MULTIDISCIPLINARY TREATMENT OF RECTAL CANCER AND OTHER PELVIC TUMOURS

Multidisciplinaire behandeling van het rectum carcinoom en andere kleine bekken tumoren

Floris Ferenschild

The publication of this thesis was financially supported by:

Nederlandse Vereniging voor Gastro Intestinale Chirurgie
Roche Nederland B.V.
Pfizer B.V.
Stichting Erasmus Heelkundig Onderzoek
Boonekamp B.V.

ISBN: XXX-XXX

Design: Legatron Electronic Publishing, Rotterdam
Printed by: Ipskamp Drukkers, Enschede

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Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.G. Schmidt
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
9 december 2009 om 15.30 uur, door:

Floris Titiaan Josef Ferenschild

geboren te Herkenbosch

Promotiecommissie

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In my beginning is my end
T.S. Elliot

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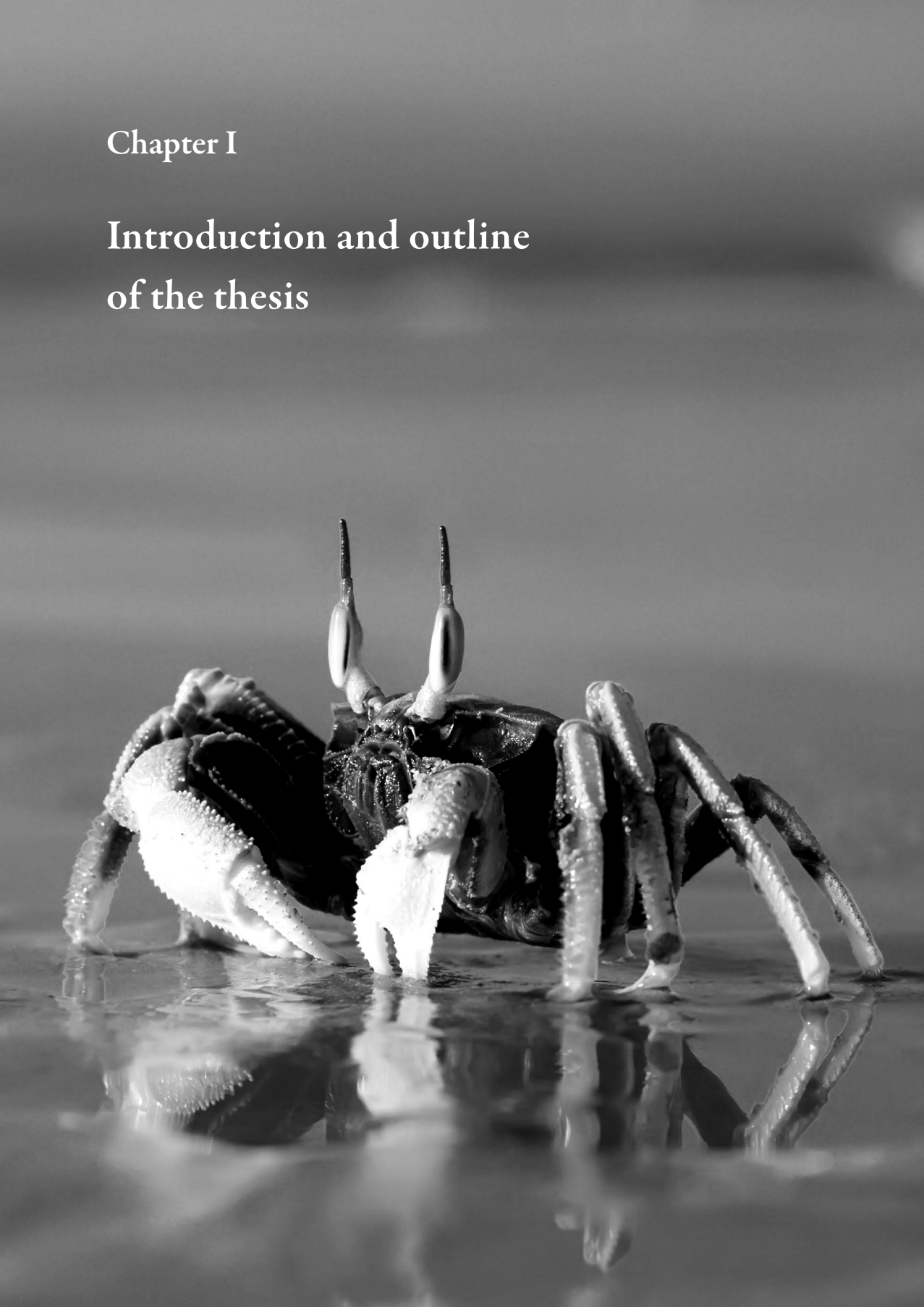
PART V | RESULTS

Chapter I

Introduction and outline of the thesis



PART I | PRIMARY RECTAL CANCER

Primary rectal cancer

Colorectal cancer is a major problem in the western world and has a rising incidence.[1,2] Approximately one third of these tumours originate in the rectum. Although colon and rectal cancer share similar features there is a distinct difference in clinical behaviour and therapeutical approach.[3] The treatment of primary rectal cancer has evolved into a multidisciplinary treatment with standardised imaging techniques, surgical procedures, pathological assessment, and (chemo)radiation therapeutical options.[1, 4-6] The introduction of total mesorectal excision (TME) has lead to a significant decreased local recurrence rate[7] in combination with preoperative short-term radiotherapy (5x5Gy).[8, 9] Based on the beneficial results reported in the Dutch TME trial[1] the treatment protocol in the Netherlands of patients with a tumour in the lower two-third of the rectum was changed in 2001.[10] Nowadays all patients are considered to be discussed in a multidisciplinary team and a short course of radiotherapy will be given prior to TME surgery. It is unclear if results in community hospitals are similar to the results presented in these multicenter trials. In **chapter 2** we report the results of rectal cancer surgery in a low volume community hospital in the region of the Comprehensive Cancer Centre Rotterdam. The aim of the study was to identify the compliance to the new standardised treatment protocol i.e. the introduction of preoperative radiotherapy. Furthermore, the results of rectal cancer treatment in the centre were analysed and compared with reference values based on selected patients from randomised trials in the recent literature.

Preoperative radiotherapy

Although long term results of preoperative radiotherapy showed a consistent significant difference in local control in the Dutch TME trial, this difference was not present in a subgroup analysis for TNM stage I and II.[9] Although short course preoperative radiotherapy has become the standard of care for rectal cancers in many centres in the Netherlands and other European countries selection criteria are still controversial.[11] Especially in T2 and T3, N0 rectal cancer patients neo-adjuvant radiotherapy seems to add little to local control or survival.[12] In **chapter 3** we assessed the outcome of a historical group of T2, 3 N0 patients treated with a TME alone and compare them with a T2, 3 N0 group who was treated with preoperative radiotherapy followed by TME. Time to local recurrence, time to distant metastases and overall survival between the different treatment groups were compared and predictors of recurrence were identified to analyse the influence of clinical variables on outcome.

PART II | LOCALLY ADVANCED RECTAL CANCER

Primary locally advanced rectal cancer

Primary locally advanced rectal cancer extends into or beyond the enveloping fascia propria of the mesorectal compartment and is estimated to account for 6-10% of all primary rectal cancers.[13] An adequate circumferential resection margin (CRM>2mm) is related to a significantly improved local control after surgery for primary rectal Cancer.[14] Especially in locally advanced rectal cancer radical margins and an adequate CRM are often difficult to obtain because of infiltration into adjacent structures. Preoperative long course radiation therapy have been developed to increase resectability by the effect of downsizing/-staging and to ameliorate outcome.[15, 16] In case of a marginal complete or incomplete resection intraoperative radiotherapy (IORT) can be applied with the aim to provide better local control. In **chapter 4** we describe our experience with the multimodality treatment of pre- and intraoperative radiotherapy and surgery for a cohort of 123 patients with primary locally advanced and initially unresectable rectal tumours.

Preoperative chemoradiation therapy

The addition of 5-FU based chemotherapy to radiation therapy has demonstrated to be feasible with an increase in pathological complete response rate and local control for locally advanced rectal cancer patients.[17, 18] Capecitabine (oral 5-FU) is a fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumour cells as the concentration of the key enzyme thymidine phosphorylase is higher in tumour cells compared with normal tissue.[19-21] Several phase II studies have been initiated to evaluate the tolerance and efficacy of chemoradiation with capecitabine.[22-24] In these studies different regimes of capecitabine were used and in some studies leucovorin was added. In **chapter 5** we describe a phase II study to evaluate the efficacy and toxicity of preoperative chemoradiation with capecitabine in large T3/T4 rectal tumours or in patients with local lymph node metastases.

PART III | RECURRENT RECTAL CANCER

Recurrent rectal cancer

Despite improvements in the treatment of primary rectal cancer, local recurrences occur and the incidence range between 3-15%.[1] When a recurrence develops in rectal cancer patient, prognosis is often poor and without adequate treatment mean survival is approximately 8 months and 5-year survival rates range between 0-30%.[25-31] Recurrences are often associated with severe symptoms, especially neuropathic pain due to ingrowth in the pelvic wall.[30] The main goals in the treatment of recurrent rectal cancer are palliation of symptoms, good quality of life and, if possible, curative surgery. In recurrent rectal cancer the visceral fascia surrounding the rectum has been resected in previous surgery, which makes a complete resection of recurrent disease more difficult.[26] Successful complete resection of recurrent rectal cancer is often restricted to selected patients, for example with an early-detected tumour or an anastomosis-limited recurrence after previous sphincter-sparing surgery.[32] Preoperative radiotherapy is used in the treatment of recurrent rectal cancer based upon the beneficial effects on local control and even overall survival in the treatment of primary rectal cancer.[33, 34] In **chapter 6** the outcome is described after treatment of 92 patients with recurrent rectal cancer, with a special interest on the effect of preoperative long-term irradiation and intra-operative radiation.

Recurrence after transanal endoscopic microsurgery (TEM)

In an attempt to avoid the morbidity and mortality of TME, local excision has been developed as a therapeutic option in the treatment of well-selected patients with early rectal cancer.[2] Early reports of operations performed through the transanal approach found unacceptably high rates of incomplete tumour removal in up to 60 percent of surgical specimens.[35-38] The introduction of transanal endoscopic microsurgery (TEM) by Buess *et al*.[39] proved to be an optimised technique for removal of rectal tumours. This technique enables excellent access and visualization of the surgical field and allows precise and full-thickness excision of the tumour. The rate of tumour resection with clear margins, even with standardised pathology, for T1 tumours has increased to more than 90%. [35, 40] Considering the very low mortality and morbidity rates, local excision by TEM is now considered a potential alternative for the surgical treatment of T1 tumours by many surgeons.[36, 41, 42] However, the wide range of local recurrences range from 0 to 24%,[43, 44] and the results of salvage surgery in recurrent tumours are matters of concern. In the literature only few series report on surgical procedures following recurrent disease after transanal surgery.[45-47] In **chapter 7** we present the results of salvage surgery for local recurrences of a large group of patients treated with TEM for T1 rectal cancer.

PART IV | EXTENDED RESECTIONS AND RECONSTRUCTIONS

Abdominoperineal Sacral resections (APSR)

Despite efforts in the early detection and intense follow-up of rectal cancer patients, primary locally advanced and recurrent rectal cancer with involvement into adjacent organs or structures is not uncommon. For patients with extraluminal tumour mass involving the pelvis or other organs, the treatment used to be strictly palliative. Because of new treatment modalities, including preoperative chemoradiation therapy and extensive resections, it is possible to obtain complete resections in this group of patients.[48, 49] If the tumour has infiltration into or a very close relation with the sacrum, an abdominoperineal sacral resection (APSR) might in some patients be the only curative treatment option. In patients with primary locally advanced rectal cancer involvement of the posterior bony pelvis almost never occurs, but this is sometimes seen in recurrent rectal cancer patients.[50] The symptoms often include severe pain in the sacral region. The 5-year overall survival of APSR is reported between 15 and 30% and the local control rate between 15 and 40%.[51] In **chapter 8** we evaluate the oncological outcome after APSR for both primary locally advanced and recurrent rectal cancer in our tertiary referral centre.

Total pelvic exenteration (TPE)

In case of a locally advanced growth pattern of a primary or recurrent rectal tumour or other pelvic tumours, major exenterative surgery might be necessary to provide complete resection margins. In case of tumour involvement of the base or trigone of the bladder or the prostate, a total pelvic exenteration (TPE) with resection of the rectum together with bladder, lower ureters and internal genital organs could salvage the patient. TPE has been performed in primary or recurrent cancer of the cervix, rectum, vagina, uterine corpus, vulva, prostate, bladder and in pelvic sarcoma.[52, 53] Since the introduction of the technique by Brunswick in 1948 the initially poor quality of life and high mortality and morbidity associated with the technique have substantially improved.[54-56] However, morbidity after this extensive surgical procedure is still high and reports between 13% and 64%.[57-59] Five-year survival rates after TPE for patients with primary disease range between 32% and 66% and in patients with recurrent disease from 0% to 23%.[49,54,59] The results of TPE in a cohort of 69 patients are described in **chapter 9.**

Pelvic reconstructions

In **chapter 10** we describe our experience with the technique of salvage APR for anal cancer patients. The treatment of anal cancer has changed radically during the past few decades, from predominantly surgery to (chemo)radiation therapy. Despite the overall excellent results of CRT in the primary treatment of anal carcinoma, a proportion of patients fail treatment. Initial treatment failure occurs in 10-15% and an additional 10-15% of patients develop a local recurrence after an initial complete response to CRT.[60-62] The majority of these failures is isolated to the primary tumour site[60, 63, 64] and are therefore curable by a salvage abdominoperineal resection (APR). A major problem of surgery in the previously irradiated anal area is poor healing of the often large perineal wound.[65] The incidence of perineal wound complications is rather high after salvage treatment with APR, and complications in more than 30% of patients have been reported.[66, 67] Similar to the report by others the VRAM flap reconstructive procedure results in primary healing with acceptable donor-site morbidity and low complication rates.[65, 68, 69] Resection margins of the perianal skin can easily be compromised when primary closure is performed. The use of a VRAM flap also enables the surgeon to remove the recurrent or persistent tumour mass with wide resection margins, as the large skin defect can easily be managed.

In **chapter 11**, the results of the studies performed in this thesis are summarised and discussed.

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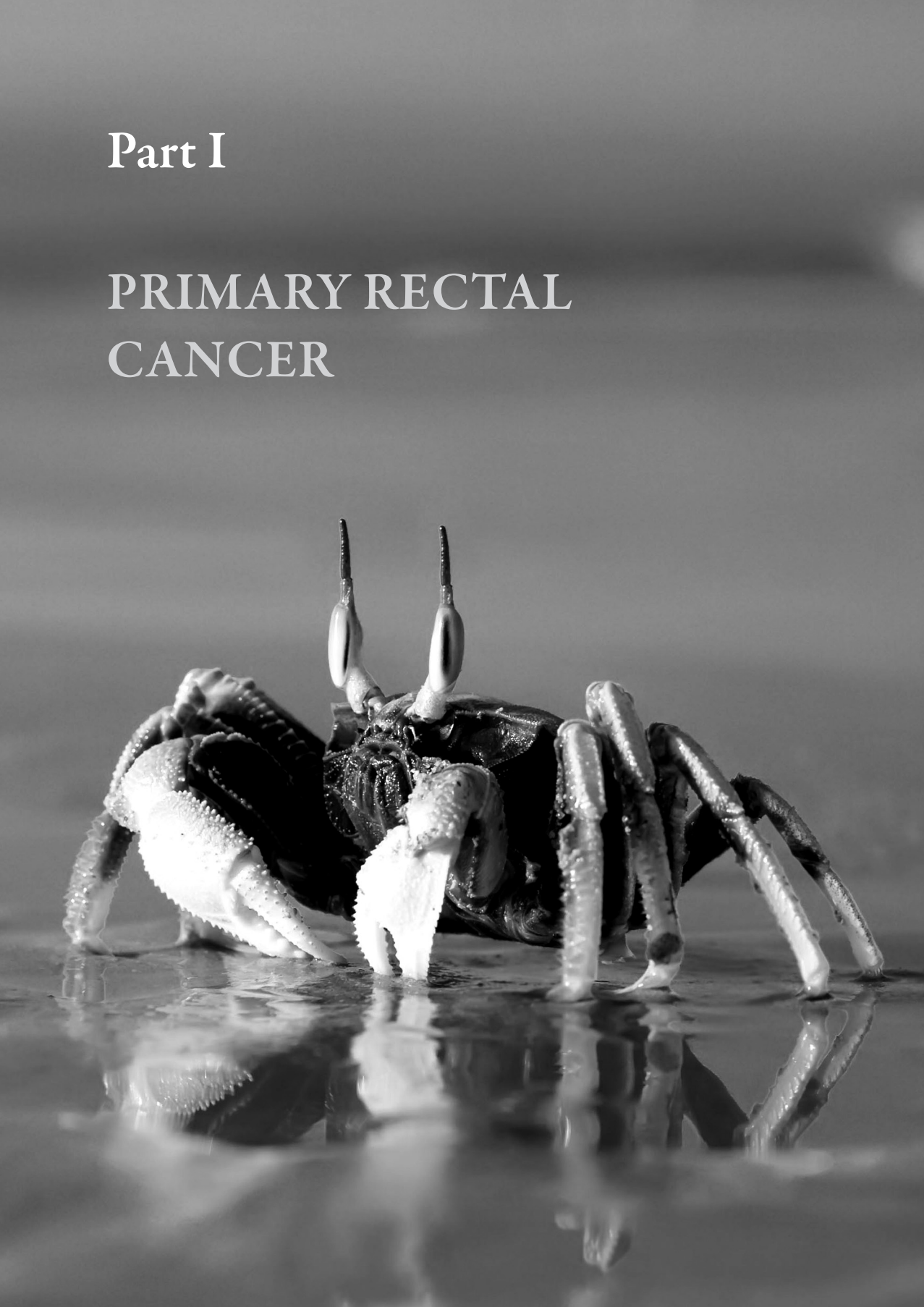
Part I

PRIMARY RECTAL CANCER



Chapter II

Total Mesorectal Excision in rectal cancer: a single institution experience with 210 patients in a low volume center

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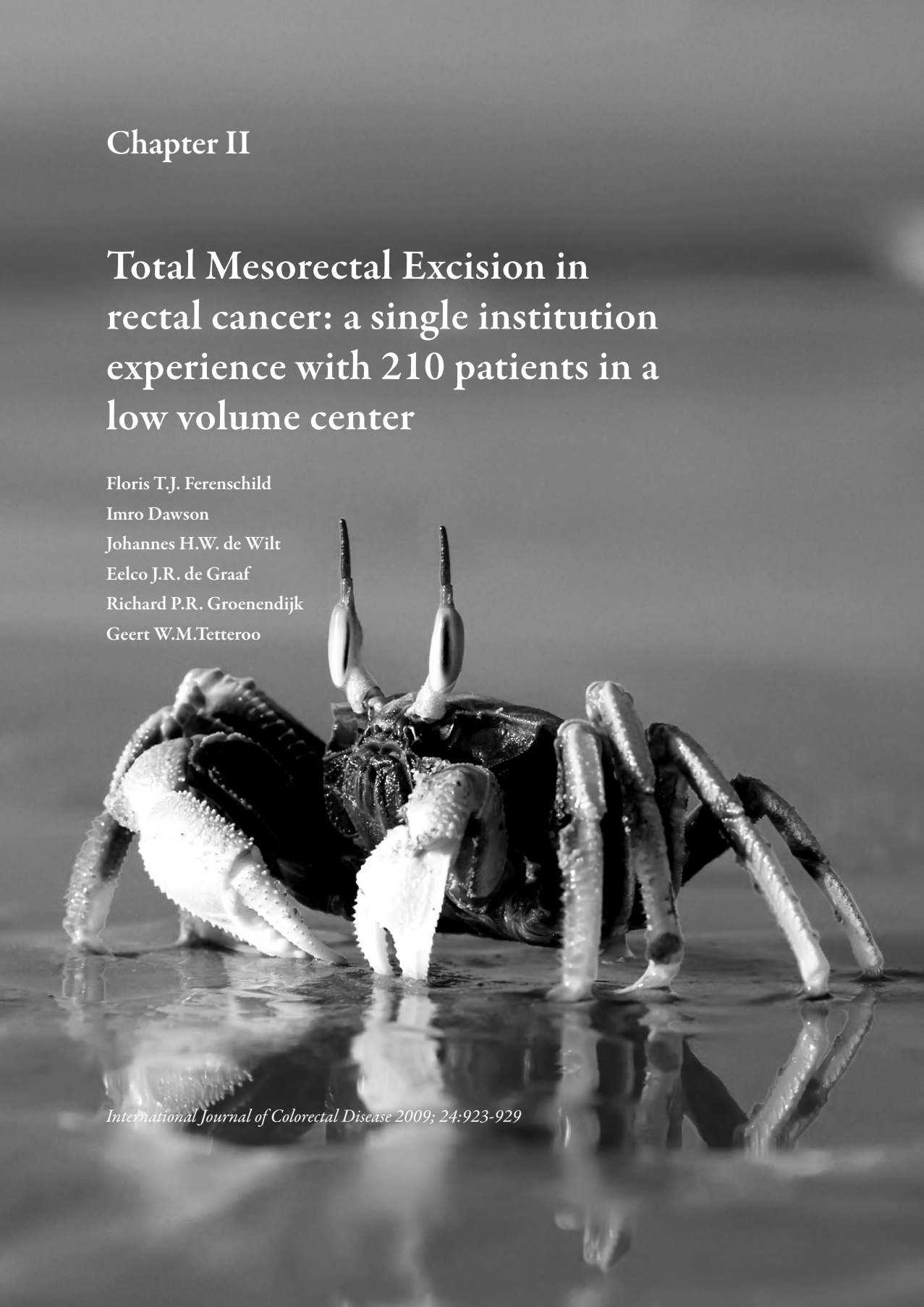

International Journal of Colorectal Disease 2009; 24:923-929

ABSTRACT

Objective

The aim of this study was to review the results and long-term outcome after total mesorectal excision (TME) for adenocarcinoma of the rectum in a community teaching hospital.

Materials and Methods

Between 1996 and 2003, 210 patients with rectal cancer were identified in our prospective database, containing patient characteristics, radiotherapy plans, operation notes, histopathological reports and follow-up details. An evaluation of prognostic factors for local recurrence, distant metastases and overall survival was performed.

Results

The mean age at diagnosis was 69 (range 40 - 91) years. A total of 145 patients were treated by anterior rectal resection; 65 patients had to undergo an abdominoperineal resection (APR). Anastomotic leakage rate was 5%. Postoperative mortality was 3%. After a median follow up of 3.6 years, the local recurrence free rate in patients with microscopically complete resections was 91%. The 5-year overall survival rate was 58%. An increased serum CEA, an APR, positive lymph nodes and an incomplete resection all significantly decreased 5-year overall survival and local recurrence rate. In a multivariate analysis age was the most important prognostic factor for overall survival.

Conclusions

Patients with rectal cancer can safely be treated with TME in a community teaching hospital and leads to a good overall survival and an excellent local control. In patients aged above 80, treatment related mortality is an important competitive risk factor, which obscures the positive effect of modern rectal cancer treatment.

INTRODUCTION

The ultimate goal in the treatment of rectal cancer is to maximise local control and to improve overall long-term survival. Local recurrence is a serious problem in the treatment of rectal cancer, since it causes disabling symptoms and is difficult to treat; besides, it is thought to be an important factor in overall long-term survival. After conventional surgery, a high incidence of local recurrence up to 40% was reported.[1, 2] Heald described a new concept in operative anatomy, the total mesorectal excision (TME) technique in which the entire mesorectum is enveloped and resected.[3-5] The introduction of this surgical technique resulted in a local recurrence rate of less than 10% in specialised centres. It was recognised that involvement of the circumferential margin by tumour cells is predictive for local recurrences.[6] With this new standardised technique, a unique chance was given to study the effect of (neo-) adjuvant therapy. Based on the good results of preoperative radiotherapy in Sweden,[7] the Dutch Colorectal Cancer Group started a randomised multicentre trial. They investigated whether the addition of preoperative radiotherapy increases the benefit of total mesorectal excision.[8-10] The outcome of this study showed a significant reduction in local recurrences with preoperative radiation compared to operation alone in patients with rectal cancer (5.6% vs.10.2% at 6.1 years).[11] Differences were not significant for tumours in the upper third of the rectum. Therefore, from the year 2001 onwards, the Comprehensive Cancer Centre Rotterdam (CCCR), decided to standardise preoperative radiotherapy for each patient with a tumour up to 10 cm from the anal verge. A course of 5 x 5 Gy was given to all these patients. However the TME study was performed in selected patients under optimal conditions and low volume centres still report higher recurrence rates.[12, 13]
This study was designed to assess the outcome after treatment of primary rectal cancer in a community teaching hospital with special emphasis on local recurrence and overall survival.

PATIENTS AND METHODS

Patients and Preoperative Assessment

Between 1996 and 2003, the hospital charts of 210 patients with primary rectal cancer were recorded in our prospective database. Medical records were examined to obtain all necessary data. All patients had histologically proven adenocarcinoma of the rectum, without evidence of distant metastases at that stage. The inferior margin of the tumour was located not further than 15 cm from the anal verge to be defined as a rectal tumour. Prior to

surgery, medical history, physical examination, and routine blood tests were assessed. Work-up consisted of colonoscopy with biopsy, followed by an x-ray of the chest in combination with abdominal ultrasound to exclude distant metastases. In most cases also a CT-scan of the abdomen was made. In selected cases, especially to rule out the suspicion of growth of the tumour into adjacent organs, a MRI of the pelvis was made. Our database consists of hospital notes, radiotherapy plans, operation notes and histopathological reports to obtain the following information: demographics, preoperative diagnostic intervention, tumour staging, radiotherapy technique, surgical details, histopathological details and complications. Follow up was registered using hospital notes, medical letters and in some cases by general practitioner information.

External Beam Radiation Therapy (EBRT)

Starting in 2001, short term EBRT was given to all patients with a tumour up to 10 cm.[8] A radiation dose of 25 Gy in 5 daily fractions was delivered. In patients with a locally advanced tumour 50Gy radiotherapy was given in 25 daily fractions of 2 Gy. Locally advanced tumour growth was defined as infiltration of the tumour in the environment and/or pathologically enlarged lymph nodes near the circumferential margins of the mesorectum on a CT-scan. Afterwards an evaluation of the effect of radiation therapy was done again by CT-scan. When thought feasible an explorative laparotomy was done with the intention to do a resection. EBRT was administered by a three-field technique, using one posterior and two lateral ports.

Surgery

All patients underwent surgery according to the TME principle, as advocated by Heald.[3] In patients with a high rectal cancer, the mesorectum was divided 5cm below the tumour and a partial mesorectal excision was performed. Surgery was planned 3–5 days after short-term radiotherapy. For locally advanced or T4 tumours re-evaluation was done after irradiation. When feasible, the patient was operated on 5-6 weeks later. Prophylactic intravenous antibiotics were given at the induction of anaesthesia in all patients. Three well-trained TME surgeons performed all operations. In case of an anterior resection, a side to end anastomosis was made using the double stapling technique. A diversion stoma was made in case of complicated procedures, a positive leakage test or incomplete doughnuts. Loop ileostomy was the preferred method in these cases. With a positive leakage test, the leakage was localised and sutured when discovered.

Pathology

The pathologists were trained to identify CRM, positive nodes and lateral spread of tumour according to the protocol of Quirke *et al.*[14]

Adjuvant Therapy

Generally patients were not treated with adjuvant chemotherapy, irrespective of nodal status. After 2005 there was a tendency to give adjuvant chemotherapy in well-conditioned patients with positive lymph nodes.

Statistics

Local control and overall survival curves were calculated from the time of TME and were based on the method of Kaplan and Meier. All statistical analyses were executed in SPSS. Univariate comparisons of survival end points were calculated using the log-rank test. Significance was defined as $P<0.05$. For multivariate analysis, Cox-regression was used to evaluate prognostic factors.

RESULTS

Patients

A total of 210 patients were operated with curative intent. One hundred and thirteen (54%) of the patients were male and 97 (46%) were female with a median age of 70 (range 40 to 90 years) The median level of preoperative CEA was 2,8 (range 0,2–142). Patient characteristics and presenting symptoms are shown in Table 1. Fifty-three patients (25%) received preoperative radiotherapy. The majority of these patients (n=42) received short-term radiotherapy. Eleven patients were treated with 50 Gy external beam radiation therapy because of preoperatively defined locally advanced tumours. Since 2001, due to changing policy in preoperative radiotherapy, a growing amount of patients received EBRT. Of the 40 patients (with a tumour below 10 cm) included in this study from 2001, 36 received short-term radiotherapy.

Table 1. Preoperative characteristics

	Total	%
– Symptoms – Bloodloss	153	73
– Mucus	38	18
– Tenesmus	47	22
– Diarrhea	44	21
– Constipation	35	17
Distance of tumour from anal verge		
– ≤ 5 cm	59	28
– 5-10 cm	87	41
– 10-15 cm	64	31

Surgical results

A LAR was done in 145 patients (69%) and an APR in 65 patients (31%). Of the 145 patients with a LAR, a diverting stoma was made in 26 patients (18%), which was closed in 18 patients. Five patients underwent a local excision of the tumour (Transanal Endoscopic Microsurgery) as initial treatment before TME was performed. Thirteen patients (6%) proved to have hepatic metastases during surgery. In 10 of these patients hepatic metastases were not diagnosed by ultra-sonography or computer-tomography during the preoperative workup, but discovered during surgery. The median duration of surgery was 110 min (range 45–210 min) and the median operative blood loss was 600 ml (range 50–4000ml). The median bloodloss was significantly lower in LAR compared to APR, 400 vs. 1000ml respectively ($P<0.001$).

Complications are depicted in Table 2. Postoperative mortality was 3%. Twelve patients underwent a relaparotomy because of abdominal symptoms. During operation an anastomotic leakage was found in 8 patients; 3 patients were treated with a loop ileostomy and in 5 patients a colostomy was performed after removal of the anastomosis. A re-anastomosis was performed, after 6 and 9 months, in 2 of these patients. Perineal infections were present in 12 patients (18%) after an APR and treated conservatively. All these 12 patients had been treated with preoperative radiotherapy.

Table 2. Postoperative complications and reinterventions

	Total	%
Minor complications		
– Urinary infection	16	8
– Bladder retention	3	1
– Wound infection abdominal	17	8
Major complications		
– Wound infection perineal	12	18*
– Anastomotic leakage	8	5
– Intra abdominal fluid collection without leak	3	1
Reintervention		
– Abscess drainage	3	1
– Relaparotomy	12	6
– Permanent colostomy	7	3
– Permanent ileostomy	2	1
– Temporary ileostomy	3	1

* 18% of 65 abdomino-perineal resections

Pathology

In 199 patients (95%) a microscopic radical resection was performed (R0). In 11 (5%) patients the resection was microscopically irradical (R1) including 4 patients with a pT4 tumour. The postoperative tumour stage is given in Table 3. Two patients had no residual disease after TME. However, these patients had undergone a TEM before TME. TME was performed because the local excision was irradical on pathology. One of these patients had a T1 and one a T2 tumour at the initial pathology. Three patients had a carcinoma in situ. A T1 tumour was seen in 23 patients, a T2 in 63, a T3 in 106 and a T4 tumour in 15 patients. One-hundred-twenty-and-eight patients were node negative, 45 had metastasis in 1 to 3 regional lymph nodes (N1), and 37 had metastasis in 4 or more regional lymph nodes (N2).

Follow-up

The median follow up was 3.6 years (range 0.4–8.4 years). In total, 21 patients developed a local recurrence, most of them (83%) discovered during the first two years of follow-up. Fourteen of 199 patients with a complete resection developed a local recurrence (7%). Seven of 11 patients with an incomplete resection developed a local recurrence (64%). A complete

resection versus an incomplete resection was of significant importance on local control (P<0.001, Figure 1). The actuarial overall 3- and 5-year local control rates were 92% and 88%, respectively. Nineteen of the local recurrences were found in tumours primary located in the lowest 2/3 of the rectum. A high level of CEA (>5), an APR, positive lymph nodes and an incomplete resection negatively influenced the local recurrence rate significantly. There was no significant difference in age, gender and preoperative radiotherapy regarding local recurrence (See Table 4). The significant prognostic factors were entered in a multivariate analysis (See Table 5). The most important factor was completeness of the resection. CEA in this multivariate analysis was not of significant importance anymore.

Table 3. Pathology

	Total	**%**
Residual tumour		
– R0	199	95
– R1	11	58
AJCC pTNM stage		
– CIS	3	1
– I	67	33
– II	53	25
– III	74	35
– IV	13	6

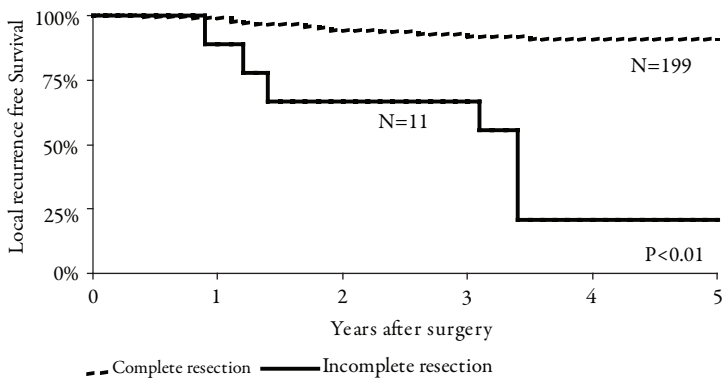

Figure 1. Local recurrence according to a complete versus an incomplete resection (P<0.01)

Distant metastases

Forty-five patients developed distant metastases, of which 40% was discovered during the first year of follow-up. Thirty-four patients developed hepatic metastases, 18 lung metastases and 5 bone metastases. Lung and/or bone metastases were in 38% synchronic with hepatic metastases.

Table 4. Univariate analysis on 5-year Local Free Recurrence (LR) and Overall Survival (OS)

	N	LFR	OS
Radiotherapy yes	53	82%	67%
Radiotherapy no	157	93% P=0.32	55% P=0.17
LAR	145	93%	61%
APR	65	63% P<0.01	50% P=0.02
CEA <5	151	90%	65%
CEA >5	59	65% P=0.05	48% P=0.04
Male	114	90%	57%
Female	96	85% P=0.55	55% P=0.60
Age < 80	173	85%	64%
Age > 80	37	75% P=0.36	30% P<0.01
Node negative	82	93%	65%
Node positive	128	79% P<0.01	34% P=0.01
Complete	199	92%	62%
Incomplete	11	20% P<0.01	17% P=0.05
Tumour height			
– 0-5 cm	59	82%	52%
– 5-10 cm	87	85%	56%
– 10-15 cm	64	95% P=0.11	65% P=0.23

Overall survival

The actuarial overall 3- and 5-year survival rates were 72% and 58%, respectively. Five-year overall survival demonstrated a statistically significant difference between the pTNM stages, type of resection, lymph nodes, CEA levels, age and completeness of the resection (See table 4). Patient's gender and preoperative radiotherapy were not of statistic significance. Increased age, advanced T-stage, positive lymph node status, increased CEA and completeness of the

resection were independent risk factors for overall survival in the multivariate analysis (See Table 5). In a Cox regression model age was the most important factor.

