MULTIMODALITY TREATMENT FOR LOCALLY ADVANCED AND RECURRENT RECTAL CANCER

Multidisciplinaire behandeling van primair lokaal uitgebreid en recidief rectumcarcinoom

Maarten Vermaas

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Chapter 1

Introduction and outline of the thesis

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 standardized surgical, pathological and radiotherapeutical procedures.[2,4-6] The introduction of preoperative short-term radiotherapy (5*5Gy) in combination with total mesorectal excision (TME) has lead to a significant decreased local recurrence rate.[7]

Based on these beneficial results the treatment protocol in the region of the Comprehensive Cancer Centre Rotterdam of patients with a tumour in the lower two-third of the rectum was changed.[2] In **chapter 2** we report the results of a registration study in the region of the Comprehensive Cancer Centre Rotterdam. The aim of this study was to identify the compliance to a new standardized treatment protocol i.e. the introduction of preoperative radiotherapy. Furthermore, the results of rectal cancer treatment in the Rotterdam region were analyzed and compared with reference values based on selected patients from randomised trials in the recent literature.

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.[8] An adequate circumferential resection margin (CRM>2mm) is related to a significantly improved local control after surgery for primary rectal cancer.[9] Especially in locally advanced rectal cancer radical margins and an adequate CRM are often difficult to obtain because of infiltration into adjacent structures. Preoperative treatment modalities have been developed to increase resectability by the effect of downsizing/-staging and to ameliorate outcome.[10,11] In case of a marginal radical or irradical resection intraoperative radiotherapy (IORT) can be applied with the aim to provide better local control. In **chapter 3** we describe our experience with the combined modality treatment of pre- and intraoperative radiotherapy and surgery for a cohort of 123 patients with primary locally advanced and initially unresectable rectal tumours.

Recurrent rectal cancer

Despite improvements in the treatment of primary rectal cancer, local recurrence rates range between 3-15%.[2] When a recurrence occurs in rectal cancer patients, prognosis is often poor and without adequate treatment mean survival is approximately 8 months and 5-year survival rates range between 0-30 %.[12-18] Recurrences are often associated with severe symptoms, especially pain.[18] 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 all recurrent disease more difficult.[17] Successful complete resection of recurrent disease is often restricted to selected patients, for example with an early-detected tumour or an anastomosis-limited recurrence after previous sphincter-sparing surgery.[19] Preoperative radiotherapy is also used in the treatment of recurrent rectal cancer with curative intent based upon the beneficial effects on local control and even overall survival in the treatment of primary rectal cancer.[20,21]

In **chapter 4** 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 intraoperative radiation.

Previously irradiated patients with recurrent rectal cancer

Since the integration of preoperative radiotherapy in the treatment of primary rectal cancer, the patients who develop a local recurrence confront us with a new problem: the treatment of previously irradiated rectal recurrences. Operating in a previously irradiated and surgically explored area is complicated by postradiation fibrosis and altered anatomy. Preoperative radiotherapy is integrated in the treatment of recurrent rectal cancer, but in this group of previously irradiated patients a smaller dosage of preoperative radiation can be applied in order not to exceed the maximum tolerated dosage. Recent studies suggest a poor prognosis of previously irradiated recurrent rectal cancer. In **chapter 5** the results of reirradiation and surgery in patients with a previously irradiated recurrent rectal tumour are described.

Intraoperative radiotherapy (IORT)

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. The use of and results after high dose rate intraoperative

radiotherapy for 37 patients with close or positive margins after resection of a primary locally advanced and recurrent tumour is reported in **chapter 6.**

Total pelvic exenteration (TPE)

In case of a locally advanced growth pattern of a primary or recurrent rectal tumour major exenterative surgery is necessary to provide complete resection margins.
A total pelvic exenteration (TPE) with resection of the rectum together with bladder, lower ureters and internal genital organs could salvage the patient, in case of tumour involvement of the base or trigone of the bladder or the prostate.
The results of TPE in a cohort of 35 patients (23 with primary locally advanced rectal cancer and 12 recurrent rectal cancer) are described in **chapter 7.**

Reconstruction after surgery

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 pre- or intraoperative radiotherapy and/or chemotherapy, chances for infection are even higher.[22-25] 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.[26,27] In **chapter 8** we describe our experience with reconstruction of pelvic defects after surgery for 25 patients with previously irradiated malignancies using a gracilis muscle flap transposition.

Radiofrequency ablation (RFA)

A selection of patients with recurrent rectal cancer does not qualify for exenterative surgery because of poor physical condition. In these patients there is a need for other techniques to provide local control. RFA nowadays is commonly used in the treatment of primary liver tumours (HCC) and liver metastases (colorectal, breast and neuro-endocrine), but the technique has also been described in the treatment of other tumours.[28,29] The mechanism of RFA is based on the conversion of radiofrequency into heat. **Chapter 9** reports for the first time on the utility of repeated RFA sessions in a single patient with recurrent rectal cancer who refused major surgery but agreed for local ablative therapy in order to provide local control.

Chapter 10, the general discussion, summarizes the results and general conclusions of this thesis.

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Chapter 2

Introduction of preoperative radiotherapy in the treatment of operable rectal cancer in the Southwest region of the Netherlands

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Abstract

Introduction

After publication of the results of the Dutch TME-trial, preoperative radiotherapy followed by TME-surgery was introduced in July 2001 in the region of the comprehensive cancer centre Rotterdam as standard treatment for rectal cancer. The aim of this study is to identify the compliance to a new standardized treatment protocol i.e. the introduction of preoperative radiotherapy and to analyze the results of rectal cancer treatment in the Comprehensive Cancer Centre Rotterdam Region.

Patients and methods

A total of 521 patients with adenocarcinoma of the rectum were included in the period from 2001 to 2003. All patients were treated with curative intent.

Results

There was a significant increase of preoperative radiotherapy for patients with a tumour in the lower two-third of the rectum (21% vs. 69%, $p<0.001$). Perioperative mortality rate was 2.7% and overall anastomotic leakage rate was 10.3%. There was a significant increase in the occurrence of anastomotic leakage in end-to-end anastomoses ($p<0.0001$). Most anastomotic leakages occurred when patients were operated in between 4 and 8 days after the end of radiotherapy. Several aspects such as continence for urine and faeces and sexual functions were poorly registered. The total number of lymph nodes registered in pathology reports was low. The rate of reported circumferential margins increased from 37% to 70% after feedback to the regional pathology working group.

Conclusion

The regional quality of rectal cancer surgery is conform preset quality-demands. There was a significant increase in the percentage preoperative radiotherapy, but still about 25% of patients who qualified for radiotherapy did not receive radiation. Pathology reports improved during registration, which illustrates the importance of registration to assess and improve quality of rectal cancer treatment.

Introduction

The average annual incidence of rectal cancer in The Netherlands is 2300 patients and this incidence is rising.[1] The treatment of rectal cancer has evolved into a multidisciplinary treatment with standardized surgical, pathological and radiotherapeutical procedures.[2-5] Total mesorectal excision (TME) leads to a decreased rate of local recurrence.[6] A randomised phase III trial performed by the Dutch Colorectal Cancer Group showed a beneficial effect of preoperative radiotherapy followed by TME-surgery on local control.[2] Based on these results the Dutch national guidelines for the treatment of rectal cancer were changed and all patients were advised to be treated with preoperative radiotherapy. However, a sub-group analysis did not demonstrate the additional effect of short-term preoperative radiotherapy for tumours in the upper third of the rectum.[2] Therefore, in the region of the Comprehensive Cancer Centre Rotterdam only rectal tumours located in the lower two-third of the rectum were treated with 5x5Gy radiotherapy followed by TME surgery since July 2001.

A registration database was started to analyze the implementation of the new treatment protocol. There is a rising interest in national and regional registration studies and the analysis of the level of quality of regional and national cancer treatment.[7] In Sweden a national registration database has been used for years to analyze national results of cancer treatment and since 1995 a specialised rectal cancer database has been introduced.[8] In the Netherlands only a few registration studies focus on the quality of national and regional treatment. Most of these projects are retrospective studies that focus on survival and therefore miss information on postoperative complications and functional results (e.g. urinary and faecal continence and sexual functions). The aim of this study is to identify the compliance to a new standardized treatment protocol i.e. the introduction of preoperative radiotherapy; furthermore, to analyze the results of rectal cancer treatment in the Comprehensive Cancer Centre Rotterdam Region and compare these with reference values based on selected patients from randomised trials in the recent literature.

Methods

The region of the Comprehensive Cancer Centre Rotterdam consists of one tertiary referral hospital and 15 general hospitals in the South-western part of the Netherlands, which is a region with 2,3 million inhabitants. All oncological colorectal surgeons join in The Regional Network of Surgeons.

All patients who underwent treatment with curative intent for a histologically confirmed adenocarcinoma of the rectum between January 2001 and December 2003 were included in the registry. The rectum was defined as the first 15 cm bowel from the dentate line measured by endoscopy or as the part underlying the virtual line between symphysis pubis and promontory during contrast imaging. National guidelines advise imaging by pelvic CT or MRI of all tumours in case of suspicion of local growth close to and into surrounding structures (T3 and T4). Treatment with curative intent required a patient without evidence of distant metastases and a rectal cancer that allowed for a radical resection based on preoperative imaging studies. A patient was not excluded when radical rectal surgery was combined with the resection of a peroperatively diagnosed distant metastases. All patient-, tumour- and operative characteristics and postoperative follow-up data were scored according to a preset list including; date of diagnosis, previous pelvic surgery, localization and distal margin of tumour, preoperative diagnostics and neo-adjuvant treatment. Operative characteristics were: type of surgery, anastomosis, surgeons and the postoperative complications. Tumours were classified according to the UICC TNM-criteria. Follow-up characteristics were: CEA serum levels, local and distant control, loss of continence of urine and faeces, and sexual functions. Anastomotic leakage was defined as a clinical observable leakage in which reintervention was necessary. Preset reference values based on literature were: postoperative mortality< 5%, anastomotic leakage < 10%, local recurrence < 10%, loss of urinary continence< 10% after 3 months, loss of faecal continence < 10% after 3 months and erection disturbances< 35% after 6 months. [2, 9, 10]

Before the start of the prospective registration a retrospective registration study was conducted in the period between January 2001 and June 2002. With the use of PALGA (a nation-wide histopathology database) all patients were selected for the retrospective part of the study. PALGA was also used in the prospective registration to verify if all rectal cancer patients were included in the registration.[11] The retrospective study was conducted by three independent research students who collected data in the participating hospitals and entered this information in a specially designed database.

Treatment

According to regional guidelines all patients treated from the first of July 2001 with a rectal tumour in the lower two-third of the rectum received radiotherapy prior to surgery. The radiotherapy was applied through a posterior-anterior field and two lateral fields with a total dosage of 25 Gy (5 x 5 Gy). The target volume of the radiotherapy consists of the primary tumour and the mesentery with the vascular

supply containing the perirectal, presacral and internal iliac nodes. According to the protocol the day of surgery should be between 1 and 7 days after the end of radiotherapy. All operations, except for transanal endoscopic microsurgery (TEM), were performed by TME-technique. This technique implies en-bloc resection of the rectum and perirectal fat and lymphoid tissue.[6] The majority of regional surgeons were previously trained in this technique. Chemotherapy was no standard neoadjuvant or adjuvant treatment in the regional or national guidelines. Pathological examination of the resected specimen was performed by the standardized technique described by Quirke.[3]

Data collection and statistical analysis

The databases were provided to regional surgeons in Microsoft Access 1997/ 2000 or Microsoft Excel. One surgeon per hospital was responsible for the registration of all data. The Comprehensive Cancer Centre Rotterdam collected all data bi-annually. A data manager first performed a data-analysis for missing data, inconsistencies and faults, which were then reported to the surgeons. After a second correction all data were integrated in a database and analyzed with SAS statistical software (version 10). During the entire process the privacy of patients was maintained.

Results

All 16 hospitals participated in the retrospective study and 12 hospitals participated in the prospective registration. Four hospitals did not participate because the surgeons said to have a shortage of time to collect the data. Patient- and tumour characteristics did not differ between these hospitals and therefore all data of the retrospective study were included for further analyses.

The PALGA pathological database indicated 900 patients with a rectal tumour in the period between January 2001 and December 2003. Three hundred and seventy-nine patients were excluded because the tumour-histology other than adenocarcinoma, the tumour was not localised in the rectum or the treatment was with palliative intent. A total of 521 patients were included of which 230 in the retrospective part and 291 in the prospective part of the study. All patient-, tumour- and operation characteristics are summarised in table 1 and 2. The number of patients included per hospital varied from 13 to 51 per two years. The number of surgeons varied from 1 to 3 per hospital.

Difference before and after introduction of new regional treatment protocol

During the study period a significant increase in the proportion of preoperatively irradiated (5*5Gy) patients with a tumour in the lower two-third of the rectum was observed (21% versus 69%, p<0,001; figure 1). In the last semester of 2003, 74% of the patients with a tumour in the lower two-third of the rectum received preoperative radiotherapy, including 5% undergoing long-term radiation (25x2Gy). The percentage of long-term irradiated patients did not change over the period. There is no significant difference in age between the irradiated and the non-irradiated patients (p=0.37).

The proportion of patients receiving preoperative radiotherapy varied between hospitals from 41% to 100% (p<0.001). The motivation for withholding radiotherapy was not recorded in this study, but was certainly influenced by stage. T1 tumours were treated by preoperative radiotherapy in 47% of the patients, against 75% of T2 tumours and 85% of T3 tumours (p<0.001). The median interval between the last day of radiotherapy and operation was 4 days, 24 patients (10%) had an interval longer than 7 days.

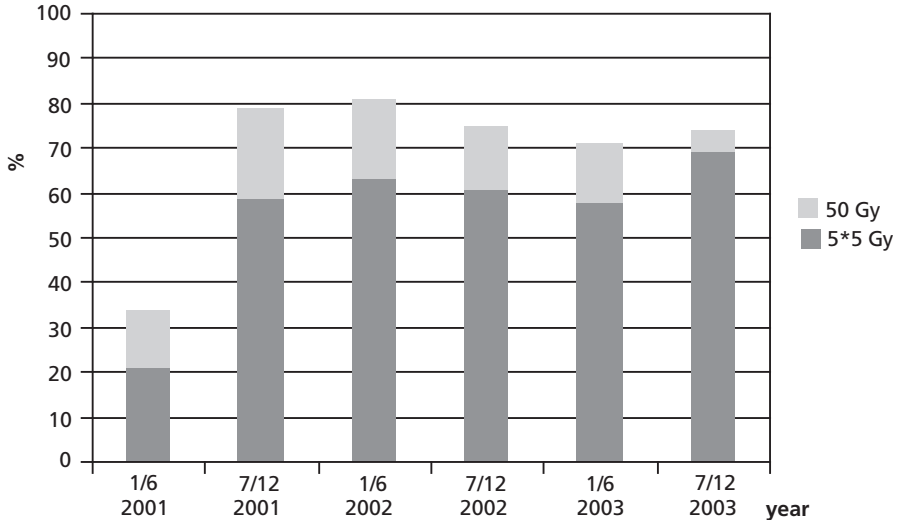

Figure 1. Percentage preoperative radiotherapy before and after introduction of a new treatment protocol

Table 1. Patient- and tumour-characteristics

		2001	2002	2003
Number of patients		155	203	163
Male/ female (%)		59/ 41	62/ 38	57/ 43
Age (median)		68 (39-91)	67 (36-90)	65 (31-94)
Prior pelvic surgery (%)		10	10	13
Localization tumour (%)				
Proximal (10-15 cm)		35	27	29
Medial (5-10 cm)		30	35	28
Distal (0-5 cm)		35	37	44
TNM staging (%)				
Tumour	T1	12	12	10
	T2	35	31	36
	T3	44	46	44
	T4	7	9	4
	Tx	2	2	6
Stage (UICC) (%)				
Stage I (T1-T2 N0M0)		39	34	37
Stage II (T3-T4 N0M0)		20	28	20
Stage III (N+)		32	30	29
Stage IV (M+)		8	6	8
Unknown		1	2	6

Histopathology reporting

The number of analyzed lymph nodes in pathology specimens remained unchanged during the study period. A median number of 6 nodes (range 0-26) were analyzed without a significant difference between irradiated and non-irradiated patients. There was also no difference in the number of positive nodes; median 3 positive nodes (range 1-16) in the irradiated group versus 2 (range 1-13) in the non-irradiated group. A substantial part of the pathology reports were not according to regional pathology guidelines. The circumferential resection margin was only reported in 37% of the reports in 2002. After feedback to the regional pathologist network this percentage increased to 70% in 2003.

Table 2. Operative- and pathological characteristics

	2001	2002	2003	
Operation (%)				
APR	30	27	31	n.s.
LAR	52	51	55	
TEM	5	5	0	
Other	12	15	11	
Protective stoma LAR (%)	56	60	55	n.s.
Type of anastomosis LAR (%)				
Hand-sewn	4	7	12	n.s.
Stapled	94	83	87	
Anastomosis (%)				
end to end	10	9	9	n.s.
side to end	86	75	74	
coloanal	1	4	6	
Circumferential margin (%)				
<= 2 mm	9	9	11	n.s.
> 2 mm	28	29	59	
unknown	64	63	30	
Completeness of resection (%)				
complete (R0)	91,4	91,5	93,8	n.s.
microscopically incomplete (R1)	3,3	3,2	3,4	
macroscopically incomplete (R2)	0,7	1,1	0	
unknown	4,6	4,2	2,7	

LAR = Low Anterior Resection, APR = Abdominoperineal resection,
TEM = Transanal Endoscopic Microsurgery, n.s. = non-significant

Surgical Management

The proportion of sphincter-sparing surgery did not differ before and after the introduction of the new treatment protocol. The numbers of sphincter-sparing operations were 92%, 81% en 27% for the proximal, middle and distal tumours. In 58% of patients who underwent a low anterior resection (LAR) a protective ileostomy was constructed. Clinical anastomotic leakage was demonstrated in 10.3% of the patients. Although there was no randomization, an analysis of the correlation between certain treatment factors and the occurrence of anastomotic leakage was performed (table 3). There seemed to be no relation between the occurrence of anastomotic leakage and the construction of a diversion ileostomy or

colostomy. There was a significant correlation between the type of anastomosis and the occurrence of anastomotic leakage (p<0.0001; table 3) Postoperative mortality remained low in the entire period (3%). Mortality was significantly higher in patients who experienced anastomotic leakage (2% versus 12.5%, p=0.02). The construction of a protective stoma did not have significant influence on mortality after occurrence of anastomotic leakage. There were no differences in the completeness of resection in the analyzed period (table 2). Patients with an interval of 4-7 days between the end of radiotherapy and the day of surgery had a significantly higher rate of anastomotic leakage compared to patients with a shorter or longer interval (p=0.04). The anastomotic leakage rates were 4.1% (1-3 days); 16.7% (4-7 days) and 4.5 % if the interval was more than 8 days. Postoperative mortality was not significantly different between the different interval groups (p=0.84).

Late Morbidity & Follow-up

Data on the loss of urinary and faecal continence and changes in sexual functions remained unknown in respectively 75%, 37% and 83% of the patients. Considering the high percentage of missing data of functional and sexual outcome no analysis of these data was performed. Pre- and postoperative CEA-values were registered in respectively 45% and 30% of the patients.

Table 3. Correlations between anastomotic leakage and specific treatment factors after low anterior resection

Patient / treatment		Patients with anastomotic leakage		p-value
		N	%	
Preoperative radiotherapy	No	13	13	
	Yes	10	9	n.s.
Protective stoma	No	10	10,6	
	Yes	13	10,3	n.s.
Localisation of tumour	Proximal	8	8%	
	Middle	10	10%	
	Distal	6	17%	n.s.
Anastomosis	end to end	6	27,3	
	side to end	18	10,1	
	coloanal	0	0	<0,0001

n.s. = non-significant

Discussion

Based on the results of the Dutch TME trial the treatment in the region of the Comprehensive Cancer Centre Rotterdam of patients with a tumour in the lower two-third of the rectum has changed to preoperative radiotherapy (5*5Gy) followed by TME-surgery.[2] This registration study identified a significant increase in the number of preoperatively irradiated patients after the introduction of the new treatment protocol. A significant percentage (25% at the end of the period) of patients, however, did not receive radiation and remained unchanged during the period of intensive registration after the introduction of the new treatment protocol. Identifying the specific reasons for not performing preoperative radiotherapy in a subgroup of patients was not the aim of our study, but reasons could be the lack of additional value of preoperative radiation in small tumours (T1).[2] Although preoperative radiotherapy was introduced in the guidelines for all rectal tumours, the study from Kapiteijn et al. demonstrated that radiotherapy did not reduce the incidence of local recurrences in the subgroup of stage I tumours. Therefore, some surgeons operated on patients with these small tumours without preoperative radiotherapy. This was clearly demonstrated in this study where the minority of patients with T1 tumours received preoperative radiotherapy versus the majority of patients with higher stage tumours ($p<0.001$). A significant difference in the percentage of patients receiving preoperative radiotherapy per hospital was also identified (range 41-100%). One of the explanations for this difference can be a personal objection of a surgeon against radiotherapy. Other reasons could be a difference in patients with co-morbidity who are sometimes withdrawn from radiotherapy. Logistical reasons could also play a role in not irradiating patients. The current registration offers the possibility to specifically analyze results per hospital or surgeons and to provide feedback. This to eventually optimize and standardize the regional treatment of rectal cancer.

