BEYOND THE MARGINS
OF RECTAL CANCER TREATMENT
PUSHING BOUNDARIES IN ADVANCED STAGES

JAN MAARTEN VAN REES

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Pushing boundaries in advanced stages

Jan Maarten van Rees

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Beyond the Margins of Rectal Cancer Treatment

Pushing boundaries in advanced stages

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INTRODUCTION

CHAPTER 1

General introduction and outline of this thesis

Parts of this chapter are adapted from: '*The incidence, treatment and survival of patients with rare types of rectal malignancies in the Netherlands: A population-based study between 1989 and 2018*'
***van Rees JM**, Elferink MAG, Tanis PJ, de Wilt JHW, Burger JWA, Verhoef C*
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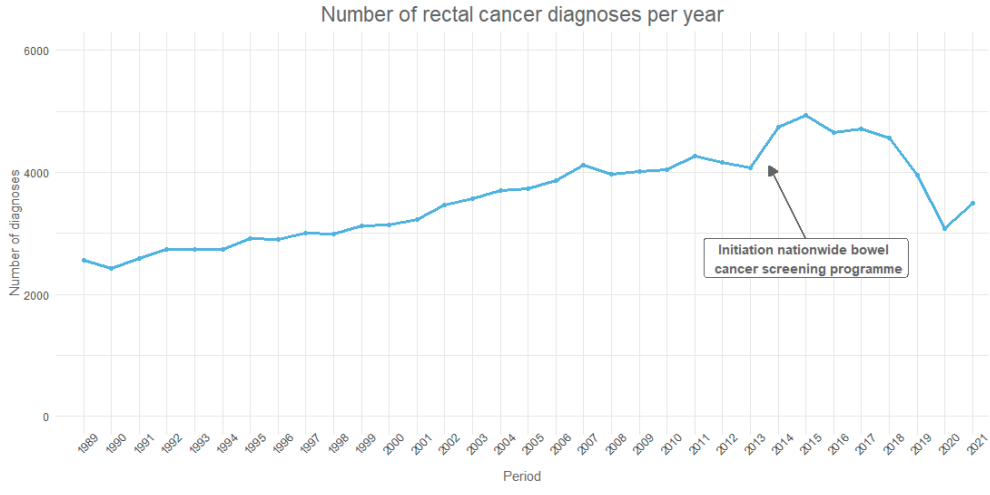
INTRODUCTION

Colorectal cancer is one of the most common types of cancer in the Western world, and was responsible for 9% of all cancer-related deaths in 2022.(1) Rectal cancer accounts for approximately one third of the cases of colorectal cancer. Unlike the amalgamated term "colorectal cancer" suggests, colon and rectal cancer are two different entities. Discriminating between the two diseases is important, because treatment methods differ considerably.

In the Netherlands, approximately 3500 patients per year are diagnosed with rectal cancer, although the incidence has decreased because of the nationwide bowel cancer screening programme that was implemented in 2014.(2) Initially, higher incidence rates of rectal cancer were observed in the years 2014, 2015 and 2016, and this was followed by a decrease in incidence the years thereafter. This is congruent with the hypothesis that screening will eventually reduce the incidence of cancer due the detection and resection of premalignant lesions before invasive cancer can occur.(3) Currently, the decreasing trend in incidence in rectal cancer appears to have reached a plateau in the Netherlands, and the Dutch Cancer Registry (NCR) expects a slow increase in the colorectal cancer incidence in the coming years.(2) The incidence of rectal cancer in the period of 1989-2021 in the Netherlands is shown in Figure 1.

Figure 1. Number of rectal cancer diagnoses per year in the Netherlands



The vast majority of rectal malignancies, around 97.5%, is histologically classified as "adenocarcinoma", and originate from intestinal epithelial cells with glandular origin.(4) The remaining, less common types of rectal malignancies include neuro-endocrine tumours (NET), sarcoma, lymphoma, melanoma and squamous cell carcinoma (SCC). These malignancies may all be located in the rectum, but have important differences in histology, disease behaviour and prognosis. These specific diseases require different treatment approaches. This thesis focuses on rectal adenocarcinoma.

Management of rectal cancer is challenging, and is reflected by the lack of international consensus on how to optimally treat this disease. All over the world, treatment methods are continually evolving and the use of various treatment modalities differs per country. Although marked improvements have been made in the management of rectal cancer in the past few decades, the disease burden of rectal cancer in the advanced stages remains high up until today. The scope of this thesis is to investigate the multimodality treatment of locally advanced, locally recurrent, and stage IV rectal cancer.

Locally advanced rectal cancer

About 10% of rectal cancer patients present with tumours that extend to, or invade the mesorectal fascia.(5, 6) These patients have locally advanced rectal cancer (LARC). Patients with LARC are treated differently compared to patients with lower staged tumours (clinically staged T1-3N0). Most importantly, a standard total mesorectal extension (TME) for tumours that involve the mesorectal fascia may not be sufficient to achieve clear resection margins. In these patients, more aggressive approaches for complete tumour resection are required, and may consist of the removal of surrounding tissues, such as bone, muscle, nerves, vascular structures or even adjacent organs, for example the bladder or the reproductive organs. Intra-operative radiotherapy (IORT) might be administrated when one of the resected margins is still considered at high risk for microscopic tumour remnants after removal of the specimen.(7, 8)

Another important difference in the treatment strategy of LARC compared to non-LARC, is the utilisation of concomitant chemotherapy and radiotherapy in the neoadjuvant setting, which is referred to as chemoradiation.(9) The rationale behind chemoradiation is to induce tumour shrinkage, and thereby improve the chance of a complete resection (R0), and to decrease the local recurrence rate. Chemoradiation prior to surgery is considered standard of care for patients with LARC.(10, 11) Current research in LARC focuses on various other neoadjuvant treatment schemes, such as oxaliplatin based systematic chemotherapy prior to, or after, (chemo-)radiotherapy. These schedules have demonstrated promising results in terms of downstaging and complete response rates, but it should be noted that these improvements are at the cost of increased toxicity.(12-14)

Moreover, no improvement in overall survival has been gained with these intensified schemes, as compared to the standard chemoradiation treatment only.(12, 15-17)