Table 5. Results of the Multivariate Cox regression analysis for Local Recurrence and Overall Survival

	Local recurrence			Overall Survival		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Type of resection						
– APR	0.20	0.1–0.5	0.000	0.74	0.4–1.2	0.284
Lymph Nodes						
– positive	3.63	1.5–8.9	0.005	1.99	1.2–3.3	0.007
Completeness						
– incomplete	0.00	0.00–100+	0.000	1.01	0.4–2.5	0.981
Level of CEA						
– >5	2.05	0.8–4.9	0.105	1.83	1.1–3.0	0.019
Age						
– > 80	-	-	-	2.76	1.5–5.0	0.000

HR = Hazard Ratio, CI = Confidence Interval

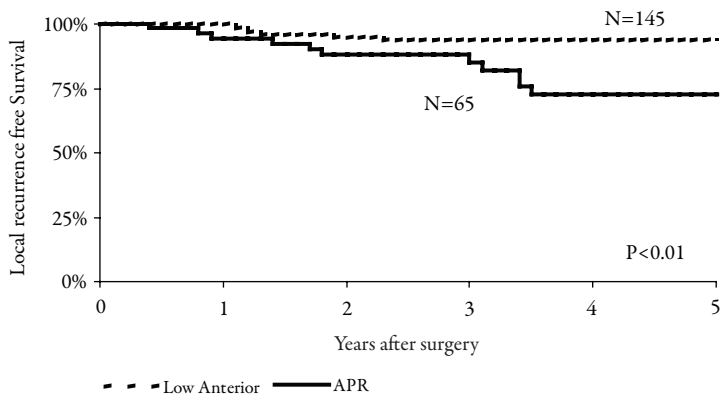

Figure 2. Local recurrence according to type of resection (P<0.01)

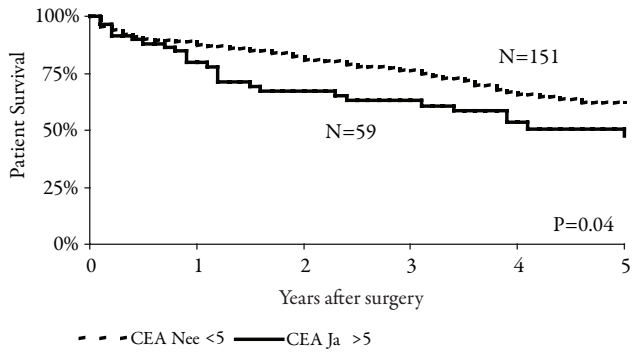

Figure 3. Overall survival according to CEA (P=0.04)

DISCUSSION

Since the introduction of TME as the standard operative technique, the rate of local recurrence after resection of rectal carcinomas spectacularly decreased from 37% in the early 1980s after conventional surgery to <10% at present.[5] TME provides sharp meticulous dissection to keep the visceral layer of the pelvic fascia intact and this is important to avoid breach in the mesorectum, which is now an important cause for local recurrence.[15-18] Neoadjuvant radiotherapy demonstrated to improve the TME results with a decreased local recurrence rate, but without an impact on survival.[11] In the present study, this impact of radiotherapy on local recurrence was not demonstrated, but the number of patients is small. To define the value of TME in a general hospital population, we decided to include all patients of all ages with a potentially resectable rectal carcinoma. Evaluation of the results, therefore, includes patients previously treated by local transanal resection and patients with postoperatively proven T4 tumours and elderly patients or patients who are not fit enough to enter clinical trials. Bearing this in mind, our results are encouraging. The local recurrence rate was 13% in the whole group at 5 years, including patients with and without preoperative radiotherapy. When considering the microscopically complete resected tumours, the recurrence rate was 9%. R1 resections showed a 21% local recurrence rate, which is similar to what has been described in the literature.[17, 19] Adequate surgery plays a key role in preventing local recurrences.[20, 21] Quirke showed a linear correlation between the development of a local recurrence and an inadequate resection with positive circumferential margins.[14, 22] It is, therefore, of crucial importance to optimise preoperative work-up

to identify those patients who will need preoperative treatment in order to downsise and downstage the tumour. In our study, four patients with a local recurrence proved to have T4 tumours, which were not preoperatively correctly diagnosed and, therefore, did not undergo preoperative chemoradiotherapy. New imaging techniques using MRI to stage these tumours accurately will improve this in the future.[23–2]

The use of sharp perimesorectal dissection and the practice of "close shave" anterior resection has not only led to fewer recurrences but also increased the sphincter saving rate. Heald *et al*.[28] reported that APR was required in 23% of patients with tumours in the lower rectum. In the present study, an APR was performed in 30% of the patients. Since there is a significantly worse outcome on both local control and overall survival and the high rate of perineal complications in patients with an APR pretreated with preoperative radiotherapy, it is favourable to have fewer APR .[8]

Anastomotic leakage is a major complication associated with TME. As the risk of leakage depends on the level of the anastomosis, the incidence of leakage is high following TME in low rectal tumours (7–9%).[29] A total of eight patients (5%) in our study developed an anastomotic leakage. Six of them (75%) were located in patients with very low anastomoses (below 5 cm), which increases the risk for leakage. All these patients had been treated with preoperative radiotherapy, which is known to increase the risk for leakage.[30-32]

The prognosis in our patient series is similar to other reported data, showing an overall survival of more than 60% after 5 years.[33, 34] To identify prognostic factors, a univariate analysis was included. As expected, TNM classification was of significant importance for prognosis.[17] As reported by many others,[8, 11, 13, 35-39] completeness of the resection was also a significant prognostic factor. New treatment protocols (neoadjuvant chemoradiation) and meticulous preoperative work-up will possibly lead to more complete resections in the future. Furthermore, in contrast with previous reports,[40] high levels of CEA levels were of significant importance on both overall survival and local recurrence in the present study.[41-44] Age >80 was also an important factor for a decreased overall survival in the present study. After 5 years, the overall survival of patients above 80 was 30% compared to 64% in patients under the age of 80. The incidence of comorbidity, which renders the patient vulnerable to postoperative complications, is also highest after this age.[45, 46] After major resectional treatment, elderly patients with rectal cancer have an increased 30-day and 6-month mortality compared with younger patients. Treatment-related mortality is an important competitive risk factor, which obscures the positive effect of modern rectal cancer treatment in those aged 75 years and above.[37, 46-48]

CONCLUSION

TME is a feasible technique with an acceptable rate of postoperative morbidity and low mortality also in a community hospital. Patients with positive lymph nodes, an incomplete resection, aged above 80, and/or a high level of CEA have a poor prognosis. Meticulous preoperative work-up is of great importance to decrease incomplete resections and improve results in future patients.

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Chapter III

Preoperative radiotherapy has no value in patients with T2, 3 N0 adenocarcinomas of the rectum

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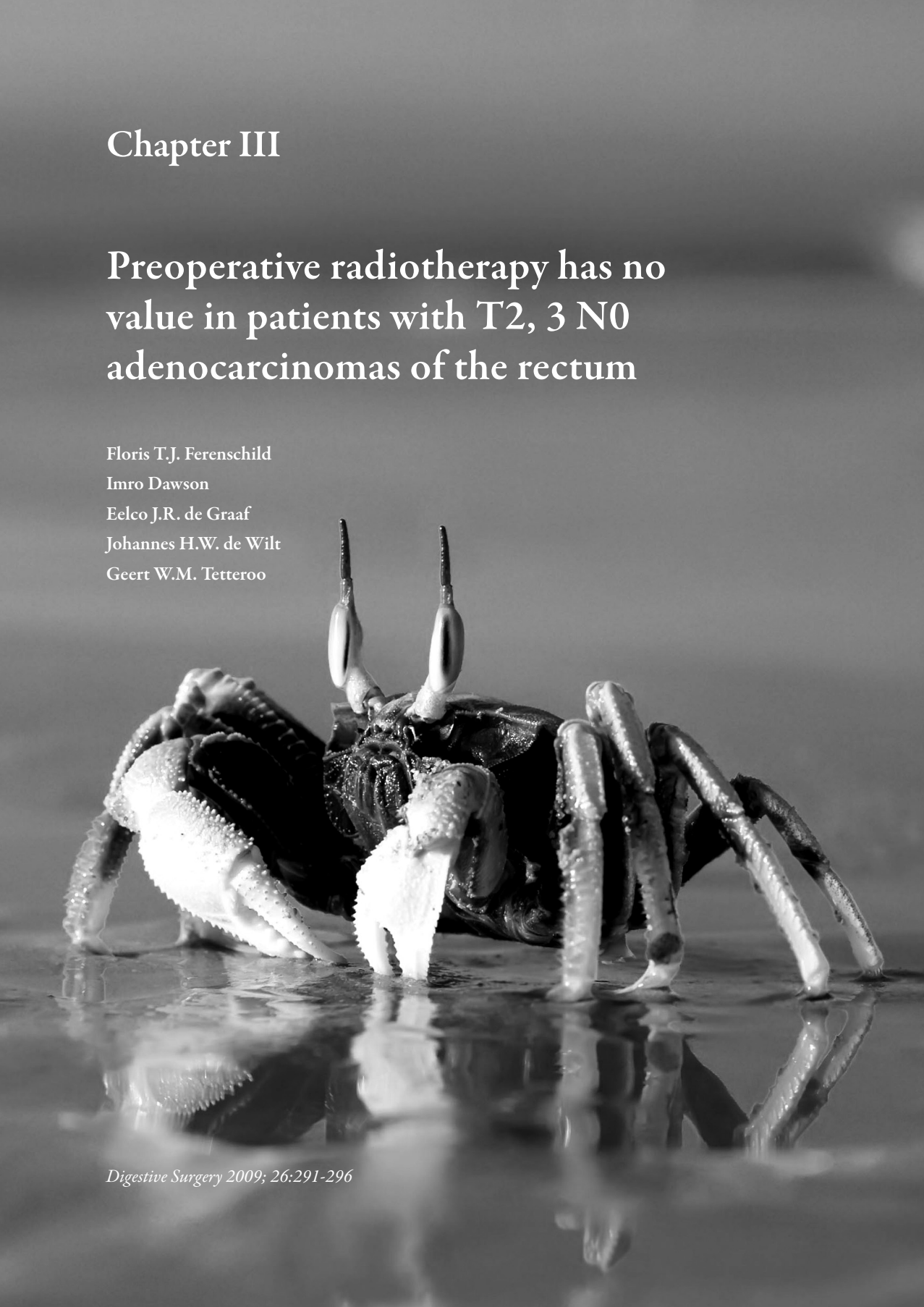

Digestive Surgery 2009; 26:291-296

ABSTRACT

Background

Treatment of rectal cancer with *preop*erative radiotherapy followed by TME is nowadays the standard treatment. It reduces local recurrences and improves overall survival. However, in patients with T2, 3 N0 rectal cancer, the role of *preop*erative radiotherapy remains controversial. The aim of this study was to review the benefit of radiotherapy in T2 and T3, N0 rectal cancer patients.

Methods

Between 1996 and 2003, 103 patients with T2, 3 N0 rectal cancer, were identified in our prospective database. This study evaluated time to local recurrence, distant metastases and overall survival.

Results

The median age at the time of diagnosis was 70 (range 40–91) years. Median follow up was 4.3 years. The 5-year local control rate was 94%. The five-year overall survival was 65%. The 5-year disease free survival rate was 82%. Preoperative radiotherapy did not show any statistic differences. Abdominal perineal resection and T3 tumours negatively influenced overall survival (P=0.02). Advanced age was of significant importance on overall survival.

Conclusions

Preoperative radiotherapy does not seem to be of significant importance in patients with T2, 3 N0 rectal cancer regarding local recurrence and survival. Since preoperative radiotherapy is associated with short- and long term morbidity, patients with T2, 3 N0 tumours should be identified and treated with surgery alone.

INTRODUCTION

The ultimate goal in the treatment of rectal cancer is to maximise local control and to improve overall long-term survival. Local recurrence is a serious complication in the treatment of rectal cancer, since it causes disabling symptoms and is difficult to cure.[1, 2] After conventional surgery a high incidence of local recurrence up to 40% was previously reported.[3, 4] Heald described a new concept in operative anatomy, the Total Mesorectal Excision (TME) technique in which the entire mesorectum is enveloped and resected.[5, 6] The Dutch Colorectal Cancer Group started a randomised multicentre trial and showed a superior local control in patients treated with *preop*erative radiotherapy followed by TME surgery.[7] Long term results showed a consistent significant difference in local control, however this difference was not present in a subgroup analysis for TNM stage I and II.[8] Since several years, preoperative radiotherapy has become the standard of care for all rectal cancers in many medical centres, but selection criteria are still controversial.[9] Although 30% of T2 and T3, N0 patients die as a result of disseminated disease, neo-adjuvant radiotherapy seems to add little to local control or survival.[10] This study was intended to assess the outcome of a historical group of T2, 3 N0 patients treated with a TME alone and compare them with a T2, 3 N0 group who was treated with preoperative radiotherapy followed by TME. Time to local recurrence, time to distant metastases and overall survival between the different treatment groups was compared and predictors of recurrence were identified to assess the influence of clinical variables on outcome.

PATIENTS AND METHODS

Patients and Preoperative Assessment

Between 1996 and 2003, the hospital charts of 210 patients with primary rectal cancer were recorded in our prospective database. Of these, 103 patients had a pT2 or a pT3 tumour with negative lymph nodes. In case of preoperative radiotherapy, a radiation dose of 25 Gy in 5 daily fractions was delivered. Radiotherapy was administered by a three-field technique, using one posterior and two lateral ports. All patients underwent complete curative resection and were observed prospectively. Follow-up, primarily obtained from the institution database, was updated by clinical chart review, physician records, patient's correspondence and telephone interviews. Clinical factors including age, gender, node status, CEA levels, radiotherapy, type of resection and completeness were correlated with time to local recurrence, distant metastases, disease free survival and overall survival.

Surgery

All patients underwent surgery according to the Total Mesorectal Excision principle, as described by Heald.[5] Surgery was planned 5–7 days after short-term radiotherapy and prophylactic intravenous antibiotics were given at the induction of anaesthesia in all patients. Three well-trained TME surgeons performed all operations. In case of an anterior resection, a side to end anastomosis was made using the double stapling technique. A diversion stoma was made in case of complicated procedures, a positive leakage test or incomplete doughnuts. Loop ileostomy was the preferred method in these cases. In case of a positive leakage test, the leakage was localised and sutured when discovered.

Pathology

The pathologists were trained to identify Cirumferential Resection Margin (CRM), positive nodes and lateral spread of tumour according to the protocol of Quirke *et al*.[11] Complete resection was defined as absence of residual disease (<1mm) after surgical resection.

Follow-up

Clinical evaluation every 3 months during the first year after surgery and yearly thereafter for at least two more years was mandatory and included yearly liver imaging and endoscopy. Physical examination was carried out and CEA levels were measured. If the patients had complaints and/or the CEA level was risen a CT-scan or MRI was made, followed by pathology if there was suspicion of recurrence. A local recurrence was defined as evidence of a tumour within the lesser pelvis or the perineal wound. Distant recurrence was defined as evidence of a tumour in any other area.

Statistics

Local control and overall survival curves were calculated from the time of TME and were based on the method of Kaplan and Meier. All statistical analyses were executed in SPSS. Univariate comparisons of survival end points were calculated using the log-rank test. Significance was defined as $P<0.05$. Multivariate analysis was done by Cox regression with significant independent univariate parameters

RESULTS

Patient and tumour characteristics

One hundred and three patients were included with a mean age of 70 (range: 40–91 years). Patient and tumour characteristics are depicted in table 1. Preoperative serum CEA levels were recorded in 91 of 103 patients (90%) with median serum preoperative CEA of 2, 6 (range: 0,2–133 ng/ml). All patients were node negative (N0) on pathologic review. Median number of lymph nodes removed at surgery was 6 (range: 0–24). All but three resections were complete, with microscopically negative circumferential and distal margins. Median distance from the circumferential- and distal margin was measured on original pathologic examination and recorded for 79 and 70 of 103 patients, respectively. Median distance from the circumferential margin was 10 mm (range 1–45 mm) and from the distal margin 25 mm (range 4–120 mm). Patients with pT2, 3 N0 lesions did not receive additional adjuvant therapy.

Table 1. Patient and Tumour Characteristics

	Rtx no*	Rtx yes	Total
Sex			
– male	42 (58%)	20 (65%)	62 (60%)
– female	30 (42%)	11 (35%)	41(40%)
AJCC T Stage			
– pT2	34 (47%)	13 (42%)	47 (46%)
– pT3	38 (53%)	18 (58%)	56 (54%)
Type of resection			
– Low Anterior Resection	48 (66%)	22 (71%)	70 (69%)
– Abdomino perineal resection	24 (34%)	9 (29%)	33 (31%)
Grade			
– well differentiated	5 (7%)	2 (6%)	7 (7%)
– moderately differentiated	51 (71%)	18 (58%)	69 (67%)
– poor differentiated	16 (22%)	11 (36%)	27 (26%)

* Rtx = radiotherapy

Follow-up

Median follow-up of all patients was 4.3 years (range 0.4–8.4 years). During follow-up 10 patients died because of ongoing or recurrent disease. Five patients died postoperatively (4.9%).

Local Recurrence

Local recurrences were demonstrated during follow-up in 4 patients. Three recurrences occurred in the patients who had an incomplete resection of the tumour. The actuarial overall 3- and 5-year local control rates were 97% and 94%, respectively. An incomplete resection significantly influenced outcome. There was a trend to a higher risk on local recurrences in patients with an elevated preoperative CEA (p=0.07). In the univariate analysis preoperative radiotherapy, age, gender, ASA classification, bloodloss during operation preoperative pain were no significant prognostic factors for the risk of local recurrence (Table 2 and Figure 1).

Distant metastases

Thirteen patients developed distant metastases during follow-up. The actuarial overall 3- and 5-year distant metastases free rates were 93% and 87%, respectively. The actuarial disease free survival rates were 86% and 80%, respectively. For T2 tumours, the 5-year disease free survival was 87% compared with 75% for patients with a T3 tumour (P=0.34). The mean time to develop distant metastases in pT2 tumours was 3,5 years. In pT3 tumours this was 1,2 years. Twelve patients developed hepatic metastases, 5 patients' lung metastases and 1 patient bone metastases. Lung and/or bone metastases were in 38% synchronous with hepatic metastases. There were no statistical significant differences for the development of distant metastases.

Overall survival

The actuarial overall 3- and 5-year survival rates were 75% and 65%, respectively. Five-year overall survival demonstrated a statistically significant difference between the pTNM stages (Figure 2), type of resection (Figure 3), completeness of the resection and age (Table 2.). Advanced age (>80 years) was also an independent negative factor in a multivariate analysis (Figure 4).

Table 2. Survival and Local Recurrence

Outcome	Number of patients	%	*P* value	95% CI
5-year local free recurrence				
All patients	103	94		0.88–0.99
– pT2	47	96		0.87–1.00
– pT3	56	91	P=0.34	0.83–1.00
– LAR	70	94		0.89–1.00
– APR	33	88	P=0.53	0.75–1.00
– CEA <5	76	95		0.92–1.00
– CEA >5	27	84	P=0.07	0.66–0.93
– Age <80	81	95		0.87–0.99
– Age >80	22	85	P=0.76	0.71–0.99
– Rtx yes	31	95		0.87–1.00
– Rtx no	72	93	P=0.69	0.85–1.00
– Complete resection	100	96		0.89–1.00
– Incomplete resection	3	0	P=0.02	0.00–1.00
5-year overall survival				
All patients	103	65		0.55–0.74
– pT2	47	77		0.62–0.89
– pT3	56	55	P=0.03	0.42–0.69
– LAR	70	75		0.58–0.82
– APR	33	52	P=0.02	0.35–0.70
– CEA < 5	75	70		0.60–0.81
– CEA > 5	28	54	P=0.14	0.16–0.51
– Age < 80	81	72		0.62–0.81
– Age > 80	22	34	P=0.00	0.16–0.51
– Rtx yes	31	73		0.54–0.87
– Rtx no	72	63	P=0.65	0.51–0.74
– Complete resection	100	77		0.66–0.82
– Incomplete resection	3	0	P=0.04	0.13–1.00

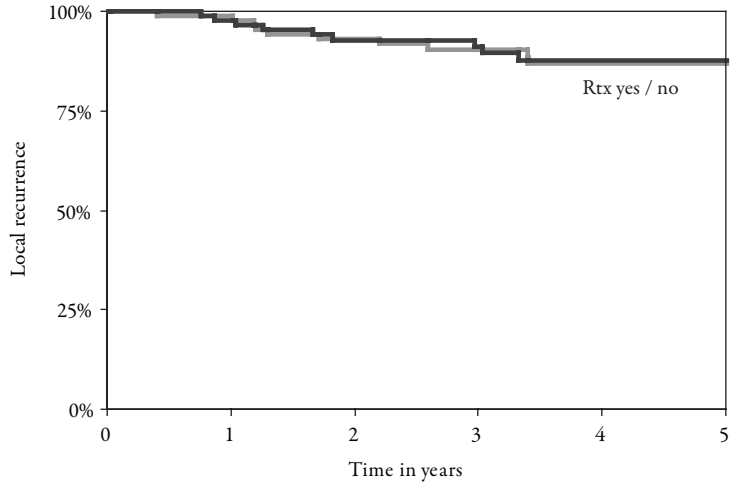

Figure 1. Local control according to pre-operative radiotherapy

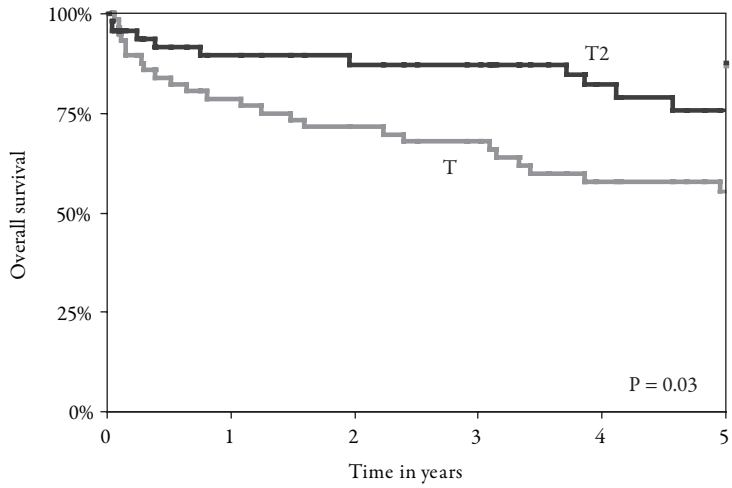

Figure 2. Overall survival according to pTNM stages

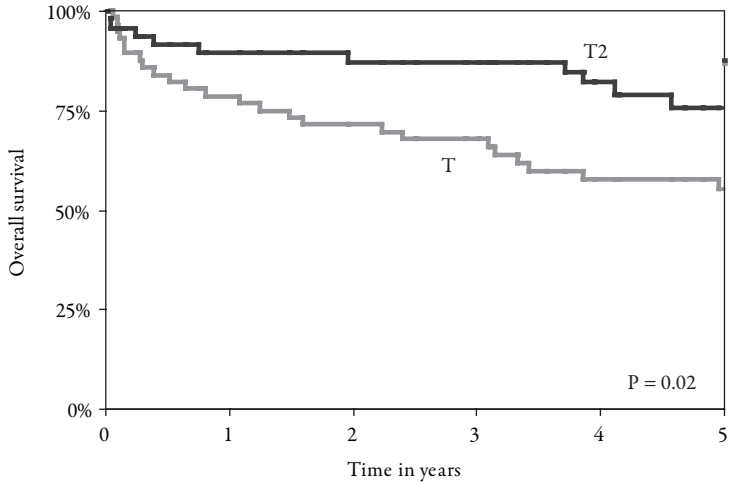

Figure 3. Overall survival according to type of resection

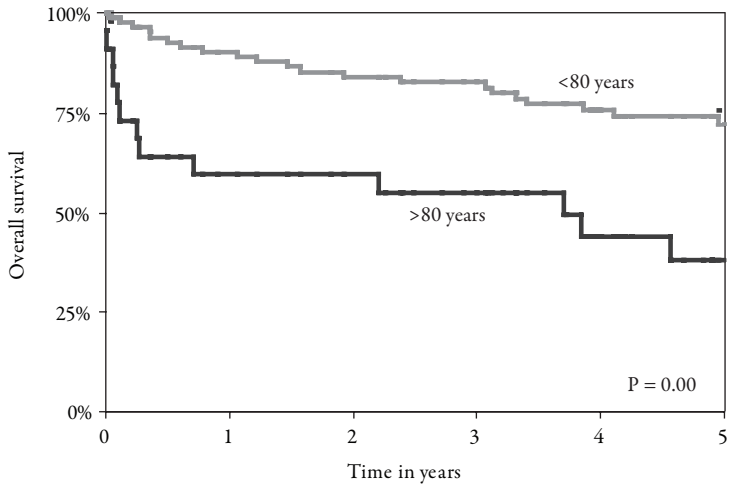

Figure 4. Overall survival according to age

DISCUSSION

Since the introduction of TME as the standard operative technique, the rate of local recurrence after resection of rectal carcinomas decreased spectacular from 30–40% in the early 80's after conventional surgery to less than 10% at present.[12, 13] In the present study 5-year local recurrence rate for T2, 3 N0 patients was 6%, without a difference between patients who did and did not underwent preoperative radiotherapy. Final results of the Dutch TME trial has demonstrated that five-year local recurrence rate of patients undergoing a macroscopically complete local resection was 5.6% in case of preoperative radiotherapy compared with 10.9% in patients undergoing TME alone (P<0.001).[8, 14] This has resulted in the administration of a short course of radiotherapy in nearly all patients with rectal cancer in the Netherlands.[15] However, preoperative radiotherapy has short- and long-term negative side effects such as increased leakage,[16] wound infections[7] and faecal incontinence.[8] Surgical nerve damage may play a major role in the development of faecal and urinary incontinence, but there is a significant additional effect of radiotherapy and faecal incontinence can worsen over time in case of radiotherapy.[17] Sexual dysfunction; erectile dysfunction, ejaculatory problems, dyspareunia and vaginal dryness, occurs frequently after rectal cancer treatment and is caused by surgical (nerve) damage with again an additional effect of preoperative radiotherapy.[18] Moreover, a recent update of the Dutch TME trial demonstrated that there is no benefit of radiotherapy on local recurrences in T2, 3 NO patients, similar as has been demonstrated in the present study.[8] Kapiteijn *et al*.[7] reported that *preop*erative radiotherapy only seems to be beneficial in patients with positive lymph nodes (*i.e.*, TNM stage III).[8] Thus, *preop*erative radiotherapy might not be indicated in early tumours of the rectum and needs to be reconsidered as standard treatment for all rectal cancer patients.

In the present study, preoperative increased serum CEA levels showed a trend for an increased local recurrence rate (p=0.07). Nissan *et al*.[10] found that serum CEA levels are a significant prognostic factor for both local control and overall survival. A significant prognostic factor for increased local recurrences and reduced survival in this study was an incomplete resection, which has already been recognised as an important factor in the literature.[8, 19-21] Furthermore, as previously reported by others[8, 10, 22-24] a significant reduced survival was identified in patients who underwent an APR.

Advanced age (>80 years) was the most important factor for a decreased overall survival in the present study. In a multivariate analysis age was the only significant independent factor. After 5 years the overall survival of patients above 80 years was 34% compared to 72% in patients under the age of 80. More importantly, 45% (10 patients) of the elderly patients died during

the first 6 months after surgery. The incidence of co morbidity, which renders the patient vulnerable to postoperative complications, is also highest after this age.[25, 26] Treatment-related mortality is an important competitive risk factor, which obscures the positive effect of modern rectal-cancer treatment in those aged 75 years and above.[26-29] Thus, surgery might not be the best option for all elderly patients with rectal cancer and alternative treatment option should be considered in the elderly frail patients such as radiotherapy only, or radiotherapy in combination with local excision, to minimise morbidity.

As we obtained the good results for T2, 3 N0 patients, it is of great importance to identify this specific group of patients before treatment is started. Meticulous *preop*erative work-up is therefore important to identify patients with lymph node involvement preoperatively, but neither clinical assessment nor imaging tools, including MRI, CT, PET an ERUS have the ability to accurately identify lymph node involvement. Recent studies demonstrated that the accuracy of preoperative imaging (including ERUS/MRI) for staging T3N0 rectal cancer was limited because 22% of patients will have undetected mesorectal lymph node involvement. [30, 31] Further studies are needed to improve the accuracy of imaging modalities to establish treatment options that will provide the best outcome for this group of patients.

CONCLUSION

Patients with limited (T2-3) rectal tumours without lymph node metastases have an excellent local control and overall survival. Preoperative radiotherapy had no demonstrable effect on local recurrence or survival, therefore patients with early, limited rectal cancers, should be treated with surgery alone. Improvements in imaging modalities are necessary to identify patients without lymph node involvement who should be refrained from preoperative radiotherapy treatment.

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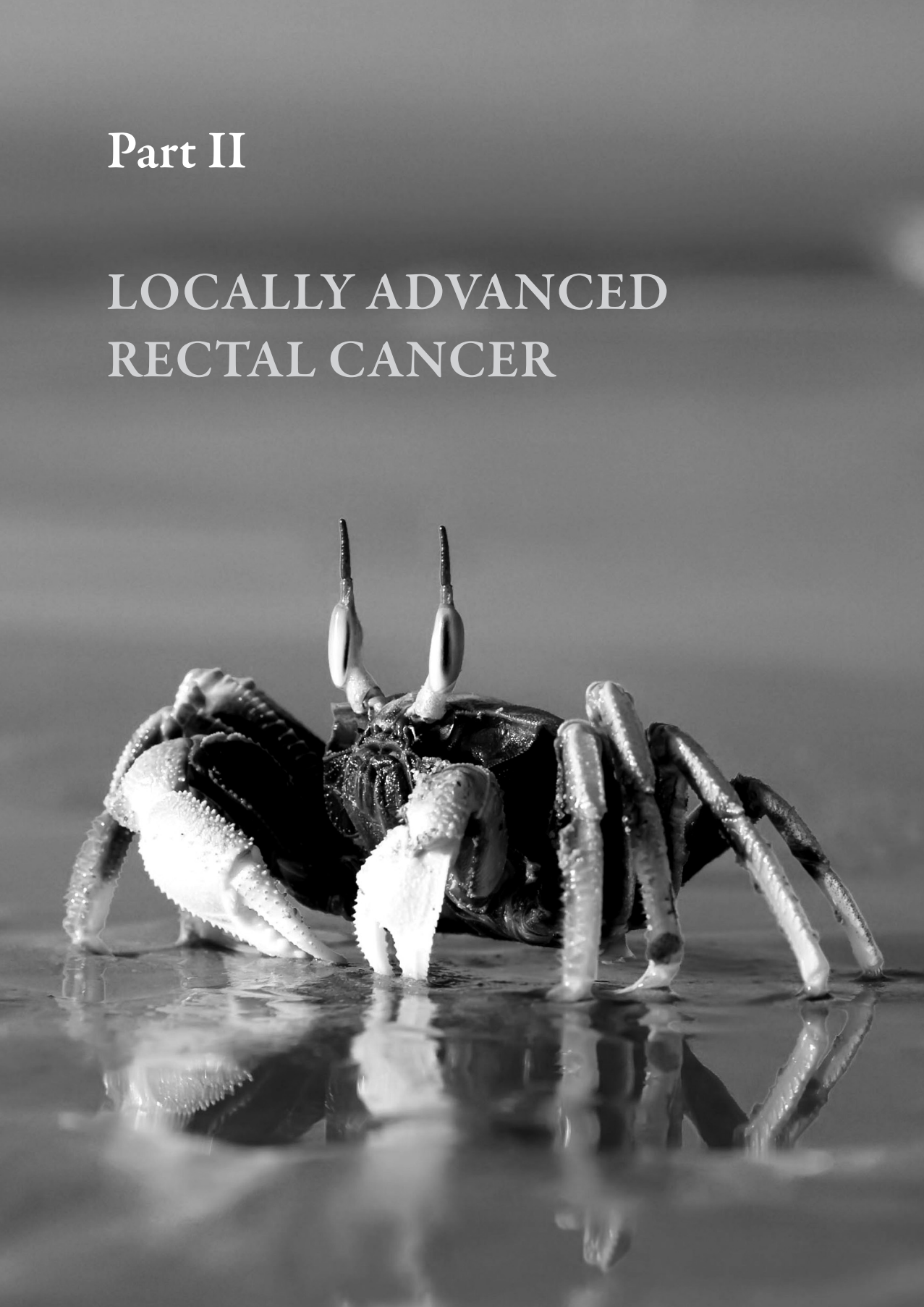
Part II

LOCALLY ADVANCED RECTAL CANCER



Chapter IV

Value of intraoperative radiotherapy in locally advanced rectal cancer

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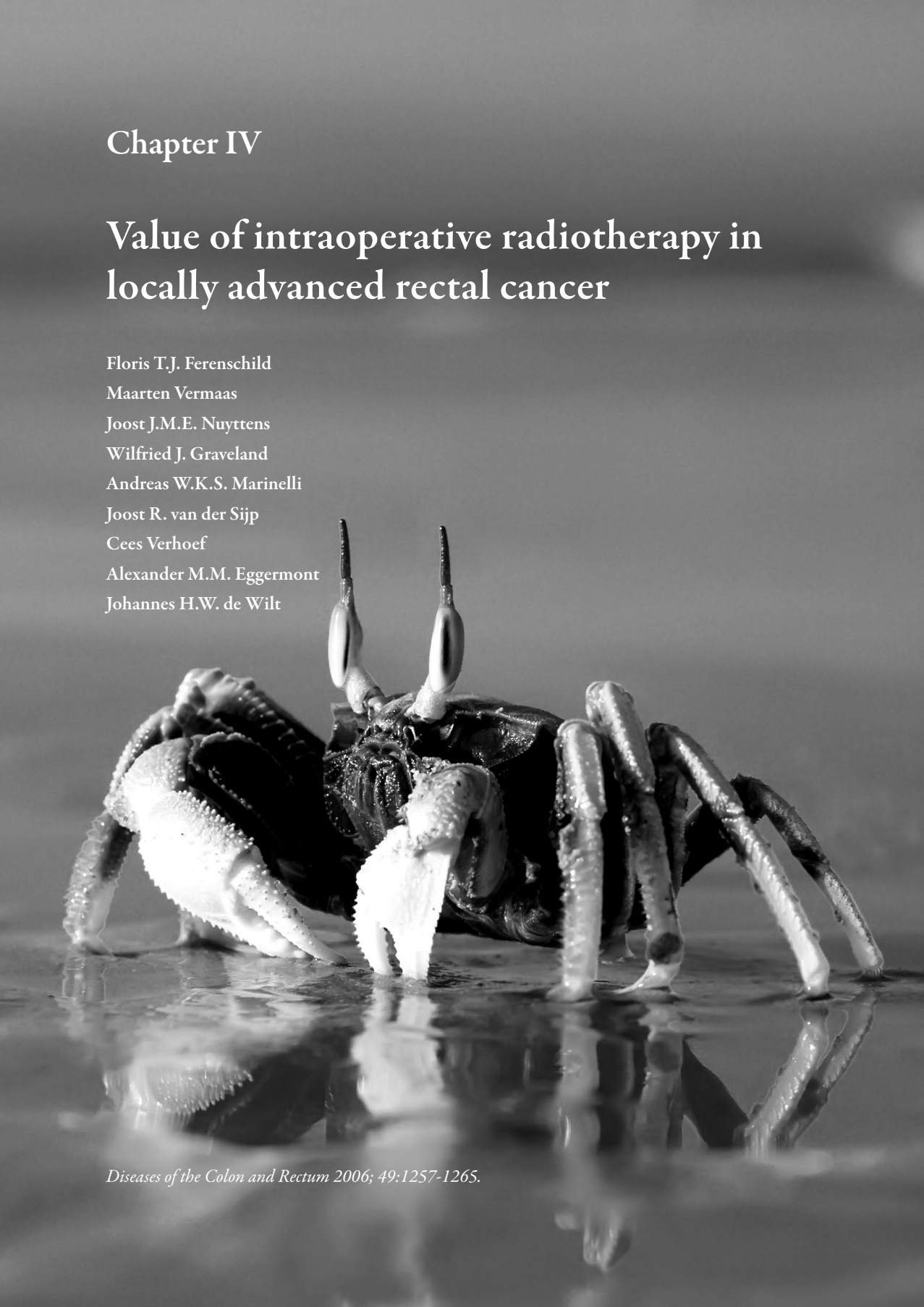

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ABSTRACT

Purpose

The study was designed to analyse the results of a multimodality treatment, using preoperative radiotherapy, followed by surgery and intraoperative radiotherapy in patients with primary locally advanced rectal cancer.