The completeness of resection did not differ over the analyzed years and is comparable with the literature.[12] Mortality and the percentage of anastomotic leakage were in the range of the preset quality reference values. The significantly higher mortality after the occurrence of anastomotic leakage concurs with known literature.[13] The percentage of created protective stomata was comparable with data from the TME-trial.[14] But, in contrast to recently published results describing a protective value of the defunctioning stoma on the occurrence of clinically relevant anastomotic leakage, a lower leakage rate in this group of patients was not experienced.[13] There seemed to be a relation between the type of anastomosis and the rate of anastomotic leakage. In the present study there was no leakage

in the small group of patients who received a colo-anal anastomosis and colonic pouch. Only few publications describe the type of anastomosis as one of the factors influencing anastomotic leakage. Hallbook et al. showed a significantly lower anastomotic leakage rate after colon J-pouch compared with straight anastomoses.[15] Other authors have hypothesized that higher leakage rates after straight (end-to-end) anastomosis can be based on impaired microcirculation at the anastomotic site.[15,16] This might be a reason for the higher anastomotic leakage rate found in the straight anastomosis in the present study.

Another interesting difference in anastomotic leakage rate was found between the different interval groups. Patients who were operated on 4-7 days after the end of radiotherapy experienced a four times higher rate of anastomotic leakage, without an impact on postoperative mortality. In the Dutch TME–trial, however, patients older than 75 who were operated after 9 days had a significantly higher postoperative mortality (personal communication, Marijnen et al.). In theory postradiation oedema and inflammation could lead to such complications and this might be influenced by the interval between radiotherapy and surgery. Until now the relevance of the total treatment time is virtually unknown and further studies are needed to fully understand this phenomenon.

The total number of lymph nodes examined by a pathologist is of importance for the accurate staging of a tumour and to accurately define the prognosis of the patient.[17] Instead of the generally accepted minimum of 12 lymph nodes examined for accurate staging only a mean of 6 nodes were examined in our region.[18] There was no analysis of the surgical quality of the resected TME-specimen; therefore, the reason for the low number of lymph nodes cannot be attributed to poor surgery or poor pathology. In contrast to the TME-trial there was no significant influence of radiotherapy on the number of lymph nodes retrieved in the specimen.[19] The percentage of reported circumferential resection margins, being one of the most important factors for local control, was low in the beginning of the study.[20] However, after feedback to the regional pathology network an increase in the reported margins was noticed.

Because of the low percentage of reported functional and sexual results during follow-up it was not possible to perform reliable analyses on these data. Better and more reliable results on functional outcome can be obtained using anonymous quality of life questionnaires, such as the EORCT QLQ C30 or CR38.[21] The outcomes of randomised studies out of a carefully selected population cannot always be translated to the population in daily practice. The evaluation of the results of treatment of the patient population in daily practice can be of additive value to the results deducted from controlled studies. A prospective cancer related database can identify regional

quality of treatment, but can also identify individual differences between hospitals and surgeons. Compliance to introduced guidelines and new treatment protocols can be identified. A problem, however, is that the high workload of surgeons creates a burden for reliable and complete data-registration. An internal audit halfway the registration identified the lack of time of the surgeon as the only factor for failure to registration.

Participating surgeons

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Chapter 3

Value of intraoperative radiotherapy in locally advanced rectal cancer

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Abstract

Purpose

This study was designed to analyze 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, histopathologic 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 media dose of 50Gy radiotherapy. Surgery was performed six to ten weeks after radiotherapy. Twenty-seven patients were treated with intraoperative radiotherapy because margins were incomplete or ≤ 2mm. Postoperative mortality was 2 percent. The median follow-up of all patients was 25.1 months. The overall five-year local control was 65 percent and the overall five-year survival was 50 percent. Positive lymph nodes and incomplete resections negatively influenced local control and overall survival. Intraoperative radiotherapy improved five-year local control (58 vs. 0 percent, p =0.016) and overall survival (38 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 five-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 histological finding.

Introduction

Colorectal cancer is a major problem in the western world; it 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 by 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 adenocarcinoma. Each tumour was clinically classified as large T3 with narrow circumferential margins to the mesorectal fascia on CT or magnetic resonance imaging (MRI) or fixed, initially unresectable T4 tumours. Our prospective database consists of hospital notes, radiotherapy plans, operation notes and histopathology reports to obtain the following information: demographics, preoperative diagnostic intervention, tumour staging, radiotherapy technique, surgical details, histopathology 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 (1 posterior and 2 lateral fields) were used. A radiation dose of 50 Gy in 25 daily fractions of 2 Gy 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 ≤ 2mm. 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, three to four 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 localizer. 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 to the anatomy of the pelvis.

Surgery

Surgery was planned six to ten 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 metastases-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 metastases were analyzed 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 < 0.05 were regarded as significant.

Results

Patients

Preoperative radiotherapy followed by surgery was performed in 123 patients (87 males). Mean age at the time of surgery was 66 (range 20-90 year) years. Presenting symptoms were pain in 12 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 before 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 of radiotherapy. The remaining patients received various doses between 25 and 52 Gy.

Surgery was performed six to ten weeks after radiotherapy and included low anterior resection in 23 patients (19 percent), abdominal-perineal 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 centre, *e.g.* 29 of 76 patients operated on had a T4 tumour *vs.* 2 of 47 patients in the community hospitals. Twenty-seven patients (22 percent) were treated with IORT because the resection was ≤ 2mm.

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%

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

Follow-up

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

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)

Local control

The overall three-year and five-year local control rates were 75 and 65 percent, respectively. There was a significant difference in the five-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 centre 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).

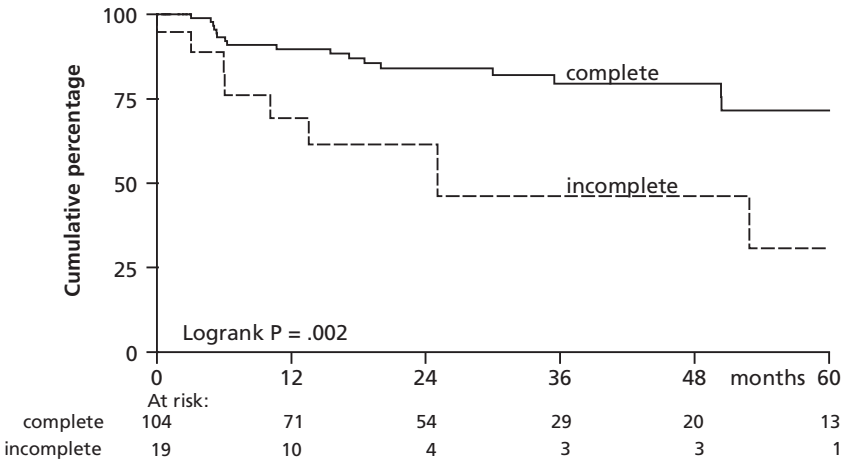


Figure 1. Local control by completeness of resection

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* = 0.02**)	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%
TPE	18	85%	47%	44%
PE	19	70% **ns**	50% **ns**	66% **ns**

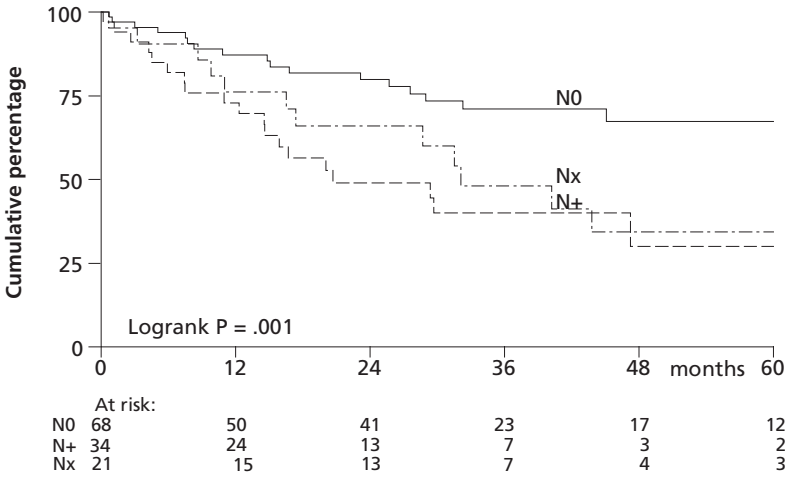
LAR Low Anterior Resection, APR Abdominoperineal Resection, APSR Abdominoperineal-sacral Resection, TPE Total pelvic exenteration, PE Posterior exenteration

Distant metastases

The overall three-year and five-year actuarial distant metastases free survival rates were 59 percent and 53 percent, respectively. The five-year metastases free survival rate was statistically significantly different for complete vs. 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).

Overall Survival

The overall three-year and five-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 significantly important (Table 3).



Legend N0: no positive lymph nodes, N+: positive lymph nodes; Nx: nodal status unknown

Figure 2. Overall survival by lymph node status

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 eight patients developed a local recurrence and all died within five 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 *vs*. 0 percent, p=0.016; 5-year overall survival 38 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, gender, 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.

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%**n.s.**	66%**n.s.**
Incomplete	8	No	0%	0%
Incomplete	11	Yes	58% (***P* = 0.016**)	38% (***P* = 0.026**)

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

Discussion

Patients with locally advanced tumours should preferably receive some form of neoadjuvant treatment in order 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 5-year overall survival of patients treated for recurrent rectal cancer is generally reported between 15 to 55 percent[6,16-19] compared to a much higher 40 to 70 percent in primary locally advanced rectal cancer.[6,7,20-22] 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 in comparison with incomplete resected patients (72 vs. 31 percent). This is in concordance with results demonstrated

in the Dutch TME trial representing mainly T2 and T3 rectal cancer patients. A margin ≤ 2mm was associated with a local recurrence risk of 16 percent compared to 5.8 percent in patients with more mesorectal tissue surrounding the tumour ($p<0.0001$).[23] 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.[24]

Lymph node status and the presentation of preoperative pain also proved to be significantly important factors for local control in the present study. Pain is not often 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.[18,25]

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.[26] 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.[27] Previous studies have demonstrated that IORT achieves good local control and high survival rates in primary locally advanced rectal cancer.[7,10,11,20,28-31] 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 to 0 percent in patients who did not receive IORT. Nakfoor et al.[21] and Gunderson et al.[32] 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.[33] Despite the fact that patients treated in the referral hospital had more advanced tumours, local control was 75 percent compared to 44 percent in community hospitals after five years ($p=0.02$). Similar results were reported by Wibe et al.[34] who demonstrated that local recurrence rate was higher in patients treated in hospitals with a low annual caseload of less than 10 procedures compared to hospitals with a high treatment volume of 30 procedures or more.[35] Patients treated in smaller hospitals also had a lower long-term survival rate than those treated in larger hospitals. Begg et al.,[36] reported that mortality rates are lower when complex surgical oncological procedures are performed by surgical teams in hospitals with special expertise. Based on these results, we

emphasize that not only volume but also the necessity of a multidisciplinary team, including a radiation oncologist, urologist, surgical oncologist, plastic surgeon, and gynaecologist is of importance for these surgical procedures, which are preferably performed in specialised centres.

The overall survival rate in the present study is comparable to what has been reported in the literature for these advanced tumours.[20,30,37] 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 are also reported.[7,11,29,30] However, these latter factors seemed not important in the present study.

IORT was applied in 19 patients who were treated with a narrow but complete resection (margin 0-2mm). The survival in these patients was similar to the total group of patients with a complete margin who did not receive IORT. Nagtegaal et al.[23] have demonstrated that circumferential margins are extremely important for developing a local recurrence. For rectal cancer patients with circumferential margin of < 1mm, a recurrence rate of 16 percent after two years was described. In the present study, addition of IORT seems to overrule the unfavourable prognostic histological 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 neo-adjuvant treatment to reduce tumour mass. Addition of chemotherapy to preoperative radiotherapy recently demonstrated to improve local control in two large randomised trials.[7,38-40] The European Organisation for Research and Treatment of Cancer (EORTC) 22921 four-arm randomised trial[41] demonstrated the benefit of preoperative chemoradiation vs. preoperative radiation alone in T3-T4 resectable rectal cancer patients. Addition of 5-fluoroucil and leucovorin to preoperative radiation slightly increased the amount of acute toxicity, but more importantly increased the number of complete responses and decreased the local recurrence rate after five years.[42] In future multimodality treatment protocols for locally advanced rectal cancer the addition of chemotherapy to radiotherapy should therefore be considered.[43]

Conclusions

IORT for patients with a narrow complete or incomplete resection seems to overrule the unfavourable prognostic histological 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 4

Preoperative radiotherapy improves outcome in recurrent rectal cancer

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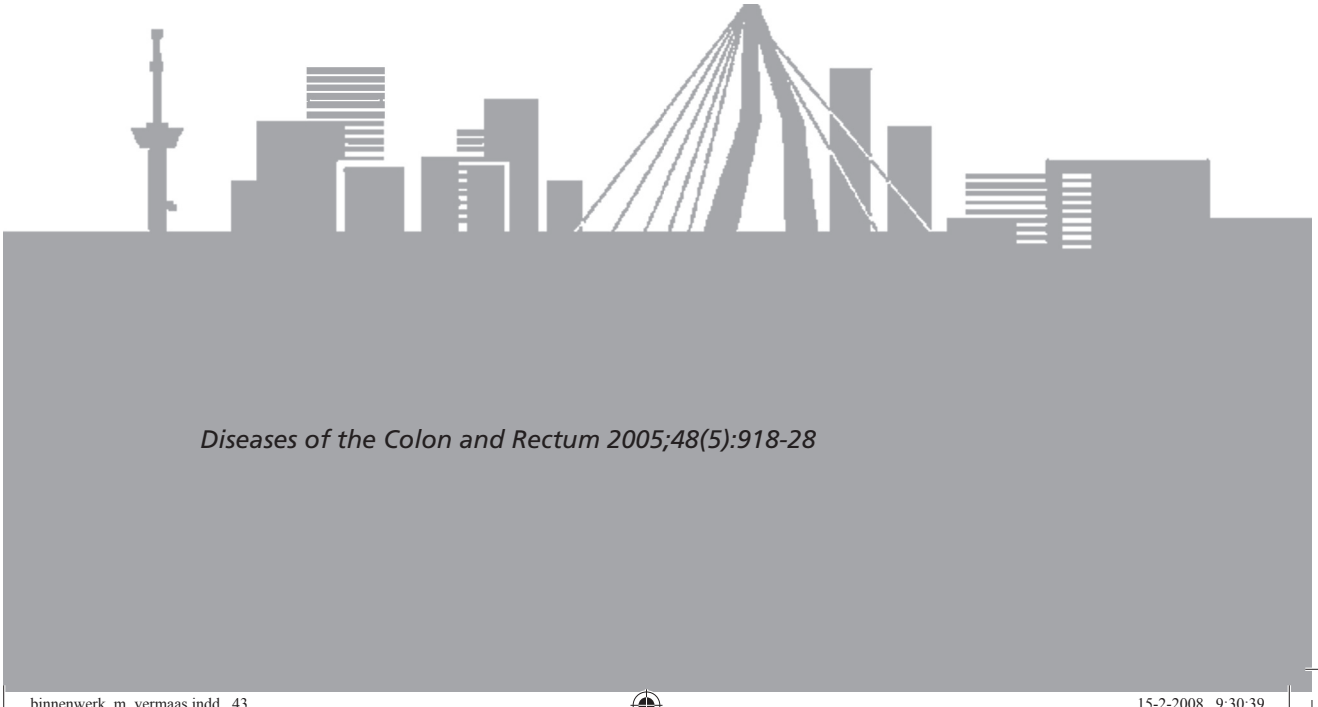

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Abstract

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 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 node-bearing 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.[2,5,6] 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 focussed 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 analyzed. 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 percent men and 42 percent 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 had a 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-field-box. 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.

Table 1. Characteristics of the primary tumour

Grade	**No pre-op RTX (33)**	**Pre-op RTX (59)**
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%
Hartmann / Transanal resection	9%	12%

Pre-op RTX = preoperative radiotherapy; No pre-op RTX = no preoperative radiotherapy;
LAR = low anterior resection; APR = abdomino-perineal resection

Table 2. Tumour characteristics of rectal cancer recurrence

Tumour status		**No preop RTX (33)**	**Preop RTX (59)**
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			
Tr1	(Limited recurrence in submucosa)	0%	2%
Tr2	(Growth in full thickness rectal wall)	3%	3%
Tr3	(Growth into surrounding soft tissue)	33%	41%
Tr4	(Penetration anterior structures)	30%	25%
Tr5	(Penetration posterior structures)	21%	19%
Unknown		12%	10%
Suzuki classification			
F0	(no contact to pelvic wall)	18%	20%
F1	(contact less than ¼ of pelvic wall)	30%	31%
F2	(contact ¼ to ½ of pelvic wall)	21%	19%
F3	(contact more than ½ of pelvic wall)	0%	5%
F4	(infiltration in bony structures/ small bowel)	15%	20%
Unknown		15%	5%

Preop RTX = preoperative radiotherapy; No preop RTX = no preoperative radiotherapy

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.

Table 3. Operation characteristics of patients treated for recurrent rectal cancer

Resection	No preop RTX (33)	Preop RTX (59)	
R0	45%	64%	
R1	36%	22%	
R2	18%	14%	
Type of resection			
LAR	0%	5%	
APR	73%	43%	
APSR	3%	19%	
Total pelvic exenteration	6%	14%	
Posterior resection	18%	19%	
Median bloodloss	3000 ml.	6000 ml.	***p<0,001***
Median operating time	255 min.	415 min.	***p=0,016***
Median hospitalization	17 days	24 days	***p=0,189***

Preop RTX = preoperative radiotherapy
No preop RTX = no preoperative radiotherapy
LAR = low anterior resection
APR = abdomino-perineal resection
APSR = abdomino-perineal-sacral resection
R0 = microscopically complete resection
R1 = microscopically incomplete resection
R2 = macroscopically complete resection

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=0,4). 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 4. Three-year actuarial local control and overall survival by IORT administration and completeness of resection

		Local control (3 yr)		Overall survival (3 yr)	
IORT					
complete (R0)	(n = 17)	45%		35%	
incomplete (R1/2)	(n = 10)	21%	***(p=0,25)***	21%	***(p=0,75)***
Non-IORT					
complete (R0)	(n = 21)	24%		41%	
incomplete (R1/2)	(n = 11)	19%	***(p=0,58)***	27%	***(p=0,45)***

IORT intraoperative radiotherapy

Table 5. Postoperative results

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

Preop RTX = preoperative radiotherapy; No preop RTX = no preoperative radiotherapy

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 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.

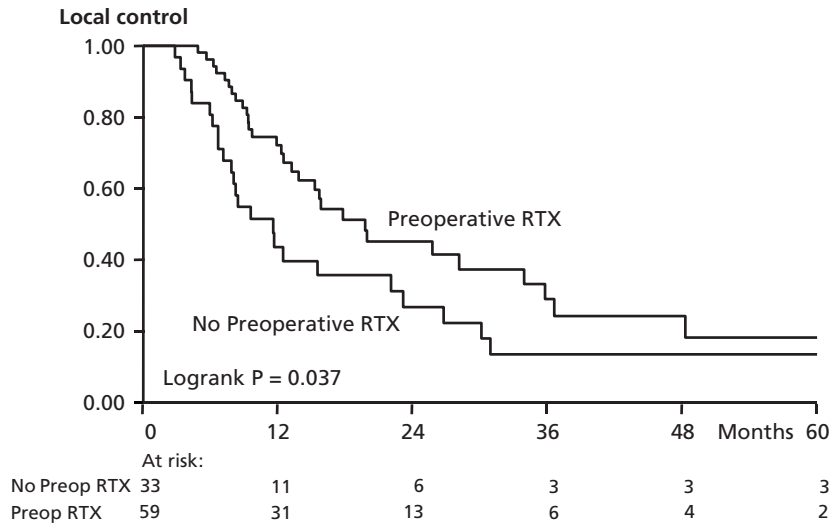

Figure 1. Local control of recurrent rectal cancer patients treated with preoperative RTX vs. no preoperative RTX

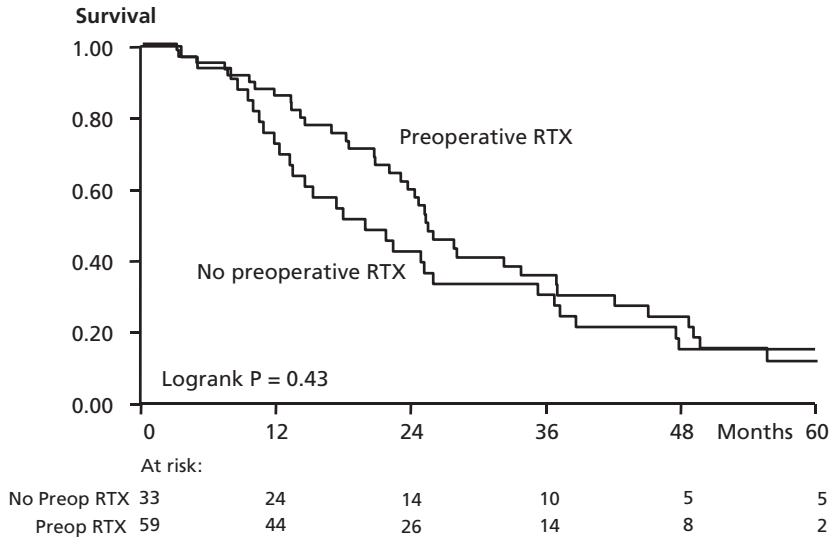

Figure 2. Overall survival of recurrent rectal cancer patients treated with preoperative RTX vs. no preoperative RTX

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 6. Local control and overall survival

	Local control			Overall survival		
	3 yr	5 yr	P	3 yr	5yr	P
Neg. lymph nodes prim. (57)	24%	20%	0.067	35%	20%	***0.009***
Pos. lymph nodes prim. (33)	14%	7%		28%	x	
No symp. Pain (61)	20%	17%	0.445	35%	16%	0.681
Symptomatic pain (30)	27%	14%		30%	9%	
Preop RTX (59)	28%	18%	***0.037***	34%	11%	0.426
No preop RTX (33)	13%	13%		30%	15%	
Suzuki stage 0,1,2 (64)	23%	23%	0.525	33%	12%	0.857
Suzuki stage 3,4 (20)	17%	x		31%	8%	
Wanebo Tr1-3 (39)	18%	18%	0.889	37%	6%	0.427
Wanebo Tr4-5 (43)	16%	5%		22%	11%	
Complete response (6)	80%	40%	0,186	100%	67%	***0,011***
No complete response (53)	20%	14%		%	0%	
Complete (R0) resection (53)	31%	26%	0.079	39%	21%	***0.036***
Incomplete (R1/2) resection (39)	11%	5%		24%	3%	
IORT (27)	34%	23%	0.084	31%	24%	0.375
Non IORT (32)	17%	14%		33%	11%	

Preop RTX = preoperative radiotherapy; No preop RTX = no preoperative radiotherapy; IORT = intraoperative radiotherapy; x = not assessable

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

		Local Control			Overall Survival		
	n	HR	p-value	CI	HR	p-value	CI
Preoperative RTX							
No preop RTX	33	1			1		
Preop RTX	59	0,529	0,020	(0,310-0,904)	0,791	0,334	(0,491-1,2373)
Interval prim-rec							
< 12months	34	1			1		
>12 months	58	0,667	0,144	(0,387-1,148)	0,880	0,606	(0,543-1,428)
Lymph node status							
Negative	59	1			1		
Positive	33	1,735	0,054	(0,989-3,041)	1,852	0,015	(1,128-3,041)

Preop RTX = Preoperative radiotherapy; Interval prim-rec = Interval between operation primary tumour and diagnosis recurrence; HR = Hazard rate; CI = Confidence interval

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 post-radiation 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 sterilize 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-dose-rate 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 equalizes 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).

