The Multimodality Treatment of Locally Advanced and Locally Recurrent Rectal Cancer

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The Multimodality Treatment of Locally Advanced and Locally Recurrent Rectal Cancer

De multimodaliteitsbehandeling van het lokaal voortgeschreden en het lokaal recidiverend rectumcarcinoom

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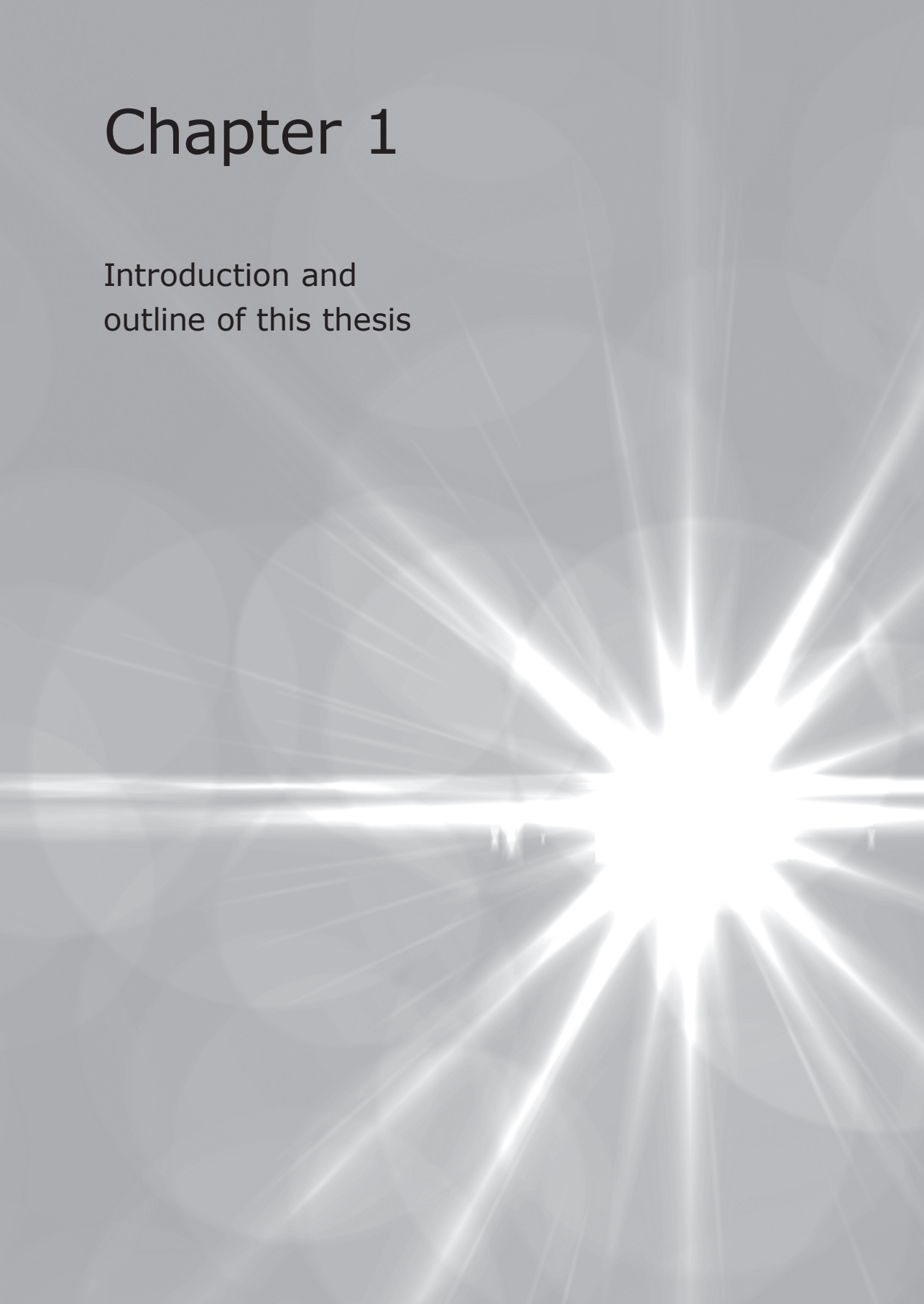
Chapter 1

Introduction and
outline of this thesis



Introduction

Although the incidence of colorectal cancer decreases in the United States and seems to stabilize in The Netherlands, it remains the third most common malignancy among women and men in most Western countries.[1,2] Rectal cancer accounts for approximately one third of the total number of colorectal cancer patients and differs substantially from colon cancer. Generally, rectal malignancies are located under the peritoneal reflection, are closely related to the surrounding vital structures and are fixed within the pelvis. Colon malignancies are located intraperitoneally and are less often related to structures nearby. This factor makes rectal cancer different than colon cancer with different surgical and therapeutic options.

The treatment of rectal cancer has improved drastically in the last 3 decades, leading to improved outcomes. Historically, the outcome of rectal cancer has been poorer than the outcome of colon cancer. However, due to advancements in the treatment of rectal cancer the long-term outcome is now similar to colon cancer.[3,4] The main advancement is the introduction of a surgical technique, called total mesorectal excision (TME). Sir Bill Heald first described the TME-technique in 1979[5] and first long-term outcome of a large cohort of rectal cancer patients treated by this procedure was published in 1986.[6] This technique comprises a complete removal of the lymph node bearing mesorectum along with its intact enveloping fascia. This procedure has two advantages attributing to an improved long-term outcome. Firstly, the TME technique leads to a higher number of complete resections by leaving the visceral fascia intact. Secondly, TME leads to a complete removal of all possible regional lymph node metastases, which could potentially evolve into local recurrences.[7] Before the introduction of TME, local recurrence rates were reported up to 45%.[8-10] Currently, the local recurrence rate rarely exceeds 10% after rectal cancer surgery. Although no randomized controlled trials are available, it is highly likely that TME is the main cause of the decreased local recurrence rate and a prolonged overall survival after rectal cancer surgery.[11]

Simultaneously with the introduction of the TME technique, radiotherapy made its entry in rectal cancer management. The first high quality meta-analysis was published in 1989 demonstrating an improvement in local control without a beneficial effect on the overall survival.[12] Since then, many randomized trials have been executed on the effect of radiotherapy. The 'Dutch TME trial' and the German trial CAO/ARO/AIO-94 were one of the most important studies. The Dutch TME trial showed that even with TME surgery a short-course radiotherapy (5x5 Gy) leads to an improved local control.[11] The CAO/ARO/AIO-94 trial demonstrated that pre-operative radiotherapy resulted in a lower local recurrence rate compared to post-operative radiotherapy.[13] This has led to the current practice only to administer radiotherapy in a neo-adjuvant manner. The last important advancement concerning radiotherapy was combining it with concurrent chemotherapy. It

was shown that radiotherapy with concurrent chemotherapy as a radiosensitizer improves local control without an effect on survival benefit.[14,15]

The third major advancement in the treatment of rectal cancer is the quality of rectal cancer imaging. Two decades ago a digital rectal examination was standard of care to determine the extensiveness of the rectal malignancy. The introduction of Magnetic Resonance (MR) imaging has greatly improved rectal cancer staging. First single center series exploring the use of MR imaging in rectal cancer staging were published in the 80s,[16,17] but MR-imaging became standard of care in the first decade of the 21th century. The accuracies of tumor staging, nodal staging and circumferential resection margin involvement are superior compared to computed Tomographic scans (CT) or endoscopic ultrasound sonography (EUS).[18-20] Moreover, the Mercury trial has showed that MR imaging could accurately assess the completeness of the surgical resection margins and that MR imaging was accurately reproducible in multiple centers.[21] These factors have led to the recommendation to use MR imaging for pre-operative local staging in all guidelines.

TME surgery, neoadjuvant radiotherapy and improved imaging modalities have brought a great quality improvement in rectal cancer management, resulting in improved local control and improved overall survival after rectal cancer surgery. Currently, the treatment has shifted towards a more personalized approach, depending on the local tumor stage. Early stages of rectal cancer require a different treatment strategy than the more advanced stages of rectal cancer. For example, early stage rectal cancer (T1-2N0) can be treated safely by performing surgery alone without neo-adjuvant radiotherapy.[22] Moreover, these patients may be offered organ-sparing procedures resulting in a lower morbidity rate.[23] Presently, there is even evidence that surgery can be omitted in highly selected patients in case of a complete clinical response after neo-adjuvant chemoradiotherapy. Several single center series have suggested that this so called 'watch and wait' approach is safe.[24,25]

The more advanced stages (e.g. locally advanced rectal cancer), on which the current thesis focuses, require a different approach. Locally advanced rectal cancer (LARC) is associated with higher local recurrence rates and poorer overall survival rates compared to the less advanced stages.[26] Therefore, LARC requires a multimodality approach with optimal staging, neo-adjuvant therapy and 'tailor-made' surgery to improve outcome. The circumferential resection margin (CRM) is often at risk and standard TME-surgery would lead to incomplete resections. Incomplete resections are detrimental for oncological outcome.[27] Neo-adjuvant (chemo-)radiotherapy is an essential part of the treatment of LARC, because it leads to lower local recurrence rates and tumor shrinkage (e.g. downstaging). Downstaging may render initially unresectable rectal malignancies into resectable tumors and thereby facilitating a complete resection.[14,15,22] Despite the downstaging effect of neo-adjuvant (chemo-)radiotherapy, a more radical

surgical approach, such as extralevatory abdominoperineal resections and partial or total exenterations, are often necessary to achieve complete resection magins.[28] These 'beyond TME' procedures are technically demanding with high complication and morbidity rates and may benefit from an experienced surgical team.[29]

Despite the advancements in primary rectal cancer treatment, 6-10% of the patients still develop a local recurrence.[11,14] Locally recurrent rectal cancer (LRRC) is usually accompanied by severe progressive pain, a poor quality of life and a poor overall survival. The treatment of LRRC is challenging. It is a heterogeneous disease varying from small central anastomotic recurrences to large pre-sacral or lateral recurrences with bony involvement of the sacrum or pelvis. A complete surgical resection is the only chance on durable local control and overall survival.[30] Several institutes across the world have explored the possibilities of the surgical treatment of LRRC and showed encouraging local control and overall survival rates when LRRC is treated in a multimodality manner.[31-33] The surgical treatment is technically demanding. Pelvic exenterative surgery is often necessary to achieve complete surgical margins but comes with a high complication and morbidity rate.[34]

The first chapters of this thesis focus on local staging. Previously mentioned, local staging is an essential part of high quality rectal cancer treatment. The accuracy of rectal cancer staging has greatly improved since the introduction of MR imaging. Unfortunately, the use of neo-adjuvant (chemo-)radiotherapy has confronted us with a new problem. Potentially, (chemo-)radiotherapy provides us the opportunity to perform less radical surgery due to the downstaging effect. However, the grade of downstaging differs per person and it seems useful to reassess the local tumor extent after (chemo-) radiotherapy. Unfortunately, the accuracy of MR imaging after (chemo-)radiotherapy is poor and this questions the usefulness of local restaging.[35,36] Fibrosis and local reactions caused by the radiotherapy makes it difficult to differentiate between viable tumor and non-malignant tissue. To improve restaging accuracy, it could be useful to add Dynamic Contrast Enhanced (DCE) sequences to MRI restaging. DCE may be helpful to differentiate between malignant and non-malignant tissue due to different contrast enhanced patterns. **In chapter 2** of this thesis we evaluated whether the addition DCE sequences resulted in an improved tumor, nodal staging and assessment of CRM involvement.

Local staging mainly determines the optimal treatment in rectal cancer management. However, detecting distant metastases is at least as important in order to offer patients optimal treatment. Approximately 20% of the patients are diagnosed with synchronous distant metastases at presentation.[37] These patients can, in case of limited metastatic disease, be offered resection of both metastases and primary tumor. If this is not the case, these patients should be referred for palliative care. Fortunately, most patients present without distant metastases and are candidates for curative surgery. In case of

LARC, patients are scheduled for neo-adjuvant (chemo-)radiotherapy and planned for surgery approximately 8-12 weeks after ending (chemo-)radiotherapy. The duration of a long course of (chemo-)radiotherapy is approximately 5 weeks and this means surgery is performed 4 to 5 months after initial staging. In this period new metastases may have developed or may become visible on imaging. This is particularly the case in LARC patients as these patients have the highest chance of developing distant metastases.[27,38,39] It could be of additional value to restage these patients by a thoraco-abdominal CT-scan after neo-adjuvant (chemo-)radiotherapy to identify patients with new distant metastases. This would have clinical impact, since these patients could be offered a different surgical approach or these patients could be spared surgery in case of extensive metastasized disease and be referred for palliative care. **In chapter 3**, we evaluated the benefit of restaging by thoraco-abdominal CT-scan after a long course (chemo-)radiotherapy for LARC.

Despite the poor accuracy of restaging techniques after (chemo-)radiotherapy, it is widely used. To evaluate the usefulness, we briefly reviewed the current literature to evaluate and question the potential benefit of restaging **in chapter 4**.

After optimal staging and neo-adjuvant therapy, patients with LARC are planned for the most suitable surgical procedure. The downstaging effect of neo-adjuvant therapy and beyond TME surgery may result in complete resections in the majority of the patients. However, due to the extensiveness of the local tumor some patients may still have involved circumferential resection margins (CRM). Involved CRMs leads to poor oncologic outcomes with high local recurrence rates and poor overall survival.[40] In an attempt to improve outcomes for these patients, several institutes across the world have implemented intra-operative radiotherapy (IORT) to their multimodality approach. The advantage of IORT is that a local radiotherapy boost can be administered at a specific area at risk, while other radiosensitive tissue, such as the small intestine and bladder, can be shielded from this radiation therapy. One single dose of IORT is considered to have a two to three times higher biological equivalent than fractioned radiotherapy. Therefore, a 10 Gy radiation dose may be able to eliminate microscopic remnants after a microscopically incomplete resection.[41,42] **In chapter 5**, we evaluated the effect of IORT in LARC on the local recurrence rate after neo-adjuvant (chemo-)radiotherapy and TME surgery.

The multimodality treatment of LARC results in improved oncological outcomes, whereas the benefit of a multimodality approach in early stage rectal cancer is limited. Moreover, the surgical treatment of early stage rectal cancer is considered to be technically less demanding. These factors render early stage and locally advanced rectal cancer to be considered as two different diseases. The most advanced stage (cT4) rectal cancer is relatively rare. In this stage radical surgical procedures are often necessary and these procedures are accompanied by high complication and morbidity rates. These

patients may potentially benefit the most from a dedicated and experienced (surgical) multidisciplinary team. Therefore, the benefit of treatment in dedicated high volume hospital may be more apparent in cT4 rectal cancer than in the more common cT1-3 rectal cancer. **In chapter 6**, we hypothesized that the effect of hospital volume in the treatment of cT4 rectal cancer was more important than in cT1-3 rectal cancer. We have analyzed the overall survival in a large population based study according to the hospital volume for cT4 and cT1-3 rectal cancer separately. A previous population based study did not find evidence that hospital volume regardless of the tumor stage was associated with a long-term overall survival in the Netherlands.[43]

Approximately 20% of the colorectal cancer patients are diagnosed with synchronous distant metastases.[44,45] Patients with limited metastatic disease can be treated with curative intent by a synchronous resection of primary tumor and metastases, by a 'liver first' approach or a resection of the metastases in a later stage.[46] Unfortunately, the majority of the patients is not suitable for a curative resection. For these patients, the best treatment strategy remains unclear. They can undergo a palliative resection of the primary tumor, which is frequently performed worldwide or they can be treated with palliative systemic therapy.[47] In case of disabling symptoms, there may be an indication for resection. In asymptomatic or mildly symptomatic tumors, the effect of primary tumor resection is questionable. Some advocate primary tumor resection, as it would lead to a prolonged survival. However, the studies suggesting a beneficial effect of primary tumor resection are often limited by selection bias. In these studies only patients in good clinical condition were considered candidates for surgery. High level evidence (e.g. randomized controlled trials) is lacking. Therefore, i**n chapter 7**, we reviewed the current evidence of primary tumor resection in stage IV colorectal cancer with unresectable metastatic disease.

The introduction of TME surgery and pelvic radiotherapy introduced a new problem of treating this new 'type' of LRRC. The optimal LCCR treatment includes neo-adjuvant (chemo-)radiotherapy to improve local control.[48] However, when the primary tumor has already been treated with radiotherapy, the radiation dose for LRRC treatment is limited. Additionally, previous TME-surgery makes complete resection of the local recurrence more demanding due to the fact that local recurrences after TME surgery may not be limited to an anatomical compartment. These factors render treatment of LRRC after TME surgery and previous radiotherapy more difficult. Furthermore it makes it questionable whether these patients still should be offered surgical treatment. **In chapter 8**, we have evaluated the outcome of LRRC in patients who received pelvic radiotherapy and TME surgery and compared it to the outcome of patients who did not receive previous pelvic radiotherapy.

In LRRC treatment, the single most important prognostic factor for overall survival and disease free survival is the resection margin status.[49] A complete resection (R0)

can lead to 5-year survival rates up to 60%, while incomplete resections (R1/2) lead to significantly poorer outcomes.[50,51] All efforts should be made to achieve a R0-resection by tumor downstaging by neo-adjuvant therapy and performing more radical surgery. In primary rectal cancer, it is unclear whether to consider 1mm or 2mm as an involved resection margin. Some authors plea to consider margins less or equal to 1mm to be involved, while others advice to consider margins less or equal to 2mm to be involved[27,52,53]. Nonetheless, there is consensus that close margins, either 1 or 2 mm, are associated with poorer oncological outcomes. If this is also the case in LRRC is unknown as it has never been evaluated. This may be important, because this could determine the extensiveness of the surgical resection and it may be helpful to inform patients more accurately after surgery about their prognosis. **In chapter 9**, we have evaluated the association between width of the tumor-free resection margin and the long term outcome after LRRC surgery.

Although surgical resection is the only durable option for long-term overall survival and local control, only 31-40% of the LRRC patients are considered to be suitable candidates for a curative surgical resection.[33,54] The majority of the patients have metastatic disease or an advanced local recurrence till such an extend that surgical resection is technically impossible or futile. These patients can be treated by pelvic radiotherapy in case of pain or may be offered chemotherapy which may prolong overall survival. Currently, a high number of patients diagnosed with LRRC have already received pelvic radiotherapy for the primary tumor. These patients represent an even more challenging group to treat palliatively. The radiation dose is limited and chemotherapy may not be as effective due to radiation induced fibrosis and scarring. The poorer response of chemotherapy in irradiated area has been previously demonstrated in recurrent cervical cancer. A meta-analysis found that the proportion of women who responded to treatment was significantly lower for recurrences within the pelvic field compared with disease outside of the pelvic radiotherapy field.[55] Whether this is also the case in LRRC is unknown and in **chapter 10**, we have evaluated the response of chemotherapy on the local recurrence in previously irradiated area and compared it to distant metastases outside the radiation field in that patient.

That study found that the proportion of women who responded to treatment was significantly lower for recurrences within the pelvic field compared with disease outside of the pelvic radiotherapy field

Due to the rarity of LRRC and the complexity of the optimal curative and palliative treatment, the treatment options for physicians in the Netherlands are relatively unknown. A multimodality approach can lead to a relatively good oncological outcome. On the other hand, even for patients with LRRC without curative options, there are several options to alleviate symptoms. In **chapter 11**, we have reviewed the current

literature to evaluate the outcome of the surgical treatment and explored the possibilities of both curative and palliative treatment of LRRC.

Summarizing, the treatment of rectal cancer has drastically improved over the last 3 decades. The treatment has shifted towards a more personalized treatment. LARC and LRRC represent a challenging group of patients who require a multimodality approach to achieve optimal oncological outcome. The current thesis aimed to further improve this multimodality treatment.

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Chapter 2

Prediction of tumor stage and lymph node involvement with dynamic contrast-enhanced MRI after chemoradiotherapy for locally advanced rectal cancer.

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Abstract

Purpose

The usefulness of restaging by MRI after chemoradiotherapy (CTxRTx) in patients with locally advanced rectal cancer has not yet been established, mostly due to the difficult differentiation between viable tumor and fibrosis. MRI with dynamic contrast-enhanced (DCE) sequences may be of additional value in distinguishing malignant from non-malignant tissue. The aim of this study was to assess the accuracy of tumor, nodal staging and CRM involvement by MRI with DCE sequences after CTxRTx.

Methods

The accuracies were assessed by MRI on T2-weighted MR images with DCE sequences in patients with locally advanced rectal cancer after long course CTxRTx. MR images were assessed by two independent radiologists.

Results

For tumor staging and CRM involvement, MRI with DCE sequences had an accuracy of 45% and 60%, respectively. The accuracy for nodal staging was 93%. On MRI, malignant lymph nodes had a median diameter of 8 mm (range, 4 – 18 and benign lymph nodes a median diameter of 4mm (range, 3 – 11). A significant indicator for benign nodes was hypointensity on T2 weighted images *(*$p < 0.001$) and early complete arterial phase enhancement on dynamic contrast-enhanced weighted images *(*$p < 0.001$). A significant indicator for malignant nodes was heterogeneity on T2 weighted images (χ^2 $p < 0.000$) and early incomplete arterial phase enhancement on dynamic contrast-enhanced ($p < 0.001$).

Conclusions

MRI with DCE is a useful tool for nodal staging after CTxRTx. The addition of DCE sequences did not improve the accuracy of determining the tumor stage, CRM involvement and in detecting complete response.

Introduction

Colorectal cancer is the third most common cancer among men and women worldwide.[1] Rectal cancer accounts for 30% of these colorectal malignancies. Surgery with total mesorectal excision (TME) is the cornerstone of treatment in rectal cancer and has led in combination with neo-adjuvant radiotherapy to a decrease in local recurrences.[2-4] Predictive factors for recurrence are depth of tumor invasion, number of malignant lymph nodes and involvement of the circumferential resection margin (CRM).[4,5] Therefore, patients with locally advanced rectal cancer (e.g. large T3 or T4 tumors or involved lymph nodes) have a higher recurrence rate. Currently, these patients are usually treated with long course radiotherapy in combination with chemotherapy followed by TME or multivisceral resections.[2,3,6,7]

Magnetic Resonance Imaging (MRI) is the most accurate imaging modality for assessment of T-stage and CRM for locally advanced tumors. MRI can accurately predict an involved CRM and the transmural invasion of the tumor.[8-10] An involved CRM is a reason to administer long course chemoradiotherapy (CTxRTx). Nodal disease may also be a reason to administer CTxRTx. However, nodal disease remains a difficult radiologic diagnosis.[11] New techniques such as high spatial MRI and ultra-small particles iron oxide (USPIO) enhanced MRI showed promising results in the detection of nodal involvement.[12,13]

The usefulness of restaging after CTxRTx by MRI has not yet been established. After CTxRTx the tumor can be downstaged to 60% and approximately 20% of the tumors show a pathological complete response (pCR).[14,15] Additional imaging may render the patient, in case of downstaging and N0 status, operable with a less extensive resection. On the other hand, in patients in whom the CRM is still involved, more aggressive surgery is justified. Unfortunately, the accuracy of MRI after CTxRTx in predicting tumor and nodal stage is poor, mostly due to the difficult differentiation between viable tumor and fibrosis.[11,16-18] Dynamic Contrast-Enhanced (DCE) MRI may be of additional value in distinguishing malignant from non-malignant tissue. Malignant tissue shows specific contrast-enhanced patterns due to the neoangiogenesis, which gives elevated perfusion and permeability, in patients without neo-adjuvant therapy.[19] The aim of this study is to assess the accuracy of DCE MRI with DCE sequences for tumor, nodal staging and CRM involvement after CTxRTx in patients with locally advanced rectal cancer.

Methods and Materials

Patients

Between June 2005 and March 2009, 101 patients with locally advanced rectal cancer were treated with neo-adjuvant long course radiotherapy followed by rectal surgery. Thirty-three patients were treated by radiotherapy without chemotherapy and 13 patients were restaged in the referring hospital, leaving 55 patients treated with CTxRTx, who were all restaged by MRI with DCE sequences.

All patients had biopsy proven adenocarcinoma of the rectum within 15 cm of the anal verge. Locally advanced rectal cancer was defined on imaging prior to the chemoradiatherapy. According to local standard of care, tumors greater than 5 cm at colonoscopy (clinically large T3), a clinically fixed tumor, tumor invasion in an adjacent organ, tumors with an involved CRM (margin <2 mm) and node positivity (lymph node larger than 8 mm on CT-scan or MRI) were considered as locally advanced rectal cancer.

All patients were evaluated including a complete history and physical examination, colonoscopy, tumor biopsy, computed tomography (CT) scan of the abdomen, magnetic resonance imaging (MRI) of the pelvis and a chest X-ray or chest CT scan.

Therapeutic regimen

Capecitabine was administered orally at a dose of 825 mg/m2 twice a day during radiotherapy days. The first daily dose was given two hours before radiotherapy and the second dose twelve hours later. Patients received a dose of 50-52 Gy radiotherapy delivered in 25-26 fractions of 2.0 Gy. Radiotherapy was administered by a three-field technique, using one posterior and two lateral beams, a four-field box or with five fields using intensity modulated radiotherapy.[7]

Radiology

Imaging was performed after CTxRTx after median interval of 5 weeks (interquartile range, 4 – 6). Magnetic resonance imaging was performed using thin-section (3 or 5 mm) high-spatial resolution, phased array coils on a 1.5 T MR systems (Siemens Vision, Erlangen, Germany; Philips Intera, Best, The Netherlands). Patients were scanned supine without gastro-intestinal tract preparation, rectal insufflation or relaxants. The following sequences were used in all patients: transverse, coronal and sagittal Surv Haste (TSE, 18877/100, 90°), transverse T2W (TSE, 4661/80, 90°), transverse T2W/ Spir (TSE, 4586/80, 90°), transverse T1W (FFE in/out, 184/2.3- 4.0, 80°), transverse Sense Dyn (TFE, 136/1.16, 90°), transverse and sagittal 3D TFE (TFE, 3.4/1.68, 15°).

Dynamic imaging was performed before and after intravenous injection of 20 ml of gadopentetate dimeglumine in the arterial dominant, venous dominant and 2-minute delayed phases.

Image interpretation

All images were assessed by a radiologist prior to surgery for determination of the operation strategy. Surgery was performed with a median of 4 weeks (interquartile range, 3-5) after restaging. Two radiologists: reader 1 (R.D.) and reader 2 (F.W.) retrospectively assessed all images independently. Both readers had over 5 years of experience in rectal cancer imaging and were blinded to the pathologic and surgical findings. The following parameters were recorded by the readers:

Tumor stage

The distance of the lower and upper border of the tumor to the anal verge, maximum axial diameter, CRM, T-stage and tumor invasion, for T2-weighted images and Dynamic contrast-enhanced images were assessed.

Nodal stage

N-stage was determined by location, size (only nodes >3 mm were evaluated), shape (round or oval), border (irregular or sharp), signal intensity (SI) on T2 weighted images (hyperintens, hypointens SI) and homogeneous or heterogeneous SI. On dynamic contrast-enhanced images the arterial phase (early or late and complete or incomplete) and possible washout effects (complete or incomplete) were evaluated. Criteria for suspect malignant lymph nodes were size ≥ 5 mm, round shape, irregular border, heterogeneity on T2 images and incomplete arterial phase and washout effects.[20,21] A lymph node was considered malignant when ≥ 3 criteria were positive.

Circumferential Resection Margin (CRM)

An involved CRM was defined as a margin ≤2 mm to the mesorectal fascia or in case of tumor invasion through the mesorectal fascia into surrounding structures.

Surgery and histopathology

Total mesorectal excision was performed in all patients. In patients whose circumferential resection margin (CRM) were considered at risk (CRM <2mm) intraoperative radiotherapy (IORT) was applied. [4,22] Pathologic examination of the histology specimen was evaluated according to the protocol of Quirke et al. [23] The report noted the depth of tumor invasion into the bowel wall and surrounding tissue, differentiation grade of the tumor, lymph node involvement and resection margin involvement.

Radiologic-pathologic comparison

The tumor, nodal status and CRM involvement determined by MRI were compared to pathologic staging of the surgical specimen.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 15.0. The data used when appropriate were mean, median, (interquartile) range and standard deviation. The diagnostic accuracy, sensitivity, specificity, negative predictive and positive predictive value of MRI was computed in determining the post-chemoradiation nodal stage. The interobserver agreement was calculated by using K statistics. K values of less than 0 indicated poor agreement, 0-0.20 indicated slight agreement, 0.21-0.40 indicated fair agreement, 0.41-0.60 indicated moderate agreement, 0.61-0.80 indicated substantial agreement and 0.80-1.00 indicated almost perfect agreement. The χ^2-test was used to determine the correlated factor to predict the nodal positivity, if the assumption of adequate cell sizes (≥5) was not met; the Fisher's exact test was applied. The results are significant at a *P*-value of less than 0.05.

Results

Surgery and histopathology

Surgery was performed in 41 males and 14 females with a median age of 61 years (range 33 – 78) The median interval of surgery after CTxRTx was 9 weeks (interquartile range, 8 – 10) Surgical and pathologic characteristics are depicted in *table I*.

Table I. Characteristics of 55 patients with locally advanced rectal carcinoma after CTxRTx

	Number of patients (%)
Surgery	
LAR	25 (46)
APR	20 (36)
Total exenteration	4 (7)
Posterior exenteration	6 (11)
Tumor staging	
T0	6 (11)
Tis	2 (4)
T1	0 (0)
T2	10 (18)
T3	32 (58)
T4	5 (9)
Nodal staging	
N0	45 (82)
N1	5 (9)
N2	5 (9)

LAR, Low anterior resection; APR, abdominoperineal resection

A pathological complete response was found in 6 (11%) patients. Five patients underwent a resection with viable tumor within 1 mm of the CRM. One patient had a positive lymph node <1 mm from the mesorectal fascia. Four patients received IORT after resection due to CRM of <2 mm. [22] In resection specimens a median of 9 (range 1 – 21) lymph nodes were retrieved. Ten (8,8%) patients had a total of 42 tumorpositive lymph nodes.

Radiologic-pathologic comparison

A comparison of preoperative MRI staging and histopathological staging for both readers is depicted in *table II.*

Tumor stage

The readers both understaged 4 (7%) patients. Reader 1 had an accuracy of 40% (22 patients) and overstaged 29 (53%) patients. Reader 2 had an accuracy of 45% (25 patients) and overstaged 26 (47%) patients. The k statistics show fair agreement (k = 0.37) for T-staging.

Table II. Comparison of T-staging by DCE MRI and histopathology

		Histopathology					
		T0	**Tis**	**T2**	**T3**	**T4**	
Reader 1	T2	3	1	3	3	0	10
	T3	3	1	6	15	1	26
	T4	0	0	1	14	4	19
	Total	6	2	10	32	5	55
Reader 2	T2	0	0	4	3	0	7
	T3	5	1	5	17	1	29
	T4	1	1	1	12	4	19
	Total	6	2	10	32	5	55

Nodal stage

The accuracy of both readers in nodal staging is noted in *table III*. Both readers accurately diagnosed the same 8 patients node positive on MRI. The accuracy for reader 1 for nodal staging 89%, sensitivity 80%, specificity 91%, a positive predictive value (PPV) of 66% and a negative predictive value (NPV) of 95%. Reader 2 showed an accuracy of 93%, sensitivity of 80%, specificity of 96%, a PPV of 80% and a NPV of 96%. K-statistics showed almost perfect agreement (k = 0.89).

Table III. Comparison of N-staging by DCE MRI and histopathology

		pN0	pN+	
Reader 1	cN0	41	2	43
	cN+	4	8	12
	Total	45	10	55
Reader 2	cN0	43	2	45
	cN+	2	8	10
	Total	45	10	55

Characteristics of lymph nodes

The median diameter of the lymph nodes was as follows: malignant lymph nodes 8.1 mm (range 4.2 - 16.2) and 8.0 mm (range 4.0 - 18.0) for reader 1 and 2 respectively, benign lymph nodes 4.8 mm (range 3.0 – 11.0) and 4.4 mm (range 3.0 - 11.0) for reader 1 and 2 respectively.

Circumferential resection margin (CRM)

The accuracy of both readers in predicting CRM involvement is depicted in *table IV.* The accuracy for reader 1 was 60%, sensitivity 86%, specificity 49%, PPV of 38% and a NPV of 91%. Reader 2 showed an accuracy of 56%, sensitivity 79%, specificity 48%, PPV of 34% and a NPV of 91%. K-statistics showed moderate agreement (k = 0.59) for predicting CRM involvement.

Table IV. Comparison of CRM involvement by DCE MRI and histopathology

		Histopathology CRM involved	CRM not involved	
Reader 1	CRM involved	12	20	32
	CRM not involved	2	21	23
	Total	14	41	55
Reader 2	CRM involved	11	21	32
	CRM not involved	3	20	22
	Total	14	41	55

CRM; Circumferential resection margin

There was a significant difference in shape of malignant and benign nodes. Reader 1 showed that a round shape is associated with benign nodes (p=0.026) and reader 2 showed that an oval shape is associated with benign nodes (p=0.008).

The border of lymph nodes did not give a significant difference in the assessment of lymph nodes for reader 1, but reader 2 showed that a sharp border is associated (p=0.005) with benign nodes. Concerning hyperintensity on T2 weighted images, both readers found no significant differences. Hypointensity was an significant indicator for benign nodes (reader 1 p=0.000; reader 2 p=0.000) and heterogeneity was an

significant indicator for malignant nodes (reader 1 p=0.000; reader 2 p=0.000) for both readers.

There were no washout effects detected and only the following characteristic on DCE images gave a significant difference for both readers; early complete arterial phase *(Fig I.)* was a significant characteristic of benign nodes (reader 1 p=0.000; reader 2 p=0.000). Early incomplete arterial phase (*Fig II.)* was a significant characteristic of malignant nodes (reader 1 p=0.000; reader 2 p=0.000).

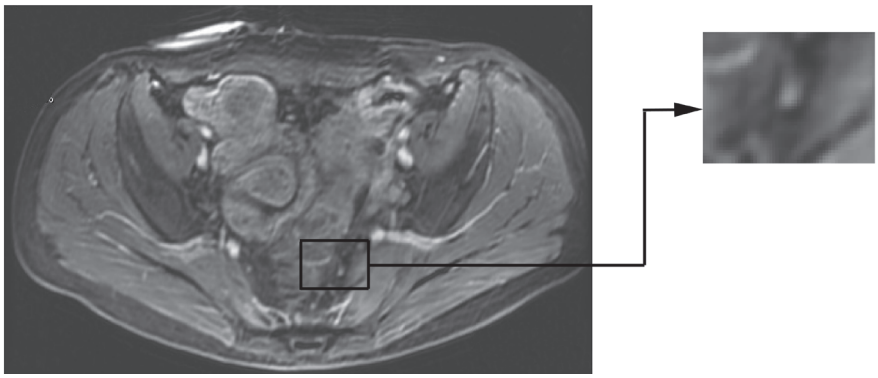

Figure I. DCE-weighted image with early complete arterial phase

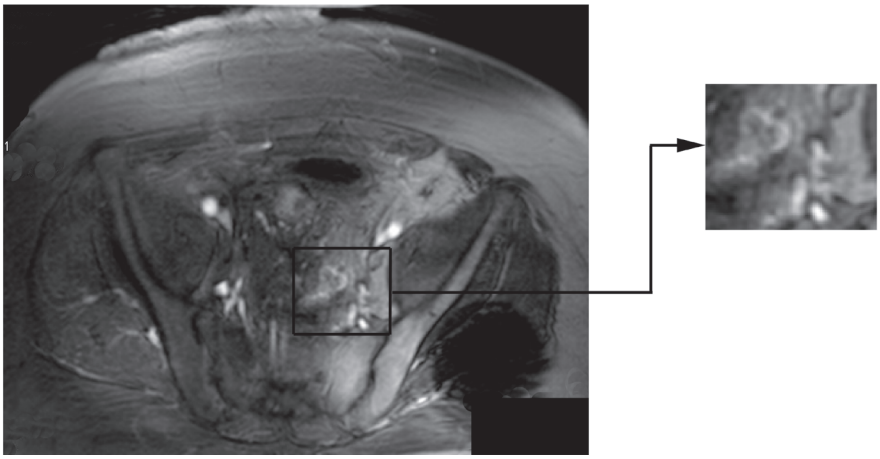

Figure II. DCE-weighted image with early incomplete arterial phase

Interval between CTxRTx, surgery and restaging

The accuracy of tumor and nodal staging in patients having surgery <9 weeks after CTxRTx compared to patients having surgery ≥9 week was not significantly different. The accuracy of tumor staging was 42% vs. 37% (p=0.85) and the accuracy of nodal staging was 87% vs. 92% (p=0.53), The accuracy of tumor and nodal staging when

restaging was performed <4 weeks compared to ≥4 weeks prior to surgery was not significantly different either. The accuracy of tumor staging was 29% vs. 46% (p=0.08) and the accuracy of nodal staging 92% vs. 87% (p=0.53)

Discussion

This study was conducted to evaluate the additional value of MRI with DCE sequences in restaging after CTxRTx in patient with locally advanced rectal cancer. Although the accuracy for T-stage was poor, the addition of DCE sequences showed a high accuracy in detecting malignant lymph nodes. Complete arterial phase on DCE was a significant indicator for benign nodes and incomplete arterial phase (enhanced rim) was significant for malignant nodes. Complete pathologic response, carcinoma in situ and T1 stage tumor could not be correctly detected.