Locally recurrent rectal cancer

Despite optimisation of primary rectal cancer treatment, for example chemoradiation for high-risk rectal cancer and short-course radiation therapy for lower stages, local recurrences in the pelvic area still occur in 5-10% of curatively treated patients.(9, 10, 18) These patients have locally recurrent rectal cancer (LRRC). Patients with LRRC usually have tumours with more aggressive behaviour, and chances for cure are low.(19, 20) Treatment of LRRC depends on resectability and whether or not (extensive) distant metastases are present. The cornerstone for LRRC without metastases is radical surgical resection (R0). This usually requires the resection of adjacent organs and structures.(21-24) As in primary advanced rectal cancer, neoadjuvant treatment plays an important role in downstaging of the tumour, and increases the chance of a complete resection.(22, 23, 25, 26) Two phase III randomised controlled trials, PelvEx II (NCT 04389088) and GRECCAR 15, are currently investigating the role of induction systemic chemotherapy and chemoradiation as pre-operative strategy.(27, 28)

AIM OF THIS THESIS

The aim of this thesis is to further improve the multimodality management of advanced stages of rectal cancer, and focuses especially on those patients with rectal cancer that is beyond the “ordinary” limits of the disease. Management of advanced disease is difficult, as it is questionable whether curative treatment is still possible, and what strategy should be preferred. The long-term outcomes and treatment of locally advanced, locally recurrent, and stage IV rectal cancer will profoundly be discussed.

OUTLINE OF THIS THESIS

This thesis focuses on three important aspects of rectal cancer. In part I, the oncological outcomes of locally advanced and locally recurrent rectal cancer are evaluated. Part II describes the morbidity that is accompanied by the treatment of advanced rectal cancer, and methods to reduce treatment-related morbidity will be discussed. Finally, considerations for the management of stage IV rectal cancer will be outlined in the third and final part of this thesis.

PART I: ONCOLOGICAL OUTCOMES OF ADVANCED RECTAL CANCER

Management of advanced rectal cancer is continually evolving. Diagnostic modalities, patient selection and treatment approaches changed during the last decades. These changes should be evaluated in real-life practice. In an era in which optimal treatment for advanced rectal cancer has yet to be established, retrospective cohort studies provide important knowledge on disease management. In **Chapter 2**, a large cohort of patients with LRRC treated in a tertiary referral centre was evaluated. Patients included were those who were eligible for curative intended treatment, as well as patients with incurable disease (e.g. due to extensive metastases or unresectable local disease) who were treated non-surgically with radiotherapy and/or chemotherapy or best supportive care. To evaluate the different IORT modalities used in the Netherlands, including intraoperative electron beam radiation therapy (IOERT) and high-dose-rate intraoperative brachytherapy (HDR-IORT), **Chapter 3** compared the long-term oncological outcomes between IOERT and HDR-IORT in patients with LARC and LRRC. The role of induction systemic chemotherapy prior to chemoradiation and surgery is retrospectively investigated in LRRC patients in **Chapter 4**.

PART II: MORBIDITY IN ADVANCED RECTAL CANCER

Whilst surgical possibilities are expanding, and neoadjuvant treatment approaches tend to be increasingly aggressive, the question arises whether the toxicity and impact on quality of life caused by treatment is still justified.(29) In advanced rectal cancer, the balance between the potential oncologic survival gain and toxicitiy of treatment should carefully be considered, preferably in a multidisciplinary team.(20) In **Chapter 5**, surgical techniques for rectal cancer in the anterior pelvic compartment are described, which is followed by a detailed overview of complications associated with this procedure, and the impact on quality of life. Morbidity is especially a problem in frail and elderly patients, as these patients have less functional capacity and cardiopulmonary resilience to endure treatment-related complications. For example, dehydration after severe diarrhea during chemoradiation, or abdominal sepsis due to an anastomosis leakage could have detrimental, even lethal consequences. Taken into account the high proportion of frail and elderly patients in the advanced rectal cancer population, risk factors for perioperative morbidity should be identified and, if possible, corrected. In **Chapter 6** and **Chapter 7**, prognostic parameters for morbidity and mortality were identified in patients with LARC or LRRC undergoing chemoradiation and pelvic exenteration surgery. In **Chapter 8**, it was investigated whether the use of an omentoplasty to fill up the pelvic space after an abdominal perineal resection (APR) could reduce perineal complications in patients with LARC or LRRC.

Part III: MANAGEMENT OF STAGE IV DISEASE

About 25% of patients diagnosed with rectal cancer have distant metastases, and another 30% will develop distant recurrence after curative treatment.(30, 31) Metastatic disease is most frequently found in the liver and lungs, followed by peritoneum, extra-regional lymph nodes, and bone.(32, 33) Chances for long-term survival in patients with colorectal metastases are low, but not absent. To achieve cure, patients require treatment with multiple interventions, sometimes combined with perioperative chemotherapy. Patients who may be offered a curative intended strategy should be selected carefully, because the benefit of local treatment in patients with aggressive metastatic disease and low life expectancy is questionable. A common strategy for treating patients with synchronous metastatic disease is the administration of chemotherapy, and subsequent observation of tumour behaviour. In case of response, surgical resection of the metastatic site(s) and primary tumour can be considered. This stepwise strategy is the logic behind the “liver-first approach” for patients with LARC and synchronous liver metastases. The liver-first approach is investigated and compared against the M1-scheme in **Chapter 10**. Colorectal cancer that has spread to the lungs regularly appears to behave rather indolently, and seldom results in pulmonary failure. Treatment modalities for colorectal lung metastases include surgery, thermal ablation, stereotactic radiotherapy (SBRT), and systemic therapy. In **Chapter 11**, these modalities are retrospectively evaluated in selected patients with limited extrapulmonal disease. The impact of indeterminate lung nodules and distant metastases on long-term outcomes in patient with LRRC is described in **Chapter 12** and **Chapter 13** of this thesis. Finally, in **Chapter 14**, the role of circulating tumour DNA (ctDNA) after treatment of LARC as predictor for recurrence and survival is described in a systematic review and meta-analyses.

