>(26)</td>
<td>(26)</td>
<td>(26)</td>
<td></td>
</tr>
</tbody>
</table>

**Incontinence**

| Median    | 69           | 21              | 0.02            | 56               | 83              | 0.05             |   |
| (Range)   | (33 - 42)    | (-31 - 72)      | (-33 - 36)      | (-44 - 42)       | (-53 - 47)      |                 |   |
| Mean      | 10           | 25              | 14              | 31               | 14              | 14               |   |
| (St.Dev.) | (19)         | (24)            | (16)            | (22)             |                 |                 |   |
| Missing   | 0            | 1               | 1               | 1                |                 |                 |   |

**Stool Related Aspects**

| Median    | 5            | 3               | 0.25            | 56               | 12              | 0.66             |   |
| (Range)   | (-31 - 58)   | (-39 - 56)      | (-53 - 47)      | (-56 - 47)       | (-49 - 75)      |                 |   |
| Mean      | 78           | 17              | -49             | 75               | 5               | 4                |   |
| (St.Dev.) | (25)         | (21)            | (26)            | (26)             |                 |                 |   |
| Missing   | 5            | 3               | 4               | 3                |                 |                 |   |

**Bowel Medication**

| Median    | 0            | 17              | 0.08            | 17               | 17              | 0.07             |   |
| (Range)   | (-4.3 - 33)  | (-33 - 100)     | (-25 - 33)      | (-33 - 67)       | (-38 - 36)      |                 |   |
| Mean      | 87           | 22              | 19              | 19               | 19              | 19               |   |
| (St.Dev.) | (14)         | (33)            | (15)            | (25)             |                 |                 |   |
| Missing   | 0            | 1               | 0               | 1                |                 |                 |   |

**Total**

| Median    | 96           | 20              | 0.04            | 11               | 11              | 0.04             |   |
| (Range)   | (-32 - 33)   | (-27 - 53)      | (-30 - 26)      | (-38 - 36)       |                 |                 |   |
| Mean      | 71           | 19              | -14             | 97               |                 |                 |   |
| (St.Dev.) | (17)         | (19)            | (17)            | (18)             |                 |                 |   |
| Missing   | 5            | 5               | 6               | 5                |                 |                 |   |
Functional outcome after rectal surgery

The results of the COREFO questionnaire summary scores reflecting bowel function as assessed at 4 and 12 months after randomisation are depicted in Table 2A. Although all scales demonstrate better functional results for the J-pouch group at 4 months, this better functionality was also present at baseline. Therefore, in Table 2B the differences from baseline are depicted, demonstrating a significantly better continence for patients with a J-pouch at 4 months (p=0.04) and a better total functional outcome for patients with a J-pouch both at 4 and 12 months postoperatively (p=0.04). The outcome parameters of secondary interest (COREFO at 4 months, the EORTC QLQ-CR38 defaecation problems score at 4 and 12 months, and the SF-36 physical functioning score at 4 and 12 months) did not show any significant differences between treatment groups (Table 2 and 3).

Table 3  EORTC QLQ-CR38 and SF-36 scores of patients with a J-Pouch (JP) or a side-to-end (STE) anastomosis

<table>
<thead>
<tr>
<th></th>
<th>JP n=48</th>
<th>STE n=44</th>
<th>JP n=22</th>
<th>STE n=25</th>
<th>JP n=30</th>
<th>STE n=22</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td>4 months</td>
<td></td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-CR38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defaecation problems</td>
<td>Mean</td>
<td>73</td>
<td>74</td>
<td>75</td>
<td>67</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>(St.Dev.)</td>
<td>(15)</td>
<td>(15)</td>
<td>(14)</td>
<td>(14)</td>
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</tr>
<tr>
<td></td>
<td>Missing</td>
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<td>7</td>
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<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Mean</td>
<td>77</td>
<td>74</td>
<td>76</td>
<td>63</td>
<td>79</td>
</tr>
<tr>
<td>symptoms</td>
<td>(St.Dev.)</td>
<td>(16)</td>
<td>(14)</td>
<td>(13)</td>
<td>(21)</td>
<td>(13)</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Micturition problems</td>
<td>Mean</td>
<td>72</td>
<td>69</td>
<td>78</td>
<td>66</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>(St.Dev.)</td>
<td>(22)</td>
<td>(18)</td>
<td>(22)</td>
<td>(22)</td>
<td>(15)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sexual functioning</td>
<td>Mean</td>
<td>77</td>
<td>73</td>
<td>78</td>
<td>78</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>(St.Dev.)</td>
<td>(24)</td>
<td>(21)</td>
<td>(21)</td>
<td>(24)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>Mean</td>
<td>87</td>
<td>80</td>
<td>83</td>
<td>66</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>(St.Dev.)</td>
<td>(15)</td>
<td>(21)</td>
<td>(14)</td>
<td>(22)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>Mean</td>
<td>74</td>
<td>72</td>
<td>69</td>
<td>54</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>(St.Dev.)</td>
<td>(21)</td>
<td>(26)</td>
<td>(23)</td>
<td>(30)</td>
<td>(21)</td>
</tr>
<tr>
<td></td>
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<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>Mean</td>
<td>67</td>
<td>59</td>
<td>66</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>(St.Dev.)</td>
<td>(21)</td>
<td>(18)</td>
<td>(21)</td>
<td>(19)</td>
<td>(22)</td>
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<td></td>
<td>Missing</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The primary endpoints as assessed at baseline were not significantly different between patients who were evaluable at 4 months and those who had stomas. There was also no association between the endpoint assessed at 12 months and tumour stage.

Surgical outcome and postoperative complications

The use of the descending colon versus the sigmoid colon for coloanal reconstruction was similar in both groups with the latter being more often performed (Table 4). Postoperative hospital stay, in-hospital mortality and overall complications did not differ between treatment groups. Details of the postoperative complications are listed in Table 5. A high number of complications occurred after the primary operation in both groups: 31 of 55 (56%) patients had a complicated course in the J-pouch group versus 26 of 52 (50%) patients in the side-to-end group. Sixty percent of all complications were minor complications, as defined in the publication of Bakx et al.15 Eight of nineteen patients with an anastomotic leakage underwent a relaparotomy with a local washout, while the other patients were conservatively treated. In four of 13 patients with an abdominal abscess surgical drainage was performed and in five of 14 patients with a small bowel obstruction conservative therapy failed and a relaparotomy was needed. In one patient the vascularisation of the J-pouch was inadequate and the pouch had to be removed. Eight re-operations were performed for other reasons. Median (range) time for reversal of the ileostomy was 12 (1 - 23) weeks for the patients with a J-pouch, and 7 (1 - 63) weeks for the patients with a side-to-end anastomosis.
In 18 (33%) patients in the J-pouch group and 14 (27%) patients in the side-to-end group the ileostomy was reversed during first admission. Complications after reversal of the ileostomy were similar for both groups and are listed in Table 5.

**Table 5** Complications after rectal resection and after stoma reversal

<table>
<thead>
<tr>
<th></th>
<th>J-Pouch</th>
<th>Side-to-End</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complications after rectal resection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leakage*</td>
<td>10/49 (5)</td>
<td>9/48 (3)</td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>6 (3)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>8 (4)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Ischemia of the J-Pouch</td>
<td>1 (1)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Recurrent haemorrhage</td>
<td>1 (1)</td>
<td>0 (-)</td>
</tr>
<tr>
<td>Thrombo-embolic complications</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td>Stoma related complications</td>
<td>2 (-)</td>
<td>2 (-)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (-)</td>
<td>2 (-)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4 (-)</td>
<td>4 (-)</td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50 (17)</td>
<td>43 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>J-Pouch</th>
<th>Side-to-End</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complications after stoma reversal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal abscess</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (-)</td>
<td>1 (-)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

All values are in absolute numbers (re-operations).

* Percentage of anastomotic leakage is calculated by comparing absolute numbers to patients with an anastomosis.

No significant differences were found between both treatment groups.

In multivariate analysis, different factors were tested for their influence on functional outcome, such as tumour stage, gender, pelvic sepsis and type of anastomosis, but no influence on functional outcome was found.

The flow diagram (Figure 1) displays mortality at different time points. At one year one patient in the J-pouch group and five patients in the side-to-end group had died (p=n.s.). In each group one patient died during the postoperative period; in the J-pouch group a pelvic bleeding resulted in a haemorrhagic shock, in the side-to-end group a septic shock resulted in multi-organ failure. During follow-up, one patient died due to metastatic disease, whereas the other three deaths were non-tumour related. After one year of follow-up, two patients in both groups were diagnosed with a local recurrence. Within the same period metastatic disease was found in 5 of 55 (9%) patients in the J-pouch group versus 9 of 52 (17%) patients in the side-to-end group.

**DISCUSSION**

In this multicentre randomised trial a better functional outcome was found in patients with a J-pouch as compared to patients with a side-to-end anastomosis. These functional differences did not influence health-related and overall quality of life. However, this better functionality should be interpreted with caution, as it reflects the results of 40% of the randomised patients.

Short term outcome of surgery did not show significant differences between the treatment groups with respect to complications, postoperative hospital stay, necessity of re-operation, hospital re-admissions and mortality. Temporary diversion of the fecal stream by creating a loop ileostomy was performed in all patients. However, reversal of the ileostomy tended to occur later in the J-pouch group than in the side-to-end group; in a substantial number of patients the ileostomy was not reversed at 4 months. This caused an unexpectedly high reduction of eligibility for postoperative functional assessment, especially at the 4 months time point. This delay in stoma reversal was due to both logistic reasons (waiting list) and the relatively high rate of complications. In future trials, by changing the time point for follow-up from date of randomisation to date of restored bowel continuity this issue can possibly be overcome.

The hypothesis that a J-pouch anastomosis provides a better defaecatory function by constructing a larger reservoir and by transecting the circular muscular fibres (thus preventing neorectal irritability) is credible. Furthermore, the superiority of the J-pouch in comparison with the end-to-end anastomosis might be contributed to the antiperistaltic direction of the fecal flow due to the double barrelled configuration. In case of a side-to-end anastomosis, the isoperistaltic fecal flow is partly diverted by the distal colonic part of the anastomosis. It is possible that the initially larger reservoir of the J-pouch is equalized by the adaptation of the side-to-end reservoir after approximately 4 months, as the peristaltic direction towards the distal colonic part of the anastomosis is creating a threshold volume which is similar to that of the J-pouch reservoir.

This phenomenon has been previously studied by barostat measurements. Fürst et al. described comparable results of maximally tolerable volume and neorectal capacity of the J-pouch and the end-to-end anastomosis. Comparing maximally tolerated volume and threshold volume of the J-pouch with the side-to-end anastomosis, higher and similar maximum results are described. Most likely, the major functional principle of the J-pouch is predominantly related to delayed propulsive motility and...
not to the increased neorectal capacity. Furthermore, by analysing barostat measurements in a subgroup of patients in the present trial, we were able to demonstrate neorectal contractions in both groups of patients, as a response to prolonged isobaric and isovolumetric distension. These contractions may contribute to an increased bowel frequency and complaints of urge.16

The recently published Cochrane systematic review compared all different anastomotic techniques and recommended the J-pouch as the procedure of choice, based on improved bowel function as compared to the end-to-end anastomosis. However, similar functional and surgical results of the side-to-end anastomosis and the J-pouch were found.6

At the onset of our trial multiple studies had indeed demonstrated the superiority of the colonic J-pouch in comparison with the end-to-end anastomosis, whereas just one study had been published comparing the colonic J-pouch with the side-to-end anastomosis. The latter found a reduction of bowel movements per day in favour of the J-pouch at three and six months postoperatively, but was performed before the era of preoperative radiotherapy and the questionnaire to evaluate functional outcome in that study was not validated.18

During the course of our trial, two other randomised controlled trials have been published, comparing the colonic J-pouch with the side-to-end anastomosis. Some shortcomings of these two trials should be taken in mind. Machado et al. retrospectively assessed baseline function, and the size of the pouch was instructed to be 8 cm, which is relatively large and might have influenced functional outcome.21 The most recently published trial of Jiang et al. did not find functional differences between the colonic J-pouch and the side-to-end anastomosis, but no validated questionnaire was used to analyse functional outcome.20 These studies are summarised in Table 6.

In the present trial, baseline results were prospectively collected and a validated questionnaire was used to analyse functional outcome. Multivariate analysis demonstrated no influence of possible confounders on functional outcome. Although the high rate of complications in our study is in contrast with these previous RCT’s,18,20,21 similar complication rates have been described in other large randomised studies. In comparison, the Dutch TME trial found a 48% complication rate22 and the MRC CLASSICC trial reported a 50% complication rate after rectal surgery.23 In the present trial, independent datamangers collected the data: the reporting was meticulous and therefore more reliable. Secondly, the use of preoperative radiotherapy in all patients, in combination with the construction of a coloanal anastomosis might have influenced our results. Finally, the majority of complications were minor complications and did not influence bowel function.

The possible advantages in the first months after the operation should be balanced against the fact that the construction of a J-pouch is technically more challenging and sometimes impossible, due to the requirement of an additional length of colon to connect the apex of the pouch to the distal anorectum. Furthermore, a short mesocolon can make this mobilization more difficult and a fat-loaded, double folded mesocolon can be too bulky to descend into a narrow pelvis, especially in male patients.24 This inability to construct a colonic J-pouch was also seen in our study group, as in three patients a side-to-end anastomosis and in one patient an end-to-end anastomosis had to be created due to technical difficulties, despite randomisation for a J-pouch. This was one of the reasons why we decided to change the protocol and preferred to randomise the patients not before, but during the operation.

In the present trial, the late restoration of bowel continuity caused a relatively large number of missing data for the primary outcome. Although unfortunate and a limitation for drawing strong conclusions, these data contribute to the body of evidence that the J-pouch provides no convincing support for its superiority in comparison with the side-to-end anastomosis. Therefore, this study does not support the preferred use of the J-pouch, but justifies the choice of the side-to-end coloanal anastomosis, because of its ease of construction.
ACKNOWLEDGMENTS

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Obituary
In November 2009, Frederik Slors past away. As a colorectal surgeon in the Academic Medical Centre (AMC) in Amsterdam, he contributed to the accomplishment of this study. We lost in him a skilful surgeon and a highly appreciated colleague.

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Chapter 2

Neorectal irritability after short term preoperative radiotherapy and surgical resection for rectal cancer
Functional outcome after rectal surgery

**ABSTRACT**

**Objectives:** Preoperative radiotherapy followed by rectal resection with total mesorectal excision (TME) and coloanal anastomosis severely compromises anorectal function, which has been attributed to a decrease in neorectal capacity and neorectal compliance. However, to what extent altered motility of the neorectum is involved, is still unknown. The aim of the study was 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 (HVs).

**Methods:** Neorectal function (J-pouch or side-to-end anastomosis) was studied in 15 patients (median age 61 years, 10 males) 5 months after short term preoperative radiotherapy (5x5 Gy) and rectal resection with TME for rectal cancer and compared with that of 10 volunteers (median age 41 years, 7 males). Furthermore, patients with a colonic J-pouch anastomosis (n=6) were compared with patients with a side-to-end anastomosis (n=9). (Neo)rectal sensitivity was assessed using a stepwise isovolumetric and isobaric distension protocol. (Neo)rectal motility was determined during prolonged distension at the threshold of urge to defaecate.

**Results:** The neorectal volume of patients at the threshold of urge to defaecate (125 ± 45 ml) was significantly lower when compared with that of HVs (272 ± 87 ml, p<0.05). The pressure threshold, however, did not differ between patients (26 ± 9 mmHg) and HVs (21 ± 5 mmHg) and neither did the pressure threshold differ between patients with a J-pouch and side-to-end anastomosis. In HVs, no rectal contractions were observed during prolonged rectal distension. In contrast, in all 15 patients, prolonged isovolumetric and isobaric distension induced 3 (range 0-5) rectal contractions/10 min, which were associated with an increase in sensation in half of the patients.

**Conclusions:** Patients who underwent preoperative radiotherapy and rectal resection with TME, but not HVs, developed contractions of the neorectum in response to prolonged distension. We suggest that this neorectal ‘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 neorectum is created using the sigmoid colon or descending colon. After this multimodality treatment, anorectal function is often compromised as reflected by an increase in the frequency and urgency of defaecation and by incontinence.3,4 Recent research shows 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 because of direct injury of the nervous supply,7,8 the low level of anastomosis,9-11 impaired neorectal capacity and decreased compliance,12,13 and the loss of rectal sensation.18-20

Feacal 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 feacal 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, is an important factor in the ability to defer defaecation.21-23 Abnormalities in rectal reservoir capacity, either because of impairment of this relaxation or decreased compliance (fibrosis because of earlier radiation therapy or inflammation), are considered as having an important function in the pathogenesis of feacal incontinence and urgency.24,25 In line with this reasoning, earlier studies have shown an increase in urgency, tenesmus and defaecation frequency because of decreased neorectal reservoir capacity and decreased neorectal 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 neorectum these contractions were followed by one or more extra contractions during distension periods of 2 min, suggesting neorectal irritability.25,26

In this study, we want to further explore the phenomenon of neorectal contractions and hypothesise that the neorectum lacks the capacity to adapt to distension. Rectal filling with feacal content would lead to prolonged distension of the neorectum inducing neorectal contractions, subsequently contributing to the feeling of urgency. To test this hypothesis, the motor response to prolonged filling of the neorectum 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.
During pouch formation, the circular muscle layer is transected 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 might reduce contractility. Therefore, the motor response to rectal filling was also compared between patients with a J-pouch coloanal anastomosis and patients with a side-to-end coloanal anastomosis.

**MATERIALS AND METHODS**

**Subjects**

Fifteen patients (10 males) with a median age of 61 years (range 33-76 years) treated for rectal carcinoma located in the lower two-thirds of the rectum were evaluated. All patients had stage II disease and treatment consisted of short term preoperative radiotherapy (5x5Gy) followed by rectal resection with TME and coloanal anastomosis. In six patients a pouch coloanal anastomosis and in nine patients a side-to-end coloanal anastomosis was created.

None of the patients received chemotherapy and/or postoperative radiotherapy. Five months (range 4-6 months) after surgery, the patients were invited to undergo an anorectal function study. Protective loop ileostomies were closed at least 6 weeks before measurements to ensure bowel function.

In addition, ten healthy volunteers (HVs, 7 males) with a median age of 41 years (19-70 years) served as controls. None of the volunteers had either defecation problems, as tested by the COREFO questionnaire, or a history of abdominal surgery and/or previous radio- or chemotherapy possibly compromising bowel function.

**Rectal barostat and anorectal manometry**

A noncompliant 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 it had a length of 10 cm when used for patients. The maximum capacity of the bag was 600 ml and it had a length of 15 cm when used in the HVs. This balloon was connected to an electronic barostat (Synetics Medical, Stockholm, Sweden) to measure rectal compliance and rectal sensory motor function. The barostat balloons were inflated up to 10 mmHg before and after 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 proximal to the (neo)rectum. This balloon was inflated with up to 150 ml of air before and after the completion of the experiment to rule out any leakage of air.

**Positioning of the catheters**

Participants received a water enema to clean the bowel and to avoid interference of stool during the measurements (Figure 2). 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 whereas 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 into the barostat catheter in the anal canal. All measurements were carried out with the subjects in the left lateral position.

After the insertion of the two catheters, a recovery period of 15 min 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.
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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 min. Thereafter, the subjects were instructed to squeeze maximally on three occasions.

Proximal colonic distension

To evaluate the response of the (neo)rectum to proximal colonic distension, the barostat balloon was set to MDP + 2 mmHg and the latex balloon was distended during 30 s in different volume steps (50 ml, 75 ml, 100 ml, 125 ml, 150 ml or until discomfort was reported).

Stepwise isovolumetric distension protocol

Isovolumetric distensions were performed beginning with volume steps of 25 ml in patients and 50 ml in HVs. Each distension lasted 1 min after which the volume was increased further until the participant reported discomfort or pain. Sensations were scored 30 s after each distension step using a 6-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 defaecate, 5 = discomfort/ pain). 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 stepwise 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.