The addition of DCE to determine T-stage after CTxRTx has not proven its usefulness in this study. The poor accuracy of the T-stage could be explained by the fact that rectal cancer has a high level of maturation of vessels, which show relatively low permeability, thus less enhancement on DCE MRI.[24] The accuracy of MRI for T-stage was 45% in this study. Other studies, using MRI with additional DCE sequences showed accuracies of 44-77%.[16,25,26] However, these studies divided patients into two T-stages to define accuracy (T0 vs. >T1 or T0-2 vs. T3-4).[16,25] MRI without additional DCE sequence, showed comparable accuracy results of 34-60%.[18,27-31]

The poor accuracy in predicting T-stage and CRM after CTxRTx is in great contrast to the high accuracy of MRI-staging in patients with rectal cancer treated without neo-adjuvant CTxRTx. A recent meta-analysis reported a sensitivity and specificity in tumor staging of 87% and 75% in patients treated without neo-adjuvant CTxRTx.[32] The tendency of post-chemoradiotherapy MRI to overstage the T-stage and CRM involvement was reported previously and may be caused by the inability of MRI to distinguish between viable tumor cells and fibrosis. Recently, Patel et al. analysed the value of MRI after CTxRTx in rectal cancer patients to analyse good versus poor responders with the histopathological standards of T stage (ypT) and tumor regression grading (TRG). Even using only 2 different t-stages (T0-T3a vs. T3b-4) 19% of the patients were under- or overstaged.[33]

The time span from the end of chemoradiotherapy to surgery has slowly increased over the years. Delaying surgery may reduce postoperative morbidity without compromising prognosis.[34] Moreover, several studies showed a higher percentage of pathological complete response and downstaging after a longer interval between ending CTxRTx and surgery.[35-37] This downstaging effect may influence the accuracy of the restaging MRI. However, we found no differences in accuracies of tumor and nodal staging between

patients in whom surgery was performed < 9 weeks or ≥9 weeks after ending CTxRTx. In addition, it has been suggested that the restaging by MRI shortly before surgery may improve the accuracy of tumor staging.[38] In our study restaging was performed with a median interval of 4 weeks before surgery. We found no higher accuracy of tumor and nodal staging for patients restaged <4 weeks compared to patients restaged after ≥ 4 weeks.

The addition of DCE to high-spatial MRI showed a high accuracy in nodal staging compared to other studies that also applied DCE. They reported accuracies of 62-65%.[16,25,26] This difference could be explained by the fact that we included different enhancement patterns to distinguish between benign and malignant nodes. One study staged a node malignant if it was bigger than 5 mm,[16] while the other 2 studies did not describe any criteria for malignant nodes.[25,26] Studies without additional DCE sequences reported accuracies of 68-71%.[28,31] One study only used the criteria > 5 mm to stage a node malignant while the other study did not note any criteria for malignant nodes. Brown et al.[21] reported that by assessing morphologic features of lymph nodes on MRI, malignant nodes can be detected with a greater degree of sensitivity and specificity compared to nodal size measurement. Studies using the morphologic criteria stated by Brown in addition to size cut-off values (> 5mm mesorectal, > 10mm extramesorectal) still showed lower accuracies of 70-78%.[27,29] Accuracies were even lower even when cut-off values were not used 75-88%[39-41]. We used the same morphologic features described by Brown et al. with a cut-off value of >3 mm. Approximately 9% of the malignant nodes are missed on MRI with a cut-off value of 3 mm in patients treated without neo-adjuvant therapy.[20] Recently, prospective assessment of imaging with MRI without DCE after preoperative chemoradiotherapy for rectal cancer showed an accuracy for nodal staging of 68% with a NPV of 78%.[30] MRI with ultra small particles iron oxide showed promising results for nodal staging with a sensitivity of 93% and a specificity of 96% when an estimated area of white region within the node that was larger than 30%.[13] This sensitivity and specificity were slightly higher than in our study. However, the study mentioned above excluded all patients who were treated with chemoradiotherapy. Therefore, these results may not be comparable to ours.

The accuracy of MRI with DCE for nodal stage was 93% with a PPV of 80% and a NPV of 96%. There was good agreement between the two readers. Nonetheless, both missed the same two histopathology node positive patients. In one patient no benign or malignant nodes were detected on MRI. In the other patient, two nodes were detected, which were staged benign on MRI with confirmation on histopathology. However, the tumor incarcerated a malignant node, undetectable on MRI. Even with the knowledge of the presence of malignant lymph nodes, both radiologists were not able to detect any suspect lymph nodes after reassessment of the MRI.

Two histopathology node negative patients were overstaged by both readers. In these two patients nodes had an axis of more than 8 mm (9.0 mm and 11.0 mm, respectively). Although the median diameter of the malignant nodes was bigger than that of the benign nodes in this study (8.0 and 4.4 mm respectively), it shows size is not a single reliable criteria to diagnose malignant nodes, which was confirmed in results by other studies.[20,21]

MRI with DCE has a good predictive value for malignant nodes. Generally, complete early arterial phase was a significant indicator of benign nodes, whereas incomplete arterial phase was a significant predictor of malignant nodes. Malignant nodes showed an intense border and hypointense core on DCE. This difference in intensity could be explained by that as tumors grow in size, their metabolic demands become too great for existing vasculature. At this stage, the centre of the mass becomes necrotic, leading to the common situation of a necrotic core and an active tumor periphery. This finding has been previously described in patients with a squamous cell carcinoma of the head or the neck. MRI with additional DCE sequences showed significantly different results in contrast intensity for their core and rim in malignant cervical lymph nodes. Benign nodes did not show significant differences, which is in concordance with our findings.[42]

Complete pathologic response, carcinoma in situ and T1 stage tumor could not be correctly detected on MRI even with the addition of DCE sequence. MRI with DCE sequences showed similar poor results in predicting pCR compared to conventional MRI. Predicting pCR after CTxRTx can be of great value for patients with rectal cancer. Patients could be spared unnecessary surgery with high morbidity. Promising results in predicting pCR are shown in adding diffusion weighted (DW) MRI to conventional MRI. Their diagnostic accuracy for the evaluation of pCR increased to 85%.[14,43,44]

Due to the retrospective nature of this study, we were not able to directly assess whether lymph nodes detected on MRI are the same lymph nodes assessed with histopathology. With prospective research a node-by-node correlation is capable to accurately link lymph nodes detected on MRI with DCE to lymph nodes retrieved at histopathology. Another drawback is the relative small amount of patients included in this study. Many of our patients were restaged by MRI without additional DCE sequences and therefore could not be included in this study.

In conclusion, the addition of DCE sequences improved the accuracy of nodal staging after chemoradiotherapy. However, additional DCE sequences did not improve the accuracy for tumor staging, CRM involvement or detecting a pathological complete response. In our opinion, the addition of DCE sequences is a significant step forward towards more accurate staging by MRI after chemoradiotherapy. We think that further development and introduction of such highly accurate preoperative staging modalities will enable us to identify those patients who are candidates for less invasive surgery for rectal cancer or even for watchful waiting.

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Chapter 3

Is Restaging with Chest and Abdominal CT Scan after Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer Necessary?

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Abstract

Background

There is no evidence regarding restaging of patients with locally advanced rectal cancer after a long course of neoadjuvant radiotherapy with or without chemotherapy. This study evaluated the value of restaging with chest and abdominal computed tomographic (CT) scan after radiotherapy.

Methods

Between January 2000 and December 2010, all newly diagnosed patients in our tertiary referral hospital, who underwent a long course of radiotherapy for locally advanced rectal cancer, were analyzed. Patients were only included if they had chest and abdominal imaging before and after radiotherapy treatment.

Results

A total of 153 patients who met the inclusion criteria and were treated with curative intent were included. A change in treatment strategy due to new findings on the CT scan after radiotherapy was observed in 18 (12 %) of 153 patients. Twelve patients (8 %) were spared rectal surgery due to progressive metastatic disease.

Conclusions

Restaging with a chest and abdominal CT scan after radiotherapy for locally advanced rectal cancer is advisable because additional findings may alter the treatment strategy.

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in men and the second in women.[1] At the time of diagnosis, approximately 25 % of patients already have liver metastases.[2,3] The lungs represent the second most common site of metastases from colorectal cancer. According to non-population-based studies, lung metastases are present in 10–15 % of patients with colorectal cancer.[4,5] A population-based study reported that lung metastases are present in 2 % of patients with colorectal cancer.[6]

Distant metastases have implications on the treatment options. For the screening of liver metastases, the Dutch Association of Comprehensive Cancer Centres (ACCC), the National Institute for Health and Clinical Excellence (NICE), and The American Society of Colon and Rectal Surgeons (ASCRS) recommend a computed tomographic (CT) scan or magnetic resonance imaging (MRI). For the screening of lung metastases, they recommend the use of a chest X-ray or a chest CT scan.[7-9]

Locally advanced rectal cancer has a higher risk of developing lung metastases than colon cancer.[6,8,10] In patients with locally advanced rectal cancer, improved local control can be achieved with a long course of preoperative radiotherapy in combination with low-dose neoadjuvant chemotherapy as a radiosensitizer.[11] However, no advice is provided by ACCC, NICE, or ASCRS in any guideline regarding restaging of patients after neoadjuvant treatment of locally advanced rectal cancer—that is, repeating the imaging, after a long course of neoadjuvant radiotherapy treatment, to ensure that in the intervening time no metastases have developed. This study evaluated the value of restaging patients with locally advanced rectal cancer with a CT scan.

Patients and Methods

Between January 2000 and December 2010, data from all newly diagnosed patients who received a long course of radiotherapy for locally advanced rectal cancer in our tertiary referral hospital were analyzed. Patients were included if they had a chest and abdominal CT scan before and after radiotherapy treatment. An MRI was used for local staging before and after radiotherapy. Neoadjuvant treatment was provided with curative intent. Patient characteristics were collected retrospectively. The database comprised data on age, gender, radiation time and dose, simultaneous chemotherapy, pre- and postradiotherapy chest and abdominal CT scan, pathological primary tumor stage, lymph node stage, and type of surgery.

CT Scan

All CT scans were assessed by radiologists in regular clinical practice. Whenever there was any doubt concerning lesions found on the CT scans, then these scans were reassessed by a panel of radiologists and discussed in a multidisciplinary meeting.

Images were acquired after intravenous injection of 150 mL contrast material at 3.5 mL/s with a delay of 80 s. In addition, an arterial phase scan of the liver was acquired at a delay of 30 s. Positron emission tomography scan is not used as standard protocol in our center.

Locally Advanced Rectal Cancer

Locally advanced rectal cancer was defined in our center as a histological proven adenocarcinoma with one of the following characteristics: tumor >5 cm at colonoscopy and MRI (clinically large T3); clinically fixed tumor or with ingrowth in adjacent organ on MRI (T4); N+ tumor (lymph node >8 mm and/or >4 nodes >5 mm on CT scan or MRI). T4 tumors, but also advanced T3 tumors with a close relation to the circumferential margin, were considered as locally advanced rectal cancer. Regardless of size criteria, any lymph node depicted on MRI with an irregular border or mixed signal intensity was considered suspicious for metastasis.

All patients with locally advanced rectal cancer were discussed in a multidisciplinary team that consisted of colorectal surgeons, hepatobiliary surgeons, gastroenterologists, surgical oncologists, medical oncologists, radiation oncologists, radiologists, pathologists, and nurse practitioners.

Chemoradiotherapy

In our center, patients with locally advanced rectal cancer have been treated with a long course of neoadjuvant radiotherapy: 45–50 Gy (in fractions of 1.8–2 Gy) with or without chemotherapy (capecitabine 825 mg/m^2 twice a day only on radiotherapy days).[12] We selected patients who did not receive chemotherapy as a result of their comorbidities. Radiotherapy was followed by surgery with a delay of 6–10 weeks. Intraoperative radiotherapy was applied if the circumferential margin was <2 mm. [13] No laparoscopic resections were performed.

Statistical Analysis

Descriptive statistics are expressed as median (interquartile range [IQR]). Pre- and post-CT variables are expressed as binary variables and compared with the McNemar test for paired data. If fewer than 25 cases change values from the first variable to the second variable, the binomial distribution is used to compute the probability. The SPSS statistical software package (version 17.0; SPSS, Chicago, IL) was used for statistical analysis, where a *P*-value of ≤0.05 was considered statistically significant.

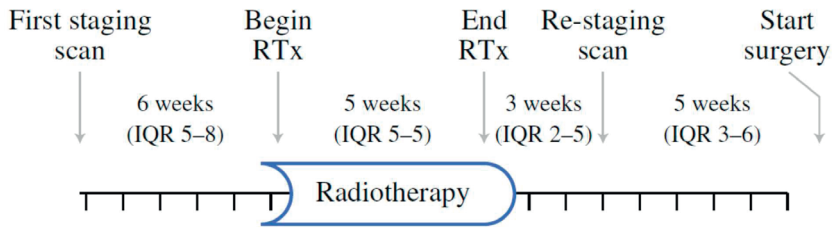
Results

Between January 2000 and December 2010 over 2000 patients were treated with neoadjuvant radiotherapy for rectal cancer. Patients were excluded for receiving radiotherapy for recurrence, palliative radiotherapy, primary radiotherapy treatment, postoperative radiotherapy treatment, and liver-first treatment[14]; and for not have imaging studies available.

A total of 153 patients with primary locally advanced rectal cancer had imaging studies available before and after radiotherapy treatment. A chest CT scan before radiotherapy treatment was not performed in 36 patients; they received a chest X-ray. All other patients had an abdominal and chest CT scan. The majority of patients were men (61 %), and the median age was 62 (IQR 53–69.5) years. All 153 patients had a chest and abdominal CT scan after radiotherapy.

The median time between the staging scan and the start of radiotherapy was 6 weeks (IQR 5–8).The time between end of radiotherapy and the postradiotherapy staging scan was 3 weeks (IQR 2–5). The median time between the two scans was 15 weeks (IQR 12.5–17). The median time between the end of radiotherapy and surgery was 9 weeks (IQR 8–10). The median time between the postradiotherapy scan and surgery was 5 weeks (IQR 3–6) *(Fig. 1).*

Figure I. Time interval of treatment



Chest and abdominal CT scans after radiotherapy demonstrated significant additional findings of metastases compared to the scans before radiotherapy, 11 patients (five liver metastases, five lung metastases, and one with both liver and lung metastases) versus 25 patients (14 liver metastases, seven lung metastases, and four with both liver and lung metastases) (P = 0.001). Details of the CT scan findings before and after radiotherapy are described in *Table I*.

Table I: Diagnostic findings of restaging after radiotherapy

Before RTx	After RTx	No. of patients
Normal	Normal	96
Normal	LrM	6
Normal	LrM + lung IL	1
Normal	LrM + lung LNS	1
Normal	LrM + LnM	1
Normal	LnM	3
Normal	Liver IL	6
Normal	Lung IL	5
Normal	Lung LNS	3
Liver IL	Normal	5
Liver IL	Liver IL	1
Liver IL	LrM	2
Liver LNS	Normal	1
Liver LNS	Liver LNS	2
LrM	LrM	2
LrM	LrM + LnM	2
LrM	LrM + lung LNS	1
LrM + LnM	LrM + LnM	1
Lung IL	LrM	1
Lung IL	Lung IL	1
Lung IL	Lung LNS	2
Lung IL	Normal	3
LnM	Normal	1
LnM	LnM	4
Liver IL + lung IL	Lung LNS	1
Liver LNS + lung LNS	Liver LNS + lung LNS	1

RTx radiotherapy, LrM liver metastases, LnM lung metastases, IL indeterminate lesions, LNS lesions not suspicious

Of the 153 patients treated with neoadjuvant radiotherapy with curative intent, 107 received a long course of chemoradiotherapy and 46 a long course of radiotherapy only. In ten patients, metastases were detected on the staging scan before radiotherapy, and in 143 patients, the scan before radiotherapy did not reveal any metastases. Of the 143 patients without metastases on the staging scan before radiotherapy, 15 patients (10 %) had metastases on the restaging scan after radiotherapy. A change in treatment strategy due to new findings was carried out in 13 patients (9 %). A resection for rectum carcinoma was not performed in 7 (5 %) of 143 patients *(Table II).*

Table II. Metastases found on restaging scan in 143 patients with previously undetected metastases

Before RTx	RTx	After RTx	Treatment	Change in treatment strategy
Normal	RTx	LrM + lung IL	Palliative CTx	Yes
Normal	CTx, RTx	LrM + LnM	Palliative CTx	Yes
Normal	CTx, RTx	LrM	LAR + liver resection	Yes
Normal	CTx, RTx	LrM	LAR + liver resection	Yes
Normal	CTx, RTx	LrM	Palliative CTx	Yes
Normal	CTx, RTx	LrM	LAR + liver resection	Yes
Normal	RTx	LrM	Palliative CTx	Yes
Normal	CTx, RTx	LrM + lung LNS	LAR + liver resection	Yes
Normal	RTx	LrM	Palliative CTx	Yes
Normal	CTx, RTx	LnM	APR + SRx	Yes
Normal	CTx, RTx	LnM	APR (palliative) + palliative CTx	Yes
Normal	RTx	LnM + other	LAR (palliative)	No
Liver IL	CTx, RTx	LrM	LAR + liver resection	Yes
Liver IL	RTx	LrM + other	Palliative CTx	Yes
Lung IL	CTx, RTx	LrM	Laparotomy, peritoneal carcinomatosis → palliative CTx	No

RTx radiotherapy, *CTx* chemotherapy, *LAR* low anterior resection, *APR* abdominal perineal resection, *LrM* liver metastases, *LnM* lung metastases, *SRx* stereotactic body radiation, *IL* indeterminate lesions, *LNS* lesions not suspicious

In the ten patients with metastases detected on the staging scan before radiotherapy, a change in treatment strategy was carried out in 5 (50 %) as a result of new findings on the postradiotherapy staging scan. A resection for rectum carcinoma was not performed in 5 (50 %) of ten patients *(Table III).*

Table III. Metastases found on restaging scan in 10 patients with previously detected metastases

Before RTx	RTx	After RTx	Treatment	Change in treatment
LrM	RTx	Progression of LrM	Palliative CTx	Yes
LrM	CTx, RTx	LrM	LAR + liver resection	No
LrM	CTx, RTx	LrM	LAR + liver resection	No
LrM	CTx, RTx	LrM + LnM	Palliative CTx	Yes
LrM	RTx	LrM + LnM	Palliative CTx	Yes
LnM	CTx, RTx	LnM	APR	No
LnM	CTx, RTx	LnM	LAR	No
LnM	RTx	Progression of LnM	Supportive care	Yes
LnM	CTx, RTx	LnM	APR + lobectomy	No
LrM + LnM	RTx	LrM + progression of LnM	Palliative CTx	Yes

RTx radiotherapy, *CTx* chemotherapy, *LAR* low anterior resection, *APR* abdominal perineal resection, *LrM* liver metastases, *LnM* lung metastases

In the total group of 153 patients, a change in treatment strategy due to new findings was carried out in 18 (12 %). None of the patients had false-positive metastases on pathology and/or follow-up. Twelve (8 %) of 153 patients were spared rectal surgery as a result of new findings.

Discussion

We evaluated the value of restaging with CT scan for distant metastases after neoadjuvant radiotherapy with or without chemotherapy in patients with locally advanced rectal cancer. A change in treatment strategy due to new findings was observed in 12 % of the patients. In the total group, 8 % of patients were spared rectal surgery due to progressive metastatic disease.Local staging of rectum carcinoma has important implications for the choice of optimal treatment. In patients with locally advanced rectum cancer, improved local control can be achieved with a long course of preoperative radiotherapy in combination with neoadjuvant chemotherapy.[15]

Distant metastases have implications on the treatment options. For the screening of liver metastases, there consensus among oncologists that CT or MRI be performed. For the screening of lung metastases, they recommend the use of a chest X-ray or a CT scan.[7-9]

It is known that locally advanced rectal cancer has a higher risk of developing metastases than colon cancer.[5,6,8,10] The recommended treatment for locally advanced rectal cancer is a long course of radiotherapy with or without chemotherapy.[8] Surgery is usually planned 6–10 weeks after finishing neoadjuvant therapy. During these 3 months, metastases can develop that previously were too small to be detected or were not present at all. Therefore, it seems prudent to restage the patient for distant metastases after radiotherapy and before commencing surgery because new findings in this relatively long period might alter the treatment options. In case of unresectable metastatic disease, resection of the primary tumor is unnecessary from an oncological point of view.[16-19] Through restaging, patients might therefore be spared an unnecessary extensive pelvic operation.

We found a large interval between the staging scan and the beginning of radiotherapy. Most patients were referred to our hospital, and this wide interval is a consequence of logistic management. We do not know whether this wide range has an influence on the outcome of our study.

Local staging techniques have previously been described for locally advanced rectal cancer.[20-25] To our knowledge, this is the first study describing restaging for distant metastases after radiotherapy and before commencing surgery in patients with locally advanced rectal cancer.

Restaging is only necessary if there are consequences for the treatment strategy in case of additional diagnostic findings. Additional findings can result in treatment of metastases, or in case of unresectable metastases, no resection of rectal tumor and optional treatment with palliative chemotherapy. In our series, 12 % of the total group of 153 patients had a change in the treatment due to findings on the postradiotherapy CT scan. A resection for locally advanced rectal cancer was prevented in 67 % of the latter patients as a result of findings on the postradiotherapy CT scan.

Several studies have demonstrated the abdominal CT scan to be a reliable diagnostic tool for detecting liver metastases, and CT scan has proven to be better than ultrasound.[26-28] There are limited data describing the optimal chest staging strategy for these patients.[29] Some authors conclude that the low incidence of pulmonary metastases and minimal consequences for the treatment plan limits the clinical value or routine staging chest CT before operation.[29,30] It has several disadvantages such as cost, radiation exposure, and prolonged uncertainty due to the frequent finding of indeterminate lesions.[30] However, these results were not assessed in the selected group of patients with locally advanced rectal cancer. Choi et al. demonstrated that staging before neoadjuvant radiotherapy with a chest CT for patients with locally advanced rectal cancer seems reasonable.[4] Moreover, these patients can benefit from resection of pulmonary metastases because resection can significantly improve survival.[31] In our specific patient population, all patients will have two CT scans at a median interval of 15 weeks. In case of indeterminate lesions, this will help differentiate between metastases and benign lesions.

We recognize the limitations of this retrospective study in our single-center database; patients were not randomized to have a restaging scan or not, with all inherent biases. Only patients who had complete imaging before and after radiotherapy were included. However, more patients received restaging scans but not all preoperative imaging was available. Not including these patients can cause bias in this study.

In conclusion, this study demonstrated that restaging with a CT scan after radiotherapy is a worthwhile step in the treatment of locally advanced rectal cancer because additional findings may alter the treatment strategy.

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Chapter 4

Challenges in determining the benefits of restaging after chemoradiotherapy for locally advanced rectal cancer

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Primary staging

Primary staging in rectal cancer is essential for determining the optimal treatment strategy and consists of local staging and screening for distant metastases. Local staging is important to determine the surgical approach and to identify individual risk factors for recurrence, such as depth of extramural spread, lymph node involvement, mesorectal fascia (MRF) involvement and extramural vascular invasion.[1-4] Patients with low risk for recurrence can be treated by surgery alone, whereas patients with a high risk for recurrence must be treated with neoadjuvant (chemo-)radiotherapy to decrease the chance of local recurrence.[5,6]

Screening for distant metastases is important to identify metastasized patients who require a different treatment approach. Patients with resectable synchronous distant metastases should be treated with curative intent by resection of the distant metastases and primary tumor. Patients with unresectable distant metastases can be safely spared rectal surgery and treated with systemic chemotherapy with a low chance of emergency surgery.[7]

For primary local staging, magnetic resonance (MR) imaging is superior compared to other imaging modalities currently available. Accuracies of tumor staging, nodal staging and MRF-involvement by MR imaging are higher compared to the accuracies of Computed Tomographic (CT) scans and endoscopic ultrasound sonography (EUS).[8-10] Moreover, the multicenter Mercury study with 12 colorectal units in 4 European countries showed MR imaging to be highly accurate and reproducible.[11] Therefore, MR imaging is recommended in all guidelines as preferred imaging modality in the preoperative assessment of rectal cancer.[12-14] For screening for distant metastases, most guidelines advise a thoraco-abdominal CT-scan.[12,14]

Chemoradiotherapy and potential benefits of restaging

Neoadjuvant chemoradiotherapy (CTxRTx) is administered to reduce local recurrence rates, to facilitate tumor downstaging and additionally leads to a pathological complete response (pCR) in 11-19%.[3,6,15-17] The identification of good versus poor responders before definitive surgery is important, because patients may be offered less radical or rather more radical surgery. Therefore, patients are increasingly being restaged after administering CTxRTx and many advocate to perform restaging routinely.[18] Restaging could have implications for surgical management. For example, tumor shrinkage may lead to sphincter sparing surgery instead of an abdominoperineal resections with a permanent stoma. Furthermore, there is a growing interest in selecting those patients who are likely to have achieved a pCR, because these patients could be offered a 'wait and see policy' and spared rectal surgery at all.

Does restaging alters treatment strategy and is it safe?

The most important problem of restaging is that generally the accuracy of predicting tumor stage is poor. This is mainly caused by the difficulty differentiating between vital tumor and radiation induced fibrosis. Other radiation-induced changes, such as edema, inflammation and necrosis also contribute to a poor accuracy. Especially, the sensitivity of tumor staging in patients after CTxRTx is concerning. A recent meta-analysis reported a poor mean sensitivity of 50% and a mean specificity of 91%, while only discriminating between T0-2 vs. T3-4.[19] Accuracies predicting exact tumor stage are even poorer.[20,21] On the other hand, the accuracy of predicting lymph node involvement in restaging is higher compared to primary staging, but still the specificity nodal restaging is concerning. The same meta-analysis reported a mean specificity of 60% and a mean sensitivity of 76%.[19]

One of the most important questions regarding the clinical use of restaging remains unanswered: Does restaging indeed alter surgical treatment? Theoretically, tumor downstaging caused by CTxRTx may result in more sphincter saving procedures, which could explain the increase of the sphincter sparing procedures in the last decades from 17% in the early 80s[22] to 79% in 2011.[23] However, none of the randomized controlled trials evaluating the effect of CTxRTx was able to demonstrate a significant increase in the rate of sphincter saving surgery. This suggests that the increase is more likely to be caused by advances in the surgical practice than by administering CTxRTx.[24] Moreover, it remains unclear whether performing less radical procedures in downstaged patients is safe, keeping in mind that imaging is insufficient to detect possible vital tumor remnants in the radiation induced fibrosis.[25] Another problem is the considerable change of under- and overstaging. Obviously, the risk of overstaging is higher due to the replacement of vital tumor into fibrosis, but understaging of tumor status occurs in 7-22% of the patients.[20,21,26] Surgeons should be cautious performing less radical resections based on restaging imaging, because understaging may lead to incomplete resections and these are disastrous for oncologic outcome.[2]

A potential interesting aspect of restaging is that in case of complete tumor disappearance treatment plan could be altered into a wait and see policy. Although the results of studies with a wait and see policy are promising,[27,28] it is important to realize that omitting surgery is no standard practice. The results of a wait and see policy are based on few studies and the majority of the studies originates from one single center with limited long term follow up. Based on these data, a wait and see policy is not proven to be safe. Therefore, restaging with the idea to alter treatment plan into a wait and see policy should only be performed in clinical trials. Moreover, due to the very poor sensitivity of predicting a pCR of 19%, restaging in a wait and see policy should only be performed as an integrated part of several examinations, including endoscopy and digital examination.[19] The diagnostic accuracy of predicting a pCR may be increased by performing local excisions by transanal endoscopic microsurgery (TEM). In the

near future, the CARTS trial will provide the answer whether this approach is safe and feasible.[29] However, not only accurate determination of tumor stage is important to safely alter treatment into a wait and see policy. Accurate assessment of possible malignant lymph nodes is at least even important. Unfortunately, the specificity of 60% of nodal restaging shows there is a considerable chance of missing malignant lymph nodes.

Benefits of local restaging

A potential involved circumferential resection margin (CRM) or the relationship of the tumor to the MRF has emerged as one of the most powerful predictors of outcome. Surgical dissection outside of this fascia has become central in the efforts to achieve CRM negativity and is possible in many cases. This is the concept behind the beyond total mesorectal exicion (TME) approach.[30] The accuracies of predicting MRF-involvement after CTxRTx are acceptable with a sensitivity of 76% and a specificity of 86%.[19] This makes restaging is useful for determining MRF-involvement in patients and to assess the need for resections beyond the TME plane. However, surgeons should keep in mind that there is a considerable change of overtreatment by performing unnecessary multivisceral resections or undertreatment by performing incomplete resections.

Another interesting and potentially useful aspect of restaging is that radiologically determined tumor response can be used as early prognostic factor. The mercury study group has demonstrated that radiologically determined poor tumor response was associated with poorer overall survival and disease free survival.[31] In these patients, post-operative follow up could be intensified to detect distant metastases in an early stage or could be offered more aggressive (neo)adjuvant therapy.

Improvements in accuracy of local restaging

Although accuracies of restaging are generally poor, there have been gains in restaging accuracies in the hands of dedicated and experienced radiologists. Recent studies have reported accuracies up to 80%.[25,32,33] This is caused by the use of high resolution MRI techniques, the use of validated reporting criteria and by diffusion weighted (DW) imaging. DWI-MRI significantly improves accuracies in tumor staging and also seems to improve the sensitivity of predicting a pCR.[19,34]

Restaging for distant metastases

Generally, rectal surgery is scheduled after an interval of 6 weeks after ending CTxRTx. However, rectal surgery is now often postponed to 9 or even 12 weeks as longer intervals may enhance tumor downstaging, increase pCR rates and reduce complication rates.[35,36] Currently, the interval between initial staging and surgery may take up to 4-5 months. Due to this long interval, restaging by a thoraco-abdominal CT-scan could detect distant metastases, which developed during CTxRTx. Also considering that only the advanced

stages of rectal cancer with subsequently the highest risk of developing of distant metastases are treated with CTxRTx. Two recently published studies have demonstrated the development of distant metastases in 7-12% of the patients being restaged by a thoraco-abdominal CT-scan.[21,37] This is essential information, because the development of distant metastases alters the optimal surgical strategy. Patients with resectable metastases can undergo resections of both rectal tumor and distant metastases, while patients with unresectable metastases can be spared rectal surgery.

Conclusions

Currently, the actual benefits of local restaging for clinical practice are limited. Accuracies of tumor and nodal staging after administering CTxRTx are too low to safely alter definitive surgical procedure or to apply a wait and see policy. However, restaging is useful to evaluate MRF-involvement in locally advanced rectal cancer and to assess whether resections beyond the TME plane are necessary. Furthermore, restaging can evaluate tumor response, which can be used as early prognostic factor. Restaging by thoraco-abdominal CT-scan is valuable to detect distant metastases developing during CTxRTx. A considerable proportion develops distant metastases during CTxRTx and these patients require a different surgical strategy. Moreover, some patients develops unresectable distant metastases and these patients can even be spared rectal surgery. Future research should focus on improvement of restaging accuracies and on evaluating the safety of performing less radical surgery in downstaged patients.

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Chapter 5

Intraoperative radiotherapy (IORT) reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer

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Abstract

Purpose

Intraoperative radiotherapy (IORT) is advocated by some for patients with locally advanced rectal cancer (LARC) who have involved or narrow circumferential resection margins (CRM) after rectal surgery. This study evaluates the potentially beneficial effect of IORT on local control.

Methods

All surgically treated patients with LARC treated in a tertiary referral center between 1996 and 2012 were analyzed retrospectively. The outcome of patients treated with IORT with a clear but narrow CRM (≤2mm) or a microscopically involved CRM was compared to patients who were not treated with IORT.

Results

A total of 409 patients underwent resection of LARC and 95 patients (23%) had a CRM ≤2mm. Four patients were excluded from further analysis due to a macroscopically involved resection margin. In 43 patients with clear but narrow CRMs, there was no difference in the cumulative 5-year local recurrence-free survival of patients treated with (n=21) or without IORT (n=22) (70 vs. 79%,p=0.63). In 48 patients with a microscopically involved CRM, there was a significant difference in the cumulative 5-year local recurrence-free survival in favor of the patients treated with IORT (n=31) compared to patients treated without IORT (n=17) (84 vs. 41%,p=0.01). Multivariable analysis confirmed that IORT was independently associated with a decreased local recurrence rate (HR 0.24, 0.07–0.86). There was no significant difference in complication rate of patients treated with or without IORT (65% vs. 52%,p=0.18)

Conclusion

The current study suggests that IORT reduces local recurrence rates in patients with LARC with a microscopically involved CRM.

Introduction

Local control is an important goal of the surgical treatment of rectal cancer. Local recurrences are usually accompanied by severe pain and poor quality of life.[1] One of the most important predictive factors for local recurrence is the circumferential resection margin (CRM).[2] The recognition of an involved CRM as one of the main causes of local recurrences has led to the introduction of total mesorectal excision (TME), resulting in less involved margins and consequently less local recurrences. A further decrease of CRM-involvement was caused by introducing neoadjuvant (chemo-)radiotherapy. Unfortunately, despite using neoadjuvant (chemo-)radiotherapy followed by TME, CRM-involvement is still reported in 17–20% of the patients with locally advanced rectal cancer (LARC) and results in local recurrence rates of 55–62% in these patients.[3,4]

Several institutes worldwide have integrated intraoperative radiotherapy (IORT) to the multimodality approach of LARC to improve outcome. IORT refers to the delivery of a boost of radiation at the time of surgery. One single IORT dose results in a two to three times higher biological equivalent than the same dose given by conventional fractionation.[5] The rationale behind IORT is that this extra radiation boost, if preceded by neoadjuvant radiotherapy, may be able to eradicate microscopic remnants after an incomplete resection. In addition to patients with microscopically involved CRMs, IORT may also be beneficial in patients with a clear but narrow CRM (≤2mm), because these patients are also known to have a higher risk of local recurrence.[6]

In the literature, the results of the effect of IORT on local control in patients with LARC are contradictory. Some retrospective studies reported a beneficial effect [7-11], but others, including a recently published randomized controlled trial, did not find any beneficial effect.[12-14] However, these studies report on patients that in the majority of cases had radical resections and some describe both LARC and locally recurrent rectal cancer patients. Comparative studies focusing on LARC with involved or clear but narrow CRMs specifically are lacking. The aim of the current study is to evaluate whether IORT after neoadjuvant radiotherapy decreases the local recurrence rate in patients with LARC with a microscopically involved CRM or a clear but narrow CRM after TME.

Patients and methods

Between 1996 and August 2012, all patients undergoing curative TME for LARC in the Erasmus Cancer institute, a tertiary referral center for T4 colorectal cancer for the southwest region of The Netherlands, were entered in a database. LARC was defined as large T3 or T4 rectal tumors with clinical suspicion of narrow or involved CRMs with or

without potentially malignant lymph nodes, or rectal tumors with potentially malignant lymph nodes outside the TME plane.

Based on the final pathology report, all patients with a CRM equal or less than 2 mm were retrospectively analyzed. These patients were divided into two groups; a group with resections with a clear, but narrow CRM (≤2mm) and a group with a microscopically involved CRM. In these groups, we compared the local recurrence-free survival and overall survival of the patients who were treated with and without IORT.