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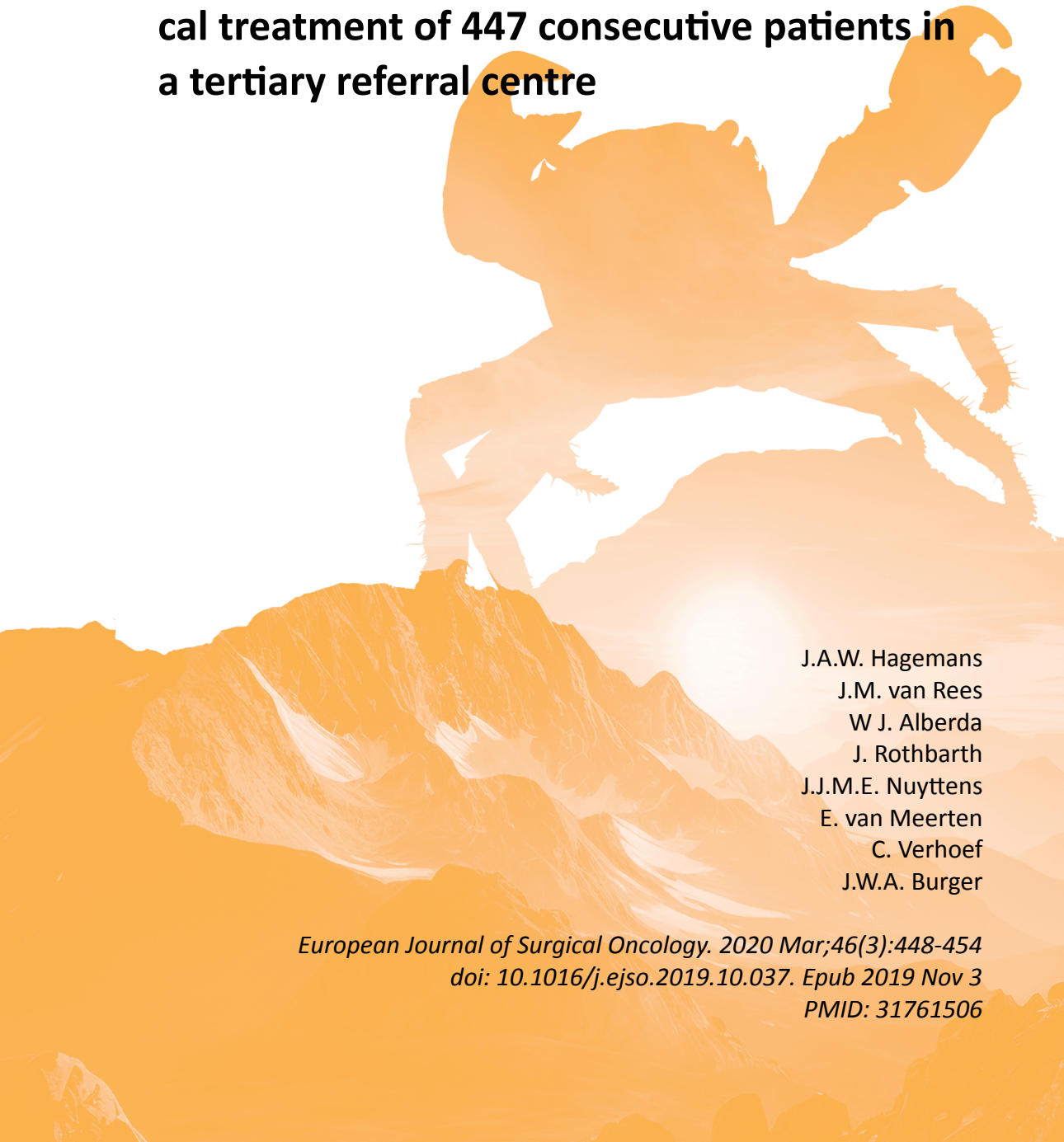
PART I

Oncological outcomes of advanced rectal cancer

CHAPTER 2

Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre



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ABSTRACT

Introduction

The majority of patients with locally recurrent rectal cancer (LRRC) present with extensive metastatic disease or an unresectable recurrence, and will be treated palliatively. Only a minority of patients will be eligible for potential cure by surgical treatment. The aim of this study is to evaluate the long-term outcome of surgical treatment and non-surgical treatment of patients with LRRC.

Methods

All patients with LRRC referred to our tertiary institute between 2000 and 2015 were retrospectively analysed. Patients were discussed in a multidisciplinary tumour board (MDT) and eventually received curative surgical or non-surgical treatment. Overall survival (OS) was compared by resection margin status and non-surgical treatment.

Results

A total of 447 patients were discussed in our MDT of which 193 patients underwent surgical treatment and 254 patients received non-surgical treatment. Surgically treated patients were significantly younger, received less neoadjuvant therapy for the primary tumour, had less metastasis at diagnosis and more central recurrences. The 5-year OS was 51% for R0-resections and 34% for R1-resections. Although numbers with R2-resections were too small to implicate prognostic significance, there was no difference in 5-year OS between R2-resections and non-surgical treatment (10% vs. 4%, p=0.282). In a subgroup analysis the OS of R2-patients was even poorer compared to optimal palliative treated patients with combined chemotherapy and radiotherapy (22 vs 29 months, p=0.413).

Conclusion

R2-resections do not result in a survival benefit compared to non-surgical treatment in this non-randomized series. Patients with a high chance on a R2-resection could be offered non-surgical treatment, without local resection.

INTRODUCTION

The introduction of total mesorectal excision (TME) and neoadjuvant (chemo-) radiotherapy have drastically decreased local recurrence rates after surgery for rectal cancer over the last decades. Locally recurrent rectal cancer (LRRC) still occurs in 6-10% of the surgically treated patients.(1-5) The development of LRRC has a major impact on quality of life, mostly by the occurrence of severe pain, bleeding and fistulation.(6)

Most patients with LRRC present with extensive metastatic disease or an unresectable local recurrence.(7-10) These patients can be offered non-surgical treatment, consisting of external beam radiotherapy, chemotherapy, a combination of both or comfort care.(11) Palliative external beam radiotherapy may relief pelvic pain complaints and chemotherapy may delay disease progression and prolong survival.(7, 8, 11-13) A minority of patients presenting with LRRC can potentially be cured by surgical resection. The long-term outcome of surgical treatment mainly depends on the ability to achieve a clear resection margin.(10, 14, 15) Management of LRRC remains a challenge both for curative surgical treatment and non-surgical treatment.

The aim of the current study is to evaluate the long-term outcome of a large cohort of patients with LRRC and determining the outcome of curative surgical treatment and non-surgical treatment in these patients.