Methods

Between 1987 and 2002, 123 patients with initial unresectable and locally advanced rectal cancer were identified in our prospective database, containing patient characteristics, radiotherapy plans, operation notes, histopathological reports and follow-up details. An evaluation of prognostic factors for local recurrence, distant metastases and overall survival was performed.

Results

All patients were treated preoperatively with a median dose of 50 Gy radiotherapy. Surgery was performed 6-10 weeks after radiotherapy. Twenty-seven patients were treated with IORT because margins were incomplete or equal or less than 2 mm. Postoperative mortality was 2 percent. The median follow up of all patients was 25.1 months. The overall 5-year local control was 65 percent and the overall 5- year survival was 50 percent. Positive lymph nodes and incomplete resections negatively influenced local control and overall survival. Intraoperative radiotherapy improved 5-year local control (58 percent *vs.* 0 percent, p=0.016) and overall survival (38 percent *vs.* 0 percent, p=0.026) for patients with R1/2 resections.

Conclusions

The presented multimodality treatment is feasible with an acceptable mortality and a 5-year overall survival of 50 percent. Addition of intraoperative radiotherapy for patients with a narrow or microscopic incomplete resection seems to overrule the unfavourable prognostic histologic finding.

INTRODUCTION

Colorectal cancer is a major problem in the western world, has a rising incidence and a mortality rate of approximately 50 percent.[1, 2] Rectal cancer is different from colon cancer because of its close relationship to surrounding structures, which leads to high local recurrence rates of 3–25 percent after resection.[3-5]

Primary locally advanced rectal cancer (*i.e.* tumour tissue extending into or beyond the enveloping fascia propria of the mesorectal compartment) represents approximately 10 percent of all rectal cancer patients. Often these tumours infiltrate adjacent structures and therefore have a higher risk to develop a local recurrence which might lead to disabling symptoms including unrelenting pain.[6]

Locally advanced rectal cancer, when left untreated, results in a median survival of 7–8 months.[7] Primary radiation therapy for locally advanced rectal carcinomas provides good palliation but a limited chance of cure. Because surgery alone has been reported to result in 5-year survival rates of only 19 to 33 percent, preoperative radiotherapy has been used to downstage advanced tumours and make it possible to perform a complete resection.[8, 9]

Primary locally advanced rectal cancer can be cured using aggressive treatment modalities including preoperative (chemo)radiotherapy, extensive surgery and intraoperative radiotherapy (IORT).[10] IORT refers to the delivery of radiation at the time of surgery and is used when resection margins are narrow or involved with tumour cells. IORT can be applied very specifically to an area at risk, under direct visual control and with the possibility to shield the surrounding structures from radiation. The biologic effectiveness of single-dose IORT is considered to be as effective as two to three times the equivalent dose of fractionated radiotherapy. Eble *et al*.[11] demonstrated that IORT was feasible, safe and resulted in very low local recurrence rates, even in patients with microscopic residual disease or close resection margins. Previous reports of treatment programs using external beam radiation therapy, surgical resection and IORT for patients with locally advanced primary rectal carcinoma described excellent local control and high survival rates.[1]

At our tertiary referral hospital we have initiated a treatment protocol for patients with primary locally advanced or recurrent rectal cancer, which combines preoperative radiotherapy followed by surgery and IORT. In this report the experience with this combined modality therapy for 123 patients with primary locally advanced and initially unresectable rectal cancer is described. Prognostic factors were evaluated for local recurrence, metastases-free and overall survival.

MATERIALS AND METHODS

Data collection

Between January 1987 and March 2003, 123 patients with locally advanced or initially unresectable rectal cancer were referred to our tertiary referral centre. All tumours were biopsy-proven invasive adenocarcinomas. Each tumour was clinically classified as large T3 with narrow circumferential margins to the mesorectal fascia on CT or MRI imaging or fixed, initially unresectable T4 tumours. Our prospective database consists of hospital notes, radiotherapy plans, operation notes and histopathologic reports to obtain the following information: demographics, preoperative diagnostic intervention, tumour staging, radiotherapy technique, surgical details, histopathologic details, and complications. Follow-up was registered using hospital notes, medical letters, and in some cases by general practitioner information.

Preoperative and intraoperative radiotherapy

In a minority (n=15) of cases a four-field technique was used to cover the treatment volume defined by the supervising radiotherapist. In the majority (n=108) of cases three fields (one posterior and two lateral fields) were used. A radiation dose of 50 Gy in 25 daily fractions of 2Gy was planned for all patients. IORT with HDR brachytherapy was given from 1997 to those patients (n=27) who had a minimal circumferential free resection margin equal to or less than two millimeters. The resection margin was judged on frozen sections taken during surgery. A boost of 10 Gy was directly given in the operation field with the Flexible Intraoperative Template (FIT) developed at our department.[12] The FIT is a 5 mm thick flexible silicon template containing parallel catheters spaced 1 cm apart. The shape of the FIT was determined by the surgeon and radiation oncologist and was adjusted to the target area. Before positioning the FIT, 3 to 4 surgical clips were placed widely around the target surface. Active dwell positions were chosen according to the size and shape of the actual FIT. The dose was specified at the reference depth (usually 10 mm from the surface of the FIT). The position of the clips was reconstructed from the reconstruction films made using a dedicated brachytherapy localiser. The individual treatment plan was calculated by importing the dwell times from the standard treatment plan in the reconstructed FIT geometry. The actually delivered dose, i.e. the treatment dose, was defined as the average dose in dose points, placed on a line perpendicular to the reconstructed FIT at the prescribed depth. This dose was expected to be 10 Gy because of the anatomy of the pelvis.

Surgery

Surgery was planned 6-10 weeks after the final radiation treatment. The majority of patients (n=76) were operated on in the Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam. When patients did not need extensive surgery or IORT was not considered necessary, surgery was in some cases performed in other hospitals (n=47).

Statistical analysis

Patient characteristics are presented by tabulation. Overall survival, local failure-free and metastasis-free survival were calculated using the actuarial method of Kaplan and Meier.[13] The IORT and non-IORT groups were compared using the log rank test. Overall survival, local control and distant metastasis were analysed as a function of completeness of the resection, lymph node stage (negative *vs.* positive), IORT (yes *vs.* no), preoperative pain (yes *vs.* no) and type of hospital (tertiary centre or community hospital). Cox regression was used to evaluate the prognostic factors for overall survival.[14] *P*-values less than 0.05 were regarded as significant.

RESULTS

Patients

Preoperative radiotherapy followed by surgery was performed in 123 patients; 87 male and 36 female. Mean age at the time of surgery was 66 year (range 20–90 year). Presenting symptoms were pain in twelve patients (10 percent), defecation abnormality in 56 patients (46 percent), perineal pressure in 9 (7 percent) and a combination of these in 36 patients (29 percent). Only 10 patients (8 percent) presented without symptoms. The tumour was clinically fixed to adjacent organs or the pelvic wall in 99 patients (80 percent).

Treatment

In 66 patients (54 percent) a diversion colostomy was performed, prior to radiotherapy. The omentum or the distal sigmoid was used to fill the pelvis to prevent the small bowel from radiation damage in 53 patients, an artificial spacer (breast prosthesis) was used in two patients. The majority of patients (n=104) received 50 Gy radiotherapy. The remaining patients received various doses between 25 and 52 Gy.

Surgery was performed 6–10 weeks after radiotherapy and included low anterior resection in 23 patients (19 percent), abdominalperineal resection in 60 (49 percent) or abdominal sacral

resection in 3 patients (2 percent). When there was tumour growth into the vagina or cervix or into the bladder or prostate, respectively a posterior- (n=19) or total exenteration (n=18) was performed. A complete resection (R0) could be performed in 104 patients (85 percent), a microscopic incomplete (R1) in 17 patients (14 percent) and macroscopic incomplete (R2) in 2 patients (1 percent). Other tumour characteristics are depicted in Table 1. There was a statistically significant difference in tumour stage between the referral hospital and the community hospitals (P=0.001). More advanced tumour stages were treated in the tertiary center, *e.g.* 29/76 patients operated on had a T4 tumour *vs.* 2/47 patients in the community hospitals. Twenty-seven patients (22 percent) were treated with IORT because the resection was incomplete or the margin equal or less than 2 mm.

The median operation time was 345 minutes (range 135–670 minutes) and the median bloodloss 3.6 liters (range 0,5–20 litres). Perioperative liver metastases were found in 3 patients. These metastases were resected during a second intervention in all patients.

Follow-up

Median follow up was 25.1 months (range 1–136 months). Postoperative complications are depicted in Table 2. Postoperative in hospital (within 30 days after surgery) mortality occurred in 3 patients (2 percent). Three (3 percent) patients complained of possible radiotherapy related late toxicity: 2 patients reported chronic perineal pain and 1 patient experienced chronic diarrhea.

Local control

The overall 3-year and 5-year local control rates were 75 and 65 percent, respectively. There was a significant difference in the 5-year local control rate between a complete resection or incomplete resection (P=0.002) (Figure 1), negative lymph nodes and positive lymph nodes (P<0.001), surgery in center or community hospital (p=0.02) and preoperative pain (P=0.002). Fixation of the tumour and type of resection were not of significant importance (Table 3).

Distant metastases

The overall 3-year and 5-year actuarial distant metastases free survival rates were 59 percent and 53 percent, respectively. The 5-year metastases free survival rate was statistically significantly different for complete versus incomplete resection (P<0.001), positive vs. negative lymph nodes (P<0.001) and preoperative pain (P=0.002). Type of hospital, fixation of the tumour and type of resection were not of significant importance (Table 3).

Table 1. Treatment characteristics of 123 patients after multimodality treatment

	N	(%)
Tumour localization (distance to anal verge)		
– <5 cm	83	67
– 6-10 cm	28	23
– >10 cm	8	7
– Unknown	4	3
Resection of adjacent organs		
– Prostate	17	14
– Prostate partial	14	11
– Seminal Vesiculae	20	16
– Bladder	18	15
– Vaginal wall	22	18
– Uterus	15	12
– Part of sacrum	4	3
– Os coccygis	10	8
TNM-classification (pathology)		
Tumour		
– T0	2	1
– T2	17	14
– T3	70	57
– T4	31	25
– Tx	3	2
Node		
– N0	68	56
– N1	24	20
– N2	9	7
– Nx	22	18
Metastases		
– M0	120	97
– M1	3	3

Table 2. Postoperative complications

	N	(%)
Postoperative complications		
– Local complications		
– Abdominal / perineal wound infection	18	15
– Intra-abdominal / perineal abscesses	12	10
– Anastomotic leakage*	4	18
General complications		
– Urinary tract infection	9	7
– Bladder retention	21	17
– Pneumonia	10	8
Reinterventions		
– Revision stoma	7	6
– Revision Bricker	2	1
– Abscess drainage	7	6

* Counted only in those patients who underwent a low anterior resection (n=22)

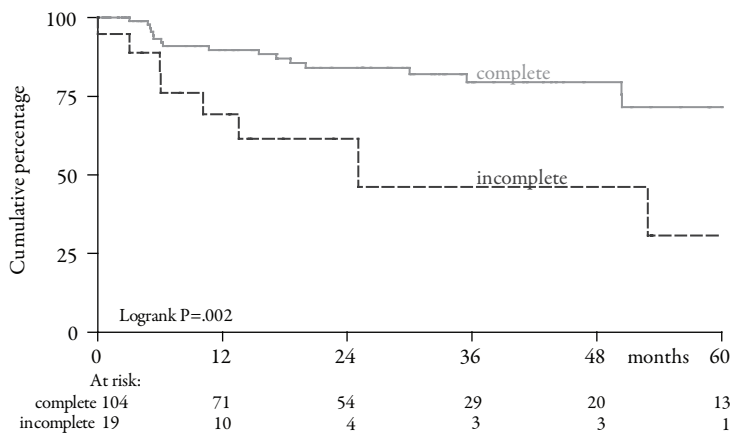

Figure 1. Local control by completeness of resection

Table 3. Univariate analysis of prognostic factors

	N	Local control (5yr)	Metastases free (5yr)	Overall survival (5yr)
Resection				
– Complete (R0)	104	72%	60%	57%
– Incomplete (R1,2)	19	31% (P=0.002)	17% (P<0.001)	20% (P<0.001)
Lymph node stage				
– N -	68	83%	77%	67%
– N +	34	0%	12%	30%
– N x	21	65% (P<0.001)	33% (P<0.001)	34% (P=0.001)
Preoperative pain				
– No	105	73%	59%	53%
– Yes	11	17% (P=0.002)	14% (P=0.002)	38% ns
Type of Hospital				
– Referral Centre	76	75%	52%	56%
– Community Hosp.	46	44% (P=0.020)	53% ns	41% ns
Fixation of tumour				
– No	23	59%	38%	48%
– Anterior	35	59%	56%	53%
– Posterior	12	89%	88%	64%
– Lateral	11	79%	79%	81%
– Multiple sites	33	65% ns	36% ns	35% ns
Type of resection				
– LAR	22	75%	78%	54%
– APR	60	54%	48%	46%
– APSR	3	100%	67%	67%
– Total exenteration	18	85%	47%	44%
– Post exenteration	19	70% ns	50% ns	66% ns

N - = no positive lymp nodes; N+ = positive lymph nodes; LAR = low anterior resection; APR = abdominoperineal resection; APSR = abdominopreineal sacral resection; ns = not significant

Overall Survival

The overall 3-year and 5-year survival rates were 58 percent and 50 percent, respectively. Five-year overall survival was significantly different between complete and incomplete resection (P<0.001) and lymph node status (P=0.001) (Figure 2). Preoperative pain had no effect on

overall survival. Type of hospital, fixation of the tumour and type of resection were also not of significant importance (Table 3).

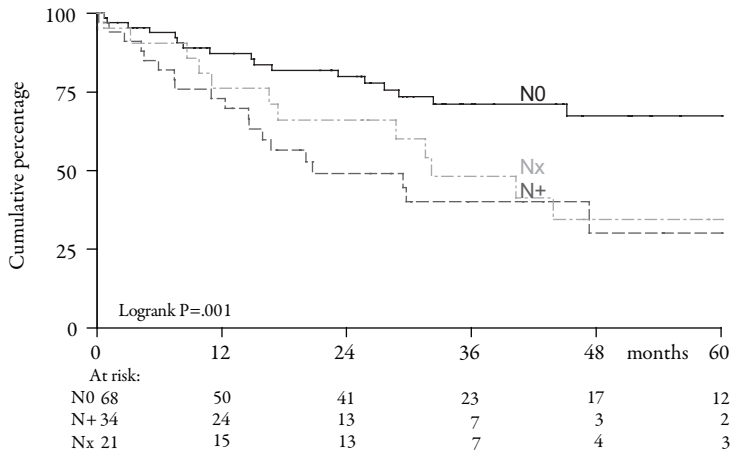

Figure 2. Overall survival by lymph node status

Table 4. Five-year actuarial local control and overall survival by IORT administration

Resection	N	IORT*	Local control	Overall survival
Complete	85	No	71%	56%
Complete	19	Yes	72% ns	66% ns
Incomplete	8	No	0%	0%
Incomplete	11	Yes	58% (P=0.016)	38% (P=0.026)

IORT = intra operative radiotherapy; ns = not significant

* IORT added for patients with margins ≤ 2mm after 1997

IORT

Of the 19 patients who underwent an incomplete (R1, 2) resection 8 did not receive IORT, because of high radiation therapy in the past (*e.g.* cervix carcinoma), poor physical situation, or because IORT was not available. All these 8 patients developed a local recurrence and all died within 5 years (Table 4). When IORT was delivered to patients with an incomplete resection, local control and survival were substantially improved relative to patients who did

not receive IORT (5-year local control 58 percent *vs*. 0 percent, P=0.016; 5-year overall survival 38 percent *vs.* 0 percent, P=0.026). Patients who underwent IORT for a marginal complete resection (margin <2 mm) had a similar local control and overall survival compared to the total group of patients who underwent a complete resection. In a multivariate Cox analysis including the factor IORT combined with completeness of resection, age, sex, and lymph node status, significant independent prognostic information was obtained from IORT and lymph node status. An incomplete resection without IORT was significantly inferior (P<0.001) to a complete resection or an incomplete resection with IORT.

DISCUSSION

Patients with locally advanced tumours should preferably receive some form of neoadjuvant treatment to downstage the tumour and enable a potentially curative resection. In the present study, a multimodality treatment consisting of preoperative radiation therapy followed by aggressive surgery with or without intraoperative radiotherapy was demonstrated to be feasible with an acceptable mortality and a five-year local control of 65 percent and an overall survival of 50 percent. In the literature, several studies do not discriminate between primary locally advanced and recurrent rectal cancer and results are described as one group.[1,15] It seems important to differentiate between these two, because five-year overall survival of patients treated for recurrent rectal cancer is generally reported between 15 to 55 percent16–20 compared with a much higher 40 to 70 percent in primary locally advanced rectal cancer.[7,20–23] A similar difference in local control in favour of locally advanced rectal cancer has been described.

In the present study, patients who underwent a complete resection had a significantly improved five-year local control rate compared with incompletely resected patients (72 *vs*. 31 percent). This is in concordance with results demonstrated in the Dutch TME trial representing mainly T2 and 3 rectal cancer patients. A margin of 2 mm was associated with a local recurrence risk of 16 percent compared with 5.8 percent in patients with more mesorectal tissue surrounding the tumour (P<0.0001).[24] Willett *et al*.[7] reported similarly high local control rates in patients with locally advanced rectal cancer who underwent complete tumour resection. Even if the tumour invades adjacent organs and a total pelvic exenteration is considered necessary, local control rates can be high as long as complete tumour resections are achieved.[25]

Lymph node status and the presentation of preoperative pain also proved to be significantly important factors for local control in the present study. Pain often is not described as a predictive factor in primary locally advanced rectal cancer but is known to be a negative prognostic factor in local recurrences and leads to a significant decrease in overall survival.[18,26]

Local control is significantly related to the dose of irradiation; however, because of toxicity to radiosensitive organs, such as small bowels, the external radiation dose should not exceed 60 Gy.[27] A combination of external irradiation and IORT allows the safe delivery of higher effective doses of irradiation than can be delivered with external beam-only techniques. IORT is a boosting technique that has been proven to be feasible to integrate in the multimodality treatment of locally advanced rectal cancer without increased normal tissue toxicity.[28] Previous studies have demonstrated that IORT achieves good local control and high survival rates in primary locally advanced rectal cancer.[7,10,11,21,29-32] Most of the results reported regarding IORT in rectal cancer originate from a few centres, and randomised trials are lacking. In the present study, IORT improves the five-year local control rate in patients with an incomplete resection to 58 percent compared with 0 percent in patients who did not receive IORT. Nakfoor *et al*.[22] and Gunderson *et al*.[33] similarly reported high local control rates with IORT even for patients who had macroscopic residual disease. The Mayo series demonstrated five-year overall survival of 55 percent in R1 resected patients and 21 percent in R2 patients.[34] Despite the fact that patients treated in the referral hospital had more advanced tumours, local control was 75 percent compared with 44 percent in community hospitals after five years (P=0.02). Similar results were reported by Wibe *et al*.[35] who demonstrated that local recurrence rate was higher in patients treated in hospitals with a low annual caseload of fewer than 10 procedures compared with hospitals with a high treatment volume of 30 procedures or more.36 Patients treated in smaller hospitals also had a lower long-term survival rate than those treated in larger hospitals. Begg *et al*.[37] reported that mortality rates are lower when complex surgical oncologic procedures are performed by surgical teams in hospitals with special expertise. Based on these results, we emphasise that not only volume but also the necessity of a multidisciplinary team, including a radiation oncologist, urologist, surgical oncologist, plastic surgeon, and gynaecologist, is important for these surgical procedures, which preferably are performed in specialised centers. The overall survival rate in the present study is comparable to what has been reported in the literature for these advanced tumours.[21,31,38] Significantly important prognostic factors for overall survival are completeness of resection and negative lymph node status. In the literature, these are known prognostic factors, but other factors, such as extent of resection and fixation of

tumour, also are reported.[7,11,30,31] However, these latter factors did not seem important in the present study. IORT was applied in 19 patients who were treated with a narrow but complete resection (margin, 0–2 mm). The survival of these patients was similar to the total group of patients with a complete margin who did not receive IORT. Nagtegaal *et al*.[24] have demonstrated that circumferential margins are extremely important for developing a local recurrence. For rectal cancer patients with circumferential margin of <1 mm, a recurrence rate of 16 percent after two years was described. In the present study, addition of IORT seems to overrule the unfavourable prognostic histologic finding in patients with narrow resection margins. In patients with incomplete resection margins (R1/2 resection), addition of IORT resulted in acceptable local control (58 percent) and overall survival rates (38 percent). This was in contrast to patients who underwent an incomplete resection and were not treated with IORT who all died within five years. In the present study, radiotherapy only was used as neoadjuvant treatment to reduce tumour mass. Addition of chemotherapy to preoperative radiotherapy recently demonstrated an improvement of local control in two, large, randomised trials.[7,39-41] The European Organisation for Research and Treatment of Cancer (EORTC) 22921 four-arm randomised trial[42] demonstrated the benefit of preoperative chemoradiation *vs*. preoperative radiation alone in T3–T4 resectable rectal cancer patients. The addition of 5-fluorouracil and leucovorin to preoperative radiation slightly increased the amount of acute toxicity and, more importantly, increased the number of complete responses and decreased the local recurrence rate after five years.[43] In future multimodality treatment protocols for locally advanced rectal cancer, the addition of chemotherapy to radiotherapy should be considered.[44]

CONCLUSION

IORT for patients with a narrow complete or incomplete resection seems to overrule the unfavourable prognostic histologic finding for local control and overall survival. The future of treatment for primary locally advanced rectal cancer will be the successful integration of IORT into multimodality treatment programs as described in this study.

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Chapter V

Preoperative chemotherapy with capecitabine in locally advanced rectal cancer

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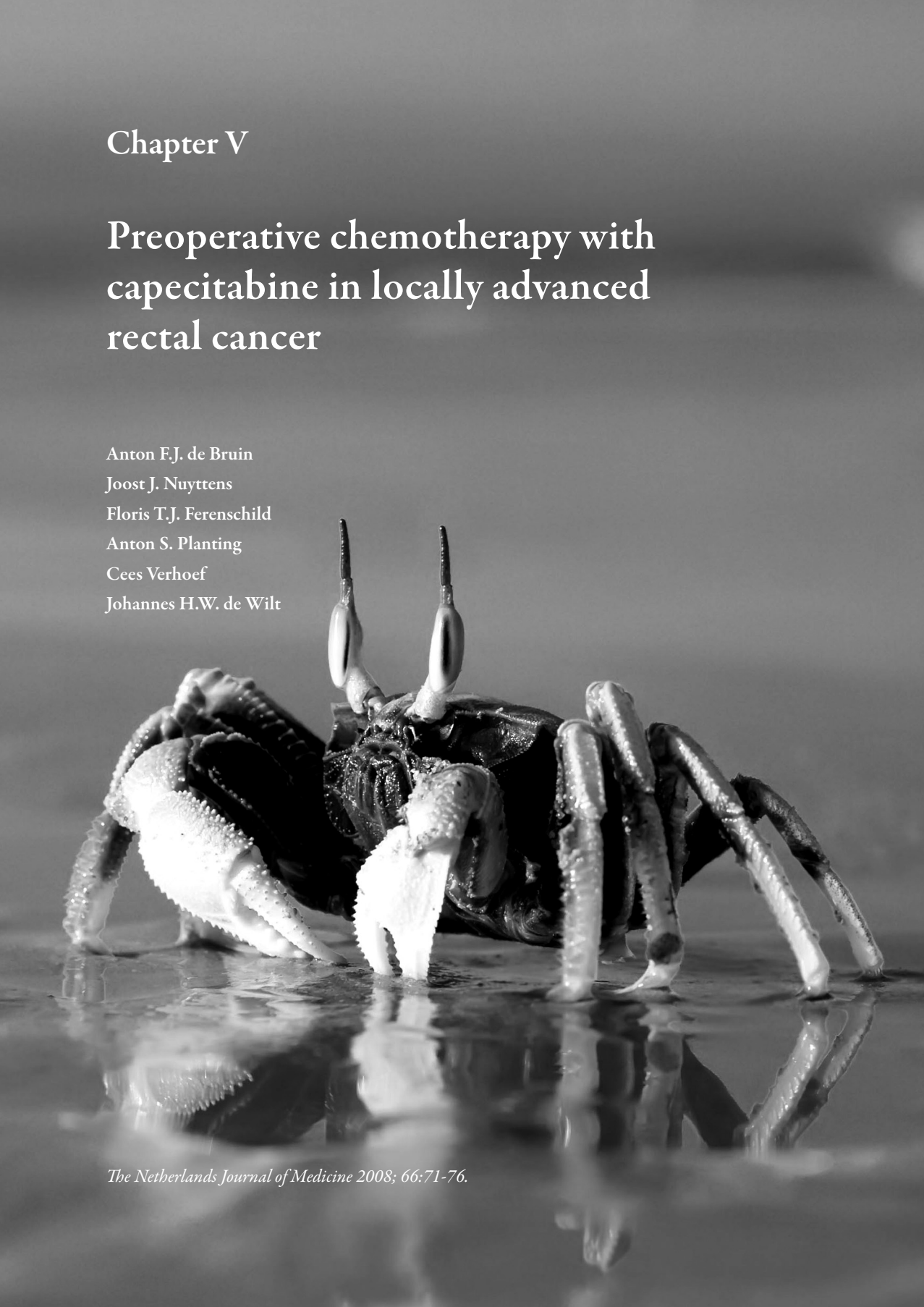

The Netherlands Journal of Medicine 2008; 66:71-76.

ABSTRACT

Background

Preoperative radiation therapy in combination with 5-fluoracil (5-FU) improves local tumour control in locally advanced rectal cancer. The aim of our study was to evaluate the toxicity and efficacy of preoperative chemoradiation using the oral 5-FU prodrug capecitabine in locally advanced rectal cancer.

Methods

Sixty patients with locally advanced rectal cancer were treated with preoperative chemoradiation. Radiotherapy consisted of a total dose of 50 Gy delivered in 25 fractions to the pelvis. Chemotherapy was concurrently administered and consisted of oral capecitabine only on radiotherapy days. Surgery was performed six to ten weeks after completion of chemoradiation.

Results

The patient population consisted of 19 females and 41 males, with a median age of 61 years. All but two patients received the full dose of chemoradiation. No grade 3 or 4 haematological toxicities developed. Two patients (3%) developed grade 3 radiation dermatitis and one a grade 3diarrhoea. All patients underwent definitive surgery; 19 patients underwent an abdominal perineal resection (APR), 25 a low anterior resection (LAR) and 16 patients a Hartmann's procedure. One patient with a low anterior resection developed an anastomotic leakage (4%). Final pathology demonstrated eight patients (13%) with a complete pathological response. Primary tumour and nodal downstaging occurred in 67 and 84% of the patients, respectively. Two patients (3%) had an R1 resection, one after an APR and one after an LAR.

Conclusion

Preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. This preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes.

INTRODUCTION

Preoperative radiotherapy with concurrent 5-fluorouracil (5-FU) based chemotherapy has received increased interest over the last decade in the treatment of locally advanced colorectal cancer. The addition of chemotherapy to radiation therapy has been demonstrated to be feasible, with an increase in pathological complete response rate and possibility of sphincter preservation. Preoperative chemoradiation therapy with 5-FU confers a significant benefit with respect to local control.[1,2] Continuous 5-FU infusion has been proven superior to bolus administration in terms of tumour response and is associated with a lower incidence of haematological and nonhaematological toxicity.[3,4] Disadvantages of continuous infusion are requirement of hospitalisation and potential complications resulting from central venous access.[5] Capecitabine is a fluoropyrimidine carbamate rationally designed to generate 5-FU preferentially in tumour cells as the concentration of the key enzyme thymidine phosphorylase is higher in tumour cells compared with normal tissue. After irradiation thymidine phosphorylase is upregulated in tumour tissue resulting in a supra-additive affect of capecitabine on radiotherapy.[6-8] Capecitabine is administered daily to mimic continuous infusion of 5-FU. A phase I study of preoperative radiotherapy with 50.4 Gy given in 28 fractions in five weeks combined with escalating doses of capecitabine was reported by Ngan *et al.*[9] For phase II studies, they recommended a capecitabine dose of 1800 mg/m^2/day. This overall dose is similar to that used when capecitabine is given as a single agent for metastatic disease either in the 42-day continuous regimen (825 mg/m^2 twice daily) or in the intermittent schedule (1250 mg/m^2 twice daily for two weeks, one every three weeks).[10,11] Dunst *et al.* also conducted a phase I study and recommended 825 mg/ m^2 capecitabine twice a day for phase II evaluation.[12] Three phase II studies have been initiated to evaluate the tolerance and efficacy of chemoradiation with capecitabine. In these studies different regimes of capecitabine were used and in some studies leucovorin was added.[13-16] We initiated a phase II study to evaluate the efficacy and toxicity of preoperative chemoradiation with capecitabine in large T3/T4 rectal tumours or in tumours with local lymph node metastasis. In this study capecitabine was only administered on radiotherapy days.

MATERIALS AND METHODS

All patients treated in this study were evaluated including a complete history and physical examination, colonoscopy, tumour biopsy, abdominal ultrasound, computed tomography (CT) scan of the abdomen and pelvis and magnetic resonance imaging (MRI) of the pelvis, a chest X-ray and/or chest CT scan. All CT and MRI images of the patients were discussed in our multidisciplinary meeting which includes a colorectal surgeon, gynaecologist, urologist, radiotherapist, radiologist and medical oncologist. Complete laboratory tests included a full blood count with differential, serum chemistries including electrolytes, liver function tests, creatinine, and carcinoembryonic antigen.

Inclusion criteria

All patients had a histologically proven adenocarcinoma of the rectum. This was defined as any tumour within 15 cm of the anal verge or a tumour located distal from the line between the promontory and symphysis on sagittal MRI. The location of the tumour was measured from the anal verge using colonoscopy. Patients with large T3 or T4, Nx or any T3, N1-2 rectal adenocarcinoma were eligible for the study. Large T3 tumours were defined on pelvic MRI as tumours with narrow margins (<2 mm) to the circumferential rectal fascia. Mesorectal and obturator lymph nodes were considered positive on pelvic MRI if a node was larger than 8 mm or multiple nodes larger than 3 mm. All patients needed to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and be aged between 18 and 80 years. Patients also had to have adequate liver, renal and bone marrow function as follows: bilirubin <30 mmol/l, aspartate aminotransferase and alanine aminotransferase less than five times the upper level of normal (ULN), creatinine <1.5 x ULN, leucocytes >3.5 x 109/l, and platelets 100 x 109/l. Patients of child-bearing age were required to practice approved methods of birth control.

Exclusion criteria

Patients with severe comorbidity such as cardiomyopathy or other cardiovascular disease were excluded. Patients with known risk of adverse reaction to fluoropyrimidines were excluded, as well as patients who were participating in other trials or receiving any investigational drugs.

TRIAL DESIGN AND ENDPOINTS

This was a single-armed, multicentre phase II study of preoperative radiotherapy with concurrent capecitabine for locally advanced rectal cancer. Primary endpoints were toxicity, grade of tumour downstaging and pathological complete response. Secondary endpoints were rate of sphincter preservation and postoperative complications. Primary endpoints were haematological and nonhaematological toxicity. Toxicity was scored with Radiation Therapy Oncology Group criteria and the National Cancer Institute Common Toxicity Criteria version 3.0. Secondary endpoints were complete pathological response, pathological downstaging and sphincter preservation. Our definition of downstaging and complete response was based on the comparison of the clinical tumour node metastasis (TNM) and the pathological TNM stage. Pathological complete response was defined as no tumour cells in the pathological specimen, but only a fibrotic mass.

Chemotherapy

Capecitabine was administered orally at a dose of 825 mg/m^2 twice a day only on radiotherapy days. The first daily dose was given two hours before radiotherapy and the second dose twelve hours later. Dose modifications were applied if the patient experienced any grade 3 or 4 haematological toxicity or any grade 3 nonhaematological toxicity, such as hand-foot syndrome, except for alopecia. Chemotherapy was restarted at a 75% dose if toxicity levels resolved to grade 1 or less. If toxicity was clearly related to radiotherapy, for example radiation dermatitis, local therapy was administered and capecitabine was not stopped.

Radiotherapy

All patients were treated with preoperative radiotherapy and received a dose of 50 Gy delivered in 25 fractions of 2.0 Gy.Radiotherapy was administered by a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy. The lateral pelvic borders were defined as 1.5 cm lateral of the bony pelvis, the cranial border was the promontory, and the caudal border was below the foramina obturatoria to 2 cm under the anus, depending on tumour position. Patients were evaluated four times during the course of chemoradiation to assess acute toxicity and compliance with the oral capecitabine. Blood tests were taken each time and consisted of full blood count, platelets, leucocytes and neutrophils.

Surgery

Surgery was performed six to ten weeks after completing chemoradiation. Patients were reassessed for respectability by pelvis CT scanning or MRI of the pelvis. Total mesorectal excision technique was performed in all patients, and extended multivisceral resections were performed in clinically T4 patients. Intraoperative radiotherapy was administered in those patients in whom the circumferential margins were considered at risk.

RESULTS

A total of 60 patients were included between July 2005 and November 2006. The median age was 61 years (range 32 to 82 years) and the majority of patients had T3N1-N2 (48%) stage of disease. Other patient characteristics are shown in table 1. Median distance to the anal verge was 5 cm (range 0 to 20 cm). Most of the tumours were located in the lower parts of the rectum, with only a minority (13%) above 10 cm (table 2). In one patient the tumour was measured at 20 cm from the anal verge, but after discussing this case in our multidisciplinary team, we considered the bulk of the tumour to be in the upper part of the rectum, in close relation to the bladder. In this case downsizing of the tumour was aimed for and chemoradiation was proposed. All patients underwent surgery and were evaluated for pathological response and downstaging.

Toxicity

Toxicity was moderate and is summarised in *table 3*. Hand-foot syndrome did not occur in any of the patients. No haematological grade 3 or 4 toxicities occurred. Haematological toxicity was mild with grade 2 anaemia, leucocytopenia and neutropenia in 7, 12 and 3% of the patients, respectively. The only grade 3 nonhaematological toxicity was radiation dermatitis (3%) and diarrhoea (2%). Chemoradiation was not stopped in two patients who developed grade 3 radiation dermatitis. This occurred at the end of therapy and was managed by applying local therapy. All but two patients received the full dose of chemoradiation. A 56-year-old male reported severe chest pain while taking capecitabine, which was absent in the weekend. There was no history of cardiac disease. Capecitabine was stopped and radiation continued. A second patient was a 49-year-old female who experienced grade 3 diarrhoea which required intravenous fluid replacement. Capecitabine was stopped and not restarted at patient's request; radiotherapy was continued.