Conclusions

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 5

Reirradiation and resection of recurrent rectal cancer in previously irradiated patients

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Abstract

Background and purpose: The optimal treatment for isolated locally recurrent rectal cancer is preoperative (chemo-)radiation followed by surgery ± IORT. However, recent studies suggest a poor prognosis of previously irradiated recurrences.

Material and methods: Of 117 patients with recurrent rectal cancer, 11 patients had been irradiated previously. After diagnosis of an isolated recurrent rectal cancer all patients were treated with reirradiation (median dose 30Gy) before surgery.

Results: In all but one patient resection of the recurrence was performed; APR (n=4), resection of recurrence (n=2) and total exenteration (n=4). One patient underwent a microscopically complete resection (R0), six patients a microscopically incomplete resection (R1) and 3 patients a macroscopically incomplete resection (R2), after which all patients received IORT. The minor and major complication rates were 80% and 10%. There was no in-hospital mortality.
The overall survival was at 1 and 3 years were 77% and 51%. Local control was after 1 and 3 years were 66% and 27%. The distant metastases free survival was after 1 and 3 years were 100% and 50%. Median pain free survival after treatment was 5 months.

Conclusion: Treatment of previously irradiated recurrent rectal cancer with reirradiation, IORT and surgery is related with high morbidity and poor local control, although some patients have long-term distant control and survival.

Background and purpose

Preoperative short-term radiotherapy (5x5Gy) has evolved into an integrated factor in the treatment of T2-3 rectal tumours because of beneficial effects on local control.[1] Long-term radiotherapy (44-50 Gy) has become standard of care in the treatment of T4 tumours because of improved local control and the effect of downsizing /-staging, thereby facilitating less invasive surgery in a subgroup of patients.[2]

The 3-15 percent of patients who do develop a local recurrence confront us with a new problem; the treatment of previously irradiated tumours.[1] In previously non-irradiated recurrent tumours the combination of preoperative radiotherapy with a dosage of 50Gy and surgery leads to improved local control.[3] This high radiation dose cannot be administered in previously irradiated patients, thus a lower dose of radiation must be applied not exceeding the maximum tolerated dosage. Previously Mohiuddin et al.[4] demonstrated that reirradiation of a rectal recurrence with 15x2Gy is feasible and a large multicentre study reported excellent results with this treatment schedule.[5]

On the other hand, data from the Dutch TME trial suggested that the clinical nature and prognosis of patients with locally recurrent rectal cancer has changed since the introduction of preoperative radiotherapy. The majority of patients who presented with a local recurrence after previous preoperative radiotherapy had simultaneous distant metastases and a poor survival (median 6 months).[6]

In our tertiary referral centre patients with locally recurrent rectal cancer are treated with reirradiation followed by surgery in combination with intraoperative radiotherapy. The aim of this study is to analyse the results of this multimodality treatment protocol for patients with recurrent rectal cancer.

Material and methods

In the period 1984 to 2006, 367 patients with primary and recurrent locally advanced rectal cancer were treated in our tertiary-referral cancer hospital. Of the total group of 117 patients with recurrent rectal cancer, 11 patients were previously irradiated and treated with reirradiation before surgery of the recurrence. The group consisted of 7 male and 4 female with a median age of 62 years (range 41-77).
Primary tumour and treatment characteristics are depicted in table 1. The median dosage of external beam radiotherapy (EBRT) applied during treatment of the primary tumour was 50 Gy (range 25-60; table 1). Six patients received preoperative radiation (3 patients 5x5 Gy, 2 patients 25x2 Gy and 1 patient 25x2 Gy in combination

with 10 Gy intraoperatively). Five patients received postoperative radiotherapy (25x2Gy) during the primary treatment due to a microscopically incomplete (R1) resection (n=3) or peroperative tumourspill (n=2). None of the patients received chemotherapy for treatment of the primary tumour.

Table 1. Pathological characteristics and treatment primary tumour

		(N)
Primary pTNM stage		
	T2N0M0	2
	T3N0M0	3
	T3N1M0	2
	T3N2M0	1
	T4N0M0	1
	T4N1M0	1
Primary radiotherapy dosage		
	25Gy	3
	50Gy	7
	60Gy	1
Primary operation		
	LAR	6
	APR	5

LAR Low Anterior Resection, APR Abdominoperineal Resection

Work-up

Patients were preoperatively analyzed and selected using a pelvic CT- and MRI-scan of the pelvis. On indication a cystoscopy was used to identify tumour growth into the bladder. Screening for distant metastases was performed using thoracic and abdominal CT-scans. Based on the preoperative examination and imaging, 5 patients were graded as Wanebo Tr4 (e.g. tumour penetrating adjacent organs) and 6 as Wanebo Tr5 (invasion of bony structures, of low pelvic side walls).[7]

EBRT and IORT

EBRT was administered in doses of 1,8 or 2 Gy per fraction up to a median dose of 30Gy (range 27-40). EBRT was delivered by either a three-field technique, using one posterior and two lateral portals or a four-field box technique. The pelvic field borders were defined as follows: the lateral borders extend 1.5 cm lateral of the bony pelvis, with the cranial border the promontory (L5-S1), and the caudal border was at least below the foramina obturatoria to 2 cm under the anus, depending on

the tumour position. The dorsal border encompassed the sacrum, and the anterior border was chosen in such a way that the tumour region was widely covered.

In 1997, an intraoperative radiation therapy (IORT) program was started in our hospital. [8] IORT with HDR brachytherapy was given to patients who had a minimal circumferential free resection margin equal to or less than two millimetres. 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.[8]

Evaluation of morbidity and mortality

Patient characteristics, operation techniques and follow-up were studied using the database and hospital charts. Surgery related morbidity was divided in major and minor complications. Major morbidity was defined as complications that required reintervention. All other complications were classified as minor.

Statistical analysis of survival and local control

All patients were bi-annually seen at our outpatient-clinic for follow-up. Survival time was calculated from the date of resection of the rectal cancer until the last follow-up attendance or until death. Local control was calculated from the date of resection of the rectal cancer until the histological or evident radiological presence of a local recurrence. The cumulative survival, disease free survival and local control rate after surgery was calculated using the Kaplan-Meier method. Because of the small size of the patient cohort no statistical analyses for prognostic significant factors were performed.

Results

Of the 11 patients in this study, 10 were diagnosed after presentation with complaints; 6 patients presented with perineal pain, 3 with an altered pattern of defecation and 1 patient with urinary problems. One patient did not have any complaints, but presented with a rise of carcinoembyonic antigen (CEA). Median interval between primary surgery and date of recurrence was 22 months (range 9-117).

Preoperative workup did not reveal any distant metastases and all patients were operated on with curative intent. Neo-adjuvant chemotherapy was applied to one patient with a presacral recurrence before reirradiation (40Gy) in combination with hyperthermia.

One patient underwent a staging laparotomy with construction of a diverting colostomy before the start of radiation to identify the resectability of the local recurrence and to avoid tumour obstruction in the preoperative workup.

Operation

All but one operation were performed in our cancer centre. Characteristics are depicted in table 2. In one patient the tumour showed massive growth into the lateral pelvic walls with fixation to bilateral ureters and fixation to the presacral plane and was therefore defined as not resectable.

Table 2. Tumour and operation characteristics

		(N)
Growth into other organs/ structures		
	prostate	1
	vesicles	2
	bladder	2
	vagina	2
	sacral bone	2
	lateral pelvic wall	6
Type of resection		
	None	1
	APR	4
	Resection recurrence	2
	Total exenteration	4
Median duration of operation	420 min	360-540
Median loss of blood	3500 ml	1100-21000
Hospital stay	14 days	11-49

IORT

All patients received intraoperative radiotherapy; 9 patients were treated with HDR-IORT (10Gy) and 1 patient with IOERT (12.5 Gy) because of incomplete or marginal complete resection margins as judged peroperatively. The radiotherapy was applied to the presacral plane in 3 patients, ventral plane in 1 patient, right lateral pelvic wall in 8 patients and left lateral pelvic wall in 5 patients.

Pathology

In one of the operated patients a microscopically complete resection could be obtained; 6 patients underwent a microscopically incomplete resection (R1) and 3 patients a macroscopically incomplete resection (R2). Pathological examination identified invasion into prostate (n=1), vesicles (n=2), bladder(n=2), vagina (n=2), sacral bone (n=2) and the lateral pelvic wall (n=6). Seven patients were without metastatic lymph nodal involvement, 3 patients were N1 and 1 patients N2.

Postoperative morbidity & mortality

There was no postoperative mortality. The two most common postoperative complications were urinary tract infection (50%) and wound infection (40%). Two patients (20%) developed sepsis due to a central venous catheter, one patient (10%) a pneumonia and one patient (10%) postradiation neuropathic pain. One patient experienced a major complication with bilateral postoperative renal stasis based on postradiation fibrosis for which bilateral renal catheters were placed.

Follow-up

Median follow-up is 22 months (range 2-66). Local control rates after 1 and 3 year were 66% and 27%, respectively. The distant metastases free survival after 1 and 3 year were 100% and 50% and the overall 1- and 3-year survival were 77% and 51%, respectively (Figure 1).

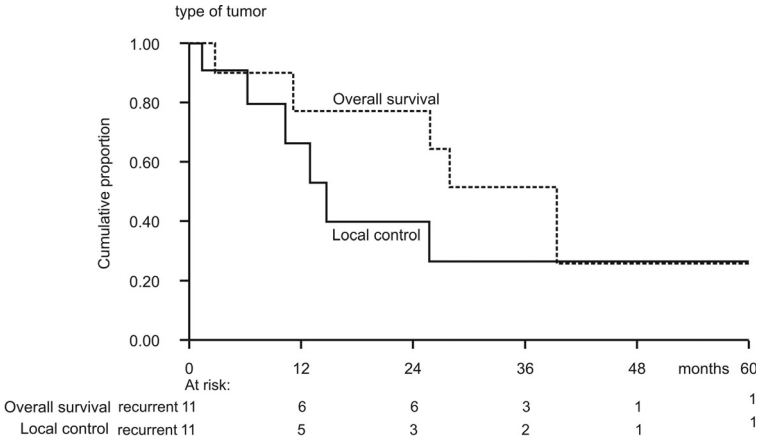

Figure 1. Kaplan Meier curve local control and overall survival

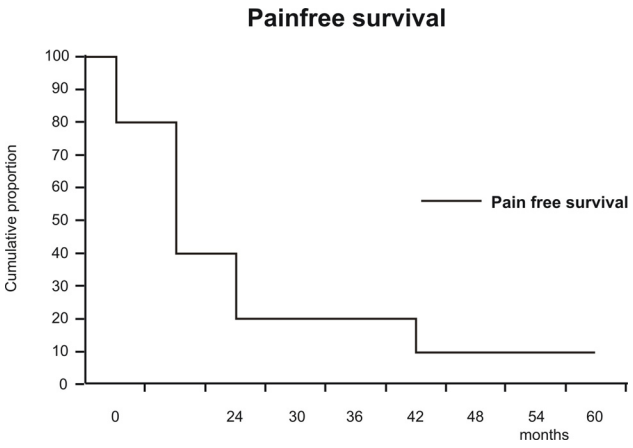

Figure 2. Pain free survival

Complaints after treatment:

Postoperatively four patients (40%) were free of pain, after a mean follow-up of 22 months (range 3-54). Three of these patients remained without recurrence and one developed a local recurrence. One patient developed complaints of local perineal pain in combination with neuropathic pain in the left leg during preoperative radiotherapy that persisted after surgery.

Six other patients with recurrent disease developed complaints of severe local perineal/ pelvic pain (n=6) and neuropathic pain in the lower extremities (n=5). The patients were all treated in collaboration with a specialised "pain-team" that consisted of a neurologist and an anaesthesiologist. All patients were treated with medication; one patient was treated with an opioid, one patient Amitriptyline (tricyclic antidepressant) and the other 4 patients received an opioid combined with other medication (Amitriptyline, Gabapentin, NSAID). One patient was treated invasively with a selective neural root block at the level of L2.

The median pain free survival after surgery was 5 months (range 0-54 months). Of the 6 patients alive two years after surgery, 3 were without symptomatic pain (50%).

Discussion

Since the integration of preoperative radiotherapy in the treatment of primary tumours, only a limited dosage of radiation can be applied in case of a recurrence. Recent data showed that reirradiation with a dosage of 30Gy is safe, even in combination with chemotherapy.[4,5] The question remains if this limited dosage of radiation is a sufficient aggressive therapy of recurrent rectal cancer. Radiation for the recurrence at a dose less than 45Gy is related with a significantly shorter survival compared to patients who received more than 45 Gy.[6] Follow-up from the Dutch TME-trial showed that the majority of patients who presented with a local recurrence after preoperative radiotherapy have simultaneous distant metastases and a poor prognosis with a median overall survival of 6 months compared with 15.9 months in the non-irradiated group. Of a total of 23 recurrences after prior radiation only 4 (17%) patients were operated.[6]

Local control

In the present study the local control rate for 10 patients operated on after reirradiation was 66% after 1 year and 27% after 3 years. These results are identical compared to our previously described results of the treatment of previously non-irradiated rectal recurrences (3 year rate of 28%).[3] Because of the small size of our patient cohort we were not able to identify prognostic factors for local control. Previous studies have identified the interval between primary surgery and local relapse and radical surgery as significant factors for local control.[5] Mohiuddin showed that local control after surgery was better compared to a non-surgical approach.[4]

Overall survival

Previously published survival outcome after treatment of patients with non-irradiated recurrences who were treated with long term preoperative radiotherapy and surgery ± IORT were respectively 34% and 11% after 3 and 5 year.[3] These results are similar to the results of the recurrences treated with reirradiation and surgery described in the present study. Valentini et al. described a median survival period of 42 months and 5 year overall survival of 39%. Macroscopically complete resections had a 5 year overall survival rate of 65%.[5] The differences in overall survival in favour of Valentini's results can be attributed to the less invasive character of the performed primary procedures (76% anterior resections) and more favourable tumour characteristics of the recurrences. In our cohort only one of the recurrences was at the site of the anastomosis, this was the only patient that underwent a R0 resection. Recurrences at the site of the anastomosis are overall more easily resectable and have a significant

better overall survival compared with pelvic wall recurrences. [6] Another option might be the fact that some patients in our study were irradiated previously with a short course (25Gy), whereas all patients in the study of Valentini et al. were previously irradiated with a long course (50Gy).

All patients were without distant metastases at the time of surgery and this distant control remained after 1 year for all patients and after 3 years for half of the patients. These results are favourable when compared to results of single modality regimens with radiotherapy only for recurrent rectal cancer, suggesting that a subset of patients do really benefit of the combination of reirradiation and surgery in this group.[4,9]

Morbidity & postoperative pain

In contrast to previously published data that indicated significantly higher postoperative morbidity rates after preoperative radiotherapy we did not experience a higher rate of wound healing complications or other complications after this regimen of extensive radiotherapy when compared to previously described results of surgery for non-irradiated recurrent rectal cancer.[3,10]

Two-third of patients developed severe perineal/pelvic pain and pain in lower extremities which required medical treatment. In our experience we could not confirm the beneficial results of Mohiuddin et al. who described a complete response of pain to radiotherapy in 55%, with a median duration of 9 months.[4] Valentini et al. described a 3 and 5-year pain-free survival of respectively 89% and 31%.[5]

Considering the morbidity, the short pain free survival, moderate local control and poor survival the question rises if reirradiation and surgery is the best option for patients who present with a recurrence after prior irradiation and if other treatment options are available. We previously reported the performance of 4 uncomplicated RFA procedures in a single patient with locally recurrent rectal cancer providing long-term local control and associated symptom control for a period greater than 4 years.[11] Other techniques as reirradiation combined with hyperthermia have been described to provide palliation in 72% of patients for a period of 6 months.[12] The use of intensity-modulated radiotherapy (IMRT), has the potential of more accurate delivery of higher dosages, avoiding the damage of critical structures surrounding the tumour. This might result in more radiation-induced necrosis and eventually in the possibility of a higher grade of tumour-downstaging.[13]

Neoadjuvant chemoradiation has lead to significantly lower local recurrence rates in primary locally advanced rectal cancer and complete response rates of 8-29% have been reported, depending on the stage at presentation.[14,15] Valentini et al. report 8% clinical complete and 36% partial response after preoperative hyperfractioned

chemoradiation for locally recurrent rectal cancer.[5] In case of the presence of locally advanced recurrent disease it might be worthwhile to perform more extensive surgery or a composite resection. These major resections are related with a significant morbidity but no mortality in experienced hands.[16,17] Whether these results can be obtained in previously irradiated patients remains to been seen.

Our results after reirradiation indicate that a more careful selection of patients with recurrent rectal cancer is of the highest importance. There is a need for a multimodality approach in which surgery, radiology, radiotherapy, medical oncology all play a crucial role. Especially after extensive radiotherapy and prior surgery adequate imaging techniques of the pelvis (with MRI of 4-phase CT-scanning) are essential for the differentiation between vital tumour and fibrosis.[18] Finally, we believe that if solid preoperative workup identifies a macroscopically completely resectable tumour (chemo)radiotherapy followed by surgery, will be the treatment of choice.

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Chapter 6

High Dose Rate Intraoperative Radiotherapy (HDR-IORT) for close or positive margins in patients with locally advanced or recurrent rectal cancer

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Abstract

Purpose

A high-dose-rate intraoperative radiotherapy (HDR-IORT) technique for rectal cancer was developed and the technique, local failure, and survival were analyzed.

Materials and methods

After the exclusion of metastatic patients, 37 patients were treated with external beam radiotherapy, surgery, and HDR-IORT between 1997 and 2000. Primary locally advanced rectal cancer was found in 18 patients and recurrent disease in 19. HDR-IORT was only administered if the resection margin was ≤ 2mm. The flexible intraoperative template is a 5-mm-thick pad with 1-cm-spaced parallel catheters. Clips were placed during surgery to define the target area. A dose of 10 Gy was prescribed at a 1 cm depth from the template surface and calculated using standard plans. After treatment, the dose at the clips was calculated using the reconstructed template geometry and the actual treatment dwell times. The median follow-up of surviving patients was 3 years. No patients were lost to follow-up.

Results

Overall, 12 patients (32%) had local recurrence, 5 (14%) of which were in the HDR-IORT field. The three-year local failure rate for primary tumours and recurrent tumours was 19 percent and 52 percent (p=0,0042). The three-year local failure rate was 37 percent for negative margins and 26 percent for positive margins (p=0,51). A high mean dose at the clip (17.3 Gy) was found. The overall survival was significantly different for primary vs. recurrent tumours, stage, and grade.

Conclusion

Because of the HDR technique, a high dose at the clips was found, with good local control. More out-of-field than in-field failures were seen. The local failure rate was significantly different for primary vs. recurrent disease.

Introduction

Primary locally advanced and recurrent rectal tumours are a heterogeneous group of tumours that include intrapelvic tethered rectum tumours, fixed tumours, enlarged nodes and, metastatic disease.

The risk of developing local recurrences after treatment of a primary increases with increased stage. Treatment of early-stage rectal cancer with preoperative radiotherapy and total mesorectal excision resulted in a recurrence free rate of 94 percent for Stage II and 85 percent for stage III tumours.[1] More advanced rectal tumours treated with postoperative radiotherapy and chemotherapy resulted in a recurrence free rate of 73 percent for low risk patients (T1-2N+ or T3N0) and 48 percent for high risk patients (T3N+ /T4, any N).[2]

Survival after recurrence depends on stage and treatment and this results in a three-year survival varying from 0 to 60 percent.[3-5] The cause of death in these patients is often systemic disease. However, a mortality of 16 to 44 percent owing to local failure has been reported.[6, 7] Fixed or tethered rectal tumours often invade the adjacent organs or pelvic wall and result in an even worse local control and survival. To treat these latter tumours, intraoperative radiotherapy (IORT) was developed, because the conventional doses and techniques were insufficient or would lead to greater incidence of radiation complications.