PATIENTS AND METHODS

All consecutive patients with confirmed LRRC discussed in the multidisciplinary tumour board (MDT) of the Erasmus MC Cancer Institute, a tertiary referral hospital, from 2000-2015 were retrospectively analysed. LRRC was defined as local recurrence of rectal cancer in the pelvic area. This MDT included experienced surgeons, radiologists, radiation oncologists and medical oncologists. If needed, gynaecologists, urologists, pathologists and plastic surgeons were invited to join the meeting.

Data was collected from all referring hospitals, general practitioners and obtained from hospital notes, operation notes, histopathological and imaging reports. The local medical ethics committee of our institution approved this study (MEC-2017-448).

Surgical treatment

Surgical treatment was considered feasible in patients with resectable metastatic disease and/or non-metastasized LRRC with a realistic chance of a R0/R1-resection, as discussed by the MDT. R0-resections were defined as any radical resection (no tumour invasion in the resection plane, tumour-free margin of >1 mm); R1-resections as microscopically involved margins (tumour invasion in resection plane on microscopic assessment, tumour-free

margin of ≤1 mm); R2-resections as macroscopically involved margins or massive invasion into the resection surface on pathology report.

Patients were usually scheduled for neoadjuvant (chemo)radiotherapy. Radiotherapy-naïve patients were planned for long course radiotherapy (44.6-52Gy) and previously irradiated patients received a short course re-irradiation (27-30Gy). From 2006 onwards, all patients received concurrent Capecitabine during radiotherapy as reported previously.(16) Induction chemotherapy was occasionally administered. After neoadjuvant therapy patients were restaged (CT Thorax/Abdomen and Pelvic MRI) and discussed in the MDT to evaluate development of distant metastases, tumour response of the local recurrence and clinical condition, which may alter the decision for surgical treatment to palliative treatment.(17) Surgical planning was made by the MDT based on imaging after restaging after neoadjuvant therapy.

Surgical procedures included low anterior resection (LAR), abdominoperineal resection (APR) with and without multivisceral resection (MVR), and both posterior exenteration and total pelvic exenteration. Surgery was usually performed at our institute and in some cases in the referring hospital. In our institute, the multimodality approach for LRRC included intra-operative brachytherapy (IOBT) with a single dose of 10Gy. Patients received IOBT in case of a positive circumferential resection margin (CRM) or a narrow margin (CRM ≤ 2mm) on frozen sections taken preoperatively. In addition patients received IOBT in case of peroperatively expected or uncertain achievement of radical margins, i.e. due to fibrosis and also patient with an expected peroperative R2-resection.(18, 19) Surgical complications were scored according to the Clavien-Dindo classification.(20)

Non-surgical treatment

Patients receiving non-surgical treatment usually had extensive metastatic disease, unresectable local recurrence or a poor clinical condition. There was no standard policy regarding the choice of non-surgical treatment. Non-surgical treatment consisted of radiotherapy or chemotherapy, either with or without hyperthermia or a combination of both and comfort care. Generally, patients with symptomatic LRRC were treated with radiotherapy and those with asymptomatic metastasized or unresectable LRRC were treated with chemotherapy. Hyperthermia was usually administered to previously irradiated patients due to the limited radiation dose available for their local recurrence. The choice of dose and fractioning of radiotherapy was largely based on the clinical judgment of the radiation oncologists and this resulted in heterogeneity in the radiotherapy management. Comfort care was provided for patients who were unable to receive or did not desire any treatment with radiotherapy or chemotherapy.

Statistical analysis

Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data were reported as count (percentage). Group comparisons were made using Chi-square or Mann-Whitney-U-test as appropriate. Survival and follow-up were calculated from the date of LRRC diagnosis till death or last follow-up. Survival rates and follow-up were calculated by the (reversed) method of Kaplan-Meier and comparisons by log-rank test. For all analyses, patients were divided into two groups: 1) patients who underwent surgery and 2) patients who received non-surgical treatment including those patients who were previously considered eligible for surgical treatment. Statistical analyses were performed using IBM SPSS Statistics v24.0.0 for Windows (IBM Corp, Armonk, New York, USA).

RESULTS

A total of 447 consecutive patients with LRRC were discussed in our MDT. A flowchart of included patients is displayed in figure 1. After discussion in the MDT, 244 patients (55%) were considered candidates for surgery. This decision was reversed in 51 patients after restaging after neoadjuvant therapy, as described in figure 1. In total, 193 patients underwent surgical treatment and 254 patients received non-surgical treatment. Patient, primary and recurrent tumour characteristics are outlined in table 1. Treatment and follow-up are depicted in table 2.

Figure 1. Flowchart of all referred LRRC patients

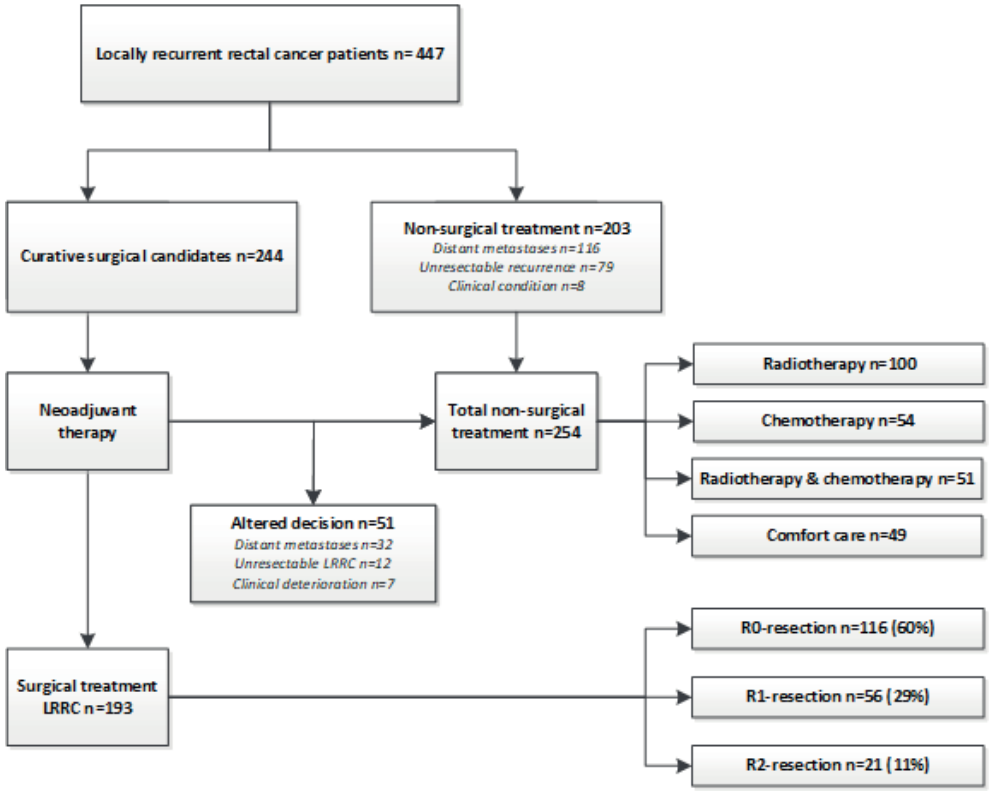


Table 1. Patients, primary and recurrent tumour characteristics of surgical and non-surgical treatment