Stepwise isobaric distension protocol

The stepwise isobaric distension protocol was performed beginning with fixed pressure steps of 3 mmHg above MDP with a maximum absolute pressure of 55 mmHg. Each distension lasted 1 min and sensation was scored 30 s after each distension. The barostat balloon was deflated if the participant indicated discomfort or pain (sensation 5).

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 the urge to defaecate (sensation 3) as scored during the preceding stepwise isobaric distension protocol. Sensations were scored every minute or when the participant indicated an increase or decrease in sensation.

Questionnaire

All participating patients were asked to complete a validated questionnaire preoperatively and 4 months postoperatively. This COREFO questionnaire was developed to evaluate postoperative problems thoroughly in a comprehensive manner for patients. The COREFO questionnaire consists of five multi-item scales: incontinence (9 questions), social impact (9 questions), frequency (2 questions), stool related aspects (3 questions) and need for medication (3 questions). The questionnaires were assessed in combination with objectively measured results to look for a potential correlation.

Data analysis

All data are given as mean ± s.d., unless stated otherwise. Continuous data were compared using Student’s t-test, whereas 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 before each sigmoidal distension, was subsequently set as 100%.

Figure 2 Schematic representation of the study protocol. HV = Healthy Volunteer, MDP = minimal distension pressure
Functional outcome after rectal surgery

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). All tracings in Figures 3 and 4 represent a period of 10 min. (Neo)rectal capacity was determined at the end of the isobaric distension protocol. The pressure volume curves were constructed using the mean volume of the last 30 s (when equilibration of the volume was reached) at each of the consecutive pressure steps during the stepwise isobaric distension protocol. The volume-pressure curves were described with the following equation: \( V = A(1-e^{-kp}) \), where \( V \) is the volume, \( A \) is the maximum volume, \( k \) is an expansion constant and \( p \) is pressure. Compliance is defined as \( \frac{dV}{dp} \) and computed at \( V_{1/2} \) which is halfway the maximum volume. The (neo)rectal compliance was calculated using a nonlinear mixed-effect model for fitting the pressure volume curves of each individual.30,31 This analysis was performed as reported earlier by our group.32 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 HVs (71 mmHg, SD 25; \( p < 0.05 \)). Although the maximum squeeze pressure was lower in patients (107 mmHg, SD 47) than in HVs (153 mmHg, SD 66; \( p = 0.15 \)), this difference was not statistically significant.

Proximal colonic distension-induced (neo)rectal contractions

Distension proximal of the (neo)rectum resulted in a volume decrease of the rectal barostat balloon in all patients except one. Volume decrease occurred immediately after minimal distension (50-75 ml) of the proximally located balloon. The percentage volume decrease (Figure 5) after proximal colonic distension was larger in patients than in HVs, but did not reach statistical significance. There was no difference in volume decrease between StE patients and JP patients (results not shown). Similarly, distension of the sigmoid induced a transient relaxation of the anal sphincter in all but 2 HVs. In contrast, in only one of 15 patients, did we observe a reduction in anal sphincter pressure in response to proximal colonic distension.

(Neo)rectal sensitivity

Volume controlled distension

Thresholds for 'first sensation' and 'urge to defaecate' and 'discomfort' during the stepwise isovolumetric distension protocol were smaller in patients than in HVs (Figure 6). Thresholds for 'first sensation', 'urge to defaecate' and 'discomfort' during the stepwise isovolumetric distension protocol were not different between StE and JP. In all ten HVs, 'discomfort' was reached during this protocol at a mean volume of 360 ± 97 ml. In 12 of 15 patients, the threshold of discomfort was not reached. In these patients, maximum (safety) pressure (55mmHg) was reached before the sensation of discomfort could be reported.
In seven of 15 patients, the onset of a neorectal 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 neorectal contraction.

**COREFO Questionnaire**

The overall score of the COREFO questionnaire did not differ between JP patients (29 ±10) and StE patients (36 ±19) at the time of the barostat measurements, and neither were there any differences in the five different subscales between JP patients and StE patients.

**Pressure-controlled distension**

Thresholds for 'sensation', 'urge to defaecate' and 'discomfort' during isobaric distension were not different between StE and JP patients. There was a significant difference in the threshold for 'first sensation' between patients and HVs (Table 1). Rectal capacity was significantly higher in HVs (308 ± 77 ml) than the neorectal capacity in patients (164 ± 47 ml; p=0.000). Compliance of the rectum in HVs (26 ± 8 ml/mmHg) was significantly higher than compliance of the neorectum in patients (12 ± 7 ml/mmHg; p=0.000). The compliance curves are shown in Figure 7. Compliance of the neorectum in StE patients (13 ± 9ml/mmHg) was comparable to that in JP patients (11 ± 4ml/mmHg; p=0.5).

**(Neo)rectal irritability**

In HVs, 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 125 ± 45 ml during isovolumetric distension and 26 ± 9 mmHg during isobaric distension. In patients, prolonged isovolumetric distension (Figure 3) at the threshold of urge to defaecate induced a median of two contractions (range 0-5) per patient with a mean increase in pressure of 21 ± 9 mmHg per contraction. During prolonged isobaric distension (Figure 4) at the threshold of urge to defaecate, a median of three contractions (range 0-5) per patient was seen with a mean volume decrease of 31 ± 16 % of the barostat balloon.

When comparing the results in the StE and JP patients, no significant differences were identified (Table 2).
Neorectal function is often compromised after radiotherapy and rectal resection with TME, resulting in urgency for defaecation and faecal incontinence. In this study, we show that, in contrast to HVs, patients who underwent TME developed neorectal contractions in response to prolonged distension (10 minutes) suggesting increased neorectal irritability. Between patients with a colonic J-pouch anastomosis and those with a side-to-end anastomosis, no significant differences could be detected. Neorectal contractions were associated with an increase in sensation in nearly half of the patients. This motor pattern in combination with the decreased neorectal capacity, decreased neorectal compliance and decreased anal resting pressure most likely explains the occurrence of urgency in these patients.

Under physiological circumstances, the rectum acts as a reservoir and accommodates rectal filling, contributing to capacity to postpone defaecation. 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 specialised intraganglionic laminar endings (rIGLEs) has been shown. 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. recently showed that these mechanoreceptors adapted to maintained distension suggesting a function 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. did not observe deviating rectal motor activity during prolonged rectal distension in healthy volunteers. In contrast to HVs, prolonged distension of the neorectum in patients at the threshold of the 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. Corsetti et al. reported a similar response during a barostat procedure in healthy volunteers 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 volunteers (7 out of 10). We hypothesise that the contractions occurring in the neorectum during prolonged distension in our study are similar to the colonic contractions described by Corsetti et al. 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. In this respect, it is important to emphasise that the rIGLEs are absent in the guinea pig colon. 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. On the basis of these findings, we hypothesise that filling of the neorectum with faecal material induces neorectal contractions, probably as an intrinsic property of the colon, contributing to the occurrence of urgency in patients after rectal resection. The influence of radiotherapy on neorectal irritability is probably limited, since radiation is not applied to the sigmoid or descending colon used to create a reservoir. 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 HVs as well as the neorectum in patients, contracted in response to sigmoidal or proximal colonic distension, representing the peristaltic reflex. This reflex consists of a smooth muscle contraction and oral and anal relaxation to the site of the stimulus, respectively, and was first described by Bayliss and Starling. The relaxation of the anal sphincter induced by distension of the sigmoid or proximal colon was observed in all but two HVs, but in only one of 15 patients. In our opinion, the transient relaxation of the anal sphincter in response to proximal colonic distension is somewhat similar to the rectal anal inhibitory reflex, and most likely represents the inhibitory wave preceding the contractile part of the peristaltic reflex, as shown earlier in studies using a double colonic barostat balloon. In addition, relaxation of the anal sphincter as part of a peristaltic wave in the colon has also been clearly shown by Herbst et al. during mass movement. We therefore believe that this relaxation of the anal sphincter indirectly shows regeneration of the enteric nervous connection between the colon and the anal sphincter. As there is no significant difference in response to sigmoidal or proximal colonic distension between HVs and patients, the peristaltic reflex seems to be undisturbed after rectal resection and does not appear to be involved in the abnormal anorectal function. This colorectal reflex has also been described in healthy volunteers in a fasting state by Ng et al.

**Clinical implications**

As the neuromuscular properties of the sigmoid and colon, especially the capacity to adapt to filling, are very different from those of the rectum, it seems unlikely that, when used to create the neorectum, it will be suitable to functionally replace the rectum or function as a reservoir. In this study, we provide evidence that the exaggerated motor response of the neorectum may have an important function in the impaired anorectal function of patients who underwent rectum resection. On the basis of this observation, two major therapeutic strategies could be proposed to improve the clinical outcome after such an operation. First, the formation of a J-pouch coloanal anastomosis could theoretically lead to a reduction in urgency. During pouch formation, the circular muscle layer is transected 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. In addition, a larger neorectal capacity is created, compared with a straight or side-to-end coloanal anastomosis, most likely also contributing to impaired urgency and/or defaecation frequency. In this study patients with a J-pouch colonic anastomosis showed fewer contractions and a slightly larger maximal volume of the neorectum than patients with a side-to-end anastomosis, although these differences were not statistically significant, most likely because of the low numbers of patients studied. Many patients did not want to participate in a barostat study, as they found the study protocol too incriminating, which might have caused a selection bias. An earlier randomised trial comparing functional results of the colonic J-pouch with the side-to-end anastomosis, however, did show a higher maximum tolerated volume and threshold volume in the colonic J-pouch group at 3 and 6 months, associated with better functional results in terms of stool frequency and urge in JP patients, especially in the early postoperative phase. Another study reported a 40% greater maximum neorectal volume in the JP group at 2 years, but could not detect an influence on the function. Therefore, the impact of the type of pouch on functional outcome remains controversial.

Apart from changing the operative technique, medication reducing gastrointestinal 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. Therefore, one might speculate that 5-HT3 receptor antagonists such as granisetron might also inhibit neorectal irritability and thus reduce urgency in these patients.

In conclusion, in patients after short term radiotherapy and rectal resection with TME, a physiological volume of stool in the neorectum will not only lead to more pronounced sensations because of the smaller neorectal capacity, but will also lead to neorectal contractions instead of neorectal accommodation. This observation does not seem to be significantly influenced by the type of coloanal anastomosis performed. We suggest that this neorectal irritability represents a new pathophysiological mechanism which contributes to urge to defaecate.

**What is current knowledge:** functional outcome after radiotherapy and TME rectal resection is impaired.

**What is new here:** neorectal irritability represents a new pathophysiological mechanism contributing to urgency.
REFERENCES


Chapter 3

Sexual and urinary functioning after rectal surgery: a prospective comparative study with long term follow-up
ABSTRACT

Purpose: The purpose of this study was to prospectively compare rectal resection with colonic resection on sexual, urinary and bowel function and quality of life in both short and long term.

Methods: Eighty-three patients who underwent a rectal resection (RR) were compared to 53 patients who underwent a colonic resection leaving the rectum in situ (RIS). A questionnaire assessing sexual, urinary and bowel functioning, with a quality of life questionnaire (SF-36) was sent to all participants preoperatively, 3 and 12 months postoperatively and approximately eight years after the onset of the study.

Results: Short term dysfunction included diminished sexual activity in female RR patients at three months and significantly more erectile dysfunction in RR patients one year postoperatively. Long term dysfunction included more frequent and more severe erectile dysfunction in RR patients as compared to RIS patients. These short and long term outcomes did not influence overall quality of life. The incidence of urinary dysfunction was comparable between both groups. Bowel functioning was significantly better in the RIS group as compared to the RR group three months and one year postoperatively.

Conclusions: Patients who underwent a rectal resection experienced up to one year postoperatively more sexual and bowel function problems than RIS patients. However, short and long term dysfunction did not influence overall quality of life. Erectile dysfunction in male RR patients persisted in time, whereas other aspects of sexual, urinary and bowel function after rectal resection and colonic resection are similar after a median follow-up of 8.5 years.

INTRODUCTION

In recent years, rectal surgery has changed dramatically. It has progressed from removal of the rectum and anus with a permanent colostomy to the present era with total mesorectal excision (TME) and sphincter saving surgery. Improvements in treatment and early detection of rectal cancer indicate that more patients will live with the consequences of this disease. Mesorectal excision improves oncological results but it may result in decreased sexual, urogenital and anorectal function, unless careful attention is given to nerve preservation.

In the Western world, similar increasing incidences are seen for inflammatory bowel disease (IBD). Although reports are inconsistent to what extent surgery is required for IBD, resections for benign disease are performed according to the total mesorectal excision principle. Therefore, this group of patients is also at risk for nerve damage, which can consequently cause functional disorders postoperatively. The impact of functional disorders, for example loss of sexual function, is probably even greater after surgery for benign disease in younger patients, although the risk of postoperative disorders is considerably lower in this population.

The awareness and a better understanding of sexual and bladder physiology and pelvic anatomy has shifted the focus of research towards nerve preserving techniques with as main clinical endpoints functional results and quality of life. However, the importance of the topic is not reflected in the relatively scarce available studies. Moreover, previous studies are difficult to interpret because data were often retrospectively collected and therefore, baseline function was not available. Therefore, the aim of the present study was to prospectively compare the long term sexual and urinary function between patients who underwent a rectal resection according to TME principles and a control group of patients after either a hemi- or subtotal colectomy or an ileocolic resection. Bowel function and quality of life were secondary endpoints.

MATERIALS AND METHODS

Between 1997 and 2000, patients of 16 years and older who underwent a rectal or colonic resection at the Academic Medical Centre in Amsterdam, the Netherlands were included in the study. Patients who underwent an emergency procedure were not included in the study, as were patients scheduled for a sigmoidal resection. Furthermore, patients who received postoperative radiotherapy were excluded from the study. To enable comparison with baseline results, only patients who returned their preope-
ative questionnaires were eligible. A total of 136 patients (63 males and 73 females) with a written informed consent were included: 83 patients in the rectal resection group (RR) and 53 in the colonic resection group with the rectum in situ (RIS). All patients received the treatment according to the group they were allocated for.

At the onset of this study, surgery without preoperative radiotherapy was the standard treatment for operable rectal cancer. For this reason and the fact that a large proportion of the patients were operated for inflammatory bowel disease, none of the patients were irradiated preoperatively. All rectal resection patients were operated according to the TME technique. Patient characteristics are listed in Table 1.

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rectum resection (n=83)</th>
<th>Rectum in situ (n=53)</th>
</tr>
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<tbody>
<tr>
<td>Age (median (range)) years</td>
<td>47 (20-81)</td>
<td>41 (18-76)</td>
</tr>
<tr>
<td>Gender (male : female)</td>
<td>45 : 38</td>
<td>18 : 35</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign†</td>
<td>58</td>
<td>39</td>
</tr>
<tr>
<td>Malignant</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Presence of a stoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperatively</td>
<td>25/84</td>
<td>1/55</td>
</tr>
<tr>
<td>3 months p.o.†</td>
<td>28/78</td>
<td>6/43</td>
</tr>
<tr>
<td>12 months p.o.‡</td>
<td>12/65</td>
<td>3/38</td>
</tr>
<tr>
<td>After long term follow-up</td>
<td>13/58</td>
<td>4/37</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>2</td>
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</tr>
<tr>
<td>Intersphincteric resection</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Ileal pouch-anal anastomosis</td>
<td>46</td>
<td>-</td>
</tr>
<tr>
<td>Low anterior resection</td>
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<td>-</td>
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<tr>
<td>Left hemicolectomy</td>
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<td>4</td>
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<tr>
<td>Right hemicolectomy</td>
<td>-</td>
<td>9</td>
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<tr>
<td>Ileoceleal resection</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

* Inflammatory bowel disease (IBD) was diagnosed in 43/83 of patients in the RR group versus 37/53 patients in the RIS group

† p.o. = postoperatively

Questionnaires were sent to all patients preoperatively, and 3 and 12 months postoperatively. All patients were contacted again after a median follow-up of eight years and six months (range 7 – 10 years), and asked to fill in the same questionnaire. General practitioners and local authorities were contacted to ask whether patients were still alive and to provide address information in order to minimise loss to follow-up. Details about the study cohort and the response rates at the different time points are listed in Figure 1.

To assess sexual and urinary functioning, a questionnaire containing specific questions on sexual and urinary function was sent to all patients preoperatively, at 3 and 12 months after the operation and after at least seven years. This disease-related questionnaire contained 26 questions subdivided in two subscales: sexual functioning (20 items) and micturition (6 items). Patients were asked about sexual activity, body image and sexual enjoyment (7 items) with additional questions for females (sexual arousal, dyspareunia, orgasm, incontinence during intercourse (6 items)) and males (erection, retrograde ejaculation, incontinence during intercourse (7 items)). To assess urinary functioning patients were asked about frequency (3 items) and incontinence (3 items). All questions described 3 to 5 possible answers; these answers were scored in a 0 - 5 range, with higher scores indicating more functional problems.
Bowel function was assessed by 12 items (the number of stools during the day and at night, stool consistency, soiling or incontinence during the day or at night, incontinence for gas, ability to distinguish between flatus and faeces, need for antidiarrhoeal medication, dietary restrictions, and incidence of perianal skin irritation), which were formulated as three- to five-option multiple-choice questions. These scores were adjusted to create a composite score that not only focussed exclusively on incontinence but also covered the complete bowel function, and were analysed by the validated Gastro-Intestinal Functional Outcome (GIFO) score. The resulting GIFO score was linearly transformed to fit in a score range from 0 - 100, with higher scores indicating a better overall function.

Patients were instructed to answer the questions based on the last three months at all time points. In the first item of the questionnaire assessing sexual function, patients were asked if they had been sexually active in the last three months. If the answer was negative, patients continued with the questionnaire assessing urinary function and bowel function. Bowel function could only be assessed in the absence of a stoma.

Furthermore, all patients received a general quality of life questionnaire (SF-36) at all time points. The SF-36 is a validated, widely used questionnaire in postoperative patients, consisting of eight multi-item scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The scores are linearly transformed to fit in a score range from 0 - 100 with higher scores indicating better health-related quality of life status. Results of the study population were compared with the general population (n = 1742) using data from a study by Aaronson et al. This study translated and validated the SF-36 health survey for the Dutch population.

Statistical Analysis

Patients were instructed to answer the questions based on the last three months at all time points. In the first item of the questionnaire assessing sexual function, patients were asked if they had been sexually active in the last three months. If the answer was negative, patients continued with the questionnaires assessing urinary function and bowel function. Male and female patients were analysed separately for sexual functioning. Furthermore, postoperative deterioration of sexual functioning was evaluated. In order to do so, relative dysfunction scores were obtained by subtracting the baseline-score from the score at each subsequent time-point. For each patient, the postoperative relative scores with respect to the several items in the questionnaire were calculated. In this way, even patients who filled in one postoperative questionnaire could be evaluated. Bowel function could only be assessed in the absence of a stoma.

Demographic data were expressed as percentages for categorical data, as mean and standard deviation (SD) for normally distributed numerical data and as median and range, for non-normally distributed numerical data. The groups were considered to be normally distributed with the Kolmogorov-Smirnov (n>50) or Shapiro-Wilk (n<50) score of >0.05. The Mann-Whitney- and independent sample t-test were used to compare data between the two groups. To analyse changes in outcome parameters over time within each group separately, the Wilcoxon test and the paired-sample t-test were used. T-test was applied when both groups were normally distributed and the Mann-Whitney or Wilcoxon test was used in the remaining cases. As the percentages of missing surveys were not significantly different between the RR and the RIS group, analysis was performed for the subset of patients that returned the questionnaire. For all analyses, a p-value less than 0.05 (two-sided) was considered significant. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Sexual Functioning

Sexual activity declined from a preoperative rate of 73% (59/81) to 57% (43/76) at three months postoperatively in the RR group (p=0.002), whereas no significant differences between pre- and postoperative sexual activity could be demonstrated in the RIS group (p=0.248; Table 2). After approximately eight years of follow-up, no significant difference in sexual activity was seen between both groups. This effect appeared to be age-dependent: median age in the sexually active RR group and RIS group was 47 (29 - 79) and 43 (27 - 68) years respectively, while a median age in the sexually inactive RR group and RIS group was 58 (37 - 78) and 57 (37 - 77) years, respectively (p<0.001). The most profound decrease in sexual activity was found in female patients of the RR group at three months postoperatively.

