Multidisciplinary approach to locally advanced and recurrent rectal cancer

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**MULTIDISCIPLINARY APPROACH TO
LOCALLY ADVANCED AND RECURRENT
RECTAL CANCER**

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MULTIDISCIPLINARY APPROACH TO LOCALLY ADVANCED AND RECURRENT RECTAL CANCER

Proefschrift

ter verkrijging van de graad van doctor

aan de Universiteit Maastricht,

op gezag van de Rector Magnificus

Prof. mr. G.P.M.F. Mols,

volgens het besluit van het College van Decanen,

in het openbaar te verdedigen

op vrijdag 27 maart 2009 om 10.00 uur

door

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Look to this day,
for it is life,
the very life of life.

In its brief course
lie all realities
and verities of existence.

The bliss of growth,
the splendor of action,
the glory of achievement
are but experiences of time.

For yesterday is but a dream
and tomorrow is only a vision.

But today well-lived
makes every yesterday a dream of happiness
and every tomorrow a vision of hope.

Look well, therefore, to this day,
such is the salutation to the ever-new dawn.

-Sanskrit proverb-

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General introduction
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CHAPTER

GENERAL INTRODUCTION

Background

Colorectal cancer is a major health problem in the Netherlands. Around 10,000 persons will develop a colorectal tumor each year and this number is expected to keep rising. It is the second most common malignancy in women and the third most common in men and almost 50% of the patients will die from this disease. About 1/3 of colorectal carcinomas is located in the rectum. Rectal cancer requires a different approach than colon cancer in terms of imaging and treatment, because of the location within the pelvis. This pelvis is a narrow space and surgical entry is more difficult. Moreover, structures are more impacted down in the pelvic cavity than in the higher abdomen (colon) thus increasing the risk of rectal tumor spread into the surrounding structures and of a positive circumferential resection margin (CRM). This was reflected in high local recurrence rates of 30-50% and a low 5-year survival rate of 31% in the 1950s¹. However, in the last 20-30 years recent developments have improved the outcome dramatically.

Recent developments

Surgery

Treatment of rectal cancer has undergone many changes during the last years due to the recognition of the importance of a clear CRM² and the understanding of the mesorectal fat package as a source for possible tumor deposits. In the past, patients with rectal cancer were treated with blunt dissection of the tumor through the mesorectal fat, often leaving tumor tissue behind leading to a high local recurrence rate. Nowadays, rectal cancer patients are treated with standardized surgery, the total mesorectal excision (TME)^{3,4}. TME is a surgical procedure in which the rectum and the enveloping mesorectal fat and lymph nodes are removed by precise dissection along the mesorectal fascia (MRF), an embryologically determined natural border.

Neoadjuvant therapy

Not only has the blunt dissection been replaced by better surgical techniques, but also neoadjuvant (chemo)radiation therapy has been introduced in order to decrease the risk of a local recurrence even further. Nowadays, two effective neoadjuvant therapy schemes are available: a short course of 5x5 Gray (Gy) and a long course of 45-50.4 Gy (5 times a week in 25 or 28 doses of 1.8 Gy) combined with 5-FU based chemotherapy. The Dutch TME trial has shown that preoperative radiotherapy with 5x5 Gy results in better local control than TME surgery alone, except for tumors that come close to or invade the mesorectal fascia and in very distal rectal cancer (these tumors need longer courses of neoadjuvant treatment)^{4,5}. Furthermore, a prospective randomized study of 823 patients with T3-4 or N+ locally advanced rectal cancer that compared preoperative with postoperative chemoradiation showed better local control and fewer toxic side effects in patients treated with preoperative chemoradiation⁶. The addition of chemotherapy to neoadjuvant radiotherapy has proven to be effective at reducing the local recurrence rate and increasing the complete response rate^{7,8}. Newer chemoradiation strategies are becoming more and more effective with complete histopathological disappearance of the tumor in 15-30% of the patients and partial response in around 50%⁹⁻¹¹.

Imaging

Imaging has become important in the preoperative management of rectal cancer. Currently used imaging techniques are endoluminal ultrasound (EUS), magnetic resonance imaging (MRI), computed tomography (CT) and positron emission

tomography (PET). For optimal patient outcome, it is essential to stratify patients into the most optimal treatment strategy, combining a good outcome with minimal morbidity. Two important prognostic factors for the development of a local recurrence are the circumferential resection margin (CRM) and lymph node involvement^{2,12}. In TME surgery, the surgeon follows the plane of the MRF. This fascia can therefore be considered as the anticipated CRM. Since a short course of radiotherapy is insufficient to prevent local recurrences when the tumor has grown through or very near the MRF, the relationship between the tumor and the MRF should be accurately predicted before surgery. Many studies have focused on primary staging of rectal cancer with MRI and have shown that high-spatial-resolution MR imaging with phased array surface coils is very accurate for the prediction of tumor involvement of the MRF and has gained a pivotal role in rectal cancer staging¹³⁻¹⁶. Prediction of lymph node status is more difficult as shown in 2 reviews^{17,18}. These reviews showed that EUS, CT and MRI are not accurate enough for clinical decision making with sensitivity estimates of 55-67% and specificity estimates of 74-78%. All modalities heavily rely on size criteria, and size on its own is insufficient to reliably distinguish between malignant and benign lymph nodes in rectal cancer. Brown et al.¹⁹ showed that 3- or 5-mm large lymph nodes still had a prevalence of positive lymph nodes of 10% and 28%, respectively. MRI using lymph node specific contrast agents (like Ultrasmall Superparamagnetic Iron Oxide (USPIO)) showed promising results for detecting malignant nodes with a sensitivity and specificity of around 95%²⁰.

Differentiated treatment

With the above mentioned preoperative staging techniques it has become possible to stratify rectal tumors in different treatment groups according to the risk of LR. One can stratify patients into low, intermediate and high risk groups for local recurrence, with the treatment options of surgery only, 5x5 Gy followed by surgery and chemoradiation with surgery (Figure 1).

Figure 1. Treatment of rectal cancer according to stage of the disease. 1=rectal wall, 2=mesorectal fat, 3=mesorectal fascia, 4=tumor, 5=positive lymph node, TME=total mesorectal excision, 5x5 RT= short course of radiotherapy, 50.4 CRT=long course of chemoradiation therapy, ETME=TME resection with extended circumferential resection margin.

There are several options how to define the three risk groups. The stratification option that is used in Maastricht, the Netherlands is as follows: patients with early tumors (T1-2No) located in the mid or high rectum are treated with TME alone. The intermediate group are patients who do not qualify as low or high risk and are treated with a short course of 5x5 Gy radiotherapy followed by TME. Patients with a high risk of LR, with locally advanced rectal cancer (LARC), have tumors with an involved or threatened CRM (≤ 2 mm on MRI), more than 3 positive lymph nodes or very distal T3 lesions. They receive a long course of 45-50.4 Gy radiotherapy combined with concurrent chemotherapy followed by either TME or a more extensive resection in case of invasion of the tumor into surrounding structures. This extensive treatment in LARC patients leads to acceptable low local recurrence rates, but is unfortunately accompanied by a relatively high morbidity rate.

In general, this differentiated treatment has led to an improvement of the 5-year survival rate up to 59% and to a decrease of the local recurrence rate to below 10%¹.

More differentiated treatment

Nowadays, the question has arisen whether even further differentiated treatment is possible. Is it still necessary to perform a standard TME or even more extended operations, with the related high morbidity rates, in patients who have responded very well to neoadjuvant treatment? The options of a local excision and even a wait and see policy are highly controversial²¹⁻²⁶. The patient is exposed to a higher risk of recurrence, but there is a lower risk of postoperative morbidity and mortality. At the same time, poor responders have to undergo the extensive treatment. This more differentiated treatment can only become successful with a staging tool that can accurately detect complete responses in the tumor and the lymph nodes and distinguish good responders from poor responders. A part of this thesis discusses the role of MRI and molecular markers in this matter. Another treatment change towards more individualized treatment may be based on the presence of histopathological factors which carry an increased risk of developing a local recurrence. The present thesis will also deal with this topic.

Local recurrences

Despite all the advances in rectal cancer diagnostics and treatment, about 10% of the patients will still develop a local recurrence²⁷. These local recurrences will be discovered at routine follow-up (e.g. increased carcinoembryonic antigen (CEA) level, suspicion at colonoscopy or CT) or with the development of symptoms (e.g. pain, rectal bleeding, changed bowel habit, weight loss) and the diagnosis will be confirmed histologically or by repeated clinical investigations. During the years, treatment emphasis has changed²⁸. In the past, many patients were denied a curative treatment as it was believed that patients were only rarely cured. Only palliative treatment, such as pain medication, radiation therapy or chemotherapy, was provided. However, there has been a general trend towards considering curative treatment, including major pelvic surgery.

When considering curative treatment, accurate information on the local and distant spread of the tumor is crucial to determine the resectability of the recurrence. It is not well established which tool is the best for preoperative local staging of locally recurrent rectal cancer (LRR). In the present thesis the preoperative assessment of extent of tumor growth by MRI is studied. Distant spread can be excluded with abdominal ultrasound and chest X-ray, with CT of the chest and abdomen and with PET. A part of this thesis studies the clinical impact of PET in recurrent rectal cancer.

Surgery is the most essential part of the treatment. The major goal is achievement of a radical resection, because this has repeatedly been shown to be the most important factor for a good outcome²⁹⁻³². However, with surgery alone still a considerable amount of patients have an irradical resection. The addition of neoadjuvant chemoradiation to surgery has resulted in a higher rate of radical resections³³. Even re-irradiation is currently being performed in patients who had already received radiotherapy for their primary tumor³⁴. Re-irradiation may result in better outcome but may also, due to tissue toxicity, result in higher morbidity rates. In some specialized centers intraoperative radiotherapy (IORT) is part of the multimodality treatment³⁵. IORT can deliver the necessary dose escalation to the area at high risk of residual tumor without damaging surrounding organs and may lead to better local control. This advantage has to be balanced against acute and late side effects of the irradiation. Survival rates have increased significantly due to the aggressive multimodality treatment^{36,37}. However, this treatment is only justifiable in strictly selected patients who might benefit from such an extensive treatment as it brings along severe morbidity. In noncurable patients palliative treatment should be provided instead.

The Catharina hospital in Eindhoven, the Netherlands is a tertiary referral center to which patients with potentially curative recurrent rectal cancer are referred from throughout the country. In 1994, multimodality treatment approach was designed for non metastasized local recurrence patients consisting of neoadjuvant (chemo)radiation, extensive surgery and intraoperative radiotherapy. The combination of the referral function and a designated treatment schedule resulted in a large group of patients treated with curative intent. The present thesis evaluates the results of multimodality treatment in these patients and investigates which patients have the best chance of a radical resection.

AIMS OF THIS THESIS

The general aim of this thesis is to assess the role of various tools to provide the optimal treatment for a patient with rectal cancer. This aim is subdivided into three specific aims.

1. To assess the accuracy of imaging in staging and restaging of primary and recurrent rectal cancer.
2. To assess the role of histopathology and molecular markers in the prediction of local recurrence and treatment outcome respectively.
3. To evaluate the results of multimodality treatment in locally recurrent rectal cancer.

OUTLINE OF THIS THESIS

Chapter 2 describes the role of post chemoradiation MRI in restaging of locally advanced rectal cancer and evaluates MRI as a tool for more individualized surgical treatment planning.

Chapter 3 evaluates the accuracy of Multi-detector row CT for the prediction of mesorectal fascia invasion in locally advanced rectal cancer with MRI as reference standard.

Chapter 4 identifies the tumor response to neoadjuvant treatment in locally advanced rectal cancer based on apoptotic tumor markers.

Chapter 5 assesses the predictive value of histopathological factors for the development of a local recurrence after primary rectal cancer treatment.

Chapter 6 studies the clinical impact of PET in patients with pelvic rectal cancer recurrence scheduled for curative treatment.

Chapter 7 evaluates the role of MRI in locally recurrent rectal cancer treatment planning.

Chapter 8 evaluates the outcomes of multimodality treatment in locally recurrent rectal cancer.

Chapter 9 investigates the relationship between the location of locally recurrent rectal cancer and its resectability and consequent outcome.

Chapter 10 summarizes and discusses the findings of the above mentioned studies. Conclusions are drawn and future research is advocated.

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Chapter 1

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**MRI for restaging after
neoadjuvant chemoradiation
in locally advanced rectal cancer.
Are we able to predict tumor
confined to the rectal wall?**

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Radiology, in press

ABSTRACT

Purpose

To retrospectively assess the accuracy of MRI after chemoradiation to determine downstaging of the primary lesion to a tumor confined to the rectal wall (ypTo-2) in locally advanced rectal cancer (LARC), using histopathology as reference standard, and to evaluate the additional value of volumetric analysis.

Patients and Methods

The institutional review board approved the study and waived informed consent. Sixty-seven patients (38 males, 29 females, mean age 63) with LARC who underwent (chemo)radiation and surgery (in all but one) were evaluated. The pre and post (chemo)radiation T2-weighted MR images were assessed for T stage by an expert abdominal radiologist, colorectal surgeon and general radiologist. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) were calculated. Tumor volume was measured by the expert radiologist. Mann-Whitney tests were used to compare tumor volumes. The findings were correlated with histopathology.

Results

The PPV for the prediction of ypTo-2 reached 91% (10/11), 86% (6/7) and 88% (7/8) for the expert abdominal radiologist, surgeon and general radiologist, respectively. Sensitivities were 42%, 25% and 29% (10, 6 and 7 of 24 respectively). ypTo-2 tumors had significantly smaller pre (chemo)radiation volumes than ypT3-4 tumors (55 versus 92 cm³, $P = 0.038$). Volume reduction rates were significantly higher in ypTo-2 than in ypT3-4 (89 versus 61%, $P < 0.001$). If pre (chemo)radiation volume was below 50 cm³ and volume reduction exceeded 75%, the excised tumor was always confined to the rectal wall (ypTo-2). Using these criteria, 42% of the cases overstaged for T stage could have been predicted as ypTo-2 correctly.

Conclusion

Tumor downsizing to ypTo-2 can be accurately predicted by combining morphological T stage predictions with volumetric analyses. Post (chemo)radiation MRI might be helpful in more individualized treatment planning.

INTRODUCTION

The standard treatment for locally advanced rectal cancer (LARC) is preoperative chemoradiation followed by a standard resection of the rectum, with surrounding organs when required^{1,2}. Neoadjuvant chemoradiation has shown to downsize and downstage the tumor, leading to improved resectability and local control^{3,4}. The most frequently used regimen, 45-50.4 Gy (Gray) combined with 5-FU based chemotherapy, results in 15-30% complete tumor response rates of the primary tumor bed and almost 50% partial response rates. Complete eradication of tumor in the lymph nodes (ypNo) also occurs, with a reported decline in the rate of node positive tumors found at histopathology from 40% before chemoradiation to 25% after chemoradiation⁴. The response rates may even be higher with the addition of new biological modifiers^{5,7}. The clinical question is what to do with good response after chemoradiation. In order to obtain maximal local control, most surgeons advocate performing a resection based on the pre chemoradiation status and disregard the response. However, major pelvic surgery is associated with a high postoperative morbidity rate of 40-50%^{8,9}. In patients in whom chemoradiation has downstaged tumors to lesions confined to the rectal wall (ypTo-2) and in whom there are no longer involved lymph nodes (ypNo) a local transanal full thickness excision of the bowel wall may be all that is required to cure the patient. This is a controversial approach, which raises the concern of exposing the patient to an undue risk of recurrence. A recent review article summarizes the experience with local excision after chemoradiation in a selected group of 237 patients¹⁰. The method of selection of patients was variable and most often based on estimation of T stage with endo-anal ultrasound (EUS), with very little role for assessment of nodal stage. The local recurrence rate varied with the histopathological T stage after chemoradiation (ypT stage): from 0% for ypTo stage to 7% for ypT2 and even 21% for ypT3. The study confirms the minimal morbidity of the local excision, as compared to the standard transabdominal resection of the rectum. Thus, the major challenge for the radiologist is to provide a tool to identify those tumors that after chemoradiation are most suitable for local excision: tumors confined to the rectal wall. Both EUS and MRI are often used for primary staging of the tumor extent, with MRI generally considered as the most accurate tool¹¹⁻¹⁴. The performance of MRI after chemoradiation is, however, less well understood. Several studies found reasonable accuracies of MRI for T staging after chemoradiation¹⁵⁻¹⁷. These studies did not focus on the assessment of residual tumor confined to the rectal wall. MR imaging of nodal involvement is more difficult, with accuracies ranging from 43% to 85%¹⁸, and accuracy data on imaging after chemoradiation are scarce. The accuracy of MR lymph node staging may improve with the recently introduced lymph node specific contrast agents. The purpose of this study was to assess the accuracy of MRI for restaging after chemoradiation in locally advanced rectal cancer. It retrospectively assessed the accuracy to determine downstaging of the primary tumor to a lesion confined to the rectal wall (ypTo-2), using histopathology as reference standard, and evaluated the additional value of volumetric analysis.

PATIENTS AND METHODS

The institutional review board approved this retrospective study and waived informed consent. Between October 1999 and August 2007 350 consecutive patients with locally advanced rectal cancer (LARC) were treated at the Maastricht University Medical Center and the Catharina Hospital in Eindhoven, the Netherlands. The inclusion criteria for our study were biopsy proven adenocarcinoma of the rectum treated with neoadjuvant therapy followed by resection of the tumor, the availability of adequate MR

examinations before and after chemoradiation and the availability of detailed surgical and histopathological reports. Furthermore, to standardize the definition of LARC, the tumor should be defined on MRI as a T3 tumor with a threatened circumferential resection margin (a distance of ≤ 2 mm from the mesorectal fascia) and/or as a T4 tumor with invasion into the surrounding organs. In total, 67 patients (Table 1, Figure 1) met these inclusion criteria and formed the population of this study. The other 283 patients were excluded because of the following reasons: 75 patients did not receive a preoperative MRI, 112 patients only had a pre chemoradiation MRI, in 83 patients the pre chemoradiation staging was performed with CT, these patients only had a post chemoradiation MRI and in 13 patients the histopathology could not be reconstructed.

Table 1. Patient, treatment and tumor characteristics

	No.	(%)
All	67	100
Median age in years (range)	64	(37-82)
Sex		
Male	38	56.7
Female	29	43.3
mrT stage		
T3	55	82.1
T4	12	17.9
Neoadjuvant therapy		
Radiotherapy	4	6.0
Chemoradiation	63	94.0
ymrT stage*		
0-2	11	16.4
3-4	56	83.6
Type of surgery		
LAR	23	34.3
APR	11	16.5
Anterior exenteration	22	32.8
Pelvic exenteration	6	8.9
ASR	4	6.0
No surgery	1	1.5
ypT stage		
0	6	8.9
1	3	4.5
2	15	22.4
3	38	56.7
4	5	7.5
TRG		
0	13	19.4
1	46	68.7
2	6	8.9
not assessable	2	3.0

Note. *cutoff 2-3 (observer 1); mrT stage, T stage on pre chemoradiation MRI; ymrT stage, T stage on post chemoradiation MRI; LAR, low anterior resection; APR, abdominoperineal resection; ASR, abdominosacral resection; ypT stage, post therapy pathological T stage; TRG, tumor regression grade according to Rödel.

Figure 1. Flow chart of patient inclusion and results of post chemoradiation MRI for the prediction of tumors confined to the rectal wall (ypT0-2) by observer 1 using morphological criteria only. * See patients inclusion criteria in Patients and Methods section. CRT, (chemo)radiation therapy.

Neoadjuvant treatment

The neoadjuvant treatment was administered according to national guidelines at that time and consisted of either radiotherapy alone or chemoradiation. A total dose of 45-50.4 Gy in 25-28 fractions of 1.8 Gy was delivered. Chemotherapy consisted of either continuous infusion of 5-fluorouracil (5-FU, 225 mg/m²/d) or the combination of 5-FU (350 mg/m²) and leucovorin (20 mg/m²) in radiotherapy week 1 and 5 or oral application of capecitabine (2x825 mg/m²/d) either alone or combined with oxaliplatin (50 mg/m²) on every first radiotherapy day of the week.

MRI techniques

MR imaging was performed on a 1.5 Tesla system (Gyroscan, Powertrack 6000 NT, Philips Medical Systems, Best, the Netherlands) using a quadrature phased array spine coil, a cardiac or body phased array coil (Philips Medical Systems, Best, the Netherlands). Sequences used were an axial T1-weighted, 2D, turbo (fast) spin echo (T1-W TSE: TR/TE 656/10 msec, 5 echo train length, 8 mm slice thickness, 0.8 mm gap, 4 signal averages, 166x256 matrix, 25 cm FOV, 1.4 min acquisition time) and a sagittal and transverse T2-weighted, 2D, fast spin echo (TR/TE 1288-3427/150 msec, 25 echo train length, 3-4 mm section thickness, 0.3-0.8 mm intersection gap, 6 signal averages, 512x512 matrix, 20-32 cm FOV). Patients did not receive bowel preparation, air insufflation or intravenous spasmolytic medication. Median time between initial MRI and the start of chemoradiation was 27 days (range 3-93). Median time between the end of the radiotherapy and the post chemoradiation MRI was 34 days (range 0-60) and between the post chemoradiation MRI and surgery 26 days (range 1-109).

Evaluation of MR images

At first, pre and post chemoradiation MRIs were retrospectively assessed for T stage by observer 1 and 2 and prospectively read in the clinical setting by observer 3 using morphological criteria. Observer 1 was a pelvic MRI radiologist with 12 years experience in reading pelvic MRI in an academic center. Observer 2 was a colorectal surgeon, who had been a member of the multidisciplinary team for 4 years in the same center. This surgeon had not treated any of the patients in this study as this could have introduced clinical bias. Observer 3 was a general radiologist working in a general hospital serving as a referral center for advanced rectal cancer and with 5 years of specific experience in reading pelvic MRI.

The terms mrT stage (= T stage on pre chemoradiation MRI), ymrT stage (= T stage on post chemoradiation MRI) and ypT stage (= T stage at post treatment histopathology) were used as proposed by Moran et al.¹⁹. All observers scored mrT stage on pre chemoradiation MRI (T3 or T4). On post chemoradiation MRI, observer 3 scored ymrT stage dichotomously to predict T stage at histology (ypT0-2 or ypT3-4), whereas observer 1 and 2 used confidence level scores to predict tumor confinement to the rectal wall at histology (ypT0-2): 0 = definitely not ypT0-2, 1 = probably not ypT0-2, 2 = possibly ypT0-2, 3 = probably ypT0-2, 4 = definitely ypT0-2. Predefined morphological criteria were used to assess T stage: ymrT0-2 was defined as complete disappearance of the tumor or as tumor surrounded by an intact dark bowel wall. ymrT3-4 was defined as residual iso-intense mass penetrating the bowel wall and/ or penetrating the mesorectal fascia and/ or invading a surrounding organ. A thickened hypo-intense bowel wall was read as a fibrotic wall. Since MRI cannot differentiate between fibrosis with or without tumor, this pattern was always scored as ymrT3. All observers were blinded to the surgical, histopathological and each other's results. T stage response to neoadjuvant treatment was determined by comparing the T stage as scored on the pre chemoradiation MRI by observer 1 with histopathological findings (Table 2).

Table 2. Tumor response to neoadjuvant treatment

	mrT3	mrT4
ypT0	6	0
ypT1	3	0
ypT2	14	1
ypT3	30	9
ypT4	2	2

Note. mrT stage, T stage on pre chemoradiation MRI; ypT stage, post therapy pathological T stage.

Subsequently, tumor volumes were assessed by observer 1. The maximum diameter was measured on 1 axial slice in two directions perpendicular to each other (length and width). The maximum height was measured on 1 sagittal slice. Tumor volume was obtained by multiplying tumor length, width and height. Volume reduction rates (%) were defined as

$$100\% \times \left(\frac{\text{pre chemoradiation} - \text{post chemoradiation volume}}{\text{pre chemoradiation volume}} \right)$$

Surgery

The median interval between the last day of radiotherapy and surgery was 8 weeks (range 6-14). Patients underwent surgery with curative intent. The resection plane was based on the initial MR staging. One patient did not undergo surgery because of complete response.

Histopathological evaluation

All specimens were evaluated according to the protocol of Quirke et al.²⁰. The specimens were received fresh, opened anteriorly and fixed in 10% formalin. Dissection consisted of 5-10 mm slicing of the whole tumor and surrounding mesorectal fat in the transverse plane. Slices were embedded in blocks and processed for hematoxylin and eosin staining in 5 µm sections. ypT stage was recorded. Tumor regression was determined semiquantitatively by the amount of viable tumor versus the amount of treatment induced fibrosis according to Rödel²¹, ranging from poor regression (Rödel 0) to intermediate regression (Rödel 1) and complete regression (Rödel 2). The single patient with a complete response who was not operated was followed with repeated endoscopy with biopsies and repeated imaging.

Statistical analysis

Histopathology served as reference standard. Receiver operating characteristic (ROC) curves were constructed and areas under the curve (AUC) were calculated for observer 1 and 2. The AUCs were compared using the method of DeLong²². After dichotomization of the 5 point scale confidence level scores (cutoff was set at: 0-2 = ypT3-4, 3-4 = ypT0-2) sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of post chemoradiation MRI for the prediction of ypT0-2 were calculated. The exact 95% confidence intervals for these values were calculated with the assumption of a binomial distribution. Inter-observer agreement was assessed by weighted kappa statistics^{23,24}, with kappa-values of 0.2-0.4 indicating fair, 0.4-0.6 moderate, and > 0.6 excellent agreements²⁵. Wilcoxon signed-rank test was used to test the statistical significance of the difference in volume before and after chemoradiation. Differences in tumor volumes before and after chemoradiation and in volume reduction rates between ypT0-2 versus ypT3-4 and between the various tumor regression grades were tested using the Mann-Whitney U test and Kruskal-Wallis test. A P-value of ≤ 0.05 (two-sided) was considered as statistically significant. Statistical analysis was performed using the SPSS statistical software program (SPSS release 15.0, Chicago, Illinois, USA).

RESULTS

Patient, treatment and tumor characteristics (Table 1)

Of the 67 patients, 38 were male (mean age 62, range 37-82) and 29 female (mean age 65, range 44-81). The mean age for the whole group was 63 (range 37-82). Four patients had long course radiotherapy only, 63 received neoadjuvant chemoradiation. All patients underwent surgery according to the TME principle²⁶ with excision of the rectum plus the surrounding mesorectal fat. When required, a more extensive procedure with resection of involved organs was performed. One patient with a clinical complete response did not undergo surgery and currently there is no evidence of disease after a 27 months period of follow-up with repeated endoscopy with biopsies and repeated MR imaging. T stage response to chemoradiation is shown in Table 2.

Prediction of ypTo-2 on post chemoradiation MRI based on morphological criteria
AUC, accuracy, sensitivity, specificity, PPV and NPV of post chemoradiation MRI for the prediction of ypTo-2 stage tumors based on morphological criteria only, for the 3 observers are displayed in Table 3. The AUCs from observer 1 (0.86) and observer 2 (0.69) differed significantly (P=0.02).

Table 3. Performance of post chemoradiation MRI for the prediction of ypTo-2

Parameter	Observer 1	Observer 2	Observer 3	T stage and volume
AUC	0.86 (0.76, 0.97)	0.69 (0.56, .82)	-	-
Accuracy (%)	78 (52/67)	72 (48/67)	73 (49/67)	87 (58/67)
95% CI	66, 87	59, 82	61, 83	76, 94
Sensitivity (%)	42 (10/24)	25 (6/24)	29 (7/24)	67 (16/24)
95% CI	22, 63	10, 47	13, 51	45, 84
Specificity (%)	98 (42/43)	98 (42/43)	98 (42/43)	98 (42/43)
95% CI	88, 100	88, 100	88, 100	88, 100
PPV (%)	91 (10/11)	86 (6/7)	88 (7/8)	94 (16/17)
95% CI	59, 100	42, 100	47, 100	71, 100
NPV (%)	75 (42/56)	70 (42/60)	71 (42/59)	84 (42/50)
95% CI	62, 86	57, 81	58, 82	71, 93

Note. Values for observer 1-3 are based on morphological T stage prediction only. The values for T stage and volume are based on the combination of morphological criteria and volumetric criteria (initial volume $\leq 50\text{ cm}^3$ and volume reduction $\geq 75\text{ cm}^3 = \text{ypTo-2}$). Numbers in parentheses are absolute numbers. ypTo-2, pathological To-2 after neoadjuvant therapy; observer 1, expert radiologist; observer 2, colorectal surgeon; observer 3, general radiologist; AUC, area under the receiver operating characteristic curve; 95% CI, exact 95% confidence intervals; PPV, positive predictive value; NPV, negative predictive value.

Figure 2. The administration of chemoradiation to a tumor with a small volume ($3.3 \times 2.6 \times 3.6 = 31\text{ cm}^3$) resulted in a complete response at histopathological examination. (a,b) Sagittal T2-weighted fast spin-echo MR images (3427/150). (a) Before chemoradiation a tumor (T) is seen in the rectum. C is cervix. (b) After chemoradiation the tumor has completely disappeared and a normal rectal wall configuration is seen with a dark outer layer (white arrow) and a hyper-intense inner layer (grey arrow). C = cervix, Co = coccygeal bone. At histopathology no residual tumor was found.

If, after chemoradiation, the rectal wall returned to its normal configuration of a 2 layered pattern on MRI (Figure 2), then this was always associated with a complete histopathological disappearance of the tumor (ypTo). In 4 of the 6 patients with a complete response (66.7%) this feature was seen.

Figure 3. Diffuse hypo-intense tissue infiltration of the rectal wall and mesorectal fat at post chemoradiation MRI, suggestive of residual tumor, lead to overstaging. (a,b) Transverse T2-weighted fast spin-echo MR images (3427/150). (a) Before chemoradiation the tumor (T) has grown into the surrounding mesorectal fat (arrows). (b) After chemoradiation a thickened rectal wall is seen with hypo-intense thickening and spiculations into the mesorectal fat (arrows), suggestive of residual tumor. However, at histopathology this corresponded to fibrosis without residual tumor.