		Total (N=447)	Surgical (N=193)	Non-surgical (N=254)	P-value
Gender	Male	289 (65%)	125 (65%)	164 (65%)	0.965
	Female	158 (35%)	68 (35%)	90 (35%)	
Age at primary tumour resection	Median (IQR)	63 (56-70)	62 (54-67.5)	64 (56-72)	0.016*
Age at diagnosis LRRC	Median (IQR)	66 (58-73)	65 (57-71)	67 (58-75)	<0.001*
Neoadjuvant treatment primary tumour	None	256 (57%)	126 (65%)	130 (51%)	0.002**
	Short course RTx	49 (11%)	18 (9%)	31 (12%)	
	Long course RTx	62 (14%)	14 (7%)	48 (19%)	
	Chemoradiotherapy	80 (18%)	35 (18%)	45 (18%)	
Primary tumour resection	LAR	244 (55%)	112 (58%)	132 (52%)	<0.001**
	APR	106 (24%)	30 (16%)	76 (30%)	
	Rectosigmoid	55 (12%)	32 (17%)	23 (9%)	
	Exenterative surgery	21 (5%)	4 (2%)	17 (7%)	
	TEM	21 (5%)	15 (8%)	6 (2%)	
Primary tumour stage	Stage I	52 (13%)	30 (16%)	22 (10%)	0.076
	Stage II	139 (34%)	58 (31%)	81 (35%)	
	Stage III	186 (45%)	86 (46%)	100 (44%)	
	Stage IV	38 (9%)	12 (7%)	26 (11%)	
	Missing***	32	7	25	
Resection margin primary tumour	R0	381 (88%)	174 (96%)	207 (83%)	<0.001**
	R1	50 (12%)	8 (4%)	42 (17%)	
	Missing***	16	11	5	
Interval primary - LRRC	Median (IQR)	23 (11-39)	24 (12-40)	21 (10-37)	0.154
Recurrence within	24 months	246 (55%)	99 (52%)	147 (58%)	
	5 years	393 (88%)	174 (90%)	219 (86%)	
	10 years	433 (97%)	191 (99%)	242 (95%)	
Symptoms at diagnosis LRRC	Yes	262 (55%)	86 (45%)	176 (69%)	<0.001**
	No	185 (45%)	107 (55%)	78 (31%)	
Metastases at diagnosis LRRC	None	285 (64%)	172 (89%)	113 (45%)	<0.001**
	Lung	55 (12%)	11 (6%)	44 (17%)	
	Liver	45 (10%)	7 (4%)	38 (15%)	
	Lung & Liver	23 (5%)	0 (0%)	23 (9%)	
	Other	39 (9%)	3 (2%)	36 (13%)	
Location LRRC	Central	74 (18%)	54 (29%)	20 (9%)	<0.001**
	Anterior	62 (15%)	31 (17%)	31 (14%)	
	Posterolateral	53 (13%)	24 (13%)	29 (13%)	
	Anterolateral	34 (8%)	14 (8%)	20 (9%)	
	Lateral	59 (14%)	29 (16%)	30 (13%)	
	Pre-sacral	133 (31%)	33 (18%)	100 (44%)	
	Missing***	32	8	24	

Mann Whitney U test ** Chi squared test * missing's not included in group comparison, percentages might not add up due to rounding.*

Abbriviations: LRRC: Locally recurrent rectal cancer; IQR: interquartile range; RTx: radiotherapy; LAR: low anterior resection; APR: abdominoperineal resection; TEM: transanal endoscopic microsurgery

Time to recurrence after primary rectal cancer resection

The median time from primary tumour resection to the diagnosis of LRRC was 23 months (IQR 11 – 39 months). In more than half of the patients (55%) LRRC developed within 2 years and in almost all patients within 5 years (88%). A total of 162 patients (36%) presented with synchronous metastases at diagnosis of LRRC: the predominant location was lung only (34%), followed by liver only (28%), other (24%) or liver and lung (14%).

The median time to diagnosis of LRRC was significantly shorter in patients with incomplete primary tumour resections compared to patients with complete resections (10 vs. 24 months, $p<0.001$) and in patients who had received neoadjuvant radiotherapy for the primary tumour compared to no radiotherapy (21 vs. 24 months, $p=0.039$). More advanced primary pathological T-stage (T3-4 vs. T1-2) did not influence the median time to LRRC (21 vs. 24 months, $p=0.172$), nor lymph node positivity (21 vs. 23 months, $p=0.776$).

Surgical and non-surgical patients

There were significant baseline differences for patients who eventually underwent surgery (n=193) compared to all non-surgically treated patients (n=254) (Table 1). Surgically treated patients were significantly younger, less symptomatic at presentation of LRRC, received less radiotherapy for the primary tumour, had fewer incomplete primary tumour resections, had less frequent synchronous distant metastasis, more differences in terms of localization of the local recurrence and underwent different procedures for the primary rectal tumour. Patients with a central localization of the local recurrence were more likely to be scheduled for surgical treatment, whereas patients with a pre-sacral recurrence were more likely to receive non-surgical treatment.

Surgical treatment

The majority of surgically treated patients received neoadjuvant therapy (90%) and more than half of the patients received (re-)chemoradiotherapy (62%). Some patients received induction chemotherapy (n=13) or radiation (n=38) or re-irradiation (n=9) without concurrent Capecitabine and 7 patients received solely induction chemotherapy. In 175 patients (91%) the surgical procedure was performed at our institute, while 18 procedures (9%) were performed in the referring hospitals. Neoadjuvant therapy and surgical procedures are described in Table 2.