Two techniques have been in use: intraoperative electron beam radiotherapy (IOERT) and high-dose-rate brachytherapy (HDR-IORT). Advantages of IOERT are the treatment depth to > 1 cm with the choice of electron energies and the quick delivery of the radiation (< 10 minutes). The flexible template in HDR brachytherapy can treat all surfaces, however, the treatment times and total procedure times are larger. The steep dose gradient between the target surface and the reference depth is another advantage, because the highest dose is at the area at risk. However, it also limits the use of intraoperative brachytherapy to target depths < 0.5 to 1 cm. Because of these differences, treatment indications can be different and results of these two techniques are not completely comparable. IOERT is the most frequent used technique. At least 14 cancer centres[5,7-19] have reported their results with IOERT, and only 3 with HDR-IORT.[4,20,21]

These 3 cancer centres used a 1-cm-thick pad as template and often prescribed a dose of 15 Gy at the surface or at 0.5 cm depth from the pad. We changed this technique to create a high dose at the surface and a steep dose gradient. We developed a 0.5-cm-thick pad and prescribed a dose of 10 Gy at 1 cm depth from the pad surface. In 1997, the HDR-IORT program was started at the Erasmus Medical Centre - Daniel Den Hoed Cancer Centre. The HDR-IORT was only performed if

resection margins on frozen section analysis were ≤ 2 mm. Thirty-nine patients with locally advanced primary or locally recurrent rectal cancer had close or positive margins on frozen section analysis and were treated during the operation with HDR-IORT. All patients received preoperative external beam radiotherapy (EBRT) to the tumour and pelvis. To evaluate our alternative HDR-IORT technique, an analysis of the local failures was made with regard to the location of the local recurrence.

Materials and methods

External beam radiotherapy and surgery

From 1997 to 2000, 97 patients with locally advanced primary or recurrent rectal tumours were treated with EBRT. After preoperative screening (CT scan of thorax, abdomen and pelvis), 23 patients were not eligible for surgery because of poor performance status, inoperable tumours or distant metastases. Of the 74 patients, 39 had close or positive resection margins and were treated with HDR-IORT. During resection, 2 patients were diagnosed with metastases and were excluded from this analysis. Of the remaining 37 patients, 18 had primary locally advanced rectal cancer and 19 had recurrence. All patients had adenocarcinoma. The patient characteristics are shown in Table 1. Five patients received 25 Gy preoperative EBRT in 5 fractions and 31 patients 50 Gy in 25 fractions. One patient with recurrent cancer was previously treated with 50.4 Gy and received for the second radiotherapy treatment an EBRT dose of 30.6 Gy in 1.8-Gy fractions. EBRT was delivered by either a three-field technique, using one posterior and two lateral portals or a four-field box technique. The pelvic field borders were defined as follows: the lateral borders extend 1.5 cm lateral of the bony pelvis, with the cranial border the promontory (L5-S1), and the caudal border was at least below the foramina obturatoria to 2 cm under the anus, depending on the tumour position. The dorsal border encompassed the sacrum, and the anterior border was chosen in such a way that the tumour region was widely covered. None of the patients received preoperative or postoperative chemotherapy. Some patients were treated with chemotherapy if metastases were diagnosed during follow up. For each patient, the selected type of surgery was based on the fixation and location of the tumour. One low anterior resection, 21 abdominoperineal and 15 abdominosacral resections were performed. Forty organs or adjacent structures were completely or partially resected (Table 2). The median follow up time of the surviving patients was 2.8 years for the patients with primary tumours and 3.3 years for those with recurrence. No patients were lost to follow up.

Table 1. Patient characteristics

		Total (%)	Primary (%)	Recurrent (%)
Number of patients		37	18 (49)	19 (51)
Median follow up of surviving patients (years)		3.0	2.8	3.3
Stage	T3 N0	20 (54)	12 (66)	8 (42)
	T4 N0	12 (32)	3 (16)	9 (47)
	T1-4 N1	5 (14)	3 (16)	2 (11)
Margin	Negative	19 (51)	11 (61)	8 (42)
	Positive	18 (49)	7 (39)	11 (58)
Gender	Male	25 (70)	12 (66)	13 (74)
	Female	12 (30)	6 (34)	6 (26)
Differentiation grade	1	3 (8)	3 (17)	0 (0)
	2	29 (78)	14 (78)	15 (79)
	3	4 (11)	0 (0)	4 (21)
	Unknown	1 (3)	1 (6)	0 (0)
Resection	LAR	1 (3)	0 (0)	1 (5)
	APR	21 (57)	15 (83)	6 (31)
	ASR	15 (40)	3 (17)	12 (63)
Age (years)	0-49	9 (24)	6 (33)	3 (16)
	50-69	18 (49)	8 (44)	10 (53)
	70-79	10 (27)	4 (22)	6 (31)

LAR = Low anterior resection; APR = abdominoperineal resection; ASR = abdominosacral resection

Table 2. Resection of organs

Resection of	no	yes	partially
bladder	28	7	2
prostate	13	7	5
posterior vaginal wall	5	7	0
uterus with adnex	8	4	0
small bowel	33	0	4
sacrum	22	0	15
psoas	33	0	4

Intraoperative Radiotherapy

The flexible intraoperative template (FIT) developed at our department is a 5-mm-thick pad made of flexible silicon 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 generously around the target surface. The size and shape of the FIT were then adjusted to the target surface. The FIT, in combination with the catheter positions, was overlaid on a paper template. The paper template was used as input for the treatment planning system (Plato BPS, versions 13.3 and 13.7, Nucletron, The Netherlands). After positioning, the FIT was pressed against the area at risk by filling the pelvis with gauze pads. This was done to avoid the bolus effect from blood and/or surgical fluid during IORT time and to push critical organs away from the FIT. Two orthogonal radiographs were taken to see whether the target surface (clips) was encompassed by the applicator. Treatment planning was performed using standard geometries present in the treatment planning system. A dose of 10 Gy was delivered, usually at 1 cm depth from the applicator surface. The prescription depth was altered to a combination of 0.5 and 1 cm for one patient and for another patient to 1 and 2 cm. After treatment, the dose at the clips was calculated using the reconstructed template geometry and the actual treatment times. IORT was only administered if resection margins to the tumour were ≤ 2 mm, which was judged on frozen section analysis. In the final pathology report, positive margins were found in 18 patients and negative margins in 19 patients. Of these 19 patients, 4 had a resection margin < 1 mm. Profuse bleeding or haemodynamic instability during surgery occurred in 7 patients. For these 7 patients, clips were not placed and/or orthogonal radiographs were not taken to reduce the operation time. In total, 129 clips were placed; 112 clips were apparently positioned directly under the FIT and 17 just at the edge of the FIT. The posterior and/or right pelvic walls were the most frequently treated with the FIT (Table 3). On average, 8 tubes with a FIT surface of 69 cm^3 were used. The mean radiation time was 27 minutes (Table 4).

Definitions and statistical method

A local recurrence was defined as tumour regrowth within the EBRT field, and an IORT in-field recurrence as a recurrence completely or partially within the IORT field, as seen on CT scan or magnetic resonance imaging. Local recurrence and distant metastases were scored until patient death and censored thereafter. Local control and survival curves were calculated using the actuarial Kaplan-Meier method. Comparisons for survival were made using the log-rank test. For other comparisons, the Kruskal-Wallis test was used.

Table 3. Place of FIT in the pelvis

Place of FIT	number
Posterior pelvic wall	1
Posterior and left lateral pelvic wall	8
Posterior and right lateral pelvic wall	9
Posterior,left and right lateral pelvic wall	2
Posterior, left and right lateral, and anterior pelvic wall	0
Anterior pelvic wall	6
Anterior and left lateral pelvic wall	0
Anterior and right lateral pelvic wall	1
Anterior, left and right pelvic wall	4
Left lateral pelvic wall	2
Right lateral pelvic wall	4

Table 4. IORT characteristics

	Median	Mean	SD
Number of catheters	7 (5-14)	8	2.7
FIT surface (cm^2)	60 (24-161)	69	35
Radiation time (min)	21 (10-66)	27	14
Number of clips	4 (2-7)	4	1.1

Results

Local control

Twelve patients (33%) developed local recurrence, five recurrences were in the IORT field and seven were out-of-field. One IORT in-field failure (1 of 18 patients; 6%) was seen in the primary locally advanced group, and four (4 of 19 patients; 21%) in the recurrence group. Three IORT in-field failures were diagnosed in patients with positive resection margins. The median time to local recurrence was 4.5 years (Figure 1). The three-year actuarial failure rate for primary tumours and recurrent tumours were 19 percent and 52 percent, respectively (p=0.042; Figure 2A). For patients with an abdominoperineal resection, the mean time to local failure was 4.2 years; for those with an abdominosacral resection, it was 2.8 years (p=0.043; Figure 2B). The three-year local failure rate was 37 percent for negative margins and 26 percent for positive margins (p=0.51; Figure 2C). Out-of-field failures were seen earlier than in-field failures (median time: 16 vs. 31 months; p=0.077).

Eight of the 12 local failures were located in the posterior pelvis (Figure 3). The median distance of the out-of-field recurrence to the area treated with the FIT was 2 cm (range 1–5). Four recurrences were found growing in the sacrum or sacral foramina.

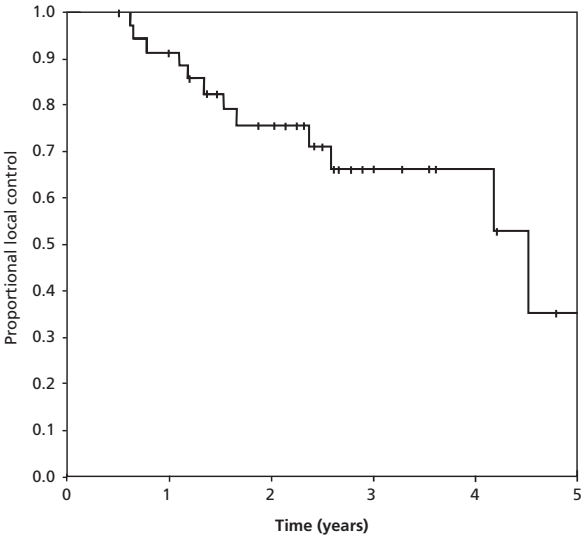
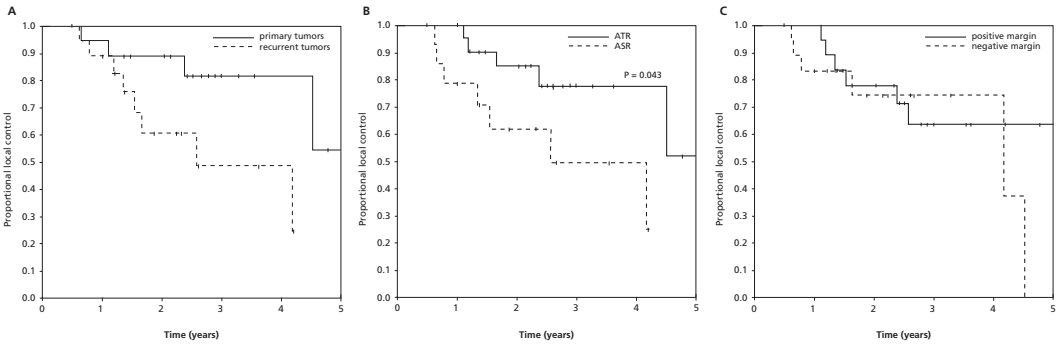
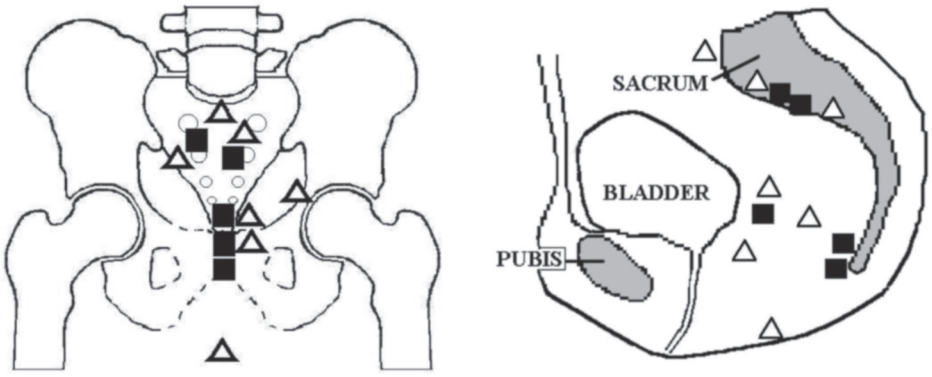


Figure 1. The overall time to local recurrence



APR: abdominoperineal resection; ASR: abdominosacral resection

Figure 2. The time to local recurrence for primary/recurrent tumours (A), resection type (B), resection margin (C)



Δ : IORT out-field recurrence; ■: IORT in-field recurrence

Figure 3. The place of recurrence after IORT treatment.

IORT technique

The mean dose of all clips was 15.79 Gy. The mean dose to the 112 clips under the FIT and 17 clips at the edge was 17.27 and 6.05 Gy, respectively. Of the 112 clips, 20 received a dose < 13 Gy. A dose < 10 Gy was calculated in 4 of these 20. Patients with and without an in-field recurrence had a mean clip dose of 18.00 Gy (range 12.39-24.42) and 17.21 Gy (range 7.15-42.64). Patients with an in-field recurrence had a mean FIT of 82 cm^2 compared to 67 cm^2 for the rest of the patients (p=0.63). No relationship between the size of the FIT, the number of resected organs, or the topography of local recurrences was found.

Complications

At the start of the EBRT, 57 percent of the patients complained of pain, 32 percent of irregular stools, 27 percent of intrapelvic discomfort, and 5 percent of urinary problems. Postoperatively, many complications were diagnosed, including delay in wound healing in 46 percent, abscesses in 16 percent, leakage at the anastomosis in 5 percent and fistulas in 8 percent. Plexopathy was found in 14 percent of the patients. Only 3 patients had late complications: 1 patient had chronic diarrhoea (Radiation Therapy Oncology Group [RTOG] 1), another chronic pain in the pelvis (RTOG 2), and the last patient had radiating pain to the lower extremities (RTOG 2). Sacral necrosis was not found.

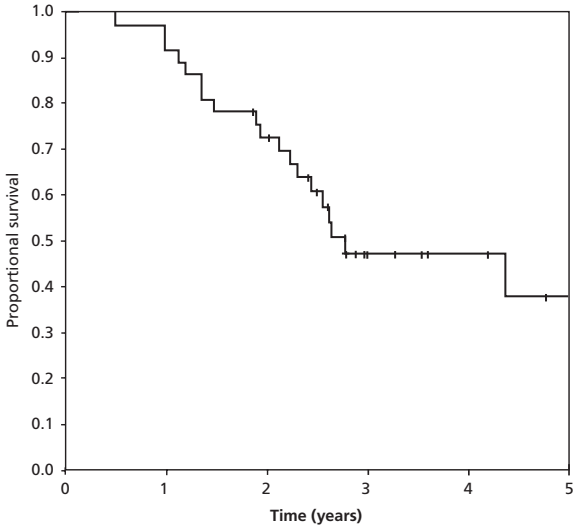


Figure 4. The overall survival

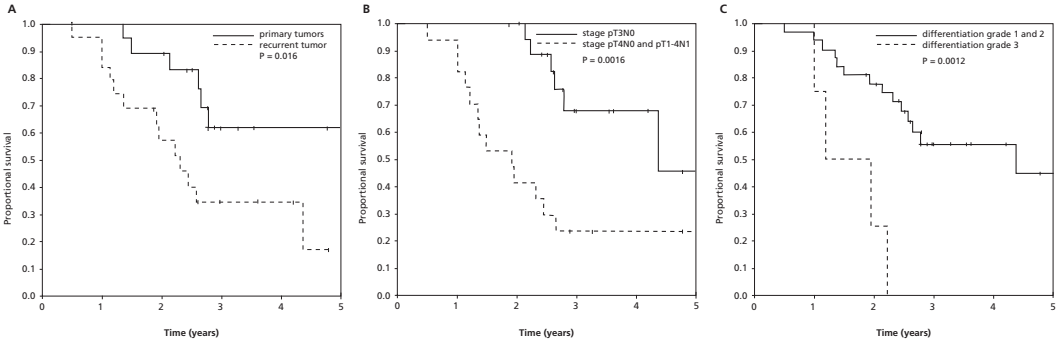


Figure 5. The survival according to primary/recurrent tumours (A), stage (B), and grade (C)

Overall survival

The actuarial five-year survival was 38 percent, with a median survival of 2.8 years (Figure 4). The three-year overall survival for patients with primary and recurrent tumours was 61 percent and 34 percent, respectively (Figure 5A), and this difference was significantly different (p=0.016). Two patients (5%) died of local disease, 17 (46%) due to metastases. Of these 17 patients, 4 died of peritonitis carcinomatosa. Seventeen patients are still alive, 13 without disease, at last follow-up. The overall survival was significantly different according to stage (p=0.0016), and grade

(p=0.0012; Figure 5B,C). Patients < 50 years had a median survival of 2.2 years compared to 4.4 years for patients > 50 years (p=0.31).

Distant metastases were found in 18 patients. Several patients had metastases in more than one organ: 5 patients had metastases in the liver, 8 in the lung, 4 in the peritoneum and 7 in other locations. No patients with liver metastases were rescued by surgery. Metastases were found in 44 percent and 53 percent of the patients with primary and recurrent tumours, respectively. The metastatic free survival was not significantly different for primary versus recurrent tumours (p=0.45).

Discussion

The use of intraoperative radiotherapy for rectal cancer has been reported by at least 17 cancer centres; however, only 3 of these 17 use HDR-IORT. Two centres[4,22] used a 1-cm-thick pad (HAM applicator) and prescribed usually a dose of 15 Gy at 0.5 cm from the pad surface. The third centre also developed a 1-cm-thick pad, but prescribed a dose of 15 Gy to the surface.[23] Our technique is different with the use of a 0.5 cm thick pad and a prescribed dose of 10 Gy to 1 cm from the pad surface. Advantages of this thinner pad are the increased flexibility and a higher surface dose. In combination with dwell time optimization, doses up to 40 Gy to the clips were found at the corners of the template, as verified by the clip doses. According to the dosimetric characteristics of our technique, a clip dose ≥ 13 Gy indicated a gap between the FIT and the area of risk of < 5 mm or a well-positioned template at the clip. An adequate dose at the clip was found in 82 percent. Although the thinner template is more flexible, we still found a gap ≥ 5mm between the FIT surface and the clips in 18 percent. But we only found a dose < 10 Gy in 3.5 percent of the clips, so we may assume that our technique is carried out well. The cause of the in-field failures was not found. No dose difference in patients with in-field or no in-field failures was found.

Although high doses were applied to the surface, only 3 patients complained of late toxicity. Two patients reported chronic radiating pain and one patient chronic diarrhoea. The postoperative toxicity of the integral treatment was high, as reported by many authors.[4,7,10,20,24,25] Many patients underwent extended resection combined with preoperative radiotherapy. It was often difficult to assign a particular complication to surgery or radiotherapy. Huber et al.[21] found a significant higher complication rate in patients treated with HDR-IORT, Hashiguchi et al.[7] described a trend and Noyes et al.[26] found no difference in his combined analysis with 220 patients.

Five of the twelve local recurrences were IORT in-field recurrences. Because more out-of-field than in-field failures occurred, it could be assumed that IORT is an effective treatment. However, a randomised trial is needed to conclude this. Nine authors[7,8,10,11,19-21,24] also reported the site of recurrence: for primary and recurrent tumours, 17 and 49 percent of the local failures were in-field recurrences (Table 5). Because out-of-field failures were more frequent than in-field failures, the question is raised how these out-field failures can be reduced. Our out-of-field failures were within 5 cm of the IORT area, and could be included by extending the FIT. However, four local failures were located in the sacrum or sacral foramina. HDR-IORT probably could not have prevented these local failures, because they are situated close to the nerves. The question arises whether higher doses or larger FIT's could have prevented the other recurrences, without increasing the toxicity.

Table 5. Number of in-field failures according to author and technique

	Author	In-field failure	Total failures	%	Technique
Primary tumours	Huber et al. [21]	0	3	0	HDR-IORT
	Gunderson et al. [11]	1	8	13	IOERT
	Calvo et al. (18)	1	3	30	IOERT
	This publication	1	4	25	HDR-IORT
	Total	3	18	17	
Recurrent tumours	Bussieres et al. [8]	9	21	50	IOERT
	Pezner et al. [19]	8	13	43	IOERT
	Haddock et al. [24]	12	18	62	IOERT
	Eble et al. [10]	4	9	67	IOERT
	Hashiguchi et al. [7]	1	9	44	IOERT
	Nag et al. [20]	7	14	11	HDR-IORT
	This publication	4	8	50	HDR-IORT
	Total	45	92	49	

HDR-IORT = High Dose Rate IntraOperative Radiotherapy; IOERT = IntraOperative Electron Radiotherapy

As opposed to other reports, we did not find that close or positive margins did differ in local recurrence rate (p=0.51). Many authors[4,8,11,14,22,7] reported a statistically significant difference in local failure rate according to the resection margin. However they usually compare negative margins with microscopic positive margins or gross total resections and not close margins (< 2 mm) with positive margins. Extended resections, such as abdominosacral resections, and total and partial

organ resections were often performed. Patients who underwent abdominosacral resections had a significant different higher local failure rate than did patients with an abdominoperineal resection (p=0.043). This can be explained by the larger amount of disease or more aggressive character of the tumour when abdominosacral resections were necessary.

Of our patients 33 percent had local failure. For primary locally advanced tumours, the three-year local failure rate was 19 percent. Other authors found a comparable three-year local failure rate of and 23 percent.[1,28] Harrison et al.[27] reported a two-year local failure rate of 19 percent. Recurrent tumours had in this study a three-year local failure rate of 52 percent. The reported three-year local failure rate varies between 53 and 79 percent.[4,6,8,19,22] A statistically significant difference (p=0.042) in the time to local failure between primary and recurrent tumours was found, but has not been previously reported.

Patients with primary tumours survived longer than patients with a recurrence (p=0.016). The two-, three-, and five-year overall survival for patients with primary tumours was 89, 61 and 61 percent, respectively. Harrison et al.[27] reported a two-year survival of 69 percent, other authors[11,14,21] reported a three-, and five-year survival of 55 and 45 percent, respectively. In this study, patients with recurrent tumours had a three-year overall survival of 34 percent. Most authors[4,5,7,8,22] reported a three-year survival of 30 to 50 percent; however, other authors[10,24] found a three-year survival of 12 and 64 percent. Patients with pathologic proven positive nodes, T4 tumours, or grade 3 differentiation had a statistically significant lower survival. Complete or partial resection,[4-7,10,11,22,27] the use of IORT plus EBRT,[4,22] concomitant chemo-radiotherapy,[11] and larger irradiated target areas[20] were found to be other significant prognostic factors by other authors.