Two of the 12 patients reported regular dyspareunia at three months postoperatively, while only 1 of 22 patients experienced regular dyspareunia preoperatively (Figure 2A). Although most females experienced diminished physical arousal, this problem was seen at all time points in both groups, and the majority of female participants stated to be satisfied with their sexual life. The ability to have orgasms did not change among female patients in both the RR and the RIS group. Faecal incontinence during sexual intercourse was not frequently reported and did not have a major influence on sexual activity.
Male sexual function was more impaired in the RR group. Five of 32 patients in the RR group experienced erectile dysfunction regularly at twelve months and another three patients reported that erectile dysfunction occurred at all times. Thus, eight of the male RR patients experienced severe erectile dysfunction at twelve months postoperatively, whereas this problem was reported by 1 of 37 patients preoperatively (p=0.025). Severe erectile dysfunction persisted in 8 of 22 patients in the RR group after long term follow-up, whereas no such dysfunction was reported in the RIS group (p=0.001; Figure 2B). Besides erection failures, patients who underwent rectal resection experienced less sufficiency of the erection and a shorter duration of the erection. At twelve months and long term follow-up, 4 and 5 patients in the RR group reported to experience less sufficiency of the erection and a shorter duration of the erection at all times, compared with two patients (one in each group) reporting regular insufficiency and a regular shorter duration of the erection preoperatively (p=0.010). Pain during an orgasm was reported incidentally; preoperatively in 3 of 47 male patients and at three months in 9 of 40 male patients (p=0.046), mainly in the RR group. None of the patients in the RR group experienced retrograde ejaculation preoperatively, but at twelve months postoperatively, three of 32 patients reported that retrograde ejaculation occurred at all times. In those patients not reporting any retrograde ejaculation or erectile dysfunction, sexual function was comparable with control patients in the RIS group. Preoperative questionnaires showed that none of the male patients experienced orgasm failures in both groups. At three months after rectal resection, one of 31 males lost the ability to have an orgasm, with orgasm failures at one year in 3 of 32 males. Orgasm failure was also seen in the RIS group: one male patient reported regular orgasm failure at three and twelve months postoperatively.

Sexual functional disturbances did not result in significant differences regarding body image, sexual satisfaction and the ability to have orgasms between the two groups, neither in female nor in male patients.
Urinary Functioning

The degree of urinary incontinence as reported in the RR and RIS group at each time interval was not significantly different, as displayed in Figure 3. Although an absolute decrease of urinary continence of 11% (68/80 to 43/58) and 15% (45/53 to 26/37) was observed after a median interval of eight and a half years, no significant impact of colorectal surgery on overall urinary functioning could be demonstrated.

Bowel Functioning

Bowel function was significantly diminished in RR patients as compared to RIS patients at three months, with a mean score of 62 (± 9) and 74 (± 8) respectively (p=0.001). These differences were still significant after one year of follow-up, with a mean score of 63 (± 11) and 72 (± 9), respectively (p=0.001). After a median time interval of eight and a half years from initial surgery, bowel function was similar in both groups, with a mean score of 65 (± 10) in the RR group and 69 (± 10) in the RIS group (Figure 4).

Quality of Life

Overall quality of life preoperatively, at three and twelve months postoperatively and after long term follow-up, is shown in Figure 5. Preoperatively, quality of life in the RR group was significantly better than the RIS group in all but one (PF) subscales.
subscale. Three and twelve months after surgery only the ‘general health perception’ subscale was significantly better in the RR group compared to the RIS group. At a median time interval of 8 years and six months after surgery, no significant differences between the RR and RIS group were found.

The quality of life scores over time within the RR group showed that only the ‘role physical’ subscale was significantly diminished at three months after surgery in comparison with the preoperative results. Six of eight scales demonstrated significant improvement at twelve months compared to corresponding scores at three months postoperatively within the RR group (PF, RP, BP, VT, SF and MH). After more than eight years of follow-up, quality of life deteriorated as compared to the twelve months results in six of eight scales (RP, BP, GH, VT, SF, MH). Within the RIS group, five of eight subscales improved at three months postoperatively in comparison with the preoperative scores (RP, BP, VT, SF, MH). From three to twelve months the ‘role physical’ scale improved significantly. More than eight years after surgery, quality of life was not significantly deteriorated in the RIS group, compared to the twelve months results.

Figure 5 demonstrates the quality of life results from the general population and the results from the RR and RIS group. In comparison with the general population, the preoperative scores from the RR group were significantly lower in three subscales (RP, GH, RE), whereas quality of life in the RIS group was significantly lower in all subscales. After three months, both the RR and RIS group scored lower in three subscales (RP, GH, RE), compared with the general population. Twelve months postoperatively, one (RP) and two (RP, GH) subscales were worse than the general population in the RR and RIS group respectively. This difference was still seen after long term follow-up: two subscales were worse in both groups (RP, GH) and one additional scale was scored worse in the RIS group (RE).

**DISCUSSION**

In the present analysis, the long term functional results of rectal resection could be reliably assessed because of the high response rate of more than 80% (95/118 patients alive) with a median follow-up of 8.5 years from surgical intervention. This study demonstrates a significant increase of male sexual dysfunction and female sexual inactivity after rectal surgery in comparison with patients who underwent abdominal surgery without dissection in the pelvic cavity. After long term follow-up, male erectile function after rectal resection was still significantly diminished, whereas other sexual and bladder functions were similar in both groups and comparable to preoperative functioning.

To our knowledge there are no prospective trials with sexual and urinary functional disorders after rectal surgery as a primary endpoint. Furthermore the retrospective nature of historical studies with the lack of baseline variables, limits the interpretation of previous results. However, we are aware of some shortcomings of the present trial. By evaluating the impact of surgery alone on sexual, urinary and bowel function we assessed patients who underwent TME for benign or malignant disease. We believe our data are not confounded, as rectal resection patients were all operated according to the same technique (TME). Sexual dysfunction can be influenced postoperatively by other factors than surgery alone, such as the recovery period after surgery, coping with disease and body image. These factors are temporary, and are not influencing results after a long term follow-up. In case of partial nerve damage, initial dysfunction can temporarily be reduced, but can recover in the first years after the initial operation. Therefore, a long term follow-up of approximately eight years is valuable and mandatory to assess whether the reduced function is definite or not.

At the onset of this study, validated questionnaires concerning specific sexual problems were not available yet. Therefore, after consultation of the department of Sexology we used a Dutch questionnaire to evaluate sexual and urinary function and compared results between and within groups to baseline scores.

Another shortcoming is caused by missing surveys: the fact that patients with a stoma or patients who are sexually inactive can not answer the questionnaire resulted in a relatively small number of patients. This might be an explanation for the fact that trends in certain functional disorders did not reach statistical significance. Avoidance to communicate about sexual problems is a known problem in most studies conducted on this subject. By excluding sexually inactive patients in the present trial, response rates to the questionnaire assessing sexual function were similar to response rates to the other questionnaires, thereby limiting the possible bias.

Decreased sexual activity was found after rectal resection, both in male and female patients, but sexual activity returned to baseline levels after one year of follow-up. Although reasons for sexual inactivity were not reported, it might be related to the frequently reported dyspareunia after rectal resection, which persisted even after long term follow-up. A retrospective study on sexual health in women following pelvic surgery for rectal cancer reported a significant influence on functional problems, but this study had a response rate of only 37%. Another retrospective study, with a high response rate of 81%, reported a decrease in sexual activity from 61% preoperatively to 32% postoperatively in female patients, which is similar to our findings. More recently, a prospective trial of sexual dysfunction after rectal cancer treatment repor-
An incidence of male sexual dysfunction of approximately 76% and female sexual dysfunction of approximately 59%. In the present study, 3 of 32 male patients experienced retrograde ejaculation at all times, and 8 of 32 patients reported severe erectile dysfunction one year after rectal resection. This seems to be comparable with other studies. A prospective study evaluated 29 male patients for functional disorders after rectal resection, by comparing baseline with postoperative results. Thirty percent experienced sexual dysfunction postoperatively; no long term follow-up data were available. In a review of 13 mainly retrospective studies, erectile dysfunction was recorded in 20% of patients and in eight of these studies loss of ejaculation occurred in 40% of patients after sphincter saving surgery for rectal cancer. Preoperative radiotherapy, which might contribute to this high rate of sexual dysfunction, was not reported in all but one of these studies. The results for benign disease are better, especially after the introduction of the restorative proctocolectomy, with erectile dysfunction rates of 0-4% and loss of ejaculation in 0-17%. The low rate of urinary problems in the present study is in contrast to the literature. The occurrence of minor or moderate urinary symptoms early after TME has been reported in up to 35% of patients, but little is known about long term bladder function. Theoretically, urinary symptoms such as voiding are associated with damage to the parasympathetic nerves leading to detrusor denervation and decreased sensitivity of the bladder. Long term improvement can be expected by a high degree of reversibility of partially damaged nerves and functional compensation by unimpaired nerve pathways.

Deprived bowel functioning is a well acknowledged phenomenon after rectal surgery. In the present study we also found major bowel dysfunction early after rectal resection. After more than eight years of adjustment, these differences were no longer significant when compared to the control group.

In this study, we could not demonstrate a significant influence of impaired function on quality of life. By comparing our baseline results for quality of life, the preoperative scores of the RIS group were significantly worse for all but one subscale (physical functioning PF) as compared to the RR group. Possibly, the large proportion of inflammatory bowel disease in the control group is explaining this finding. This difference in quality of life was less clear after three months, and was no longer present after more than eight years. Preoperative scores for quality of life were, as expected, lower than scores of the general population. Apparently, not only the functional outcome of the operation is causing a reduction in quality of life, but the patient’s underlying disease and the need for colorectal surgery as well.

Conclusion: Short term dysfunction after rectal resection included diminished sexual activity in female patients at three months and significantly more erectile dysfunction in male patients one year postoperatively. Long term dysfunction included more frequent and more severe erectile dysfunction in RR patients as compared to RIS patients. Other aspects of sexual, urinary and bowel function after rectal resection and colonic resection are similar, both in the short term as after a median follow-up of 8.5 years.

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Part II
Colorectal surgery; management of anastomotic dehiscence
Chapter 4

Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection

A. Doeksen
P.J. Tanis
B.C. Vrouenraets
J.J.B. van Lanschot
W.F. van Tets
ABSTRACT

Aim: To analyse the time interval (‘delay’) between the first occurrence of clinical parameters associated with anastomotic leakage after colorectal resection and subsequent relaparotomy.

Methods: In 36 out of 289 consecutive patients with colorectal anastomosis, leakage was confirmed at relaparotomy. The medical records of these patients were retrospectively analysed and type and time of appearance of clinical parameters suggestive of anastomotic leakage were recorded. These parameters included heart rate, body temperature, local or generalised peritoneal reaction, leucocytosis, ileus and delayed gastric emptying. Factors influencing delay of relaparotomy and consequences of delayed recognition and treatment were determined.

Results: First documentation of at least one of the predefined parameters for anastomotic leakage was after a median interval of 4 ± 1.7 d after the operation. The median number of days between first parameter(s) associated with leakage and relaparotomy was 3.5 ± 5.7 d. The time interval between the first signs of leakage and relaparotomy was significantly longer when a weekend was included (4.2 d vs 2.4 d, p = 0.021) or radiological evaluation proved to be false-negative (8.1 d vs 3.5 d, p = 0.007). No significant association between delay and number of additional relaparotomies, hospital stay or mortality could be demonstrated.

Conclusion: An intervening weekend and negative diagnostic imaging reports may contribute to a delay in diagnosis and relaparotomy for anastomotic leakage. That delay was more than two days in two-thirds of the patients.

INTRODUCTION

Anastomotic leakage after colorectal resection is an adverse event with a tremendous impact on morbidity, mortality and quality of life. Mortality rates of more than 30% in patients who developed anastomotic leakage have been reported in the literature. Clinically symptomatic leakage often requires one or more operative reinterventions with frequent need for intensive care admission and prolonged hospital stay. When a stoma is constructed at reexploration, this is meant to be temporary but often appears to be permanent. In those patients whose bowel continuity is restored, late functional consequences may be encountered.

Many studies have concentrated on risk factors for anastomotic leakage, including comorbidity and surgical technique, trying to find ways to prevent leakage in high-risk groups. When leakage occurs, it seems important to detect this complication at an early moment to minimise associated morbidity and mortality. However, the clinical diagnosis of anastomotic leakage is often difficult and it may only become evident after several days of close observation. Little is known about the incidence and consequences of a delay in the diagnosis and subsequent treatment of anastomotic leakage after colorectal resection. Therefore, we retrospectively determined time intervals between first clinical signs and relaparotomy and assessed risk factors and consequences of a delay in recognition and treatment of anastomotic leakage.

MATERIALS AND METHODS

Between January 2000 and July 2003, 289 consecutive patients underwent an ileocolic, colo-colonic or colorectal anastomosis at the Sint Lucas Andreas Hospital, a nonuniversity teaching hospital in Amsterdam, the Netherlands.

There were 158 females and 131 males with a mean age of 69 (range 20-96) years. In 15 patients (5%), the anastomosis was performed to restore colonic continuity after previous colostomy, while in the remaining patients the anastomosis was constructed immediately following bowel resection. Ileocolonic resection was performed in 27 patients (9%), right hemicolecotmy in 94 (33%), transverse colonic resection in 10 (3%), left hemicolecotmy in 20 (7%), sigmoidal resection in 72 (25%), and subtotal or total colectomy in 7 patients (3%). A low anterior resection was performed in 44 patients (15%). Patients electively planned for colonic or rectal resection were admitted to the hospital one day before surgery. Bowel preparation was given to patients undergoing left-sided resections and consisted of oral phosphate solution. In addition,
one enema was given the morning of surgery to patients who underwent low anterior resection. Antibiotic prophylaxis consisted of a cephalosporin and metronidazol and was given in a single dose during induction of anesthesia. Operations were performed by consultant surgeons in 184 patients (64%), and by trainees under supervision in 105 patients (36%). Type of anastomosis (e.g. end-to-end or end-to-side) depended on the preference of the individual surgeon.

Hand-sewn anastomoses were performed using a one layer continuous suture of propylene 3/0 in 209 patients (72%). Stapled anastomoses were performed in 80 patients (28%). Postoperative oral intake was gradually restarted depending on nausea, bowel movements, gastric tube production (if applied), and passage of flatus or stools. No fast-track recovery programs were used during the study period. Patient’s temperature, blood pressure, and heart rate were routinely recorded three times daily. The patients were seen by the attending doctor at least once daily during morning rounds, even during the weekends. Radiological examination of the anastomosis by contrast radiography or computed tomography (CT) was not performed on a routine basis, but only when leakage was suspected on clinical grounds.

For the purpose of this study, simple clinical parameters suggestive of anastomotic leakage were identified from the literature, and retrospectively collected from the records of patients who developed anastomotic leakage confirmed at relaparotomy. These parameters included tachycardia (heart rate > 100 beats per minute), fever (body temperature > 38°C), local or generalised peritoneal reaction during physical examination, leucocytosis (> 10 × 10³/mL), prolonged adynamic ileus (> 2 d) as demonstrated by symptoms and signs during physical examination or abdominal radiography, and delayed gastric emptying (increased gastric tube production of more than 200 mL per day or vomiting necessitating tube reinsertion). In addition, the postoperative day of first appearance of any of these parameters was scored, as well as the first day the attending doctor recognised these signs, resulting in a description in the patient’s files. Delay until relaparotomy was calculated from the day of first retrospective presence of clinical parameters associated with leakage and from the day the possibility of anastomotic leakage was explicitly suggested in the medical records by the attending doctor. The following factors were tested for their association with delay of relaparotomy for anastomotic leakage: age, sex, body mass index, site of anastomosis, radiological examination, and presence of a weekend in the period between first appearance of clinical parameter(s) and relaparotomy. To determine the influence of a weekend on the delay of relaparotomy, patients with a delay of more than seven days were excluded. Consequences of a delay for number of relaparotomies, hospital stay, and in-hospital mortality were assessed.

**Statistical analysis**

Univariate analyses using the Mann-Whitney test, F test and X²-test were performed to compare data of two groups. Spearman’s correlation coefficient was used to determine the correlation between two continuous variables. Significance was set at p ≤ 0.05 (two-sided). Statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS, Chicago, IL, USA).

**RESULTS**

Anastomotic leakage was confirmed during relaparotomy in 36 patients. Patient and treatment characteristics of the 36 patients are displayed in Table 1. Symptomatic anastomotic leakage occurred despite the presence of a diverting ileostomy in three patients after low anterior resection. In three patients, anastomotic leakage was not confirmed during first relaparotomy, but only after repeated laparotomy at three (‘second look’ at day one, ‘third look’ at day three), 24 and 28 d after the initial operation, respectively.

<table>
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<th>Characteristic</th>
<th>n (%)</th>
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<tr>
<td>Gender</td>
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<tr>
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<tr>
<td>Mean age (range) (yr)</td>
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<tr>
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<td>American Society of Anesthesiology score</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>16 (44)</td>
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<tr>
<td>3</td>
<td>6 (17)</td>
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<td>Transverse colonic resection</td>
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<td>Left hemicolectomy</td>
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<td>Sigmoidal resection</td>
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<td>Subtotal colectomy</td>
<td>3 (8)</td>
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<tr>
<td>Anterior resection</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Restoring continuity after colostomy</td>
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Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
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<th>p</th>
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<tr>
<td>Age (yr)</td>
<td>&lt; 70</td>
<td>19</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>≥ 70</td>
<td>17</td>
<td>4.9</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>21</td>
<td>4.5</td>
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<tr>
<td></td>
<td>Female</td>
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<td>4.9</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>&lt; 25</td>
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</tr>
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<td></td>
<td>≥ 25</td>
<td>14</td>
<td>5.3</td>
</tr>
<tr>
<td>Site of anastomosis</td>
<td>Left</td>
<td>25</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Right</td>
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<td>4.3</td>
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<tr>
<td>Radiological examination performed</td>
<td>Yes</td>
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<td>6.0</td>
</tr>
<tr>
<td></td>
<td>No</td>
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<td>2.7</td>
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<tr>
<td>Outcome of radiological examination</td>
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<td>9</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>TP/NP</td>
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<td>3.5</td>
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<td>Weekend included in period between first clinical parameter and relaparotomy</td>
<td>Yes</td>
<td>14</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>18</td>
<td>2.4</td>
</tr>
</tbody>
</table>

FN: false-negative; TP: true-positive; NP: not performed. 1Four missing values, 2Four patients excluded with delay of more than seven days. Significance of differences in delay between subgroups is determined using the Mann-Whitney test.

Apart from irrigation of the contaminated abdominal cavity, the operative procedure for leakage consisted of breakdown of the anastomosis and construction of a colostomy in 21 patients (58%), a diverting loop-ileostomy in twelve (33%), abscess drainage in two (6%), and no additional intervention in one patient (3%).

For the 36 patients with leakage confirmed at relaparotomy, the incidence and median postoperative day of first occurrence of the simple clinical parameters are displayed in Table 2. The first appearance of at least one of these signs was after a median interval of 4 (± 1.7; range 1-8) d after the operation. This interval was 5 ± 2.3 (range 2-12) d and 5.5 ± 2.8 (range 2-12) d for at least two and three signs, respectively. Relaparotomy for anastomotic leakage was performed after a median interval of 7 d after initial surgery (± 4.1; range 3-24) d. The median number of days between the first occurrence of each specific parameter, at least one parameter, at least two parameters and at least three parameters associated with leakage and relaparotomy are displayed in Table 3. The median time interval between the presence of at least one positive parameter and relaparotomy (‘the delay’) was 3.5 d; 23 relaparotomies for anastomotic leakage (64%) were performed after a delay of more than two days. The median number of days between the attending doctor’s suggestion of anastomotic leakage in the medical records and relaparotomy was one day.