Table 2. Treatment and follow up of LRRC in surgical and non-surgical treatment

	Surgical (N=193)	Non-surgical (N=254)
Neoadjuvant therapy LRRC		
None	19 (10%)	205 (81%)
Irradiation (50Gy)	38 (20%)	13 (5%)
Re-irradiation (30Gy)	9 (5%)	3 (1%)
Induction chemotherapy*	20 (10%)	9 (2%)
Chemoradiotherapy (50Gy)	61 (32%)	14 (6%)
Re-Chemoradiotherapy (30Gy)	59 (31%)	15 (6%)
Surgical procedure		
Total pelvic exenteration	43 (22%)	N/A
Posterior pelvic exenteration	27 (14%)	N/A
APR with MVR	26 (14%)	N/A
LAR with MVR	18 (9%)	N/A
Local resection with MVR	11 (5%)	N/A
APR only	25 (13%)	N/A
LAR only	26 (13%)	N/A
Local resection only	17 (7%)	N/A
IOBT**	86 (45%)	N/A
Follow up		
Alive at last FU	65 (34%)	9 (4%)
No evidence of disease at last FU	47 (24%)	N/A
Local re-recurrence	62 (32%)	N/A
Metastases (any)	88 (46%)	186 (73%)
Metastases (synchronous)	14 (7%)	138 (54%)
Metastases (metachronous)	74 (38%)	48 (19%)
Lung***	47 (53%)	63 (34%)
Liver	15 (17%)	46 (25%)
Lung and liver	10 (11%)	26 (14%)
Peritoneal	6 (7%)	15 (8%)
Lymphogenic	7 (8%)	20 (11%)
Other	3 (3%)	16 (9%)

** Combined with (chemo-)radiotherapy in 13 patients for surgical patients and 5 non-surgical patients; ** Including 16 patients with R2-resection; *** Location of metastases are reported as percentage within metastases.*

Abbriviations: N/A: not applicable; APR: abdominoperineal resection; MVR: multivisceral resection; LAR: low anterior resection; IOBT: intraoperative brachy therapy; FU: follow up;

Surgical results

R0-resections were achieved in 116 patients (60%), R1-resections in 56 patients (29%) and R2-resections in 21 patients (11%). The 30-day mortality and the in-hospital mortality rate were both 3% (n=5). Four patients died within 22 days and one patient died during admission at 67 days after surgery. Postoperative complications were registered in 176 out of 193 patients. A total of 59 (34%) patients experienced major complications (Clavien-Dindo ≥ 3). Most common complications were wound complications (23%), pre-sacral abscesses (11%) and urinary tract infections (9%). Surgical re-intervention was required in 26 patients (13%) and abscess drainage (i.e. pre-sacral or abdominal abscess) in 25 patients (13%). Complications for surgically treated patients are displayed in Table 3.

Table 3. Surgical complications

	Total (N=193)
Clavien-Dindo	
No complication	59 (34%)
Clavien-Dindo I	31 (18%)
Clavien-Dindo II	27 (15%)
Clavien-Dindo IIIA	21 (12%)
Clavien-Dindo IIIB	25 (14%)
Clavien-Dindo IVA	3 (2%)
Clavien-Dindo IVB	4 (2%)
Clavien-Dindo V	5 (3%)
Most common complications	
Wound complication	45 (23%)
Pre-sacral abscess	22 (11%)
Urinary tract infection	18 (9%)
Relaparotomy	18 (9%)
Pneumonia	15 (8%)
Sepsis	13 (7%)
Cardiac complication	12 (6%)
Nephrostomy	12 (6%)
Reintervention stoma	3 (2%)
Anastomotic leakage	3 (2%)
Any surgical reintervention	26 (13%)
Any abscess drainage	25 (13%)

Non-surgical treatment

A total of 254 patients received non-surgical treatment, including 51 patients who were first considered candidates for surgical treatment. These patients had received neoadjuvant therapy, but the aim of the treatment was altered as described previously. Patients were treated by radiotherapy (n=100), by chemotherapy only (n=54), by combined radiotherapy and chemotherapy (n=51) or comfort care (n=49).

In 63 previously irradiated patients, re-irradiation was administered in varying doses of 15 to 48 Gy delivered in 3-15 fractions. Radiotherapy-naïve patients (n=88) received radiotherapy doses varying from 6-66Gy in 4-28 fractions. Almost half of the patients experienced pain (48%) of whom the majority (56%) needed pain consultation.

Follow-up and survival surgical and non-surgical treatment

The median follow-up time for the whole cohort was 26 months (IQR 11 – 45) and median follow-up for survivors was 120 months (IQR 68 – 142).

Survival surgically treated patients

The median follow-up of the 193 surgically treated patients was 42 months (IQR 29 - 70) and the median follow-up for survivors was 117 months (IQR 67 - 140). The estimated 1-, 3- and 5-year overall survival rates were 93%, 65% and 41%, respectively. The median overall survival was 47 months (IQR 29 – 156). The estimated 1-, 3- and 5-year local re-recurrence free survival rates were 81%, 64% and 63%, respectively. The median local re-recurrence free survival was not reached. At last follow-up 65 (34%) patients were alive, of whom 50 patients with no evidence of disease. Sixty-two patients developed a local re-recurrence and 74 patients developed metastases after surgery. Thirty-one patients were diagnosed with both. Recurrence patterns and death by resection margin are demonstrated in Table 4.

Table 4. Recurrence patterns and death by resection margin

		R0 (N=116)	R1 (N=56)	R2 (N=21)	Total (N=193)	P-value
Re-recurrence		26 (22%)	26 (46%)	N/A	52 (27%)	0.001**
Distant metastasis*	Any	45 (39%)	30 (54%)	13 (62%)	88 (46%)	0.058
	Synchronous	6 (5%)	4 (7%)	4 (19%)	14 (7%)	0.078
	Metachronous	39 (34%)	26 (46%)	9 (43%)	74 (38%)	0.244
	None	71 (61%)	26 (46%)	9 (43%)	106 (55%)	0.206
	Liver	10 (9%)	5 (9%)	0 (0%)	15 (8%)	
	Lung	22 (19%)	15 (27%)	10 (48%)	47 (24%)	
	Lung and liver	5 (5%)	4 (7%)	1 (5%)	10 (5%)	
	Other	2 (2%)	1 (2%)	0 (0%)	3 (2%)	
	Lymphogenic	3 (3%)	4 (7%)	0 (0%)	7 (4%)	
	Peritoneal	3 (3%)	1 (2%)	2 (10%)	6 (3%)	
Death within 60 months		53 (46%)	35 (63%)	19 (91%)	107 (55%)	<0.001**
Cancer specific death		55 (47%)	40 (71%)	21 (100%)	116 (60%)	<0.001**