Overstaging (Figure 3) of ypTo-2 occurred in 14 patients for the observer 1, in 18 for observer 2 and in 17 for observer 3. In all these cases, diffuse hypo-intense tissue infiltration of the rectal wall and/ or the mesorectal fat was seen. Only 1 patient was understaged by all observers. In this case, only 2 small tumor cell clusters (diameter < 50 μ m) were found in the mesorectal fat, rendering the tumor an ypT3 (Figure 4). Interobserver agreement was fair to moderate with kappa values of 0.426 (95% confidence interval 0.219-0.634) between observer 1 and 2, 0.328 (0.022-0.634) between observer 1 and 3 and 0.625 (0.324-0.926) between observer 2 and 3.

Table 4. Relation between tumor volume (reduction) and ypT

Parameter	ypTo-2 n=24	ypT3-4 n=43	P value [†]
Median pre tumor volume in cm ³ (ID)	55 (32-83)	92 (50-162)	0.038
Median post tumor volume in cm ³ (ID)	5 (0.2-22)	31 (15-63)	< 0.001
Median tumor volume reduction rate in % (ID)	89 (76-100)	61 (36-77)	< 0.001

Note. [†]Mann-Whitney U test; ID, interquartile distance; ypT, post therapy pathological T stage.

Figure 4. Understaging occurred in only one patient, who had only 2 small tumor cell clusters in the mesorectal fat at histopathology. (a,b) Sagittal T2-weighted fast spin-echo MR images (3427/150). (a) Before chemoradiation a very large tumor (T) is seen in the rectum. B = bladder. (b) After chemoradiation this tumor seems to have disappeared. B = bladder. (c) The histopathological slide shows a small tumor cell cluster (arrow) in the mesorectal fat, rendering the tumor a T3 after neoadjuvant treatment (ypT3). Hematoxylin-eosin stain; original magnification, X 2.5.

Volume response to neoadjuvant chemoradiation

The tumor volume significantly decreased from a median of 67 cm³ (range 16-578 cm³) before chemoradiation to a median of 20 cm³ (range 0-198 cm³, $P < 0.001$) after chemoradiation. A median volume reduction rate of 72.8% (range -25%-100%) was found. Significant differences were found between ypT0-2 and ypT3-4 tumors for pre and post chemoradiation volumes and volume reduction rates (Table 4). These differences also applied for the various tumor regression grades (Table 5). All tumors with a pre chemoradiation volume of ≤ 50 cm³ and a volume reduction rate of $\geq 75\%$ were ypT0-2 (PPV 10/24; 42%, NPV 43/43; 100%). When considering these volumetric criteria, 6/14 (42.9%, observer 1), 8/18 (44.4%, observer 2) and 7/17 (41.2%, observer 3) overstaged by morphological T staging could have been predicted as ypT0-2 correctly. All tumors with a volume reduction after chemoradiation of less than 1/3 of their original volume were ypT3-4. The combination of morphological criteria with volumetric criteria (either one or both indicated ypT0-2) reached the best values for the prediction of ypT0-2 (Table 3). Table 6 lists criteria when to assume ypT0-2 on MRI.

Table 5. Relation between tumor volume (reduction) and tumor regression grade

Parameter	TRG 0	TRG 1	TRG 2	P value [‡]
Median pre tumor volume in cm ³ (ID)	162 (58-243)	60 (37-105)	48 (29-87)	0.031
Median post tumor volume in cm ³ (ID)	38 (24-65)	17 (9-36)	0.4 (0.0-10)	0.003
Median tumor volume reduction rate in % (ID)	70 (58-84)	72 (49-87)	99 (89-100)	0.006

Note. [‡]Kruskal-Wallis test; TRG, tumor regression grade according to Rödel; ID, Interquartile distance.

Table 6. Criteria to assume ypT0-2 on MRI

- Normal bowel wall with a 2-layered pattern (Figure 2b).
- Residual tumor but surrounded with a hypointense line corresponding with an intact muscular bowel wall.
- Initial tumor volume of ≤ 50 cm³ (Table 4).
- Volume reduction rate of ≥ 75 cm³ (Table 4).
- Combination of volumetric criteria (initial volume of ≤ 50 cm³ plus a volume reduction rate of ≥ 75 cm³) and the above mentioned morphological criteria (Table 3).

DISCUSSION

Our study investigated the accuracy of post chemoradiation MRI to predict downstaging of tumors to lesions confined to the rectal wall (ypT0-2) using histopathology as reference standard and the additional value of volumetric analysis in LARC patients. In experienced hands, post chemoradiation MRI can reach a high PPV in predicting tumor downsizing to ypT0-2, especially when combining morphological and volumetric criteria. Importantly, high tumor volume reduction correlated significantly with tumors confined to the rectal wall (ypT0-2) and with high regression grades.

Our study focused on the clinically more relevant discrimination between ypT0-2 and ypT3-4, instead of the determination of each T stage separately. Post chemoradiation MRI reached a PPV of 91% for the prediction of the more favorable tumors (ypT0-2) based on morphological criteria alone. A high PPV indicates that when a tumor is predicted as ypT0-2 it is usually true. Apparently, the visualization of an intact hypointense bowel wall on T2-W MR images is highly predictive of a tumor limited to the bowel wall, explaining the high PPV. In many ypT0-2 tumors a normal hypo-intense bowel wall was indeed visualized. However, when this bowel wall appearance cannot be delineated, for example when it has thickened due to radiotherapy, fibrosis is suggested. We chose to stage these tumors as ypT3-4 in order to prevent understaging as that is a safer approach in clinical practice. The interpretation of fibrosis with or without residual tumor remains difficult on MRI, as has also been reported by others^{15-17,27-31}. Because of the presence of fibrosis many ypT2 tumors were overstaged in this study, leading to a lower NPV. It is unclear if more sensitive techniques, such as FDG-PET, may help us in this situation. Although FDG-PET is able to discriminate responders from nonresponders after chemoradiation³²⁻³⁴, it is not able to differentiate between ypT0-2 and ypT3-4 or fibrosis with or without tumor³⁵.

Other publications on MR restaging only described accuracies for overall T staging. However, when we analyzed their results for the subgroup ypT0-2 we also found high PPVs ranging from 83 to 92% for the prediction of ypT0-2^{16,17,36}. Wotherspoon³⁷ reported that MRI could correctly predict the presence or absence of residual disease in 82% with understaging in 4% of the patients. In our study, only 1 patient (1.5%) was understaged. In this patient, in the whole specimen only 2 residual tumor cell clusters in the mesorectal fat were found. The clinical relevance of these cells surrounded by abundant fibrosis, however, remains unclear.

In our study, significant differences between ypT0-2 and ypT3-4 for pre and post chemoradiation volumes and volume reduction rates were found. The combination of a pre chemoradiation volume of $\leq 50 \text{ cm}^3$ and a volume reduction of $\geq 75\%$ was highly predictive for ypT0-2, especially when added to the morphological criteria (PPV = 94%). One could consider treating these tumors less extensively. In tumors with a volume reduction of $< 1/3$ the whole initial tumor area should be resected, with standard TME and when necessary surrounding organs, because all these tumors remained T3-4. However, the volume measurements are always somewhat biased by subjectivity and reproducibility needs to be investigated in future studies. Previous studies on volumetry and staging focused on the discrimination of responders versus nonresponders (instead of ypT0-2 versus ypT3-4) and were controversial^{29,38}. Torkzad et al.³⁹ found a significant correlation between percentage residual tumor volume at second MRI and ypT-stage when the cut-off was set at 44%. However, some T3 tumors also had a residual volume of $< 44\%$ and thus no clinically relevant cut-off could be found, as opposed to our results.

The considerable interobserver variability we observed was mainly due to small patient numbers (reflected by the relatively wide 95% confidence intervals) and related to those cases in which the expert reader was quite sure about the presence of a ypT0-2 (confidence levels 3-4). The less experienced reader was more cautious (more overstaging) in these cases leading to a variability between the readers. This is also reflected by the higher kappa (0.625) between observer 2 and 3 both of whom overstaged more cases.

Our study had some limitations. Although the reference standard was based on the combined analysis of detailed standardized histopathological and surgical reports and MR imaging studies, some inaccuracies might have been introduced due to the retrospective nature of this study. In a retrospective study, research depends on the accuracy of written reports and important data may not be available which may to some extent lead to recall and selection bias. Even so, our study may provide new guiding principles of more individualized treatment strategies based on post chemoradiation MRI findings, in contrast to the current clinical practice in which most surgical treatment decisions are based on the initial MRI findings.

Accurate ypT0-2 prediction alone provides prognostic information, because complete responders, T downstagers and patients with more tumor regression have better overall survival, disease free survival and local control than patients with poor response to chemoradiation⁴⁰⁻⁴⁴. However, in order to select patients for a local transanal excision, accurate prediction of ypT0-2 patients is not enough, as it is also crucial to be able to accurately predict ypN0 patients. The question whether MRI can be accurate in predicting ypN0 nodal status is addressed in the paper by Lahaye et al. (Radiology, in press).

In conclusion, rectal cancer downstaging after chemoradiation to ypT0-2 can be predicted accurately by MRI reaching a high PPV, although at the cost of a lower NPV. One needs to be very careful in case of diffuse fibrosis, because no distinction can be made between fibrosis with or without tumor cell nests, although the prognostic relevance of these nests remains to be determined. Significant differences in pre and post volumes and volume reduction rates were discriminative for ypT0-2 versus ypT3-4. A pre chemoradiation volume of $\leq 50 \text{ cm}^3$ together with a volume reduction rate of $\geq 75\%$ was 100% predictive for ypT0-2. The combination of morphological and volumetric criteria may thus provide an important decision tool for a more individualized surgical approach in locally advanced rectal cancer after neoadjuvant treatment.

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**The accuracy of
Multi-detector row CT
for the assessment
of tumor invasion of the
mesorectal fascia in
primary rectal cancer**

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ABSTRACT

Purpose

To evaluate the accuracy of Multi-detector row CT (MDCT) for the prediction of tumor invasion of the mesorectal fascia (MRF).

Materials and methods

A total of 35 patients with primary rectal cancer underwent preoperative staging magnetic resonance imaging (MRI) and MDCT. The tumor relationship to the MRF, expressed in 3 categories (1-tumor free MRF = tumor distance ≥ 1 mm; 2-threatened = distance < 1 mm; 3-invasion = distance 0 mm) was determined on CT by two observers at patient level and at different anatomical locations. A third expert reader evaluated the MRF tumor relationship on MRI, which served as reference standard. Receiver operating characteristic curves (ROC curves) and areas under these curves (AUC) were calculated. The inter-observer agreement of CT was determined by using linear weighted kappa statistics.

Results

The AUC of CT for MRF invasion was 0.71 for observer 1 and 0.62 for observer 2. The inter-observer agreement was kappa = 0.34. The performance of CT at mid-high rectal levels was statistically significant better compared to low anterior (observer 1: AUC = 0.88 versus 0.50; observer 2: AUC = 0.84 versus 0.31; $P \leq 0.040$).

Conclusion

Multi-detector row CT has a poor accuracy for predicting MRF invasion in low anterior located tumors. The accuracy of CT significantly improves for tumors in the mid-high rectum. There is a high inconsistency among readers.

INTRODUCTION

The prognosis of patients with rectal cancer has improved since the introduction of total mesorectal excision (TME) surgery^{1,3}. Using this surgical technique the mesorectal compartment including the rectum and perirectal fat is completely excised by sharp dissection along the mesorectal fascia (MRF)¹. Additionally, large randomized trials have shown that neo-adjuvant therapy improves local tumor control even further, regardless of optimized surgical techniques^{3,4}. The advances in rectal cancer treatment have provoked differentiated neo-adjuvant treatment strategies based on anatomical preoperative identifiable risk factors for local tumor recurrence as can be visualized with magnetic resonance imaging (MRI)⁵. One of the most important risk factors is the tumor relationship to the MRF, which actually defines the surgical circumferential resection margin (CRM) in TME surgery^{6,7}. Long courses of neo-adjuvant chemoradiation have emerged as the preferential treatment of patients with anticipated tumor invasion of the MRF on MRI in order to downstage/downsize the tumor and to obtain tumor free resection margins⁵.

Magnetic resonance imaging has become an integral part of the diagnostic work-up of patients with rectal cancer due to its proven efficacy to determine the tumor relationship to the MRF^{5,8-11}. However, the moderate availability¹² and the higher cost of MR on one hand, and improved Multi-detector row CT (MDCT) on the other hand, have revived the discussion whether to use CT or MRI for rectal cancer staging. With these state of the art CT technique it has become feasible to visualize the MRF and to perform a quick one stop shop examination of the whole abdomen including distant metastasis. At present, only a few MDCT studies have been published on the subject of rectal cancer staging¹³⁻¹⁷. To our knowledge, two studies focused on the prediction of tumor invasion of the MRF^{13,18}. One study with MDCT suggested results equal to MRI, and the other with conventional CT suggested results inferior to MRI. The question on the accuracy of MDCT remains open.

The application of chemoradiation as the preferred treatment of locally advanced rectal cancer has created a major methodological problem for the evaluation of the staging accuracy of new imaging techniques. Due to the tumor downsizing the traditional gold standard of histology is no longer valid. Subgroup analysis of patients treated with short-courses of 5x5 Gray (Gy) radiotherapy (no downstaging or downsizing effects) or without neo-adjuvant therapy obviously introduces a selection bias of small tumors in which imaging of tumor invasion of the MRF cannot be assessed because there is no invasion. Therefore, the aim of the present study was to evaluate the accuracy of MDCT for the prediction of tumor invasion of the MRF with MRI as reference standard.

MATERIALS AND METHODS

Patients

Institutional approval was obtained for this retrospective study. The records of a cohort of consecutive patients with biopsy proven primary rectal cancer were searched for patients who underwent both MRI and MDCT imaging at the University Hospital Maastricht between June 2004 and June 2006. The standard workup for patients with a rectal cancer includes a pelvic MRI. Some patients received a MDCT because of preoperative planning of radiotherapy. Inclusion criteria were availability of both MRI and contrast enhanced CT examinations of good quality prior to the application of any neo-adjuvant therapy. In total, 35 patients met these inclusion criteria and were enrolled

in the present study. Relevant clinical information such as type of neo-adjuvant therapy, type of operation, radiologic and histologic reports were recorded. There were 23 men and 12 women. The mean age of the patients was 68 years (range 44-85 years). The mean time between the MRI and CT examination was 24 days (range 1-49 days).

Technique

All CT studies were performed on a 16-slice CT system (SOMATOM® Sensation 16, Siemens, Erlangen, Germany). The scan protocol comprised a slice collimation of 16 x 0.75 mm, table feed/rotation: 15.0 mm, rotation time 0.5 s, reconstruction increment 5 mm, 5 mm reconstructed slice thickness. All the patients received 120 ml of nonionic IV contrast agent (Iobitridol 350 mg, Xenetix®, Guerbet, France) at a flow rate of 3 ml/s and oral contrast (Telebrix gastro®, Guerbet, France). The images of the pelvis were obtained in the porto-venous contrast phase (scan delay 60 s). None of the patients received a contrast enema or bowel relaxation.

Magnetic resonance (MR) imaging was performed on a 1.5 Tesla system (Gyrosan, Powertrack 6000 NT, Philips Medical Systems, The Netherlands) using a phased array sense-cardiac coil. The scan protocol consisted of a T2-weighted sequence obtained in three orientations (axial, sagittal and coronal): turbo(fast)spin echo, TR = 3427/TE = 150 msec, echo train length of 25, 4 mm slice thickness, 0.8 mm gap, 6 signal averages, 175x256 matrix, 20 cm FOV. None of the patients received Gadolinium contrast enhanced sequences, fat suppression techniques, rectal contrast enema or bowel relaxation.

Image evaluation

The CT examinations were read by two observers who were blinded to each other and to the clinical and MRI results. Observer 1 (R.V.) was a dedicated abdominal radiologist with over 8 years of experience in reading pelvic CT and MRI. Observer 2 (A.D.G.) was a general radiologist with over 5 years of experience in reading cross sectional imaging. The MRI examinations were assessed by a third observer (R.B.T.) with over 12 years of experience in rectal cancer MRI and who has read over 1500 MRIs of rectal cancer cases.

Observer 1 and 2 assessed the relationship between the rectal tumor and the MRF on the CT images, and the third observer on MRI. The MRF was defined as the fine linear structure surrounding the mesorectal compartment, hypo-intense on T2-weighted MR images and iso-intense to muscle on CT. The relation of the rectal tumor to the MRF was expressed in 3 discrete categories: 1 = tumor free MRF defined as a measured distance between the tumor periphery and the MRF of ≥ 1 mm; 2 = tumor threatened MRF defined as a distance of < 1 mm; 3 = tumor invaded MRF defined as a distance of $= 0$ mm between the tumor and the MRF^{9,11}. All image evaluations and measurements were performed on a viewing station.

Specific anatomical locations of the MRF were individually evaluated for presence of rectal cancer and, if present, the tumor relation to the MRF was assessed according to the previously described criteria 1-3. Anatomical locations were defined as:

- 1 Low anterior (anterior mesorectal quadrant at the level of the prostate and vagina)
- 2 Low lateral left, posterior and lateral right (lateral and posterior mesorectal quadrants at the level of the pelvic floor upto the level of the obturator muscles and low sacrum)
- 3 Mid anterior in males (anterior mesorectal quadrant at the level of the seminal vesicles)
- 4 Mid-high lateral left, posterior and lateral right (lateral and posterior mesorectal quadrants at the level of the obturator muscles up to the piriform muscles and high sacrum)

Statistical analysis

The CT findings at patient level and at the level of different anatomical locations were compared with the corresponding MRI findings, serving as the reference standard. Receiver operating characteristic curves (ROC curves) were constructed and areas under the curves (AUC) were calculated by using the scored categories 1-3. The difference in performance of MDCT for the prediction of MRF invasion for different anatomical locations was analyzed by means of comparison of the corresponding AUC and the calculation of a critical ratio z according to the method of Hanley¹⁹. For this analysis, only anatomical locations with abnormal rectal walls on MRI were included¹⁹. A P value of < 0.05 was considered as statistically significant. Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CT for the prediction of tumor invasion of the MRF was calculated for both observers by dichotomization of the scored discrete categories 1-3 (cutoff between category 1 vs. 2-3). The inter-observer agreement for CT was determined by using linear weighted kappa statistics based on the scored discrete categories 1-3²⁰. Statistical analysis was performed by using the software package SPSS for Windows®, release 11.5 (Chicago, IL, USA).

RESULTS

Reference standard MRI versus clinical results

In total, 15 of 35 patients had locally advanced rectal tumors with tumor invasion of the MRF on MRI. All of these 15 patients were treated with long courses of chemoradiation followed by TME in 3 of 15, APR (abdominal perineal resection) in 2 of 15, pelvic exenteration with or without sphincter preservation in 8 of 15 and no operation in 2 of 15 patients. The remaining 20 of 35 patients had a tumor free MRF on MRI. About 15 of these 20 patients received short course radiotherapy (5 x 5 Gy) followed by TME. Histologic evaluation of the surgical specimen showed in all of these 15 patients a tumor free MRF. The remaining 5 of 20 patients with a predicted tumor free MRF on MRI received long courses of chemoradiation based on adverse prognostic risk factors such as advanced nodal disease and distal location. Three of these 5 patients were treated with TME, 1 of 5 with APR and 1 of 5 received no operation.

Performance of CT at patient level

Staging failures of CT for the prediction of tumor invasion of the MRF occurred in 12/35 (34%) patients for observer 1 and 16/35 (46%) for observer 2 (Table 1). The majority of these failures was based on the overstaging of the tumor relation to the MRF (obs 1: 10/12 = 83%; obs 2: 13/16 = 81%). The area under the ROC curve, accuracy, sensitivity, specificity, PPV and NPV are displayed in Table 2. The inter-observer agreement expressed by the linear weighted kappa was 0.34 (95% CI: 0.04, 0.64).

Table 1. CT versus reference standard MRI for the prediction of the tumor relationship to the MRF at patient level.

	Free MRF	Invaded MRF*
CT observer 1		
Free	10	2
Threatened	2	1
Invaded	8	12
CT observer 2		
Free	7	3
Threatened	2	-
Invaded	11	12
Total	20	15

Note. MRF, mesorectal fascia. *None of the patients had a tumor threatened MRF on MRI. Free MRF, measured distance between tumor and MRF of ≥ 1 mm; Tumor threatened MRF, distance between tumor and MRF of < 1 mm; Invaded MRF, tumor in contact with MRF.

Table 2. Performance of CT for the prediction of tumor invasion of the MRF at patient level.

	Observer 1		Observer 2	
AUC (95% CI)	0.71	(0.54, 0.88)	0.62	(0.43, 0.81)
Accuracy	66%	(23/35)	54%	(19/35)
Sensitivity	87%	(13/15)	80%	(12/15)
Specificity	50%	(10/20)	35%	(7/20)
PPV	57%	(13/23)	48%	(12/25)
NPV	83%	(10/12)	70%	(7/10)

Note. AUC, Area under the receiver operating characteristic curve; (95% CI), 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Analysis of different anatomical locations

The results of CT for the evaluation of tumor invasion at different anatomical locations are shown in Table 3. There was a statistically significant difference between the performance of CT at the mid-high lateral-posterior rectum compared to the low anterior rectum for both observers (observer 1: AUC = 0.88 vs. 0.50, $P = 0.040$; observer 2: AUC = 0.84 versus 0.31, $P = 0.003$). Overstaging occurred in 87% (27/31) of the staging failures of CT for observer 1, 83% (33/40) for observer 2 and were mainly observed at the lower rectum (Figures 1 and 2). CT failed to visualize the rectal tumor at 1 of 4 anatomical locations with tumor invasion of the MRF for observer 1 and 5 of 7 for observer 2 (Figure 3). Additionally, observer 1 predicted in 7 of 120 anatomical locations with a normal rectal wall on MRI tumor invasion of the MRF and in 11 of 120 for observer 2 (Figure 4).

Table 3. Performance of CT for the prediction of tumor invasion of the MRF at different anatomical locations

Locations	MRF invasion		Observer 1	Observer 2
	-	+	AUC (95% CI)	AUC (95% CI)
Low anterior	3	8	0.50 (0.10, 0.90) *	0.31 (0.00, 0.64) *
Low lat-post	32	3	0.78 (0.60, 0.97)	0.58 (0.19, 0.96)
Mid anterior	10	7	0.71 (0.46, 0.97)	0.66 (0.35, 0.97)
Mid-high lat-post	77	8	0.88 (0.73, 1.00) *	0.84 (0.66, 1.00) *
All locations**	122	26	0.82 (0.73, 0.92)	0.70 (0.56, 0.84)

Note. MRF, mesorectal fascia; AUC, area under the ROC curve with 95 % confidence interval; -, number of cases with a tumor free MRF predicted on MRI; +, number of cases with a tumor threatened or invaded MRF; *Statistically significant difference: $P \leq 0.04$; **Locations with normal rectal wall on MRI were excluded from analysis (120/268).

a
Figure 1. Poor anatomical detail on CT leading to overestimation of tumor invasion of the MRF in distal rectal tumors. (a) Axial MS-CT image of distal rectal cancer. The tumor (asterisk) is difficult to delineate and no fat pad can be seen between the tumor and the pelvic floor (arrow) suggesting invasion of the MRF. (b) Axial T2-weighted MR image at the same level shows a tumor free MRF represented by a partial intact muscular rectal wall layer (arrowhead) and a minimal fat pad (white arrow) between the tumor (asterix) and the pelvic floor muscles (black arrows).

b

a
Figure 2. Another example of poor anatomical detail on CT causing overestimation of MRF invasion in difficult anatomical regions. (a) Axial MS-CT image of distal rectal cancer (asterisk) showing tumor invasion of the anterior MRF (arrow) and vagina (v). B, bladder. (b) Axial T2-weighted MR images at the same level shows a tumor free anterior MRF and vagina (v) represented by a well-defined fat pad (arrow) between the tumor (asterisk) and the anterior MRF. B, bladder.

b

a

Figure 3. Difficult visualization of the tumor localization on CT leading to underestimation of tumor invasion of the MRF. (a) Axial MS-CT image. The rectal tumor located in the anterior rectum (asterisk) at the level of the seminal vesicles (v) is difficult to appreciate due to partial collapse of the rectal lumen and suboptimal soft tissue contrast resolution. (b) Axial T2-weighted MR image at the same level illustrates an optimal visualization of the tumor in the rectal wall due high anatomical detail. Also the tumor spread into the anterior MRF (arrows) is well appreciated because of the high soft tissue contrast resolution (V = seminal vesicles).

b

a

Figure 4. Normal rectal wall staged as tumor invasion of the MRF on CT due to insufficient anatomical detail. (a) Axial MS-CT image suggests a thickened rectal wall interpreted as distal tumor (asterisk) contacting the pelvic floor (arrows) and vagina (v). (b) Axial T2-weighted MR image at the same level clearly depicts a normal rectal wall (asterisk) as well as surrounding anatomy (arrows = pelvic floor; v = vagina).

b

DISCUSSION

The present study evaluated the accuracy of MDCT for the prediction of tumor invasion of the MRF with MRI as reference standard. We found a poor accuracy (54-66%), AUC (0.62-0.71) and high inconsistency among observers for the prediction of tumor invasion of the MRF. Evaluation of the staging accuracy of CT at different anatomical locations showed very poor AUCs (0.31-0.50) for low-anterior tumors, but the

performance significantly improved for mid-high lateral-posterior located rectal tumors (AUC: 0.84-0.88; $P \leq 0.04$).

Some studies on the performance of MDCT for staging of rectal cancer have focused on the prediction of T stage (TNM staging classification)¹³⁻¹⁷. Matsuoka et al.¹⁵ found in a study of 21 patients comparing MDCT with MRI an agreement of 95% between MDCT and histology, with no difference between MDCT and MRI. Kulinna et al.¹⁶ reported an accuracy of 86% in a study of 92 patients. The results of Sinha et al.¹⁷ showed an accuracy of 87% for the prediction of T stage in 69 patients. The study of Taylor et al.¹³ addressed the clinically important prediction of the tumor relationship to the MRF and reported a poor agreement between MDCT, MRI and histology (kappa 0.06-0.15) in 42 patients treated with a short course of radiotherapy (5x5 Gy) or surgery only. The NPV of both MRI and CT was good (82% and 85%), but both modalities had a very low PPV (25% and 31%). These results confirm our findings of overstaging with CT, although the overstaging of MRI is rather surprising considering the high accuracy reported in several previous studies⁸⁻¹¹. The adopted wide cutoff (< 5 mm) for the definition of tumor threatening and invasion of the MRF might have been responsible for this substantial overstaging¹¹. Wolberink et al.¹⁸ report in a retrospective study of 125 with and without a short course of radiotherapy on the value of conventional CT in predicting MRF invasion. The area under the curve of the ROC curve ranged between 0.697 and 0.813, and is comparable to the present study. The sensitivity in this study was just below 50% and the majority of false negatives occurred in tumors located in the distal anterior rectum. The present study confirms the difficulty in interpreting these tumors even on MDCT.

Our results showed a general overstaging of the tumor relation to the MRF on CT. The main causes were: a poor localization of the tumor in the rectum, leading to misinterpretation of a thickened wall as tumor and vice versa; inability to detect a (partially) intact muscular rectal wall; and a poor appreciation of a small fat pad between the tumor and the MRF. Despite major progress of image quality with the Multi-detector row technique, its poor soft tissue contrast resolution compared to MRI remains^{21,22}. High anatomical detail is essential for the evaluation of distal tumors as we experienced in the majority of our CT staging failures. Tumor penetration of the distal rectal wall almost directly results in tumor invasion of the MRF due to its close relation²³. This close relation of anatomy restricts the application of rectal inflation by contrast enemas which has been generally used in MDCT studies in order to better appreciate the tumor location¹⁴⁻¹⁶. The inflation of the rectum causes stretching of the perirectal fat plane and reduces the distance to the MRF leading to overestimation of tumor invasion²⁴.

The soft tissue contrast resolution appeared to be far less critical in the mid-upper rectum, reflected by the high AUCs (0.84-0.88) for both observers, significantly better than for low-anterior rectal tumors. The presence of a broad non truncated fat mantle surrounding the rectum at these levels gives sufficient contrast between tumor and MRF.

A major point of concern is the poor inter-observer agreement (kappa = 0.34) of CT despite the use of objective criteria for tumor invasion of the MRF. High consistency among observers with different levels of experience is one of the most important pre-requisites for the general acceptance of a staging technique. The consistent results among observers and repeatedly reported high accuracy for the prediction of MRF invasion has contributed to the general acceptance of MRI as the most appropriate selection tool for neo-adjuvant and surgical therapy^{8,9,25}.

When considering the results of the present study, one must keep in mind that the design has some limitations. We used reconstructed CT slices of 5 mm which were evaluated in the axial plane only. The use of thinner slices might improve the prediction of MRF invasion in difficult anatomical regions, however, this has never been studied. The only reports on this subject have shown improved T staging by multi planar reconstruction (MPR)^{14,17}. The main limitation is related to the use of MRI as the reference standard, rather than histology. As argued in the introduction this has become virtually impossible since patients with a tumor that invades or threatens the MRF are currently treated with long courses of chemoradiation. Studying only patients who are treated with surgery only or a short course of preoperative radiotherapy creates selection bias of non locally advanced rectal cancer, and excludes those patients who are most at risk for involvement of the MRF^{13,16}. Other authors have compared imaging after neo-adjuvant chemoradiation with histology, but this is problematic because of the difficulties in interpreting radiofibrosis, and does not give an answer to the question of the relation of the tumor to the MRF before chemoradiation^{9,26}. MRI is the only modality that has been extensively evaluated for the prediction of tumor invasion of the MRF and several studies have agreed upon its high accuracy^{8-11,25}. Based on the current evidence, we feel that MRI gives the best available representation of the tumor extension to the MRF prior to chemoradiation and therefore could serve as a reference standard.

CONCLUSION

Multi-detector row CT has a poor accuracy for the identification of invasion of the MRF in low-anterior located tumors. The accuracy of CT significantly improves for tumors located in the mid to high rectum. There is a high inconsistency among readers.