Table 1. Baseline patient characteristics

Category	Number (%)
Gender	
– Male	41 (68)
– Female	19 (32)
Performance status (ECOG)	
– 0	40(67)
– 1	20(33)
Histological differentiation	
– Moderately	44(73)
– Poorly	3(5)
– Unknown	13(22)
Clinical Tumour stage	
– *c*T3NO	3(5)
– *c*T3N+	29(48)
– *c*T4NO	12(20)
– *c*T4N+	16(27)

ECOG= Eastern Cooperative Oncology group

Table 2. Tumour location and surgical treatment

Tumour location	Number	APR (%)	LAR (%)	Hartmann (%)
10 cm	8	1 (12)	4 (50)	3 (38)
5–10 cm	20	2 (10)	13 (65)	5 (25)
<5 cm	32	16 (50)	8 (25)	8 (25)
All tumours	60	19 (32)	25 (42)	16 (27)

APR = abdominoperineal resection; LAR = low anterior resection

Response

Surgery was performed in ten different hospitals and all patients underwent definitive surgery. In 19 patients an abdominal perineal resection (APR) was performed, in 16 a Hartmann's resection and in 25 a low anterior resection (LAR). Of the patients with T4 tumours, 18 underwent a multivisceral resection: five posterior exenterations, three total exenterations, three vagina resections, two partial bladder resections, three seminal vesicle resections and two partial prostate resections. A complete pathological response was

Table 3. Haematological and non-haematological toxicity

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin	-	4 (7)	-	-
Platelets	15 (25)	-	-	-
Leukocytes (total WBC)	22 (37)	7 (12)	-	-
Neutrophils	-	2 (3)	-	-
Hand-foot skin reaction	1 (2)	-	-	-
Radiation dermatitis	14 (23)	11 (18)	2 (3)	-
Nausea	9 (15)	1 (2)	-	-
Vomiting	0 (0)	-	-	-
Lower gastrointestinal (diarrhea)	11 (18)	1(2)	1 (2)	-
Genito-urinary	13 (22)	-	-	-

WBC = white blood count

Table 4. Distribution of clinical tumour stage compared with pathological tumour stage

Clinical: Tumour and Node	pT0N0	pT1N0	pT2N0	pT2N1	pT3N0	pT3N1	pT3N2	pT4N0	pT4N2	Total (%)
cT3N0	1	1	1	-	-	-	-	-	-	3 (5)
cT3N1	3	-	4	-	8	3	-	-	-	18 (30)
cT3N2	3	3	1	-	2	-	2	-	-	11 (18)
cT4N0	1	2	3	1	2	-	-	3	-	12 (20)
cT4N1	-	-	4	-	9	-	-	1	-	14 (23)
cT4N2	-	-	-	-	-	-	1	-	1	2 (3)
Total (%)	8 (13)	6 (10%	13 (22)	1 (2)	21 (35)	3 (5)	3 (5)	4 (7)	1 (2)	60

Table 5. Comparison of trials of preoperative chemoradiation therapy in locally advanced rectal cancer

Study	No. Patients	Treatment	Downstaging rate(%)	Responce (%)	Ro/R1 resectionts	Toxicity	T3/T4	sphincter preservation
De Paoli[15]	53	Pelvic RT (45 Gy in 25 fractions, 5 days/ week) + boost to tumour (5.4 Gy in 3 fractions) +c (825 mg/m^2 bid) 7-days/ week.	57	pCR 24%	48/3	Grade 3; 6 patients (11%) = leucopenia 4% + hand-foot syndrome 4%	46/7	59%
Kim[26]	38	Pelvic RT (45 Gy in 25 fractions, 5 days/ week) + boost to tumour (5.4 Gy in 3 fractions) + c (825 mg/m^2 bid.) +LV (20mg/m^2/day) days 1-14 week, 2 cycles of 14 days.	63%	pCR 31%	NR	Grade 3; hand-foot syndrome (7%), fatigue (4%),diarrhea (4%) and radiation dermatitis (2%)	33/4	72%
Krishnan[13]	54	Pelvic RT (45Gy in 25 fractions, 5 days/ week) + concomitant boost to tumour (7.5 Gy in 5 fractions) + c (825mg/m^2 bid.) continuous 35 days.	51%	pCR 18%	51/0	Grade 4 2% diarrhea, Grade 3 lymphopenia 70%, anemia and neu-tropenia 2%, radiation der-matitis 9%, proctitis 4%, fatigue 2%, diarrhea 2%	52/2	67%
Present	60	Pelvic RT (50 Gy in 25 fractions, 5 days/ week) + c (825mg/m^2 5days/week)	67%	pCR 13%	58/2	grade 3 2% diarrhea, 3% radiation dermatitis	32/28	50%

achieved in eight patients (13%) (table 4). Overall tumour and nodal downstaging occurred in 51 patients (85%). Tumour downstaging was seen in 40 patients (67%) and overall nodal downstaging in 38 patients (84%). Tumour progression during chemoradiation was not observed. Final pathology demonstrated T0 in eight patients (13%), T1 in six patients (10%), T2 in 14 patients (23%), T3 in 27 patients (45%) and T4 in five patients (8%). Of the 32 patients with initial tumour location less then 5 cm from the anal verge, 16 underwent an abdominal perineal resection and eight (25%) sphincter preservation by performing a low anterior resection. The majority of patients with the initial tumour location more than 5 cm from the anal verge underwent an LAR; only three patients underwent an APR, and eight a Hartmann's resection. In two patients (3%) an R1 resection was performed; one male patient with a tumour located at 3 cm from the anal verge underwent an APR and another male patient with a tumour located at 8 cm from the anal verge underwent a low anterior resection. No R2 resections were performed. Anastomotic leakage in the low anterior group occurred in one patient (4%).

DISCUSSION

Patients with locally advanced rectum carcinoma should preferably receive some form of neoadjuvant treatment to downstage the tumour and enable a potentially curative resection. 5-FU-based chemoradiation is currently a well-accepted approach in the management of locally advanced rectum carcinoma. We conducted the present study to evaluate toxicity and efficacy of preoperative chemoradiation using oral 5-FU (capecitabine) in locally advanced rectal cancer. This should potentially lead to improved local tumour control and improved chance of sphincter preservation. We demonstrated that preoperative chemoradiation therapy with capecitabine is feasible with acceptable overall grade 3 toxicity of 5% and a 13% complete response rate. All patients treated in this study completed radiotherapy and all but two completed chemotherapy. The incidence of acute toxicity in the present study was slightly lower than other phase II trials using capecitabine.[13-15] Table 5 demonstrates the results from the present study and three previously published studies. These differences can possibly be explained by the regime of capecitabine that was administered. Considering the radiation sensitising dose and effect of capecitabine in this set-up,[17] we designed the study to give capecitabine only on radiotherapy days. Because of the two-day resting period every five days, toxicity might therefore be lower than in the other series where capecitabine was administered twice daily, seven days a week. Kim *et al.*[16] used a regime consisting of two

cycles of 14 days followed by a resting period of seven days and also added leucovorin to their regime. It is noteworthy that one of the patients in the present study had severe chest pain with no history of any myocardial disease. Cardiotoxicity is a well-known but rare adverse effect of capecitabine and has been reported in several case reports.[18-20] In a previous study of locally advanced rectal carcinoma in our centre, radiotherapy was used at a similar dose (25 x 2Gy), but without capecitabine demonstrating a complete pathological response rate of only 2%.[21] In the present study a large group of patients (47%) who had a clinical T4 tumour were treated and despite this a complete pathological response of 13% and a total tumour downstaging of 67% were observed. Complete pathological response rates were slightly higher in the other reported phase II trials, but these differences can be explained by the fact that other phase II studies had considerably less patients with clinical T4 tumours. In the subgroup of patients with T4 staged tumours, one patient (4%) had a complete response and 24 of 28 patients (84%) had a total tumour downstaging. Of the 45 patients with clinical positive nodal status only eight (18%) had pathological nodal involvement. Unfortunately, there is a potential bias in all studies that report on rectal cancer downstaging. The real downstaging effect of the chemoradiation treatment can not be accurately measured, since clinical nodal staging is based on diagnostic imaging and is not pathologically proven. However, we used strict criteria for node positivity on pelvic MRI and all patients were discussed in a multidisciplinary team. All patients in our study had definitive surgery after preoperative therapy. Multivisceral resection, which was previously proven to enable good local control and acceptable survival, was performed in 18 patients.[22] The considerable downstaging effect of the addition of capecitabine to a long series of radiation may increase the chance of sphincter preservation and decrease the need for multivisceral resection. Bujko *et al.* demonstrated no significant increase in sphincter preservation after 5-FU based chemoradiation therapy, despite an increased clinical response rate.[23] Other studies demonstrated a significant correlation between chemoradiation and sphincter preservation.[24] In the present study only eight patients (25%) with a low-lying tumour (≤5 cm from anal verge) underwent sphincter preserving surgery. Therefore, conclusions regarding the benefit of chemoradiation on sphincter saving surgery can not be made based on the experience in this study. The incidence of circumferential margin involvement in patients with locally advanced rectal cancer is higher compared with rectal cancers were the tumour is confined to the mesorectum. Especially in APR patients circumferential resection margins are more often involved compared with patients who undergo an LAR.[25] In the present study, two patients (3%) had an R1 resection; one after an APR and one after an LAR. The downstaging effect of chemoradiation might decrease the risk of circumferential involvement, but surgical

technique is also important. For instance, in patients who underwent an APR resection, wide perineal resection seems to decrease the risk of involved margins and improve outcome.[26] Further improvement of outcome can be expected using new neoadjuvant chemoradiation protocols including chemotherapeutic drugs such as oxaliplatin or irinotecan.[27,28] Willet *et al.* have reported promising results using a vascular endothelial growth factor (VEGF) specific antibody (Bevacizumab) in combination with 5-FU-based radiotherapy.[29] This has lead to the conduction of a multicentre feasibility trial (RAX) in the Netherlands for which patients are currently being included.

CONCLUSION

Preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. In addition, this preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes resulting in few R1/R2 resections in large T3 and T4 rectal carcinoma. Capecitabine is used as a radiation sensitiser and there seems to be no need to administer it on nonradiotherapy days. By doing so it might minimize toxicity without influencing response.

ACKNOWLEDGEMENT

Surgeons in the Comprehensive Cancer Centre Rotterdam who operated on some of the patients: A.J. van Beek, W.F. Blom, P.P.L.O. Coene, H. Fabry, E. van der Harst, H. Kemperman, H.E. Lont, F. Logeman, G.H.H. Mannaerts, R.J. Oostenbroek, R. den Toom, W.J. Vles, W.F. Weidema.

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Part III

RECURRENT RECTAL CANCER

Chapter VI

Preoperative radiotherapy improves outcome in recurrent rectal cancer

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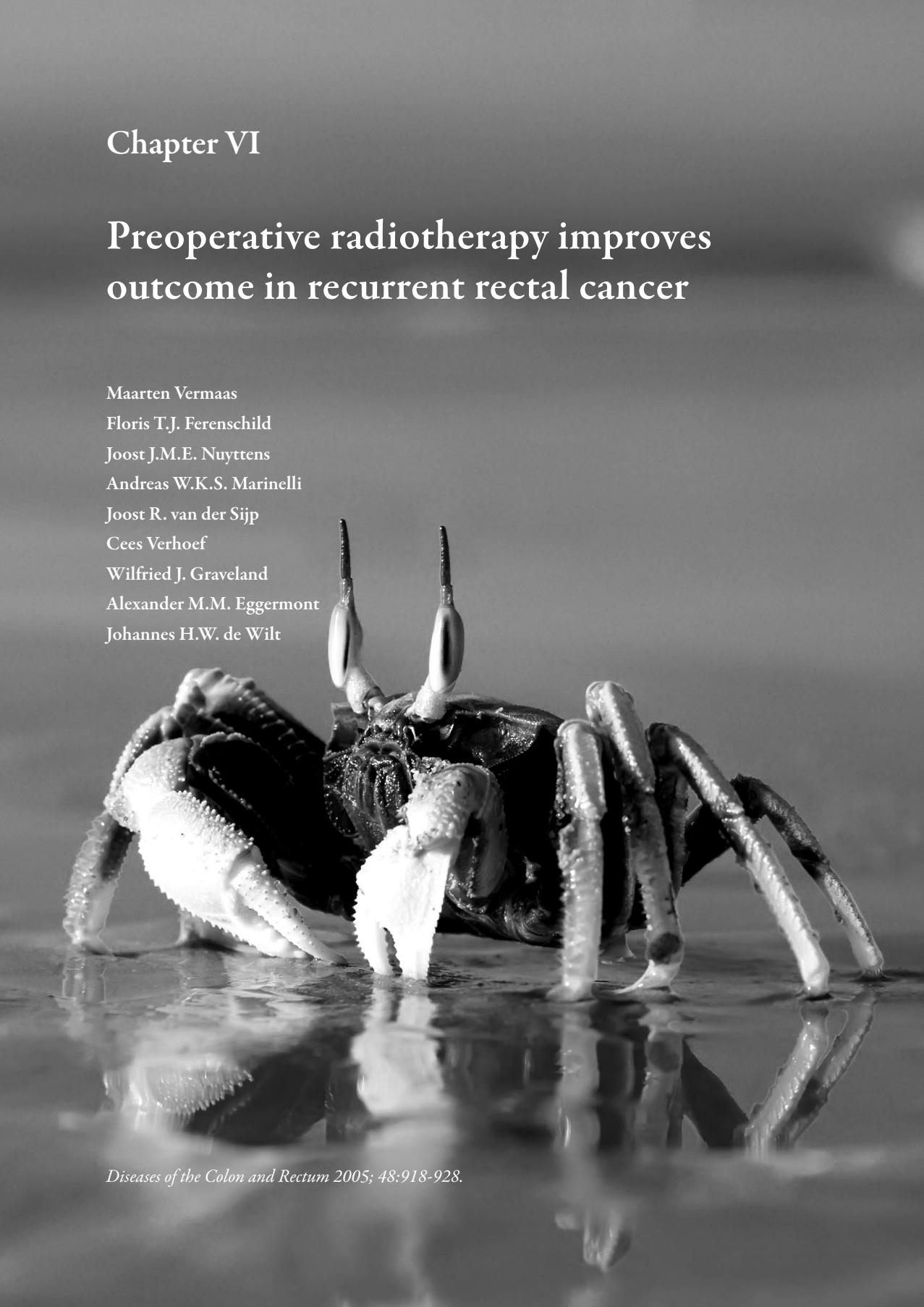

Diseases of the Colon and Rectum 2005; 48:918-928.

ABSTRACT

Background

When local recurrent rectal cancer is diagnosed without signs of metastases, a potentially curative resection can be performed. The aim of this study was designed to compare the results of preoperative radiotherapy followed by surgery with surgery only.

Methods

Between 1985 and 2003, 117 patients with recurrent rectal cancer were prospectively entered in our database. Ninety-two patients were suitable for resection with curative intent. Preoperative radiation with a median dosage of 50 Gy was performed in 59 patients and 33 patients did not receive preoperative radiotherapy. The median age of the patients was respectively 66 and 62 years.

Results

The median follow-up of patients alive for the total group was 16 (range 4–156) months. Tumour characteristics were comparable between the two groups. Complete resections (R0) were performed in 64 percent of the patients who received preoperative radiation and 45 percent of the nonirradiated patients. A complete response after radiotherapy was found in 10 percent of the preoperative irradiated patients (n=6). There were no differences in morbidity and reintervention rate between the two groups. Local control after preoperative radiotherapy was statistically significantly higher after three and five years (P=0,036). Overall survival and metastases free survival were not different in both groups. Complete response to preoperative radiotherapy was predictive for an improved survival.

Conclusions

Preoperative radiotherapy for recurrent rectal cancer results in a higher number of complete resections and an improved local control compared to patients treated without radiotherapy. Preoperative radiotherapy should be standard treatment for patients with recurrent rectal cancer.

INTRODUCTION

In the quest to obtain improved disease control and sphincter preservation the treatment of primary rectal cancer has developed in recent years to mesorectal excision, with adequate circumferential margins and excision of the lymph nodebearing area. With the introduction of this surgical technique local recurrence rates dropped from 25–40 percent in the literature[1-5] to <10 percent in recent series.[2,6 5] Preoperative short period radiotherapy (5x5 Gy) followed by total mesorectal excision (TME) further decreased local recurrence rates.[5] The ultimate goal is to increase local control, and thereby improve overall long term survival. When a recurrence occurs in rectal cancer patients, prognosis is often poor. Even with adequate treatment overall five-year survival rates reported in the literature ranges from 0–30 percent.[7,8-13] Recurrences are often associated with severe symptomatic disease, especially pain.7 For most patients, especially patients with extraluminal tumour mass involving other organs, the treatment used to be strictly palliative. Radiotherapy as a palliative treatment option has an effect on the tumour mass for a period of 6 to 11 months, without the possibility of prolonging overall survival.[4,14] Due to new treatment modalities including preoperative and intraoperative radiotherapy, it is possible to obtain a radical resection even in this group of patients.[15]

The main goals in the treatment of recurrent rectal cancer are palliation of symptoms, good quality of life and, if possible, curative surgery. In case of incomplete or marginal resection intraoperative radiotherapy can deliver an extra boost of 10 Gy, which can achieve the biologic equivalence of two or three times that of the equivalent dose of fractionated external beam therapy.[13,16,17] In several studies this has been suggested to improve both local control and overall survival, but patient numbers are often small in these series. The current treatment of the recurrent rectal carcinoma in our tertiary referral cancer centre consists of a "multimodality" approach, consisting of preoperative high dose radiotherapy, followed by resection and intraoperative radiotherapy when surgical margins are narrow or incomplete.

This study was designed to assess the outcome after treatment of recurrent rectal cancer in our cancer centre. We especially focused on the effect of preoperative long-term irradiation and intraoperative radiation in the multimodality treatment of recurrent rectal cancer.

PATIENTS AND METHODS

All patients treated between 1985 and 2003 in the Erasmus MC – Daniel den Hoed Cancer Centre for a recurrent rectal carcinoma were analysed. Medical records were examined to obtain all necessary data. A total of 117 patients with recurrent rectal cancer were examined for surgical treatment; 25 were excluded for resection. Most of the excluded patients were considered not fit enough to undergo major surgery (n=16). Two patients deteriorated after their preoperative radiotherapy treatment and were not scheduled for surgery, and another seven patients were not operated because preoperative staging after radiotherapy revealed distant metastases in lung or liver.

The remaining 92 patients were considered suitable for curative surgery of their recurrent tumour. Curative intent was defined as a surgical resection with intent of complete resection of the tumour. All patients had previously undergone resection of a primary rectal tumour located within 15 centimetre of the dentate line.

Patients were divided in two subgroups; one group with 59 patients who were treated with preoperative radiotherapy followed by surgery six to eight weeks later, and another group with 33 patients who were operated on without preoperative radiotherapy. The preoperatively irradiated group consisted of 64 percent males and 36 percent female, with a median age of 66 years, and the preoperatively nonirradiated group of 58% men and 42% women, with a median age of 62 years at reoperation. The median follow-up of all 92 patients was 16 (range 4–156) months at the moment of statistical analysis.

All patients were histologically proven recurrent rectal adenocarcinoma. Staging consisted of magnetic resonance imaging and CT scanning of the pelvis to define the localization and growth of the recurrence. Exclusion of distant disease was performed by a thoracoabdominal CT scan and by perioperative palpation of the liver and the peritoneal contents. The recurrences were classified with two different systems: the Wanebo classification and the Suzuki classification.[15,18] In general, patients were seen every three months at our outpatients department for the first postoperative year and every six months thereafter. Physical examination, carcinoembryonic antigen in serum, and an annual abdominal CT scan were performed to demonstrate local or systemic recurrences.

External Beam Radiotherapy (EBRT)

Patients who were treated with preoperative EBRT received a median dose of 50Gy (range 25–60) delivered in 25 fractions of 2.0 Gy. EBRT was administered by either a three-field technique, using one posterior and two lateral portals, or a four-fieldbox. The lateral

pelvic borders were defined as 1.5-cm lateral of the bony pelvis, the cranial border was the promontory, and the caudal border was below the foramina obturatoria to 2 cm under the anus, depending on tumour position. Preoperative EBRT was performed in all patients treated after 1997; concurrent chemotherapy was not administered in the described group of patients.

The four most recent irradiated patients in the multimodality group were irradiated with a new radiation technique: intensity modulated radiotherapy (IMRT). This technique is used to diminish the toxicity of radiation dosed to the abdominal organs.

Surgery

The objective of the surgical approach was to obtain free circumferential margins. The circumferential plane consists of four quadrants. In all quadrants recurrent tumour growth can occur and require extended surgery. In case of ventral growth, for example growth into the base of the bladder, the prostate or the seminal vesicles, a total pelvic exenterative procedure was performed. In case of growth into the posterior plane, for example into the sacrum below S2, an abdominoperineal-sacral resection (APSR) was performed. A low anterior resection or an abdominoperineal resection treated centrally located recurrences. Complications were classified as major complications, if they did extend the hospitalization or did require reintervention.

Intraoperative Radiotherapy

In 1997 the high-dose-rate intraoperative radiotherapy (HDR-IORT) program was started at the Erasmus MC – Daniel den Hoed Cancer Centre.[19-21] All patients treated with HDR-IORT were treated preoperatively with EBRT. The HDR-IORT was performed if resection margins to the tumour were ≤2 mm. This was judged perioperatively on frozen sections. A silicon template with 1-cm-spaced parallel source tubes running through the centre of the template was placed over the marginal radical or irradical spot. This irradical spot was marked by three to four surgical clips, and size and shape of the template were adjusted to the target surface. The template was positioned and pressed against the target surface using gauze pads. The radioactive source was lead through the tubes, hereby delivering a boost with a median dose of 10 Gy at 1-cm depth from the applicator surface. IORT was not available in patients treated without preoperative radiotherapy, because they were all treated before 1997.

Statistical analysis

Local failure-free survival and overall survival estimates were calculated by the method of Kaplan and Meier.[22] All statistical analyses were executed in Stata. (Statacorp, Texas, USA) Univariate comparisons of survival endpoints were executed using the log-rank test. The Cox proportional hazards analysis was used for multivariate analysis of prognostic factors for local control and overall survival.[23] Significance was defined as $P<0.05$.

RESULTS

The median interval between treatment of the primary tumour and the diagnosis of the recurrence was 15 (range 2–72) months in the preoperatively nonirradiated group and 16 (range 5–186) months in the preoperatively irradiated group. The characteristics of the primary tumours of both groups are depicted in Table 1. Tumour histology grade, stage and type of resection were statistically not significantly different. Pain as a preoperative symptom was found in 31 percent of the patients treated for a local recurrence. Tumour characteristics and classifications for the recurrent tumours were similar for both groups treated with or without preoperative radiotherapy (Table 2). A complete (R0) resection was possible in 45 percent of the preoperatively nonirradiated group and 64 percent of the preoperatively irradiated group (P=0,08; Table 3). In 46 percent of the resections in the preoperatively irradiated group IORT was performed because of a marginal complete or incomplete resection. Operation characteristics and hospitalization are summarised in Table 3.

The duration of operation was significantly longer in patients who received intraoperative radiotherapy (IORT, 445 minutes *vs.* non-IORT, 343 min; p=0,018). Loss of blood was not statistically significantly different in patients treated with IORT (median 6500 ml; range 1500–17000) in comparison with patients who did not receive IORT (median 5000 ml; range1100- 21000; P=0,402). The results of the local control and overall survival of patients who received IORT compared with patients who did not are depicted in Table 4. Both groups are divided by the completeness of the resection (R0 vs. R1/2).

In the preoperatively irradiated group, the perioperative mortality was 3 percent (n=2) and no postoperative mortality occurred. One patient died during operation because of massive bleeding caused by disseminated intravascular coagulation, and the other because of a myocardial infarction during operation. In the group of patients that did not receive neoadjuvant radiotherapy, no perioperative and postoperative death occurred. All other complications were classified as minor. Complications and reinterventions are depicted in

Table 5. In the preoperatively nonirradiated group 88 percent of the 33 patients received postoperative radiotherapy, with a median dose of 50 (range 30–60) Gy. Eight patients were administered chemotherapy postoperatively because of positive lymph nodes or distant disease.

Table 1. Characteristics of the primary tumour

	No pre-op RTX (n=33)	**Pre-op RTX (n=59)**
Grade		
– Well differentiated	15	7
– Moderately differentiated	73	86
– Poorly differentiated	3	2
– Unknown	9	5
UICC		
– Stage 1	15	20
– Stage 2	42	39
– Stage 3	36	32
– Stage 4	0	2
– Unknown	6	7
Type of resection		
– LAR	79	56
– APR	12	32
– Hartman / Transanal resection	9	12

Pre-op RTX = pre-operative radiotherapy; No pre-op RTX = no pre-operative radiotherapy; LAR = low anterior resection; APR = abdomino-perineal resection. Data are presented in percentages

Local control

After three and five years, respectively, 28 and 18 percent of the patients of the preoperative radiation group were without local recurrence. Local control is significantly higher when compared to the 13 and 13 percent of the preoperatively nonirradiated group (P=0,037; Figure 1). Prognostic factors important for local control are shown in Table 6. Preoperative radiotherapy was the only prognostic important factor studied to have a significant impact on local control. Patients of the preoperatively irradiated group who had a complete response after radiotherapy had higher local control rate (40 percent) compared to the patients who had no complete response (14 percent), but because of small numbers this failed to become statistically significant. There is a trend towards better local control after three and five

Table 2. Tumour characteristics of rectal cancer recurrence

	No pre-op RTX (n = 33)	Pre-op RTX (n = 59)
Tumour status		
– T0	0	7
– T1	0	2
– T2	3	3
– T3	42	41
– T4	45	41
– Tx	9	6
Nodal status		
– N0	15	17
– N+	15	7
– Nx	70	76
Grade		
– Well differentiated	9	2
– Moderately differentiated	73	61
– Poorly differentiated	6	20
– Unknown	12	16
Wanebo classification		
– Tr 1(limited recurrence in submucosa)	0	2
– Tr 2 (growth in full thickness rectal wall)	3	3
– Tr 3 (growth into surrounding soft tissue)	33	41
– Tr 4 (penetration anterior structures)	30	25
– Tr 5 (penetration posterior structures)	21	19
– Unknown	12	10
Suzuki classification		
– F 0 (no contact to pelvic wall)	18	20
– F 1 (contact < ¼ of pelvic wall)	30	31
– F 2 (contact ¼ to ½ of pelvic wall)	21	19
– F 3 (contact > ½ of pelvic wall)	0	5
– F 4 (infiltration in bony structures / small bowell)	15	20
– Unknown	15	5

Pre-op RTX = pre-operative radiotherapy; No pre-op RTX = no pre-operative radiotherapy. Data are percentages

years between R0 vs. R1/2 surgery (*P*=0,079) and toward negative lymph node status of the primary rectal cancer vs. involved lymph nodes (*P*=0.067). Preoperative symptomatic pain at the time of diagnosis, Wanebo-stage and Suzuki-stage, and application of IORT had no prognostic value on local control. After multivariate analysis the effect of preoperative radiotherapy on local control was also significant (*P*=0,020; Table 7). An interval between the operation of the primary tumour and the diagnosis of the recurrence longer than one year and positive lymph node status were not predictive for local control.

Table 3. Operation characteristics

	No Preop RTX (n = 33)	**Preop RTX (n = 59)**	***P* Value**
Resection			
– R0	45	64	
– R1	36	22	
– R2	18	14	
Type of resection			
– LAR	0	5	
– APR	73	43	
– APSR	3	19	
– TPE	6	14	
– PE	18	19	
Median bloodloss (ml)	3.000	6.000	<0.001
Median operating time (min)	255	415	0.016
Median hospitalization (days)	17	24	0.189

Preop RTX = pre-operative radiotherapy; R0 = microscopically complete resection; R1 = microscopically incomplete resection; R2 = macroscopically complete resection; LAR = low anterior resection; APR = abdominoperineal resection APSR = abdominoperineal sacral resection; TPE = total pelvic exenteration; PE = Posterior exenteration. Data are percentages unless otherwise indicated

Overall survival

The three- and five-year survival rates of patients who were treated with preoperative radiotherapy were respectively 34 percent and 11 percent. These results did not differ significantly when compared to the 30 percent and 15 percent of patients who did not receive preoperative radiotherapy (*P*=0,426; Figure 2). Positive lymph nodes of the primary treated rectal cancer were an important prognostic factor for a worse survival when compared

with a negative nodal stage (*P*=0,009; Table 6). A complete response after radiotherapy is a statistically significant prognostic for an improved survival (*P*=0.024). After a complete "curative" resection (R0), the overall survival was statistically significantly improved when compared with the incomplete (R1/2) resections (*P*=0,036). Patients with preoperative symptomatic pain, IORT, and Suzuki- and Wanebo-stage had no significant different overall survival. Multivariate analysis also failed to shown an impact of preoperative radiotherapy and an interval between the operation of the primary tumour and the diagnosis of the recurrence longer than one year on overall survival (Table 7). After multivariate analysis positive lymph node status seemed prognostic for a worse overall survival (*P*=0,015).

Table 4. Three-year actuarial local control and overall survival by IORT administration and completeness of resection

	No. of patients	Local control (3yr)	Overall survival (3yr)
IORT			
– Complete (R0)	17	45	35
– Incomplete (R1/2)	10	21 (P=0.25)	21 (P=0.75)
Non-IORT			
– Complete (R0)	21	24	41
– Incomplete (R1/2)	11	19 (P=0.58)	27 (P=0.45)

IORT = intraoperative radiotherapy

Data are numbers or percentages with *P* values in parentheses

Table 5. Post-operative results

Complications and reinterventions	No Preop RTX (n = 33)	Preop RTX (n = 59)
Minor	52	59
Major	21	26
Reinterventions	9	15
Postoperative radiotherapy	88	15
Postoperative chemotherapy	24	2

Preop RTX = preoperative radiotherapy. Data are percentages

Table 6. Local control and overall survival

		Local control			Overall survival		
	No. of patients	**3-year**	**5-year**	***P* Value**	**3-year**	**5-year**	***P* Value**
Negative lymph nodes primary	57	24	20		35	20	
Positive lymph nodes primary	33	14	7	0.067	28	-	0.009
No symptomatic pain	61	20	17		35	16	
Symptomatic pain	30	27	14	0.445	30	9	0.681
Preop RTX	59	28	18		34	11	
No Preop RTX	33	13	13	0.037	30	15	0.426
Suzuki stage 0,1,2	64	23	23		33	12	
Suzuki stage 3,4	20	17	-	0.525	31	8	0.857
Wanebo Tr 1 – 3	39	18	18		37	6	
Wanebo Tr 4 – 5	43	16	5	0.889	22	11	0.427
Complete response	6	80	40		100	67	
Incomplete response	53	20	14	0.186		0	0.011
Complete (R0) resection	53	31	26		39	21	
Incomplete (R1/2) resection	39	11	5	0.079	24	3	0.036
IORT	27	34	23		31	24	
Non-IORT	32	17	14	0.084	33	11	0.375

Preop RTX = pre-operative radiotherapy; IORT = intra-operative radiotherapy; - = not assessable
Data are percentages unless otherwise indicated. All bold data are significantly different (P<0.05)

Table 7. Multivariate Cox-analysis for local control and overall survival

		Local control			Overall survival		
	No. of patients	**Hazard ratio**	***P* Value**	**Confidence Interval**	**Hazard ratio**	***P* Value**	**Confidence Interval**
Radiotherapy							
– No Preop RTX	33	1			1		
– Preop RTX	59	0.529	0.02	0.31-0.90	0.791	0.334	0.49-1.24
Interval prim-rec							
– <12 months	34	1			1		
– >12 months	58	0.667	0.144	0.38-1.15	0.88	0.606	0.54-1.43
Lymph Node status							
– negative	59	1			1		
– positive	33	1.735	0.054	0.98-3.04	1.852	0.015	1.13-3.04

Preop RTX = pre-operative radiotherapy; Interval prim-rec = interval between operation primary tumour and diagnosis recurrence

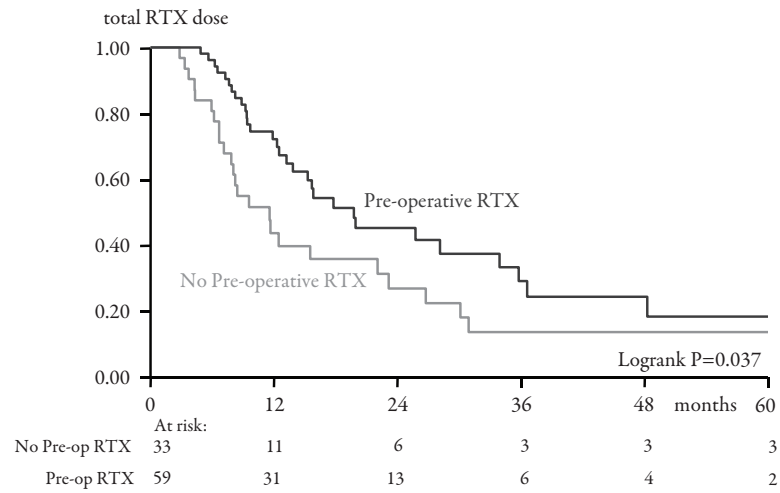

Figure 1: Local control pre-operative RTX vs no pre-operative RTX

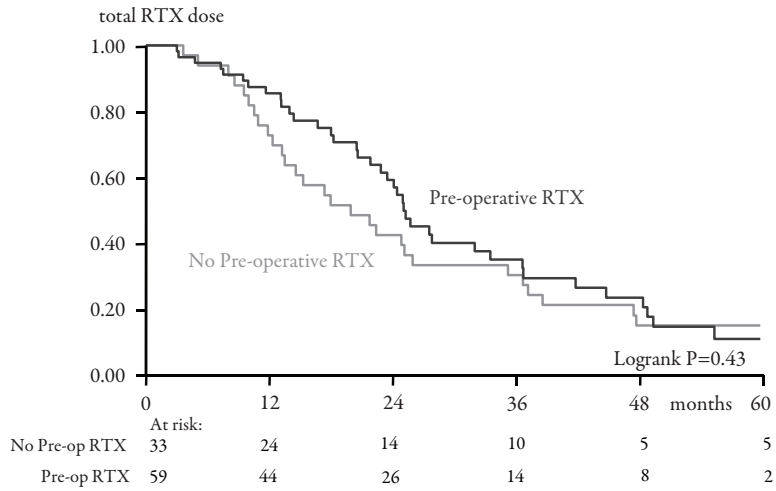

Figure 2: Overall survival pre-operative RTX vx. no pre-operative RTX

DISCUSSION

Local recurrent rectal cancer has a poor prognosis. Local radiotherapy can offer good palliation for some months, but has not been associated with long-term survival benefits.[24] A selective group of patients with recurrent disease can be operated on with curative intent.[7] The choice of therapy depends upon prior therapy and the local extent of the recurrence. Curative treatment seems best possible in selected patients with true anastomotic recurrence or those without pelvic sidewall involvement and early detection of the tumour.[18] Factors contributing to improvement of surgery for recurrent rectal cancer in the recent decade are the improved preoperative workup with advanced radiodiagnostic techniques, ameliorated preoperative treatment modalities, and the possibility of the performance of more extensive operations.[7,25-28]

The use of preoperative radiotherapy in the treatment of recurrent rectal cancer with curative intent is based upon studies in primary rectal cancer that identify a beneficial effect of radiation therapy on the resectability, the local control, and even overall survival.[29,30] However, there are no good comparative data from prospective trials in recurrent rectal cancer. In this article, we have focussed on the effects of preoperative radiotherapy, without adjuvant chemotherapy. For an identification of the effect of the neoadjuvant radiotherapy, we have compared our series of patients who were all treated by a multimodality approach

(preoperative radiotherapy, surgery, and IORT on indication) with a historical group of patient treated with surgery only, followed by postoperative radiotherapy in most patients (88 percent). Although overall follow-up for the total group of patients is relatively short for determining differences in local failure (16 months), we were able to show a significant difference in local control in favour of patients who received preoperative radiotherapy (P=0,037). Because of the nonrandomised character of our study the difference in local control cannot be entirely attributed to the preoperative radiotherapy. Both groups, however, are highly comparable concerning the tumour stages of the primary and recurrent tumours. The multivariate analysis also indicated the beneficial prognostic value of preoperative radiotherapy on local control (P=0,02). We were not able to identify a beneficial effect of the neoadjuvant radiotherapy on overall survival. Overall survival is dependent on the development of metastases, which is not influenced by local treatment modalities, but might be improved with new systemic adjuvant chemotherapy protocols. Pathological analysis of the resection specimens showed that preoperative radiotherapy was associated with multiple histological changes such as necrosis and fibrosis, resulting in a 10 percent complete response percentage. This percentage compares favourable to response rates of 5 to 9 percent reported in the literature after neoadjuvant (chemo)radiation treatment protocols.[4,7,31] Wanebo et al. described that patients with a complete response to neoadjuvant therapy showed an identical behaviour to the rest of the group.[15] In contrast to these results. Our small group (n=6) of patients with CR did not only show a trend towards improved local control but also a statistically significantly improved overall survival when compared with patients who did not have a complete response after preoperative radiotherapy.