*Location of metastases are reported as percentage within resection margin. ** Chi squared test*

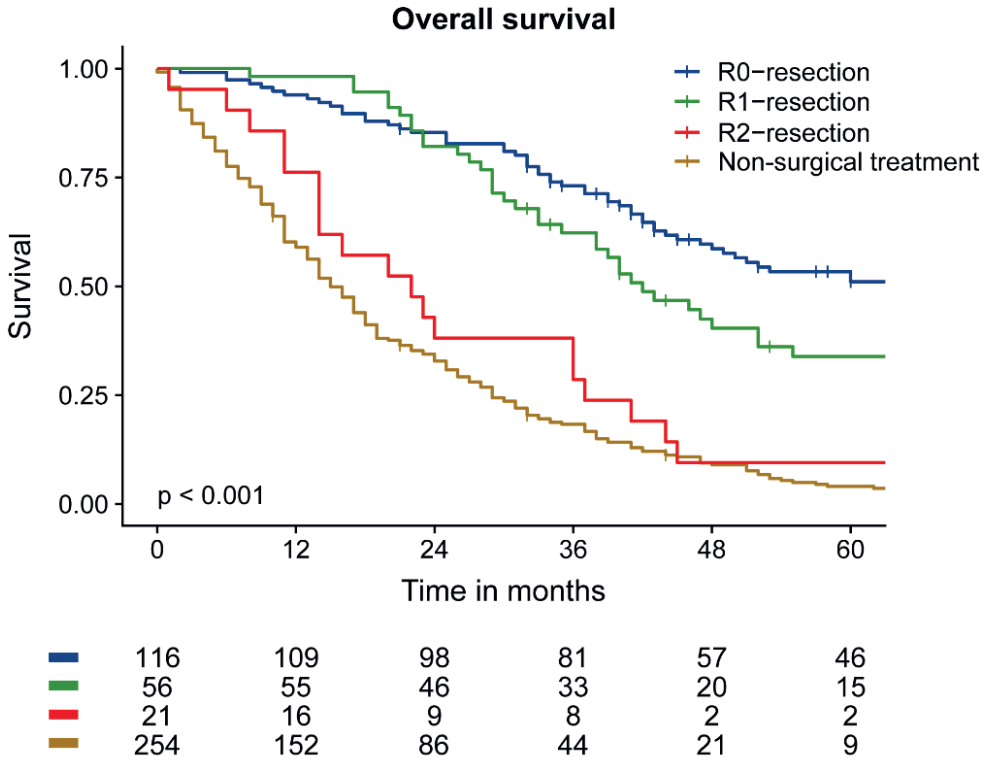
Survival non-surgically treated patients

The median follow-up of the 254 non-surgically treated patients was 15 months (IQR 7 – 29) and the median follow-up for survivors was 145 months (IQR 142-162). The estimated 1-, 3-, 5-year overall survival rates were 60%, 19%, 4%, respectively. The median survival was the highest for patients treated with combined radiotherapy and chemotherapy, followed by chemotherapy only, radiotherapy only and comfort care (29, 18, 14 and 7 months, respectively). There was no significant difference in median survival of metastasized and non-metastasized patients at diagnosis (14 vs. 18 months, p=0.293). Nine patients were alive at last follow-up. One patient, with a proven LRRC on imaging, had a complete radiologic response of the recurrence after treatment with radiotherapy and was alive at 162 months follow-up. Two patients, with histologically confirmed LRRCs, were alive at 145 and 142 months with stable systemic and local disease after an experimental chemotherapeutic treatment. Two patients, with histologically proven LRRC and systemic disease, were alive at 44- and 32-months follow-up, both receiving experimental chemotherapeutic treatment. Two patients with proven LRRC on imaging with systemic disease with highly elevated carcinoembryonic antigen were alive at 44 and 32 months with slowly progressive systemic and local disease without treatment. Another two patients with histologically proven LRRC and systemic disease were alive, but were lost to follow-up at 21 and 10 months. Distant metastases were diagnosed in 186 patients. In 141 patients distant metastases were diagnosed at presentation and 45 patients developed distant metastases during follow-up of non-surgical treatment.

Survival by resection margin vs. non-surgical treatment

Compared to patients treated non-surgically, there was a significant difference in 5-year overall survival in favour of patients with R0-resections (51% vs. 4%, p<0.001) and R1-resections (34% vs. 4%, p<0.001). There was no difference in overall survival between R2-resections and non-surgical treatment (10% vs. 4%, p=0.282). This is shown in figure 2. In a subgroup analysis, patients with a R2-resection had a prolonged median survival of 29 months (IQR 16 – 41) compared to 22 months (IQR 14 – 37) of the patients who were treated with palliative radiotherapy and chemotherapy, although this difference was not significant (p=0.413).

Figure 2. Overall survival according to surgical resection and non-surgical treatment



DISCUSSION

This large cohort of patients with LRRC, treated by surgical or non-surgical treatment, have demonstrated that R0- and R1-resections result in a 5-year overall survival rate of 51% and 34%, respectively. These survival rates are significantly prolonged compared to non-surgical treatment. Although numbers were too small to implicate prognostic significance, R2-resections did not result in a 5-year overall survival benefit compared to non-surgical treatment with a rate of 10% vs. 4%. Moreover, the overall survival of patients who underwent a R2-resection was poorer compared to patients who were treated non-surgically with combined radiotherapy and chemotherapy.

The 5-year overall survival rate for R0-resections in the present study is in line with previously reported outcomes of population-based studies and meta-analyses within a range of 43%-60%. Additionally, the poorer overall survival rate of R1-resections (range 14-36%) and the dismal overall survival rate of R2-resections(range 0-16%) are in line with the overall survival rates reported by others.(7-11, 14, 15) This confirms that resection margin status after surgical treatment for LRRC is the most important prognostic factor for overall survival. Unfortunately, not all LRRC patients are eligible for curative surgery.