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Chapter 3

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**Preoperative
radiochemotherapy
is successful also in patients
with locally advanced rectal
cancer who have intrinsically
high apoptotic tumours**

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ABSTRACT

Background

Not all patients with locally advanced rectal cancer (LARC) respond equally to neo-adjuvant radiochemotherapy (RCT). Patients with highly apoptotic less advanced rectal cancers do not benefit from short term radiotherapy. This study investigates whether this is also the case in the setting of RCT for LARC.

Patients and methods

Tissue microarrays were constructed of biopsy and resection specimens of 201 LARC patients. Apoptosis (M30) and several apoptosis-regulating proteins [p53, Bcl-2, Bax, cyclooxygenase-2 (Cox-2) and mamma serine protease inhibitor (maspin)] were studied with immunohistochemistry. Subsequently, predictive values for local recurrence (LR), overall survival (OS) and histological tumour regression were analysed.

Results

Apoptotic levels, quantified as the number of apoptotic cells/mm² tumour epithelium, were higher in posttherapy tissues compared to biopsies ($P < 0.001$). Biopsies from clinical T4 stage tumours demonstrated significantly higher levels of apoptosis than clinical T3 tumours ($P = 0.020$). Therapy-induced apoptosis was higher when the interval between the last day of irradiation and surgery increased ($P < 0.001$, correlation coefficient = 0.355). Pre- and post-therapy apoptosis, p53, Bcl-2, Bax and Cox-2 were not associated with LR, OS or tumour regression. Intense pretherapy cytoplasmatic staining of maspin indicated a higher risk on LR ($P = 0.009$) only.

Conclusion

Combined RCT is also successful in highly apoptotic tumours and is therefore independent of intrinsic apoptosis.

INTRODUCTION

Patients with locally advanced rectal cancer (LARC) are at high risk of local failure. Therefore, surgery alone is often not curative and neo-adjuvant radiochemotherapy (RCT) is required in order to improve local control and achieve a radical resection. Tumour response to RCT varies considerably and various stages of histological tumour regression can be observed in the surgical resection specimens. Markers that can predict therapy outcome would permit adaptation of the therapeutic strategy and improve treatment of LARC; e.g. poor responders could be offered a different therapy regimen or could be operated much sooner with more extensive surgery.

In order to prevent local recurrences (LRs) and improve local control, patients with mobile rectal cancer (T1-T3) currently receive short term neo-adjuvant radiotherapy (RT) as standardised treatment for rectal cancer in the Netherlands. However, not all patients benefit equally; some might experience side-effects¹. Therefore, we would like to predict tumour response. De Bruin et al.² showed that levels of apoptosis (assessed with M30) can attribute to the selection of patients with a high risk on local failure, since RT was effective in patients with low levels of intrinsic apoptosis, but patients who had high levels of intrinsic apoptosis in their primary tumour and did not receive RT had the same risk on developing a LR, as patients that did receive RT. It is, however, unclear what the prognostic implications of intrinsic and therapy-induced apoptosis are in patients with LARC in the neo-adjuvant setting.

RT and chemotherapy can both induce apoptosis in malignancies of the gastrointestinal tract. However, the complexity of the apoptotic pathway enables tumour cells to escape from apoptosis inducing therapy resistance and affecting patient's outcome. At the cellular level, the regulation of apoptosis depends on a very complex balance between pro- and anti-apoptotic proteins. Among them are p53, Bcl-2, Bax, cyclooxygenase-2 (Cox-2) and mamma serine protease inhibitor (maspin). The extensively described oncogene p53 is commonly inactivated in colorectal cancer and is a cell cycle regulator and a potent inducer of apoptosis as a response to DNA damage³⁻⁵. Bcl-2 and Bax act as antagonists and are members of the same family of proteins. While Bcl-2 is an important inhibitor of apoptosis, over- expression of Bax induces programmed cell death^{6,7}. During irradiation, Cox-2 has been described to act as a survival factor by inhibiting apoptosis⁸. Maspin is a multifaceted protein that has been described to promote apoptosis⁹.

In the present study, we evaluated the prognostic value of intrinsic and induced apoptosis (M30) and five different apoptosis-regulating proteins: p53, Bcl-2, Bax, Cox-2 and maspin in patients with LARC who were treated with RCT. LR and overall survival (OS) were the main outcome parameters. In addition, the association between these markers and histological tumour regression was investigated.

PATIENTS AND METHODS

Patient selection

The patient population consisted of a consecutive series of 201 LARC patients with biopsy-proven adenocarcinoma as described previously¹⁰. All patients received multimodality treatment at the Catharina hospital between 1994 to 2005¹¹. Treatment decision was based on the best regimen according to the national guidelines of that moment in time.

Histological assessment of therapy-induced tumour regression

Histological therapy-induced tumour regression was assessed according to the regression grading system described by Rödel et al.¹². The degree of tumour was estimated and subdivided into the following categories: (i) no regression or < 25% of tumour mass, (ii) 25% to >50% tumour regression, (iii) complete regression. The degree of tumour regression was determined semiquantitatively by an experienced pathologist (JHJMvK) who was unfamiliar with patients' clinical outcome. The investigations of the clinical value of therapy-induced tumour regression assessment in this patient population have been extensively described in a previous study¹⁰.

Tissue microarray construction

Tissue microarrays (TMA) were constructed from formalin-fixed, paraffin-embedded biopsy tissues (three 0.6-mm punches) and resection specimens (three 2-mm punches) using an Alphelys TMA booster (Westburg, Leusden, the Netherlands). Three punches have been previously described to be sufficient to overcome tumour heterogeneity¹³. Moreover, most studies validating the use of TMA for studying markers with immunohistochemistry (IHC) advise to use three to four punches of 0.6 mm¹⁴⁻¹⁶. We used an equivalent of 10 tumour punches of 0.6 mm which is well above the advised number of 0.6 mm punches. In case normal tissue was available, one punch was also taken from this area in order to construct a TMA containing normal tissues only. Preferably, normal tissue adjacent to the tumour tissue was used (55%). If this was not present, normal tissue was obtained from another paraffin block (45%).

Table 1. Immunohistochemical specifications of the antibodies used

Antibody (company)	Clone	Dilution	Antigen retrieval	IHC assessment
M30 CytoDEATH (Roche, Indianapolis, IN)	M30 specific for human cytokeratine 18	1:500	Incubation with a 10mM sodium citrate buffer (pH 6.0) for 30 min at 98°C	Number of apoptotic cells/mm ² tumour epithelial was quantified
P53 (BioGenex, San Ramon, CA)	BP53-12	1:10,000		Intensity of nuclear staining (0-3) and the proportion of negative cells: 10-30%, 30-60% or 60-90% ^a
Bcl-2 Oncoprotein (Dako, Glostrup, Denmark)		1:500		Intensity of cytoplasmic staining (0-3) ^a
Bax (Santa Cruz Biotechnology, Santa Cruz, CA)	B-9	1:1000		Intensity of cytoplasmic staining (0-3) ^a
Cox-2 (Cayman Chemicals, Ann Arbor, MI)	CX229	1:100		Combination of intensity and proportion of cytoplasmic staining ^{a 17,18}
Maspin (Becton Dickinson Pharmingen, Franklin Lakes, NJ)	G167-70	1:20,000		Intensity of cytoplasmic and nuclear staining (0-3) ^a

Note. ^astaining patterns were assessed by two independent observers. IHC, immunohistochemistry; Cox-2, cyclooxygenase; Maspin, mamma serine protease inhibitor.

Immunohistochemistry

Immunohistochemical stainings were performed on 4-µm TMA sections using the PowerVision plus method (ImmunoVision, Brisbane, Ca). Visualisation involved incubation with PowerDAB (ImmunoVision) for 5 min. Methods of antigen retrieval and the dilutions of the antibodies used can be found in Table 1. Slides were incubated in a humidity chamber with the primary antibody for 20 h (overnight) at 4 °C. Negative

controls involved incubation with phosphate-buffered saline with 2% goat serum and 0.1% sodium azide only. Slides were counterstained with haematoxylin. Staining patterns of p53, Bcl-2, Bax, Cox-2 and maspin were all evaluated semiquantitatively (Table 1) by two independent observers who were unfamiliar with patients' outcome. In case of disagreement, a consensus score was obtained which was used for further analysis.

Quantification of apoptosis

In case of M30 IHC, the number of apoptotic tumour cells/mm² tumour epithelium was assessed for each punch. In order to establish the area of tumour epithelium for each punch, TMA were stained with the pancytokeratin MAK-6 (1:10, protease antigen retrieval, Zymed Laboratories, Invitrogen, Carlsbad, CA). Microscopic images measuring 0.74 mm² were digitised using an RGB CCD camera (AxioCam MRc, Zeiss, Germany), resulting in a specimen level pixel size of 1.3 x 1.3 µm². Quantitative measurements of the tumour area or area of normal epithelium were performed using a digital image analysis system (KS400, Carl Zeiss, Germany). Punches of 0.6 mm diameter were analysed using a 10x objective and 2 mm punches using an objective of x2.5. Digitised images were corrected for unequal illumination using a stored image of an empty microscopic field. The immunopositive area (in mm²) was calculated automatically. Subsequently, the number of apoptotic cells was manually counted to calculate the apoptotic level defined as the number of apoptotic cells/mm² tumour epithelium. Values that exceeded the standard deviation two times were considered outliers and were therefore excluded from further analysis.

Statistics

Data were analyzed with the SPSS package (Statistical Product and Service Solutions 11.0 for Windows, SPSS Inc., Chicago, IL). Interobserver variability was calculated by κ statistic as described by Cohen^{19,20}. κ-values of 0.2-0.4 indicate 'fair', 0.4-0.6 'moderate', and values of >0.6 'excellent' agreements²¹. Correlations between apoptosis and the interval between the last day of irradiation and surgery were analysed according to the Spearman's rank correlation test. Univariate survival analyses of time to death or LR were performed using the Kaplan-Meier method and log-rank testing with the time of surgery as the entry date. Patient outcome parameters were (LR), and OS. P values of ≤ 0.05 were considered as statistically significant.

Multiple variable analyses involved Cox proportional hazards regression (enter method), logistic regression (enter method) and building of decision trees using the DTREG software for predictive modeling and forecasting (www.dtreg.com). Single-tree models for classification using the Gini splitting algorithm in which the variables were equally weighted were constructed. Pruning and validation of the tree model was performed with the V-Fold cross validation in order to determine the statistically optimal tree size.

RESULTS

Patient and tumour characteristics

Patient, treatment and tumour characteristics are summarised in Table 2. The majority (59%) of the patient population initially presented with a tumour invading into other adjacent organs or structures [clinical T4 stage (cT4)]. Complete histological tumour regression was observed in 21 (11%) patients. Poor (Rödel 0) and moderate (Rödel 1) tumour regression grades were observed in 50% and 39% patients, respectively.

Table 2. Patient, treatment and tumour characteristics

Factor	Category	n	(%)
Median age (range)		63	(35-86)
Sex	Male	122	(61)
	Female	79	(39)
cT stage	cT3	83	(41)
	cT4	118	(59)
Neo-adjuvant therapy	RT	74	(37)
	RCT interrupted	102	(51)
	RCT continuous	25	(12)
Median interval between last day RT and surgery		7.8	weeks
CRM	Positive	43	(21)
	Negative	158	(79)
ypT stage	ypT0	20	(10)
	ypT1s	1	(0.5)
	ypT1	2	(1)
	ypT2	15	(7)
	ypT3	132	(66)
	ypT4	30	(15)
	not assessable	1	(0.5)
ypN-stage	No	131	(65)
	N1	47	(24)
	N2	23	(11)
Histologic regression	0	101	(50)
	1	79	(39)
	2	21	(11)
Pretreatment apoptosis (mean of cells)		0	
Post treatment apoptosis (mean of cells)		10.39	

Note. Values in parentheses are percentages, unless otherwise specified. cT3, clinical T3 stage; cT4, clinical T4 stage; RT, radiotherapy; RCT, radiochemotherapy; CRM, circumferential resection margin.

Apoptosis; prognostic significance and correlations with clinicopathological factors

Representative staining patterns observed after M30 IHC are depicted in Figure 1A. The apoptotic levels in neither the posttherapy resection specimens nor the pre-treatment biopsies were associated with LR or OS. The amount of apoptotic cells was significantly higher in posttreatment resection specimens compared to pre-treatment biopsies (median 10.4 versus 0, $P < 0.001$, Wilcoxon test). M30 IHC was also carried out on TMA-containing normal tissues. This revealed that the amount of apoptosis in normal epithelium was significantly lower in patients who received the capecitabine containing continuous schedule (7.2 apoptotic cells/mm² epithelium) compared to patients who received the interrupted RCT (15.3 apoptotic cells/mm² epithelium) schedule ($P = 0.018$). Apoptotic levels did not differ between normal tissues obtained adjacent to the tumour from another paraffin block ($P = 0.163$). The amount of apoptotic tumour cells did not significantly differ between the different therapy regimens (Table 3).

Figure 1. Examples of immuno-histochemical staining patterns observed after staining with (A) M30 CytoDEATH, (B) p53, (C) Bcl-2, (D) Bax, (E) cyclooxygenase-2 and (F) mammary serine protease inhibitor. The arrows in panel (A) depict examples of apoptotic tumour cells that demonstrate intense staining with the M30 antibody. Original magnifications (A): 400x, (B)-(F): 200x.

Table 3. Correlation between apoptosis and clinicopathological factors

Factor	Category	Pre-treatment apoptosis (median/mean)	P	Post-treatment apoptosis (median/mean)	P
cT stage	cT3	0/5.89	0.020 ^a	11.37/21.12	0.57 ^a
	cT4	3.65/11.71		9.78/17.95	
Neo-adjuvant therapy	RT	0/9.51	0.12 ^b	11.45/19.23	0.97 ^b
	RCT interrupted	2.47/9.43		9.68/20.11	
	RCT continuous	6.03/2.47		10.71/18.08	
Interval between last day RT and surgery		P=0.34 ^c , cc= 0.084		P=0.001 ^c , cc=0.328	
ypT stage	ypT0, ypTis, ypT1, pT2	0/8.40	0.93 ^a	9.28/21.39	0.75 ^a
	ypT3, ypT4	0/9.52		10.39/18.84	
ypN stage	No	0/9.45	0.23 ^b	9.48/19.91	0.87 ^b
	N1	3.32/10.62		17.14/18.79	
	N2	0/5.56		11.45/16.33	
CRM	Positive	0/9.34	0.96	11.45/18.47	0.811 ^b
	Negative	0/9.28		9.48/19.50	
Histologic regression	0	0/8.94	0.041 ^b	12.40/22.11	0.003 ^a
	1	5.42/10.80		3.94/10.68	
	2	1.24/5.94		n.a.	

Note. ^aMann-Whitney U test; ^bKruskal Wallis test; ^cPearson correlation. P, P value; cT3, clinical T3 stage; cT4, clinical T4 stage; RT, radiotherapy; RCT, radiochemotherapy; CRM, circumferential resection margin; cc, correlation coefficient; n.a., not assessed.

Associations between apoptosis and the different clinicopathological factors can be found in Table 3. Tumours with a cT4 were found to have higher levels of intrinsic apoptosis than clinical T3 stage tumours (P= 0.020). In addition, M30 IHC revealed that a longer interval between last day of RT and surgery resulted in an increased number of apoptotic cells (P=0.001, Pearson correlation coefficient = 0.328), indicating a large

effect of this parameter on the posttreatment apoptosis. Apoptotic levels were found to be significantly higher in resection specimens with limited tumour regression (Rödel 0) than in specimens with 25% to >50% tumour regression (Rödel 0, $P=0.003$). Intrinsic apoptosis was not predictive for histological tumour regression since comparable levels of apoptosis were observed in patients with a poor and complete response (no residual tumour cells) (Table 3).

p53, Bcl-2, Bax, Cox-2 and maspin; prognostic significance

Representative staining patterns after staining for p53, Bcl-2, Bax, Cox-2 and maspin are depicted in panel B, C, D, E and F respectively, of Figure 1. As indicated in Table 1, IHC staining patterns for p53, Bcl-2, Bax, Cox-2 and maspin were assessed by two independent observers. In the case of the resection specimens, the calculated mean κ values of the three tumours containing punches were found to be 0.61, 0.79, 0.79, 0.71 and 0.78, respectively, of p53, Bcl-2, Bax, Cox-2 and maspin. For pretreatment biopsies these values were respectively 0.71, 0.85, 0.85, 0.58 and 0.86. These κ values mainly indicate excellent degrees of agreement. Negative IHC controls showed no staining.

Staining patterns and intensities of p53, Bcl-2, Bax, Cox-2 and maspin that were assessed in the biopsies and resection specimens did not correlate with histological tumour regression. Pre- and posttherapy levels of p53, Bcl-2, Bax and Cox-2 did not influence LR or OS rates. Stratification for the different treatment regimens resulted in similar findings

A strong cytoplasmic staining of maspin in the biopsy tissues was associated with a higher risk on developing a LR (Figure 2). This association, however, was not observed after separate analysis of each treatment regimen.

Figure 2. Kaplan-Meier curves depicting the correlation between cytoplasmic staining patterns of maspin in the pre-therapy biopsies and local recurrence.

Multiple variable analysis for prediction of patients' prognosis and therapy response

Investigation on the associations between apoptosis-regulating proteins and apoptotic levels showed that increased nuclear staining of maspin in tumour biopsies were associated with increased levels of apoptosis in biopsy specimens ($P=0.019$). Increased Cox-2 staining intensities in the resection specimens were significantly associated with increased levels of apoptosis ($P=0.028$). This, however, is not in consistency with the anti-apoptotic effect of Cox-2 that has been described in literature^{8,17}.

Cox proportional hazards regression indicated that different combinations of apoptosis and the different apoptosis-regulating proteins were not predictive for LR or OS. In order to study whether combinations of apoptosis and the different apoptosis-regulating proteins are predictive for tumour regression, logistic regression was carried out and decision tree models were built. In the case of both logistic regression analysis and the CART analysis histological tumour regression was dichotomised in two different ways; Rödel 0 and 1 versus Rödel 2 and Rödel 0 versus Rödel 1 and 2. This analysis revealed that none of the variables or variable combinations was predictive for tumour regression.

DISCUSSION

Pretherapy (intrinsic) or posttherapy (induced) levels of apoptosis, p53, Bcl-2, Bax and Cox-2 in tumour cells were not found to be associated with LR or OS in patients with LARC. Maspin was found to be correlated to LR only (Figure 2). These data implicate that success of neo-adjuvant RCT is independent of these factors. In addition, we found that apoptosis of tumour cells was not predictive for the degree of tumour response in these patients.

De Bruin et al.² also studied the prognostic value of apoptosis in TMA with M30 IHC which is similar to our study design. In concordance with that study we also found that the posttherapy apoptotic levels did not influence patients' prognosis. However, the study reported by Bruin et al was a randomised trial in which the surgery-only arm acted as a control, while we did have access to pretreatment biopsies. Tannapfel et al.²² investigated intrinsic- and therapy-induced levels of apoptosis in LARC patients who received RCT and also did not find a correlation between apoptosis and LR, OS or tumour regression after RCT which is consistent with our findings. Other studies, however, found that intrinsic levels of apoptosis were related to the degree of tumour regression and patients' outcome^{23,24} after long-term neo-adjuvant RCT. These differences in literature indicate that the prognostic implications of apoptosis in patients with rectal cancer are not established and need further research in order to determine the clinical usefulness (reviewed in²⁵). Since RT is the main therapy used in the present population, it would also be interesting to study the clinical consequences of apoptosis in the setting of systemic treatment with chemotherapy (CT).

Our finding that apoptotic levels were significantly increased in the surgical resection specimens is in consistency with other reports^{22,26}. On the basis of apoptosis-inducing potential of RT and CT, this was not an unexpected finding. Analysis of apoptotic levels in normal epithelial cells yielded the surprising result that the number of apoptotic cells significantly decreased in case of the continuous RCT schedule in comparison to the interrupted RCT schedule. This might be explained by the use of capecitabine in the continuous schedule which is, in contrast to 5-fluorouracil (5-FU), converted into the active metabolite in cells with a higher metabolism delivering the 5-FU predominately to the tumour cells^{27,28}. Another interesting finding was that when the interval between the last day of irradiation and surgery was longer, the post-therapy apoptotic levels increased. It is tempting to speculate that this observation could partially explain the positive effect of a prolonged interval between RCT and surgery as indicated by a French trial²⁹. Several studies have shown that long course RT with concurrent 5-FU based CT contributed to tumour downstaging and increased local control^{30,31}. However, the optimal doses of RT and CT of this multimodality therapy and the type of 5-FU administration and combination with other cytotoxic agents can still be improved.

Our study design has several limitations. First, investigations on posttherapy resection specimens have the general limitation that no tumour can be assessed after a complete response, especially after neo-adjuvant RCT. An added problem of TMA evaluation is that after a high degree of tumour regression tumour sampling can be problematic. This can obscure the evaluation of the IHC staining patterns in the posttherapy specimens. Secondly, the complex interactions between the different apoptosis regulating proteins interfere with the analysis of each individual marker. We, however, tried to overcome this problem by adding a multiple variable statistical approach. Numerous reports studying the predictive and prognostic role of apoptosis controlling proteins can be found. The clinical implications of these markers, however, remain elusive due to conflicting data. Our data show that the regulating proteins did not have prognostic implications and, more importantly, the downstream effect of these markers (i.e. apoptosis of tumour cells) was also clinically irrelevant. This indicates that the discussion about the individual contributions of the regulation proteins is less relevant. Finally, evaluation of apoptosis with the M30 CytoDEATH antibody detects only apoptotic events in tumour cells or normal epithelial cells³²; caspase-independent apoptosis, mitotic catastrophe and apoptosis of stroma cells are not detected. Other reports, for example used the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphatase biotin nick-end-labelling method^{12,33,34} or measured caspase activity^{35,36}. Evaluation of caspase-3 activity, measuring caspase dependent apoptosis in tumour and stroma cells, in patients with rectal cancer indicated that low caspase activity in biopsies decreased the risk on LR³⁵. These findings could indicate that apoptosis in stroma cells could be of substantial importance as previously described by others³⁷. Fresh frozen tissues, however, are required for these assays which were unfortunately not available in the present patient population.

In the present study we investigated the effect of apoptosis and five apoptosis-regulating proteins on prognosis and tumour regression in patients with LARC. We studied the effect of apoptosis in patients with LARC by quantifying M30-positive tumour cells and semiquantitatively analysing p53, Bcl-2, Bax, Cox-2 and maspin. Subsequently we analysed these data in both pre- and posttherapy tumour and normal tissues in a multiple variable fashion in a well-characterised population of 201 patients with LARC. The data show that apoptosis of tumour cells does not predict local control or tumour regression in LARC patients. This indicates that, in contrary to short-term RT, the success of long-term RCT does not depend on this parameter since RCT is also effective in tumours with high intrinsic levels of apoptosis. This could suggest that the multimodality RCT regimen can adequately manage heterogeneity with respect to intrinsic levels of apoptosis.

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Chapter 4

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**Local recurrence in
rectal cancer
can be predicted by
histopathological factors**

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ABSTRACT

Aim

The main cause of local recurrence (LR) in rectal cancer is involvement of the circumferential resection margin (CRM). However, patients with a negative CRM can also develop LR, suggesting that additional factors are important for LR. The aim of this study was to identify histopathological factors predictive for the development of LR after primary rectal cancer treatment.

Methods

Patients treated for locally recurrent rectal cancer at the Catharina hospital from 1994 to 2006 (n=92) were matched with a control group of patients who did not develop LR after primary rectal cancer treatment for at least 2 years (n=185) based on type of neoadjuvant treatment in a 1:2 ratio. The pathology of all primary rectal cancers was reviewed. Patient, treatment and histopathological characteristics were studied in relation to the development of LR with logistic regression and Cox regression analysis.

Results

Logistic regression indicated the presence of lymphovascular invasion (LVI, OR 4.66, $P<0.001$), extramural venous invasion (EMVI, OR 4.54, $P<0.001$), positive CRM (OR 2.56, $P=0.032$), serosal involvement (OR 6.74, $P=0.035$) and poor differentiation (OR 2.59, $P=0.012$) as factors with an increased risk to develop LR. Older age was a protective factor (OR 0.95, CI 0.93-0.98, $P=0.001$).

Conclusion

Apart from a positive CRM and serosal involvement, LVI, EMVI and poor differentiation are important independent predictive factors for the development of LR. Adjuvant therapy may be considered in the presence of these features in order to decrease the risk of a local recurrence.

INTRODUCTION

Patients with rectal cancer have a rather poor prognosis with a relative 5 year survival rate of 50-60%. Survival rate is mainly affected by local and/ or distant recurrences. The main causes of local recurrence (LR) after primary rectal cancer treatment are a positive circumferential resection margin (CRM)^{1,3} and positive lymph nodes⁴. Fortunately, due to the introduction of total mesorectal excision (TME), in which the rectum plus the surrounding mesorectal fat with the mesorectal lymph nodes are removed in total, the amount of resections with a positive CRM (and as a consequence the LR rate) has decreased significantly⁵. The LR rate has decreased even further due to the use of adequate neoadjuvant treatment⁶. However, even after these improvements in treatment, LRs still develop. Since treatment of rectal cancer has markedly improved, these LRs might reflect biological tumour aggressiveness rather than treatment failure. Indeed, several histopathological factors that reflect biological aggressiveness such as local extent of tumor growth (pT classification), differentiation grade and vessel invasion have been associated with local recurrence after colon or colorectal cancer treatment⁷. Only a few studies reported on rectal cancer alone. However, literature is inconsistent⁸⁻¹⁰ and not all factors with a proven influence on prognosis have been implemented in the standard histopathology reports^{7,11}.

Local recurrences are a major cause of cancer-related morbidity and mortality. In order to increase quality of life and survival, these recurrences need to be prevented. As such, patients with a high risk on LR need to be identified. Histopathological examination of the resection specimen can provide this identification and is crucial for prognostication and determination of adjuvant therapy or more intensive follow-up. Up till now, adjuvant treatment has mostly been administered in rectal cancer patients with positive lymph nodes or with an insufficient number of lymph nodes in the resection specimen. However, adjuvant treatment may also be needed in patients with a high risk on LR due to other factors in order to improve prognosis.

The present study investigated the predictive value of several histopathological factors for the development of LR after primary rectal cancer treatment by comparing patients who developed LR with patients who did not.

MATERIALS AND METHODS

Patients

In this study, primary resection specimens of patients who developed LR after primary rectal cancer treatment (cases) were compared with those of patients who did not develop LR after primary rectal cancer treatment for at least 2 years (controls). The cases consisted of patients, without metastases, treated with curative intent for locally recurrent rectal cancer at the Catharina hospital since 1994¹². The Catharina hospital is a national referral centre for the treatment of patients with locally advanced and locally recurrent rectal cancer and thus a relatively large group of non-metastasized patients with potentially curable locally recurrent rectal cancer was available for analysis¹³. Those patients who underwent surgery with curative intent for their primary rectal cancer and who had available histopathological slides and histopathology reports of the primary rectal resection specimen were included in this study (92 out of 147). The case-control matching was done in a 1:2 ratio based on neoadjuvant treatment schemes (either no neoadjuvant treatment or a short course of radiotherapy of 5x5 Gray (Gy) or a long course of radio(chemo)therapy of 50.4 Gy).

Table 1. Patient, treatment and histopathological factors in recurrent versus control group

	Recurrent (n=92)		Control (n=185)	
Sex				
Male	51	(55.4)	112	(64.9)
Female	41	(44.6)	65	(35.1)
Median age (range)	60	(33-85)	65	(36-89)
Neoadjuvant therapy				
None	44	(47.8)	85	(45.9)
Short course	22	(23.9)	44	(23.8)
Long course	26	(28.3)	56	(30.3)
Surgery				
LAR	71	(77.2)	113	(61.1)
APR	21	(22.8)	72	(38.9)
TNM stage (UICC 5)				
I	12	(13.0)	59	(31.9)
II	52	(56.5)	78	(42.2)
III	28	(30.5)	48	(25.9)
T classification				
1	1	(1.1)	13	(7.0)
2	16	(17.4)	56	(30.3)
3	62	(67.4)	108	(58.4)
4	13	(14.1)	8	(4.3)
N classification				
No	64	(69.6)	137	(74.1)
N+	28	(30.4)	48	(25.9)
Tumor type				
Adenocarcinoma	65	(70.7)	147	(79.5)
Mucinous component	17	(18.5)	23	(12.4)
Mucinous	10	(10.8)	15	(8.1)
Differentiation				
Well/ Moderate	70	(76.1)	160	(86.5)
Poor	22	(23.9)	25	(13.3)
Growth pattern*				
Circumscribed	53	(80.3)	105	(81.4)
Diffuse	13	(19.7)	24	(18.6)
Perineural Invasion	9	(9.8)	11	(5.9)
LVI	37	(40.2)	21	(11.4)
EMVI	38	(41.3)	24	(13.0)
IMVI	13	(14.1)	15	(8.1)
Tumor budding	23	(25.0)	34	(18.4)
CRM				
Negative	77	(83.7)	171	(92.4)
Positive	15	(16.3)	14	(7.6)
Serosa				
Negative	83	(90.2)	183	(98.9)
Positive	9	(9.8)	2	(1.1)

Note. Values in parentheses are percentages unless otherwise specified. LAR, low anterior resection; APR, abdominoperineal resection; LVI, lymphovascular invasion; EMVI, extramural venous invasion; IMVI, intramural venous invasion; CRM, circumferential resection margin. *not assessed in patients who received long course neoadjuvant therapy.

Control patients were retrieved from two different patient populations in the same time period as the cases. Those who received no or 5x5 Gy neoadjuvant therapy were used from the Dutch TME trial, a large multicenter trial comparing patients with or without neoadjuvant radiotherapy before standardized TME surgery¹⁴. Those who received 50.4 Gy as neoadjuvant treatment were used from a population of patients with locally advanced rectal cancer (LARC) referred to and treated at the Catharina hospital since 1994¹⁵. From both populations, consecutive patients were included until a 1:2 case-control ratio was achieved (Table 1). Approval of this study was given by the institutional review committee and informed consent was obtained.