Neoadjuvant (chemo-)radiotherapy

All patients received preoperative (chemo-)radiotherapy, either as a short course (25Gy) delivered in 5 fractions or as a long course (44,6–50Gy) delivered in 19-25 fractions. From 2006 onwards, patients received chemoradiotherapy with capecitabine administered orally at a dose of 825 mg/m^2 twice a day during radiotherapy days as reported previously.[15] Before 2006, no patient received concomitant chemotherapy. Radiotherapy was administered by a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy. The lateral pelvic borders were defined as 1.5cm lateral of the bony pelvis, the cranial border was the promontory, and the caudal border was below the foramina obturatoria to 2cm under the anus, depending on tumor position.

Surgery, intraoperative radiotherapy and adjuvant treatment

Surgical strategy was planned preoperatively in a multidisciplinary tumor board. TME was performed in all patients and multivisceral 'beyond TME' resections were performed in those with tumor ingrowth into surrounding structures. Patients in whom a CRM ≤2mm was expected were planned in an operation theatre with IORT facilities. During surgery, CRM status was evaluated on frozen sections. When the CRM was ≤2mm, IORT was applied to the resection area involved. Patients in whom a CRM >2mm was expected were planned in an operation theatre without IORT facilities and no standard frozen sections of the specimen were taken.

IORT was delivered by high dose rate (HDR) brachytherapy. The area where the resection margin was considered to be at risk was marked with surgical clips. IORT was administered to this area by a flexible intraoperative template (FIT), which was described previously.[16] a 5mm-thick pad made of flexible silicon with 1cm-spaced parallel source guide tubes running through the center of the template. The size and shape of the FIT were adjusted by surgeon and radiation oncologist. Thereafter, it was placed on the target surface. Treatment planning was performed using the standard geometries present in the treatment planning system. A dose of 10Gy was delivered, usually at 1cm depth from the applicator surface. Peri-operative morbidity was divided into surgical and non-

surgical morbidity and was graded according to the Dindo-Clavien classification.[17] Our treatment protocol for LARC does not include adjuvant chemotherapy or postoperative radiotherapy. Nevertheless, some patients received adjuvant chemotherapy or underwent postoperative radiotherapy.

Follow up

Patients visited the outpatient clinic every 3 months during the first two years. Thereafter, patients were examined biannually. The first two years CEA determination was performed every 3 months and thoracic and abdominal imaging biannually. After 2 years of follow up, CEA determination was performed biannually and thoracic and abdominal imaging yearly. Patients were usually discharged from further follow up after 5 years. During follow up, a local recurrence was established by symptoms, CEA increase or imaging. All suspected recurrences were confirmed by CT or MR imaging. Biopsies were attempted routinely.

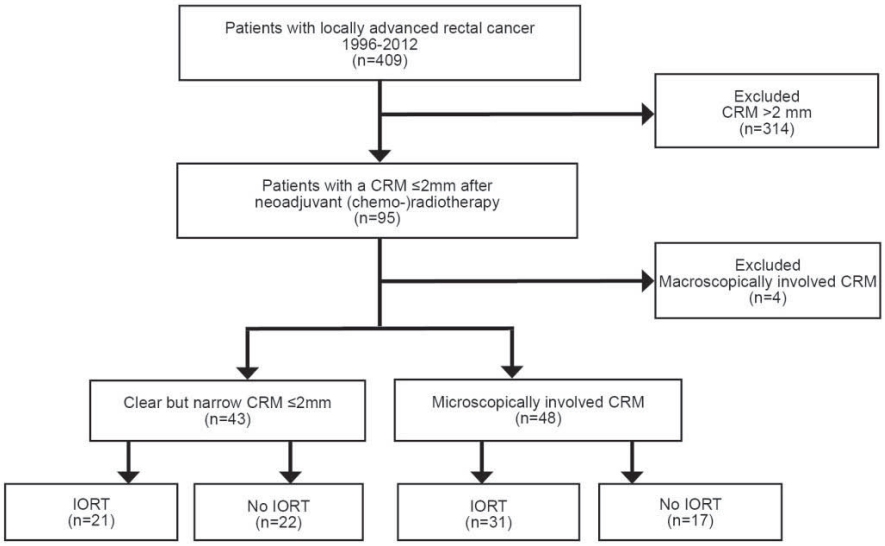
Statistical analysis

Statistical analysis was carried out using SPSS (version 20.0.0). Data was reported as median (interquartile range). Categorical data was reported as count (percentage). The Chi-square, Fisher's exact and Mann-Whitney U test were used for comparison of both groups as appropriate. Univariate local recurrence-free survival and overall survival analyses were carried out by means of Kaplan–Meier curves and log rank tests. Univariate and multivariable analyses by Cox hazard regression models were performed to determine the prognostic value of covariates.

Results

A total of 409 patients underwent TME surgery for LARC between 1996 and August 2012. Neoadjuvant (chemo-)radiotherapy was administered to 399 patients. Of these patients, 95 patients had a CRM ≤2mm on final pathology report. Forty-three patients had a clear but narrow CRM ≤2mm and 48 patients had a microscopically involved CRM. Four patients underwent a macroscopic irradical resection and were not included in this study. *(Fig. I)*

Figure I. Study flowchart of all patients



Resections with a clear but narrow CRM (≤2mm)

Patient and tumor characteristics of the patients with radical resections with a clear but narrow CRM ≤2mm are depicted in *table I*. Twenty-one patients were treated with IORT (49%), whereas 22 patients (51%) did not receive IORT. The main reasons for not administering IORT was preoperative understaging (n=14). In these patients, perioperative frozen sections were not performed and IORT was not considered. The other cause for omitting IORT was a false-negative result of the perioperative frozen sections, while the CRM proved to be ≤2mm on final pathology report (n=8).

Surgery, perioperative results and adjuvant treatment

The interval between ending radiotherapy and surgery was 9 (interquartile range, 7–12) weeks for the patients treated with IORT and 8 weeks (interquartile range, 7–11) for the patients treated without IORT (p=0.91). There were no differences in the surgical procedures and TNM stage *(table II).* Operation time was significantly longer and there was significantly more blood loss in patients treated with IORT. One patient treated with IORT received adjuvant chemotherapy compared to 2 patients who were not treated with IORT.

Local recurrence-free survival and overall survival

The median follow up was 38 (interquartile range, 15-66) months for patients treated with IORT and 39 (interquartile range, 11–73) months for patients treated without IORT. The estimated 3- and 5-year local recurrence-free survival of the 21 patients treated with

Table I. patients and tumor characteristics

	Clear but narrow CRM ≤2 mm			Resections with a microscopically involved CRM		
	Non IORT (%)	**IORT (%)**	**p-value**	**Non IORT (%)**	**IORT (%)**	**p-value**
Total	22	21		17	31	
Gender						
Male	15 (68)	18 (86)	-	11 (65)	23 (74)	-
Female	7 (32)	3 (14)	0.28*	6 (35)	8 (26)	0.73**
Age ∓	59 (17–76)	66 (43–76)	0.08***	56 (23–75)	61 (18–77)	0.84***
Neoadjuvant treatment						
Short course RTx	1 (5)	1 (4)	-	3 (18)	2 (6)	-
Long course RTx	9 (41)	12 (50)	-	9 (53)	13 (42)	-
Chemoradiotherapy	12 (55)	8 (33)	0.55**	5 (21)	16 (52)	0.24**
Tumor localization						
≤ 5 cm	12 (55)	11 (52)	-	9 (53)	16 (52)	-
> 6 cm	10 (45)	10 (48)	0.69**	8 (47)	15 (48)	0.93**
Clinical tumor stage						
T3	13 (59)	6 (29)	-	8 (47)	10 (32)	-
T4	9 (31)	15 (71)	0.04	9 (53)	21 (68)	0.31
Clinical nodal stage						
N0	10 (46)	13 (62)	-	7 (41)	13 (42)	-
N+	12 (54)	12 (38)	0.65	10 (59)	18 (58)	0.96

*CRM, Circumferential resection margin, IORT, intra-operative radiotherapy ∓, Years (interquartile range); RTx, Radiotherapy, CTx, Chemotherapy; * using Fisher's exact test; **, Using χ^2; ***, using Mann-Whitney U test*

IORT was 82% and 70% respectively. This did not significantly differ from the 3- and 5-year local recurrence-free survival of 79% and 79% respectively of patients treated without IORT (p=0.63) (*figure IA)*. Further univariate analysis for local recurrence-free survival is outlined in *table III*. Five-year overall survival did not differ significantly between patients treated with or without IORT (63 vs. 81%,p=0.28). The only independent prognostic factor for overall survival was synchronous metastatic disease (HR 5.18, CI95%: 1.27–21.2).

Resections with a microscopically involved CRM

Patient and tumor characteristics of 48 patients with a microscopically involved CRM are depicted in *table I*. IORT was administered to 31 patients (65%), whereas 17 patients (35%) did not receive IORT. In 12 patients the reasons for not administering IORT was preoperative understaging, whereas 5 patients had false-negative frozen section results. In patients not treated with IORT, stage IV disease was more common than in patients treated with IORT (52 vs. 13%,p=0.01).

Table II. Surgical, pathological results and adjuvant therapy

	Clear but narrow CRM ≤2 mm			Resections with a microscopically involved CRM		
	Non IORT (%)	**IORT (%)**	**p-value**	**Non IORT (%)**	**IORT (%)**	**p-value**
Total	22	21		17	31	
Surgical procedure						
LAR	8 (40)	4 (19)	-	6 (35)	4 (13)	-
APR	6 (27)	9 (43)	-	6 (35)	14 (45)	-
Intersphinteric	1 (5)	1 (5)	-	0	1 (3)	-
Posterior exenteration	5 (23)	3 (14)	-	3 (9)	5 (16)	-
Total exenteration	2 (9)	4 (19)	-	2 (6)	4 (13)	-
Abdominoperineal sacral	0	0	0.55**	0	3 (10)	0.40**
Operation time (minutes) ∓	317 (145–672)	481 (258–662)	0.003***	293 (220–343)	495 (433–580)	<0.001***
Blood loss (milliliters) ∓	1650 (200– 12.500)	3.300 (300 –20.000)	0.016***	1750 (790–3290)	3000 (1700–5350)	0.10***
Tumor stage						
T3	16 (72)	17 (81)	-	9 (52)	11 (35)	-
T4	6 (28)	4 (19)	0.72*	8 (48)	20 (65)	0.40**
Nodal stage						
N0	10 (45)	11 (52)	-	7 (41)	19 (61)	-
N+	12 (55)	10 (48)	0.65**	10 (59)	12 (39)	0.18**
Distant metastases	4 (18)	3 (15)	1.00*	9 (52)	4 (13)	0.01*
Pulmonary	0	0	-	1 (5)	1 (3)	-
Liver	4 (18)	3 (15)	-	8 (47)	3 (10)	-
Adjuvant therapy						
Chemotherapy	1 (5)	2 (10)	-	1 (6)	0	-
Radiotherapy	0	0	-	2 (12)	0	-

*CRM, Circumferential resection margin, IORT, Intra-operative radiotherapy; LAR, Low anterior resection; APR, Abdominoperineal resection ∓,Interquartile range; *, Using Fisher's exact test; **, Using χ^2; ***, Using Mann Whitney U test*

Surgery, perioperative results and adjuvant treatment

The interval between ending radiotherapy and surgery was 8 (interquartile range, 6–11) weeks for the patients treated with IORT and 7 (interquartile range, 6–9) weeks for the patients treated without IORT (p=0.18). Surgical procedures were similar in both groups *(table II).* Operation time was significantly longer in the IORT group. Two patients treated without IORT received an adjuvant radiation boost of 20–30Gy and one patient received adjuvant chemotherapy. No patients treated with IORT received adjuvant therapy.

Local recurrence-free survival and overall survival

The median follow up was 23 (interquartile range, 11–46) months for patients treated with IORT and 12 (interquartile range, 6–22) months for patients treated without IORT. Of the patients treated with IORT, 4 patients developed a local recurrence, whereas 14

Table III. Univariate analysis of local recurrence-free survival and overall survival of resections with a clear but narrow CRM ≤2mm

	Local recurrence-free survival			Overall survival	
	Number of patients	**Hazard ratio local recurrence (95%CI)**	**P-value**	**Hazard ratio overall survival (95%CI)**	**P-value**
Gender					
Male	33	1		1	
Female	10	2.50 (0.56 – 11.21)	0.23	1.55 (0.39 – 6.22)	0.63
Neo-adjuvant Treatment					
RTx (25-50Gy)	23	1		1	
CTxRTx (50Gy)	20	0.21 (0.09 – 11.09)	0.23	0.48 (0.10 – 2.35)	0.37
Period of surgery					
1996-2004	18	1		1	
2005-2012	25	0.26 (0.20 – 1.39)	0.18	0.92 (0.24 – 3.50)	0.91
Surgical resection					
LAR	15	1		1	
APR	28	3.05 (0.36 – 25.41)	0.27	1.81 (0.38 – 8.70)	0.52
Tumor stage					
T3	32	1		1	
T4	11	1.75 (0.34 –- 9.12)	0.51	2.12 (0.53 – 8.53)	0.66
Nodal stage					
N-	21	1		1	
N+	22	0.96 (0.19 – 4.72)	0.96	0.63 (0.14 - 2.81)	0.54
CRM					
>0 and ≤1 mm	14	1		1	
>1 and ≤2 mm	29	0.77 (0.18 – 3.56)	0.67	2.16 (0.45 – 10.42)	0.32
Metastatic disease					
No	36	1		1	
Yes	7	1.54 (0.18 – 13.14)	0.69	5.18 (1.27 – 21.22)	0.02
Tumor differentiation grade					
Well and moderate	36	1		1	
Poor	7	1.11 (0.13 - 9.58)	0.92	2.00 (0.40 – 9.98)	0.40
Vasoinvasion					
No	32	1		1	
Yes	11	1.77 (0.32 – 9.56)	0.51	1.70 (0.32 – 9.16)	0.53
Tumor localization					
≤ 5 cm	25	1		1	
> 6 cm	18	2.13 (0.42 – 10.75)	0.36	0.79 (0.15 – 4.06)	0.77
IORT					
No	22	1		1	
Yes	21	1.44 (0.32 – 6.47)	0.63	2.10 (0.53 – 8.42)	0.29

CRM, Circumferential resection margin; RTx, Radiotherapy; CTxRTx, Chemoradiotherapy; LAR, Low *anterior resection; APR,* A*bdominoperineal resection; IORT, Intraoperative radiotherapy*

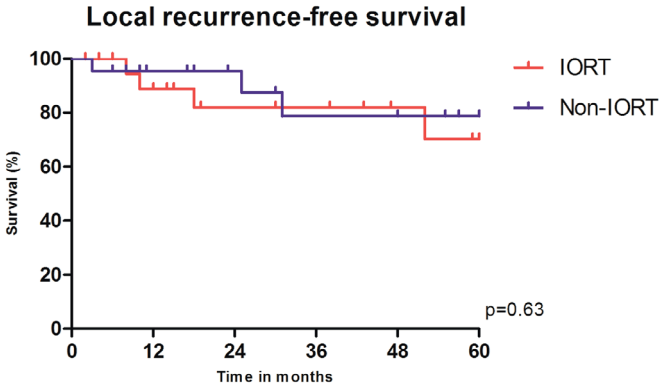
Table IV. Univariate local recurrence free survival and overall survival of resections with a microscopically involved CRM

	Local recurrence-free survival			Overall survival	
	Number of patients	**Hazard ratio local recurrence (95%CI)**	**P-value**	**Hazard ratio overall survival (95%CI)**	**P-value**
Gender					
Male	34	1		1	
Female	14	2.82 (0.86 – 9.26)	0.09	0.86 (0.38 – 1.95)	0.72
Neo-adjuvant Treatment					
RTx (25-50Gy)	27	1		1	
CTxRTx (50Gy)	21	0.51 (0.14 – 1.93)	0.32	0.46 (0.19 – 1.13)	0.08
Period of surgery					
1996-2004	21	1		1	
2005-2012	27	1.05 (0.32-3.45)	0.94	0.76 (0.37 – 1.58)	0.47
Surgical resection					
LAR	14	1		1	
APR	34	0.46 (0.14 – 1.52)	0.20	1.2 (0.53 – 2.72)	0.66
Tumor stage					
T3	20	1		1	
T4	28	0.63 (0.19 – 2.09)	0.45	1.82 (0.80 – 3.73)	0.17
Nodal stage					
N0	26	1		1	
N+	22	1.32 (0.36 – 5.01)	0.66	1.1 (0.49 – 2.41)	0.82
Metastatic disease					
No	35	1		1	
Yes	13	2.86 (0.86 – 9.27)	0.10	1.98 (0.92 – 4.28)	0.08
Tumor differentiation grade					
Well and moderate	37	1		1	
Poor	11	4.88 (1.46 – 15.12)	0.004	1.65 (0.75 – 3.6)	0.21
Vasoinvasion					
No	35	1		1	
Yes	13	1.09 (0.27 – 4.36)	0.90	1.1 (0.49 – 2.53)	0.80
Tumor localization					
≤ 5 cm	25	1		1	
> 6 cm	23	1.67 (0.45 – 6.21)	0.45	1.25 (0.56 – 2.78)	0.56
IORT					
No	17	1		1	
Yes	31	0.23 (0.07– 0.81)	0.016	0.39 0.19– 0.81)	0.01

CRM, Circumferential resection margin; RTx, Radiotherapy; CTxRTx, Chemoradiotherapy; LAR, Low anterior resection; APR, Abdominoperineal resection; IORT, Intraoperative radiotherapy

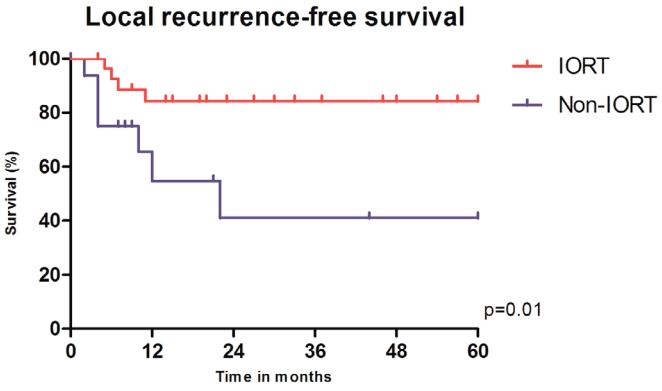
patients died without developing a local recurrence. Of the patients treated without IORT, 7 patients developed a local recurrence, whereas 7 patients died without developing a local recurrence. This resulted in significant difference in 5-year local recurrence-free survival in favor of the patients treated with IORT (84% vs. 41%,p=0.01). This is shown in *figure IB*. When 2 two patients who received a post-operative radiotherapy boost were excluded, the difference in 5-year local recurrence-free survival was more pronounced (84% vs. 33%, p=0.004). Further univariate analysis is depicted in *table IV*.

Figure IA: local recurrence-free survival of patients with clear but narrow CRMs (≤2mm)



Patients at risk						
IORT	21	16	12	11	8	5
Non-IORT	22	17	14	10	9	6

Figure IB: Local recurrence-free survival of patients with microscopically involved CRMs



Patients at risk						
IORT	31	21	15	11	8	5
Non-IORT	17	7	4	3	2	2

Multivariable analysis confirmed that IORT (HR 0.24, 95%CI: 0.07–0.86) and poor tumor differentiation (HR 4.82, 95%CI: 1.46–15.94) were independently associated with local recurrence-free survival. There was also a significant difference in 5-year overall survival in favor of the patients treated with IORT (41 vs. 13%,p=0.008). Further univariate analysis demonstrated that IORT was the only significant prognostic factor for overall survival (HR 0.39, CI95%: 0.19–0.81) *(table IV)*.

Perioperative morbidity and mortality of all patients

The perioperative morbidity and mortality is outlined in *table V.* In 52 patients treated with IORT, 38 complications occurred in 34 patients (65%). In 39 patients treated without IORT, 23 complications occurred in 20 patients (52%). There was no significant difference in number of patients with complications (p=0.18), nor in grade of complications between patients treated with or without IORT. A relaparotomy was performed in 2 patients (4%) treated with IORT compared to 1 patient (3%) not treated with IORT.

Table V. Peri-operative morbidity and mortality of all patients

	Non IORT (%)	IORT (%)	p-value
Total	39	52	
Peri-operative morbidity			
Surgical			
Abdominal/perineal wound infections	9 (23)	18 (31)	0.14*
Presacral abscess	5 (13)	3 (6)	0.28**
Relaparotomy	1 (3)	2 (4)	1.00**
Anastomotic leakage †	1 (3)	1 (2)	-
Wound dehiscence	0	1 (2)	-
Non-surgical			
Pneumonia/atelectasis	4 (10)	8 (15)	0.76**
Cardiac	1 (3)	2 (6)	1.00**
Urinary tract infection	3 (8)	5 (8)	1.00**
Grading of complications (Dindo-Clavien)			
Grade ≥2	10 (25)	17 (33)	0.16**
Grade ≥3	6 (15)	8 (15)	1.00**
Grade ≥4	1 (3)	1 (2)	1.00*
Mortality			
In hospital mortality	1 (3)	0	-

*IORT, Intraoperative radiotherapy; †, Only in patients with an anastomosis without a diverting Ileostoma; *, using Fischer's exact; **, using χ^2*

Discussion

The current study suggests that IORT reduces the local recurrence rate in patients with a microscopically involved CRM after neoadjuvant radiotherapy for LARC. This study did not find evidence that IORT reduces local recurrence rates in patients with a clear but narrow CRM (≤2mm). The complication rate is not increased in patients treated with IORT.

Patients with a microscopically involved CRM who were treated with IORT had a significantly improved 5-year local recurrence-free survival of 84% compared to 41% for the patients who were treated without IORT. This suggests that administering IORT can eradicate microscopic remnants after incomplete resections and thus improve local control.

The reduction of the local recurrence rate by IORT contradicts the results of a recently published randomized controlled trial, which demonstrated no beneficial effect of IORT after neoadjuvant radiotherapy.[12] However, that study included mostly patients with radical resections, thus providing evidence that standard administration of IORT in patients with a radical resection is not beneficial. This is in line with our finding that IORT had no beneficial effect on patients with radical resections with a clear but narrow CRM. Although the recurrence rate in these patients is increased, the recurrence rate is not as high as in patients with involved resection margins. Consequently, many more patients would be required to confirm a beneficial effect of IORT in this specific patient group; neither the randomized controlled trial, nor our study can answer this question

The literature is scarce on the effect of IORT in relation with the resection margin status and in particular in patients with R1-resections of LARC. In patients with a microscopically involved CRM, local recurrence rates of 41-100% are reported after neoadjuvant radiotherapy without administering IORT.[3,4,18,19] One comparative study demonstrated that IORT improved 5-year local control in patients with a microscopically involved CRM.[20] Non-comparative studies reported 5-year local control rates after IORT for LARC of 55-77% in patients with an involved CRM.[9,21-23] These rates are relative low compared to our 5-year local recurrence-free survival of 84%, which may be explained by the fact that we excluded patients with macroscopically involved margins. Others demonstrated that IORT did not result in a similar increase in local control after IORT for macroscopically involved resection margins as in patients with microscopically involved resection margins.[9,11,14] This suggest that IORT may be less or uneffective in patients with macroscopic involved resection margins.

Preoperative understaging and false-negative frozen section evaluation resulted in the omission of IORT in patients with involved or narrow margins. However, the erroneous omission of IORT made it possible for us to make a unique comparison of patients treated with or without IORT, which was impossible in other studies from centers that apply IORT routinely in LARC patients. Our false-negative rate of CRM-involvement on preoperative

imaging and on frozen sections seems high, but one should keep in mind that only patients with a CRM ≤2mm were selected. The overall false-negative CRM-involvement rate of 409 surgically treated patients was 6% (24/409) which is in line with a 5% false-negative rate of CRM-involvement in the Mercury trial.[24] The 7% (13/196) false-negative rate of frozen sections was slightly higher and was probably caused by sampling error. Still, this latter finding has led us to change our protocol. Currently, patients in whom we judge the risk of sampling error to be high are treated with IORT regardless of frozen section results.

Although the operation time was longer and the estimated blood loss was higher in patients who were treated with IORT, there was no significant difference in complication rate between patients who were treated with or without IORT. Administering an extra dose of radiotherapy could contribute to an increased toxicity or a higher complication rate. However, administering radiotherapy intraoperatively provides the ability to treat a specific area at risk under direct visual control with the possibility to shield surrounding structures from radiation. Previous studies from other institutes confirmed that administering IORT is safe and feasible and does not result in a higher complication rate.[10,12] Our overall complication rate of 65% in patients treated with IORT is higher compared to other institutes, reporting complications rates of 15-35%.[12,20,25] This difference may be explained by the fact that we included patients with more advanced tumors (≤2mm) and patients undergoing multivisceral resections (33%).

Due to the retrospective nature of this analysis, this study has drawbacks. Different neoadjuvant radiotherapy regimes were used in this study. Although the nature of the neoadjuvant treatment did not differ significantly, more patients who had microscopically involved CRMs treated with IORT had received neoadjuvant chemoradiotherapy. This is caused by the fact that chemoradiotherapy was introduced in 2006 and IORT was applied with an increasing frequency after 2006. Several randomized controlled trials demonstrated that adding chemotherapy during radiotherapy reduces the local recurrence rate.[26] However, these results were mainly based on radical resections. Furthermore, it could be hypothesized that patients with an involved CRM after chemoradiotherapy may have an even more aggressive tumor behavior, because this group consists of poor responders. This assumption is supported by the study of Nagtegaal et al.[2] Patients with an involved CRM after (chemo-)neoadjuvant radiotherapy had a higher chance on local recurrence than patients with a involved CRM who were treated without neoadjuvant (chemo-)radiotherapy.

Another remarkable finding was that in the group of patients who did not receive IORT for a microscopically involved CRM, significantly more patients had stage IV disease. Patients with stage IV disease were generally referred to our hospital for metastatic surgery and not for LARC specifically. Stage IV patients with involved CRMs on pathological staging were understaged preoperatively. On the other hand, patients

with a compromised CRM on preoperative clinical staging were specifically referred for IORT to our hospital, whereas the patients who were understaged preoperatively underwent surgery in other hospitals. This may explain the higher number of patients with understaged rectal cancer in the group of patients with stage IV disease. Stage IV disease was not the reason for omitting IORT; all patients were planned for a curative resection by a 'liver first' approach, synchronous resection of rectum and metastases or resection of the metastases in later stage.[27]

The presence of metastatic disease explains the shorter length of follow up in patients with an involved CRM not treated with IORT. Regardless of this shorter follow up time, patients who were not treated with IORT had a higher local recurrence rate compared to patients treated with IORT, who were followed longer. Nevertheless, metastasized disease may indicate more aggressive tumor behavior, which may also be associated with a higher local recurrence rate, even though the presence of synchronous metastases was not a significant risk factor for local recurrence in the univariate analysis. The difference in stage IV patients makes it inappropriate to draw any conclusions about the effect of IORT on overall survival, despite a significant difference between patients treated with or without IORT, because distant metastases are the most important prognostic factor for overall survival.

Several studies advocated a randomized controlled trial for definitive evidence of the effect of IORT in patients with incomplete resections. The accrual of a sufficient number of patients for such a trial would be challenging. This is illustrated by the small number of patients treated with an involved CRM over a long period of time in a high volume center in the current study. Furthermore, it is questionable whether not administering IORT in patients with involved margins may be considered acceptable in institutes currently performing IORT. Nevertheless, this study is the result of a retrospective analysis and therefore all known drawbacks of retrospective studies apply.

In conclusion, IORT does not have a benefit for patients who undergo radical resections of rectal cancer. However, our results suggest that IORT reduces the local recurrence rate in patients with microscopically involved CRMs. Patients who are at risk for a microscopically involved CRM should undergo surgery in centers with IORT facilities.

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Chapter 6

Hospital volume and outcome in locally advanced rectal cancer patients; results of a population-based study in The Netherlands

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Submitted

Abstract

Background

The treatment of rectal cancer mainly depends on the tumor stage. Clinically staged T1-3 rectal cancer (cT1-3) is treated by total mesorectal excision (TME) with or without neoadjuvant therapy, whereas cT4 rectal cancer requires a multimodality approach and often multivisceral surgery. The current study evaluates the outcome of cT1-3 and cT4 rectal cancer according to hospital volume.

Methods

This population-based study includes patients undergoing rectal cancer surgery between 2005 and 2013 in the Netherlands using data from the NCR. Cox-proportional hazards model was used for multivariable analysis of overall survival according to hospital volume. Hospitals were divided into low(1-20), medium(21-50) and high(>50 resections/year) volume for cT1-3 and into low(1-4), medium(5-9) and high(≥10 resections/year) volume for cT4 rectal cancer.

Results

A total of 14.050 confirmed cT1-3 patients and 2.104 cT4 patients underwent surgery. In cT1-3 rectal cancer, there was no significant difference in 5-year overall survival related to high, medium and low hospital volume (70% vs. 69% vs.69%). In cT4 rectal cancer, treatment in a high volume cT4 hospital was associated with a survival benefit compared to low volume cT4 hospitals (HR 0.81 95%CI 0.67-0.98) adjusted for non-treatment related confounders. There was increase in referral of cT4 rectal cancer to high volume hospitals, but the majority of patients was still treated in low volume hospitals.

Conclusion

Hospital volume was not associated with survival in cT1-3 rectal cancer. In cT4 rectal cancer, treatment in high volume cT4 hospitals was associated with an improved survival compared to low volume cT4 hospitals.

Introduction

Colorectal cancer is the third most common malignancy in the Western world and rectal cancer accounts for approximately one third of the colorectal cancer patients.[1] Outcome of rectal cancer has improved over the last two decades, mainly due to the introduction of improved imaging modalities, total mesorectal excision (TME) and neoadjuvant (chemo-)radiotherapy.[2-5]

Optimal treatment of rectal cancer is dependent on local tumor stage and the presence of distant metastases. Local tumor stage determines whether neoadjuvant (chemo-) radiotherapy should be administered to reduce local recurrence rate. In lower stages of rectal cancer, the effectiveness of neoadjuvant (chemo-)radiotherapy is limited, whereas in more advanced stages of rectal cancer (chemo-)radiotherapy is an essential part of the treatment.[6] It leads to tumor shrinkage, thereby facilitating complete resections and a decrease in local recurrence rate.[3,7]

Local tumor stage is also important to determine the optimal surgical treatment. Lower stages of rectal cancer can be treated by standard TME procedures or even rectal sparing surgery in selected patients.[8] Advanced stages of rectal cancer with tumors invading the mesorectal fascia often require a more radical surgical approach to achieve a complete resection. These procedures, such as extralevatory abdominoperineal resections and partial or total exenterations, require a surgical dissection beyond the standard TME plane.[9]

To improve the outcome of rectal cancer, the current Dutch standard indicates a minimum of 20 surgical resections of rectal cancer per year per hospital and the Dutch guideline advises centralization of care for patients with advanced stages of rectal cancer (i.e. clinically staged T4 and locally recurrent rectal cancer) in specialized colorectal cancer hospitals.[10] Due to the more complex treatment of the advanced stages of rectal cancer, a personalized 'tailor made' multimodality treatment is needed. Moreover, cT4 rectal cancer is relatively rare and exenterative surgery is technically demanding with higher amounts of blood loss, operation time and increased morbidity and mortality.[11] We hypothesize that hospital volumes may be more important in cT4 rectal cancer than in patients with cT1-3 rectal cancer. This study analyses the long-term results of cT1-3 and cT4 rectal cancer according to hospital volume in the Netherlands.

Patients and methods

Data collection

Data of all rectal cancer patients diagnosed between 2005 and 2013 in the Netherlands were retrieved from the nationwide population-based Netherlands Cancer Registry (NCR). Registration is mainly based on notification by the automated pathological archive

(PALGA) and the National Registry of Hospital Discharge Diagnosis. Trained registrars of the NCR collected data from the medical records of the different hospitals. The population based NCR database has a 95% completeness of cancer registrations.[12] Information concerning the cause of death was not available.

Study population

All patients undergoing surgery for rectal cancer were included. The following patient/tumour related variables were available: year of diagnosis, age, gender, clinical and pathological TNM stage, histopathology and the presence of synchronous distant metastases. Treatment related variables that were available were: neoadjuvant treatment, adjuvant treatment, hospital volume based on number of rectal cancer resections per year, type of surgical procedure (low anterior resection, abdominoperineal resection or proctocolectomy). Involvement of circumferential resection margin (CRM) was available from 2008 onwards.

Clinically staged T1-3 and T4 rectal cancer were analyzed separately. Patients with an unknown cT-stage were excluded from analysis, but were included in the determination of rectal cancer hospital volume. For cT1-3 rectal cancer, hospitals were divided into low volume hospitals (1-20 resections), medium volume hospitals (21-50 resections) and high volume hospitals (>50 resections), based on the total number of rectal cancer resections performed annually in one hospital. For cT4 rectal cancer, hospitals were divided into low (1-4 resections) medium (5-9 resections) and high (≥10 resections) volume based on cT4 rectal cancer resections performed annually in one hospital.

The TNM-classification was used according to the edition valid at the time of cancer diagnosis (6th edition for 2005-2009 and 7th edition for 2010-2013). The 7th edition included a distinction between cT4a (tumor penetrates the surface of the visceral peritoneum) and cT4b tumors (tumor invades or is adherent to surrounding organs or structures).

Endpoints

The primary endpoint was overall survival according to the total hospital volume for cT1-3 and cT4 rectal cancer.

Follow up

Vital status of patients was retrieved by linkage of the NCR to the nationwide municipal population registries network.

Statistical analysis

Data were reported as median (interquartile range) or mean (standard deviation) as appropriate. Categorical data were reported as count (percentage). The Chi-square was used for comparison of groups. For survival analysis, follow-up time was calculated from

date of diagnosis until date of death or end of follow-up. Patients who were alive at the end of follow-up were censored. Three and five-year survival rates were calculated by Kaplan-Meier analysis and comparisons between groups were made using log-rank tests. Multivariable Cox's proportional hazards analysis was performed to analyze differences in overall survival according to hospital volume. Variables with p-values <0.10 in the univariate analysis were included in the multivariable analysis. Only variables available for the whole study period were included in the multivariable analysis.

Results

16.154 patients underwent rectal cancer surgery and had a confirmed clinical T-stage, while in 6394 patients the cT-stage was unknown. Of those patients with a known cT-stage 14.050 patients (87%) had a cT1-3 tumor and 2.104 patients (13%) had a cT4 tumor.

cT1-3 rectal cancer

The baseline characteristics of the 14.050 patients with cT1-3 rectal cancer are outlined in *table I*. The majority of these patients underwent surgery in medium volume hospitals (62%), followed by high volume hospitals (21%) and low volume hospitals (17%). An increase was seen in patients treated in high volume hospitals (2005-2007: 13% vs. 2011-2013: 23%, p <0.001). Neoadjuvant chemoradiotherapy was administered more often to patients in high volume hospitals compared to medium volume and low volume hospitals (43% vs. 37% and 32%, p<0.001). High volume hospital hospitals performed less abdominoperineal resections (32% vs. 36% vs. 36%, p=0.002) and had a higher percentage of ypT0 stage (9% vs. 7% vs. 8%, P=0.01). There was no difference in nodal stage and CRM-involvement. Patients treated in low volume hospitals received adjuvant chemotherapy less often (11% in high and medium volume hospitals compared to 8% in low volume hospitals, p <0.001).

Outcomes

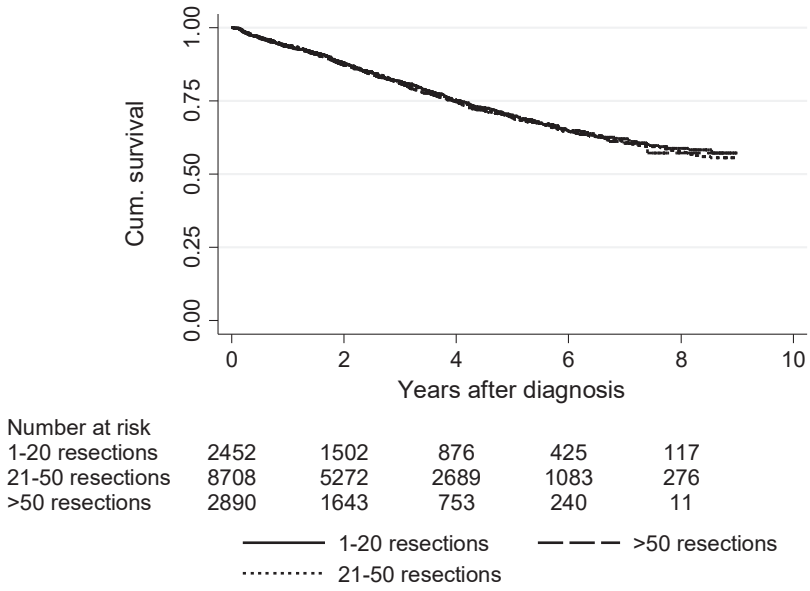
The median follow up was 31 months (IQR 15 – 54 months). The estimated 5-year survival rate of patients with cT1-3 rectal cancer who were treated in low, medium or high volume hospitals was similar (70%, 69%, 69% respectively; p=0.88). Survival curves are shown in *figure I*. Univariate Cox regression analysis showed no significant difference in survival between different hospital volumes. Univariate hazard ratios for survival of medium and high volume hospitals compared to low volume hospitals were 1.01 (95%CI: 0.92 – 1.11) and 1.03 (95%CI: 0.92 – 1.16) respectively.