Conclusion

The HDR-IORT technique for rectal cancer resulted in a high local control rate. Because of the calculation of the dose to the clips, we can conclude that our technique was well carried out. The local failure rate for those with positive margins compared to those with close margins did not differ. Because IORT out-of-field recurrences were common, a greater external beam dose, a larger FIT area, or the addition of concurrent chemotherapy may be of benefit for these patients. Patients with primary tumours had a significant higher local control and survival than did patients with recurrent tumours. Other prognostic factors for survival were stage and differentiation grade.

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Chapter 7

Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer

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Abstract

Aims

To report the role of total pelvic exenteration (TPE) in a series of locally advanced and recurrent rectal cancers.

Methods

In the period 10994-2004, TPE was performed in 35 of 296 patients with primary locally advanced and recurrent rectal cancer treated in the Daniel den Hoed Cancer Centre; 23 of 176 with primary locally advanced and 12 of 120 with recurrent rectal cancer. All but one patient received preoperative External Beam Radiation Therapy (EBRT). After 1997, intraoperative radiotherapy (IORT) was performed in case of a resection margin < 2 mm.

Results

Overall major complication rates were not significantly different between patients with primary and recurrent rectal cancer (26% vs. 50%; p=0,94). The hospital mortality rate was 3%. The five-year local control and overall survival of patients with primary locally advanced rectal cancer was 88 and 52 percent, respectively. In patients with recurrent rectal cancer three-year local control and survival rates were 60 and 32 percent, respectively. An incomplete resection, preoperative pain and advanced Wanebo stage for recurrent cancer were negative prognostic factors for both local control and overall survival.

Conclusion

TPE in primary locally advanced rectal cancer enables good local control and acceptable overall survival, thereby justifying the use of the procedure. Patients with recurrent rectal cancer showed a high rate of major complications, a high distant metastases rate, and a poor overall survival.

Introduction

In locally advanced rectal cancer, radical margins are sometimes difficult to obtain. In men, tumours located in the ventral part of the rectum near the base of the bladder, prostate and seminal vesicles make complete resections difficult. In recurrent rectal cancer patients, the outcome also depends on complete resection with negative pathological resection margins.[1-3] Curative complete surgical resection of a recurrence can provide long-term survival in selected cases.[4, 5]

Primary locally advanced and recurrent rectal cancer with involvement into adjacent organs or structures is common. Primary locally advanced rectal cancer is estimated to account for 6-10% of all primary rectal cancers.[6] 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. Since the first report by Brunschwig in 1948, TPE is considered an operation associated with a poor quality of life and considerable mortality and morbidity rates.[7] Recent reports indicate that results have substantially improved in recent years.[3,8-13] Five-year survival rates after TPE for patients with primary disease range between 32 and 66 percent and in patients with recurrent disease from 0 to 23 percent.[14,15]

The aim of this study is to evaluate the outcome after TPE for primary locally advanced and recurrent rectal cancer in a tertiary referral cancer centre and to analyze the data for prognostic factors.

Patients and methods

Between 1994 and 2004, 296 patients with primary locally advanced (large T3 and T4 tumours) and recurrent rectal cancer treated in the Erasmus University Medical Centre -Daniel den Hoed Cancer Centre were studies. Two hundred and thirty-three patients were treated with curative intent and sixty-three patients were excluded for surgery because of non-resectable distant metastatic disease, poor physical condition or demonstration of a local irresectable tumour because of ingrowth in the sacral plexus. Thirty-five TPEs were performed and reviewed; 23 of a total of 176 patients with primary locally advanced rectal cancer and 12 of a total of 120 patients with recurrent rectal cancer. All but two patients were men, with a median age of 58 years (range 40-75). Patients were preoperatively analyzed and selected using a CT and MRI scan (94% and 69%) of the pelvis. On indication a cystoscopy was used to identify tumour growth into the bladder. Screening for distant metastases was performed using thoracic and abdominal CT scans.

Preoperative radiotherapy

All patients but one received preoperative External Beam Radiation Therapy (EBRT). Neoadjuvant and adjuvant chemotherapy are not standard in the Netherlands for rectal cancer patients and were not given. EBRT was administered in doses of 2 Gy per fraction up to a median dose of 50 Gy and delivered by either a three-field technique, utilizing one posterior and two lateral portals or a four-field-box. In 22 patients a diverting colostomy was constructed before irradiation because of (near) complete faecal obstruction.

IORT

In 1997, an intraoperative radiation therapy (IORT) program was started in our hospital.[16] IORT with HDR brachytherapy was given to patients who had a minimal circumferential free resection margin equal to or less than two millimetres. 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. If the applicator was positioned appropriately, a dose of 10 Gy was delivered, usually at 1 cm depth from the applicator surface.

Evaluation of morbidity and mortality

Patient characteristics, operation techniques and follow-up were studied using the database and hospital charts. Surgery related morbidity was divided into major and minor complications. Major morbidity was defined as complications that required reintervention. All other complications were classified as minor.

Statistical analysis of survival and local control

All patients were bi-annually seen at our outpatient clinic for follow-up. Survival time was calculated from the date of resection for primary and recurrent rectal cancer until the last follow-up attendance or until death. Local control was calculated from the date of resection for primary and recurrent rectal cancer until the histological or evident radiological presence of a local recurrence. The cumulative survival, disease free survival and local control rate after surgery were calculated using the Kaplan-Meier method. 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. The level of significance was defined as $p<0,05$.

Results

Preoperative and intraoperative evaluation revealed no distant disease and all patients were in adequate physical condition. Physical condition was considered adequate after multidisciplinary team discussion and consultation by an anaesthetist. Six patients presented with pain, eight with changes in defecation, four with perineal pressure, two with changes in micturition and thirteen with a combination of these complaints. Four patients with primary locally advanced disease and one patient with recurrent disease presented with a fistula; three recto-vesical and two recto-perineal fistulas. The median distance of the tumour from the anal verge was 3 cm (range 0-14). All primary tumours were clinically fixed or tethered; in 13 patients the tumour was only fixed anteriorly and in 10 patients also to other sites such as lateral or posterior wall. In patients with recurrent disease, median interval between primary tumour and recurrence was 27 months. Prior surgery procedures for primary disease included seven abdominoperineal resections, two low anterior resection and three rectosigmoid resection with end-colostomy.

Preoperative radiotherapy

All but one patient were treated preoperatively with long course EBRT (25 x 2 Gy). One patient with a recurrent rectal cancer received postoperative radiotherapy (36Gy), but was previously treated with preoperative irradiation (30Gy) for the primary tumour.

IORT

IORT was performed in five patients with a primary tumour and seven patients with a recurrent tumour; seven with radical resection (R0) but circumferential margin < 2mm, four with microscopic residual tumour mass (R1) and one with macroscopic tumour mass (R2). Four patients with an incomplete resection did not receive IORT, because IORT was not available (one patient with a R1 resection and three with a R2 resection).

TNM-stage of the resected primary tumours and Wanebo classification for recurrent tumours is depicted in Table 1.[1] In six irradiated patients with primary disease there were no lymph nodes retrieved in the pathological specimen. The clinical T-staging, based on MRI and/or CT, was correlated with the definitive pathological T-staging (Table 2). Postradiation fibrosis instead of tumour growth into surrounding structures was observed in five of eleven patients who were clinically diagnosed as cT4. One tumour had a complete response after preoperative radiotherapy. The tumours of five patients had very close growth to the prostate or bladder (margin

range 0-3 mm), without infiltration or fibrosis. Based on the pathology reports three out of twelve recurrences were identified to be true nodal recurrences. In the nine other recurrences, no lymphoid tissue was found.

Table 1. Patients and Tumour characteristics

Primary		**(n=23, UICC TNM staging)**	
ypT-stage			
T3		8	(35%)
T4		15	(65%)
ypN-stage			
N0		13	(57%)
N1		2	(9%)
N2		2	(9%)
Nx		6	(26%)
Recurrent	**(n=12, Wanebo Classification & UICC TNM Nodal staging)**		
Tr-stage			
Tr0	*(No recurrence)*	1	(8%)
Tr3	*(Growth into surrounding soft tissue)*	3	(25%)
Tr4	*(Penetration anterior structures)*	8	(67%)
ypN-stage			
N0		5	(42%)
N1		2	(16%)
Nx		5	(42%)

ypT = Pathological T stage according to TNM after preoperative radiotherapy; ypN = Pathological N stage according to TNM after preoperative radiotherapy

Operation

Operation characteristics are depicted in Table 3. The type of fixation was not related to the completeness of resection. Complete resections were performed in all patients (n=4) where the sacrum was also resected. In all but three patients (two primary and one recurrent tumour) the dead space that occurred after resection of the tumour was filled up by transpositioning of the omentum. A gracilis muscle flap (n=5) or a sartorius muscle flap (n=1) was used in selected patients. The median duration of operation was 464 minutes (range 300-670). The median blood loss in primary and recurrent group was, respectively, 7550 millilitres (range 2300-20000) and 6193 millilitres (range 1500–14000). The median hospital stay was 17 days (range 10-64) for patients with a primary tumour and 24 days (range 16-49) for patients with a recurrent tumour.

Table 2. Correlation between clinical and pathological T-staging

Primary	**(n=23, TNM staging)**
Correct Staging	
cT3 = ypT3	1 (4%)
cT4 = ypT4	11 (47%)
Understaging	
cT3 > ypT4	4 (16%)
Overstaging	
cT4 > ypT3	7 (30%)
Recurrent	**(n=12, Wanebo classification)**
Correct Staging	
cTr4 =ypTr4	8 (67%)
Overstaging	
cTr4 > ypTr3	3 (28%)
cTr4 >ypTr0	1 (8%)

cT = Clinical T stage according to TNM; ypT = Pathological T stage according to TNM after preoperative radiotherapy; cTr = Clinical Wanebo stage for recurrence; ypTr = Pathological Wanebo stage for recurrence after preoperative radiotherapy

Table 3. Operation characteristics

	Primary (n=23)		**Recurrent (n=12)**	
Radicality				
Complete resection (R0)	19	(82%)	7	(58%)
Microscopically incomplete (R1)	2	(9%)	3	(25%)
Macroscopically incomplete (R2)	2	(9%)	2	(17%)
Resection				
TPE	20	(87%)	9	(75%)
TPE & sacral bone	2	(9%)	2	(17%)
TPE & coccygeal bone	1	(4%)	1	(8%)
Reconstruction of the pelvic space				
Omental transposition	21	(91%)	11	(92%)
Gracilis muscle transposition (direct)	3	(13%)	1	(8%)
Gracilis muscle transposition (indirect)	1	(4%)	-	
Sartorius muscle transposition (indirect)	-		1	(8%)

Table 4. Complications

	Primary (n=23)		Recurrent (n=12)	
Complications				
Minor only	8	(35%)	4	(33%)
Major only	-		3	(25%)
Major & Minor	6	(26%)	3	(25%)
No complication	9	(39%)	2	(17%)
Minor complications				
Wound infection perineal	2	(9%)	1	(8%)
Wound infection midline	4	(18%)	2	(16%)
Pneumonia	2	(9%)	1	(8%)
Sepsis by central venous cathether	1	(4%)	1	(8%)
Fever without known cause	1	(4%)	-	
Urinary tract infection	1	-	-	(4%)
Neuropathy	1	(4%)	1	(8%)
TIA	-		1	(8%)
Pressure ulcer	1	(4%)	1	(8%)
Major complications & related reinterventions				
Urostomy related				
Nefrodrain placement	2	(9%)	1	(8%)
Small bowel leakage-repair	1	(4%)	1	(8%)
Reimplantation ureter	1	(4%)	-	
Other				
Gracilis flap wound-repair	1	(4%)	-	
Sartorius flap fistula-repair	-		1	(8%)
Wound dehiscence repair	1	(4%)	-	
Ileus relaparotomy	-		1	(8%)
Abdominal abscess drainage	-		1	(8%)
Percutaneous abscess drainage	-		1	(8%)
Small bowel perforation-repair	1	(4%)	1	(8%)

Morbidity and mortality

The postoperative complications and reinterventions are described in Table 4. One patient (3%) with a primary locally advanced tumour died during the 30-days postoperative period because of sepsis and renal insufficiency. No operative mortality occurred. One patient experienced leakage of the Bricker urostomy for

which placement of two renal drains as well as persistent perineal wound-healing problems for which a bilateral gracilis muscle-transfer was performed. Complications associated with the construction of the urinary conduit were responsible for 45 percent of the major complications. These complications consist of ileo-ureteral anastomotic leakage, ureteral injury and small-bowel leakage.

Follow-up

The mean follow-up of the total group of patients was 28 months. The local control of patients with primary locally advanced rectal cancer was 88 percent at five years and in patients with recurrent rectal cancer 60 percent at three years (Figure 1). The estimated five-year overall survival of patients with primary locally advanced rectal cancer was 52 percent. In patients with recurrent rectal cancer the three- and estimated five-year overall survival were 32 and 16 percent, respectively (Figure 2). An incomplete resection and the presence of preoperative pain were both significant negative prognostic factors for local control and overall survival. Recurrences with an advanced Wanebo stage (Tr4) did have a significant lower local control and overall survival compared to stages Tr0-3. (Table 5)

Of the twelve patients who received intraoperative radiotherapy, two patients with recurrent disease developed a re-recurrence. The location of the recurrence was inside the IORT-irradiated area in one of the two patients. These patients were re-irradiated in combination with hyperthermia and both patients died 9 and 28 months later.

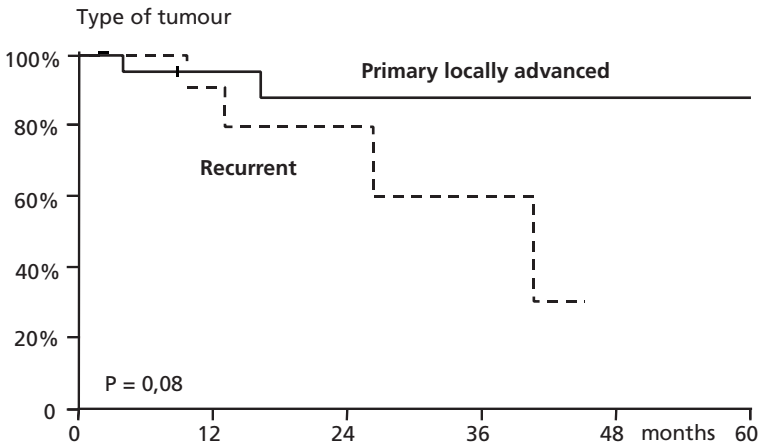

Figure 1. Actuarial curves of local control in patients with primary locally advanced (n=23) and recurrent rectal cancer (n=12)

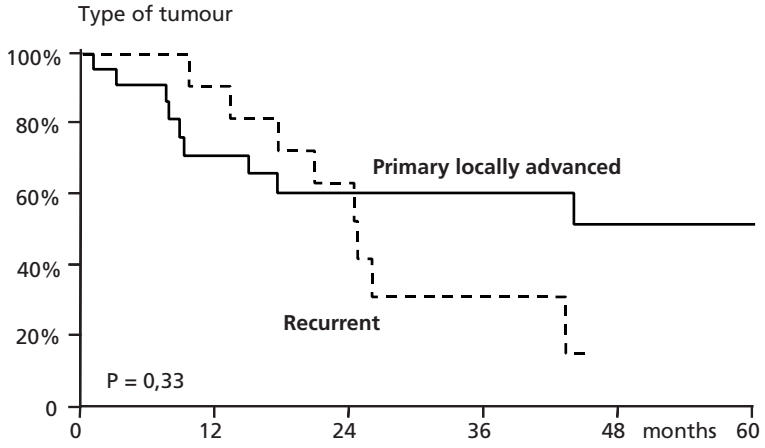

Figure 2. Actuarial curves of overall survival in patients with primary locally advanced (n=23) and recurrent rectal cancer (n=12)

Table 5. Univariate analysis for local control and overall survival

	5 yr Local Control		5 yr Overall survival	
Entire group				
Type of tumour				
Primary	88%		52%	
Recurrent	30% (#)	p=0,08	16% (#)	p=0,33
Resection				
R0	89%		54%	
R1	27%		20%	
R2	0%	***p=0,01***	0%	***P = 0,02***
Preoperative pain				
Yes	0%		0%	
No	86%	***p< 0,0001***	50%	***p=0,007***
IORT				
Yes	76%		56%	
No	59%	p=0,88	27%	p=0,59
Recurrent				
Wanebo classification				
Tr 0-3	50%		38%	
Tr 4	0% (#)	***p=0,048***	0% (#)	***p=0,032***

#: estimated rate after 5 years

Discussion

TPE started in the 1940s as a palliative technique for resection for advanced cervical cancer and developed into a widely used technique for resection of locally advanced or recurrent rectal tumours invading the bladder or prostate.[7] The five-year overall survival rate of 52 percent in the present study compares favourably to previously reported series and demonstrates that survival with excellent local control is possible after TPE for primary locally advanced rectal cancer.[6,10,13,15,17,18] The majority of resections (82%) were without microscopic or macroscopic residual tumour mass, which clearly justifies the use of TPE in selected patients with primary disease.

The curative potential of resection differs significantly between primary and recurrent tumours. 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.[19] Successful complete resection of recurrent disease is often restricted to selected patients, for example with an early-detected tumour or an anastomosis-limited recurrence after previous sphincter-sparing surgery.[20] A complete resection in patients with recurrent disease was possible in 58 percent of the patients in the present study, which was substantially lower than for patients with a primary tumour. This lower rate of complete resections is reflected in a lower local control and overall survival of patients with recurrent rectal cancer.[13-15] The three-year overall survival after TPE for recurrent tumours was 32 percent in the present study, which is not different from published results of nonexenterative surgery.[4,5]

In contrast to previous reported results of all rectal recurrences treated in our centre, advanced Wanebo stage (ingrowth in surrounding structures) is a prognostic factor for both worse local control and overall survival in this small cohort of recurrences treated with TPE.[4] Since most of these patients die of distant metastases, future studies have to focus on more adequate treatment of systemic disease in this group of patients. It is not possible from the present study to define clear criteria for performing a TPE. Non-resectable distant metastases, poor physical condition and/or irresectable local tumour are all contraindications for this type of surgery. However, each patient should be judged preoperatively by a multidisciplinary team including a surgeon, urologist, gynaecologist, radiotherapist, medical oncologist, radiologist and an anaesthetist.

Morbidity of the procedure

The overall major morbidity rate of 34 percent in the present study is in line with previous results in the literature after TPE with morbidity rates between 13 and

64 percent.[3,13,14] The complications related to the urinary conduit were a frequent cause for reintervention, which was demonstrated to occur especially in patients who previously received radiotherapy.[8] Lopez et al. reported a morbidity rate of 75 percent in irradiated patients compared to 13 percent in those without radiation.[1] All patients in the present study received long-term radiotherapy, with a median dose of 50 Gy, which might explain the high number of minor and major complications after TPE. 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.[20,22] In recent years, mortality after TPE has decreased from rates up to 33 percent down to rates varying from 0 to 10 percent.[8,13,15,21] The postoperative mortality rate of 3 percent in the present study corresponds with recent studies describing exenterative surgery, but also with results after surgery for T1-3 tumours.[2]

Local control after IORT

In contrast to Gunderson et al. no improvement of survival in the primary and recurrent group after use of IORT was observed in the present study.[23] But, patient numbers were relatively small and only twelve patients received IORT. In the analysis of our complete database of patients with both recurrent and locally advanced rectal cancer, IORT did improve local control rate. Patients who received IORT for narrow or microscopically incompletely resected tumours had a local control rate comparable to patients with wide R0 resection margins.[4,24]

Symptomatic pain in patients who underwent TPE for primary and recurrent rectal cancer is related with an inferior outcome of both local control and survival. 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.[3,5,25]

After correlation of the preoperative imaging with pathology results there was no tumour infiltration in surrounding structures in a third of the operated patients in the present study. In primary rectal cancer, circumferential margins ≥ 2 mm significantly improves local control as has been demonstrated in the Dutch TME trial.[26] Therefore, in the patients (14%) with a very narrow margin (1-3 mm) between tumour and surrounding structures (n=5) exenterative surgery was essential to obtain a complete resection with adequate margin. In 14 percent only postradiation fibrosis was found in surrounding structures in patients where preoperative imaging suggested tumour growth into these structures. This emphasizes the difficulty after preoperative radiotherapy to differentiate between fibrosis and vital tumour tissue on preoperative imaging (MRI or CT).[27]

Other adjuvant strategies

In recent studies, successful experiences have been published with the use of neoadjuvant chemotherapy in combination with radiotherapy for locally advanced and recurrent rectal cancer. Preoperative chemoradiation leads to a significantly improved local control compared with adjuvant chemoradiation and might cause downstaging of the tumour to such an extent that the cancer can be removed completely without the necessity to remove adjacent organs.[18,20,28] The use of IMRT, intensity-modulated radiotherapy, has the potential of more accurate delivery of higher dosages, avoiding the damage of critical structures surrounding the tumour. Higher radiation dosages will result in more radiation-induced necrosis and eventually in the possibility of a higher grade of tumour-downstaging.[29]

In conclusion, total pelvic exenteration can be performed safely but is associated with substantial postoperative complications and the need for reinterventions. In primary locally advanced rectal cancer a curative resection is possible in the majority of patients, and enables good local control and overall survival, justifying the use of this technique. Patients with recurrent rectal cancer showed a higher rate of major complications and a poor overall survival, demonstrating the importance of careful patient selection by a multidisciplinary team.