Neoadjuvant treatment

Neoadjuvant treatment was administered according to the national guidelines at that time or according to randomization in the Dutch TME trial¹⁴. Patients with primarily resectable cancer received either no neoadjuvant therapy or a short course of 5x5 Gy in one week. Patients with LARC were treated preoperatively with a long course of radio(chemo)therapy. Radiotherapy consisted of 50.4 Gy, 5 times a week in 28 fractions of 1.8 Gy. In 40% of the patients, the radiotherapy was combined with chemotherapy consisting 5-FU (350mg/m²) plus leucovorin (20mg/m²) in week 1 and 5 or capecitabine (2x825mg/m²/day) plus oxaliplatin (50mg/m²/week).

Surgery

All patients underwent surgery with curative intent either immediately (without neoadjuvant therapy), or one week after 5x5 Gy or 6-8 weeks after long course radio(chemo)therapy. TME trial patients underwent the standardized surgery according to the TME principle with excision of both the rectum and the surrounding mesorectal envelope along the mesorectal fascia¹⁴. In earlier patients the significance of the mesorectal fascia may not have been recognized and they underwent a more classical resection of the rectal tumour. LARC patients underwent either TME or a more extensive resection, depending on the extent of tumour growth. As cases and control patients were retrieved from the same time period, no difference in surgical techniques was found between the two groups.

Histopathology

The primary rectal cancer resection specimens were evaluated according to the protocol of Quirke and Dixon¹⁶. The following histopathological factors were assessed: invasion depth (T classification), nodal status (N classification), circumferential resection margin (CRM) status, tumour type, tumour differentiation, growth pattern, tumour budding and involvement of the serosa, neural tissue, lymphatic vessels, intramural and extramural veins. Serosal involvement could be present when the tumour was located in the higher part of the rectum (between sacral promontory and cavum douglasi), which is partially covered by serosa. The assessment was performed on haematoxylin and eosin stained slides of the primary rectal cancer specimen by two observers in consensus reading. In case of difficulty or disagreement an expert gastrointestinal pathologist was consulted. The observers were blinded to patients' outcome. T classification and N classification were assessed according to UICC 1997 (TNM 5). Classification of tumours was performed using the WHO guidelines; a tumour was scored as adenocarcinoma, adenocarcinoma with a mucinous component (mucinous component <50%) or mucinous carcinoma (mucinous component ≥50%). Tumour differentiation was scored as well/ moderately versus poorly differentiated based on the area with the least differentiated part of the tumour (not the invasive front). Growth patterns were assessed as circumscribed or infiltrating. However, in patients who

received 50.4 Gy this factor was not assessed, because tumour regression interferes with growth pattern. Lymphovascular invasion (LVI) was defined as tumour within an endothelial lined space either in the bowel wall or in the mesorectal fat. Venous invasion was defined as tumour within a space lined by endothelial cells and smooth muscle or elastic fibres and scored as either intramural (IMVI) or extramural (EMVI). In addition, an adjacent arterial structure had to be present. Tumour budding was considered to be present when small tumour cell clusters of fewer than 5 undifferentiated tumour cells were seen at the invasive front.

Statistical analysis

To compare proportions between the recurrent group and the control group Chi-Square and Fisher Exact tests were performed. To predict the development of LR by histopathological, patient (age, sex) and treatment (type of surgery) related variables logistic regression analysis was performed. Both enter method and forward step (variable entered if $P < 0.05$) method analyses were used. The results were adjusted for the matching based on type of neoadjuvant treatment. After creation of the multivariate model the predicted probabilities were saved. With these probabilities a receiver operating characteristic (ROC) curve was constructed in order to assess the accuracy of the model for the prediction of the development of a local recurrence.

In the recurrent group, local recurrence free interval (LRFI) was calculated from the primary resection date until the local recurrence resection date. Local control (LC) curves were constructed using the Kaplan-Meier method. Cox proportional hazard regression was performed to correlate the histopathological, patient and treatment related factors with LC in a multivariate manner. A P value of ≤ 0.05 (two-sided) was considered as statistically significant. Statistical analyses were performed using the SPSS statistical software program (SPSS® for Windows Release 15.0, SPSS Inc, Chicago, IL, USA).

RESULTS

Patient and treatment characteristics

In total, 277 patients (163 men, 104 women) were included in this study. Median age was 62 years (range 33-89). Patients received either no neoadjuvant radiotherapy ($n=129$), 5x5 Gy ($n=66$) or a long course of 50.4 Gy ($n=82$). This was followed by a low anterior resection (LAR) in 184 patients or an abdominoperineal resection (APR) in 93 patients. After surgery, 29 patients had a positive CRM. Ninety-two patients developed LR after primary treatment. Median interval between primary and recurrence surgery was 27.5 months (range 3-156). Patient and treatment characteristics categorized according to the recurrent and control group are listed in Table 1. Median follow-up was 58 months (range 13-289) for the recurrent group and 66 months (range 24-200) for the control group.

Histopathological factors in recurrent versus control group (Table 1)

In patients who developed LR after primary rectal cancer treatment, a positive CRM was found in 16.3% versus 7.6% in the control group ($P=0.036$). Furthermore, serosal involvement was present in 9.8% versus 1.1% in the control patients ($P=0.001$). Patients who developed LR, underwent a low anterior resection more often (77.2 vs. 61.1%, $P=0.010$) and had more tumours with a poor differentiation (23.9 vs. 13.3%, $P=0.041$) than control patients. Additionally, LVI and EMVI were found more often in the recurrent group than in the control group (40.2% versus 11.4% and 41.3% versus 13.0% respectively, both $P < 0.001$).

Table 2. Logistic regression analysis for the whole population (n=277) of patient, treatment and tumor related factors predictive for a local recurrence

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Sex						
Male	1.00			1.00		
Female	1.49	0.90-2.49	0.124	1.53	0.80-2.94	0.204
Age	0.96	0.93-0.98	0.001	0.94	0.91-0.97	<0.001
Type of surgery						
LAR	1.00			1.00		
APR	0.46	0.26-0.82	0.009	0.65	0.32-1.35	0.252
T classification						
1	1.00			1.00		
2	4.02	0.49-33.1	0.195	1.17	0.13-10.6	0.886
3	8.44	1.07-66.7	0.043	2.19	0.25-18.9	0.475
4	25.0	2.67-234	0.005	4.46	0.34-59.3	0.257
N classification						
No	1.00			1.00		
N+	1.22	0.70-2.11	0.490	0.43	0.20-0.93	0.032
Tumor type						
Adenocarcinoma	1.00			1.00		
Mucinous component	1.67	0.84-3.35	0.145	3.00	1.26-7.11	0.013
Mucinous	1.56	0.66-3.70	0.313	1.91	0.51-7.12	0.338
Differentiation						
Well/ Moderate	1.00			1.00		
Poor	2.10	1.10-4.03	0.026	2.67	1.00-7.18	0.051
Perineural invasion	1.74	0.69-4.37	0.241	1.80	0.56-5.81	0.326
LVI	5.30	2.86-9.83	<0.001	5.26	2.43-11.4	<0.001
EMVI	4.73	2.60-8.62	<0.001	4.79	2.20-10.5	<0.001
IMVI	1.86	0.84-4.11	0.124	1.87	0.69-5.08	0.218
Tumor budding	1.49	0.81-2.75	0.202	1.39	0.63-3.06	0.410
CRM						
Negative	1.00			1.00		
Positive	2.49	1.13-5.47	0.023	2.64	1.02-6.80	0.045
Serosa						
Negative	1.00			1.00		
Positive	10.2	2.15-48.8	0.004	2.76	0.29-26.6	0.375

Note. Logistic regression (ENTER method); in both univariate and multivariate analysis, the factors were adjusted for neoadjuvant treatment. OR, odds ratio; 95% CI, 95% confidence interval; P, P value; LAR, low anterior resection; APR, abdominoperineal resection; LVI, lymphovascular invasion; EMVI, extramural venous invasion; IMVI, intramural venous invasion; CRM, circumferential resection margin.

Logistic regression analysis

The whole population was analyzed in a univariate and multivariate manner with adjustment for neoadjuvant treatment (Table 2). Multivariate analysis (enter method) revealed LVI (Figure 1A, odds ratio (OR) 5.26), EMVI (Figure 1B, OR 4.79), positive CRM (OR 2.64) and a tumour with a mucinous component (OR 3.00) as independent parameters with an increased risk for a local recurrence. Poor differentiation reached borderline significance (OR 2.67, P=0.051). Patients with an older age and positive nodal status had a significantly lower risk for the development of a potentially resectable LR (OR 0.94 and 0.43 respectively). The area under the ROC curve of the predicted probabilities was 0.83 (95% confidence interval (CI) 0.78-0.88).

Figure 1A. Lymphatic invasion. Tumor invasion of a lymphatic vessel. T = tumor, arrow = lymphatic valve. Hematoxylin and eosin stain; original magnification x 10.

Figure 1B. Extramural venous invasion. Tumor invasion of a vein in the mesorectal fat. T = tumor, arrow = artery, arrowhead = venous wall. Hematoxylin and eosin stain; original magnification x 5.

The forward stepwise (LR) multivariate logistic regression analysis indicated the presence of LVI (OR 4.66, 95% CI 2.34-9.25, $P < 0.001$), EMVI (OR 4.54, 95% CI 2.30-8.95, $P < 0.001$), positive CRM (OR 2.56, 95% CI 1.08-6.07, $P = 0.032$), serosal involvement (OR 6.74, 95% CI 1.15-39.6, $P = 0.035$) and poor differentiation (OR 2.59, 95% CI 1.24-5.42, $P = 0.012$) as factors with an increased risk to develop LR. Eighty-two percent of patients in the recurrent group had either one of these factors. Older age was a protective factor (OR 0.95, 95% CI 0.93-0.98, $P = 0.001$). The same independent factors were found in CRM negative patients ($n = 248$): LVI (OR 4.27, $P < 0.001$), EMVI (OR 4.91, $P < 0.001$), serosal involvement (OR 6.31, $P = 0.040$), poor differentiation (OR 3.13, $P = 0.005$) and older age (OR 0.96, $P = 0.008$). When taking only lymph node negative (No) patients ($n = 201$) into account, those with LVI or EMVI had an even higher risk on LR (OR 7.06 and 8.56 respectively, $P < 0.001$). Furthermore, a poor differentiation had a negative impact on outcome (OR 2.61, $P = 0.044$).

Local recurrence free interval (LRFI) in the recurrent group

The median LRFI increased with the amount of neoadjuvant radiotherapy administered; 24 months (95% CI 19-29) with no radiotherapy, 27 months (95% CI 20-34) with 5x5 Gy and 37 months (95% CI 26-48) with 50.4 Gy ($P = 0.079$). Median LRFI differed significantly between the various tumour types; 30 months (95% CI 24-36) for adenocarcinomas, 22 months (95% CI 15-29) for tumours with a mucinous component and 46 months (95% CI 13-79) for mucinous tumours ($P = 0.015$). On Cox proportional hazard regression,

older age (HR 1.03, 95% CI 1.01-1.05, $P=0.007$) was a factor with an increased risk on an early LR. In contrast, mucinous tumours were more likely to have a longer LRFI (HR 0.48, 95% CI 0.24-0.96, $P=0.038$).

DISCUSSION

The present study investigated the predictive value of several histopathological factors for the development of LR after primary rectal cancer treatment by comparing cases with controls. We found that a positive CRM, serosal involvement, LVI, EMVI and poor differentiation were the most important independent factors with an increased risk on LR. As has been frequently observed², positive CRM is key factor in the development of LR. However, with the use of improved surgical techniques a positive CRM will occur less and less often and as a consequence tumour-related factors may become more important. In accordance to our findings, other authors have also shown that serosal involvement¹⁷ and poor differentiation^{11,18} have a negative influence on prognosis. The two most important factors in our analysis, also in CRM negative patients, were LVI and EMVI. LVI is regarded as a precursor of tumor growth in lymph nodes and many studies have demonstrated its prognostic significance¹⁹. However, some studies were not able to prove its independent impact on LR rate and survival^{9,10}. EMVI is regarded as early haematogenous cancer spread and has mainly been correlated with metastases^{20,21} and survival^{9,18}. In our study, however, we proved that EMVI was also strongly correlated with LR (OR 4.54, $P<0.001$). Studies as early as 1938 have addressed the presence of venous invasion²². Most, but not all studies^{23,24} found a negative correlation between venous invasion and prognosis.

The incidence of EMVI in our study was 22% (43% in recurrent and 13% in control group). The incidence described in the literature varies widely, ranging from 10-90%²¹. Quirke and Morris stated that on average a careful pathologist would find EMVI in around 30% of the patients²⁵ as was the case in our study. There are several reasons for the differences in incidence and prognosis. Intra- and extramural venous invasion are sometimes grouped together⁸, as are lymphatic and blood vessel invasion⁷. Moreover, interobserver variability may be substantial¹⁷, because of infiltration/ destruction of vessel wall. Some authors advocate the use of special elastic tissue stains for the assessment of venous invasion^{21,26}. However, there is no agreement, because this is labour intensive, time consuming, relatively expensive and results are contradictory^{7,17}. Incidence of venous invasion also depends on sampling and assessment of the resection specimen^{27,28}.

In our study, patients with positive lymph nodes had a lower risk to develop LR on multivariate analysis (enter method). At first sight, this may appear strange. However, our LR patients were sent to our hospital for recurrence treatment with curative intent (as can be indicated by the relatively good prognosis after surgery)¹² and we assume that hence there is a selection bias for patients with curable LR. Despite the presence of positive lymph nodes in the primary tumours of our patients, they might have a favourable prognosis based on other (clinical) parameters, and thus in this selected group lymph node positivity is probably not a sign of very advanced, and thus incurable disease. Similar argumentation can be used in cases treated with APR. On univariate analysis, they were less likely to develop a LR, although several studies suggest that these patients generally have a poorer prognosis than patients who underwent a LAR^{6,29}.

The retrospective nature of our study introduced some bias, because although all available haematoxylin and eosin slides were thoroughly reviewed, the selection of the slides was dependent on the accuracy of specimen sampling by the initial pathologists. However, an area under the ROC curve of the predicted probabilities of 0.83 indicates a high accuracy of our model for the prediction of the development of LR. In addition, a case-control design limits the generalization of our results. However, since the improvements in treatment have minimized the occurrence of LR, large patient populations are unavailable.

Current guidelines advocate the use of adjuvant therapy in rectal cancer patients with positive lymph nodes and sometimes also in other high risk patients²¹. We believe that administration of adjuvant chemotherapy in patients with high risk factors (in our study EMVI, LVI, poor differentiation, positive CRM and serosal involvement) might be justified. In patients who normally do not receive adjuvant treatment (No patients) we found that the negative impact of both EMVI and LVI was even more pronounced. These factors might be important for the selection of TNM II patients who will benefit from adjuvant therapy. The QUASAR collaborative workgroup³⁰ found that adjuvant treatment in all stage II colorectal cancer patients, irrespective of the presence of poor prognostic factors, improved survival and decreased both overall and local recurrence rates significantly. However, absolute improvement in survival was only 3.6%. Patients selected based on poor prognostic factors might benefit more from adjuvant treatment. Furthermore, by making those careful selections and withholding adjuvant chemotherapy in low risk patients we can prevent unnecessary morbidity. In addition to more selective application of adjuvant treatment, follow-up regimens might be differentiated, providing more intensive follow-up in high risk patients and less radical follow-up in low risk patients. This will make the treatment of rectal cancer more individualized and more cost-effective.

In conclusion, positive CRM, serosal involvement, EMVI, LVI and poor differentiation are important independent factors predictive for the development of LR after primary rectal cancer treatment. These factors should always be reported in the pathology report and patients with these factors might be treated with adjuvant chemotherapy and followed-up more closely in order to prevent the occurrence of LR.

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Chapter 5

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**Pre-operative staging with
positron emission tomography
in patients with pelvic
recurrence of rectal cancer**

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ABSTRACT

Background

The treatment of potentially curable pelvic recurrences of rectal cancer is primarily surgical. The substantial morbidity and mortality of such resections warrant stringent patient selection. Recent literature reports PET to be of additional value to CT for the detection of metastases in colorectal cancer patients. We studied the clinical impact of PET in patients with pelvic rectal cancer recurrence scheduled for curative treatment.

Methods

PET findings in 37 pelvic recurrences of rectal cancer were evaluated retrospectively. Comparison was made to CT and MRI findings. It was analyzed whether PET had been decisive in clinical decision-making or could have been so.

Results

Thirty-two patients had 37 rectal cancer recurrences. PET differed from conventional imaging in 13 cases (35%): seven PET scans showed additional lesions that were not seen with CT or MRI (lymph node metastases in 4, distant metastases in 3). In six cases where CT or MRI showed extensive disease, PET indicated more limited disease. PET alone changed management in five recurrences (14%). Four PET scans were false-positive, this had clinical implications in 2 patients.

Conclusion

In a selected population with pelvic rectal cancer recurrences scheduled for curative resection, PET had additional value to conventional imaging, mainly in detecting lymph node metastases. PET findings thus had significant impact on selection of patients for curative surgery.

INTRODUCTION

Problems caused by local recurrence of rectal cancer significantly impair the quality of life. Survival without surgical treatment is limited. When distant metastases and locally invasive expansion into irresectable structures are excluded, curative treatment is possible in carefully selected patients. The main objective of surgery is obtaining free resection margins. Downsizing by neo-adjuvant (chemo)radiation is recommended if possible (reviewed in¹). The 3-year survival rate after successful treatment of locally recurrent rectal cancer has been estimated to be between 30 and 60% in retrospective series, with local tumor control in 30-75% of patients at 3 years^{2,3}. Resection of a local recurrence is a major pelvic procedure and carries a high morbidity rate and a mortality risk of up to 10%². As the anatomical relationships have been disturbed by the primary operation, the surgery will follow extra-anatomical dissection planes, with an increased chance of morbidity. Therefore, surgical treatment of locally recurrent disease should only be undertaken with curative intent.

It is crucial to be optimally informed about the local and systemic extension of the tumor when deciding to operate. Magnetic resonance imaging (MRI) of the pelvis has been shown to be the best diagnostic modality for evaluation of the local situation (reviewed in^{4,5}). At present, computed tomography (CT) scanning of chest and abdomen is the diagnostic modality of choice for detection of distant metastases in patients with locally recurrent rectal cancer. Besides the anatomical depiction with CT, further information about the metabolic activity of the suspected lesions with positron emission tomography (PET) could be of additional value for all colorectal malignancies as was recently reviewed by Chessin et al.⁶ and by Watson et al.⁷. The main conclusions from these reviews were: (1) the PET technique has a higher specificity and sensitivity for detecting liver metastases than CT, and (2) PET can help to differentiate between malignancy, postoperative scar tissue and (chronic) infection in suspicious lesions detected by MRI or CT, especially when a biopsy specimen cannot be obtained.

Meta et al.⁸ in an earlier study reported that PET in addition to CT results in management changes in more than 40% of all patients with colorectal cancer. Kalff et al.⁹ found an even higher percentage of change in management (56%) in a group of 96 patients with colorectal cancer on the basis of PET findings. The authors conclude that 'the major benefit of PET is avoidance of inappropriate local therapies by documentation of widespread disease'.

The objective of this study was to evaluate whether PET scanning yields the same benefit in the subgroup of patients with a pelvic recurrence of rectal cancer, scheduled for treatment with curative intent, that has been staged by CT and MRI.

MATERIALS AND METHODS

Between January 2003 and October 2006, 70 patients with locally recurrent rectal cancer were scheduled for treatment with curative intent in the Catharina hospital in Eindhoven, the Netherlands. Most patients were referred from other hospitals when a local recurrence was diagnosed or suspected. All patients underwent diagnostic CT scanning of chest and abdomen (Philips SR7000 Single slice helical CT scanner; 5 mm slices) and MRI of the pelvis (Philips 1.5 Tesla; Software release 10.3). PET scans were not routinely made as part of the pre-operative workup or within the protocol of a prospective study. The use of PET, during the studied period, was at the discretion of

the treating surgeon (H.J.T.R. or G.A.P.N.) and the multidisciplinary team in which all patients were discussed.

Retrospectively reviewing the medical records, the PET scan results and the complete clinical information were available from 32 patients with 37 pelvic recurrences. In the 38 other patients who had been treated in the study period, either no PET scan was made, or other data were not available. In 26 recurrences one PET scan was made (n=17 before chemoradiation; n=9 after chemoradiation). In 11 cases 2 scans were made: before and after chemoradiation.

A whole body PET scan was made 60 minutes after intravenous administration of 18-Fluorodeoxyglucose (18-FDG) in a dose of 4-5 MBq/kg body weight. Images were made using a mobile PET camera (Siemens Exact) during the period from October 2003 to November 2004; later a mobile Siemens Accell PET-camera was used and from January 2005 onwards the hospital has used a hybrid PET/CT camera on location (Philips Gemini/Brilliance-16 slice-CT). In the stand-alone PET camera, attenuation correction was based on a transmission scan of a rotating germanium-68 source, in the PET/CT camera attenuation correction was based on a low-dose CT-scan. Tomographic reconstructed images were visually analyzed before and after attenuation correction. If the bladder 18-FDG activity was expected to interfere in the interpretation, an extra scan (bed position) was made of the pelvic region after voiding.

Principally all foci with enhanced 18-FDG uptake in excess of areas with physiologically high uptake were regarded as suspicious for malignancy. Information from PET, CT and MRI was reviewed, along with available cytological and histological (biopsy and resection) findings. Based on the outcome of these data, changes in management initiated by PET findings were evaluated.

RESULTS

Data from 32 patients with a pelvic recurrence of rectal cancer were evaluated (Table 1). All patients had a recurrence of an adenocarcinoma, for which most of them had previously been treated with an anterior or low anterior resection or with an abdominoperineal rectum amputation. One patient had undergone a transanal endoscopic local resection. There were 28 primary recurrences and 9 re-recurrences. In 4 re-recurrence patients, PET was only available for the second recurrence. In 5 patients, PET was available for both the primary recurrence and the re-recurrence. Because of these possible doubles we refer to cases or recurrences rather than to patients in the description of our analyses.

Virtually all recurrences were detected by increased levels of serum carcinoembryonic antigen (CEA) during routine follow-up. In addition, several patients had symptoms of pain or anal blood loss. For initial staging, CT or MRI was conducted in all cases. PET scans and additional MRI or CT scans were conducted in an outpatient setting after referral to the Catharina hospital. In 15 cases the definitive diagnosis was confirmed pre-operatively by cytological or histological examination. Sixteen recurrences were confirmed by intra-operative frozen-section examination. In 5 patients with irresectable tumors no histological proof of a recurrence was obtained. One patient had a complete response to induction treatment and only fibrosis was found in the resection specimen.

Table 1. Characteristics of 32 patients with 37 recurrences of rectal cancer

Mean age in years (range)	60	(41–79)
Mean interval to relapse in years (range)	4.8	(0.4–26)
Male : Female	20:12	
T stage primary tumor		
Tcis / T1	2	
T2	5	
T3	12	
T4	2	
N stage primary tumor		
No	13	
N+	8	
TNM stage of primary tumor		
not available	11	

Note. cis; carcinoma in situ

Overall concordance between PET and conventional imaging (CT and MRI) was found in 24 cases (65%). In 18 of these cases only a local recurrence was detected, whereas in 6 cases lesions other than a local recurrence were detected (lymph node or visceral metastases). The PET findings differed from CT and MRI findings in 13 cases (35%, Table 2 and 3). Seven PET scans suggested non-regional lymph node involvement or visceral metastatic lesions that were not detected with CT or MRI. In 6 cases CT or MRI showed extensive disease (local recurrence (LR) plus lymph node metastasis (LNM) n=4, LR plus ovarian metastasis n=1, extensive LNM n=1 respectively) while PET showed more limited disease (LR only n=2 and LNM only n=2, LR without ovarian metastasis n=1, less extensive LNM n=1 respectively). Table 2 lists the findings of conventional imaging and the associated PET results, showing the nature of the discrepancies. Table 3 gives details of discrepant findings per case.

Table 2. Breakdown of PET findings with conventional imaging as reference standard

MRI & CT	Recurrences	PET identical	PET different	n
LR only	22	18	LR & LNM	3
			LR & DM	1
LNM only	2	0	LNM (more extensive)	1
			LNM (less extensive)	1
LR & LNM	10	5	LR only	2
			LNM only	2
			LR & DM (visceral)	1
LR & DM (visceral)	3	1	LR only	1
			DM (more extensive)	1
Total	37	24		13

Note. PET, positon emission tomography; MRI, magnetic resonance imaging; CT, computed tomography; LR, local recurrence; LNM, lymph node metastases; DM, distant metastases.

Table 3. Discrepancies between conventional imaging and PET per case in detail (n=13)

Case	MRI & CT findings	PET findings	Consequences	Conclusion
2	LR only	LR & DM (lung)	None PET lesion disregarded	FP PET: no pulmonary disease in 2 y follow-up
11	LR & LNM (obturator foramen)	LR & LNM (inguinal)	None LR irresectable No histology of PET lesion	None possible
13	LR only	LR & LNM (inguinal)	Cytology LNM: + Palliation	TP PET
14	LR & LNM	LNM only (obturator foramen)	Curative LNM resection Limited surgery	TN PET
15	LR only	LR & LNM (iliac)	None Iliac LNM resected: +	TP PET
17	LR & DM (ovary)	LR only	None Ovary resected: -	TN PET
19	LR & DM (2 in liver)	LR & DM (mesentery, 3 in liver)	None Staging LAP: irresectable disease of the abdomen	TP PET
20	LR only	LR & LNM (iliac)	None / Palliation LR irresectable (partially on the basis of PET finding) No histology of PET lesion	None possible
21	LR & LNM (obturator foramen)	LR & LNM (para-aortal)	Curative LNM resection Limited surgery	TN PET
22	MRI: LNM (iliac) CT: LNM (iliac, inguinal)	LNM (iliac, inguinal)	Biopsy inguinal LNM: - LR resection	FP PET (and CT)
25	LR & LNM (para-aortal)	LR & LNM (para-aortal) & DM (hepatic)	None Staging LAP: irresectable disease of the abdomen	TP PET
33	LR & LNM (inguinal)	LR only	Curative resection instead of palliation. Inguinal LNM resected: -	TN PET
34	LNM (extensive)	LNM (para-caval)	Biopsy of inguinal LNM: - Curative resection para-caval LNM	TN PET

Note. PET scan findings with clinical consequences are in bold; PET, positron emission tomography; MRI, magnetic resonance imaging; CT, computed tomography; LR, local recurrence; LNM, lymph node metastases; DM, distant metastases; TP, true-positive; TN, true-negative; FP, false-positive; LAP, laparotomy.

The PET findings were the principal basis for management changes in the treatment of 5 recurrences. In 1 case the PET-positive lesion was proven to be an inguinal lymph node metastasis and further treatment was non-surgical. In 4 cases PET showed less extensive disease, supporting less extensive surgery for 3 recurrences and surgery instead of palliative therapy for 1. In 10 cases no resection was performed because of locally advanced or metastatic disease. Two patients with PET-positive and histologically proven distant lymph node metastases were regarded as having incurably disseminated disease. In 4 patients peri-operative findings were so dismal that no attempt was made at resection. In 2 of these cases, further investigation of PET-positive lesions could have resulted in an earlier decision for non-surgical management. Four patients were not operated on the basis of MRI and PET (and histology or cytology) demonstrating locally advanced irresectable disease. Thus at least 4 unnecessary operations (11% of cases) could have been prevented based on results of PET scans.

In 3 cases PET-suspected lesions were proven to be false-positive, but also CT or MRI were false-positive: 1 patient had lesions in and around the spleen, which were suspicious on both PET and CT. Resection of the spleen showed no metastases. In 1 patient, pathological ileac lymph nodes were suspected on both PET and MRI. Histological examination after resection of the recurrence showed that these nodes were not involved. In 1 patient a biopsy from an inguinal lymph node, suspected with PET and CT, was negative. One PET scan showed pulmonary metastases that were not identified with CT. The patient was followed up after resection and did not develop clinically evident pulmonary disease. This case was regarded as false-positive. All false-positive PET lesions were reevaluated by one of the authors (M.A.L.E.) and again judged as suspicious of metastasis.

DISCUSSION

The small retrospectively analyzed and highly selected patient group in this study shows that adding PET to the routine diagnostic workup of pelvic recurrences of rectal cancer is of value in a number of patients. PET was or could have been decisive in at least 14% of cases, with a substantial number of unnecessary additional diagnostic procedures. However, the specific problem of treating recurrent rectal cancer requires that we be optimally informed about the actual chances of cure. Performing an extra test or biopsy is in this context a small price for preventing unsuccessful attempts at resection. Although not quantifiable from this series, experience shows that PET findings often support MRI or clinically based suspicion of recurrence and thus may lead to a more convincing diagnosis, especially in those cases where pathological examination is impossible or non-conclusive. Several reports describe the accuracy of PET in distinguishing local recurrence from non-malignant changes in the pelvis after irradiation and rectum amputation¹⁰⁻¹².

Historical autopsy series of patients with a pelvic recurrence showed synchronous metastases in up to 50% of the cases, predominantly in the liver¹³. With the prolonged local control after TME surgery, the clinical incidence of such distant metastases appears to increase in time¹⁴. Therefore, it is remarkable that distant metastases were detected in so few patients in the study population. This clearly reflects the highly selected nature of our population with primarily pelvic recurrences. Most probably, an important contribution results from referral selection, as patients with known metastases would have been less likely to be referred for local treatment. A second contributing factor could be that patients underwent PET scan on non-objective parameters for selection. In our series, the principal benefit of PET was the more accurate detection of lymph node disease outside the immediate region of the recurrence and improved judgment of local disease. This provided important information about the necessity and possibility of a curative resection.