Table I. Baseline characteristics cT1-3 rectal cancer patients

Total patients	Low volume hospitals 1-20/year 2452	Medium volume hospitals 20-50/year 8708	High volume hospitals ≥50/year 2890	P-value
Gender				
Male	1526 (62)	5573 (64)	1824 (63)	0.25
Female	926 (38)	3135 (36)	1066 (37)	
Median age	67	67	67	0.10
Year of diagnosis *				
2005-2007	685 (24)	1791 (63)	380 (13)	< 0.001
2008-2010	780 (16)	2985 (62)	1017 (21)	
2011-2013	987 (15)	3932 (61)	1493 (23)	
Neo-adjuvant treatment				
None	252 (10)	1007 (12)	280 (9)	< 0.001
Radiotherapy	1408 (57)	4448 (51)	1359 (47)	
Chemotherapy	7 (1)	48 (1)	16 (1)	
Chemoradiotherapy	785 (32)	3205 (37)	1235 (43)	
Type of surgery				
LAR/Hartmann	1569 (64)	5575 (64)	1952 (68)	0.002
APR	854 (35)	2980 (34)	892 (31)	
Proctocolectomy	12 (1)	65 (1)	27 (1)	
Not otherwise specified	17 (1)	88 (1)	19 (1)	
Pathological tumor stage				0.010
T0	190 (8)	648 (7)	269 (9)	
T1	183 (7)	627 (7)	209 (7)	
T2	824 (34)	2788 (32)	929 (32)	
T3	1174 (48)	4270 (49)	1384 (48)	
T4	50 (2)	191 (2)	57 (2)	
TX	31 (1)	184 (2)	42 (1)	
Pathological nodal stage				
N0	1592 (65)	5519 (63)	1863 (64)	0.17
N+	835 (34)	3087 (36)	993 (35)	
NX	25 (1)	102 (1)	34 (1)	
Pathological distant metastases				
M0	2381 (97)	8317 (96)	2767 (96)	0.002
M+	71 (3)	391 (4)	123 (4)	
Tumor grade				
Well differentiated	70 (3)	259 (3)	168 (2)	< 0.001
Moderately differentiated	1009 (41)	3466 (40)	1040 (36)	
Poorly differentiated/ undifferentiated	161 (7)	532 (6)	159 (6)	
Unknown	1212 (49)	4451 (51)	1623 (56)	
CRM-involvement #				
Involved	125 (7)	477 (7)	180 (7)	0.50
Not involved	1292 (73)	4967 (72)	1779 (71)	
Unknown	349 (20)	1470 (21)	551 (22)	
Adjuvant chemotherapy	201 (8)	980 (11)	326 (11)	< 0.001

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis. #, CRM was reported in the database starting from 2008*

Figure I. Overall survival in cT1-3 patients according to hospital volume.



cT4 rectal cancer

The baseline characteristics of 2.104 patients with cT4 rectal cancer are depicted in *table II.* The majority of patients (60%) underwent surgery in low volume cT4 hospitals, followed by high volume hospitals (25%) and medium volume hospitals (15%). Eight hospitals performed less than one surgical procedure for cT4 rectal cancer per year on average (2005-2013). There was an increase in referral of cT4 rectal cancer patients for resection to any other hospital from 23% in 2005 to 38% in 2013 (p=0.003) (*figure IIa)*. CT4 patients were most often referred by low volume hospitals, followed by medium and high volume hospitals *(figure IIb)* and most often referred to high volume hospitals, but also to medium volume hospitals and even to other low volume hospitals *(figure 2c).*

The percentage of patients who received neoadjuvant therapy was higher in high volume cT4 hospitals (98%) than in medium and low volume cT4 hospitals (respectively 91% and 88%, p<0.001). In high volume cT4 hospitals, 83% of the patients received chemoradiotherapy, compared to 70% in medium volume cT4 hospitals and 62% in low volume cT4 hospitals.

Figure IIa. Referral of cT4 rectal cancer patients for resection

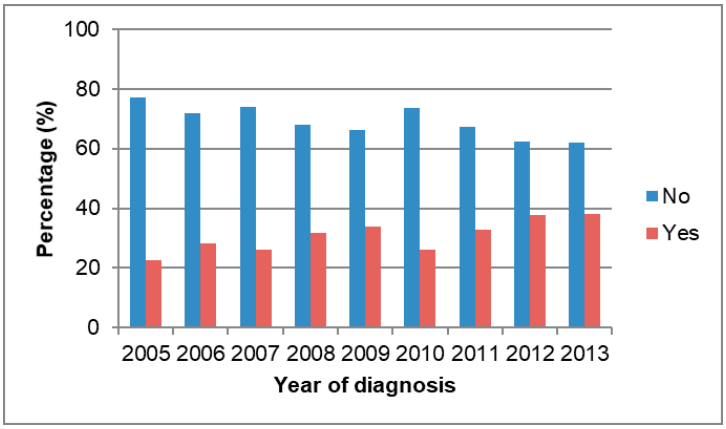


Figure IIb. Volume of hospital of diagnosis of the referred patients

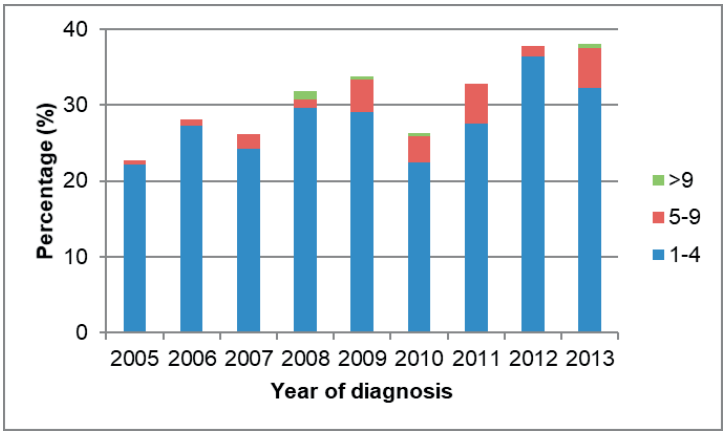


Figure IIc. Volume of hospital of resection of the referred patients

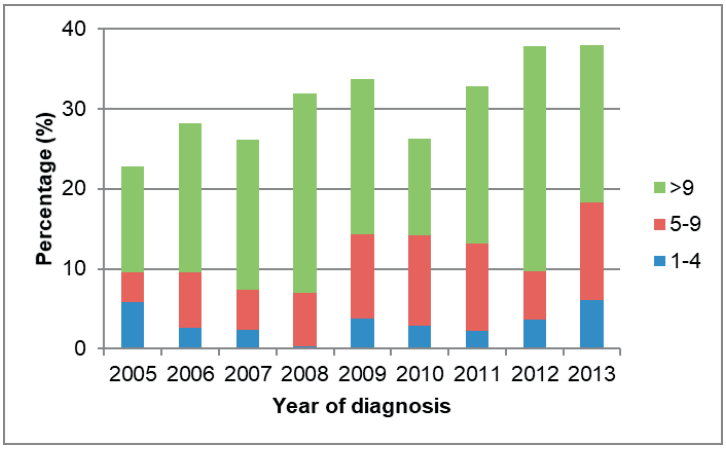


Table II. Baseline characteristics of cT4 rectal cancer patients

	Low volume hospitals 1-4/year	Medium volume hospitals 5-9/year	High volume hospitals ≥10/yea	P-value
Total patients	1.256	328	520	
Gender				
Male	622 (50)	175 (53)	294 (57)	0.02
Female	634 (50)	153 (47)	226 (43)	
Median age	67	65	63	<0.001
Year of diagnosis *				
2005-2007	433 (64)	102 (15)	142 (21)	0.03
2008-2010	442 (59)	120 (16)	188 (25)	
2011-2013	381 (56)	106 (16)	190 (28)	
Neo-adjuvant treatment				
None	156 (12)	29 (9)	13 (2)	<0.001
Radiotherapy	308 (25)	53 (16)	58 (11)	
Chemotherapy	10 (1)	16 (5)	15 (3)	
Chemoradiotherapy	782 (62)	230 (70)	434 (83)	
Type of surgery				<0.001
LAR/Hartmann	528 (42)	103 (31)	138 (27)	
APR	590 (47)	157 (48)	259 (50)	
Proctocolectomy	121 (10)	63 (19)	114 (22)	
Not otherwise specified	17 (1)	5 (2)	9 (2)	
Pathological tumor stage				
T0	87 (7)	23 (7)	47 (9)	0.02
T1	26 (2)	10 (3)	19 (4)	
T2	198 (16)	43 (13)	59 (11)	
T3	610 (49)	142 (43)	239 (46)	
T4	287 (23)	95 (29)	143 (28)	
TX	48 (4)	15 (5)	13 (3)	
Pathological nodal stage				
N0	710 (57)	204 (62)	330 (64)	0.04
N+	512 (41)	113 (34)	179 (34)	
NX	34 (3)	11 (3)	11 (2)	
Pathological distant metastases				
M0	1,174 (93)	294 (90)	461 (89)	0.001
M+	82 (7)	34 (10)	59 (11)	
Tumor grade				
Well differentiated	34 (3)	6 (2)	18 (3)	<0.001
Moderately differentiated	455 (36)	87 (27)	147 (28)	
Poorly differentiated/undifferentiated	116 (9)	25 (8)	38 (7)	
Unknown	651 (52)	210 (64)	317 (61)	
CRM-involvement #				
Involved	160 (19)	45 (20)	63 (17)	0.58
Not involved	466 (57)	131 (58)	213 (56)	
Unknown	197 (24)	50 (22)	102 (27)	
Adjuvant chemotherapy	172 (14)	52 (16)	54 (10)	0.05

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis. #, CRM was reported in the database starting from 2008*

The proportion of patients with a pathological T4-stage was higher in high volume hospitals compared to low volume hospitals (28 vs. 23%). In a subgroup analysis of the cT4 patients diagnosed between 2010 and 2013, more patients were staged cT4b in high volume hospitals compared to medium volume hospitals (82% vs. 70%, p=0.007) and low volume hospitals (82% vs. 68% p<0.001). Low volume hospitals had the highest proportion of node positive patients: 41% compared to 34% in both medium volume and high volume hospitals. The number of synchronously metastasized patients was significantly higher in high volume hospitals compared to low volume cT4 hospitals (11% vs. 7%, p=0.001) and was similar in medium cT4 hospitals (11% vs. 10%, p=0.66). In the period 2008-2013, there was no significant difference in CRM-involvement between high, medium and low volume cT4 hospitals (respectively 19%, 20%, 17%, p=0.58).

Outcomes

There was no difference in 30-days mortality and 90-days mortality according to hospital volume. Patients were followed with a median of 33 (IQR 16 - 60) months. The estimated overall survival of cT4 patients treated in high volume cT4 hospitals was significantly longer than in medium and low volume cT4 hospitals (p=0.001). The estimated 3-year survival rate was 76%, 71% and 67% respectively and the 5-year survival rate was 63%, 53% and 54% respectively (*Figure III).* Multivariable analysis demonstrated that resection in high volume cT4 hospitals was independently associated with a better overall survival compared to low volume cT4 hospitals (HR 0.81, 95%CI 0.67-0.98)), after adjusting for patient/tumour related confounders (age, pTNM-stage and tumor differentiation) *(table III).*

Figure III. Overall survival of cT4 rectal cancer according to the cT4 hospital volume

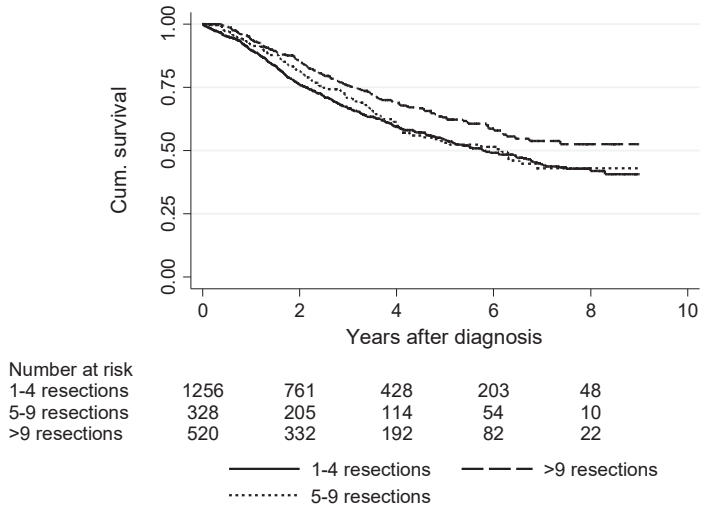


Table III. Univariate and multivariable survival analysis for overall survival of cT4 tumors with and without treatment related confounders

	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	Multivariable Hazard ratio (95%CI)
Hospital volume (procedure per year)		<0.001		
1-4	1		1	1
5-9	0.93 (0.76-1.14)		0.97 (0.79-1.19)	0.99 (0.81-1.22)
≥10	0.71 (0.59-0.85)		0.81 (0.67-0.98)	0.87 (0.71-1.05)
Gender		0.98		
Male	1		-	-
Female	1.00 (0.87-1.15)		-	-
Age	1.03 (1.02-1.04)	<0.001	1.03 (1.03-1.04)	1.03 (1.02-1.04)
Year of diagnosis	0.98 (0.95-1.02)	0.32		
Neo-adjuvant therapy		<0.001		
None	1		-	
Radiotherapy	0.58 (0.46-0.73)		-	0.70 (0.54-0.88)
Chemotherapy	0.59 (0.35-0.97)		-	0.69 (0.41-1.17)
Chemoradiotherapy	0.32 (0.26-0.39)		-	0.53 (0.42-0.68)
Type of surgery		0.02		
LAR/Hartmann	1		-	1
APR	0.81 (0.69-0.95)		-	0.99 (0.84-1.17)
Proctocolectomy	0.95 (0.78-1.16)		-	0.95 (0.77-1.18)
Not otherwise specified	1.42 (0.83-2.43)		-	1.47 (0.85-2.53)
Pathological tumor stage				
T0	1	<0.001	1	1
T1	0.89 (0.35-2.24)		0.92 (0.37-2.32)	0.87 (0.35-2.21)
T2	2.02 (1.20-3.39)		1.84 (1.09-3.10)	1.75 (1.04-2.94)
T3	3.57 (2.22-5.72)		2.73 (1.69-4.41)	2.53 (1.56-4.09)
T4	5.89 (3.65-9.50)		4.30 (2.65-6.99)	3.89 (2.38 (6.37)
TX	2.64 (1.46-4.78)		2.50 (1.38-4.56)	2.42 (1.33-4.41)
Pathological nodal stage		<0.001		
N0	1		1	1
N1	1.64 (1.38-1.95)		1.34 (1.12-1.61)	1.32 (1.10-1.58)
N2	2.74 (2.29-3.28)		2.06 (1.71-2.49)	1.95 (1.61-2.36)
NX	2.31 (1.62=3.30)		2.06 (1.43-2.97)	2.11 (1.46-3.04)
Pathological distant metastases				
M0/X	1	<0.001	1	1
M+	2.14 (1.71-2.67)		2.12 (1.68-2.69)	1.99 (1.56-2.52)
Tumor grade		<0.001		
Well differentiated	0.93 (0.62-1.42)		1.04 (0.69-1.60)	1.11 (0.73-1.69)
Moderately differentiated	1		1	1
Poorly differentiated/undifferentiated	1.66 (1.32-2.09)		1.49 (1.18-1.88)	1.47 (1.16-1.86
Unknown	0.83 (0.71-0.97)		1.01 (0.86-1.19)	1.14 (0.96-1.35)
Adjuvante chemotherapy				
No	1		-	-
Yes	1.06 (0.87-1.30)	0.54	-	*

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis. #*, CRM was reported in the database starting from 2008

When treatment related confounders were included in the multivariate analysis, neoadjuvant chemoradiotherapy was associated with improved survival. Adjustment for neoadjuvant therapy resulted in the disappearance of a significant difference between high, medium and low volume hospitals.

Discussion

The current population-based study found an overall survival benefit of cT4 rectal cancer patients treated in high volume cT4 hospitals compared to low volume cT4 hospitals. In cT1-3 rectal cancer, we were not able to find an overall survival difference related to hospital volume. In the present study patients with locally advanced (cT4) rectal cancer treated in high volume hospitals (≥10 resections annually) had a significantly improved 5-year overall survival of 63% compared to 53% in low volume (1-4 resections). This contradicts a previous study executed in the Southern part of the Netherlands, which did not found an association between hospital volume and long term overall survival for both colon and rectal cancer patients.[13] However, that study did not analyze the long-term outcome of cT4 and cT1-3 separately. This may explain why we found a survival difference, while the other study did not. Although the referral of cT4 tumors to high volume hospitals has increased during the study period, the majority of patients (56%) were still treated in a low volume cT4 hospital in the period 2011-2013

Rectal cancer is a relatively common malignancy and the majority of patients can be treated by a standard TME procedure. The Dutch TME-trial, which included a teaching program for the TME technique, showed us that this technique can be taught and rolled out nationwide and results in low recurrence rates.[4] However, only patients with cT1-3 rectal cancer are suitable candidates for a standard TME procedure, because standard TME in patients with tumor invasion through the mesorectal fascia (cT4) leads to an involved mesorectal fascia and thus incomplete resections (R1/2-resections). Involved circumferential resection margins (CRM) are uncommon in cT1-3 rectal cancer patients and reported to be <10%, whereas in cT4 patients positive CRM is demonstrated in approximately 20%.[14] Incomplete resections are deleterious for oncological outcome and all efforts should be aimed at avoiding R1/2-resections.[15] This makes more radical procedures in patients with cT4 rectal cancer necessary to achieve R0-resections. These surgical procedures beyond the TME plane are less straightforward and more technically demanding than standard TME surgery.[9,16,17] Additionally, the advanced stages of rectal cancer have the greatest benefit of a multimodality treatment, including neoadjuvant chemoradiotherapy leading to more complete resections and reduces local recurrence rates.[3,7]

Accurate staging of the rectal tumor is essential in selecting patients who should be treated with neoadjuvant therapy and to differentiate between those who can be treated by a standard TME procedure and those who require more extended surgery. The quality of this assessment may be enhanced by multidisciplinary tumor board meetings (MDT), including dedicated radiologists, radiation oncologists, medical oncologists and surgeons. Nowadays, almost all rectal cancer patients in the Netherlands are staged by MR imaging and are discussed in an MDT.[2] In an experienced MDT, cT4 tumors are potentially more accurately assessed and a more appropriate surgical procedure may be selected. Furthermore, in experienced MDTs, standardized care for patients with advanced stages of rectal cancer may result in an improved long-term outcome.

Several studies have reported survival differences according to hospital volume in complex surgical procedures in other malignancies, such as esophagus, pancreas and bladder cancer.[18-20] The hypothesis of this survival benefit is that more exposure and experience in the multimodality treatment (staging, neo-adjuvant therapy and surgical expertise) of these relatively rare malignancies results in an improved long-term outcome. In line with the findings of studies in other malignancies, the current study showed a survival benefit in the treatment of cT4 rectal cancer in high volume cT4 hospitals, but not in the more common cT1-3 rectal tumors. In a previous study from data of the NCR no difference in survival was demonstrated between high and low volume centers for all colon or rectal patients.[13] However, the results from the present study, suggest that locally advanced (cT4) rectal cancer requires a minimal number of resections per hospital, irrespective of the number of resections performed for cT1-3 rectal cancer in that same hospital.

The reason for the overall survival benefit of cT4 tumors treated in high volume cT4 hospitals cannot be defined by this population-based study. Presumably, the overall survival benefit is caused by multiple factors. Optimal staging, neoadjuvant therapy, surgical treatment and experience of the MDT may lead to superior selection, treatment and results when optimally combined. Optimal staging may results in the selection of the appropriate neoadjuvant treatment. Experience with extensive rectal resections in high volume hospitals may contribute. However, this did not lead to a lower percentage of CRM-involvement in high volume cT4 hospital compared to medium and low volume cT4 hospital in the years evaluated. This may be explained by referral of patients with more advanced tumors to high volume cT4 hospitals, which explains the higher pathological stage (pT4a and p T4b) in high volume cT4 hospitals, regardless of the higher percentage of neoadjuvant therapy administered. Another factor that may have contributed to the survival benefit is the availability of intraoperative radiotherapy (IORT). High volume cT4 hospitals in The Netherlands have the ability to apply an extra radiation dose during surgery. IORT may eradicate remaining tumor cells and this may lead to a survival

benefit.[21,22] Unfortunately, IORT was not comprehensively registered in the Netherlands Cancer Registry making further evaluation of the role of IORT impossible.

Unfortunately, the data available on different aspects of treatment is limited. The type of procedure was registered, but is limited to ''low anterior resection', 'abdominoperineal resection' and 'proctocolectomy'. Especially in cT4 rectal cancer, data on resections outside the TME plane, the need for multivisceral surgery, urinary tract reconstructions and the admission of intra-operative radiotherapy may provide more insight into what type of tumours were treated in different hospitals. However, these data are not available; only the administration of neoadjuvant therapy was registered comprehensively and indeed was identified as an independent prognostic factor for survival. We argue that when the quality of a multidisciplinary/multimodality treatment of rectal cancer is assessed, the singling out of an individual aspect, because that variable happens to be available, is inappropriate. The administration of all contributors of the multimodality treatment, at the right time, to the right patient is what defines quality of care. When important treatment related variables are lacking, a valid multivariate analysis of treatment related variables is impossible. The fact that this study identifies neo-adjuvant chemoradiotherapy as a prognostic factor for survival when randomized clinical trials did not, adds to our skepticism towards the appropriateness of a multivariate analysis of treatment related confounders in this study[23].

Although referral of cT4 rectal cancer has increased during the study period, further centralization of cT4 rectal cancer seems warranted. Remarkably, some of the patients diagnosed in low volume hospitals were referred to other low volume cT4 hospitals for treatment. To improve care for rectal cancer patients in the Netherlands, it seems logical to refer cT4 rectal cancer patients to high volume hospitals only. The total number of cT4 rectal cancer diagnosed annually in the Netherlands (approximately 250 patients) is limited and the appointment of 4 or 5 cT4 rectal cancer centers would seem appropriate. Excluding cT4 rectal cancer from the required total number of rectal cancer procedures per hospital can eliminate the stimulus to treat these patients in hospitals without T4 rectal cancer experience.

As all retrospective studies do, this study has limitations. The younger age of patients treated in high volume cT4 hospitals may indicate that the patients referred to high volume centers for extensive surgery were the ones in a relatively good clinical condition and that may improve their survival significantly. On the other hand, the pathological T-stage and the number of metastasized patients was significantly higher in high volume cT4 hospitals, suggesting that advanced stages of disease were referred to high volume cT4 hospitals, which would decrease overall survival in these patients. This type of discussion on the profile of patient groups in different hospitals is often referred to as the 'case mix' discussion. Unfortunately, for reasons described earlier, we cannot

conclude whether case mix is the driver behind the differences that we did and did not find. We stress, however, that earlier studies that suggested improved outcome in high volume centers for complex surgery also relied on retrospective data and were flawed by the same confounders. The observation that in a cohort of more than 14.000 cT1-3 rectal cancer patients, no relationship between hospital volume and overall survival was present, stands. This makes it questionable whether such a relationship, should we have missed it in this study, could realistically be clinically relevant.

In conclusion, the treatment of cT4 rectal cancer in high volume cT4 hospitals was associated with an improved survival compared to low volume cT4 hospitals after adjustment for patient and tumour related confounders. Hospital volume in cT1-3 rectal cancer was not associated with overall survival in the present study. There was a small increase in referral of cT4 rectal cancer to high volume cT4 hospitals, but further centralization of cT4 rectal cancer seems warranted to further improve outcome for this difficult group of patients.

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Chapter 7

Surgery of the Primary Tumour in Stage IV Colorectal Cancer with Unresectable Metastases

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Abstract

Since patients with incurable metastatic colorectal cancer (CRC) only have a relatively limited life expectancy, and resection of the primary tumour is accompanied by both morbidity and mortality, it is under debate whether resection of the primary tumour has an effect on survival or quality of life. The rationale behind the resection strategy is that prophylactic surgery prevents future complications. With current new chemotherapy regimens, a relatively low number of patients with metastatic CRC require surgery for their primary tumour. Many studies concerning the management of incurable stage IV CRC have been performed and most studies suggest a survival benefit for patients undergoing surgical resection of the primary tumour compared with those who received palliative treatment. However, in stage IV CRC with unresectable metastases, the role of a palliative resection of the primary tumour has never been assessed properly. Because randomised clinical trials are lacking, it is difficult to draw conclusions from the present literature.

Introduction

Colorectal cancer (CRC) is one of the two most commonly diagnosed cancers, with approximately 1.2 million new cases each year and more than 600,000 annual deaths estimated to occur worldwide.[1] In addition, roughly one-fifth of patients presents with incurable disseminated disease.[2] In the last decade, development of new chemotherapeutic biological agents has significantly improved overall survival (OS) of these patients.[3-12]

A palliative resection of the primary tumor is frequently performed[13] and there is a clear indication for surgery when patients present with symptoms of the primary tumor. However, if patients present with absence or mild symptoms, the indication for resection is less obvious. Since patients with incurable metastatic CRC (mCRC) only have a relatively limited life expectancy and resection of the primary is accompanied with both morbidity and mortality[14-16], it is under debate whether resection of the primary tumor has an effect on survival or quality of life.[17,18] Many studies concerning the management of incurable stage IV CRC have been performed; however the advantage of a palliative resection of the primary tumor has never been assessed properly.[19] Moreover, most studies do not even report whether a resection of the primary has been performed.[20]

In this paper we aim to evaluate the role of surgery of the primary in stage IV CRC with unresectable metastases.

Treatment of metastatic colorectal cancer (mCRC)

At diagnosis of CRC, approximately 20% of the patients present with synchronous mCRC, and the liver is the predilection site in half these patients.[21,22] The lungs represent the second most common site of metastases from CRC and according to non population based studies lung metastases are present in 10-15% of patients with colorectal cancer.[23,24]

When metastases are limited, a possible curative treatment can be obtained by surgical resection, however, only 15-20% of patients is resectable.[25] Median 5-year survival for patients undergoing an R0 resection of the metastases is approximately 30% (range 15-67%).[26] Despite complete resection and neoadjuvant or adjuvant chemotherapy regimens, recurrences occur in 75% of the patients.[27] Extrahepatic disease in combination with liver metastases was generally considered a contraindication for surgery.[28] However, resection of both intrahepatic and extrahepatic colorectal metastases should be considered if resection of all metastatic sites can be complete and the disease is controlled by chemotherapy.[29]

In patients with unresectable metastases, palliative systemic chemotherapy is the treatment of choice. With systemic combination chemotherapy response rates of 40-70% have been reported resulting in a median overall survival rate of approximately

22 months.[30-32] Most frequently used combinations are oxaliplatin or irinotecan plus capecitabine or 5-fluorouracil (5-FU) with or without bevacizumab. In case of K-RAS wild type tumors, anti-epidermal growth factor receptor (EGFR) antibodies such as panitumumab and cetuximab are being used.[33]

Resection of the primary tumor in patients with unresectable synchronous mCRC

Traditional surgical teaching promotes resection of the primary tumor in patients with unresectable metastases, even if the primary is asymptomatic. The rationale behind this strategy is that prophylactic surgery prevents future complications of intestinal obstruction, perforation and haemorrhage.[34] However, resection does not provide immediate palliative benefit in case of an asymptomatic primary tumor, and surgery is associated with high mortality (5-13%) and morbidity (23-48%) in patients with metastatic disease.[34-37] Some studies tried to selectively apply prophylactic surgery in patients with a low metastatic tumor burden because these patients are presumed to be at risk for obstruction because of long survival. If the metastatic tumor burden is extensive, resection of the primary is unlikely to benefit the patient and is associated with a high risk of postoperative complications. These patients are probably better served by focusing on the disseminated component of their disease and start with systemic treatment early on in their course, reserving surgery for when and if symptoms from the primary tumor are substantial.[36,38]

Other studies have shown no association between the incidence of complications and the extent of metastatic disease.[39,40] Due to recent advances in systemic chemotherapy, the risks and benefits of immediate or deferred surgical strategy are under debate.

Some clinicians in favor of the surgical approach argue that if the asymptomatic primary cancer is not resected, patients will develop disabling symptoms such as weight loss and nutritional depletion (secondary to "near" obstruction) and anemia due to bleeding of the primary tumor. Arguments supporting surgery include a lower reported operative mortality for elective surgery in patients with stage IV disease (3-6%), compared with the more threatening operative mortality rates for non-elective resections in patients with advanced and symptomatic disease (20-40%).[34,41,42] Another argument supporting this concept, is that preoperative staging is sometimes unclear and that surgery is considered the last and most effective diagnostic tool for the correct staging of abdominal tumors before treatment.[19] In addition, patients are provided with psychological comfort who feel that the "cancer" has been removed.[36]

Chemotherapy first in patients with unresectable synchronous mCRC

The advocates of a chemotherapy first approach prefer to avoid complications at least in non symptomatic patients. The argument of those who prefer "elective" surgery due to higher mortality if emergent surgery is required, was addressed in several studies, were the risk of death was found to be extremely low.[39,43-45] In fact, Poultsides et al. compared their study population with studies with elective colon resection in the metastatic setting and found that it appears that this deferred approach is associated with at least comparable perioperative mortality.[46] Another argument for chemotherapy first, is that chemotherapy will not only treat the metastases but also the primary tumor; many patients will have improvements of their symptoms and therefore evading a possible resection.[35,47] Chau et al. demonstrated that overall, 86% of patients had an improvement in symptoms. Of the patients with symptoms, 71% had diminished pelvic pain/ tenesmus, 90% had improvement in diarrhea/constipation, 100% had reduced rectal bleeding, and 93% had weight stabilization or weight gain.

Advocates of the deferred surgical approach argue that surgery at diagnosis can delay or even preclude systemic chemotherapy, and that most patients will never develop symptoms and these patients could be spared an unnecessary operation. Additionally, primary CRC surgery may alter the host immune response in such a way that tumor growth is increased in the post operative period.[56,57] An argument against resection is that patients with unresectable metastasis from colorectal cancer who have undergone palliative resection of the primary still face the prospect of further intestinal complications, which may require further surgery *(Table I).*[34,48] After resection of the primary tumor, these patients may develop local recurrence or adhesions which can result in obstruction and require subsequent surgery.

A decade ago, when patients were treated with single agent 5-FU chemotherapy, approximately 20% of patients with mCRC treated with chemotherapy required palliative surgery for symptoms related to their intact primary CRC.[39,40,46,48,51] In recent years, combinations with modern chemotherapy like FOLFOX, XELOX and FOLFIRI have attained response rates of 50% and disease control rates of 85% in prospective clinical trials.[58] With these *modern* chemotherapy regimens, approximately 7% (range 3-22%) of patients with mCRC required surgical palliation for their intact primary CRC, as stated in an elegant review by Poultsides.[43-46] These data suggest that with effective chemotherapy almost 14 asymptomatic patients need to undergo prophylactic resection of their primary tumor in order to save one patient a subsequent operation for obstruction or perforation.[46] There are indications that this has led to a decrease over time in the percentage of resection of the primary tumor in case of unresectable metastatic colorectal disease.[13]

Table I. Study results on colorectal cancer and unresectable metastases, in which the non-resection arm was treated with chemotherapy

Author	Years of study		Number of patients	Received chemotherapy (%)	Secondary palliative surgical interventions	Palliative Resection of primary
Scoggins [40]	1985-1997	resection	66	0	2 (3%)	-
		chemo	23	100	2 (9%)	0
Tebbutt [48]	1990-1999	resection	280	100	14 (5%)	-
		chemo	82	100	8 (10%)	1 (1%)
Konyalian [49]	1991-2002	resection	62	58	#	-
		chemo	47	60	17 (36%)	0
Galizia [50]	1995-2005	resection	42	100	0	
		chemo	23	100	6 (26%)	¶
Ruo [51]	1996-1999	resection	127	0	6 (5%)	
		chemo	103	83	30 (29%)	0
Michel [44]	1996-1999	resection	31	97	0	
		chemo	23	100	5 (22%)	3 (13%)
Serela [39]	1997-2000	resection	-	-	-	
		chemo	24	88	6 (25%)	4 (17%)
Benoist [43]	1997-2002	resection	32	94	0	
		chemo	27	100	4 (15%)	3 (11%)
Karoui [52]	1998-2007	resection	85	99	27 (32%)	
		chemo	123	100	15 (12%)	15 (12%)
Aslam [53]	1998-2007	resection	366	63	¥	
		chemo	281	36	128 (46%)	0
Bajwa [54]	1999-2005	resection	-	-	-	
		chemo	67	100	27 (40%)	25 (37%)
Muratore [45]	2000-2004	resection	-	-	-	
		chemo	35	100	1 (3%)	0
Poultsides [35]	2000-2006	resection	-	-	-	
		chemo	233	100	16 (7%)	8 (3%)
Seo [55]	2001-2008	resection	144	100	22 (15%)	
		chemo	83	100	4 (5%)	1 (1%)

 # Konyalian53 not described; 12 patients with complications mostly infectious; ¶ Galizia54 not described; 2 colon perforations, 1 intestinal hemorrhage, 1 bowel obstruction, 2 surgery owing to bowel perforation or stent dislocation ¥ Aslam56 not described; 11 full thickness wound dehiscence, 11 intra-abdominal collections, 11 anastomotic leak, 7 intra-abdominal sepsis, 5 hemorrhage, 4 postoperative ileus, 1 splenic tear, 1 inter-loop fistula

Survival

Several studies have been performed to analyze overall survival of patients with stage IV CRC and unresectable metastases to examine whether to resect the primary or not. Recently, Venderbosch et al. performed a retrospective analysis of two phase III studies (CAIRO and CAIRO2)[7,59] and investigated the prognostic and predictive value of resection

of the primary tumor in stage IV mCRC patients.[60] They demonstrated that resection of the primary tumor was a significantly important prognostic factor for survival in these patients. They also performed a review of the literature and identified 22 nonrandomized studies, most of which showed improved survival for mCRC patients who underwent resection of the primary tumor. These results were confirmed in a systemic review by Anwar et al.[57] An overview of these studies is presented in *table 2*.

However, in all studies presented a selection bias cannot be excluded. Most studies were not randomized, performed in single centers and were retrospective of nature. Patients with a good performance status were more likely to undergo surgery whereas those with extensive disease were more likely to be offered chemotherapy instead. In the absence of randomized controlled trials, the best evidence is obtained from case-matched studies. A case-matched study by Benoist et al. compared 27 patients with asymptomatic colorectal cancer and irresectable synchronous liver metastases who received chemotherapy, with 32 matched patients who were treated by initial resection of the primary tumor. They found no difference in survival between the operative and the non-operative management.

Prospective studies on this topic are currently planned. Recently a protocol has been developed in the Netherlands for stage IV colon cancer patients with unresectable metastases.[61] In this trial patients will be randomized to either systemic therapy until progression or unacceptable toxicity or to resection of the primary tumor followed by systemic therapy until progression or unacceptable toxicity. The endpoint of the trial is overall survival and the trial is powered to identify a survival benefit of 6 months in the surgery group. Also the National Surgical Adjuvant breast and Bowel Project has started a phase II Trial using 5-fluorouracil, leucovorin, and oxaliplatin chemotherapy plus bevacizumab for patients with unresectable stage IV colon cancer and synchronous asymptomatic primary tumor.[62] The primary endpoint is the event rate related to the intact primary tumor requiring surgery. In both trials only patients with colon cancer will be randomized and patients with rectal cancer are excluded. Also a trial from Australia/New Zealand "SUPER" is currently running: "A randomized phase III multicentre trial evaluating the role of palliative surgical resection of the primary tumor in patients with metastatic colorectal cancer".[63] Patients will be randomized to compare chemotherapy followed by surgery to surgery alone. The primary outcome is to determine whether surgical resection of the primary tumor in patients with stage IV colorectal cancer decreases intestinal complications and improves overall survival and quality of life. For patients with rectal cancer and unresectable systemic disease a phase III randomized clinical trial is recently conducted in the Netherlands. In this trial the role of radiotherapy in providing local control will be studied and patients will be randomized to either standard chemotherapy alone or short term course radiotherapy (5x5 Gy) on the primary tumor followed by standard of care chemotherapy. The primary endpoint is the number of patients requiring an unplanned surgical intervention related to symptoms of the primary rectal tumor.