Preoperative radiation causes destruction of malignant cells, but also postradiation fibrosis. Both in preoperative and perioperative staging, it is hard to differentiate between post-radiation fibrosis and tumour cells.[31] In the preoperative setting the diagnostic modalities cannot always differentiate the tumour from fibrosis.[26,32] Differentiation between tumour and fibrosis, but also growth and invasion of tumour have major consequences for the treatment and prognosis of the patient. Recent studies have shown that with the modern magnetic resonance imaging techniques a higher accuracy can be guaranteed when compared with the CT scan staging.[25,27] Perioperative staging problems consist of a limited possibility of identification of microscopically positive margins. To avoid this problem of intraoperative assessment our pathology department examines the resected material with frozen section examination during the operation when there is doubt of the surgical margins.

In the past, resections of recurrent rectal cancer that resulted in complete removal of all tumours were scarce; reported R0 resections were approximately 20 percent.[33] Studies

showed that the current multimodality treatment provides possibility for curative resection in 40 to 80 percent.[4,7,31,34-38] Our R0 resection rate of 64 percent is comparable with these published results and was nearly 20 percent higher when compared with patients who did not receive preoperative radiotherapy. We assume that this difference is caused by the effect of downstaging and downsizing after neoadjuvant radiotherapy. Both preoperative and postoperative radiation have the capability to sterilise tumour cells to a certain extend, but the effect of preoperative radiotherapy facilitates more complete resections. The higher rate of complete resections in our group can also be explained by the more extensive surgery performed in the preoperatively irradiated group. Our repertoire of surgical techniques performed to obtain negative surgical margins has developed in recent years. This development is visible in the higher rate of performed sacral resections and total pelvic exenterations. Wanebo and Marcove[28] reported in 1981 that palliative resection of tumours with invasion or tight adherence to the sacrum can be safely performed; however sacral resections are associated with a high morbidity rate that differs between 42 and 82 percent.[39,40] The value of performing a complete resection was shown by the significant better overall survival after complete (R0) resections when compared with incomplete (R1/2) resections (p=0,036). A beneficial effect on the local control was noticed in our group, however without statistical significance.

Two techniques for intraoperative radiotherapy have been developed; intraoperative electron beam radiotherapy (IOERT), and the other is the high-doserate brachytherapy (HDR-IORT). In our centre patients are treated with HDR-IORT in case of a positive or narrow surgical margin IORT, thereby delivering a radiation boost to a specific area without exceeding the radiation limits of adjacent normal tissue and with the possibility of sterilizing the pelvis from any residual tumour. Although there are no data from prospective randomised study, there are previous studies that suggest a safe performance and beneficial effect on local control. In some studies a beneficial effect on survival has been demonstrated after an intraoperative radiation boost.[4,18,41-44] In our series we applied IORT in the group of patients with marginal radical resections or irradical resections, a group with an unfavourable prognosis on local control and survival when compared with the patients with a widely resected tumour. Table 4 shows that despite this worse prognosis, local control and overall survival of the intraoperatively irradiated group were not significantly different from patients with a widely resected tumour. This pleads for the use of IORT, because IORT ameliorates and equalises the unfavourable prognosis of the patients with positive surgical margins up to the level of the group of patients with complete resections. Gross residual

remains one of the most significant predicting factors for local and systemic failure, because HDR-IORT cannot compensate for these macroscopically incomplete resections.[7,45]

In contrast to previously published data that indicate significantly higher postoperative morbidity rates after preoperative radiotherapy, we cannot demonstrate a significant difference when compared with our nonirradiated historical group.[31,46] A higher rate of complications could be expected in the preoperatively irradiated group because of the higher rate of extensive resections. Most common morbidities were minor wound infections and poor wound healing, as described in other studies.[31] The major complications rate of 26 percent in the preoperative radiation group was identical to a previous report by the Mayo Clinics.[7] Intraoperative loss of blood and operating time were high in patients who were operated on by the modern standards. These differences can be explained by the more extensive surgery that was performed. The higher operating time after the modern multimodality treatment can be attributed to the application of IORT, which is a time consuming procedure. Saito et al. reported results for blood loss that were comparable to our results, but their operating time was near twice as high.[35] Resection of the recurrent tumour was feasible with 3 percent perioperative mortality and no 30-day postoperative mortality. Both patients who died during operation were treated with preoperative radiotherapy, due to small numbers this is not significantly different from the rate in the historic nonirradiated group and is comparable to mortality rates described in the literature.[7,18,31,35,47-49]

Because of the altered anatomy after prior surgery the conventional staging systems are inadequate for recurrent rectal cancer. The UICC TNM classification, used to classify the primary tumour, cannot be used because the visceral fascia surrounding the rectum has been resected and the recurrence is not confined to the original rectal boundaries.[13]Therefore, other classification systems have been developed. Suzuki and co-workers from the Mayo Clinics use a system that is based on the degree of fixation of the tumour to the surrounding organs or structures according to pathological and/or surgical examination.[18]Wanebo *et al.* uses a modified version of the UICC TNM-classification, which resembles the original system, with an exception of the addition of an extra stage. This stage, Tr5, indicates extensive invasion of the pelvis.[15] In our study we have used both classification systems and did not find any predictive value of the two staging systems on local control and overall survival. This is in contrast with results of the Mayo-Clinics, which showed an increased number of sites were significantly associated with a decreased local control and an inferior survival.[7,18] An increasing number of sites involved, indicated by the Suzuki-classification, can point out a more advanced stage of recurrence. Until now, only two studies reported a significant influence of fixation site on the local control and survival.[7,48] When we compared the

Suzuki stages F0-F2 with the Suzuki stages F3-F4, no significant differences were found. Comparison of the Wanebo stage Tr1-3 tumours with the Wanebo Tr4-5 also showed no significant differences in local control, survival, and metastases free survival.

Symptoms accompanying the recurrence, especially pain can be related with an inferior outcome in both local control and survival. Alike, the degree of fixation, symptomatic disease indicates a more advanced recurrence, which will require more extended surgery to obtain radical margins.[7,42] Preoperative symptomatic pain had no significant prognostic value for local control and overall survival in our series.

In the choice of treatment and prognosis for patients with recurrent rectal cancer not only the current tumour stage of the recurrence is of importance. Our study shows a significant negative influence of the positive nodal stage of the primary tumour on overall survival (P=0,009).

CONCLUSION

Overall survival of the patients with recurrent rectal cancer is poor. The application of preoperative radiotherapy has lead to a significant better local control in our group. New modalities, such as neoadjuvant chemoradiation, seem promising to improve resectability and the rate of sphincter-saving procedures.[4,31] Prospective randomised studies containing these new modalities have to be conducted. A new radiotherapy technique, intensity modulated radiotherapy, which has been introduced recently in our cancer centre will offer the possibility to reduce radiation toxicity to surrounding vital structures and to deliver higher dosages to the tumour. The treatment of recurrent rectal cancer is complicated and requires the latest in modern diagnostic and operational techniques. It has to be performed in a specialised hospital with a multidisciplinary team that can provide a high quality preoperative workup and perform the complicated and often extended resections.

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Chapter VII

Treatment of recurrences after transanal endoscopic microsurgery (TEM) for T1 rectal cancer

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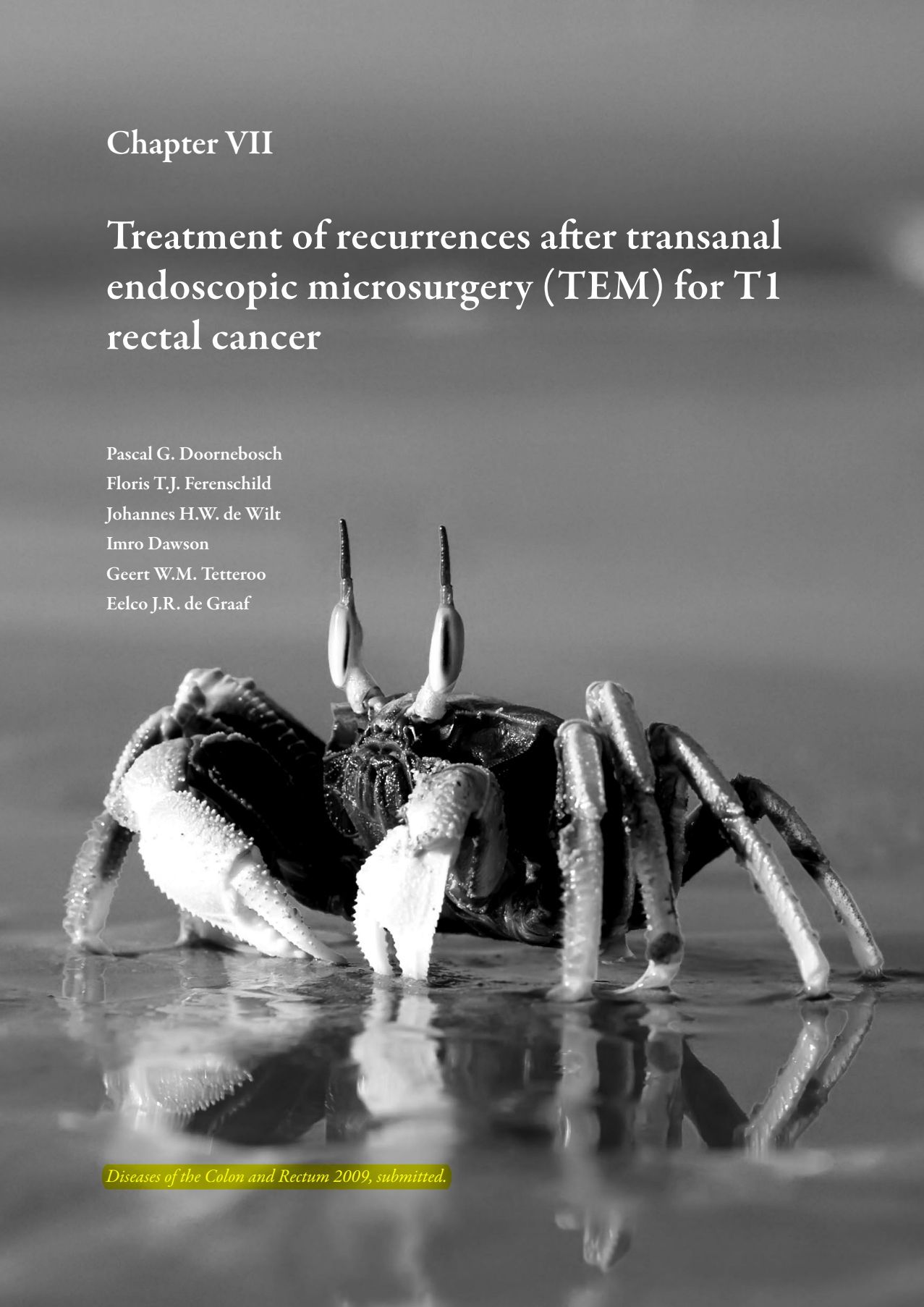

Diseases of the Colon and Rectum 2009, submitted.

ABSTRACT

Purpose

Recurrent disease after local excision of T1 rectal cancers is not uncommon, but its impact on survival is not clear. Aim of this study is to evaluate the management and outcome of local recurrences after transanal endoscopic microsurgery (TEM) for T1 rectal cancer.

Methods

A total of 88 consecutive patients who underwent TEM for pT1 rectal cancer were registered in a prospective database. Of these eighteen patients developed a local recurrence during follow-up. In this study these 18 patients were analysed with special emphasis on salvage surgery and survival.

Results

Median time to local recurrence was 10 months (range, 4–50 months). Median age at diagnosis of the recurrence was 73 years (range, 56–83 years). Two patients were not operated because of concomitant metastatic disease. All of the remaining sixteen patients underwent salvage surgery, without the need for extensive surgical procedures. In 44% of patients a permanent colostomy was created. There was no postoperative mortality. Fifteen patients had a microscopic radical resection and one patient a microscopic irradical resection. Median follow-up following salvage surgery was 20 months (range, 2–112 months). One patient developed a re-recurrence and seven patients developed distant metastases. The 3-year overall survival was 29% and the 3-year disease-free survival was 57%.

Conclusions

Recurrent disease after TEM for T1 rectal cancer is a major problem. Although salvage surgery is feasible in most of the patients, survival is impaired. A microscopic radical resection can almost always be obtained, without the need for extensive surgical procedures. In the near future we need to focus on improving selection in T1 rectal cancers suitable for TEM. Also possible adjuvant treatment strategies following salvage procedures need to be explored, in order to safe as many patients the adverse effects of TME.

INTRODUCTION

Total mesorectal excision (TME) is the gold standard for rectal cancer, because this treatment modality offers the highest chance of cure. This standardised and optimised surgical technique has lowered the recurrence rates and improved survival.[1, 2] In an attempt to avoid the substantial morbidity and mortality of TME, local excision has been suggested a therapeutic option in the treatment of well-selected patients with early rectal cancer. But, after transanal excision unacceptable high rates of incomplete tumour removal in up to 39 percent have been observed, proven to be a key predictor for recurrence.[3-7]

Transanal endoscopic microsurgery (TEM), introduced by Buess *et al.*[8], is an optimised technique for the removal of rectal tumours. This technique enables excellent access and visualization of the surgical field and allows precise and full-thickness excision of the tumour. Using TEM, the rate of microscopic radical excision margins, even with standardised pathology, for T1 tumours has increased to more than 90%.[9, 10] Because of this latter, in combination with the very low mortality and morbidity rates, TEM is nowadays considered a potential curative alternative for T1 tumours by many surgeons.[3, 11, 12]

However, even after TEM, local recurrence rates range from 0 to 24%, and the results of salvage surgery in recurrent tumours are matters of concern.[13-15] In the literature only few series report on surgical procedures and outcome of recurrent disease after transanal surgery.[16-18] To our knowledge no data exist on patients treated for a recurrence after TEM surgery. In this study we present the outcome of patients with a local recurrence after TEM for T1 rectal cancer.

PATIENTS AND METHODS

From 1996, in the IJsselland hospital, a referral centre for TEM, 88 consecutive patients underwent TEM for pT1 rectal cancer and were followed as part of a prospective, comparative study. As described previously all patients were screened according to a standard protocol. [15] The initial TEM procedure was performed by two surgeons. Full-thickness excision was performed in all lesions. All specimens were pinned on cork and were studied according to standardised pathology. None of the patients received any form of (neo-) adjuvant treatment. Only patients with microscopic complete excision margins were considered eligible for intensive follow-up. Follow-up was according to the Dutch guidelines on rectal cancer with additional rigid rectoscopy and endorectal ultrasound (ERUS) every 3 months the

first 2 years, and every 6 months thereafter for the detection of local recurrences. Magnetic resonance imaging (MRI) of the lesser pelvis was introduced as a part of the follow-up protocol during the study period., and nowadays is routinely performed at 12, 24 and 36 months following TEM. A local recurrence was defined as recurrent tumourous tissue within the lesser pelvis and endoluminally, if present, within the proximity of the scar tissue of the initial operation. Histological confirmation was mandatory. When appropriate, salvage surgery was performed. Initially patients were treated without neo-adjuvant treatment (five patients), later on with preoperative short-course radiotherapy (six patients) and nowadays with preoperative long-course chemoradiotherapy (five patients).

Following salvage surgery, patients were followed according to the Dutch guidelines for rectal cancer. Patient data were collected in a central, digital database. Percentages and continuous data were compared using the Chi-square test or the Mann-Whitney test, respectively. Patient survival was assessed using the Kaplan-Meier life-table method. *P* values given are two-tailed; $P=0.05$ was considered the limit of significance.

RESULTS

Out of 88 patients followed, in 18 patients a local recurrence occurred. Patient and salvage characteristics are depicted in table 1 and 2. Median age of patients at the time of recurrence was 74 years (range, 56 to 84), 50% of the patients were male. Median time to a local recurrence after the initial TEM procedure was 10 months (range, 4 to 50). Ten recurrences were found intra-luminal in the proximity of the scar during rectoscopy and in six patients an extra-luminal recurrence was found with ERUS during intensive follow-up visits. In two patients a late recurrence was detected only with MRI. The first patient (patient number 13) withdrew from the intensive follow-up protocol, and one year after the last visit a MRI was performed because of complaints, and a locally advanced (cT4) recurrence was diagnosed. The second patients (patients number 15) had complaints in between two (intensive) follow-up visits, and also additional MRI was performed. A locally advanced local recurrence (cT4) was diagnosed, which probably was missed at rectoscopy and ERUS. Following neo-adjuvant chemoradiotherapy a microscopic radical resection was possible in both.

Two patients were not operated. One patient (patient number 9) was initially diagnosed as having a tubulovillous adenoma. After a T1 carcinoma was diagnosed, additional investigations, focusing on metastatic disease, were not performed. Six months after the TEM procedure already a local recurrence was suspected, which could only be confirmed

half a year later, after several biopsies. At the time of diagnosis, massive hepatic metastases were found and based on these findings and patients' condition, no treatment was started. She died three months later. The other patient (patient number 6) withdrew from intensive follow-up and presented elsewhere with low back pain 20 months after the TEM procedure. A clinical T4 local recurrence was found with synchronous metastatic disease in the liver. Palliative chemotherapy was started, and the patient died ten months later.

All remaining 14 patients adhered to the intensive follow-up protocol. In two patients (patient number 3 and 6) synchronous liver metastases, initially deemed resectable, were found. Despite obtaining a microscopic radical resection in both, rapidly progressive metastatic disease developed and patients were treated with palliative chemotherapy. They died eight and respectively 22 months following the salvage procedure.

In 15 out of 16 salvage procedures, a microscopic radical resection was possible without the need for extensive surgical procedures. In one patient a microscopic irradical resection (R1) was performed, and patient received adjuvant chemotherapy. There was no post-operative mortality. Median follow up after salvage treatment of all patients with a recurrence was 20 months (range, 2-112). One of the operated patients developed a local re-recurrence and 7 patients developed distant metastases and died because of progressive disease.

The actuarial 3-year overall survival was 29% (figure 1). Patients in which a microscopic radical resection could be obtained without the presence of metastatic disease, 3-year survival was better compared to non-operated patients, stage IV disease at presentation or microscopic irradical resections (40 versus 0%; p=0.001).

The 3-year disease-free survival was 57% (figure 2).

DISCUSSION

Transanal endoscopic microsurgery (TEM) is method of choice in the treatment of rectal adenomas. Morbidity and mortality are reduced in comparison to total mesorectal excision (TME).[15] But in rectal cancer the choice for type of surgical treatment has to be based on more than differences in morbidity and mortality of the surgical procedure. When considering local excision for fit patients with rectal cancers, surgeons face a dilemma. Although, a large majority (70-85%) of patients are cured by TEM, the risk of cancer recurrence is substantially higher, varying between 10% and 28% for pT1 rectal cancer.[19-22] After TME this is reported to be only 0.4 to 1.7%.[2, 19, 23]

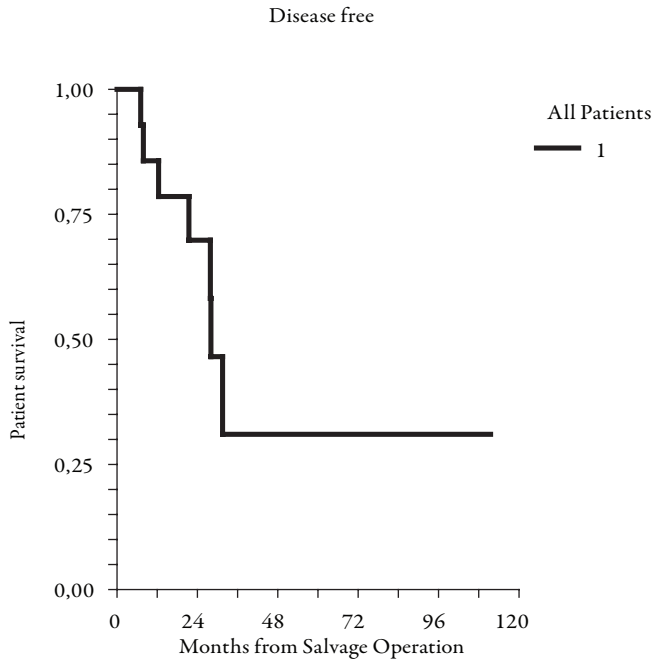

Figure 1. Overall survival following salvage operation

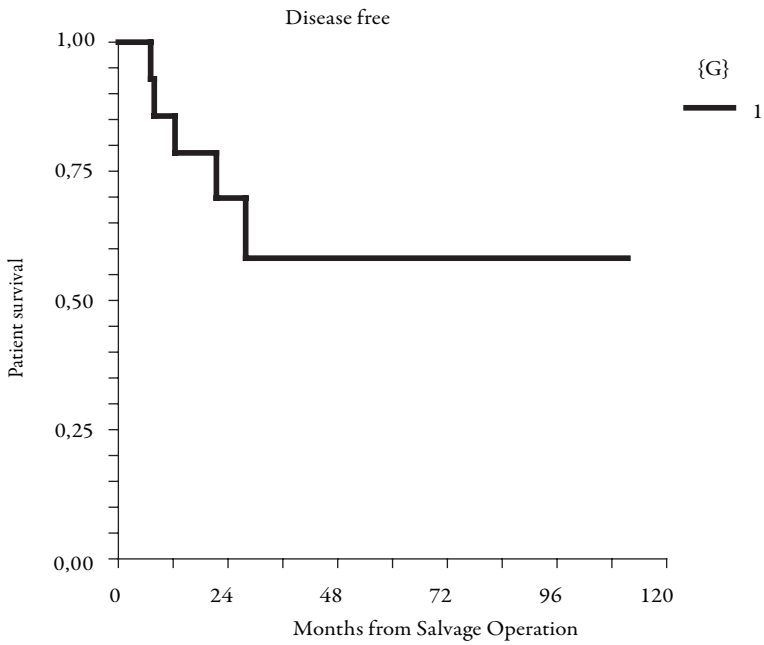

Figure 2. Disease free survival following salvage operation

Table 1. Patient- and initial tumour characteristics

Patient number	Age	Sex	Asa-classification	Low- vs high-risk	Disease free interval (months)
1	74	female	2	LR	10
2	83	female	3	LR	6
3	79	male	3	HR	19
4	82	male	3	LR	5
5	77	female	3	LR	7
6	72	female	1	LR	20
7	68	male	3	HR	5
8	61	male	3	HR	12
9	84	female	2	LR	11
10	56	male	1	LR	6
11	80	male	2	LR	11
12	71	female	1	LR	12
13	75	male	3	LR	41
14	72	female	1	LR	10
15	64	male	1	LR	50
16	80	female	1	LR	24
17	73	female	2	LR	4
18	59	male	1	LR	7

ASA= American Society of Anaesthesiology; LR= low-risk; HR= high-risk
Low-risk= good or moderately differentiated without lymf-/angioinvasion
High-risk= poor differentiated and/or lymf-/angioinvasion

In most studies reporting on local recurrences following local excision for T1 rectal cancers, there is a bias in patient and tumour selection. This is a major confounding factor when interpreting outcome. In the present series, all T1 rectal cancers excised with TEM were included, out of a consecutive group of patients and regardless of other histopathological criteria. Pathology was standardised and a microscopic radical excision (R0) had to be confirmed.[15] In contrast to primary TME, in our series obtaining a R0 excision did not prevent from a local recurrence. Therefore, improving tumour selection is of major importance. Whether basic histopathological criteria, differentiating high- and low-risk T1 rectal cancers, is able to perform this, is subject of debate. [24-27] Further studies focusing on adequate tumour selection are urgently needed.

Table 2. Salvage and survival characteristics.

Patient number	Type of salvage surgery	Neoadjuvant therapy	TNM	R0 vs R1	DM/other	FU duration (months)	Survival status
1	APR	none	pT3N0M0	R0	-	112	Alive
2	APR	none	pT2N1M0	R0	-	32	DNCR
3	HP	5x5	pT3N2M1	R0	Liver	22	DCR
4	APR	none	pT2N0M0	R0	-	28	DNCR
5	LAR	5x5	pT3N0M0	R0	-	92	Alive
6	None	none	cT4NxM1	-	Liver	10	DCR
7	APR	5x5	pT3N0M1	R0	Liver, lung	7	DCR
8	LAR	5x5	pT3N2M0	R1	Liver	13	DCR
9	None	none	cT3NxM1	-	liver	3	DCR
10	LAR	5x5	pT3N0M0	R0	-	31	Alive
11	LAR	5x5	pT3N1M0	R0	Lung, re-LR	27	DCR
12	LAR	none	pT3N0M0	R0	-	25	Alive
13	APR	CRT	pT0N0M0	R0	-	27	Alive
14	LAR	none	pT3N0M0	R0	-	20	Alive
15	APR	CRT	pT3N0M0	R0	-	18	Alive
16	LAR	CRT	pT3N2M0	R0	liver	8	DCR
17	LAR	CRT	pTisN1M0	R0	-	6	Alive
18	LAR	CRT	pT0N1M0	R0	-	2	Alive

APR= abdomino-perineal resection; LAR= low anterior resection; HP= Hartmann's procedure; TNM= tumour node metastasis classification; R0= microscopic radical resection, R1= microscopic irradical resection; DM= distant metastasis; FU= follow-up; 5x5= short-course radiotherapy, 5 times 5 Gray; CRT= chemoradiotherapy; DNCR= died non-cancer related; DCR= died cancer related; re-LR= renewed local recurrence

Besides improving patient selection, early diagnosis of a local recurrence is considered of utmost importance. Local recurrences may be intra-luminal or extra-luminal. Therefore, next to rectoscopy, endorectal ultrasound is mandatory in the follow-up regimen in patients treated with TEM for T1 rectal cancer. In our series, six out of 18 local recurrences were solely found with ERUS, which otherwise may have been missed. This was also found in other series focusing on the role of ERUS in the follow-up regimen of locally excised rectal cancers. (ref Hernandez et al, DCR 2004) ERUS however, still has its limitations and therefore MRI of the lesser pelvis is added as well in our hospital. This was mainly based on the two patients with a late recurrence, of which one was actually missed with rectoscopy and ERUS. By applying this intensive follow-up regimen in our patients, out of 16 patients who adhered to this protocol, only one was diagnosed at an advanced, incurable stage. In the remaining patients, almost always a microscopic radical resection was possible (93% R0).

The three-year overall survival in the total group of patients with a local recurrence is low (29%), and improving outcome for this initial early staged cancers is imperative. Obtaining a microscopic radical resection is a prerequisite, however does not seem to be the only parameter influencing outcome. In the present series the large number of patients diagnosed with metastatic disease is striking. Never metastatic disease occurred without a local recurrence. Maybe this actually is a biological different group, and salvage treatment should be intensified. Adding adjuvant treatment in patients with a local recurrent tumour might improve outcome, although based on this series this will be impossible to prove as only patient was given adjuvant treatment. Curative options in the presence of metastatic disease are limited and does influence the survival-rates in our series. One has to realize in our series seven patients were ASA 3 and therapeutic options were limited anyhow. This is also reflected by the higher 3-years disease-free survival of 57%, meaning patients actually died from other causes and were saved the adverse effects of a TME.

In conclusion, recurrent disease after TEM for T1 rectal cancer is a major problem. Although salvage surgery is feasible in most of the patients, survival is impaired. A microscopic radical resection can almost always be obtained, without the need for extensive surgical procedures. In the near future we need to focus on improving selection in T1 rectal cancers suitable for TEM. Also possible adjuvant treatment strategies following salvage procedures need to be explored, in order to safe as many patients the adverse effects of TME.

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Part IV

EXTENDED RESECTIONS AND RECONSTRUCTIONS

Chapter VIII

Total pelvic exenteration for primary and recurrent malignancies

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World Journal of Surgery 2009; 33:1502-1508.

ABSTRACT

Introduction

Complete resection is the most important prognostic factor in surgery for pelvic tumours. In locally advanced and recurrent pelvic malignancies radical margins are sometimes difficult to obtain, because of close relation to or growth in adjacent organs/structures. Total pelvic exenteration (TPE) is an exenterative operation for these advanced tumours and involves en bloc resection of the rectum, bladder and internal genital organs (prostate/seminal vesicles or uterus).

Methods

Between 1994 and 2008 a TPE was performed in 69 patients with pelvic cancer; 48 rectal cancer (32 primary and 16 recurrent), 14 cervical cancer (1 primary and 13 recurrent), 5 sarcoma (3 primary and 2 recurrent), 1 primary vaginal – and 1 recurrent endometrial carcinoma. Ten patients were treated with neo-adjuvant chemotherapy and 66 patients with preoperative radiotherapy to induce down staging. Eighteen patients received IORT because of an incomplete or marginal complete resection.

Results

The median follow up was 43 months (range 1–196). Median duration of surgery was 448 min (range 300-670), median blood loss was 6300 ml (range 750-21000) and hospitalization was, 17 days (range 4–65). Overall major and minor complication rates were 34% and 57%, respectively. The in hospital mortality rate was 1%. A complete resection was possible in 75% of all patients, a microscopically incomplete resection (R1) in 16% and a macroscopically incomplete resection (R2) in 9%. Five-year local control for primary locally advanced rectal cancer, recurrent rectal cancer and cervical cancer was respectively 89%, 38% and 64%. Overall survival after 5 year for primary locally advanced rectal cancer, recurrent rectal cancer and cervical cancer was 66%, 8% and 45%.

Conclusion

Total pelvic exenteration is accompanied with considerable morbidity, but good local control and acceptable overall survival justifies the use of this extensive surgical technique in most patients, especially patients with primary locally advanced and recurrent cervical cancer.

INTRODUCTION

Locally advanced pelvic tumours without distant metastases can cause severe local problems, such as pain, defecation problems and can result in a decreased quality of life.[1, 2] Extensive surgery is often the only possibility for complete resection, thereby attempting to provide local control and palliation. In case of involvement of the base or trigone of the bladder or the prostate, a total pelvic exenteration (TPE) with resection of the rectum together with bladder, lower ureters and internal genital organs could potentially salvage the patient.[3] After resection of the bladder an ileal conduit is usually constructed according to the technique described by Bricker.4 TPE has been performed in primary or recurrent cancer of the cervix, rectum, vagina, uterine corpus, vulva, prostate, bladder and in pelvic sarcoma.[5, 6]

Since the introduction of the technique by Brunswick in 1948 the initially poor quality of life and high mortality and morbidity associated with the technique have substantially improved.[7-9] However, morbidity after this extensive surgical procedure is still high and reports between 13% and 64%.[10-12] Five-year survival rates after TPE for patients with primary disease range between 32% and 66% and in patients with recurrent disease from 0% to 23%.[3, 7, 12] Hence, a careful selection in a multidisciplinary setting of patients is of paramount importance.

In the present study, all patients who underwent a pelvic exenteration were reviewed. Preoperative morbidity and mortality, local recurrence, disease free and overall survival rates were studied and prognostic factors for local control or survival were analysed.

PATIENTS AND METHODS

In the Erasmus University Medical Centre - Daniel den Hoed Cancer Centre, 69 TPE's were performed in the period between 1994 and 2008 for locally advanced primary or locally recurrent pelvic malignancies. Forty-eight patients with rectal cancer (32 primary locally advanced and 16 recurrent), 14 with cervix cancer (1 primary and 13 recurrent), 5 with pelvic sarcoma (3 primary and 2 recurrent), one primary vagina carcinoma and one recurrent endometrial carcinoma. Fifty patients were male, with a median age of 61 years (range 30–76 years).

Patients were preoperatively analysed and selected using CT- and/or MRI-scanning of the small pelvis (90% and 59%, respectively). On indication a cystoscopy was used to identify

growth into the bladder. Screening for distant metastases was performed using thoracic and abdominal CT-scan in all patients.

All 32 patients with primary rectal cancer received 50 Gy preoperative (chemo)radiation. Thirteen of twenty-six patients (10 cervical, 2 sarcoma and 1 rectal cancer patient) with recurrent cancer previously received radiotherapy during treatment of the primary tumour (median dosage 50 Gy, range 46-60 Gy). One patient was re-irradiated (27Gy) after 50Gy adjuvant radiation after primary treatment for rectal cancer. One patient with recurrent rectal cancer received chemotherapy as primary treatment. Primary surgery for patients with recurrent cancer is described in Table 1.

Table 1. Previous procedures in patients with recurrent pelvic cancer

Rectal	n=16	Abdominal perineal resection	8
		Low anterior resection	5
		Rectosigmoid resection and end colostomy	3
Cervical	n=13	Radical hysterectomy	7
		Extrafascial abdominal hysterectomy	3
		Vaginal hysterectomy	1
		Chemoradiation	2
Sarcoma	n=2	Local excision	1
		Hysterectomy	1
Endometrial	n=1	Abdominal uterus extirpation	1

In 1997 an intraoperative radiation therapy (IORT) program was started in our hospital and the technique is described previously.[13] Briefly, IORT with HDR brachytherapy was given to patients who had a minimal circumferential free resection margin equal to or less than two millimeters. The resection margin was judged on frozen sections taken during surgery. IORT was performed using the Flexible Intraoperative Template (FIT) developed at our department, delivering a dose of 10 Gy, usually at 1 cm depth from the applicator surface.

Pathology

All staging, except from the staging of sarcoma, was performed according to the AJCC TNM criteria, and completeness of resection was divided in R0 (complete resection of tumour), R1 (microscopic tumour remnant in circumferential margin) and R2 (macroscopically not complete resection). Recurrent rectal tumours were staged according to the Wanebo

classification for recurrent tumours.[14] Since 2002 all pathology examination for rectal cancer was performed by the guidelines of Quirke.15

Evaluation of morbidity and mortality

Hospital charts were studies to collect patient characteristics, operation techniques and follow-up. Surgery related morbidity is divided in major and minor complications. Major morbidity is defined as a complication that requires (surgical) reintervention. All other complications were classified as minor.

Statistical analysis of survival and local control

Survival time was calculated from the date of resection of the tumour until the last follow-up attendance or until death. Local control was calculated from the date of resection until the histological or evident radiological presence of a local recurrence. The cumulative survival and local control rate after surgery were calculated using the Kaplan-Meier method.[16] Univariate survival comparisons were executed using the log-rank test. The Cox proportional hazards analysis was used for multivariate analysis of prognostic factors for local control and overall survival.[17] The level of significance was defined as $P<0.05$.

RESULTS

At the time of diagnosis patients presented with complaints of pain (19%), changes in defecation (25%), changes in urinary miction (7%), perineal pressure (6%) and with a combination of these complaints (33%). Only 7 patients (10%) did not have complaints and were diagnosed during routine follow-up.

At preoperative physical examination 47% of the gynaecological tumours were clinically fixed to the rectum and 74% percent of the rectal tumours were clinically fixed to the prostate and bladder.

An exploratory staging laparotomy to create a colostomy or ileostomy was performed in fifteen patients (one sarcoma, one recurrent cervical, 12 primary locally advanced and one recurrent rectal cancer). No distant metastases were found during prior surgery and preoperative screening.

Preop*erative treatment*

Ten patients (14%) received neo-adjuvant chemotherapy (5 rectal cancer, 1 primary and 3 recurrent cervical and 1 vagina carcinoma). Forty-six patients (67%) received preoperative radiotherapy (median dosage 50Gy, range 27–67 Gy).

Surgery

The median duration of surgery was 448 minutes (range 300–670). The median bloodloss was 6300ml (range 750–21000ml). Fifty-eight patients received a small bowel as urostoma and 11 patients a colon conduit. In all but 6 patients an omentoplasty and in 5 patients an unilateral gracilis muscle transposition was used for primary pelvic reconstruction. Indirect reconstruction with gracilis transposition (one bilateral and three unilateral) was performed in 3 patients because of persistent perineal wounds. No flap-necrosis occurred and eventually after secondary reconstruction all perineal wounds closed in a median of 86 days (range 43–304 days).

Intra-and post-operative treatment

IORT was applied in 18 patients (6 primary rectal, 10 recurrent rectal, 2 recurrent cervical cancer): 8 with a marginal radical (R0) resection, 9 with a microscopically irradical resection (R1) and 1 with macroscopic tumour mass (R2).

One primary sarcoma and two recurrent cervical tumours were post-operatively irradiated. None of the patients received adjuvant chemotherapy.