A negative result of either contrast study or CT scanning in nine patients resulted in a significantly longer delay of relaparotomy as shown in Table 4. If a weekend (Saturday and/or Sunday) was included in the time interval between the first positive parameter suggestive of leakage and relaparotomy, delay of relaparotomy was also significantly longer in comparison with patients in whom observation and decision to reoperate did not take place during a weekend. No other factors determining the length of the delay could be demonstrated (Table 4).

After the first relaparotomy for anastomotic leakage, one additional laparotomy was performed in eight patients (22%) and more than one relaparotomy in another 10 patients (28%). Although the patients who needed at least one additional relaparotomy did have a longer delay between the first appearance of a clinical parameter and the first relaparotomy in comparison with patients who did not need additional relaparotomies (6.0 (± 7.6) d vs 3.3 (± 2.4) d), this difference did not reach statistical significance (p = 0.52). Patients with anastomotic leakage were admitted to the hospital for a mean period of 59 (range 7-259) d. There was no significant correlation between the delay of relaparotomy and duration of hospital stay (Spearman’s correlation coefficient 0.16, p = 0.34). Overall in-hospital mortality was 36% (13 of 36 patients). Delay of relaparotomy for anastomotic leakage was not significantly longer...
in patients who died postoperatively (5.5 ± 5.6 d vs 4.2 ± 5.8 d for patients who did not have a delay, p = 0.54).

**DISCUSSION**

Two thirds of relaparotomies were performed more than two days from the first appearance of at least one positive parameter suggestive of anastomotic leakage with a median delay of 3.5 d. This is similar to the median delay of 4 d in a series of 22 patients with clinical symptomatic leakage as reported by Sutton et al. Even if at least three positive parameters were present, it took a median number of 1.8 d until relaparotomy for anastomotic leakage was performed in our series. In a study by Alves et al., the risk of leakage increased to 67% if three or more signs associated with anastomotic failure were present. A remarkable finding was the increase in delay when signs and symptoms suggestive of leakage appeared just before or during a weekend. During weekends, all patients are seen by a staff surgeon and a surgical resident during morning rounds on Saturday as well as on Sunday. The higher work load, the absence of the attending surgeon who initially performed the anastomosis, and the absence of a plenary discussion of clinical problems by the entire surgical staff during weekends may explain this disturbing finding.

The routine use of radiographic imaging in diagnosing anastomotic leakage is surrounded by controversies. We found that a negative result of either contrast study or CT scanning in nine patients resulted in a significantly longer delay of relaparotomy. This observation opens the discussion whether to perform radiographic imaging before relaparotomy. Nicksa et al. retrospectively studied 36 patients who were reoperated for anastomotic leakage and found that 3 of the 18 contrast enemas (17%) and 14 of the 27 CT scans (52%) were false-negative. Another study described 16 patients with a clinical anastomotic leakage, in whom four imaging studies (25%) were initially misinterpreted. A similar sensitivity was reported by Akyol et al. in a series of 233 patients who underwent left sided colonic or colorectal anastomoses. The false-negative percentage of a routine water soluble contrast enema in the early postoperative period was 22% (11 of 51 patients with anastomotic leakage). None of these studies describe the impact of imaging on the delay of relaparotomy.

But what does eventually lead to the decision to perform a relaparotomy? Is it one specific parameter that has more impact than some others or is it a specific combination of positive parameters? Comparing the delay after each individual parameter, the presence of peritoneal reaction is the only parameter that resulted in surgical intervention within 24 h in most cases. It is unclear whether this symptom is so important in surgical decision making or it is just a relatively late sign which in combination with other earlier positive parameters makes relaparotomy inevitable. The difficulty in clinical decision making is calculating the pre-test chance of an event (i.e. anastomotic leakage) based on a number of predictive factors. In addition, a cut-off point has to be determined at which the optimum is reached in terms of benefit of an intervention on the one hand and unnecessary harm on the other. It would seem that watchful waiting as long as it is not associated with significant morbidity and mortality would be preferable to early relaparotomy and a higher negative re-exploration rate. The question is at what point the morbidity of waiting outweighs the morbidity of operating. Known risk factors, such as the level of anastomosis, chronic obstructive pulmonary disease, obesity, the use of steroids, poor nutritional state or the need for blood transfusion increase the chance of anastomotic leakage beforehand. The finding of dynamic ileus, fever or leucocytosis in high-risk patients will further increase the pre-test chance and may facilitate the decision to reoperate in these patients. However, one should take into account the risk of false-positivity of these clinical parameters which may result in a false-negative reintervention. The complete diagnostic evaluation of the clinical parameters identified from the literature (including sensitivity, specificity and positive/negative predictive value) was beyond the scope of the present study. In the previously mentioned study by Alves et al., clinical parameters suggestive of anastomotic leakage were analysed in 655 patients who underwent colorectal resection. They found a significantly higher number of patients with fever on day two, absence of bowel action on day four, diarrhea before day seven, collection of more than 400 mL of fluid through abdominal drains from day zero to three, renal failure on day three and leucocytosis after day seven in the group in which anastomotic leakage occurred compared with the uncomplicated group. No other studies on the incidence and timing of these signs and symptoms have been published to our knowledge. Ultimately, a prospective analysis should be performed of all known risk factors and clinical parameters in order to construct a decision model that can help the surgeon to make a weighed choice for the individual patient.

What can minimise the delay in diagnosis and treatment of anastomotic leakage besides simple clinical parameters? Radiological examination of the anastomosis can be misleading. Negative contrast studies and/or CT scanning undoubtedly result in a longer delay before surgical reintervention. Currently, we prospectively collect data about the additional value of radiological imaging of the anastomosis. A few investigational studies have focused on biochemical analysis of effluents of abdominal drains in patients who underwent colorectal anastomosis. Positive correlations with anastomotic leakage were found for lysozyme activity level and endotoxins. The value of these findings in daily clinical practice, however, is probably limited.
The finding that patients who ultimately died in the hospital did not have had a longer delay of relaparotomy is comparable with observations that were done by Alves et al. In that study, a non-significantly higher mortality rate was seen in patients who were reoperated on or after day five compared to those reoperated before day five. The absence of a significant association between delay of relaparotomy for anastomotic leakage and mortality is probably just a reflection of the small number of patients in both studies. It is our opinion that delay of relaparotomy in a patient with peritonitis should have an impact on outcome and that a more aggressive approach probably reduces morbidity and mortality.

In conclusion, although positive clinical parameters associated with anastomotic leakage were observed relatively early in the postoperative period, the final decision to perform a relaparotomy took a median of 3.5 extra days. The surgical team must be vigilant in the clinical observation of patients in the immediate postoperative period, also on weekends, and review carefully the interpretation of diagnostic imaging of the anastomosis. Especially patients at an increased risk of anastomotic leakage due to comorbidity, septic conditions, technical difficulties, and a distal anastomosis deserve a close clinical observation with appropriately timed surgical reintervention.

REFERENCES

Chapter 5
Radiological evaluation of colorectal anastomoses
ABSTRACT

Background and aims The purpose of this study was to determine the accuracy, interobserver variability, timing and discordance with relaparotomy of postoperative radiological examination of colorectal anastomoses.

Patient/methods From 2000 to 2005, 429 patients underwent an ileocolonic, colo-colonic, or colorectal anastomosis. Radiological examination of the anastomosis was not performed routinely, but only when there were clinically signs of leakage. Radiological imaging was reviewed by an independent radiologist and medical records were retrospectively analysed. Clinical anastomotic leakage was the standard of reference and defined as leakage confirmed during relaparotomy, drainage of pus per anum or as an anastomotic defect identified at digital examination.

Results Radiological evaluation of the anastomosis was performed in 91 patients (21%): CT in 27 patients, contrast radiography in 40, and both imaging modalities in 24 patients. The interobserver variability of CT and contrast radiography was 10% and 14%, respectively. The sensitivity and negative predictive value of imaging of the anastomosis was 65% and 73%, respectively. Anastomotic leakage was found in 11 of 21 patients (52%) who underwent relaparotomy despite negative imaging. Three of 36 patients (8%) with a diagnosis of anastomotic leakage based on radiological examination had an intact anastomosis at relaparotomy.

Conclusion Radiological imaging of the anastomosis after colorectal surgery should be restrictively applied and interpreted with caution because of the high false-negative rate and the substantial interobserver variability.

INTRODUCTION

Colorectal surgery may be complicated by anastomotic leakage that initially may present with mild and difficult to interpret symptoms. It is of utmost importance to detect failure of the anastomosis at an early stage to prevent further deterioration of the patient’s clinical condition. Symptoms and signs that should raise the suspicion of anastomotic dehiscence are fever, adynamic ileus, increased fluid collection through abdominal drains, renal failure, leukocytosis, and cardiac symptoms.1-4

In pronounced cases with clinically apparent leaks, there is no need for radiological imaging to confirm the diagnosis, but urgent relaparotomy should be performed as early intervention in order to avert potential threatening consequences.1 The diagnostic challenge is to identify anastomotic leakage early in the postoperative period and in those cases with mild or nonspecific symptoms. Because of the relatively low specificity of clinical parameters, additional diagnostic tests are often required.1 Digital examination is a test that can be simply and effectively applied in patients with a low rectal anastomosis, although some surgeons are reluctant to perform this maneuver as it may interfere with the integrity of the anastomosis.5 The alternatives in these patients and in those with a more proximal anastomosis are radiological imaging modalities or endoscopy.6-8

The primary purpose of the present study was to determine the accuracy of radiological imaging (either water-soluble contrast radiography, contrast-enhanced computed tomography (CT) or both modalities) in patients with a postoperative course suggestive of anastomotic leakage after colorectal resection. Secondary, the interobserver variability of radiological imaging of the anastomosis was determined. Finally, the timing of occurrence of clinical symptoms suggestive of leakage, radiological examination and relaparotomy as well as concordance between radiological and operative findings were assessed.

MATERIALS AND METHODS

From January 2000 to October 2005, 429 consecutive patients underwent an ileocolonic, colo-colonic or colorectal anastomosis at the Sint Lucas Andreas hospital, a large community teaching hospital in Amsterdam, the Netherlands. The type of resection in these patients is summarised in Table 1. Type of anastomosis was end-to-end, end-to-side, side-to-end, or side-to-side depending on preferences of the surgeon. Radiological examination of the anastomosis was not performed on a routine basis, but only when leakage was suspected on clinical grounds.
In general, leftsided anastomoses were examined using transanal contrast administration with radiographic imaging or CT scanning and the remaining patients underwent CT scanning with oral and intravenous contrast.

Postoperative contrast radiography was performed with water-soluble contrast (iohexol 140 mg I/ml, Omnipaque® GE Healthcare, Salt Lake City, Utah, USA). After introduction of a rectum cannula or a Foley catheter contrast was carefully administered under fluoroscopic control. Patients were in a left lateral or supine position at the start of the investigation and images were taken at different angles. CT imaging was performed on a 4-row multidetector helical CT scanner (Aquilion 4S, Toshiba Medical Systems Europe, Zoetermeer, Netherlands). Consecutive 3 mm slices were obtained and digitally archived after reconstruction at 2 mm interval to obtain adequate multiplanar reconstruction interpretation. Patients were prepared with 1 l of oral contrast fluid (30 ml megluminejoxitalamaat 300 mg I/ml, Guerbet, France, diluted in 1 l of tapwater) in 1 h and intravenous contrast fluid (Iohexol 30 mg I/ml, GE Healthcare), 100 ml in 50 s. Scanning started with 80 s delay. In patients with distal anastomoses, 500 to 1,000 ml contrast (30 ml megluminejoxitalamaat, diluted in 1 l of tap water) was administrated through a transanal Foley catheter.

All images were reviewed by a radiologist (AW) blinded for the initial report. Evaluation by the independent radiologist was compared with the original reports. In case of discrepancies, a final decision was made by concensus.

All medical records of the patients in whom radiological imaging of the anastomosis was performed were retrospectively reviewed. The presence or absence of anastomotic leakage was determined. Standard of reference was clinical anastomotic leakage, which was defined as leakage confirmed during relaparotomy, as drainage of pus per anum or as an anastomotic defect identified at digital examination. Radiological anastomotic leakage was defined as radiological features suggestive for leakage in patients who did not develop clinical leakage. These radiological features were the presence of contrast outside the bowel lumen, perianastomotic fluid collections and when air was noted directly near the anastomosis or when a pneumoperitoneum was seen more than 1 week postoperatively according to Zissin and Gayer.8

The number of clinical parameters suggestive of anastomotic leakage were retrospectively determined. These parameters included tachycardia (heart rate >100 beats per minute), fever (body temperature >38°C), local or generalised peritoneal reaction during physical examination, leukocytosis (>10×103/ml), prolonged a dynamic ileus (>2 days postoperatively), and delayed gastric emptying (nasogastric tube production of more than 200 ml per day or vomiting necessitating tube reinsertion).2 In addition, the timing of occurrence of two, three or four clinical parameters, the timing of radiological imaging, and the timing of relaparotomy were determined. To compare sensitivity and negative predictive value of contrast radiography and CT scan, 95% confidence intervals of the differences were determined. If the confidence interval did not include zero, the difference between two percentages was considered to be statistically significant.

RESULTS

Radiological imaging of the anastomosis was performed in 91 of the 429 patients (21%), whereas the anastomosis was not radiologically evaluated in 25 patients with clinically overt anastomotic leakage. The imaging modality was CT in 27 patients (30%), contrast radiography in 40 (44%), and both imaging modalities were performed in 24 patients (26%). No complications of rectally administered contrast were observed. One of the contrast radiographies could not be reviewed because of insufficient archiving. The initial evaluation and the review by the independent radiologist differed in eight of 63 valid contrast radiographies (interobserver variability, 13%) and in five of 51 CT scans (interobserver variability, 10%) as shown in Table 2.

Table 1 Type of resection of all patients (n=429) who underwent an ileocolonic, colo-colonic or colorectal anastomosis

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>No.</th>
<th>(% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocolonic resection</td>
<td>36</td>
<td>(8%)</td>
</tr>
<tr>
<td>Right hemicolectomy</td>
<td>144</td>
<td>(34%)</td>
</tr>
<tr>
<td>Transverse colonic resection</td>
<td>13</td>
<td>(3%)</td>
</tr>
<tr>
<td>Left hemicolectomy</td>
<td>35</td>
<td>(8%)</td>
</tr>
<tr>
<td>Sigmoidal resection</td>
<td>93</td>
<td>(22%)</td>
</tr>
<tr>
<td>Subtotal or total colectomy</td>
<td>9</td>
<td>(2%)</td>
</tr>
<tr>
<td>Low anterior resection</td>
<td>82</td>
<td>(19%)</td>
</tr>
<tr>
<td>Restore colonic continuity after previous colostomy</td>
<td>17</td>
<td>(4%)</td>
</tr>
</tbody>
</table>

Table 2 Discrepancies between review of independent radiologist and initial report of contrast radiography and CT scanning for suspected anastomotic leakage

<table>
<thead>
<tr>
<th>Discrepancies with initial report</th>
<th>Contrast radiography</th>
<th>CT (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No contrast leakage</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Presacral abscess</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Visualisation of side-to-end anastomosis instead of contrast leakage</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Concordance (%) (95% confidence interval)</td>
<td>87 (77–95)</td>
<td>90 (82–98)</td>
</tr>
</tbody>
</table>

* One missing value because of insufficiently printed imaging
Twenty-four patients underwent both CT scanning and contrast radiography and discordancy was found in five patients (21%). Both imaging modalities were positive for anastomotic leakage in six patients and all these patients did fulfill the criteria of clinical anastomotic leakage. Four of 13 patients (31%) without signs of anastomotic leakage by contrast radiography as well as CT scanning did have a clinical anastomotic leakage, based on relaparotomy in three of them.

Similarly, the negative predictive value was not significantly different between contrast radiography and CT scan (difference 10% (−11% to 40%)). Relaparotomy was performed in 21 of 55 patients (38%) without features of anastomotic leakage on radiological imaging. Anastomotic leakage was found in 11 of those 21 patients (52%). The correlation between radiological imaging and clinical presence or absence of anastomotic leakage is depicted in Figure 1. Table 4 shows the sensitivity and negative predictive value of radiological imaging depending on timing (<7 or ≥7 days post-operatively) and on the level of the anastomosis (proximal or distal).

Table 3 Correlation between results of radiological examination of the anastomosis and the presence or absence of clinical anastomotic leakage for each imaging modality separately and for the whole group of patients (only contrast radiography in 40, only CT in 27, and both imaging modalities in 24 patients).

<table>
<thead>
<tr>
<th>Clinical anastomotic leakage</th>
<th>Sensitivity % (CI)</th>
<th>Negative predictive value % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>65 (51–79)</td>
<td>73 (61–84)</td>
</tr>
<tr>
<td>No</td>
<td>28 (69)</td>
<td>40 (65)</td>
</tr>
<tr>
<td>All patients (n=91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leakage</td>
<td>21</td>
<td>2 (69)</td>
</tr>
<tr>
<td>No leakage</td>
<td>10</td>
<td>31 (68)</td>
</tr>
<tr>
<td>Contrast radiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=64)</td>
<td>13</td>
<td>6 (69)</td>
</tr>
<tr>
<td>Leakage</td>
<td>64 (51–84)</td>
<td>76 (62–89)</td>
</tr>
<tr>
<td>No leakage</td>
<td>13</td>
<td>6 (69)</td>
</tr>
<tr>
<td>CT (n=51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leakage</td>
<td>13</td>
<td>6 (69)</td>
</tr>
<tr>
<td>No leakage</td>
<td>11</td>
<td>11 (69)</td>
</tr>
</tbody>
</table>

CI=95% confidence interval

a Five patients with leakage by only one of both imaging modalities
b Three negative relaparotomy
c One negative relaparotomy
d Two negative relaparotomy

Figure 1 Flow chart showing the type and result of radiological examination for suspected anastomotic leakage (n=91) in a group of 429 patients who underwent an ileocolonic, colo-colonic or colorectal anastomosis. Radiological results are correlated with clinical presence or absence of anastomotic dehiscence. CT computed tomography, CR contrast radiography, plus sign radiological signs of leakage, minus sign no radiological signs of leakage, relap relaparotomy

Colorectal surgery; management of anastomotic dehiscence

Radiological evaluation of colorectal anastomoses
The timing of radiological examination of the anastomosis and relaparotomy is displayed in Table 5. The time interval between the occurrence of clinical parameters suggestive of anastomotic leakage and radiological imaging decreased with an increasing number of clinical parameters: median two, and less than 24 h for two and four clinical parameters, respectively. The median time interval between imaging and relaparotomy was less than 24 h for patients with anastomotic leakage based on contrast radiography or CT scan (n=20) as well as for patients who did not have radiological features of leakage (n=22).

**DISCUSSION**

The false-negative rate of radiological imaging of the anastomosis in colorectal surgery was 35% in the present study with a negative predictive value of 73% and these percentages seem to be lower in the early postoperative period (<7 days) and in proximal anastomoses. The limited accuracy restricts their usefulness in clinical decision making if anastomotic leakage is suspected. This is illustrated by the fact that relaparotomy was performed shortly after negative imaging in 22 patients, with half of these patients having an anastomotic leak. Three studies reported the accuracy of routine water-soluble contrast radiography. The false-negative rates were 49% (11/23) in a series of 233 colorectal and left-sided colonic anastomoses, 29% (4/14) in 117 left-sided colonic anastomoses, and 23% (7/31) in 202 contrast radiographies of low rectal anastomoses.5,9,10 Four other studies described results of radiological imaging in the subgroup of patients with clinical anastomotic dehiscence. CT was able to confirm clinical leakage in 48% to 100% and contrast radiography was positive in 40% to 83% of the patients.11–13 Our findings fit well within these rather wide ranges, but interpretation is hampered by the different clinical circumstances in which the radiological techniques were applied.