Table II: Studies Comparing Resection versus Non-resection of the Primary Tumour in Stage IV Colorectal Cancer and Unresectable Metastases

Author	Years of study		Number of patients	OS (months)	p value	Postoperative Mortality %	p-value
Makela [34]	1974-1983	Resection	66	15	—	5	—
		non-resection	30	7		17	
Scoggins [40]	1985-1997	Resection	66	14.5	0.59	5	—
		non-resection	23	16.6		—	
Liu [16]	1986-1991	Resection	57	11	—	9	—
		non-resection	6	3		17	
Tebbutt [48]	1990-1999	Resection	280	14	0.08	—	—
		non-resection	82	8.2		—	
Konyalian [49]	1991-2002	Resection	62	13	<0.0001	5	—
		non-resection	47	5		6	
Beham [64]	1993-2003	Resection	46	18	<0.001	3	—
		non-resection	21	8		0	
Costi [19]	1994-2003	Resection	83	9	<0.001	8	0.397
		non-resection	47	4		15	
Yun [65]	1994-2004	Resection	283	15.3	<0.001	3	—
		non-resection	93	5.3		—	
Stelzner [66]	1995-2001	Resection	128	11.4	<0.0001	12	0.784
		non-resection	58	4.6		10	
Galizia [50]	1995-2005	Resection	42	15.2	0.03	—	—
		non-resection	23	12.3		—	
Law [15]	1996-1999	Resection	150	7	<0.001	7	0.01
		non-resection	30	3		21	
Ruo [51]	1996-1999	Resection	127	16	<0.001	2	—
		non-resection	103	9		—	
Michel [44]	1996-1999	Resection	31	21	0.718	0	—
		non-resection	23	14		—	
Mik [67]	1996-2000	Resection	52	21	NS	—	—
		non-resection	82	14		—	
Benoist [43]	1997-2002	Resection	32	23	—	0	—
		non-resection	27	22		—	
Kaufman [68]	1998-2003	Resection	115	22	<0.0001	—	—
		non-resection	69	3		—	
Aslam [53]	1998-2007	Resection	366	14.5	<0.005	8	—
		non-resection	281	5.83		—	
Bajwa [54]	1999-2005	Resection	32	14	0.005	3	—
		non-resection	35	6		—	
Evans [69]	1999-2006	Resection	45	11	0.2056	16	—
		non-resection	57	7		36	

Table II: Studies Comparing Resection versus Non-resection of the Primary Tumour in Stage IV Colorectal Cancer and Unresectable Metastases (continued)

Author	Years of study		Number of patients	OS (months)	p value	Postoperative Mortality %	p-value
Chan [70]	2000-2002	Resection	286	14	<0.001	—	—
		non-resection	125	6		—	
Frago [71]	2000-2008	Resection	12	39.1	0.008	8	—
		non-resection	43	1.0		6	
Seo [55]	2001-2008	Resection	144	22	0.076	0	—
		non-resection	83	14		—	
Venderbosch [60]	2003-2004	Resection	258	17	0.0001	—	—
		Non-resection	141	11		—	
	2005-2006	Resection	289	21	0.0001	—	—
		Non-resection	159	13		—	

Resection was defined as resection of the primary tumour and non-resection was defined as surgical intervention without resection of the primary tumour. NS = not stated.

Summary

In stage IV CRC with unresectable metastases, the role of resection of the primary tumor remains unclear. Because randomized clinical trials are lacking, it is difficult to draw conclusions from the present literature. With current new chemotherapy regimen, including VEGF and EGF inhibitors, a relatively low number of patients with mCRC require surgery for their primary tumor. Most studies suggest a survival benefit for patients undergoing surgical resection of the primary tumor compared to those who received palliative treatment. However, these results are likely to be influenced by selection bias and therefore prospective randomized controlled trials are needed to address this question.

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Chapter 8

Outcome in patients with resectable locally recurrent rectal cancer after total mesorectal excision with and without previous neoadjuvant radiotherapy for the primary rectal tumor

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Abstract

Background

The widespread use of neoadjuvant radiotherapy (nRTx) followed by total mesorectal excision (TME) introduced the problem of treating locally recurrent rectal cancer (LRRC) after nRTx and TME. Few data exist on the outcome of the surgical treatment of this type of LRRC and the influence of nRTx for the primary tumor on the outcome is unclear.

Methods

All patients receiving multimodality treatment (including intraoperative radiotherapy) for LRRC in our center between 1996 and 2012 were retrospectively analyzed. The outcome of patients with non-metastasized resectable LRRC who received nRTx and TME for the primary tumor was compared to the outcome of patients who did not receive nRTx for the primary tumor.

Results

During this period, 139 patients underwent surgery for LRRC; 93 of these patients underwent curative surgery for LRRC after TME for the primary tumor. Sixty-five patients did not receive nRTx for the primary tumor, while 28 patients received nRTx for the primary tumor. There were no significant differences in the number of incomplete resections or peri-operative morbidities. There was no significant difference in 5-year overall survival (28% vs. 43%,p=0.81), recurrence-free survival (55% vs. 48%,p=0.50) and disease-free survival (27% vs. 40%,p=0.59).

Conclusion

Surgical treatment of carefully selected patients with non-metastasized resectable LRRC after nRTx and TME for the primary tumor is feasible and can result in sustained local control and overall survival. Patients with resectable LRRC who received nRTx for the primary tumor do not have a poorer outcome than patients who did not.

Introduction

Before the introduction of total mesorectal excision (TME) for rectal cancer, local recurrence rates after surgery varied between 15 and 45%.[1-3] Since the publication of the Dutch TME-trial, neoadjuvant radiotherapy (nRTx) followed by TME became the standard of care in the Netherlands for stage II and III rectal cancer and has led to a decrease in local recurrence rates to 6%.[4] The implementation of nRTx and TME as standard therapy introduced the problem of treating locally recurrent rectal cancer (LRRC) after nRTx and TME.

Surgical treatment of LRRC includes (chemo-)radiotherapy to improve local control.[5] When nRTX was administered for the primary tumor, the radiation dose for treatment of the LRRC is limited.[6] In addition, recurrences after TME may not be limited to the anatomical compartment lined by the visceral rectal fascia. Both factors render radical resection of these recurrences more demanding than resection in patients who did not undergo nRTx or TME previously. However, literature on the outcome of surgical treatment of LRRC after TME with and without nRTx for the primary tumor is scarce.

According to an update of the Dutch TME-trial, patients with LRRC after nRTx for the primary tumor have a shorter overall survival than patients who did not receive nRTx for the primary tumor.[7] This suggests that local recurrences after nRTx for the primary tumor have a more aggressive biological behavior than recurrences of rectal cancer that was not treated with nRTx primarily.

Because of the factors mentioned above, it is questionable whether curative treatment of LRRC in these patients is possible. On the other hand, if curative resection is possible the influence of nRTx for the primary tumor on outcome is unclear. The aim of the current study was to evaluate the outcome of resectable LRRC after nRTx and TME for the primary tumor and to demonstrate whether there is a difference in outcome of the curative treatment of resectable LRRC in patients who received nRTx and TME for the primary tumor and patients who had TME without nRTx.

Patients and Methods

Between January 1996 and July 2012, all patients undergoing surgery for LRRC in our hospital, a tertiary referral center for the southwest region of the Netherlands, were entered in a prospective database and retrospectively analyzed. All patients had a histologically proven recurrence of rectal cancer in the pelvic area.

Patients were divided into two groups; group A were patients who did not receive nRTx for the primary tumor, group B were patients who received nRTx for the primary tumor. Only primary resections that were performed by TME were included.

All LRRCs were scheduled for neoadjuvant (chemo-)radiotherapy followed by surgery. Patients who received nRTx for the primary tumor received a neoadjuvant re-irradiation dose of 27-30Gy, delivered in 15-18 fractions of 1,8-2Gy. Patients who did not receive nRTx for the primary tumor were scheduled for 44.6-52Gy in 19-28 fractions of 1.8-2.3Gy. (Re-)irradiation for LRRC was administered by a 3- or 4 field-technique or by 5 fields using intensity modulated radiotherapy. From 2006 onwards, all patients received chemoradiotherapy with capecitabine administered orally at a dose of 825 mg/m^2 twice a day during radiotherapy days as reported previously.[8] Before 2006, no patient received concomitant chemotherapy.

Before treatment, distant metastases were ruled out by a thoraco-abdominal CT-scan, which was repeated after (re-)irradiation.[9] In the majority of patients, pelvic MRI was performed for localization and progression of the recurrence prior to and after (re-)irradiation. Resectable LRRC was defined as a recurrence within the pelvic region, without distant metastases in which imaging revealed a recurrence with a high chance of a R0/R1-resection. R0/R1-resection was considered feasible when there was no apparent lateral bone-involvement, no sacral involvement above level S3, no extension through the greater sciatic notch and no encasement of common or external iliac arteries. Local recurrences were classified using the Wanebo classification.[10]

All surgical procedures were performed by a midline abdominal approach and included low anterior resections (LAR), abdominoperineal resections (APR), posterior or total exenterations and abdominoperineal-sacral resections. R0-resections were defined as resection margins >0mm; R1-resections as microscopically involved resection margins and R2-resections as macroscopically involved resection margins. Our multimodality approach for LRRC includes intra-operative radiotherapy (IORT) with a single dose of 10Gy for patients with tumor-free margins ≤2mm, evaluated during surgery on frozen sections.[11] No patient received adjuvant chemotherapy.

Peri-operative morbidity was divided into surgical and non-surgical morbidity. Abdominal wound infections were scored in case there were signs of inflammation. Wound healing problems after APR were defined as signs of inflammation of the perineal area 30 days after surgery. A presacral abscess was diagnosed by clinical symptoms in combination with a CT-scan. Small bowel obstruction and postoperative hemorrhage were considered adverse events when a re-laparotomy had to be performed. Post-operative complications were graded according to the Dindo-Clavien classification.[12] Peri-operative mortality was defined as any death occurring within 30 days of surgery. In-hospital mortality was defined as any death occurring during admission.

Statistical analysis was carried out using SPSS (version 20.0.0.1). Data was reported as median (interquartile range). The Chi-square (χ^2), Fisher's exact and Mann-Whitney U test were used for comparison of both groups as appropriate. The survival rates were calculated using Kaplan-Meier curves and significance was calculated by a log rank test.

Survival rates were calculated from the day of LRRC surgery until death or last follow-up. P-values ≤0.05 were considered significant.

Results

A total of 139 patients underwent surgery for LRRC between January 1996 and July 2012. In 98 patients primary tumor resection was performed by TME. During LRRC surgery, 5 of 98 patients were considered incurable due to metastatic disease or unresectability of the recurrence, rendering 93 patients eligible for analysis. Of these patients, 65 did not receive nRTx for the primary tumor (group A), while 28 patients received nRTx for the primary tumor (group B).

Table I. Patient and primary tumor characteristics

	No nRTx for primary tumor (group A)	nRTx for primary tumor (group B)	P-value
Total patients	65	28	
Age (years) ‡	66 (59-72)	63,5 (55-70)	0.23*
Gender			
Male	46 (65)	18 (64)	-
Female	19 (35)	10 (36)	0.54**
Primary tumor stage			
Stage I	12 (18)	5 (18)	-
Stage II	26 (40)	8 (29)	-
Stage III	22 (34)	11 (39)	-
Stage IV	3 (5)	4 (14)	-
Unknown	2 (3)	0	0.39**
Type resection			
LAR	45 (69)	17 (61)	-
APR	20 (31)	11 (39)	0.42**
Neoadjuvant treatment			
Short course RTx (25Gy)	-	10 (36)	-
Long course RTx (44.6 -50Gy)	-	10 (36)	-
Chemoradiotherapy (50Gy)	-	8 (28)	-

*Values in parentheses are percentage unless indicated otherwise; nRTx, neoadjuvant radiotherapy;‡, values are median (interquartile range); LAR, Low Anterior Resection; APR, Abdominoperineal Resection; RTx, Radiotherapy; *, using Mann Whitney U test; ** using χ^2-test*

Primary tumor and local recurrence

Patient and primary tumor characteristics are depicted in *table I*. All patients with stage IV primary rectal cancer (n=7) had undergone metastasectomy previously (median 14

months prior to LRRC, range 12-48 months) and were free of distant metastases at the time of diagnosis of LRRC. The median interval between primary tumor resection and diagnosis of LRRC was 24 (14-41) months for the patients in group A and 20 (12-30) months for patients in group B (p=0.10). The tumor characteristics of LRRC are depicted in *table II*

Table II. Tumor characteristics of locally recurrent rectal cancer

	No nRTx for primary tumor (group A)	nRTx for primary tumor group B)	P-value
Total patients	65	28	
Wanebo classification			
Tr1	7 (11)	1 (4)	-
Tr2	6 (9)	3 (11)	-
Tr3	24 (37)	12 (39)	-
Tr4	23 (36)	11 (36)	-
Tr5	5 (8)	1 (4)	0.74**
Location of recurrence			
Intraluminal	13 (20)	4 (14)	-
Extraluminal	52 (80)	24 (86)	0.51***
Location of LRRC			
Presacral	21 (32)	10 (36)	-
Lateral	18 (28)	8 (29)	-
Anterior	15 (23)	6 (21)	-
Anastomic	13 (20)	4 (14)	0.92**

*Values in parentheses are percentage; nRTx, neoadjuvant radiotherapy; Tr, Tumor stage recurrent rectal cancer; LRRC, locally recurrent rectal cancer; ** using χ^2-test, *** using Fisher's exact test*

Peri-operative results

The surgical procedures and operative results for LRRC are depicted in *table III*. There were no significant differences between both groups in the number of R0, R1 and R2-resections, although there tend to be more R1-resections in group B (26% vs. 43%,p=0.09). Intraoperative radiotherapy (IORT) was administered to all patients with an R1-resection or with a tumor-free margin ≤2mm.

Table III. Operation characteristics for locally recurrent rectal cancer

	No nRTx for primary tumor (group A)	nRTx for primary tumor (group B)	P-value
Total patients	65	28	
Neoadjuvant treatment LRRC			
RTx	41 (63)	11 (39)	
CTxRTx	24 (37)	17 (61)	0.03**
Interval nRTx and surgery‡	8 (6 – 10)	8 (8 – 10)	0.46*
Surgical procedure			
LAR	7 (11)	1 (4)	-
APR	15 (23)	7 (25)	-
Intersphinteric resection	4 (14)	1 (4)	-
Posterior exenteration ¥	17 (26)	10 (36)	-
Total pelvic exenteration	17 (26)	8 (29)	-
Pelvic recurrence resection	5 (8)	1 (4)	0.76**
Partial sacrectomy	5 (8)	2 (7)	0.93***
Omental flap	43 (66)	18 (64)	0.86**
Resection margin			
R0	41 (63)	13 (46)	-
R1	17 (26)	12 (43)	-
R2	7 (11)	3 (11)	0.26**
IORT			
R0†	16/41 (39)	6/13 (46)	0.65**
R1	17/17 (100)	12/12 (100)	-
R2	5/7 (71)	3/3 (100)	1.00***
Pathological complete response	6 (9)	1 (4)	0.67***
Operation time (minutes) ‡	408 (268 – 491)	460 (360 – 555)	0.14*
Blood loss (milliliters) ‡	2200 (1925 – 3900)	3900 (1925 – 8250)	0.16*

*Values in parentheses are percentage; †, values in parentheses are interquartile range; RTx, Radiotherapy; CTxRTx, chemoradiotherapy; LAR, Low Anterior Resection; APR, Abdominoperineal Resection;¥, only performed in women, percentage of all patients; R0, resection margin of >0 mm; R1, microscopically invclved margins; R2, macroscopically involved margins; IORT, intraoperative radiotherapy; † only in patients with margins <2mm *, using Mann-Whitney U test; **, using χ^2-test; ***, using Fisher's exact test*

In group A, 41 surgical complications occurred in 32 patients (49%). Sixteen surgical complications occurred in 13 patients (46%) in group B (p=0.80). Seventeen non-surgical complications occurred in 12 (18%) patients in group A and 11 non-surgical complications occurred in 8 patients (29%) in group B (p=0.28). There was no significant difference in grade ≥2, ≥3 or ≥4 complications.

Three patients (3%) died during admission in the hospital. There was no significant difference in in-hospital or peri-operative mortality between both groups. All deaths were caused by cardiac events. The peri-operative morbidity and mortality is further outlined in *table IV*.

Table IV. Mortality and peri-operative morbidity

	No nRTx for primary tumor (group A)	nRTx for primary tumor (group B)	P-value
Total patients	65	28	
Peri-operative morbidity			
Surgical			
Abdominal wound infections	11 (17)	5 (18)	1.00***
Presacral abscess	11 (17)	5 (18)	0.91**
Relaparotomy	10 (15)	3 (11)	0.75***
Small bowel perforation	5 (8)	1 (4)	-
Wound dehiscence	1 (4)	0	-
Abscess/hemorrhage	2 (2)	1 (4)	-
Negative	2 (4)	1 (4)	-
Non-surgical			
Pneumonia/atelectasis	9 (14)	4 (14)	0.73***
Cardiac	3 (5)	2 (8)	0.64***
Urinary tract infection	5 (8)	5 (18)	0.19**
Perineal woundhealing problems^	12 (70)	8 (66)	1.00**
Grading of complications (Dindo-Clavien)			
Grade ≥2	45 (78)	22 (81)	0.68**
Grade ≥3	24 (41)	10 (37)	0.70**
Grade ≥4	9 (16)	3 (11)	0.74***
Mortality			
In hospital mortality	1 (2)	2 (7)	0.22***
Peri-operative mortality	3 (5)	2 (7)	0.64***

*Values in parentheses are percentage; nRTx, neoadjuvant radiotherapy; ^, only in patients with an APR **, using χ^2-test; ***, using Fisher's exact test*

Survival

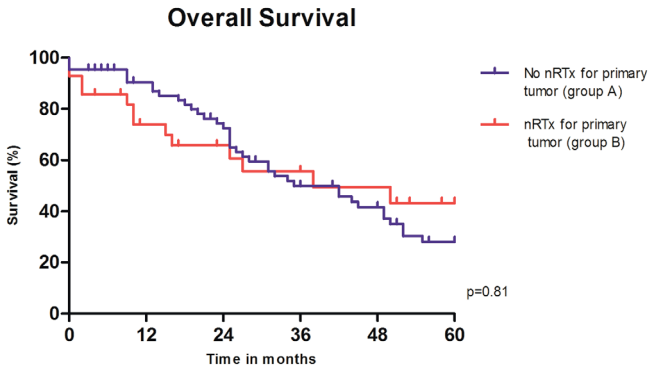
In group A, 25 patients (39%) were alive at last follow up. The median survival of surviving patients was 41 (range, 3-90) months. In group B, 14 patients (50%) were alive at last follow up. Their median survival was 32 (range, 4-86) months. The median survival of all patients in group A was 42 (95%CI 27-57) months compared to 38 (95%CI, 0-77) months for all patients in group B (p=0.81). The estimated 3- and 5-year overall survival rates of patients in group A were 50% and 28% respectively and for patients in group B 56% and 43%, respectively. *(Fig. IA)*

In group A, 23 (35%) patients suffered a re-recurrence, while 21 patients (32%) died without suffering a re-recurrence. This resulted in an estimated 5-year local recurrence-free survival of 55%. In group B, 11 patients (39%) suffered a local re-recurrence, while

5 patients (18%) died without suffering a re-recurrence. This resulted in an estimated 5-year local recurrence-free survival of 48%. This did not differ significantly from group A. (p=0.50) *(Fig. IB)*

There was a significant difference in distant metastasis free-survival after 5 years in favor of patients in group B (39% vs. 66%,p=0.05). These results are shown in *figure IC*. Disease free-survival did not differ significantly after 5 years (27% vs. 40%,p=0.59) and is shown in *figure ID.*

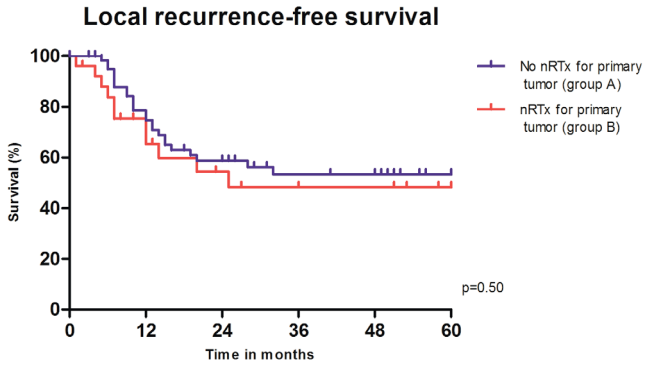
Figure Ia: Overall survival



Patients at risk

No nRTx (group A)	65	52	39	26	20	10
nRTx (group B)	28	18	13	10	8	3

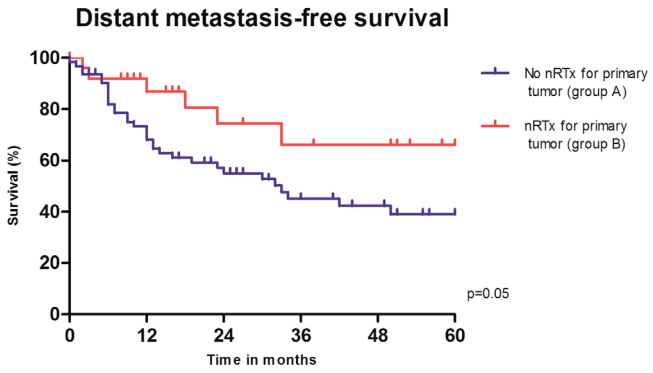
Figure IB: Local recurrence-free survival



Patients at risk

No nRTx (group A)	65	41	27	19	18	9
nRTx (group B)	28	15	9	7	7	2

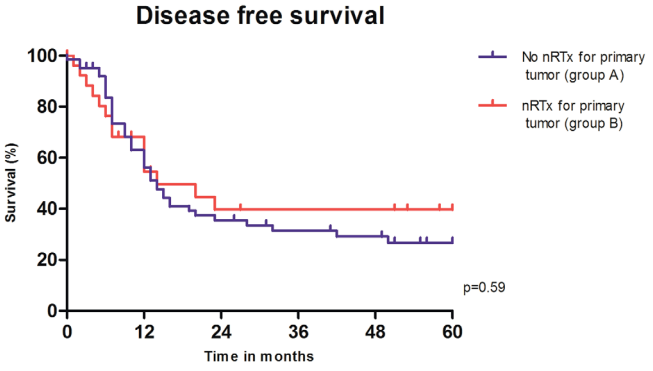
Figure IC: Distant metastasis-free survival



Patients at risk

No nRTx (group A)	65	41	27	18	14	9
nRTx (group B)	28	18	13	8	8	2

Figure ID: Disease free survival



Patients at risk

No nRTx (group A)	65	37	19	15	13	8
nRTx (group B)	28	15	9	7	7	2

Discussion

Our results demonstrate that in carefully selected patients with non-metastasized resectable LRRC who received nRTx and TME for the primary tumor, the overall survival is similar to patients who did not receive nRTx for the primary tumor. There may be more incomplete resections in patients who received nRTx for the primary tumor, but this does

not result in an increased local re-recurrence rate. The peri-operative morbidity is not increased in patients who received nRTx for the primary tumor.

These findings are complementary to updates of two large randomized controlled trials[7,13] These studies demonstrated a poorer prognosis of LRRC in case the primary tumor was treated with nRTx. However, both studies included patients that were treated curatively and those who were not, while our study focuses on resectable LRRC specifically. The poorer prognosis of LRRC after nRTx may lead to the conclusion that nRTx alters tumor characteristics resulting in more aggressive biological behavior. However, it is more likely that recurrences after nRTx may simply represent a selection of patients with unfavorable tumor characteristics. Neoadjuvant radiotherapy probably does not prevent recurrence in patients with "bad" disease (e.g. more residual disease, positive resection margins, higher tumor load). These patients are likely to have a poorer prognosis and this originates in *a high rate of distant* metastases at diagnosis or within 6 months after diagnosis of LRRC after nRTx for the primary tumor.[7] These distant metastases disqualify patients for surgery and this caused only a minority (17%) of the patients after nRTx in the update of the Dutch TME-trial to be selected for curative surgery. In our hospital, since 2002, 28% of patients with LRRC after nRTx for the primary tumor were scheduled for curative treatment (data not shown). By ruling out distant metastases prior to and after (re-)irradiation, we only selected those patients that in general have malignancies with a more benign biological behavior and this explains why this study did not find a difference in outcome of patients treated with and without nRTx for the primary tumor.

Surprisingly, we found a significant difference in 5-year distant metastasis-free survival in favor of patients who received nRTx for the primary tumor. This finding should be interpreted with caution. It is based on a small number of patients and is probably caused by the selection bias mentioned above. However, it may explain why the outcome in these patients is comparable to that of patients who did not receive nRTx for the primary tumor, even when re-irradiation doses are limited and radical resections are technically more demanding. The difference in distant metastasis-free survival did not result in a significant difference in overall survival, which is comparable to the overall survival in other centers where a multimodality approach for LRRC is adapted.[14,15]

Because resected LRRC patients in both study groups have a similar local recurrence-free survival, this implies that previous irradiation for the primary tumor does not result in decreased local control after surgery for the LRRC. This is remarkable, because the number of R0-resections in patients who received nRTx for the primary tumor was lower (although not significant) and radical resection is the most important prognostic factor for local re-recurrence and overall survival after resection of LRRC.[16-18] This lower number of R0-resections could be explained by the fact that a re-irradiation dose of 30Gy is less effective than an irradiation dose 50Gy, resulting in less downstaging and

more incomplete resections. LRRC in patients who received nRTx for the primary tumor may also evolve from radiation-insensitive tumor deposits, rendering re-irradiation less effective. Nonetheless, our R0-resection rate of LRRC in patients who did and did not receive nRTx for the primary tumor is in line with other studies that report radical resection rates of 44-59% in LRRC after TME for the primary tumor. These studies did not include patients that had received nRTx or did not differentiate between patients who did and did not receive nRTx for the primary tumor.[19,20]

IORT may be a contributing factor to the relatively low local recurrence rate after R1-resections in this study. Although no randomized control trials were published proving the value of IORT for LRRC, several retrospective studies suggested a beneficial effect of IORT on local control for locally advanced rectal cancer.[21-23] In IORT, the biological equivalent of a single dose is considered 2 to 3 times the dose given by conventional fractioning.[24] The biological equivalent dose (BED) of 30Gy re-irradiation is 36Gy, resulting in a combined BED of nRTx and IORT of 56-66Gy, which is an adequate dose to increase local control in rectal cancer. In patients who received an irradiation dose of 50Gy, which has a BED of 60Gy, the addition of IORT leads to a BED of 80-90Gy. However, this did not result in a lower local recurrence rate in our study.

Although there was more blood loss in patients with LRRC who received nRTx for the primary tumor, peri-operative morbidity and mortality rates were similar in both groups. Increased blood loss may be caused by extensive post-radiation fibrosis after previous nRTx and re-irradiation. Overall complication rates, the occurrence of wound infections and presacral abscesses were similar to those reported in the literature.[14,18,19,25]

As could be expected in a retrospective analysis, this study has methodological drawbacks. Patients eligible for surgery were selected from larger groups of patients that were not selected for surgery because of distant metastases, unresectable disease or co-morbidity. In the first years of our study period, patients often did not receive nRTx for the primary tumor, whereas in later years, neoadjuvant therapy became the standard. This resulted in a difference in length of follow-up of 9 months of the surviving patients between groups A and B (41 vs. 32 months). Despite this difference, we think both groups were followed for an adequate length of time, since no re-recurrences were reported after 32 months of follow up. Furthermore, during the study period imaging modalities have improved, possibly resulting in more accurate staging and improved patient selection.

In conclusion, surgical treatment of carefully selected patients with resectable LRRC without metastatic disease after nRTx and TME is feasible and can result in sustained local control and overall survival. Patients with resectable LRRC after nRTx and TME for the primary tumor do not have a poorer outcome than patients who did not receive nRTx for the primary tumor. Therefore, these patients should be considered candidates for curative surgery. However, only a minority of patients with LRRC after previous irradiation

are candidates for curative surgery, because the majority has distant metastases or unresectable disease. Patients after previous nRTx for the primary tumor are more likely to have an incomplete resection of the LRRC, but this does not result in an increased local recurrence rate in this series of patients who underwent multimodality treatment.

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Chapter 9

The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer

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Abstract

Background

The importance of the circumferential resection margin (CRM) has been demonstrated in primary rectal cancer, but the role of the minimal tumor-free resection margin in locally recurrent rectal cancer (LRRC) is unknown.

Objective

To evaluate the prognostic importance of a minimal tumor-free resection margin in LRRC.

Design

This was a single-institution, retrospective study.

Setting

This study was conducted in a tertiary referral hospital

Patients and methods

Based on the final pathology report, surgically treated patients with LRRC between 1990 and 2013 were divided into 4 groups: 1) Tumor-free margins of >2mm; 2) tumor-free margins of >0-2mm; 3) microscopically involved margins and 4) macroscopically involved margins.

Main outcome measures

Local control and overall survival.

Results

A total of 174 patients with a median follow up of 27 months (range, 0-144) were eligible for analysis. There was a significant difference in 5-year local re-recurrence-free survival in favor of 41 patients with tumor-free margins of >2 mm compared to 34 patients with tumor-free margins of >0-2mm (80 vs. 62%,p=0.03) and a significant difference in 5-year overall survival (60 vs. 37%,p=0.01). The 5-years local re-recurrence-free and overall survival for 55 patients with microscopically involved margins were 28% and 16% and of 20 patients with macroscopically involved margins 0% and 5%, respectively. On multivariable analysis tumor-free margins of >0-2mm were independently associated with higher re-recurrence rates (HR 2.76 95%CI1.06 – 7.16) and poorer overall survival (HR 2.57 95%CI 1.27-5.21) compared to tumor-free margins of >2mm.

Limitations

This study was limited by its retrospective nature

Conclusion

Resection margin status is an independent prognostic factor for re-recurrences rate and overall survival in surgically treated LRRC. In complete resections, patients with tumor-free resection margins of >0-2mm have a higher re-recurrence rate and a poorer overall survival than patients with tumor-free resection margins of >2mm.

Introduction

Developments in the treatment of primary rectal cancer, such as total mesorectal excision (TME) and neoadjuvant (chemo-)radiotherapy, have significantly decreased the local recurrence rate. Unfortunately, locally recurrent rectal cancer (LRRC) still occurs in 6-13% of surgically treated patients.[1-4] LRRC is associated with a poor prognosis and treatment is challenging.

Multimodality treatment of LRRC, including neoadjuvant radiotherapy and surgical resection, can lead to long-term disease-free and overall survival. However, the outcome strongly depends on whether a complete surgical resection can be achieved. Recent studies have demonstrated that complete resections can result in 5-year overall survival rates of 30-57% and local control rates of 50-80%.[5-10] On the other hand, incomplete resections leads to drastically poorer survival rates and high re-recurrence rates.[11] The treatment options for re-recurrences are limited and overall survival is usually short when re-recurrence occurs. Moreover, the development of re-recurrences has a major impact on the patient's quality of life.

In primary rectal cancer, the optimal cut-off for defining an involved circumferential resection margin (CRM) is under debate. Some authors propose a tumor-free margin of 1mm, while others propose 2mm. Regardless of this debate, there is consensus that narrows CRMs, whether 1mm or 2mm, are associated with a poorer outcome.[12-14] It is likely that narrow resection margins in LRRC may lead to a poorer outcome as well. However, the association between the minimal distance of viable tumor to the nearest resection plane and long term outcome of LRRC has not been validated.[15] This is clinically relevant, because narrow resection margins in LRRC surgery are common. Moreover, when this holds true for LRRC, a more aggressive surgical approach may be warranted. The goal of this study was to evaluate the association between width of the tumor-free resection margin and the long term outcome after LRRC surgery with curative intent.

Patients and methods

All patients undergoing surgery for LRRC between January 1990 and March 2013 in our hospital, a tertiary referral center for the southwest region of the Netherlands, were retrospectively analyzed. LRRC was defined as a histopathologically proven local recurrence of colorectal cancer within the pelvic region. Demographic data, clinical characteristics, operative procedures and histopathology were examined.

Patients were scheduled for neoadjuvant (chemo-)radiotherapy followed by surgery, either as a long course of 44.6-52Gy in 19-28 fractions of 1.8-2.3Gy or a short course of 25Gy in 5 fractions of 5Gy or were treated by surgery alone. Previously irradiated patients were scheduled for a re-irradiation dose of 27-30Gy, delivered in 15-18 fractions of 1.8-2.3Gy. After 2006, patients were treated with chemoradiotherapy with capecitabine administered orally at a dose of 825 mg/m2 twice a day during radiotherapy. Radiotherapy for LRRC was administered by a three field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy.

Patients were locally staged by pelvic MRI or CT-scan and screened for distant metastases by a thoraco-abdominal CT-scan at the time of LRRC diagnosis. The majority of patients was restaged after (re-)irradiation to evaluate the response of the local recurrence to neo-adjuvant (chemo-)radiotherapy and to detect potential distant metastases.

LRRCs were treated by local recurrence excisions, low anterior resections (LARs), abdominoperineal resections (APRs), partial exenterations, total exenterations or abdominosacral resections. Patients were considered candidates for surgical treatment in case of no extensive distant metastases, no apparent lateral bone involvement, no sacral involvement above level S3, no extension through the greater sciatic notch, and no encasement of common or external iliac arteries.

Our multimodality approach for LRRC included intra-operative radiotherapy (IORT), which became available after 1996 for patients with tumor free margins of ≤2mm, evaluated during surgery on frozen sections.[16] Frozen section evaluation became a standard part of the surgical procedure after the introduction of IORT and was taken from sites that were potentially at risk for tumor involvement evaluated on pre-operative imaging or macroscopic evaluation by surgeon and pathologist.

All resection specimens were assessed by experienced gastrointestinal pathologists, inked following a standard procedure, formalin fixed and cutsectioned in slices. The minimal tumor-free resection margin was evaluated macroscopically and microscopically as the nearest distance of viable tumor cells to the inked resection plane. The minimal resection margin of the frozen section evaluation was confirmed by final pathology evaluation. For patients where a sampling error occurred (closer or involved margins at

another resection plane), the margin of the final pathology report was considered the definitive tumor-free resection margin. For patients with a more extended resection as a result of the frozen sections, the minimal tumor-free resection margin was measured in the additional resected tissue.

Based on the final pathology report, patients with viable tumor were divided into four groups: 1) tumor-free resection margins of >2 mm; 2) tumor-free margins of >0-2 mm; 3) microscopically involved resection margins and 4) macroscopically involved resection margins. In these subgroups, we compared the local re-recurrence-free survival and overall survival.

Follow up consisted of a program in which patients generally visited the outpatient clinic every 3 months during the first two years and biannually after 2 years. The first two years CEA determination was performed every 3 months and thoracic and abdominal imaging biannually. After 2 years of follow up, CEA determination was performed biannually and thoracic and abdominal imaging yearly. Re-recurrences were established by symptoms, CEA increase or imaging. All suspected re-recurrences were confirmed by CT/MR imaging or biopsies. Confirmation of the date of death was retrieved from the death registries of the municipal register. Some patients returned to the referring hospitals for follow up. In these patients follow up data was obtained by hospital notes and information of the general practitioner.

Statistical analysis was carried out using SPSS (version 20.0.0). Data was reported as median (interquartile range). Categorical data was reported as count (percentage). Univariate analyses for local re-recurrence-free survival and overall survival were performed by using the Kaplan-Meier method and a log-rank test. Univariate and multivariable analyses to determine the prognostic value of covariates regarding local re-recurrence-free and overall survival were performed by using Cox's proportional hazards model. In these analyses, we excluded patients with a pathological complete response or an indeterminable resection margin. Multivariable analysis was stratified for period of surgery (1990-1996, 1997-2005 and 2006-2013) to rule out the effect of non-measurable covariates. For the multivariate analysis, only parameters with P-values ≤0.05 in the univariate model were entered in the Cox regression model. Backward elimination was applied and variables were removed if P-values were >0.10. Local re-recurrence-free survival and overall survival were calculated from the date of LRRC surgery to last follow-up or death. P-values <0.05 were considered statistically significant.