In conclusion, PET in patients with recurrence of rectal cancer in the pelvic area can yield decisive information for treatment planning. It should, however, be noted that at least in this series PET revealed a relatively high number of false-positive results. At present, it is our opinion that the information obtained by PET outweighs the burden of extra diagnostic tests. Additional prospective studies are needed for a better quantification of the specific benefits of PET in relation to the other diagnostic modalities and to pathological findings in these patients. When fusing PET and CT images, it is possible to directly correlate metabolically active sites with their anatomic substrates. It is likely that the use of these PET/CT scanners will increase the yield of both techniques.

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**Preoperative MRI
can predict tumor invasion
into pelvic structures in
locally recurrent rectal cancer**

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ABSTRACT

Purpose

To assess the accuracy of preoperative MRI for identification of tumor invasion into pelvic structures in patients with locally recurrent rectal cancer (LRRC) scheduled for curative resection.

Patients and Methods

Preoperative MRIs of 40 consecutive patients with LRRC scheduled for curative treatment between October 2003 and November 2006 were analyzed retrospectively. Four observers with different experience in reading pelvic MRI assessed tumor invasion into the following structures: bladder, uterus/seminal vesicles, vagina/prostate, left and right pelvic walls and sacrum. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated and a ROC curve was constructed. Surgical and/or histopathological findings were used as reference standard. Interobserver agreement was measured using kappa statistics.

Results

Preoperative MRI was accurate for the prediction of tumor invasion into structures with NPVs of 93-100% and AUCs of 0.79-1.00 for all structures and observers. PPVs were 53-100%. Overstaging occurred in 11 (observer 1), 22 (observer 2), 10 (observer 3) and 9 (observer 4) structures and understaging in 9 (observer 3) and 2 (observer 4) structures. Assessment failures were mainly due to misinterpretation of diffuse fibrosis, especially at the pelvic side walls. Interobserver agreement ranged between 0.64 and 0.99 for experienced observers.

Conclusion

Preoperative MRI is accurate for the prediction of tumor invasion into pelvic structures. MRI may be useful as preoperative road map for surgical procedure and may thus increase chances of complete resections. Interpretation of diffuse fibrosis remains difficult.

INTRODUCTION

Locally recurrent rectal cancer (LRRC) has long been regarded as a rarely curable disease. Patients were treated palliatively and subsequent median survival was 14 months and 5-year survival rate 5%¹. However, during the last twenty to thirty years, more patients were considered candidates for a curative treatment², such as neoadjuvant chemoradiation with extensive surgery and sometimes intraoperative radiotherapy³. Using these techniques, 5-year survival rates of 30-40% were obtained^{4,6}, but at the cost of a substantial treatment related morbidity. Therefore, only patients in whom the chance of a radical resection is high are likely to benefit from this aggressive approach. Otherwise, optimal palliative treatment should be considered.

Most of the imaging studies on locally recurrent rectal cancer with PET, CT or hybrid PET-CT techniques have focused on the detection of local recurrence after treatment of the primary tumor⁷⁻⁹. Tertiary referral centers who regularly treat these patients often perform additional magnetic resonance imaging (MRI) to establish whether or not a tumor is resectable. Although MRI has proven to be the preferred first choice staging modality of primary rectal cancer¹⁰⁻¹², little is known about its performance for predicting tumor extent in patients with a local recurrence. Therefore, the goal of our study was to assess the accuracy of a preoperative MRI for predicting tumor invasion into pelvic structures in patients with locally recurrent rectal cancer scheduled for curative resection.

PATIENTS AND METHODS

Patients

The institutional review board approved this study and waived informed consent because of the retrospective nature of the study. Between October 2003 and November 2006, 56 consecutive patients diagnosed with non metastasized, locally recurrent rectal cancer were scheduled for curative treatment with neoadjuvant chemoradiation, extended surgery and intraoperative radiotherapy in the Catharina hospital in Eindhoven, the Netherlands, a national referral center for these patients^{5,13}. In 45 of the 56 patients, a MRI was performed preoperatively after the chemoradiation and 28 of these patients also had a baseline MRI before chemoradiation. Five of these 45 patients did not undergo a resection, because of widespread disease and were excluded. Overall, in 40 patients MRI could be correlated with final histopathology findings.

Neoadjuvant treatment

Patients received preoperative chemoradiation with a radiotherapy dose of 50.4 Gray (Gy), 5 times a week in 28 doses of 1.8 Gy. Patients who had received radiotherapy for the primary tumor were re-irradiated (30.6 Gray, 5 times a week in 17 doses of 1.8 Gy). EBRT was delivered with a linear accelerator (10 MeV) using a three-field box technique (one posterior and two lateral portals). The pelvic field borders used were described earlier⁵. Chemotherapy consisted of either capecitabine (2x825 mg/m²/d) 5 days a week for three weeks alone or combined with oxaliplatin (50 mg/m²) on day 1, 8 and 15.

MR imaging techniques

MR imaging was performed at 1.5 T (Achieva and Intera, Philips Medical Systems, Best, the Netherlands) using a quadrature phased array spine coil, a cardiac or body phased array coil (Philips Medical Systems, Best, the Netherlands). Sequences used were axial T2-weighted TSE (T2W 2D TR/TE 3882/125; TSE factor 16; slice thickness 3.0; slice gap 0.3;

NSA 6; acq matrix 256x176; FOV 180; scan time 7:36), sagittal T2W 2D TSE (TR/TE 3882/125; TSE factor 23; slice thickness 3.0; slice gap 1.0; NSA 4; FOV 250; acq matrix 304x241; scan time 5:41), axial T1W 2D TSE (TR/TE 550/7; TSE factor 4; slice thickness 4; slice gap 0.4; NSA 1; FOV 410; acq matrix 368x306; scan time 1:32) and sagittal T1W 2D TSE (TR/TE 600/13; TSE factor 3; slice thickness 4.0; slice gap 0.8; NSA 2; FOV 320x208; acq matrix 320x145; scan time 4:00). Patients did not receive any bowel preparation, air insufflation or intravenous spasmolytic medication.

MR evaluation

The MR images were retrospectively evaluated for extent of tumor growth into surrounding pelvic structures/organs by 4 observers. Observer 1 (R.G.B.) was a dedicated pelvic MR radiologist with 12 years of experience in reading pelvic MRI in a university medical center. Observer 2 (A.W.D.) was a pelvic MR radiologist with 5 years of experience in a general hospital which served as a national referral center for locally advanced and recurrent rectal cancer. Observer 3 (V.C.C.) was a general radiologist with special interest in gastrointestinal malignancies and 1 year of experience in this field. Observer 4 (H.J.R.) was a surgical oncologist with 20 years expertise in management and surgery of (recurrent) rectal cancer. The MR images were made anonymous and were presented in a random order. The observers were blinded to surgical, histopathological and each other's results. Tumor invasion was defined as diffuse or nodular isointense tissue on the T2W FSE MR images that was at a distance of ≤ 1 mm from the structure/organ. All observers used confidence levels for the prediction of tumor invasion (1=definitely not invaded, 2=probably not invaded, 3=possibly invaded, 4=probably invaded and 5=definitely invaded). The following structures were evaluated: vagina/ prostate, uterus/ seminal vesicles, urinary bladder, sacral bone, left and right (dorso)lateral pelvic side walls. The pelvic side walls were defined as the piriform and the internal obturator muscles, the sacrotuberous and sacrospinal ligaments.

Surgery and intraoperative radiotherapy

At start of laparotomy, the abdomen was checked for liver, nodal or peritoneal metastases. The type of surgery was determined by the location of the tumor and the extent of tumor growth into surrounding structures (Table 1). The goal was to obtain an en bloc resection of the tumor and the involved structures with a tumor free margin of at least 1 mm. All patients received intraoperative radiotherapy at the area of the closest resection margin, at highest risk for residual tumor¹⁴.

Histopathology

The circumferential resection margin (CRM) of the fresh specimen was inked, the specimen was fixed in 10% formalin for 48 hours and then cut in 5-10 mm transversal slices. Slices were embedded in blocks and processed for hematoxylin and eosin (HE) staining in 5 μ m sections. On the HE stained slides the distance between the tumor and the resected organs, structures and CRM was evaluated. If the CRM in the direction of a nonresected organ/structure was free of tumor, the organ/structure was scored as noninvaded. If it showed tumor within 1 mm the organ/structure was considered as invaded. If the surgical and histopathological findings could not be reconstructed for a specific site by reviewing the reports and the HE slides, this site was excluded from analysis.

Table 1. Patient and treatment characteristics

	No.	%
All	40	100
Median age in years (range)		61 (47-77)
Sex		
Male	26	65.0
Female	14	35.0
Neoadjuvant therapy for primary tumor		
No	13	32.5
Short course (5x5 Gy)	17	42.5
Long course (45-50.4 Gy)	10	25.9
Type of primary surgery		
LAR	25	62.5
APR	15	37.5
Median interval primary-recurrence surgery in months (range)		34.0 (13-100)
MRI		
Both pre and post neoadjuvant therapy	28	70.0
Only post neoadjuvant therapy	12	30.0
Neoadjuvant therapy for recurrence		
Re-irradiation + chemotherapy	27	67.5
Full course + chemotherapy	13	32.5
Type of recurrence surgery		
LAR	6	13.3
APR	6	13.3
ASR	12	26.7
Exenteration	9	20.0
Nonanatomic resection	7	15.6

Note. MRI, magnetic resonance imaging; LAR, low anterior resection; APR, abdominoperineal resection; ASR, abdominosacral resection.

Statistical analysis

The reference standard consisted of a detailed reconstruction of all available surgical and histopathological information retrieved from the reports and by reviewing the HE slides if necessary. ROC curves were constructed for the prediction of tumor invasion of pelvic structures for all observers and the areas under the ROC curves (AUC) were calculated. The AUCs were compared using the method of DeLong¹⁵. After dichotomization of the confidence levels (1-2 = no invasion, 3-5 = invasion) sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the prediction of tumor invasion of pelvic structures were calculated. Interobserver agreement was measured using linear weighted kappa statistics^{16,17} with kappa-values of 0.2-0.4 indicating fair, 0.4-0.6 moderate, and > 0.6 excellent agreements. A difference was considered statistically significant if $P \leq 0.05$ (two-sided). Statistical analyses were performed using the SPSS statistical software program (SPSS® for Windows Release 15.0, SPSS Inc, Chicago, IL, USA).

RESULTS

Patient, treatment and tumor characteristics

The study population consisted of 26 men and 14 women with a median age of 61 years (range 41-77). The median interval between primary and recurrent surgery was 34 months (range 13-100). The median interval between the MRI and surgery was 33 days (range 7-105). The details about primary and recurrent (neoadjuvant) treatment are described in Table 1. In total, 236 structures were evaluated in 40 patients. In 6 structures (2.5%) the reference standard could not be reconstructed, because there was no information in the surgical or histopathological reports on these structures and no HE slides available containing this structure that would allow revision of the structures.

Assessment of invaded structures

Table 2 gives the AUCs, sensitivities, specificities, PPVs and NPVs of all observers for the prediction of tumor invasion into various pelvic structures at anterior, lateral and posterior locations. The AUCs for prediction of tumor growth into the left and right pelvic wall of the observer with the least experience (observer 3) were significantly lower (0.85 and 0.80 respectively) compared to those of the more experienced observers (≥ 0.94 , $P < 0.05$). Sensitivities ranged from 60-100%, with the lowest scores for the vagina/prostate (observer 3 and 4). Specificities ranged from 80-100%. PPVs ranged from 53-100%, with the lowest scores for the pelvic side walls (all observers). NPVs ranged from 93-100%, (observer 1 and 2 scored 100% for all structures).

Although tumor volume decreased substantially in the 28 patients who received both a pre and a post chemoradiation MRI, invasion into structures as judged by the observers generally remained identical on both MRIs (data not shown, example in Figure 1).

Figure 1. An example of volume downsizing and overstaging on T2W TSE (3882/125) images before (a) and after chemoradiation (b). Although the tumor volume decreased due to neoadjuvant chemoradiation, no change in the appearance of the peripheral pushing fibrotic mass was seen. Invasion into the lateral pelvic side walls and bladder was scored with the same confidence level by all observers on both pre and post chemoradiation MR images. All observers overstaged the bladder and both pelvic side walls. Histopathology revealed only limited intramucosal residual tumor cells. B, bladder.

Table 2. Prediction of tumor invasion of pelvic structures (cut-off level between 2 and 3)

	Obs.	AUC 95% CI	Accuracy 95% CI	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI
Anterior							
Vagina/ Prostate	1	1.00	100 (36/36)	100 (5/5)	100 (31/31)	100 (5/5)	100 (31/31)
		1.00-1.00	100-100	100-100	100-100	100-100	100-100
	2	0.97	92 (33/36)	100 (5/5)	90 (28/31)	63 (5/8)	100 (28/28)
		0.91-1.02	78-98	100-100	74-98	24-91	100-100
	3	0.80	94 (34/36)	60 (3/5)	100 (31/31)	100 (3/3)	94 (31/33)
		0.53-1.07	81-99	15-95	100-100	100-100	80-99
	4	0.79	92 (33/36)	60 (3/5)	97 (30/31)	75 (3/4)	94 (30/32)
		0.52-1.07	78-98	15-95	83-100	19-99	79-99
Uterus/ Seminal vesicles	1	0.98	94 (34/36)	100 (11/11)	92 (23/25)	85 (11/13)	100 (23/23)
		0.93-1.03	81-99	100-100	74-99	55-98	100-100
	2	0.93	86 (31/36)	100 (11/11)	80 (20/25)	69 (11/16)	100 (20/20)
		0.85-1.01	71-95	100-100	59-93	41-89	100-100
	3	0.94	94 (34/36)	91 (10/11)	96 (24/25)	91 (10/11)	96 (24/25)
		0.83-1.05	81-99	59-100	80-100	59-100	80-100
	4	1.00	97 (35/36)	100 (11/11)	96 (24/25)	92 (11/12)	100 (24/24)
		1.00-1.00	85-100	100-100	80-100	62-100	100-100
Urinary bladder	1	0.99	98 (39/40)	100 (4/4)	97 (35/36)	80 (4/5)	100 (35/35)
		0.95-1.02	87-100	100-100	85-100	28-99	100-100
	2	0.98	98 (39/40)	100 (4/4)	97 (35/36)	80 (4/5)	100 (35/35)
		0.94-1.02	87-100	100-100	85-100	28-99	100-100
	3	0.86	95 (38/40)	75 (3/4)	97 (35/36)	75 (3/4)	97 (35/36)
		0.60-1.12	83-99	19-99	85-100	19-99	85-100
	4	0.98	95 (38/40)	100 (4/4)	94 (34/36)	67 (4/6)	100 (34/34)
		0.94-1.02	83-99	100-100	81-99	22-96	100-100
Lateral							
Left pelvic side wall	1	0.96	92 (36/39)	100 (11/11)	89 (25/28)	79 (11/14)	100 (25/25)
		0.91-1.02	79-98	100-100	72-98	49-95	100-100
	2	0.96	85 (33/39)	100 (11/11)	79 (22/28)	65 (11/17)	100 (22/22)
		0.91-1.02	69-94	100-100	59-92	38-86	100-100
	3	0.85	87 (34/39)	82 (9/11)	89 (25/28)	75 (9/12)	93 (25/27)
		0.70-1.00	73-96	48-98	72-98	43-95	76-99
	4	0.96	95 (37/39)	100 (11/11)	93 (26/28)	85 (11/13)	100 (26/26)
		0.90-1.02	83-99	100-100	77-99	55-98	100-100
Right pelvic side wall	1	0.94	87 (34/39)	100 (8/8)	84 (26/31)	62 (8/13)	100 (26/26)
		0.87-1.01	73-96	100-100	66-95	32-86	100-100
	2	0.96	82 (32/39)	100 (8/8)	77 (24/31)	53 (8/15)	100 (24/24)
		0.90-1.02	66-92	100-100	59-90	27-79	100-100
	3	0.80	82 (32/39)	75 (6/8)	84 (26/31)	55 (6/11)	93 (26/28)
		0.61-1.00	66-92	35-97	66-95	23-83	77-99
	4	0.96	95 (37/39)	100 (8/8)	94 (29/31)	80 (8/10)	100 (29/29)
		0.90-1.02	83-99	100-100	79-99	44-97	100-100
Posterior							
Sacral bone	1	1.00	100 (40/40)	100 (10/10)	100 (30/30)	100 (10/10)	100 (30/30)
		1.00-1.00	100-100	100-100	100-100	100-100	100-100
	2	1.00	100 (40/40)	100 (10/10)	100 (30/30)	100 (10/10)	100 (30/30)
		1.00-1.00	100-100	100-100	100-100	100-100	100-100
	3	0.95	98 (39/40)	90 (9/10)	100 (30/30)	100 (9/9)	97 (30/31)
		0.84-1.06	87-100	56-100	100-100	100-100	83-100
	4	0.98	98 (39/40)	100 (10/10)	97 (29/30)	91 (10/11)	100 (29/29)
		0.94-1.02	87-100	100-100	83-100	59-100	100-100

Note. Values are percentages. Values in parenthesis are absolute numbers. Obs., observer; 95% CI; 95% confidence interval; AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value.

Assessment of failures

Overall, 82.5% (33/40) of patients were correctly assessed by observer 1, 72.5% (29/40) by observer 2, 70% (28/40) by observer 3 and 85% (34/40) by observer 4 (Figure 2). Observer 1 overstaged 11 structures in 7 patients and observer 2 overstaged 22 structures in 11 patients. Neither of these observers ever understaged. Observer 3 had 9 false negatives in 6 patients and 10 false positives in 6 patients. Observer 4 showed 2 false negatives in 2 patients and 9 false positives in 4 patients.

Table 3. Interobserver agreement for the prediction of tumor invasion of pelvic structures

Obs.	Bladder	Uterus/Seminal vesicles	Vagina/Prostate	Left pelvic wall	Right pelvic wall	Sacrum
1-2	0.98	0.88	0.72	0.93	0.88	0.99
95% CI	0.97-1.00	0.74-1.00	0.45-1.00	0.85-1.00	0.76-1.00	0.98-1.00
1-3	0.87	0.82	0.61	0.87	0.83	0.92
95% CI	0.63-1.00	0.62-1.00	0.20-1.00	0.71-1.00	0.65-1.00	0.78-1.00
1-4	0.86	0.86	0.64	0.96	0.83	0.91
95% CI	0.75-1.00	0.70-1.00	0.27-1.00	0.89-1.00	0.65-1.00	0.78-1.00
2-3	0.91	0.69	0.52	0.79	0.73	0.91
95% CI	0.75-1.00	0.46-0.93	0.14-0.91	0.62-0.97	0.52-0.94	0.77-1.00
2-4	0.85	0.72	0.54	0.88	0.81	0.90
95% CI	0.62-1.00	0.51-0.93	0.16-0.93	0.78-0.99	0.64-0.98	0.76-1.00
3-4	0.74	0.81	0.31	0.84	0.84	0.88
95% CI	0.42-1.00	0.62-1.00	0.24-0.85	0.67-1.00	0.67-1.00	0.72-1.00

Note. Obs., observers, 95% CI, 95% confidence interval.

Figure 2. An example of a true positive T2W MR image (3882/125) before (a) and after (b) neoadjuvant chemoradiation. All observers correctly scored invasion into the seminal vesicle on both pre and post chemoradiation MR images. B, bladder; V, seminal vesicle.

The majority of overstaging was due to prediction of a diffuse hypo-intense mass on T2W TSE images as fibrosis that may contain remaining tumor, while histopathology showed complete or nearly complete response without significant tumor load left (Figure 1). This occurred for observer 1 in 8 of the 11 overstaged cases (73%), for observer 2 in 55% (12/22), for observer 3 in 80% (8/10) and for observer 4 in 89% (8/9). The site where this error occurred most frequently was the lateral pelvic side wall. In two cases the right seminal vesicle was scored as definitely invaded by observer 1, 2 and 3 but histopathology showed a 4 mm free margin between the tumor and the seminal

vesicle in one case and no relationship between the tumor and the seminal vesicle in the other.

Understaging also occurred in the presence of a hypointense mass on T2W TSE MR images, which was interpreted by observer 3 as preexisting fibrosis rather than recurrent tumor (Figure 3). Observer 4 understaged 2 patients who had tumor invasion of both the uterus (cervix) and the vagina. Although this observer respected the uterine invasion, the invasion of the posterior fornix was missed.

Figure 3. An example of understaging on a T2W MR image (3882/125). Observer 3 understaged the prostate interpreting the lesion as preexisting fibrosis rather than recurrent tumor. B, bladder; P, prostate.

Figure 4. An example in which the presacral periosteal line helped to decide that the tumor did not invade the sacrum (T2W TSE MR image 3882/125). S, sacrum.

Interobserver agreement

The kappas between the observers for the bladder ranged between 0.74 and 0.98, for the uterus/ seminal vesicles between 0.69 and 0.88, for the vagina/ prostate between 0.31 and 0.72, for the left lateral pelvic wall between 0.84 and 0.96, for the right lateral pelvic wall between 0.73 and 0.88 and for the sacrum between 0.88 and 0.99 (Table 3).

DISCUSSION

Patients with locally recurrent rectal cancer benefit from accurate information on the extent of tumor growth into pelvic structures. With the exact preoperative knowledge of which pelvic structures are invaded, a detailed operative plan can be made for an en bloc resection with wide margins around the tumor, maximizing the chance of a complete resection. In patients in whom it is anticipated that this cannot be achieved, a palliative treatment can be considered with less treatment related morbidity. Our study showed that MRI was highly accurate for predicting absence of invasion into pelvic structures with NPVs of 93-100% for all observers. In other words, when MRI predicted that a structure was not invaded, it was true in 9 to 10 out of 10 cases regardless the experience of the observer. The PPV however, tended to be lower, especially at the lateral pelvic side walls (PPVs 53-85%) even for expert observers. Generally, there was a high interobserver agreement.

To the best of our knowledge only one other study has investigated the role of MRI in surgical treatment planning of recurrent rectal cancer¹⁸. In this study of 49 patients, MRI showed NPVs of 84-100% and PPVs of 71-100% for the prediction of tumor invasion into pelvic structures. Histopathology was only available for 51% of the correlations with MRI and 98/343 (28.6%) of structures were excluded because no reference standard of surgery/histopathology could be reconstructed, opposed to only 2.5% in our study. The authors reported that the main difficulty was assessment of tumor involvement of the pelvic side wall, with both false negative and false positive findings, especially after previous radiotherapy. Our findings confirm this, although the errors in pelvic side wall involvement in our study were mostly overstaging errors. After chemoradiation, tumor tissue has often been replaced by fibrosis, and it is difficult to interpret on T2W images whether or not there is still viable tumor invading the piriform and obturator muscles. To a lesser extent this fibrosis also caused staging failures of the anterior structures. Posteriorly, staging was almost perfect, probably because an intact hypointense periosteal line on the T2W TSE images almost guarantees a non involved sacral bone (Figure 4).

MR interpretation of fibrosis in recurrent rectal cancer

From studies in the setting of primary rectal cancer it is known that fibrosis after chemoradiation can cause interpretation difficulties in judging the extent of a tumor¹⁹. Within a mass of hypointense fibrotic tissue small areas of vital tumor, too small to be visible on MRI, can remain. For recurrent rectal cancer the problem of fibrosis is even more complex. The normal pelvic anatomy is often distorted because of the treatment of the primary tumor, with fibrotic changes that can be due to the primary operation, infectious complications, and prior radiotherapy. This not only hampers the detection of recurrences, but also the defining of the exact tumor extent, as it is often located within preexisting fibrosis in the presacral or lateral area. In our experience the pushing or invading fibrotic mass in front of the recurrent tumor most often did not contain malignant cells at the definitive histological examination. Our hypothesis is that this fibrosis in front of a pushing growing recurrence often is old scar tissue rather than recurrent tumor that has responded to chemoradiation. This in contrast to the fibrosis seen after chemoradiation of a primary rectal cancer, that replaces tumor and where small remnants of vital tumor can be found throughout the fibrotic tissue¹⁹. This hypothesis is supported by the fact that MR imaging showed no change in the pushing fibrotic mass after chemoradiation.

Many criteria have been proposed to differentiate between fibrosis and recurrent tumor. It has been suggested that tumor has a high and fibrosis a low signal intensity on T2-weighted images, tumor has a round border and fibrosis straight angular margins and that tumor has contrast enhancement of > 40% of the mass or a typical rim-enhancement pattern after gadolinium²⁰. Although these criteria are helpful, they are not very specific as they may occur in tumor, fibrosis, inflammation or hematoma^{21,22}.

Radiological decision making

Apart from the inherent difficulty to distinguish fibrosis from tumor, other factors can influence the judgment of the radiologist. An important factor is the understanding of the clinical consequences of the radiological report. Overstaging can lead to overtreatment, and to unnecessary treatment related morbidity, but without compromising oncological outcome. Understaging can have more serious consequences and could lead to an incomplete resection, jeopardizing the patients' cure. In our study, the least experienced radiologist had about the same number of understaging and

overstaging errors, while the two experienced radiologists and the surgeon had far more overstaging errors. This probably reflects the incorporation of clinical management issues in the radiological decision. It is our belief that active participation of radiologists in multidisciplinary meetings increases the understanding between radiologists and clinicians.

Limitations

The retrospective nature of this study presents some inherent limitations. Although the reference standard was based on detailed reconstruction of surgical and histopathological reports and review of HE slides when required, it was sometimes difficult to reconstruct the exact relation between the tumor and the surrounding structures. In the cases where the reconstruction was definitely impossible the structures were excluded from the analysis. This occurred in only 2.5% of the structures.

In conclusion, a preoperative MRI in patients with locally recurrent rectal cancer treated with neoadjuvant chemoradiation is reliable for the prediction of extent of tumor growth into surrounding pelvic structures. It can serve as a road map for the surgical procedure and increase the chances of a complete resection. Interpretation of fibrotic tissue at the latero-dorsal pelvic side walls remains difficult.

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**Radical resection after IORT-
containing multimodality
therapy is the most important
determinant for outcome in
patients treated for
locally recurrent rectal cancer**

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ABSTRACT

Background

The optimal treatment for locally recurrent rectal cancer (LRRC) is still a matter of debate. This study assessed the outcome of LRRC patients treated with multimodality treatment, consisting of neoadjuvant radio(chemo)therapy, extended resection and intraoperative radiotherapy.

Methods

One hundred and forty-seven consecutive patients with LRRC who underwent treatment between 1994 and 2006 were studied. The prognostic values of patient-, tumor- and treatment-related characteristics were tested with uni- and multivariate analysis.

Results

Median overall survival was 28 months (range 0-146 months). Five-year overall-, disease free-, metastasis free survival and local control (OS, DFS, MFS and LC respectively) were 31.5%, 34.1%, 49.5% and 54.1% respectively. Radical resection (R0) was obtained in 84 patients (57.2%), microscopically irradiable resection (R1) in 34 patients (23.1%) and macroscopically irradiable resection (R2) in 29 patients (19.7%). For patients with a radical resection median OS was 59 months and the 5-year OS, DFS, MFS and LC were 48.4%, 52.3%, 65.5% and 68.9%. Radical resection was significantly correlated with improved OS, DFS and LC ($P < 0.001$). Patients who received re-irradiation or full course radiotherapy survived significantly longer ($P = 0.043$) and longer without local recurrence ($P = 0.038$) or metastasis ($P < 0.001$) compared to patients who were not re-irradiated.

Conclusions

Radical resection is the most significant predictor of improved survival in patients with LRRC. Neoadjuvant radio(chemo)therapy is the best option in order to realize a radical resection. Re-irradiation is feasible in patients who already received irradiation as part of the primary rectal cancer treatment.

INTRODUCTION

The introduction of total mesorectal excision (TME) surgery and neoadjuvant radio(chemo)therapy (RCT) has resulted in a decrease of the incidence of locally recurrent rectal cancer (LRRC) to below 10%¹⁻⁶. However, patients who do develop LRRC still have limited treatment options and subsequent prognosis. Due to prior surgery tumor growth is not confined to a specific compartment lined by fascias, because these fascias have been damaged during the primary surgery. Therefore recurrences easily grow into surrounding compartments. Radicality can often only be achieved by a multicompartimental resection. These resections are accompanied by high morbidity and mortality rates up to 10%⁷⁻⁹. Neoadjuvant treatment options are often limited because the patients have already received RCT during the treatment of the primary tumor. Tissue tolerance for re-irradiation is limited to approximately 30 Gray (Gy) due to dose accumulation toxicity¹⁰. Furthermore, it can be hypothesized that a recurrent tumor shows a more aggressive biological behavior. It has been demonstrated that more than 50% of patients with LRRC will develop a metastasis within 6 months after the diagnosis of the local recurrence¹¹.

The inherent poor prognosis often leads to a nihilistic approach (with a high tumor-related morbidity), depriving patients of a chance of cure. However, curative treatment has improved slightly in specialized centers over the years, due to the use of neoadjuvant RCT, radical resection and in some centers intraoperative radiotherapy (IORT). IORT, either as electron beam therapy (IOERT) or as brachytherapy enables accurate delivery of a radiation dose to the tumor bed. Dose limitations of normal tissue can be minimized either by temporary removal out of the irradiation volume or by lead shielding. The use of external beam irradiation (EBRT) in combination with IORT allows local delivery of a tumorcidal biological dose up to 80-90 Gy^{12,13}. As LRRC patients constitute a highly heterogeneous group, often presenting with concomitant metastatic disease, and randomized studies are difficult to perform. Most of the knowledge about the treatment of LRRC patients is empirical and obtained from centers able to accumulate sufficient data. Since 1994, the Catharina Hospital has been a national referral center for patients with LRRC in the Netherlands.

This retrospective study of a large patient population assessed whether intensive multimodality treatment, consisting of neoadjuvant radiotherapy (often combined with chemotherapy), extended resection and IORT was useful in locally recurrent rectal cancer patients. Furthermore, the role of re-irradiation was determined.