Timing of imaging may be related to false-negative findings, as the anastomotic defect may be initially too small to allow easy flow of contrast outside the intestinal lumen (Figure 2). This is illustrated by the finding that contrast leakage was visualised only after repeated CT scanning the next day in one of 13 patients as reported by DuBrow et al.11 In distal anastomoses, inflating the balloon of the transanal catheter for contrast administration may lead to sealing of a defect, also resulting in false-negative imaging.3 In more proximal anastomoses, the rectally administered contrast has been diluted at this level and there may be not enough remaining pressure to induce contrast leakage.11 Our median time interval between index laparotomy and first imaging of 7 days (Table 5) is comparable to data in the literature, although the range was rather wide.9,10,14

Another factor determining sensitivity of radiological examination of the anastomosis is quality of the radiological technique. The higher spatial resolution of CT enables visualisation of small contrast leakage that may have been missed with conventional radiology, especially with the more recently introduced helical and multidetector row CT scanners.6 Furthermore, patient selection (routinely, based on a certain degree of clinical suspicion, or confirming clinical leakage) influences the a priori chance of leakage and thereby determines the accuracy of the imaging modality. Most patients ultimately found to have an anastomotic leak have an insidious clinical course, with low-grade fever, prolonged ileus or failure to thrive.12 Alves et al. showed that anastomotic leakage was found in only 18% of the patients with two clinical parameters suggestive of leakage.1

**Table 4**

<table>
<thead>
<tr>
<th>Sensitivity and negative predictive value of imaging of the anastomosis (CT, contrast radiography or both modalities) depending on timing postoperatively and level of the anastomosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Timing of imaging</td>
</tr>
<tr>
<td>7&lt;days postop</td>
</tr>
<tr>
<td>7≥days postop</td>
</tr>
<tr>
<td>Level of anastomoses</td>
</tr>
<tr>
<td>distal</td>
</tr>
<tr>
<td>proximal</td>
</tr>
</tbody>
</table>

CI=95% confidence interval

1 Sigmoid resection, low anterior resection and subtotal or total colectomy
2 Ileocecal resection, right hemicolectomy and left hemicolectomy

**Table 5**

<table>
<thead>
<tr>
<th>Timing of radiological examination of the anastomosis and relaparotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Primary laparotomy - first imaging modality</td>
</tr>
<tr>
<td>Primary laparotomy - second imaging modality</td>
</tr>
<tr>
<td>Primary laparotomy - relaparotomy</td>
</tr>
<tr>
<td>2 clinical parameters - first imaging</td>
</tr>
<tr>
<td>3 clinical parameters - first imaging</td>
</tr>
<tr>
<td>4 clinical parameters - first imaging</td>
</tr>
<tr>
<td>Imaging - relaparotomy</td>
</tr>
<tr>
<td>Negative imaging - relaparotomy</td>
</tr>
<tr>
<td>Positive imaging - relaparotomy</td>
</tr>
</tbody>
</table>

*a* Calculated from second imaging (nine patients with both imaging modalities before relaparotomy)
Finally, the definition of the ‘gold standard’ may explain the reported differences in sensitivity. Considerable variation in defining anastomotic leakage exists in the literature due to the lack of consensus. In a systematic review by Bruce et al., 29 separate definitions were used for leakage of lower gastrointestinal anastomoses. Lower reported incidences may be due to, for example, not relating an intra-abdominal abscess to an anastomotic dehiscence.

Only in case of a negative relaparotomy, radiological signs of leakage were defined as a false-positive result in our study. The remaining patients with positive imaging and mild signs or symptoms suggestive of anastomotic dehiscence were defined as a radiological leakage, although this could have been a false-positive result either. Therefore, we did not calculate the specificity of radiological imaging. Actually, the specificity is of only minor clinical importance, because the consequences of positive imaging are determined by the patient’s clinical condition. In other words, a patient with radiological signs of anastomotic leakage and a good and stable clinical condition will generally be treated conservatively anyway. Analysis of 135 consecutive patients from the St Mark’s hospital demonstrated that a radiological leak did not alter clinical management in the majority of cases. Similarly, DuBrow et al. concluded that the presence of radiologic abnormalities indicating leaks did not invariably lead to therapeutic intervention.

The literature is not conclusive in what is the best imaging modality in patients with suspected anastomotic leakage. Water-soluble contrast radiography and contrastenhanced CT scanning are the most frequently used diagnostic tools and are probably complimentary. These imaging modalities are sometimes elusive or at least uncertain as a spectrum of findings due to anastomotic leakage can be seen. This may explain the interobserver variability in the present study (Table 2), which is similar to the 13% disagreement as reported by Haynes et al. The advantage of CT imaging is the ability to detect other causes of the clinical symptoms, such as an intra-abdominal abscess, which offers the possibility of percutaneous drainage avoiding surgery.

In distal anastomoses not accessible for digital examination, water-soluble contrast radiography may have additional diagnostic value, although the insertion of a contrast injection catheter has to be done carefully and excessive pressure used during the examination can both precipitate and aggravate pelvic sepsis. When there is an ongoing clinical suspicion of leakage in more proximal anastomoses, CT imaging after oral administration of watersoluble contrast is the method of choice which also visualises subtle suggestion of leakage, such as perianastomotic collections.

Finally, a plain film of the pelvis is suggested to be a sensitive method in detecting disruption of a staple ring.

In conclusion, radiological imaging may be of value in case of clinical suspicion of anastomotic leakage with mild clinical symptoms, but our data suggest that the results should be interpreted with caution because of the high false-negative rate and the substantial interobserver variability. CT scanning can help to indicate alternative diagnoses and the possibility of minimally invasive percutaneous treatment.
REFERENCES


Part III

Rectal cancer; critical appraisal of current treatment
Chapter 6

Outcome of rectal cancer surgery after the introduction of preoperative radiotherapy in a low-volume hospital
**ABSTRACT**

**Background** The improvement in local control by preoperative radiotherapy for rectal cancer can be at the cost of substantial morbidity.

**Aim of the Study**: To determine the impact of short course preoperative radiotherapy on morbidity and mortality after total mesorectal excision (TME) in a low-volume hospital.

**Methods**: From 2000 to 2007, 104 patients underwent rectal resection for a proven malignancy. Outcome parameters including anastomotic leakage rate, duration of hospital stay and survival were retrospectively compared between patients who received radiotherapy followed by resection and patients who underwent resection alone.

**Results**: Anastomotic leakage occurred in 11 of 28 patients (39%) who underwent radiotherapy and in 10 of 54 patients (19%) in the surgery alone group (p=0.04). The length of hospital stay was significantly longer in the radiotherapy group in comparison with the surgery alone group (median 22 vs. 12 days; p=0.002). Independent predictors of decreased overall survival were high ASA classification, application of preoperative radiotherapy, necessity of ICU admission and advanced pathological stage.

**Conclusions**: A negative impact of preoperative radiotherapy on morbidity and mortality after rectal cancer surgery with an annual caseload of 16 was observed. Auditing of local practices is essential for quality control and potential improvement of clinical outcome.

**INTRODUCTION**

Local recurrence is a major problem in rectal cancer surgery with a substantial impact on quality of life especially due to intractable pain. Surgery is the cornerstone in the treatment of rectal cancer and a free circumferential margin is the most important factor to prevent local recurrence.1-3 The introduction of total mesorectal excision (TME) has resulted in a more than 50% reduction of local recurrence rate.4,5 Adding preoperative radiotherapy with a biological equivalent dose of at least 30 Gy led to a further decrease in local recurrence rate with an absolute risk reduction of 12% in a meta-analysis by Figueredo et al.6 Various radiotherapy schemes are used worldwide with similar results, but there is no consensus about the most optimal scheme because there are no comparative studies. For locally advanced rectal cancers (T3-4 or N2), long course radiotherapy (45-50 Gy with a daily dose of 1.8 to 2 Gy) with concurrent chemotherapy is now becoming standard of care.7

The improvement in local control by preoperative radiotherapy can be at the cost of substantial morbidity. Significantly higher rates of early postoperative adverse events have been reported after preoperative radiotherapy in comparison with surgery alone.6-8 More importantly, late side effects in irradiated patients, including faecal incontinence and sexual dysfunction, may have a negative impact on quality of life.10,11

One of the most serious complications after rectal surgery is anastomotic leakage as it can lead to life-threatening pelvic sepsis and often requires surgical reintervention. Failure of the anastomosis is also associated with long term side effects such as impaired anorectal function and sexual dysfunction and some studies find an increased risk of local recurrence.12,13 In contrast to results from large randomised studies, individual experiences from non-specialised low-volume hospitals suggested an increased risk of anastomotic leakage after preoperative radiotherapy.14-16 Because we had similar experiences this study was initiated in order to assess morbidity and mortality of total mesorectal excision with special emphasis on anastomotic leakage after the introduction of short course preoperative radiotherapy in an unselected cohort of patients.

**PATIENTS AND METHODS**

Between 2000 and 2007, 115 consecutive patients underwent a rectal resection according to TME principles for a proven malignancy at the Sint Lucas Andreas Hospital, a large community teaching hospital in Amsterdam, the Netherlands. There were 65 males and 50 females with a mean age of 70 years (range 45-95 years). For the
Cancer: critical appraisal of current treatment

Rectal cancer; critical appraisal of current treatment

The purpose of this study, data were retrospectively collected from the clinical records of all patients. Standard preoperative work-up included digital examination and colonoscopy with biopsy of the tumour, and in recent years also radiological imaging by endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI).

Thirty-nine of the 115 patients (34%) with resectable rectal cancer and the inferior tumour margin 15 cm or less from the anal verge underwent short course preoperative radiotherapy. Eleven patients (10%) underwent long course radiotherapy because of clinical T3-4 stage according to preoperative EUS or MRI findings. These 11 patients were excluded from further analysis, resulting in a study group of 104 patients. Thirty-four of 65 patients not receiving radiotherapy were treated before implementation of the results of the Dutch TME trial. The remaining 31 patients did not receive radiotherapy because of patient’s refusal or poor performance status. Clinicopathological characteristics of the patients who underwent short course preoperative radiotherapy and those who underwent immediate surgery are summarised in Table 1.

### Table 1
Clinicopathological characteristics of 104 rectal cancer patients, who underwent surgical resection according to TME principles without or with short course preoperative radiotherapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TME alone n=65</th>
<th>RT + TME n=39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median (range)) years</td>
<td>71 (47-95)</td>
<td>73 (45-88)</td>
<td>0.5</td>
</tr>
<tr>
<td>Sex (male : female)</td>
<td>40 : 25</td>
<td>19 : 20</td>
<td>0.2</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (26%)</td>
<td>17 (44%)</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>29 (45%)</td>
<td>11 (28%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19 (29%)</td>
<td>11 (28%)</td>
<td></td>
</tr>
<tr>
<td>Pathological stage according to AJCC</td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Stage 1 (T1-2N0M0)</td>
<td>19 (29%)</td>
<td>11 (28%)</td>
<td></td>
</tr>
<tr>
<td>Stage 2 (T3N0M0)</td>
<td>30 (46%)</td>
<td>14 (36%)</td>
<td></td>
</tr>
<tr>
<td>Stage 3 (T1-3N1-2M0)</td>
<td>13 (20%)</td>
<td>12 (31%)</td>
<td></td>
</tr>
<tr>
<td>Stage 4 (T1-3N1-2M1)</td>
<td>3 (5%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Type of Surgery</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Colorectal anastomosis</td>
<td>27 (42%)</td>
<td>8 (21%)</td>
<td></td>
</tr>
<tr>
<td>Colonoal anastomosis</td>
<td>27 (42%)</td>
<td>20 (51%)</td>
<td></td>
</tr>
<tr>
<td>Abdominoperineal resection</td>
<td>6 (9%)</td>
<td>9 (23%)</td>
<td></td>
</tr>
<tr>
<td>Hartmann procedure</td>
<td>5 (7%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are numbers of patients unless stated otherwise. TME=total mesorectal excision, RT=preoperative radiotherapy, ASA=American Society of Anesthesiologists, AJCC=American Joint Committee on Cancer.

Patients assigned to preoperative RT received a total dose of 25 Gy in five fractions during 5 to 7 days. The clinical target volume included the primary tumour and the mesentery with vascular supply, containing the perirectal, presacral, and the internal iliac nodes (up to the S1/S2 junction). The treatment was delivered with three portals box technique. Treatment time was from Monday to Friday, with surgery on the following week, not to exceed 10 days. No concurrent chemoradiotherapy was given.

All patients received an enema in the morning prior to surgery. Preoperative mechanical bowel preparation was not routinely applied. All operations were performed or supervised by one colorectal surgeon (WFT), who participated in the surgical quality assurance program advocated by the TME trial. All anastomoses were stapled with a side-to-end configuration, except for four patients in whom a J-pouch was constructed. A colorectal anastomosis was performed in 35 patients (34%) with a tumour located 10 to 15 cm from the anal verge. Forty-seven patients (45%) who had a distance between the tumour and the anal verge of 5 to 10 cm underwent a coloanal anastomosis. The distance to the distal tumour margin was determined on endoscopy. Patients were given a protective loop ileostomy at the discretion of the surgeon. A protective loop ileostomy was constructed more often when patients had undergone preoperative radiotherapy: 21/28 (75%) versus 10/54 (19%; p<0.001).

Fifteen patients (14%) with a tumour located in the most distal part of the rectum (0-5 cm from the anal verge) underwent an abdominoperineal resection (APR). A Hartmann procedure with permanent colostomy was performed in seven patients (7%). Postoperative oral intake was started depending on nausea, bowel movements, nasogastric tube production (if applied), and passage of flatus or stools. No fast track recovery programmes were used during this study period, although patients were stimulated to early mobilisation and to a normal diet as soon as possible.

Morbidity was quantified by four variables: anastomotic dehiscence, necessity of admittance to the Intensive Care Unit (ICU), length of stay at the ICU and length of total hospital stay. Anastomotic leakage was defined as leakage confirmed during relaparotomy, as drainage of pus per anum, as an anastomotic defect at digital examination, or as a radiological leakage with clinical symptoms suggestive of anastomotic dehiscence.

After discharge from the hospital, all patients were carefully followed every three months during the first two years, and every six months for the following three years. The status of those patients not visiting the outpatient clinic was determined by contacting the patients or their general practitioner. Follow-up was complete until April 2007, and three patients (3%) were lost to follow-up after a mean period of 31 months. Median follow-up was 35 months (range 4-70) in the radiotherapy group and 51 months (range 4-83) in the surgery alone group. Mortality was assessed based on all causes of death.
To determine significance of differences between two groups of patients, Chi-square and Fisher’s exact tests were used for categorical variables and the Mann-Whitney test for continuous variables. Survival probabilities were estimated using the Kaplan-Meier method and log rank test was used for bivariable analysis of prognostic factors. Multivariate Cox proportional hazards regression was conducted to investigate independent predictors of overall survival for the whole group of patients. Variables were entered in the multivariate model if the p-value was less than 0.2 in univariate analysis. For all analyses, a p-value less than 0.05 (two-sided) was considered statistically significant. Statistical analyses were performed with Statistical Package for the Social Sciences software (SPSS 12.0, Chicago, IL, USA).

**RESULTS**

As shown in Table 2, anastomotic leakage, hospital stay, and in-hospital mortality were significantly different in favour of the surgery alone group compared with the group who underwent resection with short course preoperative radiotherapy. The significantly higher postoperative mortality after preoperative radiotherapy had a significant impact on overall survival as shown in Figure 1 (p=0.02).

**Table 2** Clinical outcome parameters of 104 rectal cancer patients, who underwent surgical resection according to TME principles without or with short course preoperative radiotherapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TME alone n=65</th>
<th>RT + TME n=39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necessity of ICU stay</td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>Reason for ICU admittance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal sepsis</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leakage (n=54 versus n=28)</td>
<td>10 (19%)</td>
<td>11 (39%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (3%)</td>
<td>4 (10%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>3 (8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Wound abcess</td>
<td>4 (6%)</td>
<td>4 (10%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (3%)</td>
<td>2 (5%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Adynamic ileus</td>
<td>3 (5%)</td>
<td>5 (13%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fascia dehiscence</td>
<td>1 (2%)</td>
<td>3 (8%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Haematoma / bleeding</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Other*</td>
<td>5 (8%)</td>
<td>2 (5%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Duration of ICU stay (median [range]) days</td>
<td>4 (3-25)</td>
<td>5 (2-45)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>12 (5-67)</td>
<td>22 (2-93)</td>
<td>0.02</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>5 (8%)</td>
<td>10 (26%)</td>
<td>0.01</td>
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</tbody>
</table>

TME=total mesorectal excision, RT=preoperative radiotherapy, ICU=intensive care unit
* Other complications were metabolic encephalopathy, fasciitis, central venous line sepsis, glottic edema, bowel ischemia, pancreatitis, sepsis eci and a cerebrovascular accident.

**Figure 1** Overall survival of rectal cancer patients undergoing surgery alone (n=65; drawn line) or short course radiotherapy (RT) followed by surgery (n=39; interrupted line) (log rank p=0.02)
Univariate analysis of potential predictors of overall survival is depicted in Table 3. In multivariate regression analysis, high American Society of Anesthesiology (ASA) classification, application of preoperative radiotherapy, necessity of ICU stay, and advanced tumour stage according to American Joint Committee on Cancer (AJCC) were independent risk factors for poor overall survival (Table 4).

Perineal wound infection occurred in three of the nine patients who had undergone preoperative radiotherapy before APR. Two of these three patients had a deep infection with dehiscence of the perineal wound. None of the six patients in the surgery alone group developed a perineal wound complication of the APR (p=0.23). Morbidity and mortality after anastomotic leakage was evaluated in the group of 82 patients who had an anastomosis. Anastomotic leakage occurred in 21 of 82 patients: 10 of 54 patients (19%) in the surgery alone group and 11 of 28 patients (39%) in the preoperative radiotherapy group (5x5 Gy) (p=0.04). Postoperative stay at the ICU was required in eight of 54 patients (15%) with anastomosis in the surgery alone group and in six of 28 patients (21%) who underwent preoperative radiotherapy (p=0.28; Table 5). Anastomotic leakage occurred in 10 of 31 patients (32%) with a protective ileostomy versus 11 of 51 patients (22%) without ileostomy (p=0.28; Table 5). Five of the 21 patients who suffered from an anastomotic dehiscence died in hospital, of whom four patients had been treated with preoperative radiotherapy.

**DISCUSSION**

This study reports a substantial anastomotic leakage rate after preoperative radiotherapy for rectal cancer. In addition, irradiated patients had a significantly longer hospital stay and higher postoperative mortality. These alarming results suggest an association between radiotherapy and anastomotic leakage with a subsequent impact on postoperative mortality, confirming findings by Vermeulen et al. However, these results are non-randomised, single-centre studies. Several large randomised multicentre trials did not show a significant difference in anastomotic leakage between patients who underwent preoperative radiotherapy and surgery alone. How can these contradictory findings be explained? The present study has the risk of a selection bias as the patients were not randomly assigned to the two different treatment strategies. The radiotherapy group consisted of relatively more patients with ASA 1 and a low anastomosis in comparison with the surgery alone group, although these differences were not significant (Table 1). It is a striking observation that even patients who underwent surgery alone had a relatively high percentage of anastomotic leakage (Table 2). This might be partly explained by the relatively high age of our population (median age 70 years) associated with relevant comorbidity. This is demonstrated by the finding that about one third of the patients had an ASA classification higher than two, which has been identified previously as a risk factor for anastomotic leakage.

Anastomotic leakage rates and management of this complication for patients with or without loop ileostomy are displayed in Table 5.

Anastomotic leakage was observed in 7 seven of the 35 patients (20%) who had a colorectal anastomosis: six of 27 patients (22%) without preoperative radiotherapy and one of 8 patients (13%) with preoperative radiotherapy (p=0.9). In 14 of 47 patients (30%) with a coloanal anastomosis, leakage occurred in four of 27 patients (15%) without preoperative treatment and 10 of 20 patients (50%) with preoperative radiotherapy (p=0.01). Anastomotic leakage occurred in 10 of 31 patients (32%) with a protective ileostomy versus 11 of 51 patients (22%) without ileostomy (p=0.28; Table 5).