Results

A total of 174 patients underwent surgery for LRRC. During surgery, 9 patients were considered incurable due to unresectable metastatic disease or unresectability of the local recurrence, leaving 165 patients (59 women and 106 men) eligible for analysis. The baseline characteristics are depicted in *table I*. The median age at LRRC surgery was 65 years (interquartile range, 56-70).

Histopathological evaluation

Thirteen patients (8%) had a pathological complete response without viable tumor in the resected specimen after neoadjuvant therapy. Forty-one patients (24%) had a tumor-free resection margin of >2 mm (median 5mm, range, 2.1-25mm), 34 patients (21%) a tumor-free margin of >0-2mm (median 1mm, range, 0.1-2), 55 patients (33%) a microscopically involved resection margin and 20 patients (12%) a macroscopically involved resection margin. In 2 patients (1%) the resection margin could not be determined accurately. Tumor-free resection margins of >2mm were most commonly achieved in central LRRCs (14/20=70%), followed by anterior LRRCs (10/30=33%), lateral LRRCs (10/45=22%) and posterior LRRCs (6/42=14%). Six patients (4%) had a well differentiated, 102 patients (62%) a moderately differentiated and 20 (12%) patients a poorly differentiated adenocarcinoma. In 36 patients (21%) tumor differentiation was not specified. Vaso-invasion was found in 30 patients (18%).

Follow up

The median length of follow up was 27 months (range, 0-144). At last follow up, 57 patients were alive with a median follow up of 43 months (range, 3-144). The estimated 1-, 3-, 5-year overall survival was 82%, 46%, 32%, respectively. A total of 66 patients suffered a re-recurrence during follow up, while 51 patients died without a known re-recurrence.

Results of univariate and multivariable analyses of 150 patients for local re-recurrence-free survival are provided in *table II.* Univariate and multivariable analyses for overall survival are provided in *table III.* Fifteen patients with a pathological complete response or an undeterminable margin were excluded from this analysis. Multivariate analyses demonstrated that the resection margin status was an independent prognostic factor for local re-recurrence-free survival and overall survival. In addition, interval between primary tumor resection and diagnosis of LRRC and vasoinvasion were independent prognostic factors for overall survival.

Table I. Baseline patients and LRRC characteristics

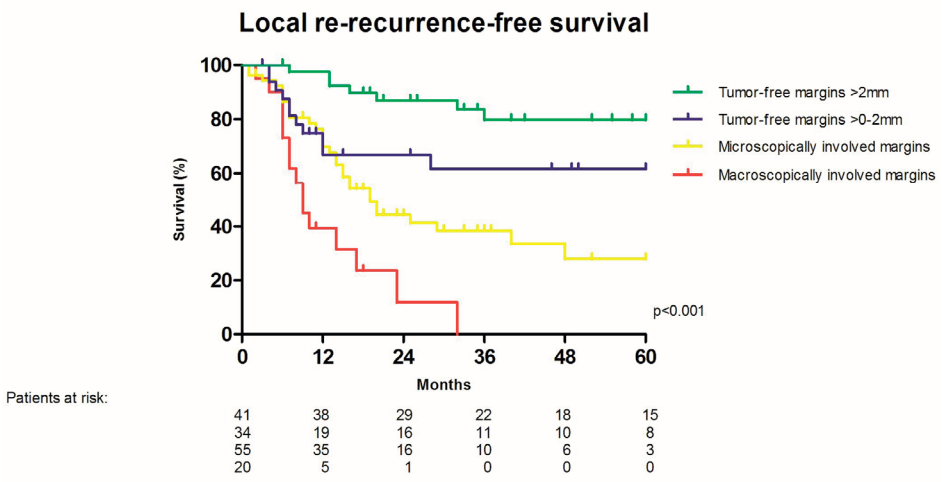
	Number of patients (%)
Total patients	165
Primary tumor resection	
Sphincter saving	127 (77)
Non-sphincter saving	38 (23)
Previous pelvic radiotherapy	
None	134 (81)
(CTx)RTx	31 (19)
Primary tumor resection	
Non-TME	65 (39)
TME	100 (61)
Interval primary tumor – LRRC*	24 (12-38)
Neoadjuvant treatment LRRC	
None	22 (13)
RTx	81 (49)
CTxRTx	62 (38)
Tumour location	
Central	20 (13)
Lateral	45 (30
Anterior	30 (20
Posterior	42 (28)
Unknown	13 (9)
LRRC surgery	
LAR	20 (12)
APR	29 (18)
Partial exenteration	61 (37)
Total exenteration	29 (18)
Abdominosacral resection	19 (12)
Recurrence resection	7 (4)
Distant metastases at diagnosis	7 (4)
Metastases-first treatment	2 (1)
Synchronous treatment	1 (1)
Delayed metastases treatment	3 (2)
Adjuvant chemotherapy	3 (2)
Blood loss***	3.000 (1.750-5.250)
IORT	76 (46)
Operation time	403 (281-499)

*LRRC, locally recurrent rectal cancer, RTx, radiotherapy; LAR, Low Anterior Resection; APR, abdominoperineal resection; CTxRTx, chemoradiotherapy.; TME, total mesorectal excision, *, Months (interquartile range)**, Weeks (interquartile range); ***, millilitres (interquartile range); IORT, intraoperative radiotherapy*

Local re-recurrence-free survival

The estimated 3- and 5-year local re-recurrence-free survival of patients with tumor-free margins of >2mm were 80% and 80% respectively, compared to 62% and 62% for patients with tumor-free margins of >0-2mm, 38% and 28% for patients with microscopically involved margins and 0% and 0% for patients with macroscopically involved resection margins. The re-recurrence-free survival of patients with tumor-free margins of >2mm was significantly longer than in patients with tumor-free margins of >0-2mm (p=0.03), microscopically involved margins (p<0.001) and macroscopically involved margins (p<0.001) (*figure I)*. In a subgroup analysis of the patients with a tumor-free resection margin of >0-2mm, there was no significant difference in local re-recurrence-free survival of patients with a tumor-free margin of <1mm (n=15) and patients with tumor-free margins of 1-2mm (n=19) (66 vs. 59%,p=0.61).

Figure I. Local re-recurrence-free survival of surgically treated LRRC patients



Overall survival

The estimated 3- and 5-year overall survival of patients with tumor-free margins of >2mm was 78% and 60% respectively, compared to 45% and 37% for patients with tumor-free margins >0-2mm, 32% and 16% for patients with microscopically involved margins and 16% and 5% for patients with macroscopically resection margins. The overall survival of patients with tumor-free margins of >2mm was significantly longer compared to patients with tumor-free margins of >0-2mm (p=0.01), microscopically involved margins (p<0.001) and macroscopically involved margins (p<0.001) (*figure II).* In a subgroup analysis of the patients with a tumor-free resection margin of >0-2mm, there was no significant difference in overall survival of patients with a tumor-free margin of <1mm and patients with tumor-free margins of 1-2mm (38 vs. 36%,p=0.57).

Table II. Univariate analysis of covariates regarding the local re-recurrence-free survival and multivariable analysis stratified for period of surgery

	Number of patients	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	p-value
Gender					
Male	94	1			
Female	56	1.04 (0.63 – 1.72)	0.88	-	
Primary tumor resection					
Non TME	58	1			
TME	92	1.04 (0.62 – 1.73)	0.89	-	
Previous pelvic radiotherapy					
No RTx	121	1			
(CTx)RTx	29	1.26 (0.68 – 2.32)	0.46	-	
Age at surgery					
<65 year	74	1			
≥65 year	76	1.17 (0.72 – 1.92)	0.53	-	
Primary tumor resection					
Sphincter saving	114	1		1	
Non sphincter saving	36	1.89 (1.13 – 3.16)	**0.015**	1.48 (0.84 - 2.61)	0.16
Interval primary tumor and diagnosis of LRRC					
<2 years	72	1			
≥2 years	78	0.71 (0.43 – 1.16)	0.17	-	
LRRC neoadjuvant treatment					
No RTx	21	1			
(CTx)RTx	129	0.56 (0.30 – 1.05)	0.07	-	
LRRC surgery					
Non sphincter saving	97	1		1	
Sphincter saving	53	1.77 (1.00 – 3.12)	**0.05**	1.48 (0.84 – 2.61)	0.17
Total exenteration					
No	122	1			
Yes	28	0.92 (0.46 – 1.80)	0.80	-	
Partial sacrectomy					
No	132	1			
Yes	18	1.80 (0.98 – 3.32)	0.06	-	
Resection margin status					
>2mm	41	1		1	
>0-2mm	34	2.82 (1.09 – 7.27)	**0.033**	2.76 (1.06 – 7.16)	**0.037**
Microscopically involved	55	5.22 (2.28 – 11.95)	**<0.001**	4.92 (2.15 – 11.26)	**<0.001**
Macroscopically involved	20	12.52 (4.97 – 31.53)	**<0.001**	11.06 (4.20 – 29.12)	**<0.001**
IORT					
No	74	1			
Yes	76	1.38 (0.84 – 2.27)	0.20	-	
Tumor differentiation grade					
Well/moderate	105	1			
Poor	18	0.92 (0.42 – 2.03)	0.83	-	
Vasoinvasion					
No	121	1			
Yes	29	2.40 (1.38 – 4.16)	**0.002**	1.60 (0.89 – 2.89)	0.12

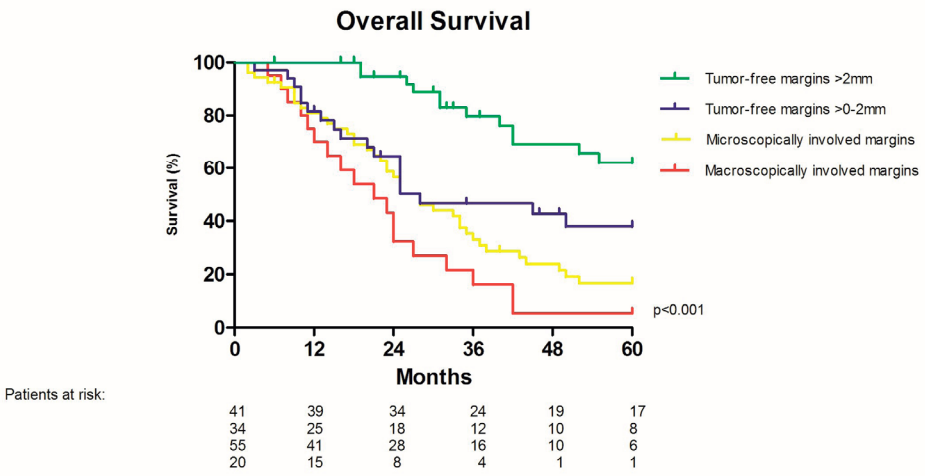
LRRC, locally recurrent rectal cancer; TME, total mesorectal excision, RTx, radiotherapy; CTxRTx, chemoradiotherapy; IORT, intraoperative radiotherapy

Table III. Univariate analysis of covariates regarding the overall survival and multivariable analysis stratified for period of surgery

	Number of patients	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI)	p-value
Gender					
Male	94	1			
Female	56	0.86 (0.56 – 1.32)	0.50	-	
Primary tumor resection					
Non-TME	58	1			
TME	92	0.83 (0.55 – 1.26)	0.38	-	
Previous pelvic radiotherapy					
No RTx	121	1			
(CTx)RTx	29	0.75 (0.43 – 1.33)	0.33	-	
Age at LRRC surgery					
<65 year	74	1			
≥65 year	76	1.21 (0.80 – 1.83)	0.36	-	
Primary tumor resection					
Sphincter saving	114	1			
Non sphincter saving	36	1.17 (0.74 – 1.85)	0.51	-	
Interval primary tumor and diagnosis of LRRC					
<2 years	72	1		1	
≥2 years	78	0.60 (0.40 – 0.90)	**0.015**	0.55 (0.36 – 0.83)	**0.006**
LRRC neoadjuvant treatment					
No RTx	21	1			
(CTx)RTx	129	0.89 (0.51 – 1.58)	0.69	-	
LRRC surgery					
Non sphincter saving	97	1			
Sphincter saving	53	1.52 (0.97-2.38)	0.07	-	
Total exenteration					
No	122	1			
Yes	28	1.17 (0.69 – 1.98)	0.56	-	
Partial sacrectomy					
No	132	1			
Yes	18	1.25 (0.70-2.25)	0.45	-	
Resection margin status					
>2mm	41	1		1	
>0-2mm	34	2.56 (1.26 – 5.20)	**0.009**	2.58 (1.26 – 5.26)	**0.009**
Microscopically involved	55	3.91 (2.09 – 7.31)	**<0.001**	3.64 (1.89 – 7.00)	**<0.001**
Macroscopically involved	20	5.95 (2.89 – 12.28)	**<0.001**	4.89 (2.29 – 10.45)	**<0.001**
IORT					
No	74	1			
Yes	76	1.37 (0.91 – 2.07)	0.14	-	
Tumor differentiation grade					
Well/moderate	105	1			
Poor	18	1.29 (0.70 – 2.39)	0.41	-	
Vasoinvasion					
No	121	1		1	
Yes	29	2.38 (1.50 – 3.81)	**0.001**	1.78 (1.06 – 2.98)	**0.029**

LRRC, locally recurrent rectal cancer; TME, total mesorectal excision, RTx, radiotherapy; CTxRTx, chemoradiotherapy; IORT, intraoperative radiotherapy

Figure II. Overall survival of the surgically treated LRRC patients



Distant metastases

Sixty-two patients (41%) developed distant metastases during follow up. The most common location was pulmonary (58%), followed by hepatic (31%) and other (20%). The 5-year distant metastases-free survival was 62% for patients with tumor-free margins of >2mm followed by 42% for tumor-free margins of 0-2mm, 28% for microscopically involved margins and 0% for macroscopically involved margins.

Discussion

The current study demonstrates that resection margins are the key to successful curative surgery for LRRC. Patients with resection margins of more than 2mm suffer less local re-recurrences and have an improved overall survival compared to patients with narrow resection margins (>0-2mm). Subsequently, patients with narrow resection margins (>0-2mm) have a more favorable outcome compared to patients with microscopically involved margins. Accurate determination of the minimal tumor-free resection margin leads to a more accurate assessment of the risk of local re-recurrence and overall survival. These data suggest that all efforts should be made to achieve resection margins more than 2 mm by downstaging with neoadjuvant treatment and by aggressive, multivisceral surgery when needed.

The association between the width of the tumor-free resection margin of LRRC and the re-recurrence rate is in line with the association of the CRM and recurrence rates in primary rectal cancer. However, re-recurrence rates after LRRC surgery are high compared to primary rectal cancer, which suggests a more aggressive local tumor

behavior of LRRC.[12] In primary rectal cancer, recurrences rates after CRMs of >2mm are reported in 2-12% of the patients compared to a re-recurrence rate of 20% after LRRC surgery. In patients with CRMs of >0-2mm, local recurrence rates of 5-28% are reported in primary rectal cancer compared to a re-recurrence rate of 38% in this study. Microscopically involved CRMs lead to a recurrence rate of 35-55% in primary rectal cancer compared to a re-recurrence rate of 72% after LRRC surgery in this study.[12-14,17]

The majority of published studies considers any microscopically uninvolved margin after LRRC surgery as a R0-resection. The local re-recurrence rates after such R0-resections are 25-50%.[6,10,18,19] These high re-recurrence rates can be explained by the fact these R0-resections probably contain a high proportion of patients with tumor-free resection margins of >0-2mm. In our series, tumor-free margins of >0-2mm were present in 46% of the patients with complete resections. In line with our results, authors who consider tumor-free margins of ≥1mm as R0-resections reported lower re-recurrence rates of 13-16%.[11,20] In the current study, re-recurrence rate and overall survival rates of patients with tumor-free margins of <1mm or tumor-free margins of 1-2mm were similar. We therefore suggest that tumor-free resection margins of >2mm should be the goal of curative surgery for LRRC.

The high frequency of narrow and involved resection margins in rectal surgery is caused by the anatomy of the pelvis. Moreover, local recurrences in the TME era are usually not confined to an anatomical compartment, since the anatomical compartment (mesorectum) was resected completely during resection of the primary rectal tumor. Consequently, local recurrences usually involve structures such as the pelvic fatty tissue and sidewalls, the bony sacrum, iliac and sacral vessels and nerves, ureters, bladder and the internal genitalia (prostate, uterus and vagina). Few patients have true intraluminal recurrences. These are the recurrences that may result in wide tumor-free resection margins as compared to recurrences that occur anterior, lateral and dorsal in the pelvis.[21] In not-centrally located LRRCs wide tumor-free resection margins can only be achieved by performing aggressive surgery, such as posterior exenterations, total exenterations or abdominosacral resections.[11,22,23]

Performing more radical surgical approaches may be the key to increase the number of patients with wider resection margins and thus improving the long-term outcome. Several experienced LRRC centers have shown that more radical surgical approaches for LRRC can be carried out with good results. A recent study of Colibaseanu et al.[24] have demonstrated that extended sacropelvic resections, for example with high sacral involvement above the level of S2 or resections in combination with hemipelvectomies, can be carried out with acceptable morbidity and results in a high complete resection rate of 93% and an excellent 5-year survival rate of 46%. Others have demonstrated previously that extensive resections of pelvic sidewall recurrences or extensive resections including sacrectomy can be carried out with excellent results.[25,26]

The introduction of multidisciplinary tumor boards and the improvement of the quality of the imaging modalities can further increase the number of complete resections by more accurate determination of the required extent of the surgical approach. It should be kept in mind that surgical planning should be performed on the initial imaging before neoadjuvant (chemo-)radiotherapy to reduce the chance of incomplete resections. Restaging imaging is unreliable to differentiate between post-radiation fibrosis and malignant tissue.

In general, the type of surgical procedure for LRRC did not change during the study period. However, developments in the treatment of primary rectal cancer, such as TME and radiotherapy, did influence the surgical treatment of LRRC. Complete resections after TME for the primary rectal tumor are considered more difficult and may result in an increased number of patients with narrow or involved resection margins. At the same time, the introduction of neoadjuvant radiotherapy for primary rectal cancer has caused re-irradiation doses for the treatment of LRRC to be limited in those patients who received radiotherapy for the primary tumor. This may result in decreased downstaging and less complete resections for LRRC. Additionally, the use of re-irradiation is still controversial, because of the potential toxicity. To evaluate the possible influence of these variables, we performed uni- and multivariable analyses, but none of these factors proved significant.

Although others have suggested a beneficial effect of IORT, the univariate analysis did not show a similar result.[27,28] However, IORT was specifically administered to patients with a high risk of local re-recurrence (i.e. involved or narrow margins ≤2mm), thus creating a selection bias to the detriment of the value of IORT.

An interval of more than 2 years between primary tumor resection and the diagnosis of LRRC was a prognostic factor for overall survival after LRRC surgery. Due to the fact that only patients with minimally of non-metastasized LRRC were selected for surgery, patients diagnosed with LRRC after an interval of more than 2 years may have tumors with a more favorable biological behavior.

Due to the retrospective nature of this analysis, this study has drawbacks. Firstly, the number of patients included is low compared to the studies that evaluated the prognostic value of the CRM in primary rectal cancer. However, this may be compensated by a higher occurrence of patients with tumor-free margins of >0-2mm. Secondly, the current study applied no standardized pathological examination to the resected specimens as was conducted in primary rectal cancer. Standardized pathological examination of LRRC is difficult due to the heterogeneity of the resected specimens, varying from specimens of total exenterations to resections of relative small local recurrences. Furthermore, the number of pathologists involved was high. The resection specimens were always evaluated by a team of 4 designated GI pathologists. However, we found that the turnover in this team has been very high, resulting in approximately 20 pathologists

evaluating the specimens. Thirdly, the long time span of this study may have introduced non-measurable variables and inherent biases, such as the quality of imaging and the experience of different surgeons. Although at all times a team of three dedicated colorectal surgeons performed resections of LRRCs (total of 8 surgeons during the study period). By stratifying for period of surgery in multivariable analysis, the influence of these variables was reduced. Fourthly, the median follow up of all patients was relative short (27 months), which was caused by a relative short overall survival. A substantial proportion of local re-recurrences may develop after this follow up period. However, the median follow up of the surviving patients was 43 months and we therefore think these patients were followed for an adequate length of time to evaluate the local re-recurrence-free survival. Fifthly, this study only included patients that underwent surgery. Since 2002, approximately 40% of the patients referred to our hospital were considered candidates for a surgical resection (data not shown). This is a potential selection bias and implies that the findings of current study are only applicable for selected patients. This may also explain the high number of patients who were treated by sphincter-saving procedures for the primary tumor.

In conclusion, resection margin status is an independent prognostic factor for re-recurrence and overall survival after curative surgery for LRRC. Patients with tumor-free resection margins of less than or equal to 2mm have a significantly higher re-recurrence rate and a poorer overall survival than patients with tumor-free resection margins over 2mm. All efforts should be directed at achieving wide tumor-free resection margins of more than 2mm.

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Chapter 10

Response to chemotherapy in patients with recurrent rectal cancer in previously irradiated area

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Abstract

Background

Tumor lesions in previously irradiated area may have a less favourable response to chemotherapy compared to tumor sites outside the radiation field. The aim of the present study was to evaluate the response to chemotherapy of locally recurrent rectal cancer (LRRC) within the previous radiation field compared to the response of distant metastases outside the radiation field.

Patients and methods

All patients with LRRC referred between 2000 and 2012 to our tertiary university hospital were reviewed. The response to chemotherapy of LRRC within previously irradiated area was compared to the response of synchronous distant metastases outside the radiation field according to the RECIST.

Results

Out of 363 cases with LRRC, 29 previously irradiated patients with distant metastases were treated with chemotherapy and eligible for analysis. Twenty-six patients (89%) suffered a first recurrence and 3 patients (11%) a second recurrence. These patients were followed with a median of 22 months (IQR, 9-40 months) and had a median survival of 33 months (IQR 14-42). In 23 patients (79%) the local recurrence showed stable disease, but the overall response rate of the local recurrences in the previously irradiated area was significantly lower than the response rate of distant metastases outside the radiation field (10% vs. 41%,p=0.034).

Conclusions

Previously irradiated patients with LRRC have a lower response rate to chemotherapy of the local recurrence within the radiation field compared to the response rate of distant metastases outside the radiation field. This suggests that chemotherapy for local palliation may not have the desired effect.

Introduction

Preoperative short-term radiotherapy (5x5Gy) has evolved into an integrated part of the treatment of stage II and III rectal cancer in the Netherlands, because of the beneficial effect on local control.[1] Long-term radiotherapy (50Gy) with or without concomitant chemotherapy has become standard of care in the treatment of locally advanced rectal cancer, because of improved local control and the effect of downsizing/-staging, thereby facilitating the possibility of a complete surgical resection.[2,3] Despite these advances, still 5–15% of the patients develop a local recurrence.[4] The widespread use of neoadjuvant radiotherapy introduced a new problem; the treatment of locally recurrent rectal cancer (LRRC) in previously irradiated area.

The treatment of LRRC is a therapeutic challenge. Complete surgical resection is considered the only chance of durable local control and long term survival.[5,6] Unfortunately, only 31-40% of the patients with LRRC have resectable disease.[7,8] The majority is considered unresectable due to the presence of extensive synchronous distant metastases or an advanced local recurrence in which complete surgical resection is technically not feasible. These patients can only be offered palliative treatment, consisting of pelvic radiotherapy in case of pain or chemotherapy in case of metastasized disease.

The palliative treatment options in previously irradiated patients with LRRC are limited. Due to the previous radiotherapy, only a limited dose of radiation can be administered and when treated with chemotherapy, the response of the local recurrence might be less favorable due to scarring and fibrosis of the pelvic tissue caused by the previous radiotherapy. This assumption is supported by a subgroup analysis of a meta-analysis, evaluating the response to chemotherapy for recurrent cervical cancer. Tumor recurrences within the previous radiation field showed a lower response rate to chemotherapy compared to the tumor recurrences outside the radiation field.[9] However, whether this also accounts for LRRC and the chemotherapeutic regimens used in this disease remains to be established.

The aim of the present study is to evaluate the response to chemotherapy of local recurrences in previously irradiated area compared to the response of distant metastases outside the radiation field within the same patient.

Patients and methods

All patients with LRRC referred between January 2000 and December 2012 to the Erasmus MC Cancer institute, a tertiary University hospital for the southwest region of the Netherlands were analyzed. Patients were discussed in a multidisciplinary tumor

board to determine the treatment strategy. At the time of diagnosis of LRRC, all patients were locally staged by a pelvic computed tomography scan (CT-scan) or by magnetic resonance imaging (MRI) and were screened for distant metastases by a thoraco-abdominal CT-scan. LRRCs were diagnosed by histological biopsies or by imaging. Criteria for LRRC on imaging were; a pelvic mass growing on consecutive imaging, a pelvic mass causing progressive ureter obstruction or a pelvic mass with sacral or lateral pelvic bone invasion.

Previously irradiated patients who presented with a first or second local recurrence with synchronous distant metastases outside the radiation field were identified. Patients who were not considered candidates for LRRC surgery and were treated with chemotherapy were included for analysis. Patients receiving palliative re-irradiation for local pain relief prior to chemotherapeutic treatment were excluded, unless re-irradiation was administered at least 1 year before the start of the chemotherapeutic treatment and the local recurrence had grown in size on radiologic imaging. Data were collected from all referring hospitals and included demographics, radiotherapeutic reports, pathological reports, radiological imaging and chemotherapeutic information.

Response to chemotherapy was assessed by two experienced medical oncologists and was scored according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[10] Tumor response was classified as a stable disease (SD), progressive disease (PD), partial response (PR) or complete response (CR). Overall response rate was defined as the sum of the patients with a PR or CR. Response evaluation was assessed after the first available follow up CT-scan after start of chemotherapy with a minimum of 3 and a maximum of 9 completed courses of chemotherapy. Baseline CT-scan had to be performed no more than 12 weeks before start of chemotherapy. Response evaluation of the local recurrence and the distant metastases was determined separately.

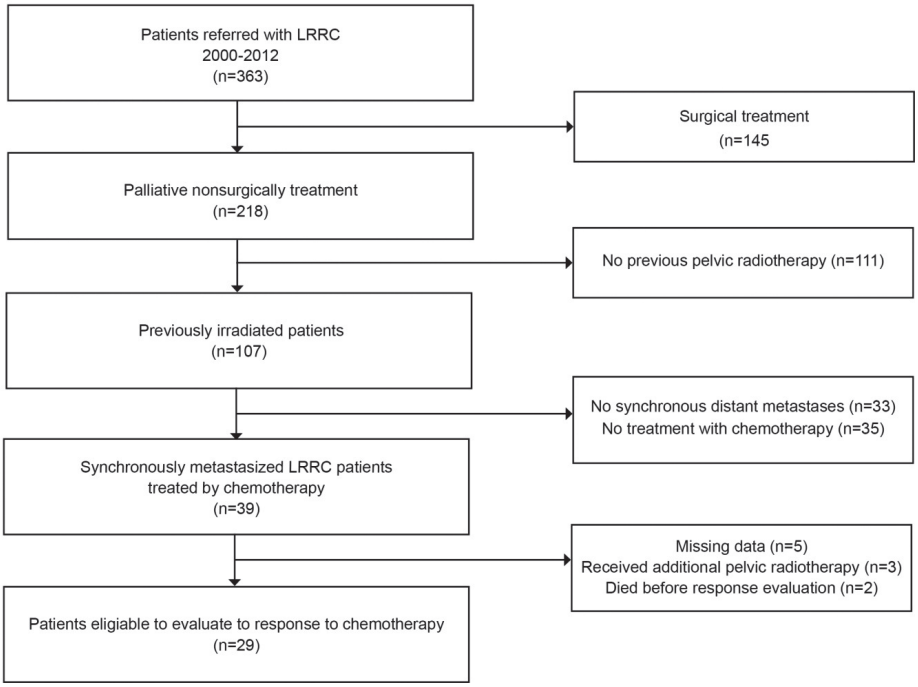
Statistical analysis was carried out using SPSS (version 20.0.0.1). Categorical data were reported as count (percentage) or median (interquartile range) as appropriate. Evaluation of distribution of response rates were performed by a chi-square test and a paired McNemar's test. P-values <0.05 were considered significant.

Results

A total 363 patients with LRRC were referred to our hospital; 218 patients (60%) were not considered candidates for curative surgery and were offered palliative treatment. One hundred and seven patients received pelvic irradiation previously of which 74 had developed synchronous distant metastases outside the previous radiation field. Chemotherapy was administered to 39 patients. Ten patients were excluded due to missing data (n=5), additional pelvic radiation within one year before the start of

chemotherapy (n=3) and death before tumor response evaluation (n=2), leaving 29 patients evaluable for analysis. *(Figure I)*

Figure I. Study flowchart of all LRRC patients



LRRC, locally recurrent rectal cancer

Patient and tumor characteristics

Patients and tumor characteristics are outlined in *table 1*. Twenty-six patients (89%) suffered a first local recurrence and 3 patients (11%) suffered a second recurrence after LRRC surgery with curative intent. LRRC was histopathologically proven in 16 patients (55%). The median interval between primary rectal surgery and LRRC diagnosis was 23 months (IQR 15-36). Previous pelvic radiotherapy for the primary tumor or first local recurrence was a long course radiotherapy (44,6-50Gy) in 12 patients (41%), chemoradiotherapy (50Gy) in 9 patients (28%) and a short course radiotherapy (25Gy) in 8 patients (28%). The localization of the distant metastases were pulmonary in 16 patients (55%), hepatic in 7 patients (24%), both pulmonary and hepatic in 3 patients (10%) and inguinal lymph nodes in 3 patients (10%).

Table I. Baseline patients and tumor characteristics

	Number of patients (%)
Total patients	29
Gender	
Male	22 (76)
Female	7 (24)
Age at diagnosis	65 (38-84)
Primary or LRRC surgery	
LAR	15 (52)
APR	11 (38)
Posterior exenteration	2 (7)
Total exenteration	1 (3)
Primary or LRRC resection margin	
R0	25
R1 (≤1mm)	3
R2 (macroscopically incomplete)	1
Tumor Stage	
T1-2	2
T3-4	27
Lymph node status	
N0	8
N+	21
Tumor differentiation	
Well	0
Moderate	17 (59)
Poor	5 (17)
Unknown	7 (24)

LAR, Low Anterior Resection; APR, abdominoperineal resection

Follow up and response to chemotherapy

Patients were followed with a median of 22 months (IQR, 9-40). At last follow up, 5 patients (17%) were alive and 24 patients (82%) died, resulting in a median survival of 33 months (IQR 14-42). The used chemotherapeutic regimes are depicted in *table II*. Chemotherapy was administered after a median of 2 months (IQR 1-8) after the diagnosis of LRRC and response evaluation was done after a median of 3 cycles. The response rates to chemotherapy of the local recurrence and the distant metastases are outlined separately in *table III.* There was a significant difference between the overall response rate of local recurrence and distant metastases (10 vs. 41%, p=0.034). On individual basis, 2 patients with CR of the distant metastases had PR of the local recurrence. Of 10 patients with PR of the distant metastases, 9 patients had SD and 1 had PD of the local recurrence. Of the 10 patients with SD of the distant metastases,

8 patients had SD, 1 patient had PD and 1 patient had PR of the local recurrence. Of the 7 patients with PD of the distant metastases, 6 patients had SD and 1 patient had PD of the local recurrence. There was no significant difference in SD rate of the local recurrences of patients with histologically proven LRRC or radiologically detected LRRC (88 vs. 70%, p=0.36).

Table II. Chemotherapeutic variables

	Number of patients (%)
Total patients	29
Number of cycles	6 (3-31)
Type chemotherapy	
Capecitabine	11
Capecitabine + Oxaliplatin	6
Iriontecan	4
Fluorouracil + Oxaliplatin + leucovorin	3
Capecitabine + Oxaliplatin + bevacizumab	2
Cetuximab	1
Capecitabine + bevacizumab	1
Fluorouracil + leucovorin	1
Switch to second line chemotherapy	
Yes	12
No	17

Discussion

The current study suggests a less favorable response rate (according to the RECIST) to chemotherapy of the local recurrence in previously irradiated area compared to the response rates of the distant metastases outside the radiation field within the same patient. The poor response rates of the local recurrences in previously irradiated area suggest that chemotherapeutic options may not have the desired effect for local palliation.

The response rate of the local recurrences in previously irradiated area was 10%, whereas the 41% response rate of the distant metastases was significantly higher. Although there is little data available about the response to chemotherapy of LRRC, the poor response is in line with studies evaluating the potential palliative effect of regional intra-arterial chemotherapy in LRRC. None of these studies were able to achieve an acceptable palliative result.[11-14] However, these studies were all conducted in the 70's and 80's before the introduction of the currently used chemotherapeutics regiments and did not solely included LRRC in previously irradiated area. Furthermore, the palliative

results of these studies were based on subjective clinical symptoms and not on objective imaging. To our knowledge, this study is the first to assess the response of LRRC to contemporary chemotherapeutic regiments and evaluating the response of the local recurrences and distant metastases separately.

A possible explanation for the difference in response rate could be that previous radiotherapy and surgery alters the environment of the pelvis in which the local recurrence is located. Previous surgery may affect vascularization of the pelvic region and radiotherapy leads to post-irradiation fibrosis and subsequently a reduced vascularization. This may prevent adequate local chemotherapeutic tissue levels, which are necessary to achieve tumor response. A comparable phenomenon was found in patients with recurrent cervical carcinoma. A pooled analysis of patients from multiple randomized controlled trials demonstrated a lower response rate to chemotherapy of tumor recurrences within the previous irradiated area compared to tumor recurrences outside the radiation field.[9] However, the analysis included studies comparing the response rates of patients with local recurrent disease after previous radiotherapy to the response rate patients who did not receive previous radiotherapy. Therefore, these results are more exposed to patient and tumor biology variability, which was minimalized in current study by comparing the response rate of the local recurrence and distant metastases within the same patient.

A second explanation for the difference in response rate may be that previous radiotherapy and surgery leads to a very fibrotic and rigid area, which makes the local recurrence within unable to shrink in contrast to the distant metastases outside the radiation and operation field. This may explain the remarkable high number of patients (79%) with stable disease of the local recurrence, but not the finding that less patients had progressive disease of local recurrences in the previously irradiated area compared to the distant metastases outside the radiation field. This suggest that chemotherapy may have some influence on the local recurrence, but in comparison to the distant metastases, the response may be different due to genetic, biological, or environmental differences, whether or not caused by the radiotherapy.

The high rate of stable disease of the local recurrences might also be caused by the fact that not all LRRCs were histologically proven and that we simply evaluated non-malignant pelvic masses. However, both histologically proven and radiologically detected LRRCs showed a high rate of stable disease and we found no difference in stable disease rate of histologically proven and radiologically detected LRRCs.

Generally, the prognosis of patients with LRRC is poor. Moreover, previously irradiated patients with LRRC represents a group with even a poorer prognosis than 'regular' not previously irradiated LRRC. This was demonstrated by an update the Dutch TME-trial. The vast majority of the patients who received radiotherapy for the primary tumor had distant metastases at diagnosis or developed them within the first 6 months after diagnosis. This resulted in a very poor median life expectancy of only 6 months.[15] In the current study,

the survival rate of previously irradiated patients was significantly longer. Presumably, the patients in the current study are a selection of patients in generally good clinical condition and were therefore also considered candidates for chemotherapeutic treatment.

The main therapeutic problem of LRRC are the often disabling- and difficult to treat symptoms, such as severe pain and fistulating or bleeding tumors. The low response rate to chemotherapy as described in the current series clearly stresses the high need for novel treatment options and in particular for those patients with symptomatic local recurrences. Pelvic re-irradiation can provide pain relief in 65-83% of the patients. Unfortunately, the duration of this pain relief is limited to a median of only 6-9 months and it can only be offered for a limited number of times.[16-18] Moreover, pelvic re-irradiation leaves distant metastases untreated and probably does not affect overall survival. A possible mechanism to improve the response to chemotherapy is to combine it with hyperthermia. Hyperthermia exposed parts of the body to high temperatures (42°C), which causes increased intracellular drug uptake, enhanced DNA damage and higher intra-tumor drug concentrations caused by an increased blood flow.[19] Future research should focus on combining hyperthermia and chemotherapy to investigate whether this approach improves the response rates of the local recurrences in previously irradiated area.