Postoperative

TNM- and Wanebo stages and completeness of resection are depicted in table 2. The median postoperative hospital stay was 17 days (range 4–65) with an increase for the recurrent tumours compared to the primary treated tumours (20 *vs.* 14 days).

Complications are depicted in table 3. The most common minor complications were a superficial wound infection (34%) and pulmonary infections (8%). Forty-eight percent of all reinterventions were performed because of complications related to the construction of the urostomy. All these patients had received radiotherapy (1 in primary treatment, 9 in neo-adjuvant setting and one as well in previous treatment, intraoperatively as in adjuvant treatment).

The major and minor complication rates were not significantly different for patients treated with or without radiotherapy.

Table 2. Pathology characteristics

		Rectal		Cervical	
		Prim	**Rec**	**Prim**	**Rec**
Total no.		32	16	1	13
T stage	T0	-	8%*	-	9
	T2	-	-	-	9
	T3	35%	25%**	-	36
	T4	65%	67%***	100%	45
N stage	N0	57%	42%	100%	45
	N1	9%	16%	-	-
	N2	9%	-	-	-
	Nx	26%	42%	-	54
Completeness	R0	82%	58%	100%	64
	R1	9%	25%	-	36
	R2	9%	17%	-	-

* no TNM-classification available

**Wanebo classification for recurrent rectal cancer stage Tr 0 *(No recurrence)*

***Wanebo classification for recurrent rectal cancer stage Tr 3 *(Growth into surrounding soft tissue)*

****Wanebo classification for recurrent rectal cancer stage Tr 4 *(Penetration anterior structures)*

Local Control

The 5-year local control of primary rectal, recurrent rectal and other cancer is 89%, 38% and 64% (Figure 1). All four patients with a soft tissue sarcoma and the patients with a primary cervical tumour and with a primary vaginal tumour remained without a local recurrence after 5 years. A recurrence at the urethra was observed 10 months after resection in the patient who was operated for a third recurrence of an endometrial tumour. The recurrence was treated with local palliative resection and the patient was systemically treated with chemotherapy.

At univariate analysis significant prognostic factors for an improved local control were the interval from primary resection to local recurrence more than 12 months (P=0.012), type of tumour (primary rectal)(P=0.009), completeness of resection (P<0.001) and absence of preoperative pain (P<0.001). Sex, age, preoperative radiotherapy and positive lymph nodes did not have prognostic value on local control.

Table 3. Complications and reinterventions

	Prim rectum (n = 32)	Rec rectum (n = 16)	Cervix (n = 14)	Others	Total (n = 69)
Complications					
– Minor only	12 (38%)	5 (31%)	2 (14%)	3 (43%)	22 (32%)
– Major only	-	4 (25%)	-	-	4 (6%)
– Major and minor	9 (28%)	4 (25%)	6 (43%)	1 (14%)	20 (29%)
– No complication	11 (34%)	3 (18%)	6 (43%)	3 (43%)	23 (33%)
Minor complications					
– Wound infection perineal	4 (12%)	1 (6%)	3 (21%)	2 (28%)	10 (14%)
– Wound infection midline	6 (19%)	3 (19%)	3 (21%)	1 (14%)	13 (19%)
– Pneumonia	4 (12%)	1 (6%)	1 (7%)	1 (14%)	7 (10%)
– Central venous catheter sepsis	1 (3%)	1 (6%)	-	-	2 (3%)
– Fever without known cause	1 (3%)	-	-	-	1 (1%)
– Urinary tract infection	3 (9%)	-	2 (14%)	1 (14%)	6 (9%)
– Neuropathy	1 (3%)	1 (6%)	-	-	2 (3%)
– TIA	-	1 (6%)	-	-	1 (1%)
– Decubitus	1 (3%)	1 (6%)	-	-	2 (3%)
Major complications/ required interventions					
– Urostomy-related	2 (6%)	2 (13%)	2 (14%)	-	6 (9%)
– Nefrodrain placement	2 (6%)	1 (6%)	1 (7%)	-	4 (6%)
– Small bowel leakage repair	1 (3%)	-	1 (7%)	-	2 (3%)
Reimplantation ureter					
Other					
– Gracilis flap wound repair	2 (6%)	-	-	-	1 (1%)
– Sartorius flap fistula repair	-	1 (6%)	-	-	1 (1%)
– Abdominal dehiscence repair	1 (3%)	-	-	-	1 (1%)
– Ileus relaparotomy	-	1 (6%)	-	-	1 (1%)
– Bleeding relaparotomy	-	-	-	1 (14%)	1 (1%)
– Abscess drainage	-	2 (12%)	3 (21%)	1 (14%)	6 (9%)
– Suture leakage repair	-	-	1 (7%)	-	1 (1%)
– Enterocutaneous fistula repair	-	-	1 (7%)	-	1 (1%)

Major complication: a complication that causes the need for reintervention or is the cause of prolonged hospitalization.

Minor complication: a complication that does not cause the need for reintervention or is the cause of prolonged hospitalization.

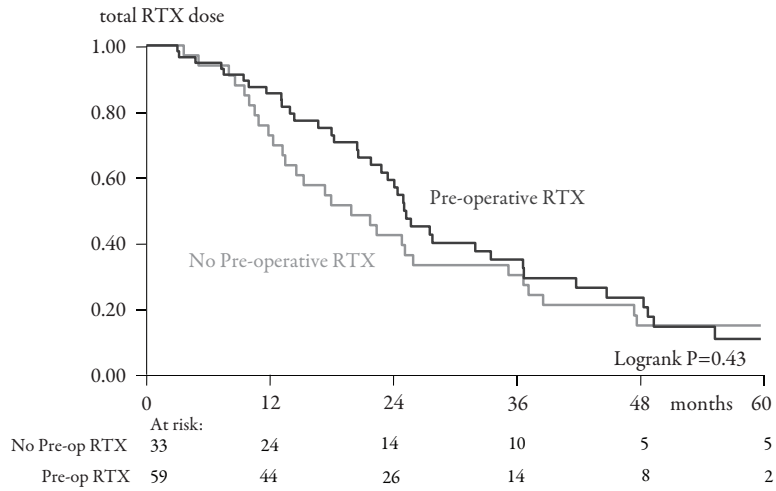

Figure 1. Kaplan-Meier curve for local control

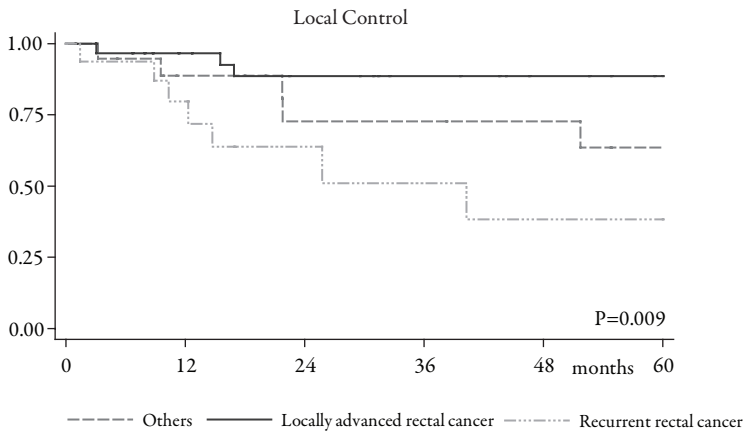

Figure 2. Kaplan-Meier curve for overall survival

Overall survival

The 5 year overall survival of patients with primary, recurrent rectal and other cancer was 66%, 8% and 45%, as depicted in figure 2. All patients with soft tissue sarcoma were alive after 5 years. At last follow-up, 46 months after resection, the patient with primary cervical cancer was alive without evidence of disease. The patient with a primary vaginal tumour remained under local control but developed bone-metastases 16 months after TPE and died

6 months later. The patient with the 3rd recurrence of endometrial cancer was lost to follow-up 9 months after developing a local recurrence.
An interval from primary resection to local recurrence more than 12 months, type of tumour (primary rectum) and completeness of resection were prognostic factors for an improved survival (P=0,010, P=0.010 and P<0.001 resp.). Sex, age, preoperative radiotherapy and positive lymph nodes did not have prognostic value on overall survival.

DISCUSSION

The technique of total pelvic exenteration was introduced as a palliative procedure for patients with advanced gynaecological cancer. Nowadays it is performed with curative intent in the treatment of locally advanced and recurrent pelvic disease (rectal, cervical, endometrial, vaginal, vulvar tumours and soft tissue sarcoma).[8] In locally advanced tumours (without distant metastasis) complete resection is the only possibility for cure and in rectal cancer patients the overall survival rate of 66% and local control rate of 89% after 5 years shows that survival with excellent local control is possible after TPE.[10, 12, 13] These results combined with the high R0-rate and acceptable complication rate justify the performance of TPE in this subgroup.[3] The results of TPE for recurrent rectal cancer, with local control of 38% and 8% overall survival after 5 years, indicate the poor prognosis and questionable benefit of major surgery in this group. The results however are comparable with rates after non-exenterative surgery for recurrent rectal cancer and the high occurrence of distant metastasis emphasises the importance of thorough patient selection.[5, 10, 12 13]
The majority of TPE in gynaecological cancer is performed in recurrent cervical cancer.[18-20] One-third of patients with primary carcinoma of the cervix will have residual disease or recurrent disease, and in up to 25% of these patients there is only local disease without systemic metastases.[21] The treatment for recurrent cervical cancer can be radiotherapy, and in a selected population, without distant metastases, exenterative surgery (posterior, anterior or total exenteration). The 5-year overall survival after treatment of recurrent cervical cancer of 45% in the present study compares to rates reported in the last decade varying from 24%–54%.[18, 19, 22] This is the same for local recurrence free rate of 64% after 5 years, which is comparable with rates varying from 40–78% in the literature.[18, 22] For more uncommon tumours, case reports or small series describe different results. Barakat *et al*. described that surgery for recurrent endometrial cancer is associated with only 20% long-term survival and high morbidity.[23] Preoperatively irradiated patients with locally advanced vaginal cancer

are appropriate candidates for TPE with >50% survival after 5 year according to Berek *et al*.[19]

Pelvic sarcoma are also rare tumours and originate from the stroma of pelvic viscera or from the retroperitoneum. Complete resection and tumour grade are the main prognostic factors for survival.[25] The four patients with sarcomas (2 primary and 2 recurrent) in the present study were all completely resected and did not recur in the pelvis. The 100% overall survival without local relapse in this small cohort compares favorably to the 66% survival after 2 years recently described by Lopes *et al*.[6]

Overall complete resection rate in the present study was 75% for all tumours. The curative potential of resection differs between primary and recurrent tumours. A complete resection in patients with recurrent disease was possible in 65% of the patients in the present study, which was substantially lower than for patients with a primary tumour (85%). Complete resection is more difficult in recurrent cancer because of primary resection of visceral fascia. Successful complete resection of recurrent disease is often restricted to selected patients, for example with early-detected or limited tumour mass. As described in previous reports, complete resection of tumour is a significant prognostic factors for local control and survival. [5, 10, 12, 26] All 4 patients with a macroscopically incomplete resection (2 primary and 2 recurrent rectal cancer) died during follow-up with a mean survival of 13 months.

Morbidity rates reported after TPE for primary and locally recurrent rectal cancer vary from 13-78%.[10, 11, 27] We have previously reported overall morbidity rates of 61% in primary rectal cancer (26% major and 35% minor) and 83% in recurrent rectal cancer (50% major and 58% minor.[3] Infectious complications as midline (14%) and perineal (19%) wound infection, fistula (4%) and abscesses (12%) are the most common complications after TPE. Preoperative radiotherapy did not lead to an increase in complications, which is in contrast to what has been described by Lopez *et al*. who identified significant higher complication rates in the irradiated group of patients.[28]

Thirty-eight percent of all major complications were related to the construction of the urinary conduit. Houvenaegel et al. showed similar complications (42%) related to the construction of a noncontinent urostomy. High complication rates after construction of a Bricker urostomy in irradiated patients have often been reported because of postradiation fibrosis. The Bricker procedure remains the most performed technique for urinary diversion. Other procedures using intestinal segment outside of the radiation field as jejunum or colon have been proposed, but each with their own related complications; use of jejunum can lead to metabolic complications and colon conduits are reserved for patients without previous colon resection, to prevent absorption problems.[29, 30] The use of continent pouches is

increasingly reported, with related functional advantages leading to improved quality of life; however also related with 46 % pouch-related complications.[30]
For many years age was considered a contraindication for the performance of TPE. In the present study patients over 70 years had similar outcome after TPE compared to younger patients, which is confirmed by other recent studies.[20, 22] Not age, but physical condition and co-morbidities are considered as the important criteria in selecting patients for TPE.
As a specialised cancer centre a weakly multidisciplinary meeting where all patients with pelvic tumours are presented and where the treatment program of each individual patient is discussed and planned.

CONCLUSION

Total pelvic exenteration is accompanied with considerable morbidity, but good local control and acceptable overall survival justifies the use of this extensive surgical technique in selected patients with primary locally advanced and recurrent pelvic tumours.

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Chapter IX

Abdominosacral resection in locally advanced and recurrent rectal cancer

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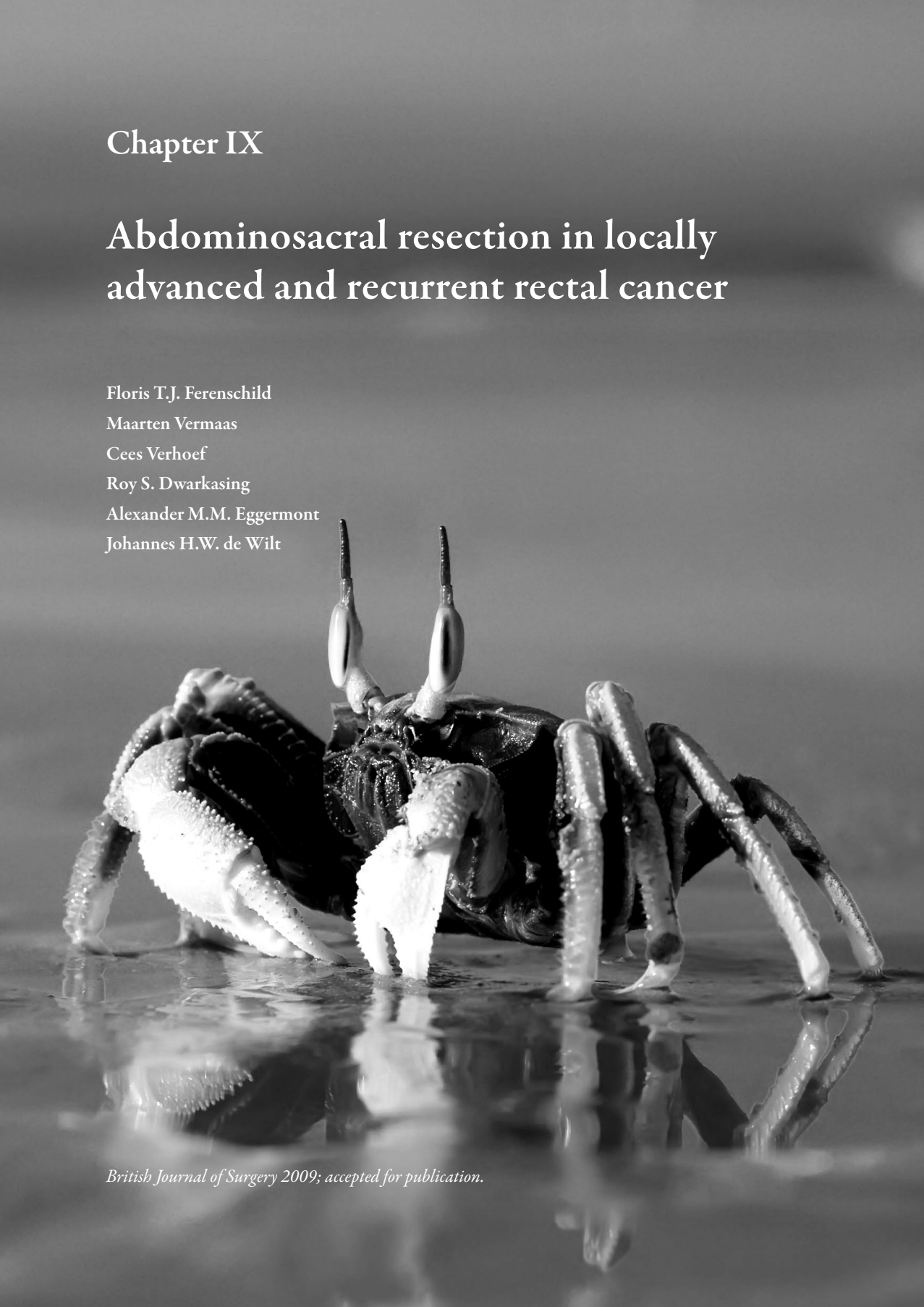

British Journal of Surgery 2009; accepted for publication.

ABSTRACT

Background

The results of resection of locally advanced and recurrent rectal cancers, including sacral resection, were analysed critically.

Methods

Between 1987 and 2007, 353 patients with locally advanced or recurrent rectal cancer, all treated in a tertiary referral centre, were identified from a prospective database. Twenty-five patients (eight primary and 17 recurrent tumours) underwent *en bloc* sacral resection.

Results

A mid sacral resection was carried out in 12 patients (level S3) and a low sacral resection in 13 (level S4/S5). Nineteen patients had an R0, four an R1 and two an R2 resection. There was no postoperative mortality. Median follow-up was 32 months. Incomplete resection had an independent negative influence on local control (5-year local recurrence rate 42 *vs.* 0 per cent in those with and without incomplete resection; $P<0{\cdot}001$). The 5-year overall survival rate was 30 per cent. Five patients with recurrent tumour had pathological invasion into the sacral bone and none survived beyond 1 year.

Conclusion

Abdominosacral resection can be performed in patients with locally advanced and recurrent rectal cancer. Patients who cannot undergo a complete resection or have clear evidence of cortical invasion have a poor prognosis.

INTRODUCTION

Despite efforts in early detection and intense follow-up of rectal cancer, primary locally advanced and recurrent rectal cancer with involvement into adjacent organs or structures is not uncommon. Primary locally advanced rectal cancer is estimated to account for 6–10 per cent of all primary rectal cancers. Local recurrence is the most common cause of failure following surgical resection of rectal cancer and occurs in 3–38 per cent.[1-3] Patients with primary cancers that do not extend beyond the muscularis propria have good clinical outcome with resection alone, but those with primary and recurrent locally advanced cancers have better outcomes if they undergo preoperative chemoradiation therapy, even those with a complete resection.[4-8] For patients with extraluminal tumour involving the pelvis or other organs, treatment used to be strictly palliative. Because of new treatment modalities, including preoperative (chemo)radiation therapy and extensive resection, it is possible to obtain complete resections in such patients.[3,9,10] Furthermore, the addition of intraoperative radiation therapy (IORT) might further improve the local control rate in patients whose rectal cancer resection was marginal.[1,4,5] The posterior bony pelvis is almost never involved in patients with primary locally advanced rectal cancer and is occasionally involved in recurrent rectal cancer.[11] The symptoms often include severe pain in the sacral region. If the tumour has infiltrated, or lays very close to, the sacrum, abdominosacral resection might be the only curative treatment option in some patients. The 5-year overall survival rate after abdominosacral resection is between 15 and 30 per cent, and the local control rate between 15 and 40 per cent.[12,13] Performing sacral resections as high as the S1–S2 interspace may lead to serious bladder and anorectal dysfunction but seems manageable without incurring musculoskeletal disability. For resections levels limited to S3–S4 there are usually no major problems with bladder or anorectal function. The aim of this study was to evaluate the oncological outcome after abdominoperineal sacral resection (APSR) for primary locally advanced and recurrent rectal cancer in a tertiary referral centre.

METHODS

Three hundred and fifty-three patients with locally advanced primary (195) or recurrent (158) rectal cancer, operated in the authors' tertiary referral centre between January 1987 and December 2007, were identified. The tumours were classified as primary locally advanced when the tumour was clinically or radiographically a large T3 lesion (larger than 5 cm) with

narrow circumferential margins, or a T4 tumour. Recurrent rectal tumours were all biopsy-proven invasive adenocarcinomas. Of these 353 patients, 25 underwent an APSR. The following information was extracted from the hospital notes, radiotherapy plans, operation notes and histopathological reports: demographics, preoperative diagnostic intervention, tumour stage, radiotherapy technique, surgical details, anaesthetic details, histopathological details and complications. Follow-up data were obtained from hospital notes, medical letters and, for some patients, from the general practitioner.

Preoperative and intraoperative (chemo)radiation therapy

One but one patient received preoperative radiotherapy. This patient was treated before preoperative radiotherapy was standard treatment at this centre. One received concomitant chemotherapy with capecitabine. A radiation dose of 50 Gy in 25 daily fractions was prescribed. From 1997, IORT was given to patients who had a minimal circumferential free resection margin of 2 mm or less. The resection margin was judged on frozen sections taken during surgery. A boost of 10 Gy was given directly in the operative field with the flexible intraoperative template (FIT) developed at this department.[14,15] This template is a 5-mm thick pad made of flexible silicone with 1- cm spaced parallel source guide tubes running through the centre of the template. Before positioning the FIT, three to four surgical clips were placed around the target surface. The size and shape of the FIT was then adjusted to the target surface. Treatment was planned using standard geometries present in the treatment planning system. Two orthogonal pelvic radiographs were taken to see whether the target surface (clips) was encompassed by the applicator. If the applicator was positioned well, a dose of 10 Gy was delivered at a depth of 1 cm from the applicator surface.[5,16]

Surgery

Determination of the surgical approach for complete resection was based predominantly on computed tomography (CT) or magnetic resonance imaging (MRI) findings. Criteria for an abdominosacral resection for either primary or recurrent cancer were invasion into the sacrum or growth into the lateral pelvic walls or pelvic floor muscles, and the need for wider dorsal access to improve visualization to enable complete tumour resection. The abdominosacral resection required a two-phase approach. The abdominal phase consisted of exploration with careful examination to exclude liver metastases or signs of extrapelvic spread. The rectum was dissected until the area of fixation was reached dorsally. From 2001 onwards, the internal iliac veins were tied or dissected routinely with an endostapler to prevent blood loss. The abdominal part of the operation has been described in detail previously. [1] After

the abdominal phase, the patient was turned around and the posterior approach started with a separate intergluteal incision through which the sacrum was exposed. The ligamentous attachments of the sacrum to the rest of the pelvis were incised. Using an osteotome the sacrum was transected at the desired level. The level of transection was based on imaging findings before neoadjuvant treatment and the intraoperative judgement of the surgeon. The entire specimen was removed *en bloc* through the sacral incision. The defect was closed primarily and, if omentum was available, an omentoplasty was carried out. In some patients a muscle flap reconstruction was used to close the perineal wound.[17]

Surgery-related morbidity was divided in major and minor. Minor morbidity was defined as a complication for which no reintervention was needed. Major morbidity required a prolonged hospital stay owing to the complication or reintervention.

Statistical analysis

Univariable analysis of predictive variables was performed using the log rank test. $P<0{\cdot}050$ was considered statistically significant. Overall survival and local control were analysed as functions of extent of resection, completeness of resection, lymph node stage (negative *versus* positive), level of sacral resection, preoperative pain and IORT (yes *vs.* no). Results were calculated from the time of operation by the method of Kaplan and Meier.[18]

RESULTS

Of 353 patients in the prospective database, 25 had an APSR for primary locally advanced (8) or recurrent (17) rectal cancer. Previous treatment in those with recurrent rectal cancer was low anterior resection in seven patients, abdominoperineal resection in nine and a Hartmann procedure in one patient. Preoperative imaging comprised CT of the thorax, abdomen and pelvis in all patients, and additional MRI of the pelvis in 16. All 25 patients were operated with curative intent. There were 19 men and six women, with a mean age of 62 (range 43–78) years. Presenting symptoms and tumour characteristics are shown in Table 1.

Treatment

All but one patient received neoadjuvant radiotherapy with a median dose of 50 (range 25–50·4) Gy. A mid sacral resection was performed in 12 patients (level S3) and a low sacral resection in 13 (level S4/S5). Total exenteration was necessary in five patients who underwent a mid-sacral excision because of combined posterior and anterior tumour

growth into the bladder. Urinary reconstruction was performed in all patients using a Bricker deviation. Seven patients who underwent a mid sacral resection had bladder-sparing surgery. Two of these patients developed urinary retention leading to recurrent urinary tract infections. Five patients had posterior exenteration because of invasion of the uterus or vagina. A permanent colostomy was fashioned in all patients. A gracilis muscle flap was constructed in three patients. IORT was given to 14 patients: eight with a complete resection (R0) but circumferential margins smaller than 2 mm and six with a microscopically (R1) or macroscopically (R2) incomplete resection. The median duration of operation was 480 (range 320–620) min. Median blood loss was 6500 (range 800–18 000) ml. The resection was complete (R0) in 19 patients; four had residual microscopic disease (R1) and two had macroscopic disease (R2). Incomplete resection was due to involvement of the presacral fascia in one patient and involvement of the lateral pelvic sidewall in the others. The pathological stage is summarised in Table 2. Two patients with liver metastases at the time of operation underwent partial liver resection, with curative intent, during a second operation. Five patients had pathologically proven cortical invasion of tumour into the sacral bone, which was demonstrated before operation in four patients (Figure 1a). All had recurrent tumours, underwent incomplete resection and died from ongoing disease within a year of the operation. In all other patients a close relationship between the tumour and sacral bone was demonstrated at pathological examination, but no tumour invasion into the bone. Preoperative imaging such as CT or MRI did not demonstrate suspicion of invasion into the cortical bone in any of these patients (Figure 1b). After surgery four patients received adjuvant radiotherapy and three had adjuvant 5-fluorouracil-based chemotherapy.

Follow-up

Median follow-up was 32 (range 2–63) months. Postoperative complications and reinterventions are shown in Table 3. Postoperative morbidity occurred in 17 patients (68 per cent). Eleven reinterventions were necessary in eight patients. Four patients with postoperative perineal wound dehiscence were treated with a muscle flap reconstruction. Three patients had a gracilis muscle flap reconstruction and one a vertical rectus abdominus musculocutaneous flap reconstruction. No patient died within30 days of operation.

Local recurrence

The median time to local recurrence was 36 (range 6–120) months. The overall 3- and 5-year local control rates were 49 and 34 per cent respectively. The 5-year local control rate was 10 per cent for patients with recurrent tumour compared with 88 per cent for those

with a primary locally advanced tumour ($P = 0{\cdot}011$). Positive lymph nodes and incomplete resections had a negative influence on local recurrence; the 5-year local control rate was 43 *versus* 0 per cent in those with and without positive lymph nodes, and 42 *versus* 0 per cent in those with complete and incomplete resections ($P < 0{\cdot}001$). Preoperative pain, previous surgical procedure (low anterior resection *versus* abdominoperineal resection), IORT and the level of sacral resection had no impact on the local control rate.

Table 1. Patient Characteristics

	N	(%)
Total	25	100
Presenting symptoms		
– Pain	9	36
– Rectal bleeding	7	28
– Diarrhea	2	8
– Combination	7	28
Tumour height (distance to anal verge or perineum)		
– < 5 cm	19	76
– 6-10 cm	6	24
Fixation tumour		
– Posterior	10	40
– Lateral	2	8
– Multiple sites (lateral and posterior or completely fixed)	13	52

Overall recurrence

The median time to the development of local and/or distant recurrence was 33 (range 12–120) months. Overall 3- and 5-year overall recurrence-free survival rates were 48 and 41 per cent respectively. The 5-year overall recurrencefree survival rate was 0 per cent in patients with positive lymph nodes compared with 77 per cent in node-negative patients ($P<0{\cdot}001$). Preoperative pain, IORT, operating time, blood loss and the level of sacral resection had no influence on overall recurrence.

Table 2. pTNM / Wanebo Classification

	Primary	%		Recurrence	%
pTNM stage	n=8		Wanebo classification	n=17	
Tumour stage			Tr stage		
– T3	6	75	– Tr3	3	18
– T4	2	25	– Tr4	9	53
			– Tr5	5	29
Nodal stage			Nodal stage		
– N0	1	12,5	– N0	2	12
– N1, 2	7	87,5	– N1, 2	2	12
– Not found	-	-	– Not found	13	76
Metastases stage			Metastases stage		
– M0	7	87,5	– M0	16	94
– M1	1	12,5	– M1	1	6

Overall survival

Median survival of the whole group was 32 (range 7–120) months. The overall 3- and 5-year survival rates were 46 and 30 per cent respectively. Five-year survival differed significantly in patients who had complete versus incomplete resection (38 *vs.* 0 per cent; P=0·011) and locally advanced versus recurrent rectal cancer (56 *vs.* 19 per cent; P=0·036). Lymph node stage and other studied factors such as preoperative pain, IORT, operating time, blood loss and the level of sacral resection had no effect on overall survival. Multivariable analysis revealed that only incomplete resection was an independent predictor of overall survival (P= 0·053). Patients with an incomplete resection or pathological invasion into the sacral bone had a median survival of 9 months and none survived for 5 years.

Table 3. Post-operative morbidity and reinterventions

Total number of patients	25	100%
Major complications	10	40%
– Perineal wound dehiscence	4	16%
– Abscess	5	20%
– Anastomotic leakage (Bricker)	2	8%
Minor complications		
– Wound dehiscence (superficial)	23	92%
– Urinary Tract Infection	10	40%
– Pneumonia	6	24%
– Fistula	3	12%
– Neuropathy	2	8%
– XXXXXXXX	2	8%
Reinterventions	11	44%
– Percutaneous abscess drainage	5	20%
– Percutaneous nephrostomy	2	8%
– Muscle flap reconstruction	4	16%
– Revision stoma (Bricker)	1	4%

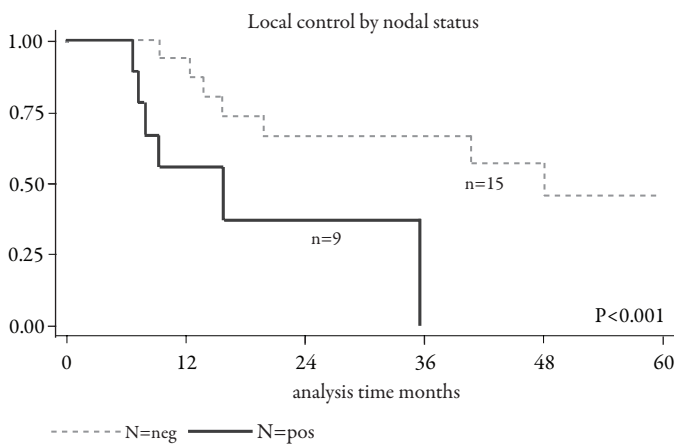

Figure 1. Local control by nodal status

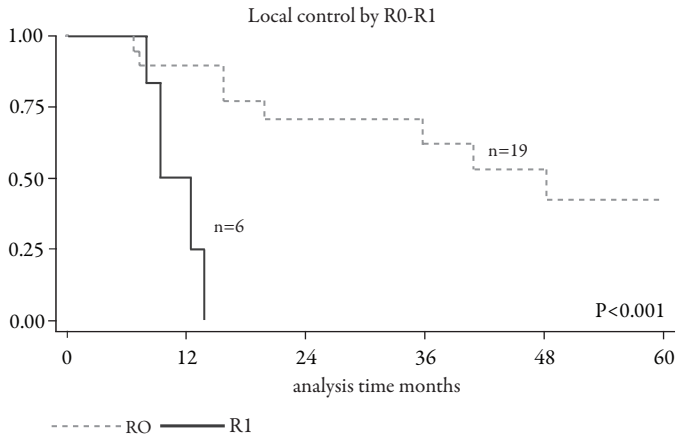

Figure 2. Local control by resection status (R0 versus R1)

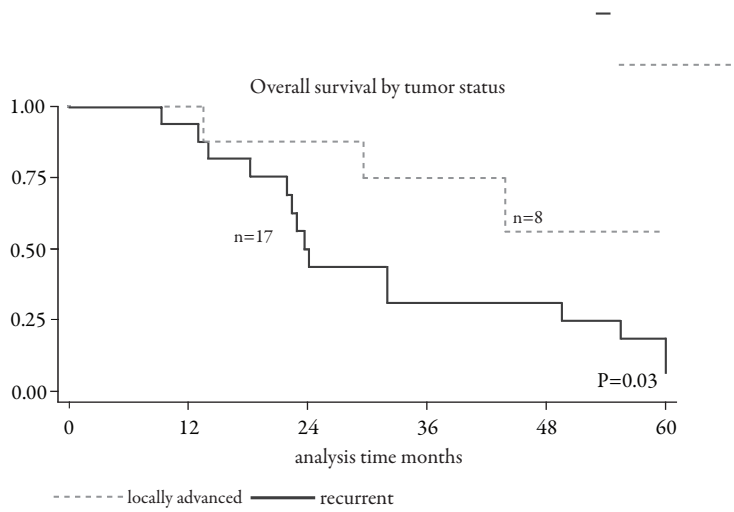

Figure 3. Overall survival by tumour status

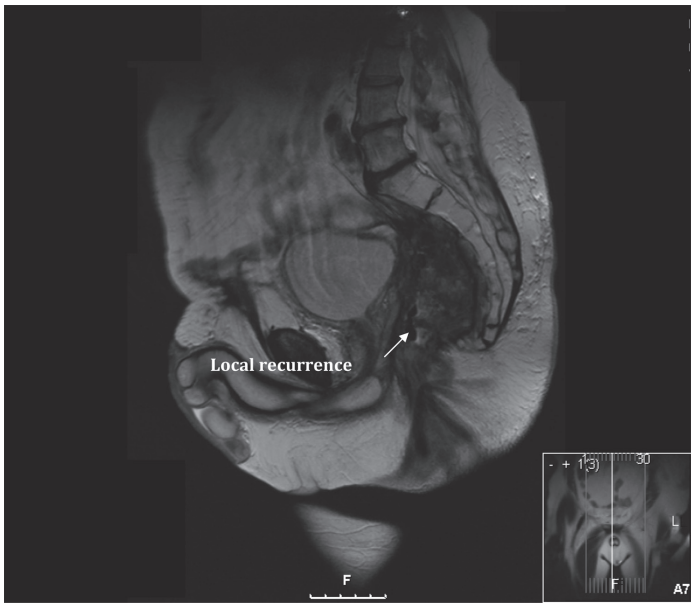

Figure 4a MRI: recurrent rectal cancer with close relation of the tumour with the sacrum

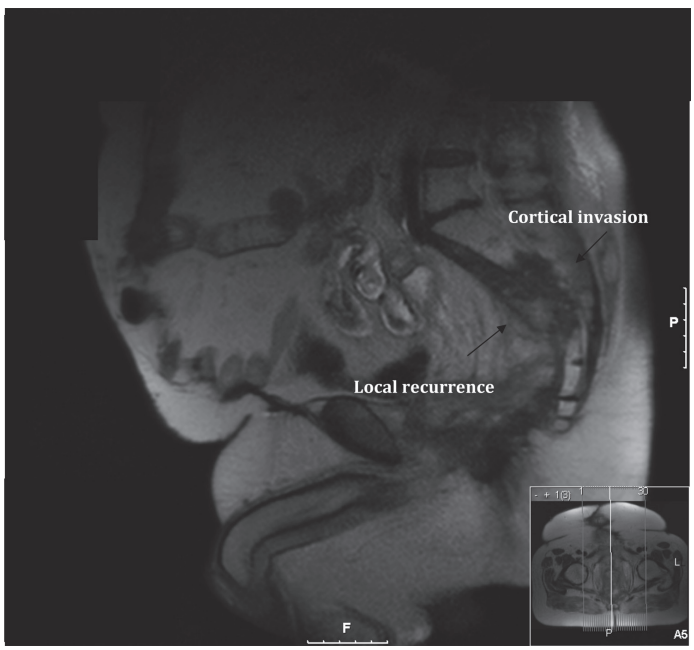

Figure 4b MRI: recurrent rectal cancer with cortical invasion in sacrum

DISCUSSION

Primary locally advanced or recurrent rectal tumours that involve or are close to the sacral bone are often considered unresectable and incurable, and are therefore treated with palliative intent. Complete resection of such tumours requires extended surgical techniques, with removal of part of the sacrum *en bloc* with the tumour. In this series, APSR with curative intent in 25 patients resulted in a 5-year overall survival rate of 30 per cent. This is comparable to published rates of 18–37 per cent.[11-13,19-22] In line with previous findings,[1,12] in the present study patients with primary locally advanced tumours had significantly better survival than those with recurrent rectal tumours (56 and 19 per cent respectively at 5 years). The results in patients with primary rectal cancer seem comparable to those for patients who underwent a rectal amputation without sacral resection.[23] Although promising results after treatment of local recurrence have been described in recent studies,[10,13] those with recurrent rectal tumours did exceptionally poorly in the present series, especially the five patients with pathological invasion of the sacral bone who did not survive more than 1 year. In another study cortical bone invasion was present in 38 per cent of patients and was associated with worse disease-specific survival.[12] Invasion into the sacral bone probably reflects aggressive tumour behaviour and such tumour is difficult if not impossible to remove completely.[24] High-resolution MRI is highly accurate and superior to CT in predicting infiltration of locally advanced primary or recurrent rectal tumours into surrounding structures, and is recommended in the preoperative investigation of such lesions. MRI can correctly predict sacral bone invasion, which may be missed by CT.[25] It is therefore important to perform meticulous preoperative evaluation using positron emission tomography-CT and pelvic MRI to judge whether bone invasion is present. If so, palliative treatment can be considered because surgery might not improve survival compared with current (radio)chemotherapy protocols.[26] This study has confirmed the importance of complete resection of rectal tumours, as reported by others,[1,4,5,10–13,15,20,27] because local control and overall survival were significantly better for patients who had an R0 resection. Although it has been shown previously that IORT improves local control of locally advanced and recurrent rectal cancers,[4,5,16,28-30] this was not the case in the present series. Mannaerts and colleagues [1] also failed to show an increase in local control or survival when IORT was used patients who underwent sacral *en bloc* resection, although the number of patients was small. Other prognostic factors such as preoperative pain or raised carcinoembryonic antigen levels, as mentioned in other studies,[9,20] were not independent prognostic factors for overall survival in the present study. The abdominosacral approach

permits a wide resection in the pelvis, as it allows resection of the large part of the bony pelvis posteriorly. The major problems of such extensive resection are the risk of neurological defects involving bladder, anorectal and sexual functions, and the potential musculoskeletal defects relating to wound dehiscence. In the present study the morbidity rate was 68 per cent and there were no deaths within 30 days. As reported by Wanebo and co-workers[11] serious neurological defects depend on the level of resection. Among twelve patients who had resection of S3 in the present study, seven underwent total exenteration with a Bricker reconstruction and four had bladder-sparing surgery. Two of the latter patients developed urinary retention, but there was no bladder dysfunction in the other two patients or in any of those who had lower dissections. Most major complications in the present study were musculoskeletal defects or perineal wound dehiscence, as reported in other series.[10,31,32] A secondary muscle flap reconstruction was needed to close the perineal wound in four patients. Nowadays, the present authors[17] and others[33] always perform a vertical rectus abdominal muscle flap as the preferred reconstruction in major pelvic surgical procedures. Other techniques, such as gluteus maximus muscle transfer, might be useful for closing the perineal defect and decreasing pelvic infections.[34]

CONCLUSION

APSR can be performed as a potentially curative resection in selected patients without mortality but with substantial morbidity. Meticulous preoperative evaluation is essential for judging whether complete resection is feasible. If the tumour lies close to the bony structures, resection with sacrectomy seems justified. Surgery might not be the best option when there is clear evidence of sacral cortical invasion by recurrent rectal tumour as outcome in such patients is poor.