PATIENTS AND METHODS

Patients

From March 1994 to July 2006, 184 consecutive patients with LRRC within the pelvis, without identified distant metastases at time of diagnosis, were scheduled for treatment with curative intent. For most patients this treatment comprised multimodality treatment, but some patients in early years did not receive neoadjuvant treatment. Multimodality treatment consisted of neoadjuvant radio(chemo)therapy, extended surgery and IOERT. Patients were referred to our institution from 42 hospitals throughout the Netherlands. Upon referral, all data about the primary and recurrent rectal tumor were available. Thirty-seven patients were excluded from further analysis because of the following reasons: 27 patients proved to have irresectable disease because of tumor growth into S2 or higher (n=20), intraperitoneal metastases (n=10)

and infiltration into the neural plexus, which extended beyond the infrapiriform foramen (n=2). Ten patients were excluded because they had a history of metastasectomy. The remaining 147 patients form the basis of this study. Patients' charts, operation and pathology reports were reviewed in order to obtain patient demographics and treatment history. After resection of the LRRC, most patients returned to their initial hospital for follow-up. Follow-up data could be completed in all patients either by medical record review or by contacting patients or their treating physicians by phone. Median follow-up time for survivors was 34.0 months (range 6-146). Our institutional review committee approved this analysis and waived informed consent, because of the retrospective nature of the study.

Preoperative evaluation

The local recurrences were discovered by routine follow-up or symptoms. In most patients histological confirmation could be obtained by either direct or computed tomography (CT)-guided biopsy. Progressive growth on repeated magnetic resonance imaging (MRI) or CT scans, especially in combination with increased carcino-embryonic antigen level or positive positron emission tomography (PET), was sometimes considered as sufficient evidence for the diagnosis of a local recurrence. All patients received a CT and/ or a MRI of the pelvis in order to assess the localization of the recurrence and the extent of growth into surrounding structures. In order to exclude disseminated disease patients underwent a liver ultrasound and a chest X-ray and since the year 2000 a CT scan of the chest and abdomen, in difficult cases supplemented with a PET scan.

Neoadjuvant therapy

Neoadjuvant treatment regimen has changed over the years, because of changes in treatment protocol. In the early years (1994-1999), patients received preoperative radiotherapy alone as external beam radiation therapy (EBRT) with a dose of 50.4 Gray (Gy), 5 times a week in 28 doses of 1.8 Gy. If the patient had already received radiotherapy for the primary tumor, no re-irradiation was given to the recurrent tumor. In 1997, re-irradiation (30.6 Gray, five times a week in 17 doses of 1.8 Gy) was introduced in previously irradiated patients. EBRT was delivered with a linear accelerator (10 MeV) by using a three-field technique, utilizing one posterior and two lateral portals. The pelvic field borders were: the lateral borders extending 1-1.5 cm lateral of the bony pelvis, the cranial borders being the promontory (L5-S1), the caudal border was below the obturator foramen. The dorsal border encompassed the sacrum and the anterior border was chosen in such a way that the initial tumor region was widely covered. If the local recurrence was low seated, the perineum was included in the radiation volume. If necessary, a spacer was placed and a stoma was constructed. The spacer was placed to displace the small bowel out of the pelvis as much as possible. A biological spacer like the omentum or the distal sigmoid was preferred and if not feasible an artificial spacer (mamma prosthesis) was used instead.

Since 1999, patients received neoadjuvant radiochemotherapy instead of radiotherapy alone. From 1999 until 2004, this consisted of 5-FU (350 mg/m²/d) combined with leucovorin (20 mg/m²/d) during the first 5 days of re-irradiation or during the first and last 5 days of full course radiotherapy. Since 2004, patients received either capecitabine (2x825 mg/m²/d) 5 days a week for three weeks combined with oxaliplatin (50 mg/m²) on day 1, 8 and 15 or continuous capecitabine (2x825mg/m²/d) 5 days a week alone. No adjuvant chemotherapy was administered, as this was not part of treatment guidelines in the Netherlands.

Table 1. Patient and treatment characteristics

	No. of patients (n=147)	
Median age in years (range)	62	(39-87)
Gender		
Male	84	(57.1)
Female	63	(42.9)
Stage of primary tumor		
I	17	(11.6)
II	68	(46.3)
III	60	(40.8)
unknown	2	(1.3)
Number of LR		
First LR	133	(90.5)
Second LR	11	(7.5)
Third LR	3	(2.0)
Median interval primary-recurrent surgery in months (range)	28	(3-207)
Type of primary surgery		
Low anterior resection	80	(54.4)
Abdominoperineal resection	44	(30.0)
Rectosigmoid resection	18	(12.2)
Exenteration	2	(1.4)
Local procedure	3	(2.0)
Type of LRRC surgery		
Low anterior resection	26	(17.7)
Abdominoperineal resection	48	(32.7)
Abdominotranssacral resection	39	(26.5)
Pelvic exenteration	17	(11.6)
Nonanatomic	17	(11.6)
EBRT for primary tumor		
No		
-EBRT for LRRC (FC)	66	(44.9)
-no EBRT for LRRC	3	(2.0)
Yes		
-EBRT for LRRC (RI)	57	(38.8)
-no EBRT for LRRC	21	(14.3)
Neoadjuvant treatment for LRRC		
No	24	(16.3)
RI without chemo	13	(8.9)
RI with chemo	44	(29.9)
FC without chemo	23	(15.6)
FC with chemo	43	(29.3)
Dose IOERT (Gy)		
0	11	(7.5)
10	72	(49.0)
12.5	35	(23.8)
15	18	(12.2)
17.5	11	(7.5)
Radicality of resection		
R0	84	(57.2)
R1	34	(23.1)
R2	29	(19.7)

Note. Values in parentheses are percentages unless indicated otherwise. LR, local recurrence; LRRC, locally recurrent rectal cancer; EBRT, external beam radiation therapy; Gy, Gray; RI, re-irradiation; FC, full course radiotherapy; IOERT, intraoperative electron beam radiotherapy; R1, microscopically radical; R1, microscopically irradiated; R2, macroscopically irradiated.

Surgery

Surgery was planned 8 to 10 weeks after completion of EBRT. At the start of the laparotomy, the abdomen was carefully checked for liver, nodal or peritoneal metastases. In all patients a radical resection was intended. In order to obtain this, resection with extended circumferential margins was necessary¹⁴. The different surgical procedures are described in Table 1. Radicality of resection was defined as follows: a R0 resection had free surgical margins, a R1 resection had focally microscopically involved margins and a R2 was defined as more than 1 cm² involved margins, in most cases macroscopically visible tumor was left behind. As specimens of locally recurrent cases had no clearly defined anatomical borders, any free margin was considered as R0.

Intraoperative radiotherapy

From 1994 until 2004, IOERT was given in a dedicated radiotherapy suite. In 2004-2005, a mobile unit was used in the operating theatre (Mobetron, Intraop). Since 2006 IOERT was delivered in a dedicated operating room using a fixed accelerator; an Elektra SL-25 linear accelerator with an in-house developed fixed applicator system. The accuracy of dose delivery with this system is within the range of $\pm 5\%$. The applicator diameter was chosen in such a way that it covered the area at risk within a margin of ± 1 cm. If necessary, bolus material was used to ensure sufficient surface dose at the area at risk for possible residual tumor. The outcome of frozen sections taken during surgery determined IOERT dose and target. When negative, 10 Gy was administered, when positive with microscopic residual disease 12.5 Gy, with macroscopic residual disease (< 2 cm²) 15 Gy was applied, and when positive with gross residual disease (> 2 cm²), 17.5 Gy was delivered. The IOERT dose was specified on the 90% isodose along the central beam axis. The depth of potential tumor involvement of the area at risk was estimated to select the energy needed to obtain an isodose of $90\% \pm 1$ cm beyond this tumor involvement. The energy being used ranged from 6-18 MeV, corresponding to an isodose depth of 1.4 to 2.8 cm depending on the diameter of the applicator (5-9 cm), bevel end of the applicator (0° - 30°), the need of bolus material and the angle between applicator and surface to be irradiated. Eleven patients did not receive IOERT; 6 patients had excessive blood loss, in 3 patients no area at risk could be identified, one patient already received IOERT as part of the primary treatment and in one patient the risk for morbidity was too high.

Statistical analysis

Survival time was calculated from the LRRC resection date until the last follow-up attendance or until death. Time to recurrence, either local (within the pelvis) or distant, was calculated from the LRRC resection date until the histological or evident radiological presence of a local or distant recurrence. Overall, cancer-specific, disease-free, metastasis free survival and local control (OS, CSS, DFS, MFS, and LC, respectively) curves were constructed using the Kaplan-Meier method. Differences in observed survival between groups were tested for statistical significance using log-rank testing. Factors of which the P-value was less than 0.10 in the univariate analysis were included in the multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards regression model. Relations between various parameters were analyzed using χ^2 method. A difference was considered statistically significant if $P \leq 0.05$ (two-sided). Statistical analyses were performed using the SPSS statistical software program (SPSS[®] for Windows Release 15.0, SPSS Inc, Chicago, IL, USA).

RESULTS

Patient and treatment characteristics

Details of the patients and treatment are listed in Table 1. Median anaesthesia time, including time for IOERT, was 375 minutes (range 170-660 min). Median blood loss was 4,750 ml (range 420-34,000ml). Median hospital stay was 19 days (range 2-105 days). Mortality rate within 1 month after operation was 4.8% (n=7), within three months it was 8.2% (n=12). During hospital admission, 95 complications were observed in 86 patients (58.5%, Table 2). Twenty-nine patients experienced urinary retention, requiring prolonged catheterization. Another common complication was a pelvic abscess (n=22), needing a re-intervention in the majority of patients. For the long term complications, standardized questionnaires were regularly sent to the surviving patients (EORTC QLQ C 30 and CR 38 and a more specific postoperative surgical morbidity questionnaire (own design). We found that patients experienced long term complications (Table 2) to some extent, but with the increase of time since the operation, the complaints decreased. We did not find any differences with regard to morbidity for the various IORT doses. However, the number of the higher doses was too low for a statistical analysis.

Table 2. Postoperative complications per type of neoadjuvant therapy

	Total (n=147)	No (n=24)	Re-irradiation (n=57)	Full course (n=66)
Postoperative				
No	61	9	22	30
Urinary retention	29	4	13	12
Abscess	22	2	11	9
Wound infections	17	2	5	10
Sepsis	6	0	4	2
Urinary tract infection	5	0	2	3
Ileus	4	2	1	1
Haemorrhage	3	0	2	1
Venous embolus	3	2	1	0
Fistula	2	1	0	1
Urinary leakage	2	1	1	0
Pneumonia	2	0	1	1
Late postoperative				
Lower extremity neuropathy	32	4	12	16
Ureter stenosis	8	0	4	4
3 months mortality	12	2	4	6

Note. Values are absolute numbers.

Univariate analysis

Median overall survival was 28 months (range 0-146 months). Actuarial 5-year OS, CSS, DFS, MFS and LC were 31.5%, 38.6%, 34.1%, 49.5% and 54.1% respectively. For patients with a Ro resection, median OS was 59 months and the actuarial 5-year OS, CSS, DFS, MFS and LC were 48.4%, 57.5%, 52.3%, 65.5% and 68.9%.

Patient-, primary tumor treatment-, and recurrence treatment-related factors were analyzed in relation to 3-year overall survival, local control and metastasis free survival (Table 3). Radical resection was correlated with significantly better OS (Figure 1), CSS, LC (Figure 2) and MFS (Figure 3) (all $P < 0.001$). Patients who received re-irradiation or full course radiotherapy as part of the treatment of LRRC survived significantly longer ($P = 0.043$) and longer without local recurrence ($P = 0.038$) or metastasis ($P < 0.001$) compared to patients who were not re-irradiated. Patients who had neoadjuvant radio(chemo)therapy experienced fewer metastases ($P < 0.001$), but did not survive longer ($P = 0.170$) than patients who did not receive neoadjuvant treatment. Early TNM stage was associated with increased OS and MFS rates ($P = 0.008$ and $P = 0.023$, respectively). If patients previously underwent an anterior resection, they survived 20 months longer without metastasis ($P = 0.007$) than patients who underwent an APR as primary surgery, but no statistical difference was found in OS ($P = 0.107$) or LC ($P = 0.069$). Patients who could be treated with LAR for the local recurrence survived 1.5 times longer than patients in whom a more extensive resection was required ($P = 0.013$).

Figure 1. Overall survival (OS) analysis. ALL, All patients ($n=147$); R0, radically resected patients ($n=84$); R1-R2, irradically resected patients ($n=63$). R0 patients had a significantly better OS than R1-R2 patients ($P < 0.001$).

Figure 2. Local control (LC) analysis. ALL, All patients ($n=147$); R0, radically resected patients ($n=84$); R1-R2, irradically resected patients ($n=63$). R0 patients had a significantly better LC than R1-R2 patients ($P < 0.001$).

Figure 3. Metastasis free survival (MFS) analysis. ALL, All patients ($n=147$); R0, radically resected patients ($n=84$); R1-R2, irradically resected patients ($n=63$). R0 patients had a significantly better MFS than R1-R2 patients ($P < 0.001$).

Table 3. Univariate analysis of patient-, tumor-, and treatment-related factors

	No.	OS at 3y*	P†	LC at 3y*	P†	MFS at 3y*	P†
All patients	147 (100)	43.8		57.0		53.1	
Age (years)							
<60	55 (37.4)	52.3	0.195	54.1	0.724	58.6	0.525
≥60	92 (62.6)	38.0		58.9		49.6	
Gender							
Male	84 (57.1)	46.5	0.822	56.7	0.636	54.8	0.332
Female	63 (42.9)	40.3		59.4		51.3	
Stage of primary tumor							
I	17 (11.6)	80.1	0.008	57.7	0.599	85.7	0.023
II	68 (46.3)	46.9		54.2		54.3	
III	60 (40.8)	29.8		58.3		39.4	
Unknown	2 (1.3)						
Type of primary surgery							
AR	98 (66.7)	46.0	0.107	64.3	0.069	58.4	0.007
APR	44 (30.0)	37.9		40.7		38.9	
Interval							
≤2 years	68 (46.3)	48.7	0.728	57.9	0.917	60.6	0.221
>2 years	79 (53.7)	40.1		55.9		47.8	
Symptoms at diagnosis							
S0	40 (27.2)	49.9	0.275	59.6	0.031	55.0	0.363
S1	47 (32.0)	47.7		74.7		58.8	
S2	58 (39.5)	36.8		43.3		46.1	
Unknown	2 (1.3)						
Dose EBRT for LRRC (Gy)							
0	24 (16.3)	25.0	0.043	37.6	0.038	17.8	<0.001
30.6 (re-irradiation)	57 (38.8)	47.6		48.9		58.7	
45-50 (full course)	66 (44.9)	49.3		69.0		61.2	
Neoadjuvant RCT for LRRC							
No	24 (16.3)	25.0	0.170	37.6	0.119	17.8	<0.001
RI without chemo	13 (8.9)	53.8		53.3		60.0	
RI with chemo	44 (29.9)	44.9		46.9		54.8	
FC without chemo	23 (15.6)	52.2		69.0		58.8	
FC with chemo	43 (29.3)	47.5		69.1		64.2	
Type of LRRC surgery							
LAR	26 (17.7)	65.1	0.013	80.4	0.055	66.2	0.175
More extensive	121 (82.3)	39.4		51.4		50.0	
Radicality of resection							
R0	84 (57.2)	58.7	<0.001	74.9	<0.001	71.6	<0.001
R1	34 (23.1)	26.5		29.2		30.6	
R2	29 (19.7)	24.1		28.5		18.8	

Note. Values in parentheses are percentages; *values are percentages of patients at three years after the operation. †log rank test. OS, overall survival; LC, local control; MFS, metastasis free survival; AR, anterior resection; APR, abdominoperineal resection; S0, asymptomatic; S1, symptomatic without pain; S2, symptomatic with pain; EBRT, external beam radiation therapy; LRRC, locally recurrent rectal cancer; Gy, Gray; RCT, radio(chemo)therapy; RI, re-irradiation; FC, full course radiotherapy; LAR, low anterior resection; R0, microscopically radical; R1, microscopically Irradical; R2, macroscopically Irradical.

Multivariable analysis

The most important factors influencing overall survival were radicality of resection and stage of the primary tumor (Table 4). After irradical resection the hazard ratio (HR) for early death was 2.11 (CI 1.37-3.24, $P = 0.001$). In patients with a stage II or stage III primary rectal cancer the mortality risk was about three times higher than in patients with a stage I disease ($P = 0.014$ and $P = 0.008$, respectively). Patients who had to undergo a more extensive resection for LRRC had a significantly worse prognosis (HR 2.11, CI 1.09-4.08, $P = 0.027$) than patients only needing a LAR. No significant survival difference was found for neoadjuvant radiotherapy. In the multivariable analysis for local control, radical resection was the only significant factor ($P = 0.001$). The results of the multivariable analysis for metastasis free survival are displayed in Table 5.

Table 4. Multivariable analysis for overall survival

	Hazard ratio	P
Radicality of resection		
Ro	1	
R1+R2	2.11 (1.37-3.24)	0.001
Stage of primary tumor		
I	1	
II	3.00 (1.25-7.19)	0.014
III	3.28 (1.37-7.88)	0.008
Dose EBRT for LRRC (Gy)		
0	1.17 (0.67-2.03)	0.588
30.6 (RI)	0.94 (0.58-1.54)	0.818
45-50 (FC)	1	
Type of LRRC surgery		
LAR	1	
More extensive	2.11 (1.09-4.08)	0.027

Note. Values in parentheses are 95% confidence intervals. Ro, microscopically radical; R1 microscopically irradical; R2, macroscopically irradical; EBRT, external beam radiation therapy; LRRC, locally recurrent rectal cancer; Gy, Gray; RI, re-irradiation; FC, full course radiotherapy; LAR, low anterior resection.

Table 5. Multivariable analysis for metastasis free survival

	Hazard ratio	P
Radicality of resection		
Ro	1	
R1+R2	2.05 (1.13-3.72)	0.018
Stage of primary tumor		
I	1	
II	2.87 (0.85-9.77)	0.091
III	3.41 (1.00-11.67)	0.050
Dose EBRT for LRRC (Gy)		
0	2.24 (1.14-4.39)	0.019
30.6 (RI)	1.01 (0.52-1.97)	0.983
45-50 (FC)	1	
Type of primary surgery		
AR	1	
APR	1.81 (1.00-3.24)	0.048

Note. Values in parentheses are 95% confidence intervals. Ro, microscopically radical; R1 microscopically irradical; R2, macroscopically irradical; EBRT, external beam radiation therapy; LRRC, locally recurrent rectal cancer; Gy, Gray; RI, re-irradiation; FC, full course radiotherapy; AR, anterior resection; APR abdominoperineal resection.

Factors influencing radicality of resection (Table 6)

As our results showed radicality of resection being the most important predictor for survival, we decided to analyze which factors were of influence on the achievement of a radical resection. Neoadjuvant treatment increased the radical resection rate; in patients who received radiotherapy (either full course or re-irradiation) or radiochemotherapy significantly more radical resections were performed than in patients who did not. After previous anterior resection, the achievement of a radical resection of the LRRC was 20% higher than after previous abdominoperineal resection ($P = 0.044$). No pain at time of diagnosis was also correlated with a higher rate of resections with a negative margin ($P = 0.030$).

Table 6. Factors influencing radicality of LRRC resection

	Radical	Irradical	p*
Gender			
Male	46 (54.8)	38 (45.2)	0.614
Female	38 (60.3)	25 (39.7)	
Age (years)			
<60	30 (54.5)	25 (45.5)	0.731
≥60	54 (58.7)	38 (41.3)	
Interval			
≤2 years	42 (61.8)	26 (38.2)	0.319
>2 years	42 (53.2)	37 (46.8)	
Primary TNM stage			
I	11 (64.7)	6 (35.3)	0.189
II	43 (63.2)	25 (36.8)	
III	29 (48.3)	31 (51.7)	
Type of primary surgery			
AR	61 (62.2)	37 (37.8)	0.044
APR	19 (43.2)	25 (56.8)	
Previous EBRT (Gy)			
0	41 (59.4)	28 (40.6)	0.232
25 (short course)	20 (66.7)	10 (33.3)	
45-50 (long course)	23 (47.9)	25 (52.1)	
EBRT for LRRC (Gy)			
No	7 (29.2)	17 (70.8)	0.009
30.6 (re-irradiation)	37 (64.9)	20 (35.1)	
45-50 (full course)	40 (60.6)	26 (39.4)	
Radio(chemo)therapy			
No	7 (29.2)	17 (70.8)	0.008
Radiotherapy	21 (58.3)	15 (41.7)	
Radiochemotherapy	56 (64.4)	31 (35.6)	
Symptoms at diagnosis			
S0	24 (60.0)	16 (40.0)	0.030
S1	33 (70.2)	14 (29.8)	
S2	26 (44.8)	32 (55.2)	

Note. Values in parentheses are percentages. * χ^2 test. LRRC, locally recurrent rectal cancer; AR, anterior resection; APR abdominoperineal resection EBRT, external beam radiation therapy; Gy, Gray; LRRC, locally recurrent rectal cancer; S0, asymptomatic; S1, symptomatic without pain; S2, symptomatic with pain.

Patterns of failure

Median time to local recurrence was 13 months (range 1-87) and to metastasis 11 months (range 1-86). Thirty patients (20.4%) developed metastases within 1 year, 22 (15.0%) had a local recurrence within 1 year. In the long run, around 50% developed a local recurrence or a metastasis (Figures 2 and 3). Twenty-three patients survived more than 5 years

(median 82 months; range 64-146 months). Of these patients, 7 died of the disease, 2 died of another cause and 14 are currently alive with no evidence of disease.

DISCUSSION

This retrospective study of a large patient population assessed whether intensive multimodality treatment was useful in locally recurrent rectal cancer patients. Furthermore, the role of re-irradiation was determined. Multimodality treatment for LRRC has been described as the most encouraging method to improve survival and local control in selected patients^{15,16}. In the present study, an actuarial 5-year survival rate of 31.5% was achieved. This outcome compares favorably to historical reports in which patients were treated with surgery alone (24%)⁷ or with palliative treatment (0%)¹⁷, but still remains somewhat disappointing.

Several factors influencing the outcome of patients with locally recurrent rectal cancer were identified. The most important prognostic factor was radicality of resection. In many studies with fewer patients the importance of a radical resection was already reported^{16,18-22}. In this study, in 57.2% of patients a radical (R0) resection was accomplished. This percentage is consistent with the proportion of circumferential margin free resections reported in literature^{21,23-27}. Median overall survival (OS) and cancer specific survival (CSS) after R0 in this study were 59 and 76 months, respectively. This compares favorably to previous studies which showed survival ranging from 17 to 50 months^{7,9,22,28-31}. Unlike the finding of other authors³² that a difference may be found after gross or microscopic residual disease we did not find a difference in oncological outcome after R1 or R2 resection (Table 3). The major variable was a tumor-free margin. This may be the result of the fact that even minor residual disease represents an aggressive tumor type in our series after intensive neoadjuvant treatment. Another explanation may be the difference in staging. In our R0 group more patients with close margins were present, leaving worse patients in the R1 group.

Another important factor with a positive influence on the outcome was re-irradiation. After re-irradiation significantly more radical resection could be performed (64.9 versus 29.2%, $P = 0.004$) and a significantly better metastasis free survival (MFS) (at 3 years: 58.7 versus 17.8%, $P < 0.001$) was observed compared to surgery alone in patients who had been irradiated for their primary tumor. Other studies report a lower rate of R0 resections when using surgery alone³³⁻³⁵. These findings stress the need for renewed radiotherapy in patients who have previously been irradiated. Our data suggest that re-irradiation even in combination with chemotherapy and intraoperative irradiation boost can be applied safely and may result in a considerable survival benefit and even cure rate. The major concern of re-irradiation is the fear of toxicity^{24,36}. However, as confirmed by others, patients can undergo re-irradiation with an additional dose of 30-40 Gy with acceptable risks, provided that the small intestine is located outside the irradiation field and the interval between previous irradiation and re-irradiation is more than 6 months^{10,26,37-39}. As we found earlier¹⁴, the intensive treatment brings along complications. However, it is difficult to find out if these complications are due to the tumor itself or due to the treatment. In the perspective of severe symptoms of untreated locally recurrent rectal cancer, the intensive multimodality treatment is justified.

Other studies found a benefit of the addition of chemotherapy to the neoadjuvant radiotherapy^{26,40}. However, no statistically significant difference between radiotherapy

and radiochemotherapy was demonstrated in our study. This might be due to small patient numbers.

Furthermore, higher TNM stage of the primary rectal cancer was an important negative prognostic factor. It did not influence local control, but was a significant predictor of OS and MFS on both univariate and multivariable analysis. These findings suggest that positive lymph nodes are representative of further metastatic spread of the disease at the time of primary tumor resection. Vermaas et al.³⁰ and Hruby et al.⁴¹ reported similar results. Primary node positive disease resulted in a significant worse prognosis ($P = 0.0009$ and $P < 0.001$, respectively). This might be an indication to deliver adjuvant chemotherapy after LRRC resection in order to control or prevent systemic disease. Other publications showed only a trend towards improved survival with a lower primary TNM stage^{11,37} or no relation at all^{18,21,25,40,42}.

Not all LRRC patients described in the literature can be compared to those studied in this paper. For example, van den Brink et al.¹¹ described patients from the Dutch TME trial who developed a LRRC. They found an early metastasis rate that approximated 75%, with 40% of these patients already having a distant metastasis at time of LRRC diagnosis. In contrast, the patients in this study were already screened for concomitant metastases before they were referred to our hospital. Therefore, it is not surprising that the number of early metastases was lower in this study. Despite the favorable selection, 50% of these patients still developed metastases over time (Figure 3). The multimodality treatment used focuses primarily on local control. The relative high rate of systemic disease may be an argument to include systemic treatment in the multimodality strategy. If systemic treatment would be administered in a neoadjuvant fashion, response to this treatment might be used as a selection criterion for further invasive procedures: local responders not developing metastases may be better candidates for extended surgery, whereas those who show local progression or even develop metastases under chemotherapy could be spared unnecessary extended surgery. The intensive multimodality treatment is not intended to compensate for macroscopically residual tumor. Therefore, a R2 resection may be considered as a treatment failure. However, at present there is still no modality to reliably discriminate between tissue fibrosis with and without tumor cells. Excluding all patients with severe fibrosis would mean that a proportion of these patients would have been denied a potentially curative resection. Therefore, it is impossible to avoid R2 resections, given the limitations of preoperative staging.

Some comments can be made about this study. It was a retrospective analysis, but the data have been collected prospectively. Heterogeneity in terms of neoadjuvant treatment was due to changes in treatment perspectives (e.g. introduction of total mesorectal excision and preoperative radio(chemo)therapy in primary rectal cancer treatment) in this long period of patient accrual. For example in the early years of the study, re-irradiation was not considered to be a treatment option, but because of more evidence of the feasibility of this approach in later years³⁹, it was started in 1997. Furthermore, the benefit or advantage of IORT could not be discussed in our study as no comparison was possible between patients who received IORT and those who did not, since nearly all patients received IORT (and those who did not had specific reasons for it). Hashiguchi and co-workers⁴³ found a significant survival benefit in patients who received IORT compared to patients who did not (3-year survival rate of 43 versus 5%, $P = 0.0007$). This was also confirmed on multivariate analysis. Several studies describe an increase of the 5-year survival rate of 15% or more after the introduction of IORT as a component of multimodality treatment^{32,44,45}. However, the role of IORT remains

debatable^{29,46}. Careful delivery of IORT is important. The ureters, blood vessels, soft tissue, bone and pelvic nerves are structures at risk of injury from IORT^{13,44,47,48}. IOERT doses of 10-20 Gy are the maximum tolerable doses when combined with EBRT. Data from MGH showed that for primary rectal cancer the combined use of high-dose preoperative EBRT, surgical resection and IOERT was tolerated well¹³. However, in locally advanced recurrent disease the complication rate was higher. Nevertheless, Krempien et al.⁴⁹ described very low long term complications in patients with locally advanced primary rectal cancer treated with TME, IOERT and pre- or postoperative EBRT. The 5-year and 10-year actuarial incidence of $\geq$ grade 3 late complications for the entire group was 9% and 13%, respectively. IORT in combination with re-irradiation leads to a high radiobiological dose and our data support the assumption that this dose can be applied safely. However, large prospective randomized controlled studies are lacking. As local re-recurrence is a great problem after treatment for local recurrence, the administration of high tumorcidal irradiation doses at the areas of risk follows a sound radiobiological principle. The potential contribution of IORT to the improved cure rates reported by others has also been achieved in this analysis.

In summary, in this patient population with a general poor prognosis, the use of multimodality treatment and radical resection has resulted in a more favorable prognosis. Due to the rarity of this entity and the inability to perform randomized studies, the additional values of radiochemotherapy (versus radiotherapy), re-irradiation and IORT (versus no IORT) were not clearly identifiable. Further evaluation is required. However, high rates of radical resections have been reached leading to a significantly improved survival in patients with LRR. Unfortunately, development of metastatic disease remains a great problem. In the future, attention has to be paid to better patient selection and appropriate systemic treatment in order to ameliorate the prognosis even further.

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**Radicality of resection
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PRELIMINARY

ABSTRACT

Purpose

The purpose of this study is to analyze the treatment results of multimodality treatment, in relation to subsite of locally recurrent rectal cancer (LRRC).

Methods

170 patients with LRRC who underwent treatment between 1994 and 2008 were studied. The basic treatment principle of multimodality treatment was preoperative (chemo)radiotherapy, intended radical surgery and intraoperative radiotherapy (IORT). The subsites of LRRC were classified into presacral, postero-lateral, (antero)lateral, anterior, anastomotic or perineal. Subsites were related to radicality of the resection, local re-recurrence rate, distant metastasis rate and cancer-specific survival.

Results

R0-resections were achieved in 54% of the patients and 5-year cancer-specific survival was 40.5%. Worst outcomes were seen in presacral LRRC, with only 28% complete resections and 19% 5-year survival ($P = 0.03$ compared to other subsites). Anastomotic LRRC resulted in the most favorable outcomes, with 77% R0-resections and 60% 5-year survival ($P = 0.04$). Generally, if a complete resection was achieved, survival improved, except in postero-lateral LRRC. Local re-recurrence and metastasis rate were lowest in anastomotic LRRC.

Conclusion

Classification of the subsite of LRRC is a predictor of potentially resectable and consequently curable disease. Treatment of posterior LRRC imposes poor results, while anastomotic LRRC location shows most superior results.