**Table 5** Anastomotic leakage and its management in patients with or without a ‘protecting’ loop ileostomy who underwent TME alone or TME preceded by short course radiotherapy (5x5 Gy)

<table>
<thead>
<tr>
<th>Management of complication</th>
<th>TME alone n=54</th>
<th>short course RT + TME n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ileostomy</td>
<td>ileostomy</td>
<td>No ileostomy</td>
</tr>
<tr>
<td>Colorectal anastomosis</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Coloanal anastomosis</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>8 (18%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>

Level of anastomosis

<table>
<thead>
<tr>
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<th>short course RT + TME n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ileostomy</td>
<td>ileostomy</td>
<td>No ileostomy</td>
</tr>
<tr>
<td>Colorectal anastomosis</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Coloanal anastomosis</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>8 (18%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Management of complication</th>
<th>TME alone n=54</th>
<th>short course RT + TME n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ileostomy</td>
<td>ileostomy</td>
<td>No ileostomy</td>
</tr>
<tr>
<td>Colorectal anastomosis</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Coloanal anastomosis</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>8 (18%)</td>
<td>2 (20%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management of complication</th>
<th>TME alone n=54</th>
<th>short course RT + TME n=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ileostomy</td>
<td>ileostomy</td>
<td>No ileostomy</td>
</tr>
<tr>
<td>Relaparotomy with ileostomy</td>
<td>3*</td>
<td>0</td>
</tr>
<tr>
<td>Relaparotomy with abscess drainage</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Relaparotomy with breakdown of the anastomosis and colostomy</td>
<td>4*</td>
<td>1</td>
</tr>
<tr>
<td>Digital transanal drainage</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Conservatively</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

TME=total mesorectal excision, RT=radiotherapy, *=one patient initially underwent ileostomy, but colostomy was constructed at second relaparotomy.

It has been suggested that the accelerated fractionation of the preoperative radiotherapy, as developed in Scandinavia three decades ago, is associated with an increased acute toxicity. The Stockholm I trial showed a higher postoperative mortality in the group of patients with short course 5x5 Gy radiotherapy in comparison with surgery alone. The Uppsala trial, however, did not show any influence on mortality of short course preoperative radiotherapy. Because of the difference in radiotherapy...
of rectal surgery is related to surgical volume. In the present study, a total number of rectal cancer patients were treated over a 7-year time period (annual caseload of one to five) and should be considered as low-volume surgeons according to other investigators. Diversity of definitions for hospital and surgeon volume makes the 'volume-outcome' relationship difficult to interpret. Volume seems to be only a surrogate measure of quality, and the literature is replete with reports of postoperative complications and mortality observed in the present study. There are no randomised studies at present comparing short course preoperative radiotherapy with preoperative conventionally fractionated schedules. A trial from the Polish Colorectal Study Group almost fits this study design; concurrent 5-fluorouracil and leucovorin was added to the long course radiotherapy group. Similar percentages of postoperative complications, local control, survival, and late toxicity were found. Craven and Sebag Montefiore conclude from their recently published review that there is no convincing evidence to suggest that modern radiotherapy increases postoperative mortality, small bowel obstruction, pelvic fractures, or fistulae. Several studies have shown that outcome of rectal surgery is related to surgical volume. In the present study, a total number of 115 patients were treated over a 7-year time period by a single surgeon, resulting in an average hospital and surgeon volume of 16 patients per year. In the Northern Region Colorectal Cancer Audit Group of the United Kingdom perioperative death per 1000 hospital admissions was higher below an annual caseload of 18.5 rectal cancer resections per surgeon. However, the authors conclude that a specialist colorectal surgeon not having a large cancer workload may still obtain excellent results. Analysis of a colorectal cancer database from Maryland, USA showed that high-volume surgeons (annual caseload > 10) had a significant lower in-hospital mortality and hospital stay in comparison with low-volume surgeons (annual caseload ≤ 5) irrespective of hospital volume. Schrag et al. showed that not hospital volume, but only surgeon-specific volume was related to 2-year mortality after rectal cancer resection. Neither of the volume parameters was associated with 30-day mortality.

However, even high-volume surgeons in this study had a caseload of only six to 26 in the 5-year study period (annual caseload of one to five) and should be considered as low-volume surgeons according to other investigators. Diversity of definitions for hospital and surgeon volume makes the 'volume-outcome' relationship difficult to interpret. Volume seems to be only a surrogate measure of quality, and the literature is unable to determine how accurate volume is in predicting outcome after rectal cancer surgery in terms of the individual centre or surgeon.

Education, training, and auditing are essential for quality improvement. In the Dutch TME trial, all participating hospitals were given information by workshops, symposia and instruction videos and the first five TME procedures had to be supervised by an instructor surgeon. This has led to a substantial reduction in local recurrence rates and improved long term outcome. A comparable surgical training program was launched in Sweden and Norway, where similar results were found. In addition, a valid and reliable registration system is crucial to improve quality of care as shown by the Swedish population-based rectal cancer registry. As stated by Wexner and Rotholtz, surgeons should be aware of their own practice patterns and their results should be audited. In Sweden, local or regional problems are discussed at yearly meetings with those responsible for registration at each hospital. We are currently implementing a national colorectal cancer registry in the Netherlands (the Dutch Surgical Colorectal Audit; http://www.dasca.nl). Based on this registry, standards can be set, and those not within the limits are stimulated to re-evaluate and improve their treatment strategies.

Changes in practice to improve surgical quality and outcome might include further specialisation and modification of technique. In our study, a loop ileostomy was not protective for anastomotic dehiscence, but it might alleviate the clinical course, as stated by others. A study by Matthiessen et al., in which patients who underwent low anterior resection were randomised between loop stoma or no loop stoma, showed a significantly different symptomatic anastomotic leakage rate of 10% and 28%, respectively. Decisions concerning faecal diversion should include patient’s comorbidity, ease of the operation, level of anastomosis, intraoperative blood loss, and the use of preoperative and postoperative adjuvant therapy. In the present study, the negative impact of radiotherapy on anastomotic leakage was mainly found in patients who had a low colorectal anastomosis and, therefore, we now create a defunctioning stoma more liberally in these patients.

In addition, it may be helpful to have two or three surgeons involved in rectal surgery who supply mutual perioperative support. Debes et al. reported adequate results in a low-volume hospital (annual case load of four), where the main surgeon and first assistant were both certified gastrointestinal surgeons in 85% of the resections. As a consequence of the findings in the present study, rectal surgery is now performed by two senior staff surgeons, who are specialised in colorectal surgery.

The initial enthusiasm regarding the favourable impact of preoperative radiotherapy on local recurrence has somewhat tempered over the last years. Besides the early and late side effects as already mentioned, an increased risk of radiation induced second primary cancers has been described. Furthermore, treatment options in case of locally recurrent disease are limited, as irradiated patients cannot be treated with further radiotherapy. With no difference in median time between surgery and diagno-
sis of local recurrence, median life expectancy of irradiated patients who developed a local recurrence was shortened from 16 to 6 months compared to patients who underwent TME alone.41

With the recently published 5-year results of the Dutch TME trial, there is still a persistent and highly significant effect of radiotherapy on local recurrence rates. In subgroup analysis, although potentially biased, radiotherapy seems only effective in patients with lesions between 5 and 10 cm from the anal verge, nodal involvement, TNM stage III, and uninvolved circumferential resection margins.42 Especially as mortality is not influenced by radiotherapy, adequate patient selection seems important to prevent overtreatment with its possible adverse events. Clearly, the decision to treat rectal cancer patients with preoperative radiotherapy should be a weighed balance between potential benefits and harms.43

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Chapter 7
The different clinical entities of locally recurrent rectal cancer and its implications for radiotherapy of the primary tumour
ABSTRACT

Introduction: The ultimate goal of (chemo)radiotherapy for primary resectable rectal cancer is to reduce symptomatic and untreatable local recurrence. The purpose of this systematic review was to specify the different clinical presentations of locally recurrent rectal cancer and the various options for treatment and prevention.

Methods: A literature search using databases Pubmed and Embase (1990 to 2009) was performed with selection of cohort studies, randomised controlled trials (RCTs), and meta-analyses relevant to the purpose of this study.

Results: Half of the patients with locally recurrent rectal cancer present with pain (S2), and 50%-60% have synchronous distant metastases. Current literature is lacking adequate prospective data on pain-free survival after developing local recurrence. Macroscopically complete resection (R0/R1) of local recurrence can be achieved in one third of the patients. After treatment with curative intent, up to 60% of the patients develops systemic disease and 5-year overall survival is 30-40%. Previous pelvic radiotherapy limits the possibilities for local treatment of recurrence.

Conclusion: Only part of the total reduction in local recurrence resulting from routinely adding radiotherapy to TME surgery for primary resectable rectal cancer favours the subgroup with intractable symptomatic recurrence. There is an urgent need to identify patients who are best treated by TME surgery alone. This patient selection would have been facilitated by including S-classification and pain-free survival in RCTs on (neo)adjuvant treatment.

INTRODUCTION

Substantial progress has been made in local control of rectal cancer over the past decades. Firstly, anatomical consideration of the mesorectal fascia and the lateral tumour spread has lead to the development of a different surgical resection technique: total mesorectal excision (TME). The TME technique has become widely accepted, as local recurrence rates declined to 5-10%, while these were over 20% when conventional blunt dissection was applied. Secondly, the use of neoadjuvant therapy further reduced local recurrence rates as clearly shown by a meta-analysis of randomised controlled trials. The combined treatment modality with short course preoperative radiotherapy followed by TME surgery became standard of care for resectable rectal cancer in many European countries.

Local recurrence rate is the most relevant endpoint for interventional studies on (neo)adjuvant radiotherapy in rectal cancer, because survival is not or only marginally improved. It has been argued that a decrease in local recurrence rate of 5% is already worthwhile to strive for, given the severe symptoms, especially pain, associated with pelvic tumour recurrences. Although distant disease is often the determining factor for prognosis in these patients, local recurrence will generally affect QOL. But not all local recurrences from rectal cancer present with pain and some patients will die from synchronous distant metastases without suffering from pelvic recurrence either without any local treatment or with adequate palliative care. Other patients have recurrent disease confined to the pelvis and can be treated with curative intent. Finally, there remains a subgroup of patients with symptomatic local recurrence without curative therapeutic options and with inadequate relief of symptoms by palliative treatment. It is only this subgroup that really benefits from prevention of local recurrence by adding radiotherapy to adequate TME surgery for primary resectable rectal cancer.

Neoadjuvant radiotherapy in rectal cancer has a significant negative impact on the long term functional outcome, especially urge and faecal incontinence. The benefit of neoadjuvant radiotherapy by reducing the risk of (symptomatic) local recurrence should therefore be balanced against its negative impact on functional outcome. In order to enable a rational advice to individual patients, one needs to have a clear picture of the different clinical presentations of locally recurrent rectal cancer and the various options for treatment and prevention. The aim of this systematic review is to summarise the available literature on these three main issues.
Methods

A literature search was performed using Pubmed and Embase databases from 1990 to 2009 and restricted to papers written in the English language. Detailed information on incidence of symptoms and synchronous distant disease in locally recurrent rectal cancer requires unselected cohorts of patients with adequate prospective data registration. For the purpose of this part of the current review, population based studies and RCTs on treatment for primary resectable rectal cancer with detailed analysis of the group of patients who developed a local recurrence during follow-up were selected. To determine resectability and success of treatment for local recurrence with curative intent, cohort studies of locally recurrent rectal cancer with surgery as the principal treatment or as part of a multimodality approach were identified. Selection of these studies was based on consecutive patient inclusion, sufficient patient numbers, availability of outcome parameters, and absence of substantial duplication of reported patients (>80%). A minimum of 50 patients undergoing resection of local recurrence was chosen, in order to limit the width of the confidence intervals of outcome data. Finally, meta-analyses of RCTs were used to determine the impact of preoperative (chemo)radiotherapy for primary resectable rectal cancer on local recurrence. Outcome of surgery alone was determined by selection of cohort studies and surgery alone arms of RCTs specifically describing the use of TME surgery. The following MeSH and free text terms were used: ‘rectal neoplasms’ [MeSH] AND ‘local neoplasm recurrences’ [MeSH]; ‘rectal’, ‘rectum’, ‘cancer’, ‘local’, ‘recurrence’, ‘surgery’, and ‘radiotherapy’. The ‘related articles’ term in Pubmed was used to expand the searches. All retrieved articles were reviewed, and the reference lists of selected articles were systematically screened for additional studies of interest. The date of the most recent search was August 1st, 2009.

Results

Clinical presentation of local recurrence

Related symptoms and synchronous distant disease are the two most important clinical aspects of locally recurrent rectal cancer because of the significant impact on quality of life and survival respectively. Literature search on the first topic revealed only two prospective studies describing symptom scores for the whole group of patients who eventually develop local recurrence (Figure 1). Patients are classified as S0 (asymptomatic), S1 (symptomatic without pain) and S2 (symptomatic with pain). In an analysis by the Stockholm Rectal Cancer Study Group of 156 patients with locally recurrent rectal cancer who had been included in a randomised trial, the percentages for S0, S1 and S2 were 13%, 33% and 54% respectively.7 In a more recent population based study also performed in Sweden including 141 local recurrences, the percentage S0 was 35% without specification of S1 and S2.8 Other studies providing incidences of symptoms are cohorts of patients who were potential candidates for surgical treatment and are probably not representative for the whole group of patients who initially present with locally recurrent disease. Reported percentages of S2 ranged from 27% to 100% with an overall percentage of 49% (453/934 patients) in nine cohorts including at least 50 patients (Figure 1).9-17 Selection bias makes these data less reliable.
Pain may develop during follow-up after diagnosis of an initially asymptomatic recurrence, either with or without local treatment. No unselected prospective studies on pain-free survival of locally recurrent rectal cancer could be identified in order to determine incidences of S2 in time.

Severity of pain can be scored in terms of analgesic drug use and impact on quality of life (QOL). Only a few small studies with selected cohorts of patients have been done to investigate these relevant clinical aspects, thereby limiting the value of the available data. In a group of 59 patients who had proven pelvic recurrence after previous irradiation, but without bony involvement and absence of extrapelvic disease, analgesic drugs were used in 41% at time of diagnosis: 27% used nonopioid drugs and 14% opioid drugs. Camilleri et al. demonstrated that developing any recurrence from rectal cancer resulted in significantly lower QOL in most dimensions in comparison with no recurrent disease. However, no measurable differences were found in QOL scores including pain between patients with exclusively distant recurrence (n=12) and those with local recurrence (n=13).

Literature search revealed three RCTs providing data on incidence of synchronous systemic dissemination. In the Dutch TME trial, 83 of 129 patients with local recurrence had also distant metastases. The Swedish Rectal Cancer Trial and Stockholm I trial reported distant disease in 66 of 143 patients and 86 of 156 patients with local recurrence, respectively. Curative treatment of both local and distant recurrence is achievable in only a very small subgroup.

In summary, recurrent rectal cancer is accompanied by pain in about half of the patients and presents with synchronous distant disease in approximately 50% to 60% of the patients.

Table 1
Consecutive cohort series of patients with locally recurrent rectal cancer published between 1990 and 2009 reporting on the proportion of macroscopically complete resection in the end

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Period (y)</th>
<th>Total No. of recurrences</th>
<th>Irresectable or M1</th>
<th>Curative intent</th>
<th>R0 / R1</th>
<th>% R0 or R1 of initial group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gagliardi</td>
<td>1995</td>
<td>19</td>
<td>82</td>
<td>25</td>
<td>57</td>
<td>1/12</td>
<td>30</td>
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<tr>
<td>Wiggers</td>
<td>1996</td>
<td>92</td>
<td>163</td>
<td>128</td>
<td>35</td>
<td>1/13</td>
<td>17</td>
</tr>
<tr>
<td>Salo</td>
<td>1999</td>
<td>99</td>
<td>194</td>
<td>62</td>
<td>132</td>
<td>5/6/13</td>
<td>43</td>
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<td>155</td>
<td>429</td>
<td>125</td>
<td>304</td>
<td>5/1/9</td>
<td>38</td>
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<tr>
<td>Asoglu</td>
<td>2007</td>
<td>7</td>
<td>72</td>
<td>22</td>
<td>50</td>
<td>2</td>
<td>50</td>
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<tr>
<td>Total</td>
<td></td>
<td></td>
<td>940</td>
<td>362</td>
<td>578</td>
<td>3/29/77</td>
<td>36</td>
</tr>
</tbody>
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y=number of years in which patients were included, M1= distant metastases not considered to be resectable, R0=macroscopically complete resection, R1=macroscopically incomplete resection

Figure 2 Flow chart of the selection of cohort studies on treatment with curative intent for locally recurrent rectal cancer
Treatment of locally recurrent rectal carcinoma with curative intent

Five cohort studies reporting the percentage of macroscopically complete resection in a consecutive series of locally recurrent rectal cancer were identified by literature search. Individual data of these five studies are displayed in Table 1. Overall, pelvic recurrence could be resected without gross residual tumour in 337 of the initial 940 patients, of which 260 had an R0 resection.

Literature search revealed 66 studies reporting on surgical treatment of locally recurrent rectal cancer either with or without (neo)adjuvant radiotherapy or chemoradiotherapy, intra-operative radiotherapy, and adjuvant chemotherapy. To evaluate outcome, eleven studies were selected as shown in Figure 2. Clinical and treatment characteristics of these eleven studies are displayed in Table 2. If the percentage of macroscopically complete resection was at least 80% (Table 2B), corresponding 5-year overall survival ranged between 30% and 40% (Table 2C). These survival probabilities are a reflection of the substantial number of patients who develop distant metastases during follow-up (Table 2C). Microscopic incompleteness of resection (R1/R2 versus R0) is the most important predictor of impaired survival after treatment of locally recurrent rectal cancer.9-11,15,21-27

Summarising these data, macroscopically complete resection can be achieved in one third of the patients who initially present with locally recurrent cancer. Approximately half of the patients will develop distant disease after treatment with curative intent with reported 5-year overall survival between 30% and 40%.

Table 2A
Unselected cohort series (published between 1990 and 2009) of locally recurrent rectal cancer, including at least 50 patients who underwent surgical resection with or without (chemo)radiotherapy or intraoperative radiotherapy; clinical characteristics

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Period (y)</th>
<th>N</th>
<th>Primary therapy</th>
<th>Characteristics local recurrence</th>
<th>Interval (months)</th>
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<tr>
<td>Bussières</td>
<td>1996</td>
<td>73</td>
<td>51</td>
<td>-</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>Salo</td>
<td>1999</td>
<td>221</td>
<td>57</td>
<td>0</td>
<td>22</td>
<td>33</td>
</tr>
<tr>
<td>Hashiguchi</td>
<td>2001</td>
<td>11</td>
<td>28</td>
<td>32</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Garcia-Aguilar</td>
<td>2002</td>
<td>100</td>
<td>16</td>
<td>50</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Shoup</td>
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<td>155</td>
<td>23</td>
<td>54</td>
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<td>33</td>
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<td>65</td>
<td>0</td>
<td>31</td>
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<td>52</td>
<td>46</td>
<td>-</td>
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<td>Heriot</td>
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<td>160</td>
<td>7</td>
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<tr>
<td>Dresen</td>
<td>2005</td>
<td>123</td>
<td>147</td>
<td>30</td>
<td>53</td>
<td>28</td>
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</tbody>
</table>

Values of follow-up represent median (range), M1=crude rate of patients with distant metastases during follow-up. * =4-year, f=disease-specific survival

Table 2B
Unselected cohort series (published between 1990 and 2009) of locally recurrent rectal cancer, including at least 50 patients who underwent surgical resection with or without (chemo)radiotherapy or intraoperative radiotherapy; treatment characteristics

<table>
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<th>Radiotherapy for resection</th>
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<td>N/y</td>
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<tr>
<td>Salo</td>
<td>103</td>
<td>104</td>
</tr>
<tr>
<td>Hashiguchi</td>
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N/y=number of resections per year, sacral=abdominosacral resection, IORT=intra-operative radiotherapy, EBRT=preoperative and/or postoperative external beam radiotherapy, CRT=chemoradiotherapy, i.e. concurrent chemotherapy during EBRT as percentage of the whole study group. * = multicentre study (Bussières 6 centres, Palmer 9 centres, Wells 2 centres, Heriot 3 centres), † = percentage of 43 R0 resections

Relief of symptoms by treatment of local recurrence

There are only a few prospective studies dealing with symptom relief by treatment of locally recurrent rectal cancer. These are relatively small selected series, mostly including both curatively and palliatively treated patients. It is questionable whether these data are representative for the whole group and whether these can be extrapolated. The largest study by Miner et al. determined pre- and postoperative symptoms in 105 surgically treated patients of whom 24 were operated with palliative treatment.
intent. Although improvement of pain after one month was found in 40% of curatively treated patients, 33% had recurrent pain and 60% developed pain during follow-up. Improvement of bleeding and obstruction was found in 88% and 78% respectively, but about half of the patients had recurrent or newly experienced bleeding or obstruction during follow-up. An analysis of 103 patients who were reirradiated for recurrence, followed by resection of residual disease in 34 of these 103 patients, revealed better results with respect to symptom relief: 55% complete and 28% partial response with a median duration of 9 months and 33% palliation until death. In that study, complete response for bleeding was 100% with 80% of patients palliated until death. In a multicentre Italian study, hyperfractionated chemoradiation was applied in 59 previously irradiated patients, of whom 39 underwent subsequent resection of the local recurrence. Pain relief was 83% at one month, with a 2-year and 5-year pain-free survival of 89% and 31% respectively.