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Chapter X

Salvage abdominoperineal resection and perineal wound healing in local recurrent or persistent anal cancer

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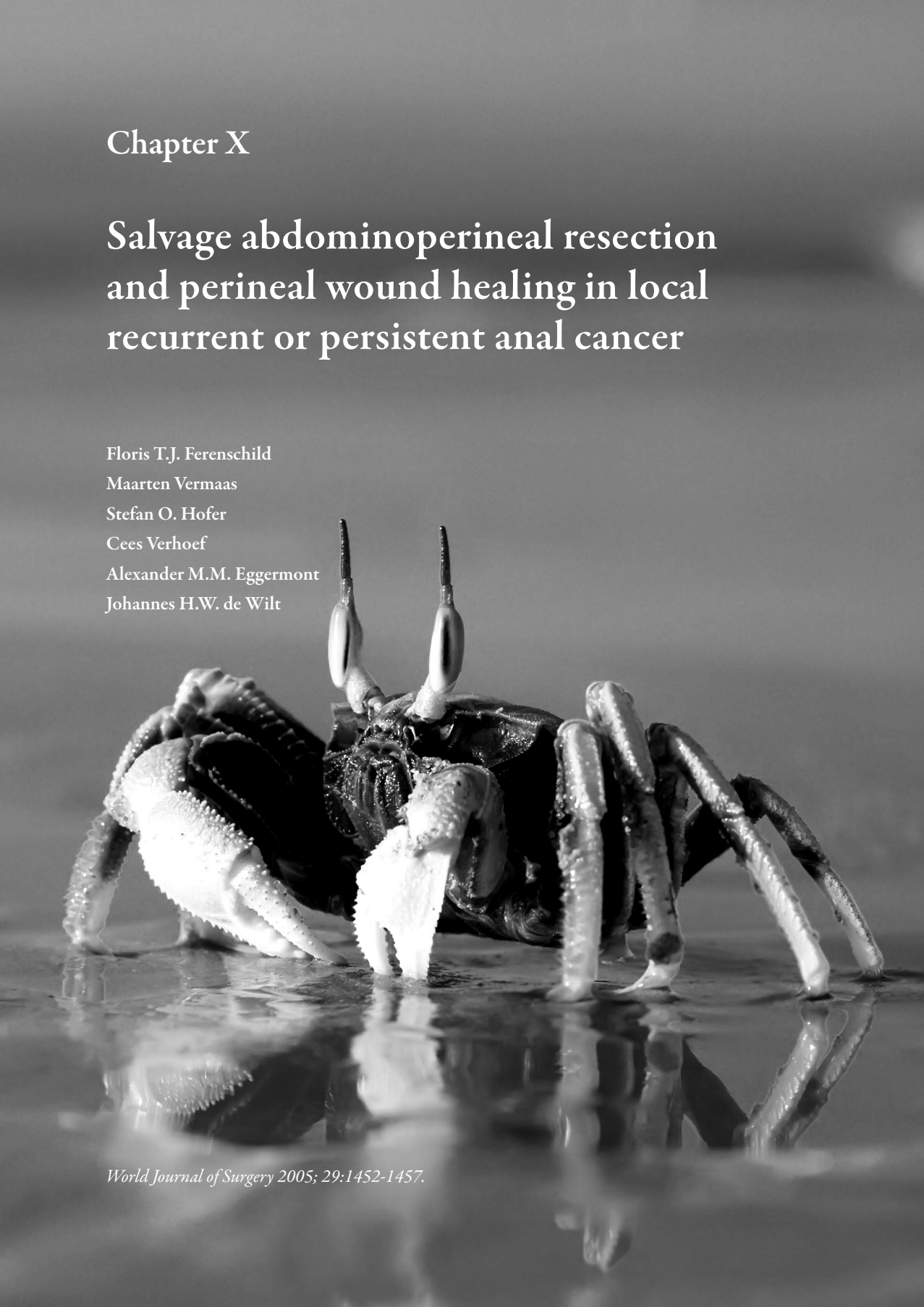

World Journal of Surgery 2005; 29:1452-1457.

ABSTRACT

Background

The primary treatment for anal cancer is chemoradiation (CRT). Failures after CRT are potentially curable with an abdominoperineal resection (APR). A major problem of surgery in the anal area is poor healing of the perineal wound.

Study design

Between 1985 and 2000, 129 patients treated for anal cancer were retrospectively reviewed. Of the 24 patients with local failure, 18 patients were treated with an APR. The aim of this study was to review the results and long-term outcome after salvage APR with special emphasis on perineal wound healing.

Results

Mean age at diagnosis was 59 (range 41–83) years. After a median follow up of 16 months, only 2 patients developed a local recurrence. The 5-year overall survival was 30%. In 11 patients the perineal wound was closed primary, in 3 patients the perineal wound was left open and in 4 patients a vertical rectus abdominus musculocutaneous (VRAM) flap was used. Perineal wound breakdown occurred in 5 of the 14 patients not treated with primary muscle reconstruction (36%). In all patients treated with a VRAM flap the perineal wound healed primarily.

Conclusions

Salvage APR in recurrent or persistent anal cancer results in good local control and 5-year overall survival in the present study of 30%. When performing an APR a VRAM flap reconstruction should be considered to prevent disabling perineal wound complications.

INTRODUCTION

Cancers of the anus originate either in the perianal skin, between the anal verge and the dentate line or proximal to the dentate line. In comparison with adenocarcinoma of the rectum, anal cancer is relatively uncommon.[1] Cancer of the anal canal constitutes 1.5% of gastrointestinal neoplasm's.[2] Different series report similar frequencies of the different histology subtypes: squamous cell 60%–65%; cloacogenic 20%–25%, adenocarcinoma 5%–10% and others (e.g. melanoma or basal cell carcinoma) are sporadic.[2-5] The treatment of anal cancer has changed radically during the past few decades, from predominantly surgery to radiotherapy or radiotherapy combined with chemotherapy. An abdominoperineal resection (APR) was found to be curative in 45 to 60% of patients,[6-8] whereas chemoradiation therapy (CRT), introduced by Nigro *et al*.[9] in 1974 reported to eradicate tumours in 75% to 95%.[10-13] Despite the overall excellent results of CRT in the primary treatment of anal carcinoma, a proportion of patients fails treatment. Initial treatment failure occurs in 10%–15% and an additional 10%–15% of patients develop a local recurrence after an initial complete response to CRT.[9,14,15] The majority of these failures is isolated to the primary tumour site[14,16,17] and would therefore seem to be curable by an abdominoperineal resection (APR). A major problem of surgery in the previously irradiated anal area is poor healing of the often large perineal wound.[18] The aim of this retrospective study was to review the results of salvage abdominoperineal resection in patients with local recurrent or persistent anal cancer and to evaluate healing of the perineal wound in these patients.

PATIENTS AND METHODS

Between 1985 and 2000 the hospital charts of 129 patients treated at our tertial referral centre for anal cancer were retrospectively reviewed. All patients had biopsy proven anal carcinoma and were treated with curative intent by radiotherapy with or without concomitant chemotherapy. Twenty-four (19%) patients subsequently presented with a local failure, in 2 cases with combined regional metastases. Failure of chemoradiation therapy (CRT) was defined as the presence of histologically proven persistent disease within 6 months or recurrent disease after an initial complete response to CRT. Of the 24 patients with local failure, 18 patients were treated with salvage abdominoperineal resection. The other 6 patients received different treatment for their failure of CRT (e.g. local excision, chemotherapy or radiotherapy) and were excluded from further analysis.

Prior treatment

All 18 patients were initially treated with chemoradiation therapy delivered in a split course. The median delivered total radiation dose was 60 Gy (range 40-80Gy). The pelvis was treated with 40 Gy (2Gy/fraction) during 4 weeks, with concomittant chemotherapy administered on day 1 to day 4. Thereafter, a break of 2 weeks was scheduled. In the last 2 weeks a boost was given to the tumour bed with a dose of 20 Gy (2Gy/fraction). During the boost concomittant chemotherapy was given on day 43 to 47. Chemotherapy consisted of 5-Fu (1000mg/m^2) and Mitomycine C (10mg/m2).

Surgery

Because the tumour was isolated in the anal canal or in the pelvis and therefore potentially curable, APR was the treatment of choice. None of the patients had distant metastases at the time of surgery. In a majority of cases the perineal wound was closed primarily. If available, the omentum was used to create an omentoplasty to fill the perineum. In a few patients the wound was left open and in four patients a vertical rectus abdominus musculocutaneous (VRAM) flap was used to fill the perineal and pelvic defect. Technique of distal placement of VRAM flaps has been described previously.[19-21] In summary the flap is freed entirely from the posterior sheath of the rectus muscle. The anterior sheet of fascia is incised from the umbilicus to the pubic bone and the flap is isolated. The flap is then tunnelled retroperitoneally to the pelvis and positioned paravesically (in women posterior to the uterus) to facilitate the reconstruction of the perineum.

Statistical methods

Local control and overall survival curves were calculated from the time of APR and were based on the method of Kaplan and Meier.[22]

RESULTS

Of the 18 surgically treated patients, 9 (50%) were men and 9 (50%) were women. Mean age at diagnosis was 59 (range 41–83) years. Seven (39%) patients presented with persistent local disease and 11 (61%) with local recurrence. The median interval, between the end of CRT and the diagnosis of failure, was 12 (range 0–98) months. Two (11%) patients presented with concurrent regional lymph nodal disease. The initial (before CRT) tumour stage was

T2 (n=13), T3 (n= 4) and T4 (n=1). The initial lymph node status was N0 (n=16) and N1 (n=2) (table 1).

Table 1. Patient characteristics

	Patients (n=18)	
Type of disease		
– Persistent	7	39%
– Recurrence	11	61%
Initial stage		
– T2	13	72%
– T3	4	22%
– T4	1	6%
– N0	16	89%
– N1	2	11%
Pathology stage		
– T0	2	11%
– T1	2	11%
– T2	6	33%
– T3	6	33%
– T4	1	6%
– N0	8	44%
– N1	3	17%
– Nx	6	33%
Histology		
– Squamous	11	72%
– Cloacogenic	3	17%
– Adenocarcinoma	2	11%

Surgical results

The median duration of surgery was 210 (range 150–456) min and the median operative blood loss was 1250 (range 500–7500) ml. In eleven patients the perineal wound was closed primary, in 3 (17%) patients the perineal wound was left open and in 4 (22%) patients a VRAM flap was used. An omentoplasty to fill the pelvic defect after APR was used in 10 (56%) patients.

Fourteen (78%) patients underwent a complete excision of the tumour (R0) and 4 (22%) patients had a microscopic irradical resection (R1). The postoperative tumour stage is demonstrated in table 1. In one patient with a T0 tumour stage, preoperative biopsies demonstrated malignant cells, but in the final pathology report after the resection no tumour was found. In another patient, with a T0 tumour stage, an APR was performed because of multiple abscesses in the anal area thought to be a recurrence. According to the lymph node status, three patients were diagnosed with positive lymph nodes in the mesorectum. In 6 patients there were no lymph nodes retrieved. Pathology reports showed squamous carcinoma in 11 (61%) patients, cloacogenic carcinoma in 3 (17%) patients and adenocarcinoma in 2 (11%) patients. Two patients did not show malignancy as mentioned above and will be excluded of local control and survival analysis.

Follow-up

The median follow up of 18 patients was 16.3 months (range 1–170 months). Complications and re-interventions are shown in table 2. Twelve patients (67%) developed a post-operative complication. Perineal wound breakdown occurred in 5 patients (45%) with median duration of 278 (range 126–427) days. In 4 patients treated with a VRAM flap the perineal wound healed primarily and no herniation was observed. Figure 1 depicts a VRAM flap 3 months after surgery. One patient developed an umbilical necrosis, due to the incision left from the umbilicus, which compromised blood flow after preparation. This patient also developed a CVC infection. A surgical re-intervention was needed in 8 (47%) patients. In two patients with perineal dehiscence a gracilis flap from both sides was used to cover the perineal defect. In two patients with a perineal hernia a mesh repair was needed to close the hernia. There was no peri-operative or post-operative mortality.

Recurrence

In the present study only two of 16 patients (13%) developed a local recurrence during follow up. Local control was achieved in all 12 patients who underwent a complete (R0) resection, but 2 out of 4 patients with an incomplete (R1) resection failed. Seven patients developed loco-regional metastases in the groin, which were treated with regional excision in one patient, chemotherapy in 3 patients and radiotherapy combined with hyperthermia in 3 cases. Seven patients developed distant metastases during follow-up.

Table 2. Complications and reinterventions after salvage APR

	Patients	
	No VRAM (n = 14)	**VRAM (n = 4)**
Complication		
– Total	15	3
– Perineal dehiscence	5	0
– Perineal hernia	4	0
– Abdominal dehiscence	1	1
– Stenosis stoma	2	0
– Necrosis umbilicus	0	1
– Pulmonary embolism	1	0
– UTI	1	0
– Urine retention	1	0
– CVC infection	0	1
Reintervention		
– Total	7	1
–		
– Mesh repair perineal	2	0
– Gracilis muscle repair	2	0
– Correction stoma	2	0
– Abdominal hernia	1	0
– Nettoyage umbilicus	0	1

VRAM = Vertical Rectus Abdominis Muscle; UTI = Urine Tract Infection; CVC = Central Venous Catheter

Overall survival

The median survival was 27 months. The actuarial overall 3- and 5-year survival rates were 50 and 30% respectively (Figure 1). Five-year overall survival of persistent disease was 63% in contrast to 13% in recurrent disease. Because patient numbers are small, a statistical analysis was not performed on these results.

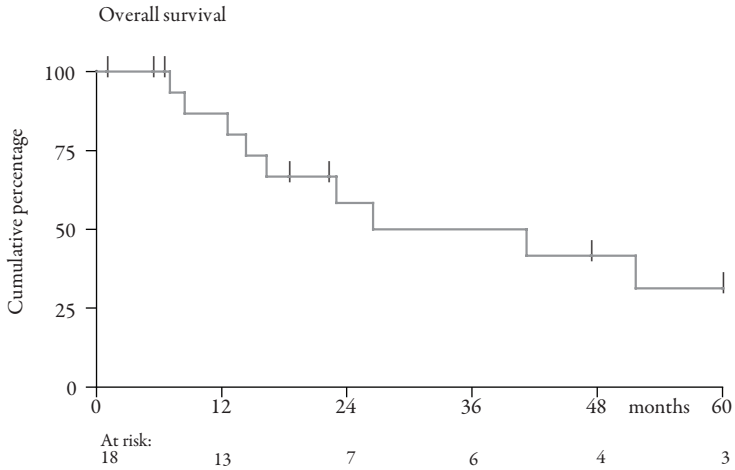

Figure 1. Overall survival after salvage APR for anal carcinoma. APR = abdominoperineal resection

DISCUSSION

Since the publication of Nigro *et al*.[9] chemo-radiation therapy (CRT) has become the treatment of choice for primary anal cancer.[16,23,24] Locoregional failures after primary treatment with CRT are reported to occur in 17–45% 23,24 and was 19% in the present study (24 of 129 patients). Although APR as a therapeutic option in patients with primary anal cancer is obsolete, it is often the only possible treatment option in patients who fail CRT.[5,15] Flam *et al*.[25] demonstrated that an additional boost of radiation therapy and concurrent cisplatin based chemotherapy could also be used in treating recurrences, but only in 4 out of 24 patients an APR could eventually be avoided with this modality. Salvage APR offers good local control, demonstrated by only two patients with a local recurrence in the present study. Five year overall survival rate after salvage APR was 30% in the present study, which is comparable to previous reports in the literature (see Table 3).[23,24,26-29] Salvage APR seems therefore the treatment of choice for patients with persistent or recurrent disease after CRT.

Table 3. Overall survival after salvage APR

Reference	No.	Median survival (mo)	5-year survival (%)
Nilsson et al. (2002)	35	33	52
Van der Wal et al. (2001)	13	33	47
Allal et al. (1999)	23	22	45
Pocard et al. (1998)	21	35	33
Ellenhorn et al. (1994)	38	41	44
Zelnick et al. (1992)	9	20	24
Current study	18	27	30

APR = abdomino perineal resection

Although there are only few reports in the literature after salvage APR for recurrent or persistent anal cancer, there is discussion regarding prognostic factors that might influence outcome. In our study, involved lymph nodes in the mesorectal excision specimen was the only important prognostic factor and resulted in a statistically significantly impaired prognosis compared to patients with uninvolved lymph nodes (p=0.01). Previous reports have suggested that patients with regional (inguinal) lymph node metastases at initial presentation have a very poor prognosis and the biology of this disease differs greatly from patients who did not have lymph node metastases.[30] This could not be confirmed in the present study, but only two patients presented with positive lymph nodes at initial presentation, which makes statistical analysis difficult. Regarding the difference in survival between persistent and recurrent anal cancer, Allal *et al*.[27] found an improved overall survival of recurrent disease compared patients presenting with persistent disease. A more aggressive biologic phenotype of tumours was suggested to reflect this outcome since many patients with persistent disease after CRT presented with advanced initial disease stage. In contrast with this other authors[23] demonstrated no difference in survival and this was also demonstrated in the present study. Other risk factors for survival were studied but not found to be significant such as resection margin, age and sex.

The incidence of perineal wound complications is rather high after salvage treatment with APR and complications in up to 30% of patients[23,24,27] have been reported previously. In the present series perineal breakdown occurred in 5 of 14 patients (36%) who were not treated with direct VRAM transposition. When perineal breakdown occurred, median duration was long (278 days) and needed secondary reconstruction using gracilis muscle transposition in two patients. Four patients treated with a VRAM flap reconstruction did not show a perineal wound breakdown or perineal hernia. Similar to Tei *et al*.,[18] the

VRAM flap reconstructive procedure resulted in primary healing with acceptable donor-site morbidity and low complication rates. Especially in anal cancer resection margins of the perianal skin can easily be compromised when primary closure is performed. The use of a VRAM flap also enables the surgeon to remove the recurrent or persistent tumour mass with wide resection margins, since large skin defect can easily be managed.

CONCLUSION

This retrospective study demonstrated that salvage abdominoperineal resection in anal cancer is feasible offering good local control and a 5-year overall survival of 30%. A VRAM flap reconstruction should be considered when performing salvage APR in persistent or recurrent anal cancer. In contrast to primary closure or no closure, this reconstructive procedure results in primary healing without perineal complications and a good functional and aesthetic outcome.

ACKNOWLEDGEMENTS

The authors thank Wilfried Graveland for his support with the statistical analysis.

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Part V

RESULTS

Chapter XI

General discussion

Parts of this chapter are adapted from:

'Management of locally advanced primary and recurrent rectal cancer'

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Clinics in Colon and Rectal Surgery 2007; 20:253-262

INTRODUCTION

The majority of patients with primary rectal cancer present with a tumour located within the mesorectal fascia. The treatment of these tumours has evolved from simple tumour resection into a multidisciplinary treatment with standardized surgical, pathological and radiotherapeutical procedures.[1-7] Since the introduction of TME-surgery by Dr Heald significant lower rates of local recurrences have been reported varying between 3 and 15 percent.[8-10] The addition of preoperative short-term radiotherapy (5x5Gy) delivered one week prior to surgery has been shown to further improve local control, without an effect on survival.[1, 11] Introduction of preoperative radiotherapy in the treatment protocol of the Rotterdam Comprehensive Cancer Registry Region in 2001showed an increase of preoperative radiotherapy from 21 to 69%.[12] Results from a community hospital in this region showed that TME with short-term preoperative radiotherapy was feasible with an acceptable rate of postoperative morbidity and low mortality .[7] In this and other studies risk factors of poor prognosis after rectal surgery have been identified, such as positive lymph nodes, an incomplete resection, aged above 80 and/or a high level of CEA.[1, 11, 13-21 22-24] In an attempt to avoid the morbidity and mortality of TME, local excision has been developed as a therapeutic option in the treatment of well-selected patients with early rectal cancer (T1).[25-29] The introduction of transanal endoscopic microsurgery (TEM) by Buess *et al*.[30] proved to be a feasible technique for removal of rectal tumours, although local recurrences are reported to be high.[31-34] Other techniques of rectal saving surgery such as chemoradiation treatment followed by TEM surgery are currently being explored.

Most rectal cancers are located within the mesorectal fascia, but in approximately 10% of all rectal cancer patients the tumour extends into or beyond the enveloping fascia propria of the mesorectal compartment.[35] Often these tumours infiltrate adjacent structures and therefore have a higher risk to develop a local recurrence.[36] Patients with these primary locally advanced rectal cancers are historically difficult to treat with surgery alone, but outcome has significantly improved using multimodality treatment options. Although preoperative, intraoperative and adjuvant (chemo) radiation therapy is important in these patients, the mainstay of treatment in rectal cancer is complete surgical removal if the tumour. In both locally advanced and recurrent rectal cancers this involves not only the removal of the total mesorectum, but en bloc resection of involved structures is often needed. This involves extended resections such as posterior or total exenterations and abdominoperineal sacral resections. Especially after these extended resections reconstruction of the perineal defect is of great concern and warrants careful selection of patients and surgical strategies.

IMAGING AND STAGING

At present, MR imaging is considered 'gold standard' for rectal cancer imaging because it has been demonstrated to be superior to CT for prediction of tumour invasion in surrounding pelvic structures.[37-42] This is important to identify locally advanced rectal cancers that not only need other preoperative treatment strategies, but also other surgical procedures. Based on clinical information it is difficult to distinguish patients with locally advanced tumours although certain patient complaints such as pneumaturia, haematuria and vaginal bleeding suggest involvement of other organs. Also digital rectal examination can provide useful information such as large bulky lesions or lesions that are tethered or fixed to the pelvic wall.[43] However, accurate and detailed anatomic information of the tumour extent is essential to select locally advanced rectal tumours for neoadjuvant treatment modalities and planning of the optimal surgical procedure. Few studies have addressed the problems of predicting rectal tumour infiltration into adjacent organs.[44] CT scan has long been used to evaluate the local tumour extent because of initial optimistic results and the advantage of a single investigation to combine local, regional and systemic staging.[45] The large difference in outcome between MR and CT in the comparative studies could be partially attributed to the fact that a state-of-the-art MR technique was compared with conventional CT techniques. In theory new generation multi-detector row spiral CT scanners, with superior contrast and spatial resolution and capability for reconstructions in multiple planes, are expected to provide better performances. Results of further studies are awaited to determine if new-generation CT can compete with MR imaging.

Neither clinical assessment nor imaging tools, including MRI, CT, PET an ERUS have the ability to accurately identify or exclude lymph node involvement. It might clinically be important to identify lymph node negative patients for instance to perform rectal saving procedures or treat them with surgery only (without preoperative radiotherapy). On the other hand in case of true positive mesorectal or extra-mesorectal nodes more extensive preoperative and operative procedures might be indicated. Recent studies demonstrated that the accuracy of preoperative imaging (including ERUS/MRI) for staging T3N0 rectal cancer was limited because 22% of patients will have undetected mesorectal lymph node involvement.[46, 47] According to Lahaye *et al*,[48, 49] the white region within the node seen by USPIO-enhanced MR images is the most accurate and practical predictive criterion for malignant lymph nodes. Their results suggest that USPIO-enhanced MR imaging could become a promising tool for nodal malignancy prediction not only for experienced but also for less experienced readers. However, the use of USPIO is not (yet) commercially available

for MR imaging and until that time further studies are needed to improve the accuracy of imaging modalities to establish treatment options that will provide the best outcome for this group of patients.
Probably the most important factor is using the most optimal imaging techniques in combination with preoperative multidisciplinary team discussions. This enables a tailor-made treatment for each rectal cancer patient and has demonstrated to decrease the number of positive resection margins.[48-50]

PREOPERATIVE TREATMENT

After the Dutch TME trial in 20011 most patients with rectal cancer in the Netherlands are treated preoperatively with short-term radiotherapy. With additional data from randomized trials and increasing follow-up, a highly significant effect of short-term preoperative radiotherapy remained on local recurrence rate without an effect on overall survival.[6, 11] The value of preoperative radiotherapy on local recurrence rates in small- and lymph node negative tumours is under debate.[17, 51] Because of the excellent results in these patients treated without radiotherapy, it would be helpful to identify these patients before treatment is started. Meticulous pre-operative work-up is of major importance helping to identify patients with small tumours and without positive lymph node involvement to save them from the early and late complications of radiotherapy.
Patients with evidence of lymph node involvement or tumour growth close to or into the mesorectal fascia are supposed to be treated with a more aggressive approach. In many European centers radiotherapy was used as neo-adjuvant treatment for locally advanced rectal cancer[35] but addition of chemotherapy has recently demonstrated to improve local control in two large randomized trials.[52, 53] Addition of 5–FU and leucovorin to preoperative radiation increased the amount of acute toxicity in T3–T4 resectable rectal cancer patients, but it increased the number of complete responses and decreased the local recurrence rate after 5 years.[54] Important is to notice that overall survival did not differ in these studies and that sphincter preservation was not increased. Postoperative chemo-radiotherapy has long been recommended for locally advanced and node positive rectal cancer patients, but preoperative treatment has demonstrated improved compliance, reduced toxicity and increased local control[55] New chemoradiation strategies are now published in numerous phase II trials including the use of oral 5–FU[56-58] and the addition of irinotecan[59, 60] and oxaliplatin[61] to 5–FU-based regimens. A recent British trial has demonstrated high

response rates in non-resectable rectal cancer patients after induction systemic chemotherapy followed by chemoradiation.[62] Although this was accompanied with considerable toxicity the number of patients with a (near) complete response was promising. Not only new chemotherapeutic drugs, but also a VEGF specific monoclonal antibody in combination with chemoradiation was recently reported by Willet et al. to increase downstaging of the tumour.[63] Other modalities such as the use of intensity-modulated radiotherapy (IMRT) which has the potential of more accurate delivery of higher radiotherapy dosages, avoiding the damage of critical structures surrounding the tumour are currently tested in rectal cancer. Higher radiation dosages could result in more radiation-induced necrosis and eventually in the possibility of further tumour downstaging.[64] These and other phase II and III trials are ongoing, but until randomised phase III trials demonstrate improved results, 5–FU based chemoradiation therapy is the golden standard for locally advanced and recurrent rectal cancer patients.[65]

SURGERY

Primary rectal cancer

Since the introduction of TME by Heald et al. this technique became the gold standard for surgery in rectal cancer.[66] TME provides sharp meticulous dissection to keep the visceral layer of the pelvic fascia intact and this is important to avoid breach in the mesorectum, which is an important risk factor for a local recurrence.[9 67, 68] With the introduction of TME the recurrence rate dropped to approximately 10%. Even in low volume centers, TME is a feasible technique with an acceptable rate of postoperative morbidity and low mortality.[7] It was recognised that involvement of the circumferential margin by tumour cells is predictive for local recurrences.[69] Other important factors for both survival and local recurrence rate are lymph node involvement, elevated CEA and age.[7, 24, 70]

Although short course radiotherapy followed by TME surgery is considered gold standard, complications are not uncommon. Serious clinical problems such as anastomotic leakage and fecal incontinence are described after this treatment and should be carefully discussed with the patient prior to treatment.[71, 72] New rectumsaving techniques are currently explored to improve short- and longterm quality of life while oncological outcome is uneffected. Examples of such strategies are TEM surgery for small T1 tumours[34, 51, 73, 74] and chemoradiation followed by TEM surgery for larger distal rectal cancers.[75, 76] Long-term

follow-up and well designed phase II and III trials are necessary to evaluate the benefits and risks of such strategies.

Primary locally advanced rectal cancer

Primary locally advanced rectal cancer is sometimes defined as stage III rectal cancer, which also represents resectable tumours with clinically suspicious lymph nodal involvement. Although these patients are treated in many centers with aggressive chemoradiation protocols, surgery can be performed with standard TME surgery[66] and after short course radiotherapy (5x5Gy) local recurrence rates and survival were demonstrated to be excellent. [1, 6] Locally advanced rectal cancer is here characterized as tumours invading or extending close to the mesorectal fascia. A complete excision of the tumour is of significant beneficial influence on local control and survival, especially in patients with locally advanced tumours. [2, 35, 77] During surgery distinction between benign adherence and malignant invasion is difficult to make, especially after neo-adjuvant therapy. Because of this difficulty the surgeon must resect en bloc the adjacent structures depending on the location and depth of invasion. [43] In case of clear lateral lymph node involvement, dissection of these nodes or parts of the pelvic wall sometimes including autonomic nerves is inevitable, but in these cases prognosis is generally poor.[78] Direct invasion in iliac vessels and obturator space is even more uncommon and only in selected cases resection of these structures might be indicated.[79]

In case of dorsal invasion abdominosacral resections can be performed,[80, 81] but this is a demanding procedure not often necessary in primary rectal cancer. Ventral invasion in a female patient usually requires resection of the uterus and/or part of the vaginal wall. In men partial removal of the prostate is possible in case of ventral invasion but a total pelvic exenteration is more commonly performed in patients with involvement of the prostate or bladder, which is discussed later in this review.

In the literature, completeness of resection, negative lymph node status, extent of resection, fixation of the tumour and presentation of pain are reported as prognostic factors for survival and local control.[35, 82-86]

Distant metastases were traditionally contraindications for surgical treatment of patients with locally advanced rectal cancer. Recent improvements in systemic chemotherapy and a more aggressive surgical approach have made patients with resectable distant metastatic disease candidates for curative surgery.[87] Especially in patients with oligometastatic liver metastases complete resection of the metastases can lead to long-term survival and cure.

Recurrent rectal cancer

Despite improvements in the treatment of primary rectal cancer, recurrences occur in approximately 5–15% of the patients. The development of a local recurrence depends on various factors such as surgical technique88, lymph node involvement1, resection margins2 and location of the tumour.[1, 89] Locally recurrent rectal cancer is often associated with severe symptomatic disease, especially pain.[85] Due to neoadjuvant treatment modalities a selective group of patients with recurrent disease can be operated on with curative intent.[81, 85] Curative treatment seems best possible in selected patients with true anastomotic recurrence or those without pelvic sidewall involvement and early detection of the tumour.90 Recent studies show that the current multimodality treatment provides possibility for curative resection in 40–80%.[85, 91-97] This lower rate of complete resections is reflected in a lower local control and overall survival of patients with recurrent rectal cancer compared to primary rectal cancer. [36, 85 86, 91, 98-102] Symptomatic disease indicates a more advanced character of tumour growth, which will result in a higher rate of incomplete resections and an associated lower local control and survival.[85, 92, 103] Symptoms such as pain or hydronephrosis104 are therefore considered to be a relative contraindication for resection of recurrent rectal cancer due to poor outcome.

Since most patients are nowadays treated with radiotherapy for their primary rectal cancer, most recurrences occur in a previously irradiated pelvis. This changes the clinical nature and prognosis of patients who develop locally recurrent rectal cancer. Overall prognosis is poor in these patients, but some patients can be reirradiated. An Italian multi-center study reported promising results after hyperfractionated chemoradiation in previously irradiated patients with an overall survival of 39% in all patients. Survival was exceptionally good in 21 patients were a R0 resection was performed with a 67% 5 years survival.[105] Further studies are needed to identify those patients with recurrent rectal cancer that are candidates for multimodality treatment protocols and extensive surgery.[85]

Recurrences after local excision for T1 rectal cancer

In an attempt to avoid the morbidity and mortality of TME, local excision has been developed as a therapeutic option in the treatment of well-selected patients with early rectal cancer.[73, 106] The introduction of transanal endoscopic microsurgery (TEM) enables excellent access and visualization of the surgical field and allows precise and full-thickness excision of the tumour.[30] The rate of tumour resection with clear margins, even with standardised pathology, for T1 tumours has increased to more than 90%.[107, 108] Considering the very low mortality and morbidity rates, local excision by TEM is now considered a potential

alternative for the surgical treatment of T1 tumours by many surgeons.[25, 109, 110]However, the wide range of local recurrence rates from 0 to 24%,[111, 112] and the results of salvage surgery in recurrent tumours are matters of concern. In the literature only few series report on surgical procedures following recurrent disease after transanal surgery.[31-33] Conclusion as written in abstract chapter VII.