Chemotherapy is increasingly used in a potential curative preoperative setting for LRRC. Pre-operative chemotherapy is administered to facilitate tumor downstaging and thus enhancing the chance of a complete resection. Complete resections are the most important prognostic factor for overall survival and it is hypothesized achieving wider resection margins may improve outcome.[6,20] The results of the current study contradicts the potential downstaging effect of chemotherapy in previously irradiated patients. Therefore, the use of pre-operative chemotherapy to induce tumor downstaging in previously irradiated patients needs further investigation.

Due to the retrospective nature of this analysis, this study has limitations. Moreover, there was no standard policy regarding the palliative treatment of patients with LRRC. Chemotherapy was only considered a suitable option in a small proportion of the patients with LRRC. This is illustrated by the fact that only 39 patients out of 74 LRRCs with synchronous distant metastases were treated with chemotherapy. This resulted in a relative small number of patients eligible for analysis. Furthermore, different chemotherapeutic regiments were used in the current study, which could lead to differences in response rate. However, this potential bias was ruled out by evaluating the response rate of distant metastases and local recurrence within the same individual patient.

In palliative treatment of LRRC, chemotherapy is administered to prolong survival and to achieve local symptom palliation. However, the current study did not evaluate the effect of chemotherapy on local symptom palliation, because evaluating local palliation

is subjective and highly patient and clinician dependent. Moreover, evaluating local palliation in a retrospective manner is highly unreliable. By using RECIST, we were able to evaluate response to chemotherapy in an objective manner.

In conclusion, previously irradiated patients with LRRC have a lower response rate to systemic chemotherapy of the local recurrence within the previous radiation field compared to the response rates of distant metastases outside the radiation field. This suggests that chemotherapeutic therapy for local palliation may not have the desired effect. Further studies are needed to improve treatment results, for example by combining chemotherapy with hyperthermia.

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Chapter 11

De behandeling van het lokaal recidiverend rectumcarcinoom

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Abstract

- Het lokaal recidiverende rectumcarcinoom (LRRC) heeft een slechte prognose.
- De incidentie is in de afgelopen decennia gedaald door verbeteringen in de behandeling van patiënten met een primair rectumcarcinoom, maar LRRC komt nog steeds bij 6-10% van deze patiënten voor.
- Het LRRC gaat vaak gepaard met hevige en progressieve pijn en heeft een grote impact op de kwaliteit van leven.
- Door een chirurgische resectie gecombineerd met chemo-radiotherapie is er een kans op curatie.
- Een radicale resectie is de belangrijkste prognostische factor in de curatieve behandeling.
- Neo-adjuvante systemische therapie kan mogelijk de uitkomsten van het LRRC verder verbeteren.
- Veel patiënten komen niet in aanmerking voor chirurgische behandeling door de aanwezigheid van metastasen of een te groot of te uitgebreid lokaal recidief. Zij moeten vanwege de invaliderende pijn optimaal palliatief worden behandeld.
- Radiotherapie is effectief tegen lokale pijn bij ongeveer 75% van de patiënten, maar de duur van de palliatie is beperkt.

Casus ter inleiding

Een 66-jarige man wordt via de Spoedeisende Hulp opgenomen met een urosepsis en een gestoorde nierfunctie. Hij heeft 2,5 jaar geleden een rectumamputatie ondergaan vanwege een rectumcarcinoom. Een echo laat een hydronefrose links zien en een aanvullende CT-scan toont een massa aan ter plaatse van de distale ureter. Hij wordt behandeld met antibiotica en er wordt een percutane nefrostomiedrain (PCN) geplaatst, waarna hij opknapt. De afwijking wordt op geleide van CT aangeprikt en blijkt een adenocarcinoom van colorectale origine te zijn. Er is sprake van een lokaal recidiverend rectumcarcinoom. Dit artikel bespreekt de diagnostische en therapeutische mogelijkheden voor een patiënt met deze aandoening.

Inleiding

De afgelopen decennia is de behandeling van het rectumcarcinoom verbeterd. Verbetering van de operatietechniek, preoperatieve chemo-radiotherapie en verbeterde beeldvormende technieken hebben geleid tot een sterke daling van het percentage lokale recidieven. Desondanks ontwikkelt 6-10% van de patiënten na resectie van een rectumcarcinoom een lokaal recidief.[1,2] Door de stijgende incidentie van het primaire rectumcarcinoom, met name veroorzaakt door de vergrijzing, kan de komende tijd het aantal patiënten met een lokaal recidiverend rectumcarcinoom (LRRC) toenemen.

Het LRRC is echter voor velen een onbekend ziektebeeld. De prognose is slecht, maar er is tegenwoordig een kans op curatie door chirurgie gecombineerd met pre-operatieve en intra-operatieve radiotherapie. Toch komt slechts een deel van de patiënten hiervoor in aanmerking; bij de aanwezigheid van afstandsmetastasen of irresectabiliteit van het lokale recidief is chirurgische behandeling niet mogelijk. Het huidige artikel bespreekt de mogelijkheden, onmogelijkheden en resultaten van de curatieve en palliatieve behandeling van patiënten met een lokaal recidiverend rectumcarcinoom.

Het lokaal recidiverend rectumcarcinoom

Het LRRC wordt gedefinieerd als tumorgroei in het kleine bekken na resectie van een primair rectumcarcinoom. De meerderheid van de patiënten (65-70%) heeft klachten op het moment dat de diagnose wordt gesteld.[3,4] De meest voorkomende klachten zijn een veranderend ontlastingspatroon, rectaal bloedverlies, mictieklachten en pijnklachten. Bij 30-35% van de patiënten wordt de diagnose gesteld terwijl zij geen klachten hebben, door een rectaal toucher, een stijgende CEA-waarde of beeldvormend onderzoek tijdens de follow-up.

Het natuurlijke beloop van een onbehandeld LRRC kenmerkt zich door progressieve pijn als gevolg van ingroei van de tumor in zenuwen van de sacrale plexus of ingroei in ossale structuren. Deze pijn is invaliderend; bovendien ontstaan vaak fistels en bloedingen uit de tumor. Dit resulteert doorgaans in een slechte kwaliteit van leven en een pijnlijke dood.

Een 'nieuw' lokaal recidiverend rectumcarcinoom

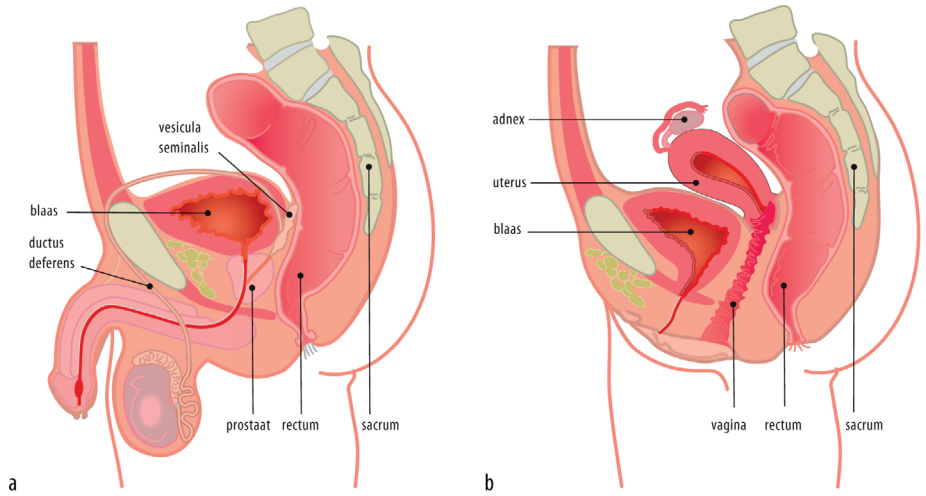
Er zijn 2 ontwikkelingen in de behandeling van het primaire rectumcarcinoom die de uitkomsten na rectumresectie sterk hebben verbeterd: zogenoemde totale mesorectale excisie (TME), een nieuwe operatietechniek, en de voorbehandeling met chemo-radiotherapie.

Totale mesorectale excisie

De introductie van TME is de belangrijkste ontwikkeling van de afgelopen decennia in de behandeling van patiënten met een primair rectumcarcinoom. Bij deze techniek wordt het anatomische compartiment rondom het rectum, waarin zich meestal alle aangedane lymfeklieren bevinden, in zijn geheel gereseceerd. Hierdoor is het percentage lokale recidieven sterk gedaald. Ook wordt tegenwoordig bij lage rectumtumoren een deel van de bekkenbodemspieren gereseceerd, omdat bleek dat voortzetten van de TME bij lage rectumtumoren juist tot een hoog aantal irradicale resecties leidde.

De introductie van TME en resectie van de bekkenbodemspieren heeft ook het karakter van het LRRC veranderd, omdat na een TME in het kleine bekken geen duidelijk

Figuur I. Schematische weergave van de anatomische structuren van (a) de man en (b) de waar alwaar een lokaal recidief kan ingroeien



afgrensbare compartimenten meer bestaan. Dit betekent dat een LRRC vaak direct ingroeit in omliggende structuren, zoals prostaat en vesikels bij de man en uterus, adnexen en vagina-achterwand bij de vrouw *(figuur I).* Ook kan de tumor in de blaas of het sacrum ingroeien. Hierdoor is een radicale resectie na TME vaak lastig te realiseren en zijn uitgebreide resecties nodig.

Preoperatieve chemo-radiotherapie

De tweede verbetering in de behandeling van primair rectumcarcinoom is de introductie van preoperatieve chemo-radiotherapie. Nederlands onderzoek heeft aangetoond dat preoperatieve radiotherapie het lokale recidiefpercentage vermindert.[2] Daarom worden tegenwoordig veel primaire rectumcarcinomen voorbehandeld met chemo-radiotherapie. Hierdoor manifesteert een LRRC zich tegenwoordig vaak in een gebied dat al eerder bestraald is geweest. Dit bemoeilijkt verdere behandeling, omdat er door eerdere radiotherapie minder ruimte is voor preoperatieve radiotherapie van het LRRC.

Daarnaast vormen recidieven in eerder bestraald gebied waarschijnlijk een groep van tumoren met biologisch ongunstig gedrag. Patiënten met een LRRC na eerdere preoperatieve radiotherapie hebben een slechtere overleving en vaker metastasen op afstand dan patiënten die geen preoperatieve radiotherapie hebben ondergaan.[5]

Tot slot wordt bij patiënten met een rectumcarcinoom in een vroeg stadium soms volstaan met een beperkte transanale resectie en bij een complete respons op chemo-radiotherapie kan worden besloten om helemaal geen operatie uit te voeren. Enerzijds kan dit leiden tot een verhoogde incidentie van LRRC; anderzijds bevinden die recidieven zich dan, in tegenstelling tot na TME, vaak wel in een nog afgrensbaar en resectabel compartiment.

Zoekstrategie

Met betrekking tot diagnostiek en behandeling van het LRRC voerden wij een zoekactie in PubMed uit met de zoekterm 'locally recurrent rectal cancer'. Wij beperkten ons tot klinisch onderzoek, gepubliceerd in het Engels en verschenen in de periode 2004-2014. Van de 200 artikelen die aan deze criteria voldeden waren er 128 niet relevant. Van de 72 overgebleven artikelen werden de grootste patiëntenseries geselecteerd als referentie, mits zij niet in strijd waren met vergelijkbare series. De referenties uit deze artikelen werden nagezien om te voorkomen dat belangrijke series over het hoofd gezien werden. Gezien de relatieve zeldzaamheid van de ziekte blijkt de bewijskracht van de studies niet hoger dan niveau 3 (cohortonderzoek of patiënt-controle-onderzoek van lage kwaliteit).

Diagnostiek en stagering

Gedetailleerde lokale stagering van het LRRC is essentieel om de resectabiliteit te beoordelen. In vergelijking met het primaire rectumcarcinoom is de beoordeling van tumoruitbreiding van het LRRC minder accuraat. Dit wordt veroorzaakt door fibrose en littekenvorming door eerdere operaties en chemo-radiotherapie. MRI heeft de hoogste accuratesse: 73-85%.[6] Een PET-CT kan helpen om littekenweefsel te onderscheiden van tumorweefsel.[7]

Disseminatieonderzoek in de vorm van CT van thorax en abdomen is net zo belangrijk. Ongeveer de helft van de patiënten heeft afstandsmetastasen op het moment dat de diagnose 'LRRC' wordt gesteld.[8] Of curatie en overlevingswinst bij LRRC met uitgebreide afstandsmetastasen mogelijk is, is onzeker.

Het beoordelen van de scans en ander beeldvormend onderzoek en het bepalen van de behandeling is vaak complex. Daarom moeten patiënten met een LRRC in een gespecialiseerd multidisciplinair overleg besproken worden, zoals dat ook geldt voor het primaire rectumcarcinoom.[9]

Curatieve behandeling

De curatieve behandeling van LRRC is een multimodaliteitsbehandeling, die bestaat uit preoperatieve chemo-radiotherapie, chirurgische resectie en eventueel intra-operatieve radiotherapie (IORT).

Preoperatieve chemo-radiotherapie

Preoperatieve chemo-radiotherapie is een belangrijk onderdeel van de curatieve behandeling. Het leidt tot meer radicale resecties en verlaagt de kans op een volgend lokaal recidief.[10] Tegenwoordig wordt de meerderheid van de patiënten met een primair rectumcarcinoom met preoperatieve chemo-radiotherapie behandeld. Vanwege de toxiciteit van radiotherapie voor organen als de blaas en de dunne darm is de maximale dosis radiotherapie die daarna nog gegeven kan worden voor het LRRC beperkt. Het lijkt echter veilig om het LRRC na eerdere radiotherapie nogmaals te behandelen met een dosis van 30 Gy, zonder dat dit resulteert in hoge toxiciteit.[11]

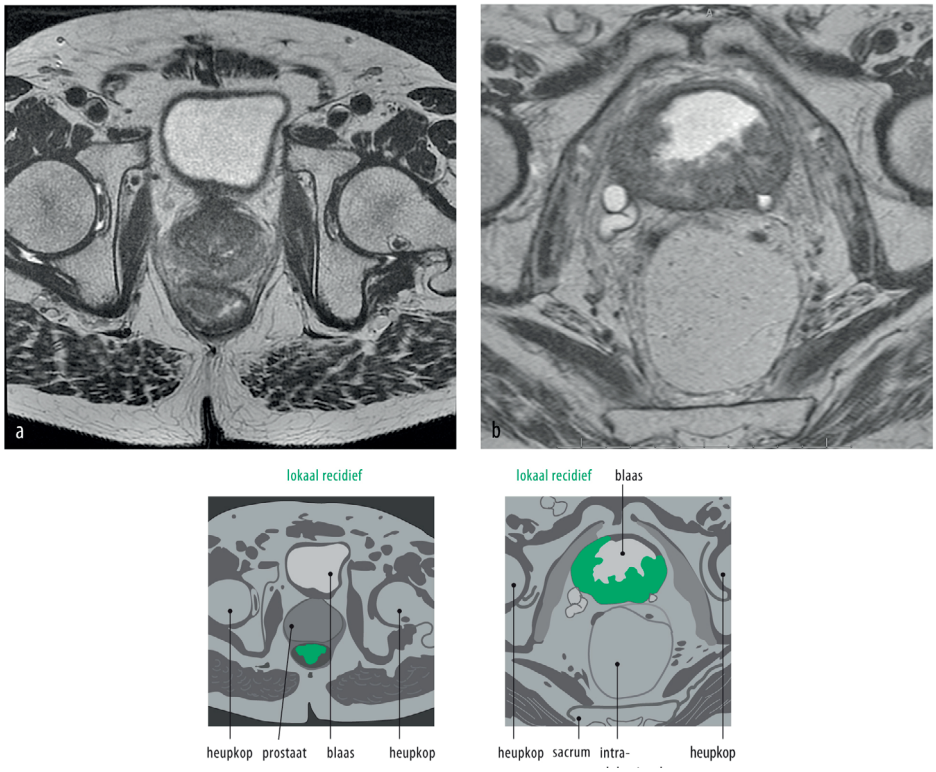
Chirurgie

Radicale resectie is de basis van de curatieve behandeling.[12] Na TME lukt dit bij 44-59% van de patiënten.[13,14] Dit percentage is ongeveer gelijk aan het percentage radicale resecties van primaire tumoren vóór de introductie van TME. Dit resultaat is waarschijnlijk behaald door een verbeterde patiëntselectie en uitbreiding van chirurgische technieken.

De lokalisatie van het LRRC in het kleine bekken is belangrijk voor de chirurgische planning en de inschatting of radicale resectie haalbaar is. Daarnaast wordt de locatie

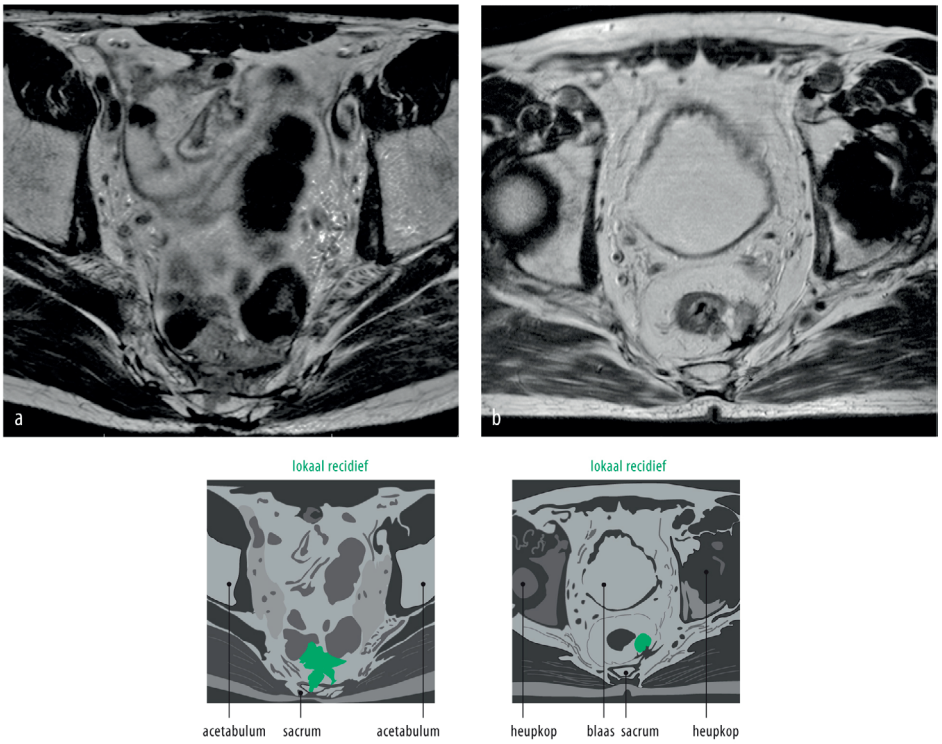
gebruikt om het LRRC te classificeren. Hierbij is een indeling gemaakt in centraal, anterieur, dorsaal en lateraal gelokaliseerde recidieven *(figuur II en III).*

Figuur II: MRI-Scan (transversale coupes) van het bekken met (a) een centraal gelegen recidief en (b) een anterieur gelokaliseerd recidief van een rectumcarcinoom bij patiënten die een totale mesorectale excisie hebben ondergaan



De kans op een radicale resectie is het hoogst bij centraal gelokaliseerd recidieven *(zie figuur 2a),* zoals het naadrecidief. Deze kans is kleiner bij anterieur, dorsaal of lateraal gelokaliseerde recidieven.[15] Bij een anterieur gelokaliseerd LRRC is er vaak ingroei in de interne genitalia. Bij vrouwen zijn dat de vagina-achterwand, de uterus of adnexen. Een radicale resectie kan dan bereikt worden door middel van een achterste exenteratie, waarbij deze structuren worden gereseceerd. Bij mannen groeit een LRRC vaak in de prostaat. Een radicale resectie betekent dan een totale exenteratie, wat ook onvermijdelijk is bij uitgebreide ingroei in de blaas. Een totale exenteratie is een resectie van blaas en rectum, waarbij bij vrouwen uterus en adnexen worden meegenomen en bij mannen de prostaat. Reconstructie van de urinewegen en aanleg van een urostoma is noodzakelijk. Totale exenteraties kunnen leiden tot langdurige overleving en curatie, maar gaan gepaard met aanzienlijke morbiditeit.[16]

Figuur III: MRI-scans (transversale coupes) van het bekken met (a) een dorsaal gelokaliseerd recidief en (b) een lateraal gelokaliseerd recidief van een rectumcarcinoom die een totale mesorectale excisie hebben onderdaan.



Dorsaal gelokaliseerde recidieven hebben een nauwe relatie met of groeien in het sacrum *(zie figuur 3a).* In dat geval is het mogelijk een deel van het sacrum te reseceren; dit is de abdominosacrale resectie. Het sacrum, bestaande uit 5 vergroeide wervellichamen, kan relatief veilig gereseceerd worden vanaf wervelniveau S2. Het probleem bij partiële sacrumresecties is dat de uittredende zenuwwortels worden meegereseceerd. Dat leidt doorgaans tot blaasfunctiestoornissen, waardoor katheterisatie vaak levenslang nodig blijft. Bij een totale sacrumresectie worden ook de wortels van S1 doorgenomen, wat leidt tot motorische uitval van de benen. Deze procedure is vanwege de ernstige morbiditeit slechts bij hoge uitzondering gerechtvaardigd. Ook abdominosacrale resecties kunnen leiden ook tot langdurige ziektevrije overleving, maar het complicatiepercentage is hoog.[17]

Lateraal gelokaliseerde recidieven hebben vaak een nauwe relatie met de iliacale vaatbundel en de ureter. Soms kan een radicale resectie alleen bereikt worden door een deel van deze vaten of de ureter te reseceren. Het is mogelijk de A. iliaca communis en externa, die essentieel zijn voor de circulatie in de benen, te reconstrueren met een interponaat om daarmee een radicale resectie te behalen. Dit soort procedures zijn goed

uitvoerbaar en veilig.[18] Resectie van een ureter wordt doorgaans opgelost door de blaas te mobiliseren en de ureter dan opnieuw met blaas te anastomoseren.

Intraoperatieve radiotherapie (IORT)

Enkele ziekenhuizen in Nederland hebben de mogelijkheid om tijdens de operatie een extra dosis radiotherapie toe te dienen. Met IORT kan een specifiek doelgebied extra bestraald worden zonder dat andere radiotherapiegevoelige structuren onbedoeld beschadigd worden. Het toedienen van IORT resulteert in een 2-3 keer hogere biologische dosis dan conventioneel toegediende radiotherapie. Een intra-operatieve dosis van 10 Gy leidt dus tot een biologische dosis van 20-30 Gy. In combinatie met een herbestralingsdosis van 30 Gy kan zodoende toch een effectieve dosis van 50-60 Gy op een specifieke locatie behaald worden, terwijl conventionele herbestraling met een dosis van 50-60 Gy zou leiden tot onacceptabele weefseltoxiciteit. Verschillende studies hebben aangetoond dat het toedienen van IORT veilig is. Het is daarnaast aannemelijk dat achtergebleven vitale tumorcellen op deze manier gedood kunnen worden.[19]

Preoperatieve en adjuvante systemische therapie

Adjuvante systemische therapie kan worden toegevoegd aan de multimodaliteitsbehandeling.[20] Dit is in Nederland ongebruikelijk, omdat er geen bewijs is dat adjuvante systemische therapie leidt tot overlevingswinst. Daarnaast is adjuvante systemische therapie niet altijd haalbaar, vanwege de hoge postoperatieve morbiditeit. Wel wordt steeds vaker preoperatieve systemische therapie toegepast om maximale tumorreductie te bereiken. Daarnaast kan een goede respons op preoperatieve systemische therapie duiden op een gunstig biologisch tumorgedrag, wat mogelijk tot betere patiëntselectie leidt. Of preoperatieve systemische therapie daadwerkelijk de uitkomsten verbetert, is niet bekend.

Prognose en morbiditeit

Radicale resecties gecombineerd met een multimodaliteitsbehandeling leiden tot een 5-jaarsoverleving van 43-55%.1[2,13,20-22] De overleving is slechter na een irradicale resectie. Microscopische irradicale resecties hebben een 5-jaars overleving van 0-27% en macroscopisch irradicale resecties hebben een overleving die vergelijkbaar is met die van palliatief behandelde patiënten.[12,13,20-23] Het complicatiepercentage na chirurgische resecties van LRRC is hoog. Het betreft voornamelijk infectieuze complicaties, zoals perineale wondinfecties en presacrale abcessen, maar ook naadlekkages komen voor.

Palliatieve behandeling

Bij veel patiënten is resectie niet mogelijk of niet zinvol door de aanwezigheid van uitgebreide afstandsmetastasen, irresectabiliteit van het lokale recidief of onvoldoende fitheid van de patiënt. Deze patiënten kunnen palliatief behandeld te worden.

Radiotherapie, hyperthermie en systemische therapie

Het kenmerkende probleem van LRRC is de pijn die veroorzaakt worden door het lokale tumorproces. De effectiefste manier om deze pijn te behandelen is palliatieve radiotherapie. Dit leidt tot verlichting bij ongeveer 75% van de patiënten, maar de duur van deze pijnverlichting is beperkt tot slechts 3-9 maanden.[24] Patiënten met recidiverende klachten van pijn kunnen wel opnieuw bestraald worden, net als patiënten die voor het primaire rectumcarcinoom al radiotherapie ontvingen.[25]

Het effect van herbestraling kan versterkt worden door hyperthermie. De temperatuur van het tumoreuze weefsel wordt daarbij verhoogd tot 40-43°C door microgolfstraling. Hyperthermie heeft een schadelijk effect op tumorcellen en versterkt het effect van radiotherapie.[26]

Palliatieve systemische therapie kan overwogen worden. Er is echter weinig bekend over het effect hiervan op pijnklachten. Oudere studies laten teleurstellende resultaten zien en de verwachting is dat ook moderne systemische therapie weinig effect op de pijn heeft. Systemische therapie leidt waarschijnlijk wel tot overlevingswinst bij patiënten met een gemetastaseerd LRRC, vergelijkbaar met de resultaten van systemische therapie bij het primaire gemetastaseerde colorectale carcinoom.

Mogelijk kunnen nieuwe therapeutische ontwikkelingen voor het primaire colorectale carcinoom, zoals de ontwikkeling van ‘targeted agents’, ook waardevol blijken voor de behandeling van LRRC. Daarmee is wellicht toch winst te behalen, hoewel het opzetten van gerandomiseerd onderzoek naar behandeling van patiënten met LRRC vaak niet haalbaar is.

Huisarts

De huisarts vervult een belangrijke rol in de behandeling van patiënten met een LRRC. Uiteindelijk zullen voor een groot deel van de chirurgisch behandelde en de palliatief behandelde patiënten geen behandelingsopties meer zijn. Deze patiënten kan ‘best supportive care’ worden aangeboden, waarbij de huisarts onmisbaar is voor adequate pijnbestrijding, vaak in samenwerking met de pijnspecialist. Daarnaast vragen deze patiënten met oncontroleerbare en progressieve pijn hun huisarts nogal eens om euthanasie.

Conclusie

Het LRRC is een lastig klinisch probleem met ingrijpende gevolgen voor de patiënt. De chirurgische behandeling is uitdagend, maar in gespecialiseerde centra kan met een multimodaliteitsbehandeling een relatief goed oncologisch resultaat bereikt worden bij geselecteerde patiënten. Veel patiënten komen niet in aanmerking voor chirurgische behandeling en kunnen palliatief behandeld worden met radiotherapie, hyperthermie en systemische therapie. Iedere patiënt met een LRRC dient te worden besproken in een gespecialiseerd centrum voor een optimale curatieve en palliatieve behandeling.

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Chapter 12

General discussion and
future perspectives

Discussion

This thesis focused on several aspects to further improve locally advanced and recurrent rectal cancer management. During last decade, rectal cancer treatment has shifted increasingly towards a personalized treatment depending on the local tumor and the presence of distant metastases. A multimodality treatment can result in relatively good long-term outcomes for both LARC and LRRC. This thesis aimed to further improve the multimodality treatment in order to offer patients the best oncological care. Briefly, the first part of this thesis, focusing on staging, showed a beneficial effect of restaging by thoraco-abdominal CT-scan after (chemo-)radiotherapy. It resulted in newly discovered distant metastases altering treatment in a substantial number of patients. Unfortunately, the beneficial effect of adding DCE sequences to local restaging by MR imaging after (chemo-)radiotherapy was limited. The second part, which focused on LARC, suggested that applying IORT leads to improved local control in patients with a microscopically involved circumferential resection margin (CRM). Furthermore, the treatment of cT4 rectal cancer in high volume cT4 hospitals may lead to an improved overall survival, while the effect of the hospital volume in cT1-3 rectal cancer is limited. The third part, focusing on LRRC, demonstrated that patients with local recurrences after previous pelvic radiotherapy and TME surgery should also be considered candidates for curative surgery. Additionally, it showed that complete resections with close margins between 0-2mm have a poorer outcome than wider resection margins of >2mm and that the effect of systemic therapy on the local recurrence in previously irradiated area was limited.

The first part of this thesis focused particularly on restaging of patients with LARC after a long course of (chemo-)radiotherapy. Accurate staging is essential for high quality rectal cancer management. The accuracy of Magnetic Resonances (MR) imaging of tumor staging and CRM involvement is high in those who did not receive neo-adjuvant treatment. MR imaging can accurately differentiate between low tumor stage (T1-2) and high tumor stage (T3-4) with a high sensitivity of 87%.[1] Moreover, a specificity of 94% in CRM involvement shows that MR-imaging can accurately detect patients at risk for incomplete resections when performing a standard TME procedure. Given the knowledge that (chemo-)radiotherapy does not only leads to a reduced local recurrence rate, the fact that it leads to tumor downstaging made it interesting to reassess the local tumor extent after (chemo-)radiotherapy.[2,3] Potentially, these patients can be offered less radical resections in case of a good response to (chemo-)radiotherapy. Additionally, (chemo-)radiotherapy may lead to a complete pathological response (pCR). A pCR is seen in 11-19% of the patients after chemoradiotherapy.[4-7] Accurate determination of patients with a pCR may be valuable, because these patients can be offered a 'watch and wait' approach. In a 'watch and wait' approach, rectal cancer surgery is omitted and patients are closely surveilled. The results of close surveillance after a complete clinical

response are promising.[8-10] However, when considering applying a 'watch and wait' approach or performing less radical surgery, it is important to accurately stage rectal cancer after (chemo-)radiotherapy. For this reason patients, are increasingly restaged after neo-adjuvant (chemo-)radiotherapy. Unfortunately, the accuracy of restaging is poor. The sensitivity of differentiating between low tumor stage (T1-2) and high tumor stage (T3-4) tumor staging drops from 87% without neo-adjuvant therapy to 50% after (chemo-)radiotherapy.[1,11] Therefore, new techniques are necessary to accurately reassess the local stage or to predict a pCR. Dynamic Contrast Enhanced (DCE) sequences may improve the accuracy of MR restaging. Malignant tissue shows specific contrast-enhanced patterns due to the neoangiogenesis, resulting in elevated perfusion and permeability.[12] This may help in differentiating between malignant and non-malignant tissue. Unfortunately, adding DCE sequences did not improve accuracy of tumor restaging, CRM-involvement or predicting a pCR. The accuracy of Tumor staging (45%) was similar to other series without the addition of DCE sequences (34-60%).[13-18] Moreover, the accuracy of CRM-involvement was low and the radiologists were unable to detect a pCR. On the other hand, the accuracy of nodal staging was high. It is known that nodal staging after chemoradiotherapy is more accurate than at primary staging. This is caused by the lower prevalence of positive nodes, leading to a higher negative predictive value and thus a more accurate selection of the node negative patients after chemoradiotherapy.[19] Nonetheless, the accuracy of nodal staging in this study was high compared to other restaging studies. The fact early incomplete arterial phase enhancement was predictive for malignant nodes, makes DCE MR imaging promising for selecting patients for less radical surgery, such as Transanal Endoscopic Microsurgery (TEM) procedures. In TEM-procedures nodal staging is important to prevent local tumor regrowth due to positive lymph nodes, since a lymph node dissection is omitted in TEM procedures. Despite of the high accuracy of nodal staging, it is doubtful to carry out standard DCE MRI's in LARC restaging due to its poor accuracy of T- staging, CRM-involvement and predicting a pCR. MR imaging with extra DCE sequences is time-consuming and brings extra costs. The results of diffusion weighted (DW) MRI sequences are more promising. DW MRI has a sensitivity of 70% and a specificity of 98% in detecting a complete pathological response.[20] Future research should focus on the combining different MR techniques to increase restaging accuracy and on finding new tumor labeling agents to more accurately detect vital tumor. Furthermore, the optimal timing to perform restaging by MR imaging should be evaluated. It could be hypothesized that restaging shortly prior to surgery may improve diagnostic accuracy, because downstaging is an ongoing process after ending chemoradiotherapy.

Although the accuracy of local restaging after (chemo-)radiotherapy is generally poor, it is widely used as it seems to be a logical step in improving rectal cancer management. In line with local restaging, it also seems logical to restage by a thoraco-abdominal

CT-scan after chemoradiotherapy to detect distant metastases. Surprisingly, the number of studies concerning the effectiveness of local restaging are numerous, but studies assessing the usefulness of restaging by a thoraco-abdominal CT-scan after chemoradiotherapy are extremely rare. The chance of developing distant metastases is associated with the local tumor stage. LARC has the highest risk of developing distant metastases, since higher tumor and nodal stage are associated with distant metatases.[21-23] In LARC, the time interval between diagnosis and surgical resection is approximately 4 to 5 months. In this period occult metastases on primary imaging may become visible or new metastases may have evolved. Restaging could identify these patients. Our study found new metastases altering the treatment in 12% of the patients and surgery was cancelled in 8% of the patients. After publication of this study, other studies have reported their results of restaging to detect distant metastases during neo-adjuvant treatment. Even though new distant metastases were detected in all these studies, the reported percentages varied between 3 and 12%.[24-27] Some supported our findings concerning the usefulness of restaging to detect distant metastases[24]. However, others state that the yield was too low.[25,27] Davids et al.[25] found distant metastases in 5% of the restaged patients. Surprisingly, it did not lead to an alteration of the surgical plan. This is remarkable, as there are several options for patients with distant metastases opting for curation.[28] The fact that others studies did not find a beneficial effect of restaging by thoraco-abdominal CT-scan give room for a thought. Presumably, thoraco-abdominal restaging is only beneficial for patients with an advanced stage of disease. Our institute is a tertiary referral center for the Southwest region of Netherlands and this possibly explains the higher yield in our study compared to others studies with less advanced stage of disease. There are several well-known prognostic factors for developing distant metastases, such as T-, N-stage and extramural venous invasion.[21-23] These prognostic factors could identify patients at high risk for developing distant metastases during neo-adjuvant treatment. Future research should evaluate whether these prognostic factors are also applicable for the development of early distant metastases evolving during neo-adjuvant treatment. It would be interesting to develop a nomogram to select only those patients with a high chance of early metastases during neo-adjuvant therapy. This will save costs, radiation exposure and uncertainty concerning the curability of their disease.