Table 3 Published cohort studies of TME surgery for rectal cancer without neoadjuvant or adjuvant (chemo) radiotherapy or selective application of such combined treatment

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<th>Author</th>
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<th>APR</th>
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<td>L +/- D 12† 8† 7†</td>
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RT=radiotherapy with or without concurrent chemotherapy, Pre=preoperative, Post=postoperative, N+=lymph node positive / TNM stage III, M1=distant metastasis / TNM stage IV, APR=abdomino-perineal resection, Curative=macroscopically radical resection performed or irresectable distant metastases, Def=definition of local recurrence, L +/- D=overall local recurrence rate including those patients with distant disease, *crude rate after a median follow-up of 69 months (Dixon et al.), 42 months (Jatzko et al.), 29 months (Wibe et al.), 37 months (Tagliazio et al.), 35 months (Enker et al.), 45 months (Martling et al.) not available (Cawthorn et al.), †=actuarial rate at 5 years (Head et al., Hall et al., Nesbakken et al., Piso et al., Law et al., Peeters et al., Ferenschild et al.), 3 years (Böla et al.) and 2 years (Jeyarajah et al.)

These data demonstrate that initial symptom relief of 80% to 90% can be achieved, but a substantial proportion of patients experience recurrent symptoms.

Prevention of local recurrence by (neo)adjuvant treatment in resectable rectal cancer

Published series of TME surgery without or with only highly selectively applied radiotherapy show local recurrence rates ranging from 2% to 17% (Table 3). The adequacy of complete excision of the mesorectum is of prognostic value for predicting local recurrence.

Radiation therapy has proven to reduce local recurrence rates compared to surgery alone for primary resectable rectal cancer. There is considerable variability in (neo)adjuvant therapy schedules and nationwide protocols when studying the literature. Meta-analysis of 19 RCTs of preoperative radiotherapy versus surgery alone in resectable rectal cancer showed a significantly lower local recurrence rate in favour of the combined therapy (pooled Hazard Ratio 0.71 (0.64-0.78)). However, state-of-the-art radiotherapy techniques (>2 fields) were applied in only four studies, biologically effective dose of more than 30 Gy in 12 studies, and TME surgery was required in only one study (Dutch TME trial). Non-TME surgery resulted in local recurrence rates of up to 54% in the control arms, while this was 11% in the Dutch TME trial. Overall survival was not significantly affected by preoperative radiotherapy with a pooled Hazard Ratio of 0.95 (0.89-1.02) using individual patient data analysis. Addition of concurrent chemotherapy to preoperative radiotherapy further improves local control. Meta-analysis of four RCTs showed that local recurrence significantly decreased from 16.5% to 9.4% by adding chemotherapy. This did not translate into a better overall or disease free survival, while grade III/IV toxicity significantly increased from 5.1% to 14.9%. Based on three RCTs, preoperative radiotherapy has shown to be more effective for local control with less treatment related toxicity in comparison with postoperative radiotherapy.

Toxicity from rectal cancer radiation is well documented for both immediate and late adverse effects. Acute toxicity consist of skin erythema, fatigue, nausea, diarrhoea and neurological pain, which are reported in 20% to 84% of patients. Perineal wound healing problems after APR are greater if preoperative radiotherapy is added to TME surgery. Bowel obstructions, bowel dysfunction presenting as continence or evacuation problems or urgency, and sexual dysfunction are encountered late side effects. The Swedish Rectal Cancer Trial and Dutch TME trial reported faecal incontinence in 50% and 62% after short course preoperative radiotherapy and in 24% and 38% after surgery alone. Emptying difficulties and bowel frequency of more than 4
times a day were found in 52% and 20% after preoperative radiotherapy, while these percentages were 36% and 8% respectively after surgery alone in the Swedish Rectal Cancer Trial. Increased risk of femoral neck and pelvic fractures, venous thromboembolism and cardiovascular death was found in the preoperative radiotherapy arm of the Stockholm I trial, but not confirmed in subsequent trials using state-of-the-art multifield techniques.

In conclusion, preoperative (chemo)radiotherapy results in a substantial relative risk reduction of local recurrence without or with only marginal improvement of overall survival. However, this relative risk reduction translates in an absolute risk reduction of only a few percent in case of adequate TME surgery, while it increases toxicity, especially long term bowel dysfunction.

**DISCUSSION**

**Clinically relevant impact of preoperative radiotherapy on local recurrence**

The 5% absolute risk reduction of local recurrence by routinely adding preoperative radiotherapy to TME surgery, based on the results of the Dutch TME trial, is not the ultimate gain in terms of clinical relevance. One subgroup of patients will die from disseminated disease without local complaints of their (asymptomatic) recurrence until death, and another subgroup will receive adequate multimodality treatment for their recurrence, either with curative or with palliative intent. Until now, there are no high quality studies available to elucidate this clinical issue. Based on data provided in the present review, an estimation of the ultimate clinically relevant effect of neo-adjuvant radiotherapy can be made. Assuming 50% disseminated disease with 50% symptomatic local recurrence, the first subgroup will be one quarter. As stated previously, the second subgroup is about one third. These two subgroups together comprise more than half of the entire group with local recurrence. So, there will remain an estimated difference of 2 - 3% in the proportion of patients with symptomatic local recurrence without effective further treatment options.

**The impact of primary treatment on management of local recurrence**

Success of secondary local treatment depends on several factors that are beyond control, except for previous radiotherapy. Abuchaiba et al. demonstrated that complete resection of local recurrence was higher in patients who were not irradiated previously. Van den Brink et al. did a similar observation, although not statistically significant: surgical resection of local recurrence was performed in 25 of 71 patients primarily treated by TME alone and in 4 of 23 patients who underwent preoperative radiotherapy for primary rectal cancer. Patient selection may partly explain this difference. Without previous radiotherapy, patients can be optimally treated by full dose (chemo)radiotherapy for local recurrence. Downstaging by adequate neoadjuvant treatment facilitates salvage surgery. Furthermore, chemoradiotherapy can be used for local control in patients with synchronous local and irresectable distant recurrences, as well as in patients with locally irresectable disease without systemic dissemination. In the Dutch TME trial, radiotherapy at a dose of 45 Gy or higher was applied in 42% of the patients for local recurrence after TME alone, while this was only 4% for the preoperative radiotherapy group. Radiotherapy dose of less than 45 Gy was associated with shorter survival in both univariable and multivariable analysis. Again, this observation should be interpreted with caution because of potential selection bias.

**Improving harm/benefit ratio of preoperative radiotherapy by risk stratification**

The small absolute decrease in intractable symptomatic local recurrences should be weighed against negative side effects and costs of standard neoadjuvant (chemo)radiotherapy for primary resectable rectal cancer. As previously described, standard preoperative (chemo)radiation is associated with an increase in late functional problems of 20% to 30%.

These data suggest an imbalance between the harm and benefit for preoperative radiotherapy in resectable rectal cancer, at least if no risk stratification is applied. Phase III trials on neoadjuvant treatment for resectable rectal cancer until now have provided overall results for all tumour locations and pathological stages. There is growing support for not applying preoperative radiotherapy in patients with clinical T2N0 and low risk T3N0 tumours, especially in case of proximal location. In rectal cancer patients who do not exceed a 10% risk of local recurrence with TME alone for their primary tumour, radiotherapy should probably be reserved for treating locally recurrent disease when occurring. However, accurate preoperative risk stratification is difficult. Refinement of preoperative locoregional staging has been achieved by adding magnetic resonance imaging (MRI), although further improvement of the technique is necessary for adequate patient selection. With the currently available options of multimodality treatment, it is necessary to have a multidisciplinary team deciding on the extent of surgery and the indication for preoperative therapy. Patients at relatively low risk of local recurrence are best treated by TME surgery alone. Short course radiotherapy and immediate TME surgery seems to be most suitable in case of intermediate risk without the need for downstaging. Long course radiotherapy with concurrent chemotherapy followed by TME surgery is now increasingly used for downstaging in patients with advanced nodal disease (N2) or at high risk for positive circumferential resection margin, which appears to be one of the most important prognosticators for local recurrence.

The different clinical entities of locally recurrent rectal cancer and its implications for radiotherapy of the primary tumour
Summary

Local recurrence of rectal cancer is often a manifestation of disseminated disease. Some of these patients will die from disseminated disease without suffering from their local recurrence. This is important to realise when considering toxic neo-adjuvant treatment for primary resectable rectal cancer that does not improve survival. Furthermore, previous pelvic radiotherapy limits the possibilities of local treatment for recurrence. From this perspective, RCTs on neo-adjuvant (chemo) radiotherapy for resectable rectal cancer should have included S-classification and pain-free survival of local recurrence for better defining the clinically relevant effect. Pretreatment diagnostic modalities are evolving, thereby enabling the use of clinical tumour stage and tumour location to select patients who benefit most from preoperative radiotherapy, resulting in an improvement of the harm/benefit ratio.

REFERENCES

Rectal cancer; critical appraisal of current treatment

Rectal cancer; critical appraisal of current treatment

The different clinical entities of locally recurrent rectal cancer and its implications for radiotherapy of the primary tumour


Chapter 8
Discussion and future perspectives
FUNCTIONAL OUTCOME AFTER RECTAL SURGERY

Rectal cancer surgery has evolved from destructive amputative procedures at the beginning of the last century to sphincter saving surgery with improved oncological results. However, the performance of a coloanal anastomosis causes a diminished anorectal function in most patients, particularly in the first postoperative year. As has been shown in Chapter 2, the capacity of the neorectum is less than the capacity of the normal rectum of healthy volunteers. In addition, hypercontractibility of the neorectum is observed. It was hypothesised that a colonic J-pouch anastomotic reservoir has a larger volume compared to the side-to-end coloanal anastomotic reservoir and might reduce neorectal contractions since the circular muscles are transected during the creation of a pouch. However, these presumed pathophysiological mechanisms were not supported by barostat measurements or by studying functional outcome for each of the two types of reconstruction (Chapter 1). A complex interplay exists between the rectum, the anal sphincter complex, the musculature of the pelvic floor and the nerve endings to the anal canal. The latter are sensitive to pain, temperature and touch, and enable differentiation between solid or liquid stool and flatus, allowing for selective passage. Disturbing the integrity and delicate balance of these physiological processes by rectal resection is the main cause of anorectal dysfunction and the type of anastomosis seems to play an insignificant role.

Alternative reconstruction techniques have been used but the available data suggest that, despite initial differences, outcome is generally comparable at two years postoperatively. For example, the transverse coloplasty did not show an advantage in bowel function over a straight anastomosis in a randomised trial. Our data contribute to the body of evidence that the J-pouch provides no convincing support for its superiority in comparison with the side-to-end anastomosis. Therefore, this study does not support the preferred use of the J-pouch, but justifies the choice of the side-to-end coloanal anastomosis, because of its ease of construction.

In all types of anastomoses, nerve preservation will probably be of utmost importance. Nerve preservation can be facilitated by the use of peroperative nerve stimulating devices which seems to be a promising approach to improve functional outcome. Training enables surgeons to improve nerve identification and preservation. Nerve identification is facilitated by using laparoscopy because of magnification of the operative field and 30 degree angulation of the camera in the narrow pelvis. However, there have been contradictory findings suggesting a worse functional outcome for laparoscopic rectal surgery, which may be related to a different use of electrocautery and sealing devices with the risk of indirect thermal damage to the nerves.
Furthermore, as a feedback and quality control to the surgeon, pathologists should be instructed and trained in identifying nerves in the resection specimen.

Besides bowel function disturbances, sexual and urinary dysfunctions are also associated with nerve damage during rectal resection.28 Our long term data could not demonstrate an influence of rectal surgery on urinary function if compared to colonic surgery. However, sexual dysfunction was seen after rectal surgery for both benign and malignant disease (Chapter 3). The main problem in studies evaluating sexual function by questionnaires is avoidance of questions related to this topic and the fact that a substantial proportion of patients state not to be sexually active.8,9 Reasons for not being sexually active are often not provided, suggesting that the latter group of patients possibly encounters severe dysfunctional problems. Furthermore, the retrospective nature of most studies conducted on this subject causes biased results, as baseline variables are not available. Although the occurrence of urinary and sexual dysfunctions is well recognised, properly designed prospective studies are awaited in order to have insight in the quantified risk of these dysfunctions. In this perspective it is also important to realise that patients seldom remember discussing the risk of diminished sexual function preoperatively.10

An interesting development in the field of rectal cancer therapy is the shift from ‘sphincter saving’ to ‘organ saving’ approaches. There is a subgroup of patients that have a complete response to neoadjuvant chemoradiotherapy or at least a significant downsizing of their primary tumour. There are some preliminary data available suggesting that these patients may be safely treated by local excision or even watchful waiting.11-13 It is to be expected that this will have a significant impact on functional outcome for those patients in a positive way.

In conclusion, not only aiming at a better local control and survival, but also focussing on improvement of anorectal, sexual and urinary function could further improve rectal cancer treatment.

COLORECTAL SURGERY;
MANAGEMENT OF ANASTOMOTIC DEHISCENCE

Anastomotic leakage causes an increased morbidity and mortality in the postoperative course and is in the long term associated with an impaired functional outcome and increased local recurrence rate.14-21 Considering all available literature on this subject, anastomotic leakage has been shown to remain a not completely evitable complication of colorectal surgery. In Chapter 4 we therefore not focused on the prevention of anastomotic leakage but on the recognition of clinical symptoms accompanying anastomotic leakage. By assessing these symptoms on a day-to-day basis, the often subtle deterioration of the clinical course of a patient becomes more apparent. This can potentially lead to a shorter delay of appropriate treatment and thus less morbidity and mortality. It should be emphasised that this day-to-day evaluation holds true for all seven days a week as we found the weekend to be significantly associated with a delay in the recognition of anastomotic leakage. Although being the first group to study anastomotic leakage from this perspective, the major weakness of our study is its retrospective nature and the lack of information about symptoms in patients without an anastomotic leakage. Both questions are currently answered by others: the latter has been described by a French group, finding the occurrence of symptoms significantly more often in the group with anastomotic leakage.22 Recently, den Dulk et al. prospectively compared all patients with a colorectal anastomosis to a historical control group by the use of a protocol for standardised postoperative surveillance. They found a shorter delay between the first signs and symptoms to the confirmation of anastomotic leakage and a higher mortality rate in patients with non-standardised postoperative monitoring. Furthermore, patients were subjected to several additional tests, which were not primarily useful to make a final diagnosis.23

This finding is in line with Chapter 5, in which the accuracy, interobserver variability, timing and discordance of postoperative radiological examination of colorectal anastomoses is described. The high false-negative rate and the substantial interobserver variability are arguments in favour of a restrictive use of diagnostic imaging and a cautious interpretation of results of radiological imaging of the anastomosis after colorectal surgery. On the other hand, several factors might influence the reliability of diagnostic imaging, such as timing of the tests, location of the anastomosis and the quality of the radiological technique.

Although our data suggest a limited additional value of radiographic imaging in the detection of anastomotic leakage, it certainly plays a role to indicate alternative diagnoses and provides the possibility of minimally invasive percutaneous treatment of an intra-abdominal abscess. However, one should keep in mind that false-negative results lead to a delay in proper treatment of (sub)clinical leakages, which might cause an unnecessary deterioration in the clinical situation of the patient.

From the currently available data, it has become clear that careful clinical judgement of the clinical course of the patient with daily standardised postoperative surveillance is the main diagnostic tool in the diagnosis of anastomotic leakage, enabling early treatment.
The surgeon plays a key role in rectal cancer treatment, as the most influential prognosticator for local recurrence after rectal resection and short course preoperative radiotherapy is adequate resection with radical circumferential resection margins (CRM). The skill level of surgeons is hereby the most variable factor as it differs between surgeons and varies in time.

In this perspective, education, training and auditing are essential for quality improvement. In the Dutch TME trial and in Scandinavia, a surgical training program was launched, which has led to a substantial reduction in local recurrence rates and improved long term outcome.\(^{24-26}\) The TME technique has become widely accepted, as local recurrence rates declined to 5-10%, while these were over 20% when using conventional blunt dissection. Ahead of the recently implemented national colorectal cancer registry in the Netherlands (the Dutch Surgical Colorectal Audit; www.dsc.nl), Chapter 6 describes morbidity and mortality of total mesorectal excision after the introduction of short course preoperative radiotherapy in an unselected cohort of patients. Reporting of a substantial anastomotic leakage rate with a prolonged hospital stay and a higher postoperative mortality contributed to the awareness of own practice patterns and resulted in re-evaluation and improvement of treatment strategies.

Furthermore, multidisciplinary treatment of rectal cancer is essential in the present era of quality assurance. Meta-analysis of 19 randomised controlled trials of preoperative radiotherapy versus surgery alone in resectable rectal cancer showed a significantly lower local recurrence rate in favour of the combined therapy (pooled Hazard Ratio 0.71 (0.64-0.78)).\(^ {27}\) In many European countries, the combined treatment modality with short course preoperative radiotherapy followed by TME surgery became the standard of care for resectable rectal cancer.

However, as described in Chapter 7, several aspects should be addressed before deciding on routine application of neoadjuvant radiotherapy. First of all, preoperative radiotherapy causes an increased rate of perineal wound infections after abdominopereineal resections and acute toxicity is reported in 20 - 84% of patients.\(^ {28}\) Secondly, bowel obstruction, bowel dysfunction presenting as continence or evacuation problems or urgency, and sexual dysfunction are encountered late side effects from preoperative radiotherapy.\(^ {29}\) Thirdly, preoperative radiotherapy does not or marginally influences overall survival.\(^ {30}\) Finally, it is questionable whether prevention of a local recurrence is really beneficial for all patients to whom this applies. In general, local recurrence is the reflection of an aggressive biological behaviour of the primary tumour as it is accompanied by synchronous distant metastasis in 50% to 60% of the patients.\(^ {29-31}\) Patients may have highly progressive systemic disease which prevents the patient from suffering of a local recurrence. A second group of patients have recurrent disease confined to the pelvis and can be treated with curative intent, especially if those patients were not irradiated for their primary tumour and full dose chemoradiotherapy is still an option.\(^ {31}\) In the end, there remains a subgroup of patients with symptomatic local recurrence without curative therapeutic options and with inadequate relief of symptoms by palliative treatment.\(^ {30,33}\) It is only this subgroup that really benefits from prevention of local recurrence by adding radiotherapy to adequate TME surgery for primary resectable rectal cancer. Therefore, the benefit of neoadjuvant radiotherapy in resectable rectal cancer should not only be balanced against its negative side effects, but also against the subgroup specific incidence, related symptoms and treatment possibilities of a locally recurrent rectal cancer. More selective application of neoadjuvant radiotherapy will improve its harm/benefit ratio.