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Chapter 8

Primary and secondary reconstruction after surgery of the irradiated pelvis using a gracilis muscle flap transposition

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Abstract

Introduction

The aim of this study is to describe our experience with reconstruction of pelvic defects after surgery for previously irradiated malignancies using a gracilis muscle flap transposition.

Patients and methods

Between 1993 and 2002, 25 patients were treated by primary (n=7) or secondary reconstruction (n=18) using a gracilis muscle transfer. All patients were previously irradiated with a median dosage of 50 Gy.

Results

Direct reconstruction following resection of the tumour was accompanied with minor complications in three patients and without major complications. Median time to complete healing of the donor site and perineal defect was 11 and 46 days, respectively. Reconstruction of persistent perineal infections resulted in minor complications at the donor site (n=3) and at the perineal wound (n=11). Three patients experienced a major complication. Median time to complete healing of the donor site and perineal defect was respectively 17 and 190 days. Necrosis of the gracilis muscle flaps was not observed.

Conclusion

Direct reconstruction with a gracilis transfer resulted in primary wound healing with low morbidity, hereby preventing potentially disabling persistent defects. After debridement of persistent wounds, indirect reconstruction with gracilis muscle resulted in the majority of patients in healing of the defects with acceptable morbidity.

Introduction

An aggressive multimodality approach to pelvic malignancy is increasingly performed both for the possibility of curation and for palliative management of disabling pelvic conditions. 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.[1-4] 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.[1,5-7] After extended pelvic surgery a large pelvic dead space can exist. Filling 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.[8,9] 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.[1,10-12]

Another possible indication for using a myocutaneous flap is in secondary reconstructions after persistent infected pelvic necrosis. If surgical debridement is ineffective, the gracilis muscle transposition might offer a solution by partially filling the gap, facilitating drainage and providing well-vascularised tissue.[11]

The aim of this article is to show our experience with the transfer of the gracilis muscle in direct reconstruction and in secondary reconstruction in patients after surgery for malignancies in the previously irradiated pelvis. Recommendations for the management of pelvic wounds are described on the basis of these results and an overview of the literature.

Patients and methods

Between 1995 and 2001, 25 patients were operated on for primary or secondary reconstruction with a gracilis muscle-transposition after pelvic surgery. Patient characteristics, operation techniques and follow-up were studied using hospital charts. Surgery related morbidity is divided in major and minor complications. Minor morbidity is defined as a complication for which no reintervention is needed. Major morbidity is defined as complications that lead to prolonged hospitalization or required reintervention.

Anatomy

The gracilis muscle originates from the pubis symphysis and inserts on the medial tibial condyle. The vascular anatomy has been well described in cadaver-studies and radiological documentation.[5] The blood supply derives from the medial circumflex branch of the profunda femoris artery.[13] This branch can be found 8-10 cm from its origin (Figure 1). The location of the pedicle can sometimes limit the rotation of the flap, and thereby limit the volume. In addition the cutaneous element allows for instance for restoration of the vaginal lining when necessary. The gracilis is a minor leg adductor, and transposition will not result in functional disability.[14]

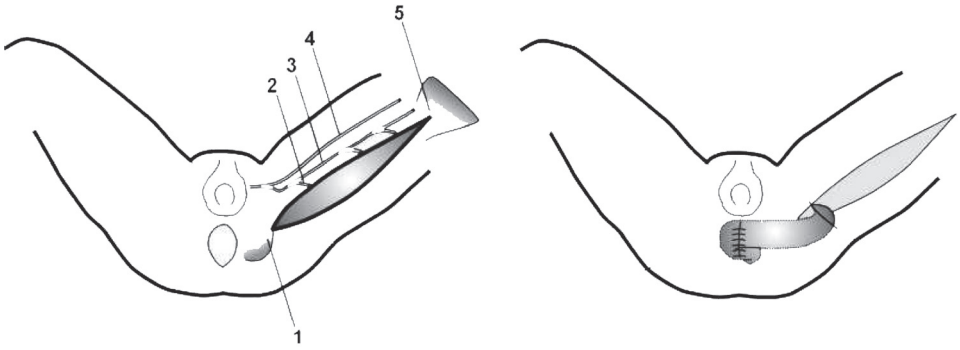

Figure 1. Schematic drawing of the technique of the transfer of the gracilis muscle

1: pubis symphysis
2: branch of medial circumflex femoral artery
3: medial circumflex branch of the profunda femoris artery
4: profunda femoris artery
5: medial tibial condyle

Surgical technique

The gracilis flaps are mobilised using the standard technique described by McCraw in 1976.[15] The patient is placed in the "Jack-knife"-position or the "lithotomy"-position. Along the medial side of the thigh a longitudinal incision is made, making it possible to identify the distal part of the gracilis muscle and to mobilise it proximally. The most proximal neurovascular pedicle is preserved. To reach the pelvic area, the muscle flap is tunnelled subcutaneously and fixed into position in the presacral space with absorbable sutures, as depicted in Figure 1. After fixation the thigh-incision is closed in one layer over a suction drain.[11]

Results

Direct reconstruction after surgical removal of a pelvic malignancy was performed in seven patients and secondary reconstruction in eighteen patients after a median interval of 12 months. In the majority of patients (n=17) rectal cancer was the primary tumour type. Other primary tumours were gynaecological cancers (n=4), anal cancer (n=2) and pelvic sarcoma or desmoid (n=2). Six patients presented with a persisting defect that was classified as a low perineal defect and eleven patients presented with pre-sacral defects.

Primary closure

Primary closure with the use of a muscular or musculocutaneous gracilis flap was performed in three men and four women, with a median age of 56 years (range 32-69). All operated patients were preoperatively treated with 50 Gy radiotherapy on the pelvis. In one patient the intraoperative resection margin, judged on frozen section, was ≤ 2 mm and this patient received a dose of 10 Gy intraoperative radiotherapy. A total pelvic exenteration was performed in four patients with a curative intent followed by the gracilis muscle flap. An abdominoperineal resection, a posterior exenteration and an anterior exenteration were all performed in one patient, respectively. In five patients the gracilis muscle was used and in two patients a musculo-cutaneous gracilis flap was used. One patient received postoperative brachytherapy on the vaginal wall with a dose of 14 Gy. Postoperative chemotherapy was administered in two patients. The median duration of the operation was 460 minutes (range 305-615). This is the total time of resection of the tumour followed by the gracilis transposition. All but one patient were operated in lithotomy-position. After closure of the wound in the thigh, a suction drain was positioned in six patients and removed when discharge was minimal. A pelvic drain was left behind in five patients. Median postoperative stay was 15 days (range 14-19).

Secondary closure

The secondary closure group consisted of thirteen men and five women, with a median age of 61 years (range 35-77). An abdominoperineal resection was previously performed in nine patients. A total exenteration was previously performed in three patients and other different types of pelvic cancer surgery were performed in the other six patients. All operated patients had been previously irradiated, with a median dose of 60 Gy (range 25-70). Three patients had received chemotherapy after their primary operation.

The median interval between primary operation and gracilis transposition was 12 months (range 1-351). The patient with the interval of 351 months had developed a recurrent radiation necrosis after a vulvectomy 29 years previously. In two patients a myocutaneous flap was used, and in 16 only a muscular flap.

After closure of the wound in the thigh, a suction drain was positioned in fifteen patients and removed when discharge was minimal. A pelvic drain was left behind in fourteen patients. All patients were operated on via perineal incision and laparotomies were not performed. The median duration of operation for the transfer of the gracilis muscle was 96 min (range 60-155). Ten patients were operated on in Jack-knife position and eight patients in lithotomy-position. Median postoperative stay was 9 days (range 4-90).

Follow-up

Median follow-up of all patients was 22 months (range 2-79). All flaps remained vital and no perioperative or postoperative mortality occurred after surgery. Table 1 depicts minor and major postoperative morbidity. Most minor complications were managed in the outpatient clinic. Prolonged stay in the hospital occurred in two patients and was considered a major complication; one patient needed reoperation because of severe perineal herniation.

Table 1. Postoperative morbidity

	Primary closure (n=7)	Secondary closure (n=18)
Minor		
Infection donor site	1	3
Perineal infection	1	6
Perineal abscess	1	1
Perineal fistula	-	4
Major		
Perineal herniation	-	1
Perineal infection	-	1
Perineal abscess	-	1

After direct closure primary healing of the pelvic wound occurred in all patients within a median of 46 days (range 17-75). After secondary closure the defects healed "per primam" in ten patients in a median period of 94 days (range 43-190). In six patients the defects healed "per secundam" in a median period of 484 days (range 304-1606). One patient did not experience healing of his persistent wound before

he deceased after a follow-up period of 234 days. Another patient was lost of follow-up after 189 days before healing of his defect. Closure of the wound at the donor-site at the thigh was achieved after a median period of 11 days (range 10-17) after primary closure and 17 days after secondary reconstruction (range 9-94). Three patients experienced persistent infections of the wound at the thigh. One patient experienced dehiscence of the donor wound, which prolonged healing of the donor site to 94 days.

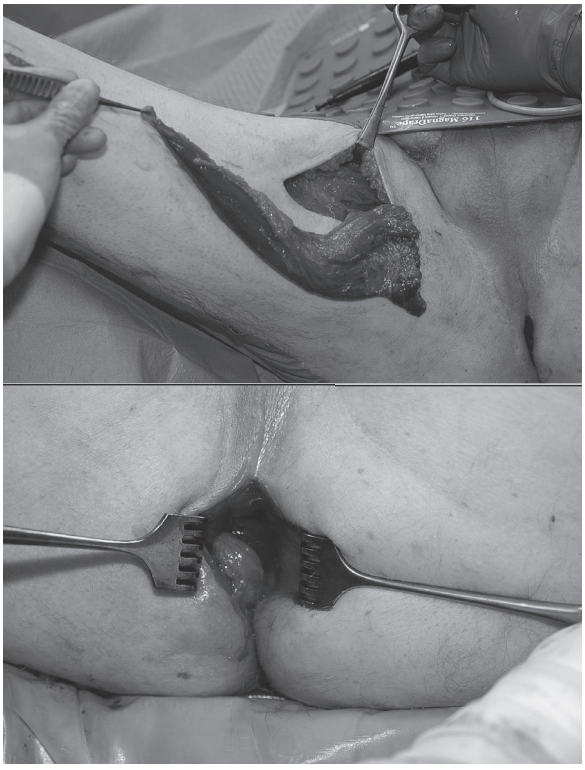

Figure 2. Two pictures of the transpositioning of the gracilis muscle

Discussion

Surgical treatment of pelvic malignancies and surrounding structures often leave defects that cannot be closed primarily. Reported morbidity rates for tumours that require extensive pelvic surgery range from 23 to 76 percent.[1] Late complications include perineal hernia, evisceration or fistulae between the perineum and the

gastrointestinal or genito-urinary tract. There is a correlation between the incidence of late complications and the dosage of absorbed radiation in combination with extensive surgery.[16] A history of pelvic irradiation causes a 10-fold increase in the incidence of wound complications.[17]

After pelvic surgery the perineal wound was traditionally left partly open and packed with gauzes, but this results in a high rate of pelvic infections and delayed wound healing.[18-20] The last decades the usual technique in primary treatment of the perineal wound is direct closure of the wound with drainage. [1] After extended resections large perineal defects can occur, which are too big for direct closure. In these circumstances filling of the perineal space can be favourable using an omentoplasty because it provides an excellent source of well-vascularised and nonirradiated tissue. Although there is no evidence that the omentoplasty directly promotes primary healing, it does reduce the incidence of the perineal dehiscence and it reduces the need for secondary opening of the perineal wound.[21,22] When the omentum is not available transposition of a myocutaneous flap can offer a solution to obliterate the pelvic space.[12,23] Because of superior abilities to provide healing factors and to combat the effect of bacterial contamination, muscular flaps are selected over skin and fasciocutaneous techniques.[24-29] Many flaps have been described, but the inferior based rectus abdominis flaps, the inferior gluteal thigh fasciocutaneous flaps and the gracilis muscle- and myocutaneous flaps have emerged as the most reliable for use in the pelvis.[14,25]

A significant difference in major complications after primary closure with gracilis muscle versus primary closure alone has been described.[1] Direct transposition of the gracilis muscle resulted in closure of the perineal wound in all patients in the present study. These results compare favourable to those described by others. [1, 3] The morbidity rate after gracilis transfer in combination with resection of the malignancy was not higher than previously reported morbidity after abdominoperineal resection for rectal cancer.[1] Flap necrosis was not found in the present study, in contrast to the first reported use of the gracilis flap by Mc Craw et al., who reported a flap necrosis of 27 percent.[15] Previous comments on the technique by Tei et al. on the unacceptable high complication ratio could not be confirmed.[30]

If the pelvic defect is too large for gracilis muscle transfer or no gracilis muscle can be harvested, other muscles can be transpositioned into the pelvic area. Inferiorly based rectus abdominis musculocutaneous flap can be used for reconstruction of the larger pelvic defects, because of the voluminous tissue bulk that can be transferred. When an abdominal approach is not required the gluteal thigh flap is an alternative option.[31] The gluteal flap can be used for medium and small sized

pelvic reconstruction but the gracilis muscles is favourable because it is a minor leg adductor, and transposition will not result in functional disability.[14] Another approach to fill the pelvis is using a colon pull-through technique. This enables not only transfer of well-vascularised tissue to the pelvis, but in combination with dynamic gracilis muscle repair restoration of continence can sometimes be obtained in a selective group of very motivated patients.[32,33]

After pelvic surgery some patients develop chronic pelvic wounds associated with pain and complications, which can even lead to narcotic dependence and a social handicap.[34] Usual treatment of these wounds consists of waiting, administration of antibiotics and the occasional surgical debridement and nettoyage. The best treatment for complications of delayed wound healing in the previously irradiated area is adequate debridement followed by reconstruction with well-vascularised, nonirradiated tissue.[23,34] The uni- and bilateral gracilis muscle for secondary reconstruction have successfully been used in the majority of patients with small and medium sized pelvic defects in the present study. Transposition of the gracilis muscle resulted in closure of the perineal wound in all but two patients.

A known disadvantage of the gracilis muscle is the variation in the anatomy of the vascular pedicle. This might give limitations in length and rotation of the transplantation graft. But the comments from other authors on the low reliability of the vascular pedicle cannot be confirmed in the present study.[5] The gracilis was not only used in the lower perineal defects but also in "higher" pre-sacral infections, without compromising the vascular supply of the flap. One patient had a gracilis muscle flap successfully transpositioned to the inguinal area, where she suffered from persistent radiation necrosis after high dose irradiation after vulvectomy. A major advantage of the gracilis muscle is its position outside the external radiation field. The ideal position of the gracilis muscle outside the radiation field enables transposition of well-vascularised tissue into the pelvic space. With a median operation time of 96 minutes, including the anaesthetics, the procedure of the harvesting and transpositioning of the gracilis graft is not time-consuming and does not lead to long postoperative hospitalization.

In conclusion, pelvic wounds are severe complications after pelvic surgery and occur more in previously irradiated tissue. Direct reconstruction with omentum or muscular transfer improves healing of the pelvic wound and prevents a potentially disabling condition for the patient. Although assessment of the outcome is limited because of the retrospective nature of this study, we want to plead for direct reconstruction after pelvic surgery in previously irradiated patients using the gracilis muscle, when the omentum is not available.

In persistent pelvic wounds, the use of secondary reconstruction by muscular

transfer ameliorates healing, with acceptable complications. Because the gracilis muscle lies outside the external radiation fields, it can be mobilised relatively simple without major complications, the transposition will not result in functional disability and it results in a high percentage of wound closure.

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Chapter 9

Utility of repeat radiofrequency ablation to provide long-term local control in recurrent rectal cancer

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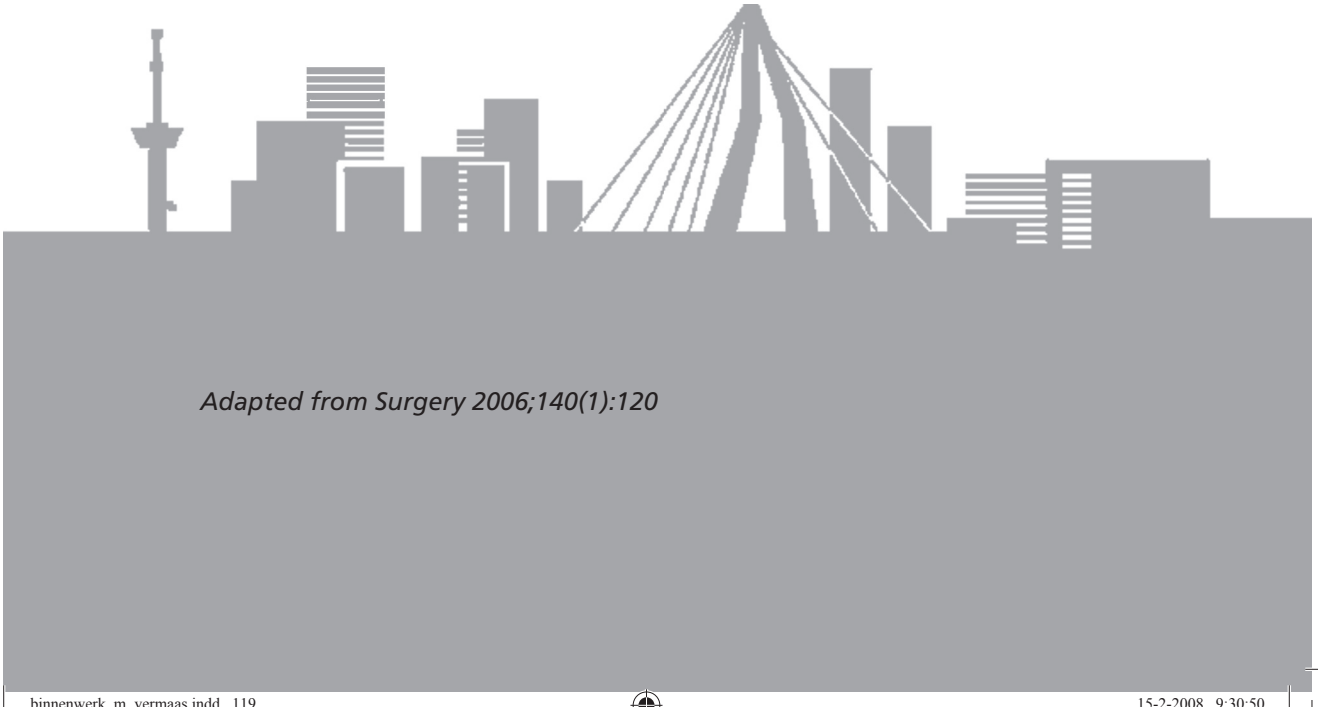

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Introduction

After total mesorectal excision for rectal cancer, local recurrence rates vary between 3 and 15 percent.[1] The standard treatment for a local recurrence without distant metastases is preoperative (chemo)radiation followed by surgical resection with intraoperative radiotherapy on indication. Local recurrences that remain isolated for a long time without the manifestation of distant metastases are observed in a sizable subgroup of patients. These local recurrences are associated with severe morbidity with dramatic impact on quality of life and often cause debilitating pain. Surgical procedures to deal with these recurrences may be difficult or even impossible and can be associated with serious morbidity. Thus, there is a need for alternative modalities to provide local control.

RFA nowadays is commonly used in the treatment of primary liver tumours (HCC) and liver metastases (colorectal, breast and neuroendocrine), but the technique has also been described in the treatment of other tumours. The mechanism of RFA is based on the conversion of radiofrequency into heat. An alternating current passes down an electrode tip into surrounding tissue, thereby causing electrons to vibrate at high frequency, which results in frictional heating and irreversible damage of surrounding cells. Tumours up to five centimetres can be treated, using powerful generators, pulsed RFA, cooled-tip-electrodes, clustered electrodes, multiple needles and saline-perfused needles.

Only a few results regarding the use of RFA in the treatment of recurrent rectal cancer have been published.[2,3] We report here for the first time on the utility of repeated RFA sessions in a single patient with recurrent rectal cancer.

Material and methods

51-year-old male patient presented 28 months after long course neoadjuvant radiotherapy followed by abdominoperineal resection for a pT3N0M0 rectal cancer, with a rising CEA. On MRI a local recurrence of 3.6 x 4.3 cm was diagnosed in the pelvis, invading prostate and left seminal vesicle. Thoracic and abdominal CT scans did not reveal distant metastases. The patient was without symptoms and refused a total exenteration but agreed to an alternative treatment with RFA of the local recurrent tumour.

Results

First RFA

Three months after diagnosis of the recurrence the first RFA was performed. After placement of a single needle (Cool-tip ®, Valleylab, Boulder) via para-sacral route centrally in the tumour under CT guidance a RFA procedure of nine minutes was performed, in which the maximum temperature reached 85°C. Saline at a temperature of 20°C was infused via a transurethral catheter in the urethra to prevent potential thermal damage to the urethra. After a short observation the patient was discharged at the day of RFA.

A decrease of CEA from 11,0 ug/l to 3,6 ug/l was observed after this procedure (Figure 1).

A two-month control MRI showed regression of the lesion from 3.6 x 4.3 cm to 3.5 x 3.4 cm. The aspect of the lesion was unchanged hypodense, without contrast-uptake in T1- and T2-weighted images, suggesting a total ablation of the tumour.