INTRODUCTION

Since the introduction of total mesorectal excision combined with neoadjuvant (chemo)radiation, locally recurrent rectal cancer (LRRC) has become less common. Whereas primary rectal cancer treatment is gradually standardizing, based on preoperative evaluation of the tumor extent, LRRC treatment is still controversial. However, the general idea has shifted from non-intervention or palliative (chemo)radiation to more aggressive multimodal approaches combined with intended radical surgery^{1,2}.

Recent studies have described that radicality of the resection of the LRRC is the most significant predictor of improved survival^{3,5}. Irradical resection is associated with 5-years survival percentages between 0 and 15%, while this is up to 52% in radical resections. Similar improvements in local re-recurrence and distant metastases rates are associated with Ro-resections of LRRC.

Since these extensive treatment strategies can cause serious morbidity, selection of potentially resectable LRRC thus has to receive major emphasis in the preoperative work-up. Modern MRI-techniques can determine the exact location and invasion patterns of the tumor, which allows tailored surgical resection and intraoperative radiotherapy application. It has been reported that central localization of the LRRC results in Ro-resections most often, while peripheral LRRC seems more difficult to resect completely^{6,7}. However, these studies are small and the consequent cumulative local re-recurrence rate (LRR), distant metastases rate (DMR) and cancer-specific survival (CSS) has not been described.

In a previous study patients operated for LRRC in the Catharina Hospital between 1994 and 2006, a national referral center for LRRC in the Netherlands, were analyzed³. In this study the main conclusions were that radicality of the LRRC surgery is the main prognostic factor and that neoadjuvant (chemo)radiotherapy is the best regimen before surgery. However, the effect of the location of the LRRC on radicality remains to be elucidated. Therefore, in this study patients operated between 1994 and 2008 were studied in order to determine the role of the location of the LRRC and its resectability and consequent LRR, MFS and CSS.

METHODS AND MATERIALS

Patients

From March 1994 to February 2008, 209 consecutive patients with LRRC within the pelvis without identified distant metastases at the time of diagnosis, were scheduled for multimodality treatment with curative intent. They were referred from 52 hospitals throughout the Netherlands. The treatment consisted of neoadjuvant (chemo)radiation, extended surgery and intraoperative radiotherapy (IORT) to the area most at risk for residual tumor. Details on this strategy have been described before^{3,8}.

Thirty-nine patients were excluded from further analysis because of the following reasons: 21 proved to have irresectable disease because of tumor growth into S2 or higher or extension beyond the infrapiriform foramen and 8 patients had intraperitoneal metastases. Ten patients were excluded because they had a history of metastectomy before LRRC diagnosis. The data of the remaining 170 patients were analyzed for this

study. Fifteen of these patients did not receive IORT, because of massive blood loss during the operation (6 patients), 4 patients had no area at risk after resection, 2 patients had previous IORT and 3 patients were expected to have too much morbidity from IORT.

Methods

As the Catharina Hospital is a national referral center for patients with LRRC, data on primary surgery and pathology were retrieved from the referring hospitals. A LRRC was defined as any recurrence of rectal cancer in the lesser pelvis. All patients underwent a CT and/or MRI of the pelvis in the preoperative evaluation of the local recurrence before neo-adjuvant treatment. Examining the images the site of the local recurrence was determined and classified into one of the following regions: 1) Presacral: predominantly midline, in contact with the sacral bone, 2) Postero-lateral: laterally located, near to or invading the piriform muscle, in contact with the sacral bone, 3) (Antero)lateral: laterally located, in association with anterior organs or along the iliac vessels or in the obturator lymph node compartment, 4) Anterior: predominantly midline, involving bladder, uterus, vagina, seminal vesicles or prostate, 5) Anastomotic: midline, after low anterior resection, low Hartmann procedure or local excision, at the staple line, 6) Perineal: midline, perineum or anal sphincter complex with surrounding perianal and ischiorectal space, 7) other location.

Details in local recurrence treatment and pathology outcomes were collected retrospectively. After LRRC treatment most patients returned to their initial hospital for follow-up. By contracting these hospitals, follow-up data could be completed in all patients. When patients had developed local re-recurrence, radiologic data were retrieved in order to determine the site of re-recurrence. These were classified into the same subsites as mentioned above.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 16.0 for Windows; SPSS Inc, Chicago, IL, USA). T-tests and chi-square tests were used to compare individual variables. Cumulative local recurrence rate (LRR) was calculated with the time between LRRC surgery and local re-recurrence. Distant metastasis rate (DMR) was calculated with the time between LRRC surgery and time of discovery of distant metastasis. The cancer-specific survival was defined as the time between LRRC surgery and death caused by cancer. 5-Year LRR, DFS and CSS were calculated using the Kaplan-Meier method. Differences were assessed using the log-rank test. Interaction analysis was performed using the cox regression model. All P values were two-sided and considered statistically significant at a value of 0.05 or less.

RESULTS

Patient and treatment characteristics

Median follow-up time for surviving patients was 35 months (range 3-146). No patients were lost to follow-up, 73 patients (43%) died from cancer and 28 (17%) from other causes. Patient and treatment characteristics are listed in Tables 1 and 2. Depending on the subsite of the LRRC, varying types of surgery had been performed. Presacral and postero-lateral recurrences were mostly treated by an abdominotranssacral resection (ASR), anastomotic recurrences by a low anterior resection (LAR) and anterior and perineal recurrences by an abdominoperineal resection (APR). Exenterations were most frequently conducted in anterior recurrences. One patient with a mesosigmoid lymph

node recurrence treated by a debulking of the tumor is not listed in Tables 2-4. Post-operative mortality within three months after surgery occurred in 4 of 20 patients (20%) with postero-lateral recurrences, in 4 of 39 (10%) with presacral, in 3 of 28 (11%) with anterior recurrences and in 3% with (antero)lateral and anastomotic recurrences (both in 1 of 39 patients).

Table 1. Patient and treatment characteristics

	No. of patients (n = 170)	
Median age, years (range)	62	(39-87)
Gender		
Male	99	(58.2)
Female	71	(41.8)
Stage of primary tumor		
I	19	(11.2)
II	72	(42.4)
III	75	(44.1)
Unknown	4	(2.4)
Type of primary surgery		
Local procedure	6	(3.5)
Rectosigmoid resection	20	(11.8)
Low anterior resection	90	(52.9)
Abdominoperineal resection	52	(30.6)
Exenteration	2	(1.2)
Median interval primary-LRRC surgery, months (range)	29	(3-283)
Subsite of LRRC		
Presacral	39	(22.9)
Postero-lateral	20	(11.8)
(Antero)lateral	39	(22.9)
Anterior	28	(16.5)
Anastomotic	39	(22.9)
Perineal	4	(2.6)
Other: lymph node recurrence in mesosigmoid	1	(0.6)
Neoadjuvant treatment for LRRC		
No	25	(14.7)
RI without chemo	15	(8.8)
RI with chemo	56	(32.9)
FC without chemo	23	(13.5)
FC with chemo	51	(30.1)
Dose of IORT (Gy)		
0	15	(8.8)
10 (R0)	83	(48.8)
12.5 (R1)	41	(24.1)
15 (R2)	20	(11.8)
17.5 (R2)	11	(6.5)

Note. Values in parentheses are percentages; LRRC, locally recurrent rectal cancer; RI, re-irradiation (30.6 Gy); FC, full course radiotherapy (50.4 Gy); IORT, intraoperative radiotherapy; R0, microscopically radical resection; R1, microscopically irradiated resection; R2, macroscopically irradiated resection.

Table 2. Type of LRRC surgery for type of LR

	Presacral	Postero-lateral	(Antero)-lateral	Anterior	Anastomotic	Perineal	Total
LAR	3 (7.7)	1 (5.0)	7 (17.9)	2 (7.1)	17 (43.6)	0 (0)	30 (17.6)
APR	9 (23.1)	6 (30.0)	6 (15.4)	13 (46.4)	16 (41.0)	3 (75.0)	53 (31.2)
ASR	19 (48.7)	10 (50.0)	5 (12.8)	1 (3.6)	6 (15.4)	1 (25.0)	42 (24.7)
Ext	6 (15.4)	1 (5.0)	9 (23.1)	10 (35.7)	0 (0)	0 (0)	26 (15.3)
N-A	2 (5.1)	2 (10.0)	12 (30.8)	2 (7.1)	0 (0)	0 (0)	18 (11.2)
Total	39	20	39	28	39	4	169

Note. Values in parentheses are percentages; LRRC, locally recurrent rectal cancer; LR, local recurrence; LAR, low anterior resection; APR, abdominoperineal resection; ASR, abdominotranssacral resection; Ext, exenteration; N-A, non-anatomic.

Radicality

A radical (Ro) resection could be achieved in 54% of all patients. Factors influencing radicality of the LRRC resection significantly in our previous study³ are listed in Table 3. The factors that were not significant in this previous study were also not significant in this analysis. There was a significant interaction between the site of the LRRC and the radicality of the resection ($P = 0.012$). In anastomotic recurrences a complete resection could be achieved most often, while in presacral recurrences only one-fourth of the resections was radical ($P < 0.001$).

Table 3. Factors influencing radicality of resection

	Radical		Irradical		P value
Type of primary surgery					
Sphincter-saving	21	(70)	9	(30)	0.059
Non sphincter-saving	71	(51)	68	(49)	
Subsite of LRRC					
Presacral	11	(28)	28	(72)	<0.001
Postero-lateral	9	(45)	11	(55)	
(Antero)lateral	22	(56)	17	(44)	
Anterior	18	(64)	10	(36)	
Anastomotic	30	(77)	9	(23)	
Perineal	2	(50)	2	(50)	
EBRT for LRRC					
No	9	(36)	16	(64)	0.121
RI	39	(56)	21	(44)	
FC	44	(60)	30	(40)	
(Chemo)radiotherapy					
No	9	(36)	16	(64)	0.103
Radiotherapy	20	(53)	18	(47)	
Chemoradiotherapy	63	(59)	43	(41)	
Symptoms at diagnosis					
S0	24	(57)	18	(43)	0.005
S1	40	(69)	18	(31)	
S2	27	(40)	40	(60)	

Note. Values in parentheses are percentages of the rows; LRRC, locally recurrent rectal cancer; EBRT, external beam radiotherapy; RI, re-irradiation (30.6 Gy); FC, full course radiotherapy (50.4 Gy); S0, asymptomatic; S1, symptomatic without pain; S2, symptomatic with pain.

Table 4. Local re-recurrence rate, distant metastasis rate and cancer specific survival after local recurrence treatment

	All/Ro	N	LRR	DMR	CSS
Presacral	All	39	57	59	19
	Ro	11	38	40	50
Posterolateral	All	20	55	38	37
	Ro	9	43	36	18
(Antero)lateral	All	39	56	62	36
	Ro	22	45	73	33
Anterior	All	28	49	58	39
	Ro	18	29	43	52
Anastomotic	All	39	28	40	60
	Ro	30	24	25	73
Perineal*	All	4	33	0	100
	Ro	2	0	0	100

Note. Values are percentages calculated by the Kaplan Meier method 5 years after local recurrence treatment; All, all patients; Ro, microscopically radical resection; LRR, local re-recurrence rate; DMR, distant metastasis rate; CSS, cancer-specific survival; *At maximum follow-up of 20 months.

Figure 1. Local re-recurrence rate after treatment according to subsite (top left).**Figure 2.** Distant metastasis rate after treatment according to subsite (top right).**Figure 3.** Cancer-specific survival rate after treatment according to subsite (bottom left).

Local re-recurrence

Local re-recurrence occurred in 54 (46%) of all patients after 5 years. Re-recurrence developed in the presacral subsite in 28 of the 54 (52%) cases; in the postero-lateral in 11 (20%), in the (antero)lateral in 9 (17%) and in another subsite in 6 (11%) patients. Re-recurrence developed in 30 (71%) of the 77 R1/R2 resections and in 22 (32%) of the 93 Ro resections after 5 years ($P < 0.001$). After resection of presacral, postero- and (antero)lateral recurrences re-recurrence was between 55 and 57% (Table 4, Figure 1). Anastomotic recurrences developed least re-recurrences; 24% after 5 years. Anastomotic, anterior and perineal LRRC resulted in significantly fewer local re-recurrences, compared to presacral, postero- and (antero)lateral LRRC ($P = 0.05$). Of the 154 patients who received IOERT, 51 developed local re-recurrence (47% 5-year rate). Of these 51 re-recurrences, 28 were located outside the IORT-field and 23 were in the IORT-field. Re-recurrences outside the IORT-field occurred in 14 (22%) of the 93 Ro resections and in 12 (30%) of the 77 R1/R2 resections ($P = 0.24$) after 5 years. 5-Year re-recurrence rate in the IORT-field was 54% ($n = 17$) in the R1/R2 resections, which was higher than 9% ($n = 6$) in Ro resections ($P = 0.003$).

Distant metastases rate and cancer-specific survival

Overall 5-year metastases rate and cancer-specific survival rate were 51.6% and 40.5%, respectively. The distant metastasis rate was 74.2% after an irradical resection and 37.1% after a radical resection ($P < 0.001$). In Table 4 distant metastasis rate according to LRRC location is listed. Anastomotic and postero-lateral recurrences together resulted in a 38% 5-year distant metastases rate, significantly lower than presacral, (antero)lateral and anterior recurrences together with a rate of 61% ($P = 0.03$, Figure 2). In subgroup analyses, comparing only patients with a radical resection, the location of LRRC did not statistically influence distant metastases rate. 5-Year cancer-specific survival was 18% after irradical resections, compared to 58% after radical resections ($P < 0.001$). Cancer-specific survival in anastomotic recurrences was significantly better (58%), compared to other recurrences with a combined survival rate of 34% (Figure 3) after 5 years ($P = 0.04$). Presacral recurrences resulted in 19% cancer-specific survival, significantly worse ($P = 0.03$) than other recurrences (48%). Comparing only patients with a radical resection, posterolateral LRRC resulted in a significantly worse prognosis (18% cancer-specific survival), compared to other LRRC sites (62%, $P = 0.01$).

DISCUSSION

The purpose of this study was to relate the location of LRRC treated with aggressive multimodality treatment with the oncological results in 170 patients, in terms of radicality, local re-recurrence, distant spread and survival. Few studies have reported on radicality in relation to subsites of pelvic recurrences, but it is difficult to draw conclusions from these, as they also reported on recurrences of other than rectal cancer⁶ or selected the most favorable patients for a resection⁷. In this study only patients with extra-pelvic extended LRRC or distant metastases were excluded, giving unbiased outcomes on treatment results.

This study showed that presacral local recurrences are most difficult to resect radically, with only 28% complete resections. Anastomotic local recurrences resulted in the highest Ro resection percentage (77%), while other types of recurrences resulted in 54-64% complete resections. This radicality was reflected in survival after LRRC resection, which varied from 19% after 5-years in presacral recurrences to 60% in anastomotic recurrences. If a complete resection was achieved no significant

differences existed in survival between the LRRC types, except a significantly worse survival in postero-lateral recurrences. Local re-recurrence and metastasis rate were lower in anastomotic recurrences compared to other types, but this difference disappeared when only R0 resections were selected.

Radicality of a LRRC resection is still the most significant prognostic factor. Depending on the operation and careful selection for surgery, percentages of complete resections in the literature vary from 26 to 79%^{1,4-7,9-12}. In this study the overall complete resection rate was 54%, which is high, keeping in mind no patients were excluded from multimodality treatment. Factors affecting potentially complete microscopic resection are reported to be initial APR-surgery, advanced stage of the primary tumor, pain at LRRC diagnosis and the presence of hydronephrosis^{1,3,13,14}. These characteristics of primary disease and symptoms at LRRC diagnosis are directly related to subsite of local recurrence, as advanced disease and APR-surgery are often associated with presacral local recurrence and most of the mentioned symptoms logically occur more often in peripheral than in central tumor location¹⁵. Consequently, the best way of judging the potential resectability in the preoperative work-up might be by classification of the subsite of LRRC.

Anastomotic LRRC show superior results in terms of LRR, DMR and CSS after multimodality treatment, compared to other types of LRRC. This is in concordance with the findings of other authors^{7,16,17}, in which central LRRC seemed to behave more as a 'localized' local recurrence than peripheral LRRC. Mechanisms causing anastomotic LRRC are most probably surgical, such as inadequate distal margin or incomplete local excision. (Antero)lateral and anterior tumor extension requires a more extended resection and there seems to be a trend towards more distant spread in (antero)lateral tumors, but small patient numbers make this debatable.

Presacral and postero-lateral recurrences impose a major problem in LRRC-surgery, as also described by Moore et al.⁶. Irradical resection rates and consequent cancer-related death rates are considerable. In this study 20% of the patients with a postero-lateral recurrence died within three months after surgery, due to surgery-related complications. This might be due to the highly advanced character of the posterior recurrences in this study, which retrospectively might have been too large to attempt curative resection. Furthermore, that most local re-recurrences occurred in the posterior compartment, stresses the fact that very advanced pelvic disease is inherent to posterior location. The question is whether or not the 5-year survival rate of around 20% weighs up against the surgery-related morbidity and mortality in these patients. Abdominotranssacral resection is a high risk procedure with post-operative complications in 60-80% of the patients^{10,11,18,19}. Post-operative mortality has been reported to be around 3-6%. On the other hand, non-intervention leads to a reduced quality of life with debilitating pain and severe complications. As a consequence of the findings of this study, patients with posterior LRRC should be approached differently in future. A PET SUV scan before and after two courses of chemotherapy can differentiate between responders and non-responders. Responders should then be offered aggressive treatment, with consequent chemoradiotherapy, surgery and IORT. In non-responders optimal palliative treatment should be considered instead.

Because of heterogeneity of the patients with respect to treatment dose and the fact that some patients were not treated with IORT, the additional effect of IORT is difficult to quantify. It is obvious however, that as much as 29% of the patients with a R1/R2

resection did not develop a local re-recurrence after 5 years. This suggests that IORT could have sterilized these residual tumor deposits. It is logical that re-recurrence rate in the IORT-field was higher in irradiated resections, compared to radical resections. However, the finding that 22-30% of the patients developed pelvic re-recurrence outside the IORT-field, not significantly different between R0 and R1/R2 resections, is striking. Somehow, even after a radical resection, tumor particles must have been left behind in areas not considered at risk. One could hypothesize that in transit tumor cells in the lateral lymph flow routes leak back into the surgical volume, as it was shown that Japanese patients had more local recurrences when the lateral lymph nodes on one side were left behind, than when a bilateral lymph node dissection was performed²⁰. Of course this theory remains speculative. But if the theory can be proven right and patients at risk for re-recurrence originating from lateral lymph flow routes can be selected pre- or intraoperatively, a lateral lymph node dissection or a boost of IORT on the lateral pedicles might prevent re-recurrence.

In conclusion, a multimodality treatment strategy is essential to achieve curation in the treatment of locally recurrent rectal cancer. In a previous study we showed that margin involvement is an important prognostic factor in LRRRC treatment³, but evidence of how to predict this preoperatively was lacking. Classification of the subsite of LRRRC is a good predictor of a radical resection, and consequently curable disease.

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Summary/Discussion
Conclusions
Future research

Chapter 10

The general aim was to assess the role of various tools to provide the optimal treatment for a patient with rectal cancer. This aim was subdivided into three specific aims.

1. To assess the accuracy of imaging in staging and restaging of primary and recurrent rectal cancer.
2. To assess the role of histopathology and molecular markers in the prediction of local recurrence and treatment outcome respectively.
3. To evaluate the results of multimodality treatment in locally recurrent rectal cancer.

Accuracy of imaging in (re)staging of primary and recurrent rectal cancer

In this thesis, we addressed the issue whether a Multi-Detector row Computed Tomography (MDCT), routinely performed in the staging of disseminated disease, could be valuable as a first line locoregional staging method of the primary rectal cancer (**chapter 3**), and on the value of a restaging magnetic resonance imaging (MRI) in locally advanced rectal cancer (LARC) patients after neoadjuvant chemoradiation for the selection of the good responders for further tailoring of treatment (**chapter 2**). For recurrent rectal cancer, the accuracy of MRI for the prediction of tumor invasion into pelvic structures (**chapter 7**) and the role of positron emission tomography (PET) in distant staging (**chapter 6**) were assessed.

Staging in primary rectal cancer

Imaging is very important in the preoperative management of rectal cancer. The identification of risk factors such as the chance of a positive circumferential resection margin (CRM) allows a stratification of the treatment for different risks of recurrence. In TME surgery, the chance of a positive CRM is represented by the distance of the tumor to the mesorectal fascia (MRF), the standard plane of resection¹. The relationship between the tumor and the MRF should be accurately predicted before surgery. Many studies focused on primary staging of rectal cancer with MRI and showed that high-spatial-resolution MR imaging with phased array surface coils is very accurate for the prediction of tumor involvement of the MRF and has gained a pivotal role in rectal cancer staging²⁻⁷. Apart from MRI, the local tumor extent could also be assessed with MDCT. A clear advantage of MDCT is the quick acquisition of detailed whole body data in order to devise an integral treatment plan by providing both local and distant tumor information simultaneously. Although the staging capabilities of MDCT for metastatic colorectal disease such as liver metastasis have been established⁸, little is known about the important prediction of the tumor relationship to the MRF. When MDCT is a good alternative to MRI, its performance for the prediction of MRF invasion should be comparable to the present standard MRI. The study in **chapter 3** assessed the performance of MDCT for the prediction of MRF invasion in 35 patients at patient level and at different anatomical locations by two observers. MRI served as reference standard. Our data demonstrated a poor accuracy at patient level (54-66%) of MDCT for the prediction of tumor invasion of the MRF. It had a reasonably high accuracy for the prediction of an invaded MRF (AUC 0.84-0.88) in mid-high located tumors, but the staging accuracy appeared poor for distal tumors (AUC 0.31-0.50). The inherent suboptimal tissue contrast resolution of CT is insufficient in the provision of anatomical detail critical in regions where structures are close to each other such as the distal rectum. Based on our results, CT cannot be considered as a good alternative for MRI for prediction of tumor invasion of the MRF, especially not for staging advanced rectal cancer at high risk for local recurrences. MRI is known to have a far better contrast

resolution than CT and is very reliable for the prediction of the circumferential resection margin. Prediction of lymph node status is more difficult, and 2 reviews showed comparable results for lymph node staging with endorectal ultrasound (EUS), CT and standard MRI^{7,9}. However, lymph node staging with USPIO enhanced MRI shows more promising results¹⁰. This means that identification of the other important risk factor, the lymph node status, may improve, and could be used for risk assessment and further treatment stratification. This has been studied in a multicenter study (unpublished data) that assessed the outcome of a differentiated treatment protocol, based primarily on MRI. The multicenter study included all rectal cancers, and defined three basic treatment groups of surgery only, 5x5 Gray (Gy) and surgery, and chemoradiation followed by surgery. The number of complete resections was significantly higher than in the Dutch TME trial, in which a standard preoperative imaging was not required (95.6% versus 84%, $P < 0.0001$). Furthermore, the actuarial local recurrence rate of 2.8% at 2 years seems promising.

Restaging in primary rectal cancer

Patients with locally advanced rectal cancer are treated with a long course of neoadjuvant chemoradiation to decrease the local recurrence rate^{11,12}. The patient is operated about 6-8 weeks after completion of the chemoradiation course. With radiotherapy alone there was little need for restaging after neoadjuvant treatment, as major downsizing and downstaging was not often observed. However, with the present neoadjuvant chemoradiation schemes a much more pronounced effect is present in the majority of patients. A less extensive resection could be considered in these patients. cT4 tumors that no longer appear to invade surrounding organs could undergo a TME instead of a more extensive resection. cT3-4 tumors that have responded very well with only a small remnant in the bowel wall (ypT0-2N0) may even be treated with a local excision. This is controversial and accurate restaging tools are required. In **chapter 2** we focused on the question whether MRI is accurate in the prediction of a tumor remnant after chemoradiation that is confined to the rectal wall. Three observers retrospectively evaluated MR images of 67 patients who underwent a MRI prior to their resection. MRI has a PPV of 91% for the prediction of ypT0-2 using morphological criteria, with an interesting finding that volume measurements have a supplementary value for ypT0-2 prediction, improving the PPV from 91% to 94% and NPV from 75% to 84%. The advantage of volumetric measurements above other more complex and time consuming tools like functional imaging or metabolic imaging is, apart from its restricted cost, the easy implementation in clinical practice where the radiologist can increase his/her level of confidence with 3 simple measurements of tumor height, width and depth. The accuracy of MRI assessment of a tumor remnant that is limited to the bowel wall was further prospectively evaluated in a multicenter study, described in two related theses on MR imaging of rectal cancer by M.J. Lahaye and S.M.E. Engelen. They also addressed the accuracy of MRI for lymph node staging after chemoradiation.

Staging in recurrent rectal cancer

Two questions have been addressed. 1: is MRI accurate for the prediction of local extent of the tumor and can it provide a surgical roadmap? 2: Is PET reliable in the detection or exclusion of distant metastases and does it influence patient management?

In primary rectal cancer, MRI can reliably predict the distance between tumor and other pelvic structures³. Local staging of recurrent rectal cancer with MRI has not gained much attention in the literature. Most imaging studies have focused on the detection of a local recurrence¹³, rather than on the staging once it has been diagnosed. In **chapter 7**,

4 observers (3 radiologists and a surgeon) assessed the accuracy of preoperative MRI for the prediction of tumor invasion of pelvic structures in 40 patients scheduled for treatment with curative intent. MRI was very accurate, with negative predictive values (NPVs) of above 90% and AUCs of 0.79-1.00. The major staging difficulty was interpretation of diffuse hypo-intense tissue at the pelvic side walls, which could be read as either fibrosis or tumor. Many other studies on restaging after chemoradiation in primary rectal cancer and on detection of local recurrence also acknowledge the difficulty of interpreting fibrosis^{14,15}. Although many criteria have been proposed for the distinction between tumor and fibrosis¹⁶, none has proven to be very specific^{17,18}. In recurrent rectal cancer the interpretation of fibrosis is more complex than in primary rectal cancer, because it is caused by various factors: primary irradiation, surgery and re-irradiation. Overall, however, we believe that MR imaging is useful as preoperative road map providing information on the exact tumor extent and on the structures that require resection.

18 FDG-PET has been found to have role in discrimination between responders and non responders after neoadjuvant chemoradiation in primary rectal cancer, for the differentiation between scar and local recurrence and for staging liver metastases before curative liver surgery^{19,20}. However, its role in distant staging in patients with a local recurrence is less well known. **Chapter 6** describes the clinical impact of PET compared with conventional imaging (CT and MRI) in 37 pelvic recurrences of rectal cancer. PET and conventional imaging were identical in 24 cases (65%). In 13 cases (35%) PET findings differed from CT/MRI; in 7 of these cases PET showed more extensive disease (upstaging of the disease) and in 6 PET showed more limited disease than CT/MRI (downstaging the disease). PET was most helpful in detecting disease outside the pelvis that was not clear on CT/MR, like involved inguinal lymph nodes. The PET findings influenced the management in 5 patients. In our opinion PET can yield information that is important for treatment planning in patients scheduled for curative resection of the local recurrence. Still, additional prospective studies are needed for a better quantification of the specific benefits of PET in relation to the other diagnostic modalities.

Role of histopathology and molecular markers

In **chapter 5** we report on histopathological prognostic factors predictive for the development of a local recurrence by comparing primary rectal cancer resection specimens of patients who developed a recurrence with a matched control group who did not develop a local recurrence. The presence of lymphovascular invasion, extramural venous invasion, positive CRM, serosal involvement and poor differentiation were identified as factors with an increased risk to develop a local recurrence. Our findings are in agreement with prior studies^{21,22}. In **chapter 4** it was investigated whether treatment outcome could be predicted by intrinsic and induced apoptosis and by 5 apoptosis-regulating proteins (p53, Bcl-2, Bax, Cox-2 and maspin) in patients with locally advanced rectal cancer who received neoadjuvant chemoradiation. Immunohistochemistry was performed on pre-therapy and post-therapy tissues. Apoptosis was investigated with the M30 antibody. Apoptosis or the related proteins (p53, Bcl-2, Bax, Cox-2) were not related with survival, local recurrence or tumor regression grade in this population. A strong cytoplasmatic staining pattern of maspin in the pre-treatment biopsies significantly correlated with an increased risk of local recurrence but was not associated with survival. These data lead to the conclusion that success of chemoradiation is independent of the intrinsic levels of apoptosis or the apoptosis regulation proteins

studied. The literature is not conclusive on the clinical implications of apoptosis and the apoptosis regulating proteins so it is advisable to further investigate this issue²³⁻²⁶.

Results of multimodality treatment in locally recurrent rectal cancer

Specialized referral centers who treat patients with non metastasized local recurrence of a rectal cancer have used a multimodality treatment that consists of neoadjuvant chemoradiation followed by extensive surgery, and in some centers intraoperative radiotherapy (IORT)^{27,28}. In the past, treatment resulted in low rates of radical resections with low survival rates²⁹. Recent studies show that with the current multimodality treatment the chances for a complete resection are 40-80%^{30,31}. We studied the outcome of patients who underwent multimodality treatment in the Catharina Hospital from 1994 onwards. The overall outcome is reported in **chapter 8**. A radical resection could be achieved in 57% of 147 patients, with a 5-year cancer specific survival rates of 39% for all patients and 58% in patients in whom a complete resection was obtained. The achievement of radical resection was the most important prognostic factor for survival. After re-irradiation significantly more radical resection could be performed (64.9 versus 29.2%, $P = 0.004$) and a significantly better metastasis free survival (MFS) (at 3 years: 58.7 versus 17.8%, $P < 0.001$) was observed compared to surgery alone in patients who had been irradiated previously for their primary tumor. The major concern of re-irradiation is the fear for a toxic dose to the surrounding normal tissues, that could lead to an increased short and long term complication rate^{31,32}. It is our belief that the advantages of an improved outcome outweigh these possible disadvantages. Re-irradiation with an additional dose of 30-40 Gy has been reported to be feasible with acceptable risks³³. Proper attention to both radiation and surgical techniques are essential. The use of small radiation fields, carefully fractionated radiation doses, exclusion of bowel and bladder and a time interval between initial irradiation and re-irradiation of at least 6 months minimize potential morbidity.