Subgroup analyses of the Dutch TME trial, although potentially biased, showed that short course radiotherapy followed by TME surgery within one week seems only effective in patients with lesions between 5 - 10 cm from the anal verge, nodal involvement, TNM stage III and uninvolved circumferential resection margins.\(^ {31}\) This trial was conducted at the time magnetic resonance imaging (MRI) was not routinely used for locoregional staging. Furthermore, a one-size-fits-all approach for rectal cancer as used in the Dutch TME trial is no longer applicable. The Dutch guidelines are predominantly based on the results of this trial. The shift towards a more tailor-made treatment in current daily practice suggests the need for revising our guidelines.
Discussion and future perspectives

MRI has become indispensable for pre-treatment evaluation of rectal cancer by assessing tumour level, relation to the CRM, lymph node status and relation to surrounding structures such as prostate, sacrum and vagina. Each individual patient will then be discussed in a multidisciplinary team consisting of a surgeon, radiation oncologist, medical oncologist and radiologist. The decision to apply short course preoperative radiotherapy or to administer long scheduled preoperative radiotherapy with concurrent chemotherapy is mostly based on MRI results, despite its limitations. Magnetic resonance imaging with lymph node specific contrast enhancement may be the most promising preoperative tool for better distinguishing between N0, N1 or N2 stage rectal cancer. The current evaluation of MRI contrast agents, like superparamagnetic iron oxide (UPSIO) and MS 325, might solve the problem of lymph node metastasis identification in the future.34-36 These novel diagnostic modalities will facilitate not only the exact localisation of the primary tumour, but also of the lymph node status. Both factors probably determine the potential advantage of preoperative radiotherapy in an individual patient. Randomised studies are needed to objectively determine the efficacy of preoperative radiotherapy in N0 rectal cancer patients and for tumours at each different level from the anal verge.

Although selection criteria are not yet fully evidence based, treatment plans for individual patients can be best made in a multidisciplinary setting and should be based on currently available suboptimal evidence, while awaiting further trials.

REFERENCES

In Chapter 1 the results of a multicentre randomised trial are described comparing functional and surgical results of the colonic J-pouch with the side-to-end anastomosis after rectal resection and their impact on quality of life. Patients with a histologically proven rectal carcinoma (cT2-T3) located in the middle and/or distal part of the rectum were included, resulting in 55 patients in the J-pouch group and 52 patients in the side-to-end group. All patients received preoperative radiotherapy in a dose of 5x5 Gy, followed by a Total Mesorectal Excision (TME). Primary endpoint was the function of the neorectum as assessed by the validated COloRECTal Functional Outcome (COREFO) questionnaire; secondary endpoints were surgical results as registered by operation reports, pathology reports and events during the postoperative course and quality of life as assessed by the EORTC-QLQ-CR38 and SF-36 questionnaires. The questionnaires were completed by all patients preoperatively and at 4 and 12 months postoperatively. The COREFO incontinence scale at 4 months and the total functional outcome at 4 and 12 months showed better results for the J-pouch group in comparison with the side-to-end group. The remaining COREFO scales (frequency, social impact, stool related aspects and bowel medication), surgical outcome (complications, re-operations, length of hospital stay, re-admissions and mortality), and quality of life did not show significant differences between treatment groups. Although functional results are slightly better by constructing a J-pouch, overall results of a colonic J-pouch and a side-to-end anastomosis are comparable. The side-to-end anastomosis is technically less demanding and therefore a justified alternative in sphincter saving surgery.

In Chapter 2 further research is described that was conducted to gain insight in the pathophysiological mechanism contributing to the impaired functional results after rectal resection. (Neo)rectal function of ten healthy volunteers (HVs) and fifteen patients (J-pouch or side-to-end anastomosis) 5 months after short term preoperative radiotherapy and total mesorectal excision for rectal cancer were evaluated by manometry and barostat studies. Furthermore, patients with a colonic J-pouch anastomosis (n=6) were compared to patients with a side-to-end anastomosis (n=9). (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 defaecate. The neorectal volume of patients at the threshold of the urge to defaecate (125 ± 45 ml) was significantly lower when compared with that of HVs (272 ± 87 ml). The pressure threshold, however, did not differ between patients (26 ± 9 mmHg) and HVs (21 ± 5 mmHg), neither did the pressure threshold differ
between patients with a J-pouch and a side-to-end anastomosis. In HVs, no rectal contractions were observed during prolonged rectal distension. In contrast, in all 15 patients, prolonged isovolumetric and isobaric distension induced 3 (range 0-5) contractions/10 min. This hypercontractility or neorectal irritability represents a pathophysiological mechanism contributing to the impaired anorectal function (mainly urgency for defaecation) after preoperative radiotherapy and total mesorectal excision.

Not only bowel function problems are seen after rectal resection, but also sexual and urinary dysfunctions. In Chapter 3 we prospectively evaluated patients after rectal resection and patients after colonic resection based on sexual, urinary and bowel function and quality of life in the short and long term. Eighty-three patients who underwent a rectal resection (RR) with total mesorectal excision were compared to 53 patients who underwent a colonic resection leaving the rectum in situ (RIS). A questionnaire assessing sexual, urinary and bowel functioning, with a quality of life questionnaire (SF-36) was sent to all participants preoperatively, 3 and 12 months postoperatively and approximately eight years after onset of the study. Short term dysfunctions included diminished sexual activity in female RR patients at three months and significantly more erectile dysfunctions in male RR patients one year postoperatively, did not influence overall quality of life. The incidence of urinary dysfunction was comparable between RR and RIS patients. Bowel functioning was significantly better in the RIS group compared to the RR group after three months and one year of follow-up. Erectile dysfunctions in male RR patients persisted in time; other sexual, urinary and bowel functions after rectal resection and colonic resection are similar after long term follow-up.

PART II
COLORECTAL SURGERY; MANAGEMENT OF ANASTOMOTIC DEHISCENCE

In Chapter 4 the time interval (‘delay’) between the occurrence of clinical parameters associated with anastomotic leakage after colorectal resection and subsequent relaparotomy was analysed. In 36 of 289 consecutive patients with colorectal anastomoses, leakage was confirmed at relaparotomy. The medical records of these patients were retrospectively analysed and type and time of appearance of clinical parameters suggestive of anastomotic leakage were recorded. These parameters included heart rate, body temperature, local or generalised peritoneal reaction, leucocytosis, ileus and delayed gastric emptying. Factors influencing delay of relaparotomy and consequences of delayed recognition and treatment were determined. First documentation of at least one of the predefined parameters for anastomotic leakage was a median interval of 4 ± 1.7 days after the first operation. The median number of days between first parameter(s) associated with leakage and relaparotomy was 3.5 ± 5.7 days. The time interval between the first signs of leakage and relaparotomy was significantly longer when a weekend was included (4.2 days vs. 2.4 days) or radiological evaluation proved to be (false-)negative (8.1 days vs. 3.5 days). The delay caused by an intervening weekend or negative diagnostic imaging to diagnosis and relaparotomy was more than two days in two-thirds of the patients. No significant association between delay and number of additional relaparotomies, hospital stay or mortality could be demonstrated.

In Chapter 5 more insight was gained in the accuracy, interobserver variability, timing and discordance with relaparotomy of postoperative radiological examination of colorectal anastomoses. Radiological examination of the anastomosis was not performed routinely, but only when there were clinical signs of leakage. Radiological imaging was reviewed by an independent radiologist and the interpretation was compared to the initial interpretation. Medical records were retrospectively analysed. Clinical anastomotic leakage was the standard of reference and defined as leakage confirmed during relaparotomy, drainage of pus per anum or as an anastomotic defect identified at digital examination. Radiological evaluation of the anastomosis was performed in 91 of 429 patients (21%) who underwent an ileocolonic, colo-colonic, or colorectal anastomosis: CT in 27 patients, contrast radiography in 40 patients, and both modalities in 24 patients. The interobserver variability of CT and contrast radiography was 10% and 14%, respectively. The sensitivity and negative predictive value of imaging of the anastomosis was 65% and 73%, respectively. Anastomotic leakage was found in 11 of 21 patients (52%) who underwent relaparotomy despite negative imaging. Three of 36 patients (8%) with a diagnosis of anastomotic leakage based on radiological examination had an intact anastomosis at relaparotomy. Therefore, we concluded that radiological imaging of the anastomosis after colorectal surgery should be restrictively applied and interpreted with caution because of the high false-negative rate and the substantial interobserver variability.

PART III
RECTAL CANCER; CRITICAL APPRAISAL OF CURRENT TREATMENT

Auditing of local practices is essential for quality control and potential improvement of clinical outcome. In contrast to results from large randomised studies, individual experiences from non-specialised low-volume hospitals suggested an increased risk of anastomotic leakage after preoperative radiotherapy. Therefore, we described morbidity and mortality of total mesorectal excision with special emphasis on anasto-
motic leakage after the introduction of short course preoperative radiotherapy in an unselected cohort of patients in Chapter 6. One hundred and four patients (annual caseload of 16) underwent rectal resection for a proven malignancy. Outcome parameters including anastomotic leakage rate, duration of hospital stay and survival were retrospectively compared between patients who received radiotherapy followed by resection and patients who underwent resection alone. A negative impact of preoperative radiotherapy on morbidity and mortality after rectal cancer surgery was observed in this cohort with an annual load of 16 cases. Anastomotic leakage occurred in 11 of 28 patients (39%) who underwent radiotherapy and in 10 of 54 patients (19%) in the surgery alone group (p=0.04). The length of hospital stay was significantly longer in the radiotherapy group in comparison with the surgery alone group (median 22 vs. 12 days; p=0.002). Independent predictors of decreased overall survival were high ASA classification, application of preoperative radiotherapy, necessity of ICU admission and advanced pathological stage.

In Chapter 7 the role of routinely adding radiotherapy to adequate TME surgery is critically appraised for primary rectal cancer, by a systematic review of current literature from the point of view of the different clinical entities of locally recurrent rectal cancer. A literature search using the databases of Pubmed and Embase (1990 to 2009) was performed with selection of cohort studies on locally recurrent rectal cancer, cohort studies and randomised controlled trials for treatment of primary resectable rectal cancer, and meta-analyses relevant to the purpose of this study. Half of the patients with local recurrence from rectal cancer present with pain, and 50%-60% have synchronous distant metastases. Macroscopically complete resection (R0/R1) of local recurrence can be achieved in one third of the patients. After treatment with curative intent, up to 60% of the patients develops systemic disease and 5-year overall survival is 30-40%. Previous pelvic radiotherapy (at the time of the initial treatment) limits the possibilities for local treatment of recurrence.

As only part of the total reduction in local recurrence resulting from routinely adding radiotherapy to TME surgery for primary resectable rectal cancer favours the subgroup with intractable symptomatic recurrence, we advocate a more selective application of neoadjuvant (chemo)radiotherapy to improve the harm/benefit ratio.
In colorectale chirurgie, naadlekkage wordt waargenomen. Bij patiënten die een rectumresectie (RR) ondergingen met totale mesorectale excisie werden vergeleken met 53 patiënten die een colonresectie ondergingen waarbij het rectum in situ bleef (RIS). Vragenlijsten ter beoordeling van seksueel, urologisch en stoelgang gerelateerde functies en de invloed op de kwaliteit van leven van de anastomose tijdens rectaal toucher. Radiologisch onderzoek van de anastomose tijdens rectaal toucher. Radiologisch onderzoek van de colorectale anastomose. Radiologisch onderzoek werd beoordeeld door een onafhankelijke radioloog en de interpretatie werd vergeleken met het initiële radiologische verslag. Medische statussen werden retrospectief geanalyseerd. Klinisch optreden van de anastomose werd geëvalueerd na een rectumresectie en colonresectie. 83 patiënten die een ileocolische, colocolische, of ileoileale anastomose bij relaparotomie was meer dan twee dagen in twee derde van de patiënten. Er kon geen significant verband worden aangetoond tussen de vertraging en het aantal relaparotomieën, opnameduur of mortaliteit.

In Hoofdstuk 3 worden prospectief de seksuele, urologische en stoelgang gerelateerde functies en de invloed op de kwaliteit van leven op korte en lange termijn bij patiënten geëvalueerd na een rectumresectie en colonresectie. 83 patiënten die een rectumresectie (RR) ondervonden en met totale mesorectale excisie werden vergeleken met 53 patiënten die een colonresectie ondergingen waarbij het rectum in situ bleef (RIS). Vragenlijsten ter beoordeling van seksueel, urologisch en stoelgang gerelateerd functioneren en een kwaliteit van leven vragenlijst (SF-36) werden naar alle patiënten (RIS) aangevraagd en zorgvuldig worden geïnterpreteerd, in verband met het hoge doel van deze patiënten zijn retrospectief verzameld en type en timing van het optreden van klinische parameters passend bij naadlekkage werden geanalyseerd. Deze parameters betreffen hartfrequentie, temperatuur, lokale of gegeneraliseerde peritonitis, leukocytose, ileus en een vertraagde maagontleding. Factoren die van invloed waren op de vertraging tot relaparotomie en de consequenties van vertraagd herkennen en behandelen van de naadlekkage werden bepaald. Eerste documentatie van tenminste een van de vooraf bepaalde parameters passend bij naadlekkage werd gedaan na een mediaan interval van 4 ± 1.7 dagen na de initiële operatie. Het mediaan aantal dagen tussen de eerste parameter(s) passend bij naadlekkage en relaparotomie was 3.5 ± 5.7 dagen. Het tijdsinterval tussen de eerste tekenen van lekkage en relaparotomie was significant langer door een weekend (4.2 versus 2.4 dagen) of (fout)-negatief radiologisch onderzoek (8.1 versus 3.5 dagen). Deze vertraging veroorzaakt door een weekend of negatief radiologisch onderzoek vanaf het optreden van symptomen tot aan relaparotomie was significant langer dan de normale periode. Sensitiviteit, vergelijkbaar zijn na lange termijn follow-up.

DEEL II
COLORECTALE CHIRURGIE; MANAGEMENT VAN NAADLEKKAGE

In Hoofdstuk 4 is het tijdsinterval (‘delay’) vanaf het optreden van klinische parameters geassocieerd met naadlekkage en de daaropvolgende relaparotomie geëvalueerd. Bij 36 van de 289 opeenvolgende patiënten met een colorectale anastomose werd een naadlekkage geconstateerd bij relaparotomie. De medische statussen van deze patiënten zijn retrospectief verzameld en type en timing van het optreden van klinische parameters passend bij naadlekkage werden geanalyseerd. Deze parameters betreffen hartfrequentie, temperatuur, lokale of gegeneraliseerde peritonitis, leukocytose, ileus en een vertraagde maagontleding. Factoren die van invloed waren op de vertraging tot relaparotomie en de consequenties van vertraagd herkennen en behandelen van de naadlekkage werden bepaald. Eerste documentatie van tenminste een van de vooraf bepaalde parameters passend bij naadlekkage werd gedaan na een mediaan interval van 4 ± 1.7 dagen na de initiële operatie. Het mediaan aantal dagen tussen de eerste parameter(s) passend bij naadlekkage en relaparotomie was 3.5 ± 5.7 dagen. Het tijdsinterval tussen de eerste tekenen van lekkage en relaparotomie was significant langer door een weekend (4.2 versus 2.4 dagen) of (fout)-negatief radiologisch onderzoek (8.1 versus 3.5 dagen). Deze vertraging veroorzaakt door een weekend of negatief radiologisch onderzoek vanaf het optreden van symptomen tot aan relaparotomie was significant langer dan de normale periode. Sensitiviteit, vergelijkbaar zijn na lange termijn follow-up.
DEEL III
RECTUM CARCINOOM; KRITISCHE BESCHOUWING VAN DE HUIDIGE BEHANDELING

Monitoring van de dagelijkse praktijk is essentieel voor de kwaliteitscontrole en potentiële verbetering van klinische resultaten. In tegenstelling tot de resultaten van grote gerandomiseerde studies, zijn er enkele publicaties van individuele ervaringen van niet-gespecialiseerde laag-volume ziekenhuizen, waarbij een hoger risico op naadlekkage wordt gezien na preoperatieve radiotherapie. Derhalve beschrijven we de morbiditeit en mortaliteit na totale mesorectale excisie met specifieke nadruk op het optreden van naadlekkage na de introductie van een kortdurend schema van preoperatieve radiotherapie in een niet-geselecteerde groep patiënten in Hoofdstuk 6. 104 patiënten (jaarlijkse caseload van 16) ondergingen een rectumresectie in verband met een rectumcarcinoom. De uitkomstparameters naadlekkage, opnameduur en overlijden werden retrospectief vergeleken tussen patiënten die preoperatief radiotherapie ondergingen gevolgd door een resectie en patiënten die alleen een resectie ondergingen. Een negatieve invloed van preoperatieve radiotherapie op zowel morbiditeit als mortaliteit na rectumchirurgie werd gevonden in deze cohort met een jaarlijkse caseload van zestien patiënten. Naadlekkage trad op bij 11 van de 28 patiënten (39%) die preoperatief radiotherapie ondergingen gevolgd door een resectie en bij 10 van de 54 patiënten (19%) die alleen een resectie ondergingen (p=0.04). De opnameduur was significant langer in de bestraalde groep ten opzichte van de chirurgiegroep (mediaan 22 versus 12 dagen; p=0.002). Onafhankelijke voorspellers van een verkorte algemene overleving waren een hoge ASA classificatie, ondergaan van preoperatieve radiotherapie, noodzaak tot opname op de ICU en een hoger tumorstadium.

In Hoofdstuk 7 wordt de rol van het routinematig toepassen van preoperatieve radiotherapie bij adequate TME chirurgie voor het primaire rectumcarcinoom kritisch geëvalueerd, door een systematische review van huidige literatuur vanuit de verschillende klinische entiteiten van het lokale recidief van het rectumcarcinoom. Een literatuuronderzoek is verricht gebruik makend van de databases van Pubmed en Embase (1990 tot 2009) met een selectie van cohort studies over het lokale recidief van het rectumcarcinoom, cohort studies en gerandomiseerde studies over de behandeling van het primair resectabel rectumcarcinoom en voor het doel van deze studie relevante meta-analyses. De helft van de patiënten met een lokaal recidief presenteerde zich met pijnklachten en 50%-60% presenteerde zich met synchrone afstandsmeta-stasen. Macroscopisch complete resectie (R0/R1) van een lokaal recidief kan worden verkregen bij een derde van de patiënten. Na behandeling met curatieve intentie, ontwikkelt tot 60% van de patiënten systemische ziekte en de 5-jaars algehele overleven is 30-40%. Eerdere bestraling van het bekken (bij de initiële behandeling van de primaire tumor) limiteert de mogelijkheden voor lokale behandeling van het recidief. Aangezien de routinematige toepassing van preoperatieve radiotherapie in het geval van een primair resectabel rectumcarcinoom slechts een deel van de totale reductie van het optreden van een lokaal recidief voorkomt, pleiten we voor een meer selectieve applicatie van neoadjuvante (chemo)radiotherapie ter verbetering van de balans tussen voor- en nadelen.
Appendices
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LIST OF PUBLICATIONS

Doeksen A, Tanis PJ, van Tets WF, van Lanschot JJB
The different clinical entities of locally recurrent rectal cancer and its implications for radiotherapy of the primary tumour
Submitted

Doeksen A, Bakx R, Vincent A, van Tets WF, Sprangers MAG, Gerhards MF, Bemelman WA, Slors JFM, van Lanschot JJB
Colonic J-pouch-anal versus side-to-end coloanal anastomosis after preoperative radiotherapy and total mesorectal excision in rectal cancer: a multicentre randomised trial
Submitted

Doeksen A, Gooszen JAH, Tanis PJ, van Duijvendijk P, van Lanschot JJB, Slors JFM
Sexual and urinary functioning after rectal surgery: a prospective comparative study with long term follow-up
Submitted

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Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection
World J Gastroent. 2007; Jul; 13(27):3271-5
Het ongelooflijke is gebeurd. Het boekje is af. En ik ben chirurg. Niet zonder de steun, het vertrouwen en de begeleiding van velen, waarvoor DANK!

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