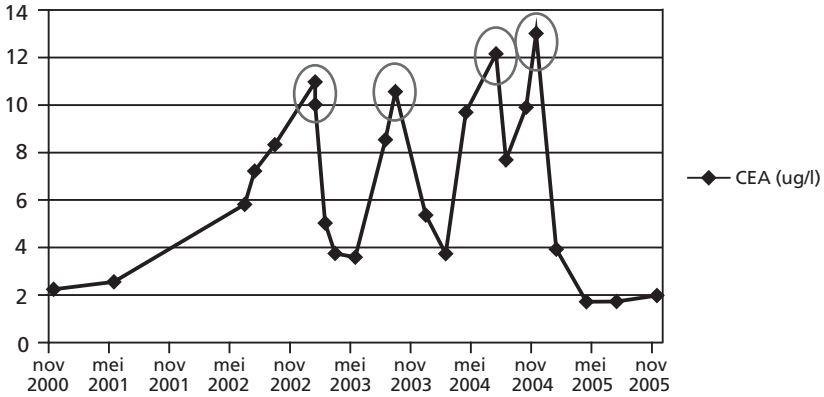

Figure 1. Carcinoembryonic antigen values in the reported patient. Circles are around the four different RFA-sessions

Second RFA

Ten months after the initial RFA, following a rise of CEA-levels (Figure 1) and suspicion of tumour re-recurrence on CT scan, a second RFA procedure was performed. Total body PET scan revealed no extrapelvic disease. Again a single needle was placed under CT-guidance centrally in the tumour and a 12-minutes RFA procedure was performed with cooling of the urethra. The patient showed no complaints after the procedure and was discharged the same day. Again a decrease of CEA from 10,6 ug/l

to 3,8 ug/l was observed after the second RFA procedure (Figure 1). A pelvic MRI scan after performance of the second RFA showed a lesion without any contrast-uptake in dynamic series, in contrast to the MRI before RFA.

Third RFA

Seven months later an increase of CEA to 12,2 ug/l (Figure 1) suggested a third re-recurrence, although radiological findings with MRI showed no changed aspect and no contrast-absorption of the lesion. Again screening did not reveal systemic metastases. Therefore, assuming that a local re-recurrence was responsible for the rise in CEA, a third RFA was performed 8 months after the second RFA.

A CT guided RFA was performed for 12 minutes, after which the temperature inside the tumour raised to 86°C. The initial decrease in CEA from 12,2 ug/l to 7,7 ug/l was followed after two months by an increase to 13,0 ug/l (Figure 1).

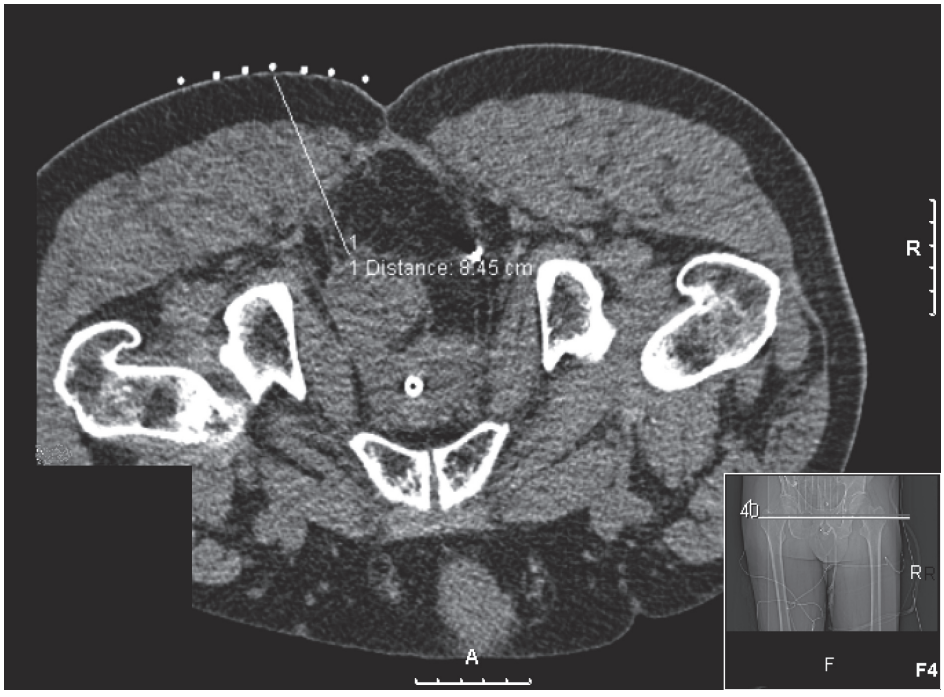

Figure 2. RFA probe positioning under CT guidance

Fourth RFA

The fourth RFA procedure was performed 5 months after the third RFA in two 12-minute sessions. The ablation was done in two parts of the tumour to enable a

larger area of tissue ablation. After the first session the end-temperature reached 61°C, the end-temperature was 87°C after the second session. Alike the previous three sessions, the patient was discharged that same day without any complaints. Three months after the fourth RFA a PET scan did not demonstrate any tumour activity and CEA levels were low (2,0 ug/l) at last follow-up one year after last RFA.

Discussion

The overall prognosis of recurrent rectal cancer is poor and the standard therapy is surgery after neoadjuvant (chemo)radiation, which can lead to good local control with survival rates of 11 to 25 percent after five years.[4] Some patients do not qualify for major surgery but do need local treatment. Based upon good results of the use of RFA in the local treatment of primary tumours and metastases in the liver, this technique has been described in recurrent rectal cancer. The aim of the treatment is to provide local control and avoid local recurrence associated morbidity. Ohhigoshi *et al.* were the first to publish results of fourteen RFA procedures in ten patients with pelvic recurrence. The overall complication rate was 36 percent (abscess formation, neuralgia and bleeding). The complete response rate was 75 percent in tumours smaller than 4 cm. Only one of the six patients who were treated in a palliative setting showed benefit (pain relief and improvement in Quality of Life) after local ablation.[2] Kalil et al. described the use of RFA in 2 patients with successful palliation in both, although one patient developed a pelvis abscess.[3]

In this report, we describe four RFA procedures over a period of 3 years in a single patient with recurrent rectal cancer without complications. Long-time local control, ongoing for more than 4 years, and associated symptom control was provided. Based upon this single patient experience we consider RFA as a possibility for selective patients with an isolated local recurrence of rectal cancer who refuse or do not qualify for surgery.

Recent literature suggests that the clinical nature and prognosis of patients with recurrent rectal cancer has changed since the introduction of preoperative radiotherapy.[5] The majority of patients who received preoperative radiotherapy in the treatment for their primary tumour presented with distant metastases at time of diagnosis of the recurrence (74%). Their survival is poor compared to patients who did not receive preoperative radiotherapy. The median survival of primarily irradiated patients was 6 months, compared to 16 in patients who did not receive radiation. The poor prognosis of patients with a recurrence emphasizes the importance of thorough patient selection before surgery for recurrent rectal cancer. An extensive

surgical procedure with high associated morbidity and mortality can not be justified in patients with a poor prognosis; because these patients derive little, if any, benefit from surgery.

This single-patient experience demonstrated that radio frequency ablation is a safe procedure to repeat in recurrent rectal cancer. More than four years after the diagnosis of the recurrence, the described patient has no evidence of disease after four RFA procedures.

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Chapter 10

General Discussion

Management of locally advanced primary and recurrent rectal cancer

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Primary rectal cancer

The majority of patients with primary rectal cancer presents 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.[1-4] Since the introduction of TME-surgery by Dr Heald significant lower rates of local recurrences have been reported varying between 3 and 15 percent.[5] The addition of preoperative short-term radiotherapy (5x5Gy) delivered one week prior to surgery performed by TME-technique has been shown to improve local control even more.[1]

After the introduction of preoperative radiotherapy and TME-surgery a region wide registration study was carried out in the South-western part of the Netherlands, which identified a significant increase of patients receiving preoperative radiotherapy. Despite this rise still a reasonable percentage (25%) of patients did not receive radiation.[6] Reasons for not performing preoperative radiotherapy remain unclear, but could be the lack of additional value of preoperative radiation in small tumours (T1).[1] Results also showed that pathology reports often lack crucial information (circumferential resection margin, adequate number of lymph nodes examined). These results emphasise the importance of analysis of region- or nation-wide treatment results, outside of large randomised trials, and also indicate the difficulty of translating new treatment protocols based on results of these trials to the daily practice.[6]

Primary locally advanced and recurrent rectal cancer

In approximately 10 percent of all rectal cancer patients the tumour extends into or beyond the enveloping fascia propria of the mesorectal compartment. Often these tumours infiltrate adjacent structures and therefore have a higher risk to develop a local recurrence.[7]

Patients with these primary locally advanced or recurrent rectal cancer are historically difficult to treat with surgery alone, but outcome has significantly improved using multimodality treatment. Although preoperative and adjuvant 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.

Imaging and Staging

Based on clinical information it is difficult to distinguish patients with locally advanced tumours although certain patients' 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 [8]. 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.[9] 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.[10]

At present, MR imaging is demonstrated to be superior to CT for prediction of tumour invasion in surrounding pelvic structures which is important in locally advanced and recurrent rectal cancer.[11-16] Although, the large difference in outcome between MRI and CT in the comparative studies could be partially attributed to the fact that a state-of-the-art MRI 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. Probably the most important factor is using adequate imaging in combination with preoperative multidisciplinary team discussions to decrease the number of positive resection margins as has been demonstrated by Burton *et al*.[17]

Preoperative treatment

Although postoperative chemoradiotherapy has long been recommended for locally advanced and node positive rectal cancer patients, preoperative treatment is now widely used worldwide. A recent German trial has demonstrated the benefits of preoperative chemoradiotherapy with improved compliance, reduced toxicity and increased local control.[18] In many European centres radiotherapy only was used as neoadjuvant treatment for locally advanced rectal cancer,[19] but addition of chemotherapy has recently demonstrated to improve local control in two large randomised trials.[20,21] Addition of 5-FU and Leucovorin to preoperative radiation slightly increased the amount of acute toxicity in T3-T4 resectable rectal cancer patients.[22] However, it increased the number of complete responses and decreased the local recurrence rate after 5 years. Important is to notice that overall survival did not differ in these studies and that sphincter preservation was not increased.

New chemoradiation strategies are now published in numerous phase II trials including the use of oral 5-FU[23,24] and the addition of Irinotecan[25,26] and Oxaliplatin[27] to 5-FU-based regimens. A recent British trial has demonstrated high response rates in nonresectable rectal cancer patients after induction systemic chemotherapy followed by chemoradiation.[28] Although this was accompanied with considerable toxicity complete response rates were promising. Neoadjuvant chemotherapy only, might also be an option for previously irradiated patients as has been reported in a recent case report, where a complete resection could be achieved.[29]

Not only new chemotherapeutic drugs, but also a VEGF specific monoclonal antibody in combination with chemoradiation was recently reported by Willet et al. to lead to considerable downstaging of the tumour.[30] 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 tested in rectal cancer. Higher radiation dosages could result in more radiation-induced necrosis and eventually in the possibility of further tumour downstaging.[31] 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.[32]

Surgery

Primary locally advanced rectal cancer

Some studies do not discriminate between primary locally advanced and recurrent rectal cancer and results are described as one group.[33] It is important to differentiate between these two since five-year overall survival of patients treated for recurrent rectal cancer is generally reported between 15 and 55 percent[7,34,35] compared to a much higher 40 to 75 percent in primary locally advanced rectal cancer.[19-21,36-40] A similar difference in local control in favour of locally advanced rectal cancer has been described.[7,34,35]

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 centres with aggressive chemoradiation protocols, surgery can be performed with standard TME surgery[36] and after short course radiotherapy (5x5Gy) local recurrence rates and survival were demonstrated to be excellent.[1] Locally advanced rectal cancer is here characterised 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.[19,41,42] During surgery distinction between benign adherence and malignant invasion is difficult to make, especially after neoadjuvant therapy. Because of this difficulty the surgeon must resect en bloc the adjacent structures depending on the location and depth of invasion.[8] 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.[43] Elective lateral lymphadenectomy has been extensively studied by Japanese surgeons and standard dissection yields generally a 10 to 15 percent involvement. In low rectal cancer and T3-4 tumours the frequency is even reported to be higher and an improved locoregional control for this extensive surgery is claimed.[44-50] On the other hand, low positive lateral lymph node yields, questionable prognostic significance, and high morbidity (urinary and sexual dysfunction) are main reasons against this procedure. Due to major improvements in preoperative chemoradiation protocols and surgical technique (TME), only a few patients may profit from lateral lymph node dissection and in western centres this technique is no routine use.[51-53] In fact, lateral pelvic lymph node metastases were in very few cases the cause of a local recurrence in a large Swedish database study.[51] Therefore, dissection of the lateral lymph nodes should only be restricted to patients with enlarged suspicious nodes. Direct invasion in iliac vessels and obturator space is even more uncommon and only in selected cases resection of these structures might be indicated.[54]

In case of dorsal invasion abdominosacral resections can be performed,[33,55] 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.[19,35,56-59]

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.[60] Especially in patients with isolated liver metastases complete resection of the metastases can lead to long-term survival and cure. In case of synchronous metastases logistic issues play an important part in the treatment of patients. Locally advanced rectal cancer

patients are treated with preoperative chemoradiation in a course of 5 weeks, followed by surgery 6 to 10 weeks later. Sometimes small liver metastases can be removed in combination with a surgical procedure of the rectal cancer. If morbidity of combined surgery is considered to be high, staged resection could be considered. Treatment of the synchronous metastatic liver disease that is decisive for survival may be postponed for over three to six months after diagnoses when the rectum is treated first. For these reason, the proposed reversed approach by Mentha *et al.*[61] is for these patients an attractive option. In this approach, patients are first treated with systemic chemotherapy, followed by liver surgery in those patients who respond. Since liver surgery is generally with minimal morbidity, chemoradiation treatment of the primary rectal cancer can commence shortly after discharge from the hospital. After finishing the chemoradiation treatment, surgery of the rectal cancer can be performed after the usual six to ten weeks. In our hospital we treated eleven patients with locally advanced rectal cancer and multiple synchronous liver metastases according to this approach.[62] One patient was progressive on Oxaliplatin-based chemotherapy and 10 patients underwent a subsequent liver resection and received after the liver resection (chemo)radiotherapy for the rectal tumour. After radiotherapy, imaging demonstrated new extensive pulmonary and/or hepatic metastases in 3 patients and they were subsequently treated with palliative chemotherapy. Seven patients underwent radical rectal surgery and are alive without evidence of disease after a median follow-up of 23 months (range 6-39). Long-term data from Mentha *et al.* and other series are needed to find the optimal strategy for this group of patients that are difficult to treat.

Recurrent rectal cancer

Despite improvements in the treatment of primary rectal cancer, recurrences occur in approximately 5 to 15 percent of the patients. The development of a local recurrence depends on various factors such as surgical technique,[63] lymph node involvement [1], resection margins[42] and location of the tumour.[1,64] Locally recurrent rectal cancer is often associated with severe symptomatic disease, especially pain.[35] 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.[65-68] Due to neoadjuvant treatment modalities a selective group of patients with recurrent disease can be operated on with curative intent.[35,55] Curative treatment seems best possible in selected patients with true anastomotic recurrence or those without pelvic sidewall involvement and early detection of the tumour.[69] In the past, resections of recurrent rectal cancer that

resulted in complete removal of all tumour tissue were scarce, with reported R0-resections around 20 percent. Recent studies show that the current multimodality treatment provides possibility for curative resection in 40 to 80 percent.[35,66,70-75] 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.[7,35-34,59,70,76-79]

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.[35,71,80] Symptoms such as pain or hydronephrosis[81] are therefore considered to be a relative contraindication for resection of recurrent rectal cancer due to poor outcome. Tumour infiltration in bony structures is not uncommon in recurrent rectal cancer and used to be another contraindication for these patients. Some studies have reported long term survivors after sacrectomy or composite resections and for highly motivated and carefully selected patients this procedure be indicated.[82]

Previously irradiated recurrent rectal cancer

Since most patients are nowadays treated with radiotherapy for primary rectal cancer, most recurrences occur in a previously irradiated pelvis. In a Dutch multi-centre study, the majority of patients who presented with a local recurrence after previous radiotherapy had simultaneous distant metastases. All patients who developed a localised recurrence died within 3 years despite multimodality treatment in some of these patients.[83] The authors conclude that the clinical nature and prognosis of those patients who do develop locally recurrent rectal cancer has been changed and that meticulous imaging for distant metastases should be performed before aggressive treatments for local recurrence are administered. Some patients can be reirradiated, although this has long been discouraged because it is thought to be associated with high incidence of late normal tissue complications. Recent data showed that reirradiation with a dosage of 30Gy is safe, even in combination with chemotherapy.[84,85] The question remains if this limited dosage of radiation is a sufficient aggressive therapy of recurrent rectal cancer. Radiation for the recurrence at a dose less than 45Gy is related with a significantly shorter survival compared to patients who received more than 45 Gy.[83] An Italian multi-centre 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.[84] These beneficial results however cannot be confirmed by our experience, which resulted in only 10% microscopically complete resections, a median pain free survival

after surgery of 5 months and an overall survival of 51% and a local control of 27% after 3 years.

The previously described beneficial effects of neoadjuvant chemoradiation (lower local recurrence and complete response rates of 8-29%) in the treatment of primary locally advanced rectal cancer deserve attention in the treatment of recurrent rectal cancer. Downstaging effects can facilitate less invasive resections of the tumour recurrence. Valentini et al. report 8% clinical complete and 36% partial response after preoperative hyperfractioned chemoradiation for locally recurrent rectal cancer.[84]

Considering the overall poor results after reirradiation and surgery a more careful selection of patients with recurrent rectal cancer is important. Recurrences at the site of the anastomosis are overall more easily resectable and have a significant better overall survival compared with pelvic recurrence.[83] If decent workup identifies a macroscopically resectable tumour, radiotherapy and surgery, in the future combined with chemotherapy, will be the treatment of choice.

Minimal invasive treatment for recurrence

Considering the morbidity, the short pain free survival, moderate local control and poor survival the question rises if major surgery is the best option for patients who present with a previously irradiated recurrence. An extensive surgical procedure with high associated morbidity and mortality cannot be justified in poor-prognosis patients or patients in poor physical condition, as these patients derive little, if any, benefit from surgery. Small cohort experiences with the use of RFA (radiofrequency ablation) in rectal tumour recurrence have been published describing long-term local control and associated symptom control.[86-88] Reirradiation and hyperthermia have also been described to provide palliation in a subgroup of patients.[89]

Total pelvic exenteration

Total pelvic exenteration (TPE) is a widely used technique for resection of locally advanced or recurrent rectal tumours invading the bladder and/or prostate.[90] Long term survival with excellent local control is possible after TPE for primary locally advanced rectal cancer (table 1).[76,78,91-97] The majority of resections in primary cancer are without microscopic or macroscopic residual tumour mass, which clearly justifies the use of TPE in selected patients with primary disease. Although, current guidelines for colorectal cancer surgery advocate TPE, only one-third of the patients in a recent 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.[91]

Table 1. Selected series of total pelvic exenteration for rectal cancer from 2001-2006.

Author	N	Morbidity (%)	Mortality (%)	5 yrs survival (primary) (%)	5 yrs survival (recurrent) (%)
Chen and Sheen-Chen[96]	50	37	2	49	-
Wiig et al.[92]	47	38	4	36	18
Yamada et al.[76]	64	50	2	60	23
Jiminez et al. [8]	55	78	5	77	28
Kecmanovic et al.[77]	28	43	10	32	17
Ike et al.[95]	71	66	4	54	-
Ike et al.[97]	45	77	13	-	14
Lopez and Luna-Perez[107]	19	67	0	-	44*
Kakuda et al.[131]	22	68	5	-	12
Moriya et al.[108]	57	58	4	-	36*
Vermaas et al.[91]	35	70	3	52	16

* composite exenteration

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.[92,78,98,99,77,93,100] Successful complete resection of recurrent disease is often restricted to selected patients, for example with an early-detected tumour or an anastomosis-limited recurrence after previous sphincter-sparing surgery.[72] Non-resectable distant metastases, poor physical condition and/or irresectable local tumour are all contraindications for this type of surgery. Symptomatic pain or leg oedema in patients who underwent TPE for primary and recurrent rectal cancer is related with an inferior outcome of both local control and survival.[101]

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.[92,102] 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.[72,103] In recent years, mortality after TPE has decreased from rates up to 33% down to rates varying from 0-10%.[76,78,92,102,104]

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[55,105-108] 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%.[108,109] Since most of these patients develop a second recurrence 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 surgery.

Pelvic reconstruction

Reconstruction of the pelvis after an extended resection is another challenge. Postoperative morbidity rates are high and vary between 23-76%, including perineal hernia, evisceration or fistulae between the perineum and the gastrointestinal or genito-urinary tract.[110-112] When a low rectal anastomosis is possible after an extended resection it should be performed when conditions permit. This gives the patients not only the opportunity for a restored continence, but also fills the pelvis with vital tissue. When an abdominoperineal resection is performed an omentoplasty might reduce the incidence of the perineal dehiscence and the need for secondary opening of the perineal wound,[113,114] although there is no direct evidence that this promotes primary healing.[115] If the omentum is not available transposition of a myocutaneous flap can offer a solution to obliterate the pelvic space. Many flaps have been described, but the inferior based rectus abdominis flaps, the inferior gluteal thigh fasciocutaneous flaps and the gracilis muscle- and myocutaneous flaps have emerged as the most reliable for use in the pelvis.[116-120] The gracilis muscle lies outside the external radiation field and can be mobilised relatively simple without major complications, the transposition will not result in functional disability and it results in a high percentage of wound closure.[117] For large pelvic defects especially the vertical rectus abdominis muscle (VRAM) can be used. It is beneficial in reconstruction of vagina and/or pelvic reconstruction and should routinely be used after extensive resections.[82]

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.[100,121] 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.[122] Different centres 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.[38,39,41,56-58,79,122-125] 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.[7,19] Published rates of in-field recurrences after treatment of primary locally advanced and recurrent rectal cancer vary respectively between 0-30% and 1-67%, comparable with our overall percentage of 42%.[57,122,126-128] 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

Treatment for patients with locally advanced and recurrent rectal cancer differs significantly to patients with rectal cancer with tumours restricted to the mesorectum. Therefore, preoperative imaging using MRI of the pelvis is important to identify those patients who are candidates for multimodality treatment including preoperative chemoradiation protocols, intraoperative radiotherapy and extended surgical resections. Because only a third of the patients with locally advanced rectal tumours are treated with the appropriate resection,[91] much effort should be made to select these patients for treatment in specialised referral centres. This has been shown to reduce morbidity and mortality, but also improved long term survival rates.[129-131] Not only volume but also the necessity of a multidisciplinary team, including a radiation oncologist, urologist, surgical oncologist, plastic surgeon and gynaecologist is of importance in these surgical procedures.