Unfortunately, a considerable amount of patients still underwent an irradical resection that will offer little benefit, and in many patients distant metastases are discovered within a year after the operation. This suggest that not all patients were suitable for a curative resection. In **chapter 9** the relation between the outcome of resection of locally recurrent rectal cancer and the anatomical subsite was investigated in a larger group of patients ($n=170$). The subsite of LRRC proved to be a predictor of potentially resectable and consequently curable disease. In anastomotic recurrences a complete resection could be achieved most often (77%), while in presacral recurrences only one-fourth of the resections was radical. Furthermore, the 60% survival in anastomotic recurrences was significantly better, compared to other recurrences with survival rates between 19-39% after 5 years. Presacral recurrences resulted in only 19% survival. Nearly all patients in both studies (**chapter 8** and **9**) received IORT. Therefore, the additional effect of IORT was difficult to quantify. In **chapter 9**, it is reported that 29% of the patients with a R1/R2 resection did not develop a local re-recurrence after 5 years. This suggests that IORT may have sterilized residual tumor deposits in some of the patients. The significant difference between renewed recurrence in the field of IORT between Ro and R1/R2 resections (9% versus 54%) suggests on the other hand that it cannot sterilize all of the remaining tumor deposits. It could however well be that the good local control in the IORT field after a Ro resection is not only the result of the surgeon obtaining a free margin, but also of the additional IORT. With the diffuse growth pattern of a local recurrence and the re-irradiation effect, evaluation of the margins is not always easy for the pathologist, and even after Ro resection small tumor deposits may be left behind.

CONCLUSIONS

1. MRI is very accurate in the prediction of tumor extent after neoadjuvant chemoradiation in locally advanced primary and recurrent rectal cancer.
2. MDCT has a poor accuracy for predicting mesorectal fascia invasion in distal rectal tumors. The accuracy of CT significantly improves for proximal tumors.
3. Histopathological factors can help in predicting the chances of a local recurrence. Success of neoadjuvant chemoradiation is independent of apoptosis (regulating proteins).
4. In a selected population with pelvic rectal cancer recurrences scheduled for curative resection, PET has additional value to conventional imaging, mainly in detecting lymph node metastases.
5. Radical resection is the most important factor for improved survival in patients treated with multimodality treatment for locally recurrent rectal cancer. Radicality is dependent on neoadjuvant chemoradiation and subsite of the recurrence.

FUTURE RESEARCH

It is a well-known fact that a radical resection is the ultimate goal of rectal cancer management. In our study MRI proves to be a good predictor of tumors downsized to lesions confined to the rectal wall (ypT0-2) by combining morphological and volumetric criteria. Our volumetric criteria are still tentative and require further research. A good prediction of ypT0-2 tumors may lead to a more limited surgery of these tumors without decreasing the chance of a radical resection. Further research should investigate the outcomes of this MRI based treatment strategy.

Although MRI is very accurate in the prediction of tumor extent as shown in chapter 2 and 7, it still has difficulty in the interpretation of diffuse fibrotic tissue. The early detection of metastatic disease is yet another area that should be improved. Dynamic contrast-enhanced MRI, diffusion weighted MRI or molecular MRI, new molecular nuclear imaging techniques and hybrid MR-PET techniques, some of which can provide whole body scanning, may provide a solution to this problem and should be studied.

High resolution MRI is the method of choice for staging of primary rectal cancer. Our study in chapter 3 revealed that MDCT should not be used for rectal cancer staging as a standard procedure. However in exceptional cases, when MRI is not available or contraindicated, MDCT may be a good alternative if the tumor is expected to be located in the proximal rectum. The presently used MDCT techniques may yield better results than the techniques described in our study. This needs to be examined.

Staging of rectal cancer may be refined with the use of specific molecular markers. These markers may provide more detailed information about patient and tumor characteristics with which better assessment of the diagnosis and the prognosis can be accomplished. The combination of multiple markers is likely to yield even more useful information as demonstrated with the microarray techniques in breast cancer. Other markers may provide a prediction of the response to a certain treatment, such as wild

type versus mutated K-ras in cetuximab and will allow a more tailored treatment with a higher therapeutic ratio. Progress in this field of translational research is eagerly awaited.

Though treatment of locally recurrent rectal cancer has taken many steps forward, metastatic disease is still a major problem after local recurrence surgery. Despite the aggressive treatment of the local recurrence, a great number of patients develop early metastases. The hypothesis is that many local recurrence patients already have undetectable distant metastases. Therefore, it is advisable to perform studies in which early systemic treatment is included in the management of these patients.

The central question of this thesis was how to provide the most optimal treatment for each rectal cancer patient. It is of utmost importance to approach rectal cancer management in a multidisciplinary manner.

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ACHTERGROND

In Nederland krijgen ongeveer 10.000 mensen per jaar dikkedarm/endeldarm kanker (colorectaal carcinoom). Bij vrouwen is het de 2^e meest voorkomende maligniteit na borstkanker, bij mannen de 3^e meest voorkomende maligniteit na prostaat- en longkanker. Ongeveer 50% zal overlijden aan deze ziekte. Een derde van de colorectaal tumoren bevindt zich in het rectum. De behandeling van rectum carcinoom is de laatste jaren sterk verbeterd door invoering van de totale mesorectale excisie (TME) en voorbehandeling met radiotherapie en chemotherapie. Hierdoor is de overleving gestegen van 31% in de jaren '50 tot 59% in het begin van deze eeuw. De effectiviteit van de behandelingstechnieken roept de vraag op of de behandeling nog verder aangepast kan worden om tot een optimale behandeling van iedere individuele rectum carcinoom patiënt te komen.

SAMENVATTING/DISCUSSIE

Het algemene doel van dit proefschrift was om de rol van verschillende instrumenten vast te stellen bij het optimaliseren van de behandeling voor een patiënt met endeldarm kanker (rectum carcinoom). Dit doel werd onderverdeeld in drie specifieke doelen.

1. Het bepalen van de nauwkeurigheid van beeldvorming in staging en herstaging van primair en recidief rectum carcinoom.
2. Het bepalen van de rol van histopathologie en moleculaire markers voor het voorspellen van het ontstaan van een lokaal recidief en de uitkomst van de behandeling.
3. Evaluatie van de resultaten van multimodale behandeling voor lokaal recidief rectum carcinoom.

Nauwkeurigheid van beeldvorming in (her)staging van primair en recidief rectum carcinoom

In dit proefschrift hebben we bekeken of een Multi-Detector row Computed Tomography (MDCT), welke routinematig gebruikt wordt bij het stageren van uitzaaiingen (metastasen), ook waardevol kan zijn als eerste lijns techniek voor de locoregionale staging van primair rectum carcinoom (**hoofdstuk 3**). Verder hebben we gekeken naar de waarde van magnetic resonance imaging (MRI) bij lokaal voortgeschreden rectum carcinoom (LARC) na voorbehandeling met radiotherapie en chemotherapie (chemoradiatie) om de patiënten die goed reageren op deze voorbehandeling te selecteren en zodoende verdere geïndividualiseerde behandeling te geven (**hoofdstuk 2**). Bij recidief rectum carcinoom werden de nauwkeurigheid van MRI voor het voorspellen van tumor invasie in de bekkenstructuren (**hoofdstuk 7**) en de rol van positron emission tomography (PET) in staging van metastasen (**hoofdstuk 6**) bepaald.

Staging van primair rectum carcinoom

Beeldvorming is essentieel bij de preoperatieve benadering van rectum carcinoom. Het identificeren van risicofactoren, zoals bijvoorbeeld de kans op een positieve circumferentiële resectiemarge (CRM), helpt om de behandeling te stratificeren aan de hand van de verschillende kansen op een recidief. Bij totale mesorectale excisie (TME)

chirurgie wordt de kans op een positieve CRM weergegeven door de afstand tussen de tumor en de mesorectale fascie (MRF), de standaard resectie marge. Het is belangrijk om deze relatie zorgvuldig te voorspellen voor de operatie. Veel studies hebben zich gericht op de primaire staging van rectum carcinoom met behulp van MRI en lieten zien dat MRI met hoge spatiële resolutie en met phased array oppervlakte spoelen zeer nauwkeurig is in het voorspellen van tumorinvasie van de MRF en dat MRI een centrale rol heeft ingenomen in de staging van rectum carcinoom. Behalve met MRI kan de lokale uitgebreidheid van de tumor ook vastgesteld worden met MCDT. Een duidelijk voordeel van MCDT is de snelle afbeelding van het gehele lichaam zodat er meteen informatie beschikbaar is van zowel de lokale tumor als de metastasen op afstand, waardoor het behandelplan snel gemaakt kan worden. Hoewel het vaststaat dat MDCT goed is in het stageren van metastatische colorectale ziekte, zoals levermetastasen, is er maar weinig bekend over de nauwkeurigheid van MDCT voor de belangrijke voorspelling van tumorinvasie van de MRF. Als MCDT een goed alternatief zou zijn voor MRI zou MDCT tumorinvasie van de MRF even goed moeten kunnen voorspellen als de huidige standaard MRI. De studie in **hoofdstuk 3** bepaalde bij 35 patiënten de nauwkeurigheid van MCDT om MRF invasie te voorspellen. Er werd door 2 radiologen gescoord op patiënt niveau en op verschillende anatomische lokaties. MRI was de referentie standaard. Onze gegevens toonden een lage nauwkeurigheid van MCDT op patiënt niveau (54-66%) voor het voorspellen van tumorinvasie van de MRF. MCDT had een redelijk hoge nauwkeurigheid voor het voorspellen van de tumorinvasie van de MRF (AUC (area under the receiver operating characteristic curve) 0.84-0.88) bij middelhoog gelokaliseerde tumoren, maar de nauwkeurigheid was laag bij laaggelegen tumoren (AUC 0.31-0.50). De inherente suboptimale weefsel contrast resolutie van CT is onvoldoende om anatomische details te geven die beslissend zijn wanneer structuren dicht bij elkaar liggen zoals in het lage rectum. Gebaseerd op onze resultaten kan CT niet beschouwd worden als een goed alternatief voor MRI voor het voorspellen van tumorinvasie van de MRF, vooral niet bij staging van lokaal voortgeschreden rectum carcinoom met een hoog risico op het ontstaan van een lokaal recidief. Het is bekend dat MRI een veel betere contrast resolutie heeft dan CT en zeer betrouwbaar is voor het voorspellen van de CRM. Het voorspellen van de lymfklier status is moeilijker. Twee reviews toonden vergelijkbare resultaten voor lymfklier staging met endorectale echo, CT en MRI. Lymfklier staging met MRI met lymfklierspecifiek contrast (USPIO) laat echter veelbelovende resultaten zien. Dit betekent dat het identificeren van de andere belangrijke factor, de lymfklier status, verbeterd kan worden en gebruikt kan worden om het risico op een lokaal recidief te bepalen en de behandeling verder te stratificeren. Dit is bestudeerd in een multicentrische studie (waarvan de gegevens nog niet gepubliceerd zijn) waar de uitkomsten van een op MRI gebaseerd gedifferentieerd behandelprotocol werden bepaald. Deze multicentrische studie includeerde alle rectum carcinomen en definieerde drie behandelgroepen namelijk alleen chirurgie, een kort periode van bestraling (5x5 Gray) gevolgd door chirurgie en een lang schema van chemoradiatie gevolgd door chirurgie. Het aantal complete resecties was significant hoger dan in de Nederlandse TME trial waarin standaard preoperatieve beeldvorming geen vereiste was (95.6% versus 84%, $P < 0.0001$). Bovendien lijkt een lokaal recidief percentage van 2.8% in twee jaar veelbelovend.

Herstaging van primair rectum carcinoom

Patiënten met lokaal voortgeschreden rectum carcinoom worden voorbehandeld met langdurige neoadjuvante chemoradiatie om de kans op het ontstaan van een lokaal recidief te verkleinen. Zes tot acht weken na chemoradiatie wordt de patiënt geopereerd. Toen de patiënten nog voorbehandeld werden met alleen radiotherapie

was herstagering na voorbehandeling niet zo belangrijk, omdat de radiotherapie geen duidelijke afname van het tumorvolume bewerkstelligde. Met de huidige chemoradiatie neemt het tumorvolume echter wel degelijk aanzienlijk af bij de meeste patiënten. Bij deze patiënten zou een beperktere operatie overwogen kunnen worden aangezien de tumor geslonken is. Patiënten met initieel een T4 tumor die na chemoradiatie niet meer lijkt in te groeien in omringende organen zouden een TME kunnen ondergaan in plaats van de zeer uitgebreide resectie die nodig zou zijn voor de T4 tumor. cT3-4 tumoren die zeer goed gereageerd hebben en waarbij er alleen nog maar een kleine tumorrest in de darmwand (ypT0-2No) aanwezig is zouden zelfs met een lokale excisie behandeld kunnen worden. Dit is controversieel en accurate beeldvorming is noodzakelijk om dit beleid in te voeren. In **hoofdstuk 2** hebben we gekeken of MRI nauwkeurig is voor het voorspellen van een tumorrest die beperkt is tot de rectumwand na chemoradiatie (ypT0-2). Drie scoorders hebben de MR beelden van 67 patiënten die een MRI hadden ondergaan voor de tumorresectie retrospectief beoordeeld. Met gebruik van morfologische criteria had MRI een positief voorspellende waarde (PPV) van 91% voor het voorspellen van tumoren beperkt tot de rectumwand. Als daar de volumemetingen bij betrokken werden steeg de PPV van 91% naar 94% en de negatief voorspellende waarde (NPV) van 75% naar 84%. Het voordeel van volumemetingen boven andere ingewikkelde en tijdrovende metingen zoals functionele of metabolische beeldvorming is, behalve lage kosten, de makkelijke toepasbaarheid in de dagelijkse kliniek. Door eenvoudigweg tumor hoogte, lengte en breedte te meten kunnen de voorspellingen verbeterd worden. Een prospectieve multicentrische studie heeft de nauwkeurigheid van MRI voor het voorspellen van tumor beperkt tot de rectumwand verder bepaald. Dit staat beschreven in twee gerelateerde theses over MR beeldvorming van rectum carcinoom door M.J. Lahaye en S.M.E. Engelen. Zij hebben ook gekeken naar de nauwkeurigheid van MRI voor lymfklier stagering na chemoradiatie.

Stagering van recidief rectum carcinoom

We hebben twee vragen proberen te beantwoorden. 1: Kan MRI de uitgebreidheid van tumorgroei nauwkeurig voorspellen en kan het dienen als leidraad waarop chirurgie kan worden gebaseerd? 2: Is PET betrouwbaar in het aantonen van uitzaaiingen (metastasen) en heeft het invloed op de behandeling?

Het is aangetoond dat MRI de afstand tussen de tumor en de omgevende structuren nauwkeurig kan voorspellen in primair rectum carcinoom. De rol van MRI bij stagering van recidief rectum carcinoom is echter nog niet uitgebreid onderzocht. De meeste studies hebben zich gericht op het ontdekken van een lokaal recidief en niet zozeer op het stageren van het recidief als dat eenmaal is gediagnostiseerd. In **hoofdstuk 7** hebben 4 scoorders (3 radiologen en 1 chirurg) de nauwkeurigheid van MRI bepaald voor het voorspellen van tumoringroei in omringende structuren bij 40 patienten die ingepland waren voor een curatieve behandeling. MRI was zeer nauwkeurig met NPVs van boven de 90% en areas under the ROC curves (AUCs) van 0.79-1.00. Het grootste struikelblok was de differentiatie tussen tumor en fibrose in het geval van diffuus hypointens weefsel, met name ter hoogte van de bekkenwand. Veel studies over herstagering van primair rectum carcinoom na voorbehandeling met chemoradiatie erkennen het probleem van de interpretatie van fibrose. Ondanks dat er al veel criteria zijn voorgesteld voor het onderscheid tussen tumor en fibrose, is er geen enkele die erg specifiek blijkt te zijn. Bij recidief rectum carcinoom is de interpretatie van fibrose zelfs nog moeilijker dan bij de primaire tumor, omdat de fibrose door verschillende factoren wordt veroorzaakt: primaire bestraling, operatie en herbestraling. In het algemeen zijn wij van mening dat MRI toch bruikbaar is in de preoperatieve setting door het

verschaffen van exacte informatie over de uitgebreidheid van de tumorgroei en over de structuren die verwijderd moeten worden.

18 FDG-PET heeft een rol in het onderscheiden van responders en nonresponders na voorbehandeling met chemoradiatie in primair rectum carcinoom, in het onderscheid maken tussen littekenweefsel en lokaal recidief tumor weefsel en in het stageren van uitzaaiingen in de lever voor curatieve lever chirurgie. Het is echter minder bekend wat de rol van PET is in het stageren van patiënten met een lokaal recidief. **Hoofdstuk 6** beschrijft de klinische relevantie van PET in vergelijking met conventionele beeldvorming (CT en MRI) bij 37 lokale recidieven. PET was gelijk aan de conventionele beeldvorming in 24 gevallen (65%). In 13 gevallen (35%) was er een verschil tussen PET en CT/MRI, waarbij PET in 7 gevallen uitgebreidere ziekte aantoonde (upstaging van de ziekte) en in 6 gevallen liet PET een beperktere ziekte zien dan op CT/MRI (downstaging van de ziekte). PET had de meeste toegevoegde waarde bij het aantonen van tumor buiten het kleine bekken, zoals positieve lymfklieren in de liezen. In 5 patiënten had de uitkomst van de PET een invloed op de behandeling. Wij vinden dat PET informatie kan verschaffen die belangrijk is voor het plannen van de behandeling van patiënten die ingepland staan voor een curatieve resectie van een lokaal recidief. Er zijn echter aanvullende prospectieve studies nodig om de specifieke voordelen van PET te bepalen.

Rol van histopathologie en moleculaire markers

In **hoofdstuk 5** vergelijken we de resectiepreparaten van patiënten die wel een recidief hebben ontwikkeld met die van patiënten die geen recidief hebben ontwikkeld om te onderzoeken of er histopathologische factoren zijn die voorspellend zijn voor het ontstaan van een recidief. Tumor ingroei in de lymfevaatjes (lymfovasculaire invasie), in de bloevaten in het omliggende mesorectale vet (extramurale veneuze invasie), in de circumferentiële resectie marge en in de serosa en slechte tumor differentiatie blijken factoren te zijn met een verhoogd risico om een lokaal recidief te ontwikkelen. Eerdere studies hebben dit ook gevonden. In **hoofdstuk 4** hebben we onderzocht of de uitkomst van de behandeling voorspeld kan worden door geprogrammeerde celdood (apoptose) en 5 apoptose gerelateerde eiwitten (p53, Bcl-2, Bax, Cox-2 en maspine) in patiënten met lokaal voortgeschreden rectum carcinoom die voorbehandeld werden met chemoradiatie. Onbehandelde bipten en posttherapie resectiemateriaal werd onderzocht met behulp van immunohistochemie. Apoptose en de apoptose gerelateerde eiwitten (p53, Bcl-2, Bax en Cox-2) bleken geen correlatie te hebben met overleving, het optreden van een lokaal recidief of tumorregressie in deze populatie. Een sterke cytoplasmatische aankleuring van maspine in de bipten was significant gecorreleerd met een verhoogd risico op het ontstaan van een lokaal recidief, maar was niet gecorreleerd met overleving. Dit alles heeft geleid tot de conclusie dat het succes van chemoradiatie onafhankelijk is van het intrinsieke niveau van apoptose of de onderzochte apoptose gerelateerde eiwitten. Aangezien de literatuur niet conclusief is over de klinische toepasbaarheid van apoptose en de apoptose gerelateerde eiwitten is aanvullend onderzoek hiernaar gewenst.

Resultaten van multimodale behandeling van het lokale recidief van rectum carcinoom

De behandeling van patiënten met een lokaal recidief zonder metastasen in gespecialiseerde verwijscentra bestaat uit multimodale behandeling: voorbehandeling met chemoradiatie gevolgd door uitgebreide chirurgie en soms intraoperatieve radiotherapie (IORT). Vroeger waren de uitkomsten van de behandeling van een lokaal recidief niet zo goed, werden er maar weinig radicale resecties bereikt en waren de overlevingscijfers laag. Recente studies tonen aan dat met de huidige multimodale

behandeling de kans op een radicale resectie 40-80% is. Wij hebben de uitkomsten onderzocht van patiënten die een multimodale behandeling ondergingen in het Catharina ziekenhuis vanaf 1994. De uitkomsten worden beschreven in **hoofdstuk 8**. In 57% van de patiënten kon er een radicale resectie bereikt worden. De kanker specifieke 5-jaarsoverleving was 39% voor alle patiënten en zelfs 58% in patiënten met een radicale resectie. Het behalen van een radicale resectie was de belangrijkste prognostische factor voor overleving. Na herbestraling konden er significant meer radicale resecties (64.9 versus 29.2%, $P = 0.004$) en een betere metastase vrije overleving (bij 3 jaar: 58.7 versus 17.8%) bereikt worden in vergelijking met alleen chirurgie bij patiënten die al bestraald waren voor hun primaire tumor. Bij herbestraling is het belangrijk om erop te letten dat het normale weefsel rondom de tumor geen toxische bestralingsdosis krijgt hetgeen zou kunnen leiden tot toegenomen korte en lange termijn complicaties. Wij geloven dat de voordelen van een verbeterde uitkomst de mogelijke nadelen overtreffen. Het is beschreven dat herbestraling met een dosis van 30-40 Gy toepasbaar is met acceptabele risico's mits er goed gelet wordt op de bestralings- en operatietechnieken. De mogelijke morbiditeit wordt geminimaliseerd door het gebruik van kleine bestralingsvelden waarbij de dunne darm en de blaas buiten het bestralingsgebied liggen, door goed gefractioneerde doses en door een tijdsinterval tussen de primaire bestraling en de herbestraling van minimaal 6 maanden.

Helaas is er nog een aanzienlijke hoeveelheid patiënten die een irradicale resectie heeft ondergaan en worden er bij veel patiënten metastasen ontdekt binnen een jaar na de operatie. Dit suggereert dat niet alle patiënten geschikte kandidaten zijn voor een curatieve resectie. In **hoofdstuk 9** wordt de relatie onderzocht tussen de uitkomst van resectie van het lokale recidief en de anatomische lokatie van het recidief. De lokatie bleek een voorspeller te zijn van potentieel resectabele en dus curabele ziekte. Bij recidieven ter hoogte van de naad (anastomose) kon in 77% een radicale resectie bereikt worden, bij presacrale recidieven maar in ¼ van de gevallen. De eerstgenoemde recidieven hadden ook een significant betere 5-jaars overleving van 60% ten opzichte van 19-39% bij lokale recidieven op een andere lokatie. De 5-jaars overleving van presacrale recidieven was slechts 19%. In beide studies (hoofdstuk 8 en 9) kregen nagenoeg alle patiënten IORT, waardoor het additionele effect van IORT moeilijk quantificeerbaar was. Uit hoofdstuk 9 blijkt dat 29% van de patiënten met een R1/R2 resectie geen lokaal recidief ontwikkelde in 5 jaar. Dit suggereert dat IORT in sommige patiënten de resttumor heeft gesteriliseerd. Aan de andere kant, het significante verschil in re-recidief binnen het IORT veld tussen radicale (R0) en irradicale (R1/R2) resecties (9% versus 54%) suggereert dat IORT niet alle resttumor kan steriliseren. Het kan echter zo zijn dat de goede lokale controle in het IORT veld na een R0 resectie niet alleen het resultaat is van het verkrijgen van een vrije marge door de chirurg maar ook van het additionele effect van de IORT. Door het diffuse groeipatroon van een lokaal recidief en door het effect van de herbestraling is de evaluatie van de resectie marge niet altijd even makkelijk voor de patholoog, zelfs na een R0 resectie kunnen er kleine tumorresten achtergebleven zijn.

CONCLUSIES

1. MRI is zeer nauwkeurig in het voorspellen van de uitgebreidheid van tumorgroei na voorbehandeling met chemoradiatie in lokaal voortgeschreden en recidief rectum carcinoom.

2. MDCT is niet nauwkeurig in het voorspellen van tumorinvasie van de mesorectale fascia in laaggelegen rectum tumoren. De nauwkeurigheid neemt significant toe voor hooggelegen tumoren.
3. Histopathologische factoren kunnen behulpzaam zijn bij het voorspellen van de kans op een lokaal recidief. Succes van chemoradiatie is onafhankelijk van apoptose (gerelateerde eiwitten).
4. In een geselecteerd groep patiënten met een lokaal recidief van het rectum carcinoom die ingepland zijn voor een curatieve resectie heeft PET een toegevoegde waarde naast conventionele beeldvorming, met name in het detecteren van positieve lymfklieren.
5. Een radicale resectie is de belangrijkste factor voor verbeterde overleving in patiënten die multimodaal worden behandeld voor hun lokale recidief van het rectum carcinoom. Radicaliteit is afhankelijk van voorbehandeling met chemoradiatie en de lokatie van het recidief.

TOEKOMSTIG ONDERZOEK

Het is algemeen bekend dat een radicale resectie het ultieme doel is van de behandeling van rectum carcinoom. Met onze studie hebben we aangetoond dat MRI een goede voorspeller is van tumoren die beperkt zijn tot de rectumwand (ypT0-2) door het combineren van morfologische en volume criteria. Verder onderzoek is nodig om onze volume criteria te valideren. Een goede voorspelling van ypT0-2 tumoren zou kunnen leiden tot beperktere chirurgie van deze tumoren zonder de kans op een radicale resectie te verlagen. Verder onderzoek is nodig om de uitkomsten van deze op MRI gebaseerde behandeling te bestuderen.

Hoewel MRI zeer nauwkeurig is in het voorspellen van de uitgebreidheid van tumorgroei, zoals aangetoond in hoofdstuk 2 en 7, blijft de interpretatie van diffuus fibrotisch weefsel moeilijk. Ook de vroege detectie van metastasen verdient verbetering. Dynamic contrast enhanced MRI, diffusie gewogen MRI of moleculaire MRI, nieuwe moleculaire nucleaire beeldvormingstechnieken en hybride MRI-PET technieken, waarvan enkele technieken scans van het hele lichaam kunnen bieden, kunnen wellicht hier een oplossing voor bieden en moeten bestudeerd worden.

Stagering van primair rectum carcinoom dient gedaan te worden met hoge resolutie MRI. Onze studie in hoofdstuk 3 liet zien dat MDCT niet gebruikt zou mogen worden als standaard procedure voor het stageren van rectum carcinoom. Echter, in uitzonderlijke gevallen als MRI niet beschikbaar of gecontraïndiceerd is, kan MDCT een goed alternatief zijn als de verwachting is dat de tumor zich hoog in het rectum bevindt. De huidige MDCT technieken zullen wellicht betere resultaten geven dan de technieken die beschreven zijn in onze studie. Dit moet onderzocht worden.

Het stageren van rectum carcinoom zou verder verfijnd kunnen worden door het gebruik van specifieke moleculaire markers. Deze markers zouden een gedetailleerdere informatie kunnen geven over de patiënt en tumor gerelateerde factoren waarmee een betere vaststelling van de diagnose en prognose verkregen zou kunnen worden. De combinatie van multi-pele markers zou zelfs nog bruikbaarere informatie kunnen

verschaffen, zoals blijkt uit de microarray technieken bij borstkanker. Andere markers zouden een voorspelling kunnen geven over de respons op bepaalde behandeling, zoals wild type versus gemuteerde K-ras bij cetuximab. Hiermee zou verdere geïndividualiseerde behandeling met een hogere therapeutische ratio bewerkstelligd kunnen worden. Voortgang op dit gebied is zeer welkom.

Ondanks dat er veel bereikt is op het gebied van behandeling van het lokale recidief van rectum carcinoom, is het ontstaan van metastasen na chirurgie nog een groot probleem. Ondanks de agressieve behandeling ontwikkelen veel patiënten metastasen snel na de operatie. De hypothese is dat veel patiënten met een lokaal recidief mogelijk al metastasen hebben die niet te detecteren zijn. Het is aan te raden om studies uit te voeren waarbij patiënten in een vroeg stadium van hun behandeling systemisch worden behandeld.

De centrale vraag van dit proefschrift was op welke manier elke rectum carcinoom patiënt de beste behandeling geboden kon worden. Het is van cruciaal belang om het rectum carcinoom op een multidisciplinaire manier te benaderen.

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CURRICULUM VITAE

De schrijver van dit proefschrift is geboren op 22 juli 1982 in Maastricht. In 2000 behaalde ze haar VWO diploma aan de scholengemeenschap Sophianum in Gulpen. In hetzelfde jaar startte ze met de opleiding Geneeskunde aan de Universiteit Maastricht. Haar wetenschapsstage en keuzeonderwijs volgde ze op de afdeling Radiologie van het Maastricht Universitair Medisch Centrum, onder begeleiding van Dr. R.F.A. Vliegen en Prof. dr. R.G.H. Beets-Tan. In augustus 2006 startte ze haar promotieonderzoek in het Catharina ziekenhuis in Eindhoven onder begeleiding van Dr. H.J.T. Rutten en later in het Maastricht Universitair Medisch Centrum onder begeleiding van Dr. G.L. Beets en Prof. dr. R.G.H. Beets-Tan. Haar thesis is het resultaat van een succesvolle multidisciplinaire samenwerking in research ter verbetering van de behandeling van de patiënt met een (recidief) rectum tumor. Het omvat studies die zijn uitgevoerd niet alleen op de afdelingen Chirurgie en Radiologie van het Catharina ziekenhuis Eindhoven en Maastricht Universitair Medisch Centrum, maar ook op de afdeling Pathologie van beide ziekenhuizen en het Universitair Medisch Centrum St. Radboud in Nijmegen, dit laatste onder begeleiding van Dr. I.D. Nagtegaal en Prof. dr. H.J.M.H. van Krieken. Sinds november 2008 is zij in opleiding tot radioloog in het Maastricht Universitair Medisch Centrum (opleiders Dr. M.W. de Haan en Prof. dr. J.E. Wildberger).

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