Due to the fact that restaging is often common practice in most Western countries, it is important to critically appraise the benefit of local restaging. Theoretically, patients could be offered less radical surgery in case of tumor downstaging. However, as mentioned earlier, the accuracy of local restaging is poor.[1,11] Commonly, radiologists overstage rectal cancer after neo-adjuvant radiotherapy due to the difficulty to differentiate between viable tumor and fibrosis. However, 7-22% of the patients are understaged at restaging.[17,26,29] Surgeons should be cautious on performing less radical surgery based on

restaging imaging, as this could result in incomplete resections. Moreover, MR imaging is not able to detect microscopic remnants in radiotherapy induced fibrosis. Furthermore, it is important to realize that none of the Randomized Controlled Trials concerning the effect of chemoradiotherapy were able to demonstrate a significant increase in the rate of sphincter saving surgery.[30] This makes it even more doubtful to assume that restaging may contribute to less radical surgery when even chemoradiotherapy itself does not lead to less radical procedures. Momentarily, the 'watch and wait' is much debated as an option for patients with a complete clinical response. Unfortunately, MR imaging is unable to accurately identify patients with a complete clinical response.[31] However, when combining MR imaging with a digital examination and endoscopy, it leads to a probability of predicting a complete response of 98%.[32] This makes MR imaging an essential part of a set of examinations for a complete clinical response to be diagnosed. Restaging can be used as an early prognostic factor. Radiologically detected poor response is a strong prognostic factor for overall survival and disease free survival.[33] It should be evaluated whether these patients could benefit from a more intensified neo-adjuvant regime by adding an extra radiation boost or by adding induction chemotherapy after neo-adjuvant chemoradiotherapy. Furthermore, radiologically detected tumor response should be evaluated as a predictive factor for early distant metastases, since these patients may benefit from thoraco-abdominal restaging. Summarizing the current literature, there is limited evidence that local restaging is beneficial for patient or surgeon and there is conflicting literature that restaging by thoraco-abdominal CT-scan is useful to detect distant metastases. According to our data, restaging by thoraco-abdominal CT-scan is advisable.[34]

Even though rectal cancer management has improved drastically, patients remain with such advanced tumors, that complete resection is not possible. Incomplete resections are less common than 10 or 20 years ago due to the use of neo-adjuvant therapy and an improved surgical technique. However, CRM-involvement was still found in approximately 6% of the surgically treated patients in 2013 in The Netherlands.[35] Additionally, we are increasingly able to accurately select those patients at risk for incomplete resections. Intra-operative radiotherapy (IORT) may be beneficial when complete resection is not possible. IORT was first described in 1937.[36] Since the 1980s several institutes across the world published their experience with IORT.[37-39] The rationale behind IORT is that the biological equivalent of one single dose of IORT is two to three times higher than fractioned radiotherapy.[40] For example, an IORT dose of 10 Gy results in a biological equivalent of 20-30 Gy. This results in a total dose of 70-80 Gy when combined with a long course pre-operative radiotherapy of 50 Gy. This radiation dose cannot be achieved by external beam radiotherapy alone, since this would lead to extensive radiotherapy induced toxicity. The advantage of IORT is that an extra boost of radiotherapy can be administered at a specific area, while other radiotherapy sensitive structures, such as

small bowels, can be shielded from the radiotherapy. Previous studies have shown that IORT can be safely administered during surgery.[41,42] Although several studies suggested a beneficial effect of IORT on local control, comparative studies focusing on LARC and R1-resections are scarse. Our study suggests a beneficial effect on local control in patients with a microscopically involved CRM (tumor invading the resection planes on microscopic assessment), while no benefit was found in patients with a clear but narrow CRM (0.1-2mm). This finding is conform to previous studies from our institute.[43,44] The estimated 5-year local recurrence free survival of 84% in our study was higher than the local recurrence free survival rate of 65% reported in the previous study from our institute. This can be explained by the fact that our study only included R1-resections, while R2-resections were included in the previous studies as well. IORT is unlikely to be beneficial in R2-resections and these were therefore excluded from our analysis. Others studies have suggested a benefit of IORT on outcome, which is in line with our results,.[45,46] However, some did not find any evidence of a beneficial effect and skepticism about the effect of IORT remains.[47,48] Similar to our study, most published studies are retrospective with a relatively small amount of patients. This results in the lack of high level evidence of the benefit of IORT, making a future prospective randomized controlled trial necessary. Unfortunately, the accrual for such trial would be difficult. Since only R1-resections may benefit of IORT, solely 6% of all rectal cancer patients in the Netherlands would be candidates to participate in such trial. Moreover, results from retrospective studies indicate that it would be unethical to withhold IORT for patients with a R1-resection. Furthermore, incomplete resections are becoming less common due to the current high quality surgery.[35] Although our study focused on LARC, LRRC may also profit from IORT since incomplete resections are more frequent in LRRC surgery. Previously, others have found a benefit of adding IORT to the multimodality treatment compared to historical controls.[49]

Rectal cancer is a relatively common malignancy with approximately 3500 new patients in The Netherlands per year. However, there is a big difference between the treatment of the early stages of rectal cancer or the advanced stages of rectal cancer. Approximately 90% of the patients with rectal cancer are diagnoses with a cT1-3 stage.[50] These stages can be treated by a standard TME procedure. The treatment of the most advanced stage (cT4) is more difficult. Ingrowths into the surrounding structures are common in cT4 rectal cancer, such as prostate in men and vagina or uterus in women. In these cases exenterative 'beyond TME' surgery is often necessary to achieve complete resections.[51] These procedures are technically demanding and time consuming. Additionally, these procedures are accompanied by a high morbidity and a high post-operative complications rate.[52] Moreover, accurate high quality imaging is essential to determine the extent of the 'beyond TME-surgery'. These advanced stages may profit from a multidisciplinary team with experience in performing these radical surgical procedures. Our study

suggests a survival benefit for patients treated in high volume cT4 rectal cancer hospitals compared to low volume cT4 hospitals. This finding is in line with the results of studies of hospital volumes in other complex malignancies, such as pancreatic cancer and esophageal cancer.[53-55] However, in rectal cancer a survival difference according to the hospital volume has never been demonstrated. Although a recent study found a higher percentage of involved CRM's in low volume hospitals compared to high volume hospitals, a recent population based study for the Southern part of The Netherlands found no benefit of treatment of colorectal cancer in high volume hospitals.[50,56] The fact that we found a survival difference in contrast to other studies can be explained by that our study analyzed cT1-3 and cT4 separately. It is not naturally evident that experience in standard rectal cancer treatment also leads to sufficient experience for the treatment of the most advanced stages of rectal cancer. Our data suggests that cT4 rectal cancer should be considered as a separate entity within rectal cancer. Therefore, it would be more appropriate to apply a minimal number of cT4 rectal cancer patients treated per hospital annually than applying a minimal total number of rectal cancer patients per hospital.

The most appropriate approach for patients with stage IV colorectal with unresectable distant metastases is still under debate. It is clear that there is an indication for surgery in symptomatic patients. However, the indication is less clear in asymptomatic or mildly symptomatic patients. It could be hypothesized that surgery of the primary tumor will prevent future emergency surgery in case of obstruction or perforation during systemic therapy. Furthermore, some retrospective studies suggested a survival benefit when the primary tumor was resected.[57-59] However, these retrospective studies are limited due to selection bias. Patients in poor clinical condition were excluded for surgery, while relatively fit patients were selected for surgery. We assessed the current evidence for surgery of the primary tumor in patients with stage IV colorectal cancer. The lack of Randomized Controlled Trials, makes it difficult to conclude whether primary tumor resection leads to a survival benefit. Surgeons should take notice that systemic therapy will probably contribute the most to a prolonged survival in metastasized colorectal patients. Complications of primary tumor surgery will postpone the administering of systemic therapy.[60] For example, anastomotic leakage or surgical site infections will lead to a delay in the administering of systemic therapy. In addition, some patients will never be able to receive systemic therapy due to ongoing infectious complications. One of the most important goals of the treatment for incurable patients is to offer these patients the best possible quality of life. Surgery has a negative impact on quality of life up to 6 months after surgery.[61] The median survival of stage IV colorectal cancer patients in The Netherlands is only 12 months.[62] This median survival can be prolonged up to 22 months in patients who are in a good clinical condition due to the current systemic therapy.[63-65] Nevertheless, this means that these patients suffer a loss of quality of life caused by the surgical treatment during a substantial period of their life expectancy. Additionally,

complications after surgery have a long-term negative impact on the patients' quality of life.[66] Obstructive complications or tumor perforation during palliative systemic therapy are arguments to perform surgery. However, the chance of emergency surgery with the current systemic therapy is limited.[60,67,68] Nevertheless, high level of evidence is warranted to offer these patients the best treatment. Several Randomized Controlled Trials are recruiting patients, such as the SYNCHRONOUS trial[69], the CAIRO4 trial[70] and a Korean multicenter trial.[71] We are awaiting the results of these trials and hopefully, these studies will provide us the answer if we should perform primary tumor resection in case of unresectable distant metastases.

The introduction of TME and neo-adjuvant (chemo-)radiotherapy reduced the number of patients with a local recurrence after rectal cancer surgery. However, the introduction of these advancements also introduced the problem of treating LRRC after TME-surgery and radiotherapy. LRRC has a poor overall survival, a great impact on quality of life and often leads to severe pain with fistulating and bleeding tumors.[72,73] Surgical resection provides the greatest probability on durable overall survival and local control.[74] Unfortunately, TME surgery and neo-adjuvant radiotherapy makes surgical resection of the local recurrence more demanding. The dose of radiotherapy for the local recurrence is limited due to the previous pelvic radiotherapy and the use of TME surgery is causing that the local recurrences are no longer confined to an anatomic compartment. In agreement with most other studies, our results show that these local recurrences can be treated with acceptable overall survival and local re-recurrence rates. However, the complete resection rate seems to be lower in previously irradiated patients. Although this did not result in a higher re-recurrence rate in our series, others have reported higher re-recurrence rates in previously irradiated patients.[75,76] A recent study showed also a poorer overall survival and a higher complication rate in previously irradiated patients.[77] However, that study particularly did not administer re-irradiation to previously irradiated patients. This may explain the fact that our study did not find a survival difference while they did. The results of our study were in line with a previous study from our institute.[78] Although the local control rate in the previous study was poorer, the 3-year overall survival rate of the current and previous study were similar. Presumably, the results of the previous study led to a more thorough patient selection for LRRC surgery. Thorough patient selection is an important aspect of LRRC treatment, as morbidity and mortality rates of LRRC surgery are high.[77,79-81] However, if the selection of patients is too strict, an opportunity for curation for these patients may be suppressed. The selection of patients is one of the most important explanation of the overall survival differences of LRRC surgery reported in the literature. Re-irradiation might contribute to an improved outcome after LRRC surgery in a previously irradiated area.[75] The main goal is to induce tumor downstaging and to improve local control. However, it also provides an opportunity to restage these patients after the end of re-irradiation. Major abdominal surgery can be

spared in patients with a progressive local recurrence during re-irradiation or in patients who have developed distant metastases during re-irradiation. This could result in an improved patient selection for LRRC surgery. Future research in LRRC treatment should focus on achieving higher numbers of complete resections. For example, patients can be offered induction chemotherapy prior to neo-adjuvant therapy to maximize the chance of a complete resection. Others have demonstrated promising results of LRRC surgery after induction chemotherapy.[82]

In LRRC surgery, a complete resection is the most important prognostic factor. Generally, resections in LRRC surgery are classified as R0-resections (complete resections), R1-resection (microscopically involved margins) or R2-resections (macroscopically involved margins). In this thesis, we have demonstrated that the minimal tumor-free resection margin is of prognostic value. In line with primary rectal cancer, we found a superior oncological outcome after surgery with wide tumor-free resection margins of more than 2mm.[23,83,84] Sampling error may be a possible explanation for this phenomenon. For example, patients with close resection margins may actually have microscopically involved margins at another location. Another explanation may be that close margins are accompanied by a higher chance of tumor deposits outside the resected area. Nevertheless, the resection margin classification in our study could be used as an alternative for the currently used standard R0/R1/R2 classification of LRRC's. In the current study, more radical procedures were not associated with a survival benefit. Ideally, the surgical procedure should be as minimal as possible. To determine the optimal approach and extensiveness of the surgical procedure accurate staging is essential. Unfortunately, the accuraracy of staging of the local recurrence is limited due to the difficulty of differentiating between tumor and fibrosis. This is similar to the difficulties seen in the restaging of LARC after (chemo-)radiotherapy. In the future, fluorescence guided surgery may be helpful to achieve a higher number of complete resections in LRRC surgery. It may help to distinguish between viable tumor and scarring or fibrosis. In several other malignancies, fluorescence guided surgery has already been evaluated and has shown to a potential benefit in some cases.[85,86] Further investigation concerning the use of fluorescence guided surgery is needed in LARC and LRRC patients.

Unfortunately, approximately 60 to 70% of the diagnosed patients are not suitable candidates for surgical treatment due to distant metastasis or local recurrence that is too extended.[87,88] These patients should be offered palliative care. Pelvic radiotherapy can relief pain in a high number of symptomatic patients.[89] In case of metastasized disease, patients can be offered systemic therapy. However, the effect of palliative chemotherapy on local symptoms and overall survival is not well established. Furthermore, the widespread use of pelvic radiotherapy may have a negative impact on the effectiveness of systemic therapy on the local recurrence. Our results showed that the response of the local recurrence in previously irradiated area was less than the distant metastases

outside the irradiated area. This suggests that the effect of chemotherapy with palliative intent for symptomatic LRRC may be limited. However, the effect of chemotherapy on overall survival in LRRC remains unclear. The overall survival of the patients in this cohort treated with systemic therapy was 33 months, while the median survival of metastasized colorectal cancer is 22 months in trials with highly selected patients. [64] This suggests that systemic therapy in metastasized LRRC patients may be effective. However, the patients in our study were highly selected. It should also be realized that this study focused on LRRC in previously irradiated area, while the effectiveness of chemotherapy on the local recurrence in patients without previous radiotherapy is not fully established. Future research should focus on the potential benefit of systemic therapy on overall survival in LRRC patients and to evaluate the response of systemic therapy on the local recurrence without previous pelvic radiotherapy.

LRRC is a relatively uncommon and unknown disease for physicians worldwide and in the Netherlands.[2,90] As this thesis pointed out, there is a chance for cure in dedicated hospitals. Therefore, it is necessary to refer all LRRC patients to one of the dedicated referral centers in the Netherlands. By referring a higher number of LRRC patients to these centers, the experience of the surgeons will be extended, leading to improved results and this will provide the opportunity to perform high quality research for these patients suffering from this relative rare disease. Simultaneously, performing high quality research will provide us more necessary data on the quality of life of patients treated curatively by surgery and palliatively by radiotherapy or systemic therapy.

In summary, this thesis aimed to further improve the multimodality treatment of LARC and LRRC by focusing on several aspects of the treatment. Restaging by a thoraco-abdominal CT-scan after (chemo-)radiotherapy, applying IORT in R1-resections and performing cT4 rectal cancer surgery in high cT4 volume hospital seems to improve LARC treatment. In LRRC, applying a minimal tumor-free resection margin and considering patients with LRRC after previous radiotherapy and TME surgery candidates for LRRC surgery seem to improve LRRC treatment. The accurate selection of the most suitable treatment is the most important challenge in LARC and LRRC treatment. This means that imaging plays a key role in the multimodality treatment. Improving imaging quality will result in a more accurate selection of patients to administer neo-adjuvant treatment, applying IORT and more radical surgery.

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Chapter 13

Summary
Samenvatting
Portfolio
Dankwoord
Curriculum Vitae

Summary

The treatment of rectal cancer has drastically improved the last decades. The three main advancements made, are the improvement of the quality of imaging, the use of neo-adjuvant therapy and a surgical technique, called total mesorectal excision (TME). Locally advanced rectal cancer (LARC) comprises a difficult to manage subgroup due to a high chance of an incomplete resection and subsequently high recurrence rates and a poor overall survival. In line with LARC, locally recurrent rectal cancer (LCCR) is a challenging group to treat. It is a heterogenetic disease with a poor prognosis and often disabling symptoms. Surgery is the only chance on durable local control and overall survival. Unfortunately, surgery is accompanied by significant morbidity and high recurrence rates. A multimodality treatment has increased the chance for cure for LARC and LRRC. Historically, the outcome of the surgical treatment was poor. However, optimal staging, neo-adjuvant (chemo-)radiotherapy and personalized surgical procedures have resulted in improved outcomes. This thesis aimed to further improve staging, multimodality treatment and surgical treatment of LARC and LRRC.

In **chapter 1**, the current management of rectal cancer and the advancements made in the last decades are outlined. Additionally, the aims of the studies included in this thesis are outlined.

In **chapter 2,** we aimed to improve the accuracy of local staging by adding dynamic contrast enhanced (DCE) sequences to standard MR imaging after neo-adjuvant chemoradiotherapy. DCE may improve the ability to distinguish between viable tumor and non-malignant fibrosis. Unfortunately, adding DCE did not result in more accurate tumor staging, determining CRM involvement or detecting a complete pathological response. On the other hand, the accuracy of nodal staging was high, making it potentially useful in the current era of rectal sparing treatment and 'watch and wait' approach.

In **chapter 3,** we evaluated the additional value of restaging after a long course (chemo-)radiotherapy by thoraco-abdominal CT-scan in patients with LARC. LARC represent a subgroup of patients with a high chance of developing distant metastasis. The identification of distant metastases is important, as it may alter the treatment strategy. A change in treatment strategy due to new findings on the CT scan after radiotherapy was observed in 18 (12%) of 153 patients. Twelve patients (8%) were spared rectal surgery due to progressive metastatic disease. The makes restaging by thoraca-abdominal CT-scan a worthwhile step in LARC management.

In **chapter 4,** we briefly summarized the benefits and limitations of local restaging after neo-adjuvant therapy. Unfortunately, the accuracy of restaging is poor. Currently, these accuracies of restaging are too poor to alter your surgical plans. The main concer is the chance of understaging of the local tumor, which occurs in 7-22% of the patients. This may lead to incomplete resections and poor oncological outcomes Radiological detected response to (chemo-)radiotherapy on MR imaging appears to be a valuable early prognostic factor and the accuracy of predicting mesorectal fascia involvement is reasonable. Future research should focus on intensifying neoadjuvant treatment in poor responders and increasing the staging accuracy by combining different techniques.

In **chapter 5,** we evaluated the potential benefit of intra-operative radiotherapy (IORT) after neo-adjuvant (chemo-)radiotherapy in patients with LARC. A single intra-operative radiation dose may be able to eradicate microscopic remnants. This retrospective analysis compared the outcome of patient treated with or without IORT. In patients with clear but narrow margins, IORT did not lead to an improved local recurrence-free survival. However, in patients with a microscopically incomplete resection, adding IORT did result in an improved local recurrence-free survival (84% vs. 41%). This suggests that IORT improves local recurrence-free survival in patient with microscopically involved circumferential resection margins.

In **chapter 6,** we hypothesized that hospital volume was associated with outcome after rectal cancer surgery. The management and treatment of cT4 rectal cancer is considered more difficult than the earlier stages of rectal cancer (cT1-3). LARC requires optimal staging, multimodality treatment and often personalized 'tailor made' surgery. Therefore, a survival difference may be more apparent in cT4 rectal cancer. In this population based study, we divided rectal cancer into a cT1-3 or a cT4 group and evaluated the long-term outcome according to the cT1-3 hospital volume or the cT4 hospital volume. In cT1-3 rectal cancer, hospital volume was not associated with overall survival. In cT4 rectal cancer, treatment in a high cT4 hospital volume (more than 20 cT4 procedures per year) was associated with a superior overall survival rates compared to the treatment in a low volume cT4 hospital after adjusting for patient and tumor variables. Furthermore, we analyzed the referrals patterns of cT4 rectal cancer within The Netherlands. Unfortantely, cT4 rectal cancer patients are often referred incorrectly, regardless of the advice in the national guideline to refer these patients to dedicated tertiary centers.

In **chapter 7,** we evaluated the effect of surgery for the primary tumor in stage IV colorectal cancer patients with unresectable metastases. Several studies suggested a beneficial effect of primary tumor resection on overall survival. This review summarized the available literature of the effect of surgery on the outcome in stage IV patients.

However, the role of resection of the primary tumor remains unclear. Randomized Controlled trials are lacking and this makes it difficult to draw conclusions. With the current new chemotherapy regiments, including VEGF and EGF inhibitors, a relatively low number of patients with metastasized colorectal cancer require surgery for their primary tumor. The studies who are suggesting a survival benefit are likely to be influenced by selection bias and therefore prospective randomized controlled trials are urgently needed to answer this question.

In **chapter 8,** we focused on the treatment of locally recurrent rectal cancer (LRRC) after previous pelvic radiotherapy and TME surgery. TME surgery leads to local recurrences that are not confined to an anatomical compartment and neo-adjuvant radiotherapy for the primary tumor limits the dose available for the treatment of the local recurrence. This study evaluated the peri-operative outcomes and long-term outcome of patients treated after previous TME surgery with or without radiotherapy for the primary tumor. The long-term outcome, complication rate and mortality rate were similar in both groups. This demonstrates that surgery in highly selected patients is feasible and that these patients should be considered candidates for curative multimodality treatment and surgery.

In **chapter 9**, we evaluated the prognostic factors affecting the long-term outcome after LRRC surgery. It is well known that the resection margin status is the most important prognostic factor after LRRC surgery. In primary rectal cancer, patients with close margins have a higher risk of developing local recurrences. We hypothesized that close margins in LRRC surgery may result in poorer oncological outcomes as well. In this study, we have evaluated the long-term outcome according to the minimal resection margin. We found that close margins of less than 2mm were associated with a poorer outcome than patients with wide resection margins of more than 2mm. This finding makes that all efforts should be made to achieve wide resection margins by neo-adjuvant downstaging and the use of radical surgery when necessary.

In **chapter 10**, we focused on the systemic therapy in the treatment of patients with LRRC. Some patients with LRRC with distant metastases are treated with systemic therapy to increase their life expectancy. This made it possible to evaluate the effect of systemic therapy on the local recurrences in previously irradiated area compared to the response of distant metastases outside the irradiated area. Previous radiotherapy may result in poorer response rates due to fibrosis and impaired vascularization. This study found a lower response rate of the local recurrence in previously irradiated area according to the radiological RESIST criteria. The poor response in previously irradiated makes it questionable whether systemic therapy is suitable for local palliation and whether neo-adjuvant induction therapy for LRRC may be useful.

In **chapter 11,** we summarized the latest literature of the treatment of LRRC for the Dutch physicians. Currently, multimodality treatment and surgery gives a chance for cure to patients who were considered incurable 2 to 3 decades ago. Even patients who underwent TME surgery and previous radiotherapy should be considered candidates for curative treatment. However, LRRC surgery is accompanied by significant morbidity and relative high mortality rates. Unfortunately, the majority of the patients are diagnoses with metastatic disease or a too extensive local recurrence. These patients should be offered optimal palliative treatment. Untreated LRRC leads often to disabling symptoms and severe pain. Pelvic radiotherapy can bring local symptom relief in approximately 75% of the patients. Unfortunately, the duration of the effect of radiotherapy is limited.

Nederlandse samenvatting

De behandeling van het rectumcarcinoom is de afgelopen decennia sterk verbeterd. Hoofzakelijk zijn er drie factoren verantwoordelijk voor deze verbetering, namelijk een verbeterde kwaliteit van de beeldvorming, pre-operatieve behandeling met (chemo-) radiotherapie en een optimale gepersonaliseerde chirurgie. Het lokaal voortgeschreden rectumcarcinoom omvat een subgroep binnen het rectumcarcinoom, waarbij de behandeling lastiger en uitdagender is vanwege de kans op een irradicale resectie en de hierbij behorende hogere kans op een lokaal recidief. Evenals het lokaal voortgeschreden rectumcarcinoom is de behandeling van het lokaal recidiverend rectum carcinoom zeer uitdagend. Een multimodaliteitsbehandeling voor het voortgeschreden rectum carcinoom en het lokaal recidiverend rectumcarcinoom heeft de kans op curatie vergroot. Van oudsher was de kans op curatie bij beide aandoeningen slecht. Optimale beeldvorming en stagering, neoadjuvante behandeling leidend tot tumorverkleining en gepersonaliseerde chirurgie, inclusief uitgebreide chirurgische procedures, heeft geresulteerd in een sterk verbeterde oncologische uitkomst. Dit proefschrift heeft als doel om verschillende aspecten van de multimodaliteitsbehandeling te analyseren en te verbeteren.

In **hoofdstuk 1** zetten we de verschillende onderzoeksvragen en onderbouwing uiteen waar de verschillende hoofdstukken van dit proefschrift een antwoord op probeert te geven.

In **hoofdstuk 2** hebben we geëvalueerd of het toevoegen van dynamische contrast series bij een standaard MRI onderzoek na het toedienen van neo-adjuvante (chemo-) radiotherapie, de accuratesse van tumor, lymfeklier stagering en het voorspellen van complete respons kan verbeteren. Uit dit onderzoek bleek dat het toevoegen van deze series niet leidt tot verbeterde lokale tumor stagering of het voorspellen van een complete pathologische respons. Aan de andere kant lijkt het toevoegen van dynamische contrast series wel tot een meer accurate beoordeling van de lymfklier status. Dit kan mogelijkheden bieden in de huidige periode, alwaar we de mogelijkheden van 'watch and wait' procedure of rectumsparende chirurgie na neo-adjuvante therapie aan het onderzoeken zijn.

In **hoofdstuk 3** hebben we de toegevoegde waarde bekeken van herstagering na een lang schema (chemo-)radiotherapy door middel van een thoraco-abdominale CT-scan. Patiënten met een lokaal voortgeschreden rectumcarcinoom hebben de hoogste kans op het ontwikkelen van afstandmetastasen. Gedurende de neo-adjvante periode die ongeveer 4-5 maanden kan duren, kan het van toegevoegde waarde zijn om te beoordelen of deze patiënten afstandsmetastasen hebben ontwikkeld. Uit deze studie

bleek inderdaad dat 12% van de patiënten (progressieve) afstandmetastasen ontwikkelde en dat leidde zelfs in 8% van de patiënten in de beslissing om geen rectumchirurgie meer uit te voeren. Dit maakt het herstageren door middel van een thoraco-abdominale CT-scan een zeer waardevolle stap in de behandeling van het lokaal voortgeschreden rectumcarcarinoom.

In **hoofdstuk 4** hebben we uiteengezet wat de beperkingen en uitdagingen zijn van het lokaal herstageren van het rectumcarcinoom na neo-adjuvante (chemo-)radiotherapie. Helaas is de accuratesse van de stagering van de tumor na (chemo-)radiotherapie slecht. Deze accuratesse is nu nog te laag om hier je behandelplan op aan te passen. Het gevaar van onderstageren is te groot en dit heeft mogelijk grote consequenties, omdat dit kan leiden tot irradicale resecties. Herstageren met MRI is wel een belangrijk onderdeel van het beoordelen van een complete klinische respons, maar slechts als onderdeel van meerdere onderzoeken. Aan de andere kant is de respons van het rectumcarcinoom op chemoradiotherapie gemeten op MRI wel een zeer vroege en accurate prognostische factor. Dit kan in de toekomst mogelijk gebruikt worden om de behandeling te intensiveren bij patiënten met een slechte respons op (chemo-)radiotherapie. Daarnaast is de accuratesse om betrokkenheid van de mesorectale fascie te beoordelen redelijk.

In **hoofdstuk 5** hebben we naar het mogelijke effect gekeken van het toepassen van intra-operatieve radiotherapie (IORT) bij patiënten met krap radicale of microscopisch irradicale resecties. Het toedienen van zo'n intra-operatieve radiotherapie dosis kan mogelijk microscopische overblijfselen neutraliseren. Deze retrospectieve studie toont aan dat IORT bij patiënten met een krap radicale resectie de lokale controle niet lijkt te verbeteren. Echter bij patiënten met een microscopische irradicale resectie is de lokale controle significant beter bij de patiënten die behandeld zijn met IORT in vergelijking bij patiënten bij wie per ongeluk geen IORT is toegepast. Dit suggereert dat IORT de kans op een lokaal recidief bij microscopische irradicale resecties kan verminderen.

Hoofdstuk 6 is gebaseerd op de hypothese dat het ziekenhuis volume bij de behandeling van het rectumcarinoom van invloed is op de oncologische uitkomsten. De behandeling van het lokaal voortgeschreden rectumcarcinoom (cT4) is complexer en chirurgisch lastiger dan de behandeling van de meer vroegere stadia (cT1-3) van het rectumcarcinoom. Het voortgeschreden rectumcarcinoom behoeft een multimodaliteitsbehandeling met optimale stagering en beeldvorming om zodoende tot het beste oncologisch resultaat te komen. Wij hebben de cT4 rectumcarcinomen en de cT1-3 rectumcarcinomen afzonderlijk van elkaar geanalyseerd in een Nederlandse populatie database. In cT1-3 rectumcarcinomen was het cT1-3 ziekenhuisvolume niet geassocieerd met de overleving. In cT4 rectumcarcinomen was een hoog

cT4 ziekenhuisvolume wel geassocieerd met een betere overleving in vergelijking met ziekenhuis met een laag volume met cT4 rectumcarcinomen. Dit was dan wel gecorrigeerd voor patiënt en tumorkarakteristieken. Daarnaast hebben we de verwijzingen binnen Nederland van cT4 rectumcarcinomen geanalyseerd en hieruit bleek dat patienten regelmatig niet juist worden doorverwezen, ondanks de adviezen in de Nederlandse richtlijnen.

In **hoofdstuk 7**, hebben we een literatuurstudie gedaan naar het effect van chirurgie van het primaire colorectaal carcinoom op de overleving bij patiënten met een stadium IV ziekte en irresectabele afstandsmetastasen. Verscheidene studies hebben een positief effect op overleving aangetoond. Dit review toont aan dat de rol van resectie nog steeds onduidelijk is, omdat er geen gerandomiseerd onderzoek beschikbaar is. Daarnaast komt er met de huidige nieuwe systemische therapie maar een heel klein gedeelte van de patiënten in aanmerking voor (spoed) chirurgie van de primaire tumor wegens klachten. Desondanks suggereren de meeste studies een overlevingswinst bij resectie van de primaire tumor.

In **hoofdstuk 8** hebben we ons toegespitst op het lokaal recidiverend rectumcarcinoom. We hebben specifiek gekeken naar de uitkomst van een lastig te behandelen subgroep van het lokaal recidiverend rectumcarcinoom na totale mesorectale excisie en radiotherapie. TME leidt tot lokaal recidieven die niet gelimiteerd zijn tot een specifiek anatomisch compartiment omringd door een fascie. Neo-adjuvante radiotherapie voor de primaire tumor leidt tot een beperktere beschikbare radiotherapie dosis voor de behandeling van het lokale recidief. Deze studie heeft de peri-operatieve resultaten en lange termijn resultaten van het lokaal recidiverend rectumcarcinoom na TME chirurgie met of zonder eerdere radiotherapie voor de primaire tumor met elkaar vergeleken. De resultaten toonden aan dat de lange termijn oncologische uitkomst hetzelfde was en dat er ook dat er geen significant verschil was in het aantal complicaties percentage. Dit houdt in dat ook deze specifieke groep ook in opzet curatief behandeld moet worden met een multimodaliteitsbehandeling en chirurgie.

In **hoofdstuk 9** hebben we de prognostische factoren na de chirurgische behandeling van het lokaal recidiverend rectumcarcinoom geëvalueerd. Het is bekend dat de resectiemarge de belangrijkste prognostische factor na chirurgie van het LRRC is. In het primaire rectumcarcinoom leiden echter niet alleen daadwerkelijke irradicale resecties tot een slechtere prognose, maar ook een krap radicale hebben een slectere uitkomst. Deze studie heeft geanalyseerd of een krap radicale resectie (≤2mm) leidt tot een oncologische slechtere uitkomst dan een ruim radicale resectie van meer dan 2 mm. Uit deze studie blijkt dat in overeenstemming met met het primaire rectumcarcinoom

dat krap radicale resecties leiden tot een oncologisch slechtere uitkomst. Dit toont het belang aan van een ruim radicale resectie. Dit kan bereikt worden door middel van neo-adjuvante inductie behandeling en indien noodzakelijk uitgebreide radicale multiviscerale chirurgie

In **hoofdstuk 10** is het effect van systemische therapie op de behandeling van het lokaal recidiverend rectumcarcinoom geanalyseerd. In enkele gevallen zijn patiënten met een lokaal recidiverend rectumcarcinoom met afstandsmetastasen behandeld met systemische therapie. Dit maakte het mogelijk om het effect van systemische therapie op het lokale recidief in al eerder bestraald gebied te beoordelen en dit te vergelijken met afstandmetastasen buiten dit bestraalde gebied. De eerdere radiotherapie maakt het effect van chemotherapie mogelijk minder effectief door de aanwezigheid van fibrose en een mogelijk verminderde vascularisatie van dit gebied. Deze studie toont inderdaad een lagere respons van het lokale recidief aan in vergelijking met de afstandmetastasen buiten het bestraalde gebied. Deze slechte respons maakt het discutabel of systemische therapie zinvol is als palliatie. Daarnaast maakt dit het twijfelachtig of systemische therapie als inductietherapie zinvol is.

In **hoofdstuk 11** hebben we de meest recente literatuur van de behandeling van het lokaal recidiverend rectumcarcinoom beoordeeld en samengevat voor de Nederlandse beroepsbeoefenaar. Een multimodaliteitsbehandeling kan tegenwoordig leiden tot genezing. Dit is in tegenstelling tot een jaar of 25 geleden toen al deze patiënten ongeneesbaar werden geacht. Zelfs patiënten die eerder TME chirurgie en radiotherapie hebben ontvangen zijn mogelijke kandidaten voor een curatieve chirurgische behandeling. Helaas is de meerderheid van de patiënten niet geschikt voor chirurgische behandeling. Dit komt vanwege de aanwezigheid van afstandsmetastasen of een te uitgebreid lokaal recidief. Deze patiënten dienen optimaal palliatief behandeld te worden, vanwege de zeer invaliderende en hevige pijn die vaak geassocieerd is met een lokaal recidief. Radiotherapie is hier het meest geschikt voor. In ongeveer 75% van de patiënten geeft radiotherapie vermindering van de klachten. Helaas is de duur van deze palliatie beperkt.

PhD Portfolio

1. PhD training	**TOTAL:**	**31.9 ECTS**
General courses	Year	Workload
- Biomedical Enlish Writing and communication	2013	3 ECTS
- Good Clinical Practice (GCP)	2013	1 ECTS
- Basic introduction Course SPSS	2013	1 ECTS
- Biostastics for clinicans	2013	1 ECTS
Specific Courses		
- ANIOS surgery ikazia ziekenhuis	2013-2014	
Seminars and workshops		
- Fundamental Critical Care Support (*FCCS*)	2015	1 ECTS
Presentations		
National conferences		
- NVvH chirurgendagen	2012	1 ECTS
- NVvH chirugendagen	2013	1,5 ECTS
- NVvH Chirugendagen	2014	1,5 ECTS
- NVvH najaarsdagen	2013	2 ECTS
- Wetenschapsdag Erasmus MC	2014	1 ECTS
- Daniel den Hoed Wetenschapsdag	2014	1 ECTS
International conferences		
- ESMO World Congress on Gastrointestinal Cancer	2013	2 ECTS
- ECCO European Cancer Congress	2014	2 ECTS
Attendence (inter)national conferations		
- NVvH chirurgendagen	2012-2017	3.6 ECTS
- NVvH najaarsvergadering	2012-2017	1.8 ECTS
- ESMO World Congress on Gastrointestinal Cancer	2013	1.2 ECTS
- ECCO European Cancer Congress	2014	1.3 ECTS
2. Teaching		
Supervising practicals and excoursons, tutoring		
- Basic life support examintor	2014	1 ECTS
- Supervising Master's theses	2014	2 ECTS
- Clinical teaching medical students (klinisch redeneren)	2013-2014	2 ECTS

Dankwoord

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Curriculum Vitae

Wijnand Jochem Alberda werd op 6 november 1983 geboren in Rotterdam. Hij groeide op in Krimpen aan den IJssel, alwaar hij onder de rook van Rotterdam in Capelle aan den IJssel in 2002 zijn atheneum diploma behaalde. Direct hierna werd hij helaas uitgeloot voor de studie geneeskunde waardoor hij 1 jaar economie en business administration heeft gestudeerd aan de Erasmus Universiteit in Rotterdam.

In 2003 werd hij alsnog ingeloot voor Geneeskunde waar hij uiteindelijk in 2010 zijn arts-examen heeft behaald. Gedurende de studie werkte hij als Forgeron op de Spoed Eisende Hulp in het Ikazia Ziekenhuis, waar zijn interesse voor het vak Heelkunde werd geboren. Zijn interesse werd verder aangewakkerd doordat hij na het behalen van zijn arts-examen in 2010 als ANIOS startte in het Ikazia Ziekenhuis op de afdeling heelkunde (opleider P.T. den Hoed)

Gedurende zijn ANIOS-schap kwam hij in contact met Prof. Verhoef en dr. Burger. Deze boden hem de kans om een promotietraject in de Daniel den Hoed kliniek in Rotterdam te starten. Eind 2012 startte hij aan zijn promotie onderzoek wat hij het eerste jaar combineerde met diensten als ANIOS in het Ikazia Ziekenhuis. In zijn compensatietijd had hij zo de kans de basis voor dit proefschrift te leggen. Na 1,5 jaar full time onderzoek te hebben gedaan mocht hij in juni 2014 starten aan zijn opleiding tot chirurg. Hij begon zijn eerste jaar in het Erasmus MC (opleider B. Wijnhoven), waarna hij in 2015 terug mocht komen op het oude nest in het ikazia ziekenhuis waar hij tot op heden zeer blij is met de keuzes die hij heeft gemaakt.

Hij woont met veel plezier in Rotterdam met zijn vriendin Nathalie Roost en zijn zoon Max (24-8-2016).