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Chapter 11

Summary

Introduction

Most patients with rectal cancer present with tumours located within the mesorectal fascia and are generally treated with total mesorectal excision (TME). Results of TME are excellent 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.

In this thesis the multimodality approach for locally advanced primary and recurrent rectal cancer is discussed with a focus on preoperative radiotherapy, IORT, reirradiation of recurrent rectal cancer, reconstruction of the pelvis after surgery and minimal invasive RF- ablation in recurrent rectal cancer.

Primary rectal cancer

Based on the results of the Dutch TME trial, the treatment in the region of the Comprehensive Cancer Centre Rotterdam 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 compliance to a new protocol i.e. the introduction of preoperative radiotherapy and the results of treatment of 521 patients with primary rectal cancer in the region of the Cancer Centre Rotterdam were analyzed. This registration study identified a significant increase ($p<0.001$) in the number of preoperatively irradiated patients after the introduction of the new treatment protocol. Mortality (2.7%) and the percentage of anastomotic leakage (10.3%) were in the range of the preset quality reference values. The mortality after the occurrence of anastomotic leakage was significantly higher (12.5% versus 2%, $p=0.02$).

Several aspects such as continence for urine and faeces and sexual functions were poorly registered. Instead of the generally accepted minimum of 12 lymph nodes examined, which is of importance for the accurate staging and prognosis, only a mean of 6 nodes were examined. The percentage of reported circumferential resection margins, being one of the most important factors for local control, was low in the beginning of the study, but increased after feedback to the regional pathology network. The improvement in pathology reports illustrates the importance of registration to assess and improve quality of rectal cancer treatment.

Primary locally advanced rectal cancer

Primary locally advanced rectal cancer is characterised in our cancer centre as a tumour invading in or extending close to the mesorectal fascia. In **chapter 3** the results of a multimodality treatment of 123 patients with primary locally advanced, using preoperative radiotherapy (median dose of 50 Gy), followed by surgery and on indication intraoperative radiotherapy (n=27) 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. Intraoperative radiotherapy (IORT) significantly improved 5-year local control (p=0.016) and overall survival (p=0.026) for patients with R1/2 resections. Addition of intraoperative radiotherapy for patients with a narrow or microscopic incomplete resection seems to overrule the unfavourable prognostic histological finding. The presented multimodality treatment for primary locally advanced rectal cancer was feasible with an acceptable mortality and 5-year overall survival.

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 4** 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 preoperative irradiated patients. Complete response to preoperative radiotherapy was predictive for 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 metastases 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.

Previously irradiated patients with recurrent rectal cancer

In **chapter 5** the results of 11 patients treated with reirradiation (median 30Gy) and surgery for locally recurrent rectal cancer were presented. After only one microscopically complete resection (R0) the local control rate was 66% after 1 year and 27% after 3 years. These results and the overall survival rates of 77% and 51% after 1 and 3 years did not significantly differ from local results of previously non-irradiated recurrences treated with long-term preoperative radiotherapy and surgery. The patients did not experience a higher rate of wound healing complications or other complications after this regimen of extensive radiotherapy. The majority of patients presented during follow-up with complaints of severe local perineal/ pelvic pain or neuropathic pain in the lower extremities, for which all received continuous treatment. Median pain free survival after treatment was 5 months. The morbidity, the short pain free survival, moderate local control and survival indicate that careful selection of patients with recurrent rectal cancer is of highest importance. An extensive surgical procedure with high associated morbidity and mortality can not be justified in poor-prognosis patients, as these patients derive little, if any, benefit from surgery.

Intraoperative radiotherapy (IORT)

HDR-IORT (high-dose-rate IORT) is applied in case of a positive or narrow surgical margin (<2mm), 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. The results of 39 patients treated with HDR-IORT using a 5mm template are described in **chapter 6**. A dose of 10 Gy could be applied to 1 cm from the pad surface, with advantage of an increased flexibility of the thin template and a higher surface dose.

And an inadequate dose (<10 Gy) was only applied in 3.5%. Forty-two percent of the local recurrences were IORT in-field recurrences. There were no differences in local control rate between a close or a positive resection margin (p=0.51).

In conclusion, HDR-IORT technique for rectum cancer resulted in an acceptable local control rate. Since IORT in-field recurrences were common, a higher external beam dose, a larger FIT area or the addition of concurrent chemotherapy as a radiosensitizer can be of benefit for the future.

Total pelvic exenteration (TPE)

In **chapter 7** results of total pelvic exenteration, a technique for resection of locally advanced or recurrent rectal tumours invading the bladder and/or prostate, are presented. Long-term survival of 52% after 5 years and excellent local control of 88% after 5 years is possible after TPE for primary locally advanced rectal cancer. These results clearly justify the use of TPE in selected patients with primary disease.

The curative potential of resection differs significantly between primary and recurrent tumours. A complete resection in patients with recurrent disease was possible in 58% of the patients. This low rate of complete resections is reflected in a lower local control and overall survival of patients with recurrent rectal cancer. The 3 years overall survival after TPE for recurrent tumours was 32% and the local control 60% after 3 years.

Growth into surrounding structures (Wanebo stage 4-5), incomplete resection and preoperative pain were prognostic factors for both worse local control and overall survival in this small cohort of recurrences treated with TPE.

The overall major morbidity rate was 34% and these complications were frequently related to the urinary conduit, which was previously been demonstrated to occur especially in patients who previously received radiotherapy. In recent years, mortality after TPE has decreased from published rates up to 33% down to only 3% in our cohort, which corresponds to mortality rates after surgery for T1-3 tumours.

In conclusion TPE in primary locally advanced rectal cancer enables good local control and acceptable overall survival, thereby justifying the use of the procedure. Patients with recurrent rectal cancer showed a high rate of major complications, a high distant metastases rate, and a poor overall survival, demonstrating the importance of careful patient selection by a multidisciplinary team.

Reconstruction after surgery

After extended resections large perineal defects can occur, which are too big for direct closure. Filling of the perineal space can be favourable using an omentoplasty or muscle- and myocutaneous transpositioning, providing well-vascularised and non-irradiated tissue. Results in **Chapter 8** show that direct transposition of the gracilis muscle resulted in closure of the perineal wound in all patients. The morbidity-rate after gracilis transfer in combination with resection of the malignancy was not higher than morbidity after abdominoperineal resection alone for rectal cancer. Previously described limitations in length and rotation of the transplantation graft, high flap necrosis rates and low reliability of the vascular pedicle of the gracilis muscle could be contradicted by results of the present study. The uni- and bilateral

gracilis muscle transpositioning for secondary reconstruction have successfully been used in the majority of patients with small and medium sized pelvic defects in the present study. Transposition of the gracilis muscle resulted in closure of the perineal wound in all but two patients. The gracilis was not only used in the lower perineal defects but also in "higher" pre-sacral locations, without compromising the vascular supply of the flap. Direct reconstruction with a gracilis transfer resulted in primary wound healing with low morbidity, hereby preventing potentially disabling persistent defects. After debridement of persistent wounds, indirect reconstruction with gracilis muscle resulted in the majority of patients in healing of the defects with acceptable morbidity.

Radiofrequency ablation (RFA)

Some patients with recurrent rectal cancer do not qualify for major surgery but do need local treatment. Based upon good results of the use of RF-ablation in the local treatment of primary tumours and metastases in the liver, this technique has been described in recurrent rectal cancer. The main aim of the treatment is to provide local control and avoid local recurrence associated morbidity. In **chapter 9** the results of four RF-ablation procedures in a single patient over a time period of 3 years for recurrent rectal cancer without complications are described. Long-time local control, ongoing for more than 4 years, and associated symptom-control was provided. Based upon this single patient experience we consider RFA as a possibility for selective patients with isolated local recurrent rectal cancer who refuse or do not qualify for surgery.

Chapter 12

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). Locale controle is significant beter na TME in combinatie met preoperatieve bestraling (5*5Gy). 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.

In dit proefschrift wordt de multidisciplinaire behandeling van het primair lokaal uitgebreid en recidief rectumcarcinoom bediscussieerd, met hierbij speciale aandacht voor de effecten van preoperatieve radiotherapie, intraoperatieve radiotherapie (IORT), reirradiatie van recidief rectum tumoren, reconstructie van het bekken na uitgebreide chirurgie en radio frequente ablatieve (RFA) behandeling van recidief rectum tumoren.

Primair rectumcarcinoom

Na de publicatie van de resultaten van de TME-trial is de standaard behandeling in de IKR-regio van tumoren gelegen in het distale twee-derde deel van het rectum gewijzigd in preoperatieve radiotherapie (5*5Gy) gevolgd door chirurgie volgens het TME principe. In **hoofdstuk 2** wordt de introductie van het regionale behandelingsprotocol en de lokale resultaten van de behandeling van 521 patiënten met een primair rectumcarcinoom geanalyseerd. Deze registratiestudie toonde een significante toename ($p<0.001$) van de patiënten die preoperatieve bestraling ontvingen sinds de introductie van het nieuwe regionale protocol. De mortaliteit (2.7%) en het percentage naadlekkage (10.3%) waren binnen de grenzen van voorafgestelde streefwaarden. De mortaliteit was significant hoger na het optreden van een naadlekkage (12.5% versus 2%, $p=0.02$).

Continentie voor urine en faeces en de seksuele functies werden matig geregistreerd. Het totaal aantal lymfklieren dat onderzocht wordt door een patholoog is van belang voor een nauwkeurige stadiëring en de prognose van de patiënt; echter in tegenstelling tot het algemeen aanvaarde minimum aantal van 12 klieren werd er een gemiddeld aantal van 6 klieren geanalyseerd. Het gerapporteerde percentage van de CRM (circumferentiële resectie marge), een van de belangrijkste

prognostische factoren voor lokale controle, was laag in het begin van de studie. Na terugrapportage van deze getallen naar het regionale netwerk pathologen toonde dit echter een stijgende trend. Deze verbetering in de kwaliteit van pathologie rapportage benadrukt het belang van registratie, met als doel het identificeren en zo mogelijk verbeteren van de kwaliteit van de regionale behandeling van het rectumcarcinoom.

Primair lokaal uitgebreid rectumcarcinoom

Het primair lokaal uitgebreid rectumcarcinoom is in ons centrum gedefinieerd als een tumor die tot aan of door de mesorectale fascie groeit. In **hoofdstuk 3** worden de resultaten van 123 patiënten met een primair lokaal uitgebreid rectumcarcinoom beschreven die behandeld werden met preoperatieve radiotherapie (mediane dosis 50Gy), gevolgd door chirurgie en op indicatie tevens IORT (n=27). De lokale controle en overleving waren respectievelijk 65% en 50% na 5 jaar. Positieve lymfklieren en een irradicale resectie hadden een significant negatieve invloed op de lokale controle en overleving. De aanwezigheid van pijn bij presentatie had een significant negatieve invloed op de lokale controle. Intraoperatieve radiotherapie (IORT) zorgde voor een significante verbetering van de lokale controle (p=0.016) en overleving (p=0.026) na 5 jaar voor patiënten met een incomplete (R1/2) resectie. Samenvattend is de behandeling van deze uitgebreide rectumtumoren mogelijk met een beperkte mortaliteit en acceptabele overleving na 5 jaar.

Recidief rectumcarcinoom

Het voornaamste doel van de behandeling is het palliëren van de symptomen en voorzien van een goede kwaliteit van leven voor de patiënt en, indien mogelijk, een radicale resectie van het tumorrecidief. Potentieel curatieve chirurgie kan verricht worden bij een patiënt die zich presenteert met een lokaal recidief zonder aanwijzingen voor metastasen op afstand. In **hoofdstuk 4** worden de resultaten beschreven van 92 patiënten die behandeld zijn met preoperatieve radiotherapie gevolgd door chirurgie (n=59) en door middel van alleen chirurgie (n=33). Er was geen verschil in de morbiditeit en het aantal reïnterventies tussen deze twee groepen. Een radicale resectie (R0) werd bereikt in 64% na voorbestraling gevolgd door chirurgie en in 45% na alleen chirurgie. In 10% van de patiënten bleek er een complete respons van de tumor op de voorbestraling te zijn. Een complete respons na preoperatieve radiotherapie was voorspellend voor een verbeterde lokale controle en overleving. De lokale controle na preoperatieve radiotherapie was significant

hoger na 3 en 5 jaar vergeleken met de lokale controle van de niet voorbestraalde patiënt. (p=0,036). De overleving en metastasevrije overleving verschilden niet tussen beide groepen. Overeenkomstig de goede resultaten van voorbestraling bij primair rectumtumoren, kan geconcludeerd worden dat preoperatieve bestraling bij patiënten met een recidief rectumtumor resulteert in meer complete resecties en een verbeterde lokale controle. Preoperatieve radiotherapie moet derhalve ook een onderdeel zijn van de standaard behandeling van recidief rectumcarcinoom.

Reirradiatie en chirurgie voor recidief rectumcarcinoom

In **hoofdstuk 5** worden de resultaten van 11 patiënten beschreven die behandeld zijn met reirradiatie (mediaan 30Gy) en chirurgie voor een lokaal recidief rectumcarcinoom. Deze groep patiënten, waarvan slechts één patiënt een microscopisch complete resectie (R0) onderging, toonde een lokale controle van 66% en 27% na respectievelijk 1 en 3 jaar follow-up. Deze resultaten en de overleving na 1 en 3 jaar (77% en 51%) kwamen overeen met eerder beschreven resultaten na de behandeling middels bestraling en chirurgie van voorheen niet bestraalde recidief rectumcarcinomen. Er was geen toename van wondgenezingsstoornissen en overige complicaties na deze uitgebreide reirradiatie therapie. Tijdens de follow-up presenteerde de meerderheid van de patiënten zich met pijn ter plaatse van het perineum of het bekken of met neuropathische pijn in de onderste extremiteiten, die in alle gevallen medicamenteuze behandeling behoefde. De gemiddelde pijnvrije overleving periode na behandeling was 5 maanden.

De geassocieerde morbiditeit, het beperkte pijnvrije interval na chirurgie, de matige lokale controle en overleving zijn indicatief voor het feit dat een zorgvuldige selectie voorafgaande aan chirurgie van belang is. Een uitgebreide chirurgische procedure, met daaraan gerelateerde morbiditeit en mortaliteit, is niet geïndiceerd bij patiënten met een slechte prognose, aangezien deze hiervan een beperkt of geen voordeel ondervindt.

Intraoperatieve radiotherapie (IORT)

Intraoperatieve radiotherapie wordt toegepast na resectie van een tumor met een irradicale of minimale marge (<2mm). Hierbij wordt een hoge dosis bestraling toegediend in een specifiek gebied met het doel resterende tumorcellen te vernietigen zonder dat omliggend weefsel blootgesteld wordt aan radiatie. De resultaten van 39 patiënten die behandeld werden met HDR-IORT worden in **hoofdstuk 6** beschreven. Op 1 cm afstand van het oppervlak van de mal werd een gemiddelde dosis van 10 Gy

toegediend en er werd slechts in 3.5% een inadequate dosis (<10 Gy) toegediend. Intraoperatieve radiotherapie leek de morbiditeit na de multidiscliplinaire behandeling niet te verhogen. Tweeënveertig procent van de lokale recidieven waren gelegen in het gebied waar IORT was toegepast. Er was er geen verschil in lokale controle tussen patiënten met een krappe radicale resectie en patiënten met een irradicale resectie (p=0.51). Concluderend leidt de multidisciplinaire behandeling van het rectumcarcinoom waarbij HDR-IORT toegepast wordt tot een acceptabele lokale controle. Aangezien recidieven in het intraoperatief bestralingveld frequent voorkwamen, kan worden overwogen om een hogere bestralingsdosis of een groter IORT gebied te gebruiken. Ook de toevoeging van chemotherapie als zogeheten "radiosensitiser" zal onderzocht moeten worden, gezien het potentieel gunstige effect op de lokale controle.

Totaal exenteratie (TPE)

In **hoofdstuk 7** worden de resultaten gepresenteerd van de totaal exenteratie, een operatieve techniek voor de resectie van rectumtumoren die de blaas en/of de prostaat ingroeien. Een overleving van 52% na 5 jaar en een lokale controle van 88% na 5 jaar was mogelijk na TPE uitgevoerd bij primaire lokaal uitgebreide tumoren. Deze resultaten rechtvaardigen het gebruik van TPE in een geselecteerde groep patiënten met een primair lokaal uitgebreid rectumcarcinoom. De mogelijkheid tot curatie verschilt tussen het primair lokaal uitgebreid rectumcarcinoom en het recidief rectumcarcinoom. Een complete resectie na TPE was slechts mogelijk in 58% van de patiënten met een recidief rectumcarcinoom. Dit lage percentage radicale resecties weerspiegelt zich in een lage lokale controle en overleving; 60% lokale controle na 3 jaar en 32% overleving na 3 jaar. Groei in omliggende structuren (Wanebo stadium 4-5), een irradicale resectie en preoperatieve pijnklachten waren negatief prognostische factoren voor zowel lokale controle als overleving.

Het percentage majeure complicaties was 34% en deze bleken vaak gerelateerd te zijn aan de constructie van de neoblaas. De mortaliteit na TPE is in de jaren afgenomen van 33% tot slechts 3%, hetgeen vergelijkbaar is met de mortaliteit die optreedt na chirurgie van T1-3 tumoren. Samenvattend is het verrichten van TPE bij patiënten met een primair lokaal uitgebreid rectumcarcinoom gerechtvaardigd gezien de goede lokale controle en acceptabele overleving. Patiënten met een recidief rectumcarcinoom tonen echter veel postoperatieve complicaties, een hoog percentage metastasen op afstand en een matige overleving. Deze resultaten benadrukken de zeer selectieve indicatiestelling voor TPE bij patiënten met een recidief rectumcarcinoom.

Reconstructie na uitgebreide chirurgie

Na uitgebreide bekkenchirurgie kunnen grote defecten resteren die te groot zijn om primair te sluiten. Het opvullen van het defect met een omentumplastiek of een spier- of spierhuidplastiek biedt de mogelijkheid tot reconstructie met goed gevasculariseerd en onbestraald weefsel. Resultaten in **hoofdstuk 8** toonden dat een directe transpositie van de gracilis spier resulteerde in een sluiting van de perineale wonden in alle patiënten. De morbiditeit van de gecombineerde resectie van maligniteit en directe reconstructie was niet hoger dan de morbiditeit beschreven na abdominoperineale resectie alleen. Bekende beperkingen in de lengte en rotatie mogelijkheden van het transplantaat, hoge necrose percentages van het transplantaat en een beperkte betrouwbaarheid van de vasculaire steel van de gracilis spier kunnen door deze resultaten niet worden bevestigd. De uni- en bilaterale gracilis spierplastiek voor secundaire reconstructie waren succesvol voor pelviene defecten van beperkte grootte. Transpositie van de gracilis spier resulteerde in op twee na alle patiënten in volledige genezing van de perineale wond. De gracilisplastiek werd niet alleen in perineale defecten, maar ook in "hogere" presacrale defecten gebruik, zonder dat hierbij de vascularisatie gecompromitteerd werd.

Resumerend resulteerde transpositie van de gracilis spier in goede primaire wondgenezing zonder evidente morbiditeit. Na debridement van persisterende wonden resulteerde indirecte reconstructie met een gracilis plastiek in genezing in de meerderheid van de patiënten met een acceptabele morbiditeit.

Radiofrequente ablatie (RFA)

Patiënten die door bijvoorbeeld een beperkte lichamelijke conditie of eigen wens niet in aanmerking komen voor resectie van een recidief rectumcarcinoom behoeven wel lokale behandeling om de symptomen van het recidief rectumcarcinoom te voorkomen of te palliëren. In navolging van positieve resultaten behaald bij verschillende primaire tumoren en levermetastasen is het gebruik van RFA beschreven bij recidief rectumtumoren. Het voornaamste doel van de behandeling is het streven naar lokale controle en het voorkomen van aan recidief rectumtumor geassocieerde morbiditeit. In **hoofdstuk 9** worden de resultaten gepresenteerd van vier ongecompliceerde RFA-procedures, verricht over een periode van de 3 jaar, bij een patiënt met een recidief rectumcarcinoom. Deze patiënt bleef vrij van een lokaal recidief en symptomen voor een periode van meer dan 4 jaar. Gebaseerd op deze gunstige resultaten kan RFA overwogen worden als alternatieve behandeling voor patiënten die niet in aanmerking komen voor majeure chirurgie.

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Curriculum vitae

Maarten Vermaas

Maarten Vermaas werd geboren op 29 juni 1977 in Doorn. In 1995 behaalde hij zijn Gymnasium diploma aan het Revius Lyceum te Doorn. Wegens uitloting studeerde hij één jaar Beleid & Management in Gezondheidszorg. In 1996 werd hij toegelaten tot de studie geneeskunde. Na een afstudeeronderzoek op de afdeling Kinderchirurgie onder begeleiding van Prof.dr. D. Tibboel haalde hij in 2001 het doctoraal examen. Na enkele maanden onderzoek op de afdeling Experimentele Heelkunde onder begeleiding van Prof.dr. H.J. Bonjer werden de co-schappen gestart. Een deel van de co-schappen voerde hij uit in het Tygerberg ziekenhuis te Stellenbosch, Zuid Afrika. Halverwege de co-schappen startte hij het huidige promotieonderzoek onder begeleiding van Prof.dr. A.M.M. Eggermont en dr. J.H.W. de Wilt.

Sinds 1 januari 2006 is hij in opleiding tot algemeen chirurg in het Reinier de Graaf Gasthuis te Delft (opleider dr. L.P.S. Stassen). Deze opleiding zal voortgezet worden in het Erasmus MC te Rotterdam (opleider Prof.dr. J.N.M. IJzermans).

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