Pelvic exenteration

Total pelvic exenteration (TPE) is a widely used technique for resection of locally advanced pelvic tumours, invading the bladder and/or prostate.[113] Long term survival with excellent local control is possible after TPE for primary locally advanced rectal cancer.[98, 100, 114-121] In recurrent rectal cancer the visceral fascia surrounding the rectum has been resected in previous surgery, which makes a complete resection of all recurrent disease more difficult. [115 100, 122 123 99, 116, 121, 124]

Morbidity is generally high after TPE with morbidity rates between 37-78%. The complications related to the urinary conduit are frequent causes for reintervention, which was demonstrated to occur especially in patients who previously received radiotherapy.[115, 121, 125] Although the refinements in the radiation therapy (3D-planning and exclusion of small-bowel from the irradiated field) may have resulted in a decreased toxicity, radiotherapy is still considered as one of the reasons for a high complications rate.[93, 126] In recent years, mortality after TPE has decreased from rates up to 33% down to rates varying from 0–10%. [98, 100, 125, 127] Although, current guidelines for colorectal cancer surgery advocate TPE, only one-third of the patients in a study based on SEER data underwent the appropriate surgical resection. These patients had a clinically significant overall survival benefit with no increase in short-term mortality compared with similar patients who did not receive a multi-visceral resection.[114]

Abdominoperineal Sacral Resection

In selected cases patients have large tumours attached or infiltrating the bony structures of the dorsal pelvis. Some of these patients are candidates to undergo a sacro-pelvic resection or composite resection as developed and described by Wanebo et al. and others.[81, 128-131] This procedure is even more demanding than a total pelvic exenteration and is accompanied with a high morbidity rate and mortality rate of approximately 10%.[131, 132] Some authors have reported long term survivors after sacrectomy or composite resections and for highly motivated and carefully selected patients even in patients with tumour infiltration in bony structures.[133] We and others (ref) have demonstrated that patients with pathological

tumour ingrowth in the bony sacrum do not survive more than 3 years and APSR seems only indicated for patients with a close relation to the sacrum. Since most of these patients develop secondary recurrences and die of distant metastases, future studies have to focus on more adequate treatment of systemic disease in this group of patients. Each patient should carefully be judged preoperatively by a multidisciplinary team including a surgeon, urologist, gynaecologist, radiotherapist, medical oncologist, radiologist and an anaesthetist before these extended surgical procedures are commenced.

Reconstructions

After extensive pelvic surgery, wounds too large for primary closure will require complex closure. These wounds can take several months to heal and bring with them a high chance of infection. In combination with preoperative or intraoperative radiotherapy and/or chemotherapy, chances for infection are even higher.[134, 135] Reported minor complication rates after treatment of primary or recurrent rectal cancer range from 25 to 60 percent, with major complication rates around 12 percent.[136-138] After extended pelvic surgery a large pelvic dead space can exist andfilling of this space has a favourable influence on the postoperative morbidity. In these circumstances the transfer of a myocutaneous flap has successfully been used for the management in primary reconstruction, preventing wound infections by directly filling up the pelvic space after surgery.[139] Bartholdson and Hulten in 1975 were the first to report the use of the gracilis myocutaneous flap, and since their report others have used this technique with excellent results.[140-142] A vertical rectus abdominus muscle (VRAM) transpostion can fill up larger defects and should be considered in case of a large dead perineal space after wide perineal AP(S)R for rectal cancer and salvage APR for other pelvic cancers. In contrast to primary closure or no closure, this reconstructive procedure results in primary healing without perineal complications and a good functional and aesthetic outcome.[139, 143, 144]

INTRAOPERATIVE RADIOTHERAPY

Local control in rectal cancer patients is related to the dose of irradiation, but because of toxicity to radiosensitive organs such as small bowels, the external radiation dose should not exceed 60 Gy. A combination of external radiation and intraoperative radiation therapy (IORT) allows the safe delivery of higher effective doses of irradiation than can be delivered with external beam only techniques. IORT is used when resection margins are narrow or

involved with tumour cells and can be applied very specifically to an area at risk, under direct visual control and with the possibility to shield the surrounding structures from radiation. The biological effectiveness of single-dose IORT is considered to be as effective as two to three times the equivalent dose of fractionated radiotherapy.[124, 145] IORT can be delivered using intraoperative electron beam radiotherapy (IOERT) or high-dose-rate brachytherapy (HDR-IORT). The advantages of IOERT are the treatment depth of >1 cm with a choice of electron energies and quick delivery of the radiation. The flexible template in HDR-IORT can treat all surfaces with the highest dose at the area at risk, however, treatment time is longer.[146] Different centers worldwide use one of these techniques. Although no randomised trials concerning IORT have been performed, several studies have reported that IORT was feasible, safe and improved both local control and overall survival, but patient numbers are often small in these series.[77, 82-84, 102, 146-152] In the analysis of our complete database of patients with both recurrent and locally advanced rectal cancer, patients who received IORT for narrow or microscopically incompletely resected tumours had a local control rate comparable to patients with wide R0 resection margins.[35, 36] Since there is a good rationale for dose escalation in locally advanced and recurrent rectal cancer, IORT is one of those promising techniques for further improving local control and overall survival.

CONCLUSIONS

A multidisciplinary approach in patients with rectal cancer or other pelvic tumours is of major importance. A meticulous work-up, tailor-made preoperative and postoperative treatment and highly specialised surgery will potentially lead to better results. Multidisciplinary treatment has shown to reduce morbidity and mortality, but also improved long-term survival rates.[153-155] To futher improving results in rectal cancer patients specialists should work and generate trials together.

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Chapter XII

Summary

INTRODUCTION

Patients with rectal cancer mostly present with tumours located within the mesorectal fascia and are generally treated with total mesorectal excision (TME). Results of TME are good with a significant improvement of the local control when preoperative short-term radiotherapy (5x5Gy) is delivered one week prior to surgery. In approximately 10% of all rectal cancer patients the tumour extends into or beyond the enveloping fascia propria of the mesorectal compartment. These tumours often infiltrate adjacent structures and therefore have a higher risk to develop a local recurrence. Patients with these primary locally advanced or recurrent rectal cancer were historically difficult to treat with surgery alone, but results have significantly improved using multimodality treatment. A multidisciplinary approach for patients with rectal cancer or other pelvic tumours reduces morbidity and mortality, but also improves long-term survival rate. A meticulous work-up, tailor made preoperative treatment and highly specialised surgery will lead to better results. In this thesis the multimodality treatment for rectal cancer and other pelvic tumours is discussed with a focus on preoperative (chemo) radiation therapy for primary and locally advanced rectal cancer, multimodality treatment including IORT for recurrent rectal cancer and extended resections and reconstructions after pelvic surgery.

PART I | PRIMARY RECTAL CANCER

Based on the results of the Dutch TME trial the treatment in The Netherlands of patients with a tumour in the lower two-third of the rectum has changed to preoperative radiotherapy (5*5Gy) followed by TME-surgery. In **chapter 2** the results preoperative radiotherapy and surgery in the treatment of 210 patients with primary rectal cancer in a low volume centre were analysed. A total of 145 patients were treated with an anterior rectal resection and 65 patients underwent an abdomino perineal resection (APR). Anastomotic leakage rate was 5% and postoperative mortality was 3%. The 5-year the local recurrence-free rate in patients with microscopically complete resections was 91% and the overall survival rate was 58%. An increased serum carcinoembryonic antigen (CEA), an APR, positive lymph nodes, and an incomplete resection all significantly influenced the 5-year overall survival and local recurrence rate negatively. In a multivariate analysis, age was the most important prognostic factor for overall survival. It was concluded patients with rectal cancer can safely be treated

with TME in a community teaching hospital and leads to a good overall survival and an excellent local control.

In patients with T2–3, N0 rectal cancer, the role of preoperative radiotherapy remains controversial. In **chapter 3** a review of the benefit of radiotherapy in T2 and T3, N0 rectal cancer patients was studied. Between 1996 and 2003, 103 patients with T2–3, N0 rectal cancer were identified in a prospective database. The 5-year local control rate was 94% and the overall survival was 65%. Preoperative radiotherapy did not show any statistical differences. Abdomino perineal resection, T3 tumours and advanced age negatively influenced overall survival. Preoperative radiotherapy does not seem to be of significant importance in patients with T2–3, N0 rectal cancer regarding local recurrence and survival. Since preoperative radiotherapy is associated with short- and long-term morbidity, identification of patients with T2–3, N0 tumours should be improved and preferably treated with surgery alone.

PART II | LOCALLY ADVANCED RECTAL CANCER

Primary locally advanced rectal cancer is characterised as a tumour invading or extending close to the mesorectal fascia. In **chapter 4** the results of a multimodality treatment of 123 patients with primary locally advanced rectal cancer, using preoperative radiotherapy (median dose of 50 Gy), followed by surgery and on indication intraoperative radiotherapy (IORT) were described. The 5-year local control was 65% and the 5-year overall survival was 50%. Positive lymph nodes and incomplete resections negatively influenced both local control and overall survival. Preoperative pain also proved to be a significantly important factor for local control. IORT significantly improved 5-year local control (P=0.016) and overall survival (P=0.026) for patients with R1/2 resections. Addition of IORT for patients with a narrow or microscopic incomplete resection seems to overrule the unfavourable prognostic histological findings. The presented multimodality treatment for primary locally advanced rectal cancer was feasible with an acceptable mortality and 5-year overall survival.

Recent studies have demonstrated that preoperative radiation therapy in combination with 5-fluoracil (5–FU) improves local tumour control in locally advanced rectal cancer. The aim of **chapter 5** was to evaluate the toxicity and efficacy of preoperative chemoradiation using the oral 5–FU prodrug capecitabine in locally advanced rectal cancer. Sixty patients with locally advanced rectal cancer were treated with preoperative chemoradiation. Radiotherapy consisted of a total dose of 50 Gy delivered in 25 fractions to the pelvis. Chemotherapy was concurrently administered and consisted of oral capecitabine only on radiotherapy

days. Surgery was performed six to ten weeks after completion of chemoradiation. All but two patients received the full dose of chemoradiation. No grade III or IV haematological toxicities developed. Two patients (3%) developed grade III radiation dermatitis and one a grade III diarrhoea. All patients underwent definitive surgery and one patient with a low anterior resection developed an anastomotic leakage (4%). Final pathology demonstrated eight patients (13%) with a complete pathological response. Primary tumour and nodal downstaging occurred in 67 and 84% of the patients, respectively. It was concluded preoperative chemoradiation with oral capecitabine is safe and well tolerated in locally advanced rectal cancer patients. This preoperative treatment has a considerable downstaging effect on the tumour and lymph nodes.

PART III | RECURRENT RECTAL CANCER

The main goals in the treatment of recurrent rectal cancer are palliation of symptoms, good quality of life and, if possible, curative surgery. When local recurrent rectal cancer is diagnosed without signs of metastases, a potentially curative resection can be performed. In **chapter 6** the results of 92 patients with recurrent rectal cancer treated with preoperative hyperfractioned radiotherapy followed by surgery (n=59) or with surgery only (n=33) were described. There were no differences in morbidity and reintervention rate between the two groups. Complete resections (R0) were achieved in 64% of the patients who received preoperative radiation and 45% of the non-irradiated patients. A complete response after radiotherapy was found in 10% of the patients and improved local control and survival. Local control after preoperative radiotherapy was statistically significantly higher after 3 and 5 years compared to the non-irradiated patient (P=0,036). Overall survival and metastasis free survival were not different in both groups. In concurrence with beneficial results of preoperative radiotherapy on local control in the treatment of primary rectal cancer, it was concluded that preoperative radiotherapy for recurrent rectal cancer resulted in more complete resections and improved local control. Preoperative radiotherapy should therefore be standard treatment in recurrent rectal cancer.

Recurrent disease after transanal excision for T1 rectal cancers is not uncommon, but its impact on survival is not clear. The aim of **chapter 7** was to evaluate the management and outcome of local recurrences after transanal endoscopic microsurgery (TEM) for pT1 rectal cancer. From 1996, 88 consecutive patients who underwent TEM for pT1 were registered in a prospective database. Eighteen patients developed a local recurrence during follow-up.

Median time to local recurrence was 16 months (range, 4–50 months). Two patients were not operated because of concomitant metastatic disease. abstract chapter VII result section: All remaining 14 patients adhered to the intensive follow-up protocol. In two patients (patient number 3 and 6) synchronous liver metastases, initially deemed resectable, were found. Despite obtaining a microscopic radical resection in both, rapidly progressive metastatic disease developed and patients were treated with palliative chemotherapy. They died eight and respectively 22 months following the salvage procedure. In 15 out of 16 salvage procedures, a microscopic radical resection was possible without the need for extensive surgical procedures. In one patient a microscopic irradical resection (R1) was performed, and patient received adjuvant chemotherapy. There was no post-operative mortality. Median follow up after salvage treatment of all patients with a recurrence was 20 months (range, 2 – 112). One of the operated patients developed a local re-recurrence and 7 patients developed distant metastases and died because of progressive disease.

The actuarial 3-year overall survival was 29% (figure 1). Patients in which a microscopic radical resection could be obtained without the presence of metastatic disease, 3-year survival was better compared to non-operated patients, stage IV disease at presentation or microscopic irradical resections (40 versus 0%; p=0.001).

The 3-year disease-free survival was 57%. Although survival in T1 rectal cancer patients is generally good, recurrence after TEM for T1 rectal cancer leads to a limited survival. A microscopic radical resection can almost always be obtained, without the need for extensive surgical procedures. In the near future we need to focus on improving selection in T1 rectal cancers suitable for TEM. Also possible adjuvant treatment strategies following salvage procedures need to be explored, in order to safe as many patients the adverse effects of TME.

PART IV | EXTENDED RESECTIONS AND RECONSTRUCTIONS

Despite efforts in the early detection and the intense follow-up of rectal cancer, primary locally advanced and recurrent rectal cancer with involvement into adjacent organs or structures is not uncommon. Radical margins are sometimes difficult to obtain because of close relation to or growth in adjacent organs/structures. Total pelvic exenteration (TPE) is an exenterative operation for these advanced tumours and involves en bloc resection of the rectum, bladder, and internal genital organs (prostate/ seminal vesicles or uterus, ovaries and/ or vagina). **Chapter 8** describes the results of TPE in our tertiary referral centre. Between 1994 and 2008, a TPE was performed in 69 patients with pelvic cancer; 48 with rectal

cancer (32 primary and 16 recurrent), 14 with cervical cancer (1 primary and 13 recurrent), 5 with sarcoma (3 primary and 2 recurrent), 1 with primary vaginal, and 1 with recurrent endometrial carcinoma. Overall major and minor complication rates were 34% and 57%, respectively. The in-hospital mortality rate was 1%. A complete resection was possible in 75% of all patients. Five-year local control for primary locally advanced rectal cancer, recurrent rectal cancer, and cervical cancer was 89%, 38%, and 64%, respectively. Overall survival after 5 years for primary locally advanced rectal cancer, recurrent rectal cancer, and cervical cancer was 66%, 8%, and 45%, respectively. Total pelvic exenteration is accompanied with considerable morbidity, but good local control and acceptable overall survival justifies the use of this extensive surgical technique in most patients, especially patients with primary locally advanced rectal cancer or recurrent cervical cancer.

In **chapter 9** a critical analysis of the results of resection of locally advanced and recurrent rectal cancers including the sacrum was evaluated. Between 1987 and 2007, 25 of 353 patients with locally advanced or recurrent rectal cancer underwent an en-bloc sacral resection in our tertiary referral centre. A mid sacrum resection was performed in 12 patients (level S3) and a low sacrum resection in 13 patients (level S4/5). A R0 resection was performed in 19/25 patients; R1 in 4/25 patients; R2 in 2/25 patients. There was no postoperative mortality. Positive lymph nodes and incomplete resections independently negatively influenced local control ($P<0.001$). The 5-year overall survival was 30%. Five patients with a recurrent tumour had pathological invasion in the sacral bone and no survival beyond 1 year. In conclusion abdomino sacral resections can be performed in patients with locally advanced and recurrent rectal cancer. Patients who cannot undergo a complete resection or have clear evidence of cortical invasion should not be scheduled for these extensive procedures.

After APR or extended pelvic resections large perineal defects can occur which are difficult to manage. Filling of the perineal space can be favourable using an omentoplasty or muscle- and myocutaneous transpositioning, providing well-vascularised and nonirradiated tissue. Results in **chapter 10** show that direct transposition of the vertical rectus abdominus muscle (VRAM) resulted in closure of the perineal wound in all patients treated with salvage APR for anal cancer. The morbidity-rate after VRAM transfer in combination with resection of the malignancy was not higher than morbidity after abdominoperineal resection alone. Perineal wound breakdown occurred in 5 of the 14 patients (36%) not treated with primary muscle reconstruction. In all patients treated with a VRAM flap the perineal wound healed primarily. In the present study salvage APR in recurrent or persistent anal cancer results in good local control and 5-year overall survival of 30%. When performing an APR a VRAM flap reconstruction should be considered to prevent disabling perineal wound complications.

Chapter XIII

Samenvatting

INTRODUCTIE

In de meerderheid van de patiënten die zich presenteert met een rectumcarcinoom is er sprake van een tumor beperkt tot de mesorectale fascie en bestaat de behandeling uit totale mesorectale excisie (TME). De resultaten van deze chirurgische behandeling zijn goed met een significante daling van het recidiefpercentage als kortdurende preoperatieve radiotherapie wordt toegepast. Tien procent van de rectumtumoren reikt tot in of buiten de fascia propria van het perirectale vet. Deze tumoren groeien vaak in omliggende structuren en hebben een grotere kans op het ontwikkelen van een lokaal recidief. Curatieve behandeling van primair lokaal uitgebreide tumoren en lokale recidieven was voorheen niet mogelijk met een behandeling die alleen uit chirurgie bestond. De resultaten verbeteren echter sinds de introductie van de multidisciplinaire aanpak. Een multidisciplinaire behandeling van deze patiënten leidt tot verminderde morbiditeit en mortaliteit en verbetert de lange termijn overleving. In dit proefschrift wordt de multidisciplinaire behandeling van het rectumcarcinoom en andere kleine bekken tumoren bediscussieerd, met hierbij speciale aandacht voor de effecten van preoperatieve (chemo)radiotherapie, intraoperatieve radiotherapie (IORT), lokale excisie van beperkte rectum tumoren, reconstructie van het bekken na uitgebreide chirurgie en sacrale resecties bij uitgebreide rectum tumoren.

DEEL I | PRIMAIR RECTUM CARCINOOM

Naar aanleiding van de Nederlandse TME trial, worden patiënten met een rectum tumor van 0 – 10cm vanaf de anus kortdurend voorbestraald waarna een resectie volgens het TME principe plaatsvindt. In **hoofdstuk 2** worden de resultaten van deze behandeling bij 210 patiënten geanalyseerd. Honderdvijfenveertig patiënten werden behandeld met een lage anterieure resectie (LAR) en 65 patiënten ondergingen een abdomino perineale resectie (APR). Klinische relevante naadlekkage kwam voor in 5% en de postoperatieve mortaliteit was 3%. De 5-jaars kans op een lokaal recidief bij patiënten met een microscopisch radicaal verwijderde tumor was 9% en de 5-jaars overleving was 58%. Een gestegen CEA, een APR, positieve lymfeklieren en een incomplete resectie hadden een significante negatieve invloed op de overleving en op het krijgen van een recidief. In een multivariate analyse was leeftijd de meest prognostische factor voor overleving. Concluderend kan men zeggen dat deze categorie patiënten veilig kan worden behandeld in een gespecialiseerd ziekenhuis en er een goede overleving en zeer goede lokale controle is.

Bij patiënten met een T2-3, N0 rectum carcinoom is de rol van preoperatieve radiotherapie controversieel. In **hoofdstuk 3** wordt de waarde van preoperatieve radiotherapie bij deze patiënten geëvalueerd. Vanaf 1996 tot en met 2003 werden 103 patiënten met een T2-3, N0 rectum carcinoom geïdentificeerd in een prospectieve databank. De 5-jaars lokale controle was 94% en de totale overleving 65%. Het geven van preoperatieve radiotherapie liet geen statistisch voor- of nadeel zien. Een APR, T3 tumoren en oudere leeftijd hadden een significante negatieve invloed op de overleving. Preoperatieve radiotherapie lijkt geen significante positieve invloed te hebben op patiënten met een T2-3, N0 rectum carcinoom met betrekking tot overleving en lokale controle. Vanwege het feit dat preoperatieve radiotherapie wel is geassocieerd met verhoogde morbiditeit is het van groot belang om deze patiënten preoperatief te identificeren en bij voorkeur alleen chirurgisch te behandelen.

DEEL II | PRIMAIR LOKAAL UITGEBREID RECTUM CARCINOOM

Een primair lokaal uitgebreid rectum carcinoom wordt gekenmerkt door een tumor die tegen of door de mesorectale fascie heen groeit. In **hoofdstuk 4** worden de resultaten beschreven van 123 patiënten met een lokaal uitgebreid rectum carcinoom, voorbehandeld met radiotherapie (mediane dosis 50 Gy), gevolgd door chirurgie en op indicatie intraoperatieve radiotherapie (IORT). Het percentage lokale controle na 5 jaar was 65% en de 5-jaars overleving 50%. Er was een negatieve invloed van positieve lymfeklieren en een incomplete resectie op de lokale controle en overleving. Preoperatieve pijn had een significante negatief voorspellende waarde t.a.v. lokale controle. IORT had een positieve invloed op de lokale controle ($P = 0.016$) en de overleving ($P = 0.026$) bij patiënten met een R1-2 resectie. Het toevoegen van IORT bij patiënten met een incomplete resectie lijkt de prognostisch ongunstige histologie teniet te doen. De in deze studie gepresenteerde multidisciplinaire behandeling van het primair uitgebreide rectum carcinoom is uitvoerbaar met een acceptabele mortaliteit en 5-jaars overleving.

Recente studies laten zien dat preoperatieve radiotherapie in combinatie met 5-FU een positief effect heeft op de lokale controle bij uitgebreide primaire rectumcarcinomen. In **hoofdstuk 5** wordt de toxiciteit en effectiviteit van preoperatieve chemoradiotherapie m.b.v. orale 5-FU (capecitabine) onderzocht. Zestig patiënten met een lokaal uitgebreid rectum carcinoom werden behandeld met preoperatieve chemo- en radiotherapie. Radiotherapie bestond uit een totale dosis van 50 Gy over 25 fracties verdeeld. Chemotherapie werd alleen gegeven op de dag van de radiotherapie. Patiënten werden 6-10 weken na de laatste gift

geopereerd. Op 2 patiënten na kreeg iedereen de volledige dosis chemo- en radiotherapie. Er trad geen graad III of IV haematologische toxiciteit op. Twee patiënten ontwikkelde graad III radiatie dermatitis en 1 graad drie diarree. Alle patiënten werden uiteindelijk geopereerd en 1 patiënt had een naadlekkage (4%). Uiteindelijke pathologie liet bij 8 patiënten een complete pathologische respons zien. Downstaging van zowel de primaire tumor als de lymfeklieren trad respectievelijk op in 67% en 84% van de patiënten. Preoperatieve chemoradiatie met orale capecitabine is veilig en wordt goed verdragen door patiënten met een lokaal uitgebreid primair rectum carcinoom. Deze preoperatieve heeft een aanzienlijk downstaging effect op de tumor en de lymfeklieren.

DEEL III | RECIDIEF RECTUM CARCINOOM

De belangrijkste doelstellingen bij de behandeling van het recidief rectum carcinoom zijn palliatie van de symptomen, kwaliteit van leven en indien mogelijk curatieve chirurgie. Als een lokaal recidief wordt aangetoond zonder tekenen van afstandsmetastasering. In **hoofdstuk 6** worden de resultaten besproken van 92 patiënten met een recidief rectum carcinoom uitgesplitst naar wel (n=59) of geen preoperatieve radiotherapie (n=33). Er was geen verschil in morbiditeit en het percentage reinterventie tussen de 2 groepen. Complete resecties werden uitgevoerd in 64% van de patiënten die preoperatieve radiotherpie kregen en in 45% van de patiënten zonder preoperatieve radiotherapie. Een complete respons werd gevonden in 10% en zorgde voor een verbeterde lokale controle en overleving. Het percentage lokale controle was significant hoger bij bestraalde patiënten zowel na 3 als na 5 jaar (P = 0.036). Overleving en metastase vrije overleving lieten geen verschil zien in beide groepen. In overeenstemming met eerder beschreven resultaten heeft preoperatieve radiotherapie voor recidief rectum carcinomen een positief effect op zowel lokale controle als op het aantal complete resecties. Preoperatieve radiotherapie moet derhalve standaard gegeven worden bij de behandeling van het recidief rectum carcinoom.

Recidieven na transanale excisie bij T1 rectum carcinomen is vaker beschreven, maar de invloed op de overleving is niet bekend. De doelstelling van **hoofdstuk 7** was evaluatie van de behandeling en uitkomst van recidief rectum tumoren na initiële transanale endoscopische microchrirugie (TEM) voor T1 rectum carcinomen. Vanaf 1996 werden er 88 patiënten met een pT1 rectum tumor geregistreerd in een prospectieve databank. Achttien patiënten ontwikkelde een recidief tijdens de follow-up. De mediane tijd voor het ontwikkelen van een recidief was 16 maanden. Twee patiënten werden niet geopereerd i.v.m. metastase

op afstand. Alle overige 16 patienten ondergingen "salvage" chirurgie zonder dat er een uitgebreide resectie nodig was. In 44% van de patienten werd er een definitief eindstandig stoma aangelegd. Er was geen post-operatieve mortaliteit. Vijftien patienten werden radicaal geopereerd en 1 patient onderging een microscopisch irradicale resectie. De mediane follow-up na "salvage" chirurgie was 20 maanden (2–112 maanden). Een patient ontwikkelde opnieuw een recidief en 7 patienten ontwikkelde afstandsmetastasen. De 3-jaars overleving was 29% en de 3-jaars ziekte vrije overleving 57%. Alhoewel de overleving na TEM voor T1 rectum carcinomen goed is leidt het optreden van een recidief tot een beperkte overleving. Echter, recidief chirurgie is uitvoerbaar en als men in staat is een complete resectie uit te voeren is er een substantiële overlevingswinst.

DEEL IV | UITGEBREIDE RESECTIES EN RECONSTRUCTIES

Ondanks het streven om rectum kanker vroeg op te sporen en intensief te vervolgen is ingroei in de omgevende organen of structuren bij zowel het primair uitgebreide- als recidief rectum carcinoom niet zeldzaam. Radicale resectie randen zijn soms moeilijk te verkrijgen vanwege deze ingroei in de omgeving. Een totale bekken exenteratie (TPE) is een uitgebreide operatie voor deze type tumoren en bestaat uit een en bloc resectie van het rectum, blaas en genitaliën. Hoofdstuk 8 beschrijft de resultaten van TPE in het Erasmus Medisch Centrum, lokatie Daniel. Tussen 1994 en 2008 werden er 69 TPE's verricht bij kleine bekken tumoren. Het totale percentage grote- en kleine complicaties was respectievelijk 34% en 57%. De mortaliteit was 1%. Een complete resectie was mogelijk in 75% van de patiënten. Het percentage lokale controle na 5 jaar voor respectievelijk primair lokaal uitgebreid rectum carcinoom, recidief rectum carcinoom en het cervix carcinoom was 89%, 38% en 64%. De 5-jaars overleving was respectievelijk 66%, 8% en 45%. Een TPE gaat gepaard met een aanzienlijke morbiditeit, echter een goede lokale controle en een acceptabele overleving rechtvaardigt deze extensieve chirurgische techniek bij de meeste patiënten, zeker als er sprake is van het primair lokaal uitgebreid rectum carcinoom of het cervix carcinoom.

In hoofdstuk 9 worden de resultaten van sacrale resecties in verband met een primair of recidief rectum carcinoom kritisch geëvalueerd. Tussen 1987 en 2007 ondergingen in het Erasmus Medisch Centrum, lokatie Daniel, 25 patiënten op een totaal van 353 patiënten een sacrale resectie bij een primair- of recidief rectum carcinoom. Een mid-sacrum resectie werd verricht bij 12 patiënten (niveau S3) en een laag-sacrum resectie bij 13 patiënten (niveau S4/5). Een complete resectie werd verricht bij 19/25 patiënten; R1 in 4/25 patiënten; R2 in

2/25 patiënten. Er was geen postoperatieve mortaliteit. Positieve lymfeklieren en incomplete resectie randen beïnvloedde onafhankelijk van elkaar de lokale controle in negatieve zin ($P < 0.001$). de 5-jaars overleving was 30%. Vijf patiënten met een recidief tumor hadden daadwerkelijk ingroei in het sacrum bij pathologisch onderzoek. Al deze patiënten overleden binnen 1 jaar. Concluderend zijn abdomino sacrale resecties uitvoerbaar bij patiënten met een rectum carcinoom. Indien er een incomplete resectie wordt verricht of als er sprake is van evidente corticale ingroei dient afgezien te worden van deze uitgebreide chirurgische procedure.

Na een APR of uitgebreide kleine bekken chirurgie kunnen er grote perineale ontstaan die moeilijk te behandelen zijn. Het opvullen van deze peritoneale ruimte kan een oplossing bieden door gebruik te maken van een omentum plastiek of een spier- of huidspier transpositie. Deze transpositie heeft als voordeel dat hij goed gevasculariseerd is en niet in bestraald gebied heeft gelegen. De resultaten van hoofdstuk 10 laten zien dat de directe transpositie van een vertical rectus abdominus muscle (VRAM) leidt tot primair sluiten van de perineale wond in alle patiënten die een APR ondergingen vanwege een anus carcinoom. De morbiditeits percentage na een VRAM in combinatie met een resectie van de maligniteit was niet hoger dan de morbiditeit na een APR zonder VRAM. Bij 5 van 14 patiënten waarbij primair geen VRAM werd gebruikt ontstond er een groot perineaal defect. In al de patiënten die primair werden behandeld met een VRAM herstelde de perineale wond primair. In deze studie was er sprake van een goede lokale controle en een 5-jaars overleving van 30%. Indien men een APR uitvoert dient men een VRAM reconstructie te overwegen.

Dankwoord

Hooggeleerde heer Alexander M.M. Eggermont. Als mijn promotor wil ik u danken omdat u degene was die het aandurfde "Die jongen met de zachte 'g' en gitaar" als anios aan te nemen in Rotterdam. Woorden die in mij opkomen als ik aan u denk zijn: turbulent, charisma, inspirator, Babylonische spraakwaterval, aanwezig (als aanwezig?), helder, duidelijk etc. De enorme kracht waarmee u de chirurgische oncologie internationaal voortstuwt is soms onnavolgbaar maar bovenal bewonderenswaardig. Dank voor de mogelijkheden die u mij heeft geboden om mijzelf te ontplooien tot wie ik nu ben.

Hooggeleerde heer de Wilt, Hans. Opleiding heelkunde, promotie, KWF-fellowship; zonder jou was deze trilogie nooit tot stand gekomen. De volharding waarmee jij mij hebt geholpen, jouw snelheid, je chirurgische vaardigheden, je gedrevenheid zullen mij altijd bijblijven. Het is voor mij een grote eer dat jij, sinds je benoeming tot hoogleraar chirurgische oncologie, niet mijn co-promotor maar mijn promotor bent.

Hooggeleerde leden van de grote & kleine commissie, professor Kuipers, professor Levendag, professor Wiggers, professor van Lanschot, professor Lange en dr. Cats en dr. Kirkels. Allen dank voor het doornemen van dit proefschrift, uw aanwezigheid en uw inbreng op deze voor mij grootse dag.

Maarten Vermaas, paranimf, wetenschapsbroeder! Erop en erover en daar stond jij als promovendus reeds in 2008. Gelukkig heb ik nu ook de eindstreep gehaald. Maarten, dank voor je grote bijdrage in dit proefschrift, maar met name voor jouw betrokkenheid. Ik ken weinig mensen die zo uitgebalanceerd door het leven gaan en dan ook nog dat leven met humor, vrolijkheid en warmte vullen. Binnenkort maar weer op de fiets, rondje Rotte!?

Rob Zuidwijk, paranimf! De allereerste promotie die ik in mijn leven meemaakte was die van jou aan de Erasmus Universiteit Rotterdam. Na 5 minuten moest ik inhoudelijk al afhaken maar was desalniettemin diep onder de indruk van deze promotie en de ceremonie. Nu 15 jaar later in precies hetzelfde gebouw, dezelfde zaal sta ik voor dezelfde taak. Dank voor de ondersteuning en wetenschappelijke wind die jij met je meevoert.

Dr. I Dawson, beste Imro; mijn opleider in de periferie. Het duurde even maar dan heb je ook wat... Dank voor de immer stimulerende, ietwat repeterende evaluatiegesprekken: "Het

gaat goed Floris, alleen wetenschappelijk vaart gaan maken, jongen." Een opleider zoals een opleider moet zijn: betrokken, stimulerend, kritisch.

Hooggeleerde heer J.N.M. IJzermans, Jan. Dank voor de tijd die jij mij gunde om een en ander af te ronden.

Dr. G.W.M. Tetteroo en dr. E.J.R. de Graaf, Geert en Eelco. Colorectale chirurgische ingrepen leerde ik van jullie. Mijn eerste LAR, eerste APR, eerste TEM-procedure, allemaal onder jullie bezielende begeleiding. Ik zal jullie 'aan tafel' nog vaak citeren! Natuurlijk wil ik ook de rest van de maatschap bedanken: Milko, Richard, Steven en Piet die mij het vak hebben geleerd. Pascal voor de laatste "spannende" wetenschappelijke ondersteuning en last but not least, Cees, net gepensioneerd, maar tot het einde een gepassioneerd chirurg.

Zeergeleerde heer C. Verhoef, Kees en natuurlijk de dames van het "Daniel" secretariaat, dank voor vele jaren krachtige ondersteuning.

Dr. A.W.K.S. Marinelli, Andreas, jij hebt het initiatief genomen om de rectumdatabase op te starten en mij hier vanaf het eerste uur in te betrekken waarvoor dank.

Wilfried Graveland, statisticus. Een echte Graveland; het uiterlijk van een beer, innerlijk intelligent, zachtmoedig en behulpzaam. Zeer veel dank voor jouw hulp zelfs nadat je al weg was uit de Daniel. Ze hadden je nooit moeten laten gaan!

Mijn zus Wendel, voor 8 bijzondere jaren samen in de stad van onze grootvader; Rotterdam. Fijn dat je erbij kunt zijn vanuit Los Angeles.

Annalies, mamma, nu ik samen met Ruth twee kinderen poog op te voeden groeit steeds meer het besef wat voor uitzonderlijke taak jij hebt volbracht. Dank voor de nimmer aflatende steun en liefde die ik van jou krijg. Ik verheug me op je bezoek in Australië.

Roos en Jonas, de schoonheid en troost die jullie mij schenken is onvoorstelbaar. Door jullie bruist het leven. Ik hou van jullie.

Ruth, zonder jou was ik allang verdronken in een zee van activiteiten. Dank voor een stukje grensbewaking maar bovenal voor het feit dat jij er bent.

Curriculum Vitae

FLORIS FERENSCHILD

Floris Ferenschild werd geboren op 19 juli 1973 te Herkenbosch. Na het eindexamen HAVO begon hij in 1990 met de studie fysiotherapie te Heerlen die hij in 1994 afrondde. Na een jaar vervangende dienstplicht te hebben vervuld startte hij in 1995 met de studie geneeskunde aan de universiteit van Maastricht. In 5 jaar tijd behaalde hij zijn arts diploma. Hierna was hij kort werkzaam als anios chirurgie in Ede waarna hij als anios in de Daniel den Hoed kliniek ging werken. Hier werd het huidige promotieonderzoek gestart onder de bezielende leiding van prof.dr. A.M.M. Eggermont en prof.dr. J.H.W. de Wilt.
Sinds 1 januari 2004 is hij in opleiding tot algemeen chirurg. De eerste 4 jaar werd hij opgeleid in het IJsselland Ziekenhuis (opleider dr. I. Dawson). De laatste 2 jaar doorloopt hij in het Erasmus MC te Rotterdam (opleider prof.dr. J.N.M. IJzermans). Het laatste jaar differentieert hij in de oncologische chirurgie. Begin 2010 zal hij in het kader van een klinisch KWF-fellowship een jaar naar het Royal Prince Alfred Hospital te Sydney gaan om zich verder te verdiepen in de colorectale- en kleine bekkenchirurgie.

Floris is in juni 2006 getrouwd met Ruth en heeft een dochter Roos en een zoon Jonas.

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