The 5-year survival rate of 4% for all non-surgically treated patients in this study seems relative high compared to other series, which rarely exceeds 4%.(21, 22) However, a recently published study by Bhangu et al.(23) demonstrated a 3-year overall of approximately 35% for patients who did not undergo surgery, which is even higher compared to our 3-year overall survival of 19%. In line with our study they reported an overall survival benefit in favour of R0- and R1-resections compared to non-operative management. In R2-resections they were not able to find a survival benefit compared to non-operative management. Neither a large meta-analysis by their group was able to demonstrate a survival benefit for R2-resections compared to non-surgical treatment.(14, 23). These results are similar to our study, where we were not able to find a survival benefit of R2-resection compared to non-surgical treated patients. In a subgroup of patients who were treated by radiotherapy and systemic chemotherapy, a prolonged median survival was found compared to R2-resections (29 vs 22 months). Nevertheless, in our study the results of R-resections our limited by the small number of patients and cannot implicate statistical significance.

The survival benefit of R0- and R1-resections compared to non-surgical treatment seems clear in the current study. However, it is important to realize that these results may be influenced by a selection bias. This study includes patients who are referred and discussed in our MDT, the number of patients not suitable for surgery, and not referred to our MDT, may be even higher. The group of non-surgically treated patients contains a higher

proportion of patients with unfavourable characteristics compared to the surgically treated patients. Non-surgically treated patients had more synchronous distant metastases and more advanced local recurrences. These unfavourable characteristics may contribute to a poorer prognosis of the non-surgical group. In line with others, the overall survival of patients receiving only comfort care was poor with a median survival of 7 months. This median survival was poorer compared to R2-resections.(8, 10, 14, 23) However, it is important to realize these patients were generally in such poor clinical condition that they were not able to receive any form of treatment.

Untreated LRRC can cause severe impairment in quality of life mainly due to severe pain, but also fistula, obstruction or bleeding.(6, 24) There may be a role for palliative surgery in these patients to reduce pain, and relief symptoms of obstruction by stenting or a diverting stoma as reported by others.(11, 25, 26) However, surgery is accompanied by high morbidity and mortality rates, occurring mainly perioperative or in the first 3 months after surgical treatment. This impairment in quality of life persists till one year after surgery. Thereafter, surgically treated patients tends to have a better quality of life.(27) This fact and the lack of a survival benefit of R2-resections suggest that LRRC surgery with a high chance on R2-resections should be abandoned and should only be performed when the potential benefit is clear.

Regarding the secondary findings, this study identified several factors associated with resectability of LRRC. Obviously, age is a factor to be considered candidate for LRRC surgery due to the high morbidity and mortality rates of LRRC surgery. Previous irradiation for the primary tumour was also associated with resectability. Presumably, neoadjuvant radiotherapy for the primary tumour is not able to prevent local recurrences in patients with unfavourable primary tumour characteristics, such as more residual disease or higher tumour load. These patients do also have a higher risk of developing distant metastases and were therefore disqualified for LRRC surgery.(28) Patients with a more extensive primary procedure had a lower chance to be considered candidates for LRRC surgery. Extensive primary surgery leads to local recurrences closely related to structures which cannot be resected completely, while low anterior resections or local excisions (TEM, transanal endoscopic microsurgery) may lead to central recurrences. This makes localization of the local recurrence also associated with resectability, because central recurrences results more often into R0-resections.(29)

A promising strategy to improve resectability of LRRC is induction chemotherapy. However, improved resectability does not automatically guarantee a survival benefit. Other factors, such as tumour behaviour, have more impact on overall survival as well. In our study few patients received induction chemotherapy, but a retrospective cohort study by van Zoggel et al.(30) compared outcomes of resection of LRRC in patients with induction

chemotherapy followed by chemoradiotherapy to patients who received solely chemoradiotherapy. The R0-resection rate did not differ significantly, but a higher rate of pathologic complete response was found in patients with combined treatment. Van Zoggel et al.(30) suggested that response rate to induction chemotherapy may be used as guidance to avoid overtreatment in patients with progressive disease under induction chemotherapy. Otherwise, in a previous study, our institute showed a lower response to chemotherapy of the local recurrence compared to the response of distant metastases in a small cohort of previously irradiated rectal cancer patients.(31) Further research is warranted to evaluate the potential benefit of induction chemotherapy for treatment of LRRC.

Due to the retrospective nature of this analysis, this study has drawbacks. There was no standard protocol for non-surgical treatment. The choice of non-surgical treatment consisting of radiotherapy, chemotherapy, or only comfort care was judged on clinical factors. This resulted in a heterogenetic group of patients from critical ill patients not able to receive any form of treatment, to patients in good clinical condition, refusing surgery. Follow-up data of patients treated non-surgically was limited, because treatment was usually performed in the referring hospitals. Therefore, data of complication rates and quality of life in non-surgically treated patients was limited.

Furthermore, this study was only able to demonstrate survival differences. As mentioned above, quality of life may be even more important in the management of LRRC. Future research should focus on quality of life of surgical or palliative management of LRRC.

In conclusion, R0- and R1-resections of LRRC resulted in 5-year overall survival rates of 51% and 34%, respectively. Although numbers with R2-resections were too small to implicate prognostic significance, there was no significant difference between the 5-year overall survival for R2-resections and palliative treatment (10% vs. 4%). Moreover, the median survival may be poorer for surgically treated patients with a R2-resection compared to optimal palliatively treated patients. Patients with a high chance on a R2-resection could be offered palliative treatment, without local resection.

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CHAPTER 3

Intraoperative electron beam radiotherapy (IOERT) versus high-dose-rate intraoperative brachytherapy (HDR-IORT) in patients with an R1 resection for locally advanced and locally recurrent rectal cancer

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ABSTRACT

Introduction

Intraoperative radiotherapy (IORT), delivered by intraoperative electron beam radiotherapy (IOERT) or high-dose-rate intraoperative brachytherapy (HDR-IORT), may reduce the local recurrence rate in patients with locally advanced and locally recurrent rectal cancer (LARC and LRRC, respectively). The aim of this study was to compare the oncological outcomes between both IORT modalities in patients with LARC or LRRC who underwent a microscopic irradical (R1) resection.

Methods

All consecutive patients who received IORT because of an R1 resection of LARC or LRRC between 2000 and 2016 in two tertiary referral centers were included. In LARC, a resection margin ≤2 mm was considered R1. A resection margin of 0 mm was considered R1 in LRRC.

Results

In total, 215 LARC patients were included, of whom 151 (70%) received IOERT and 64 (30%) received HDR-IORT; further, 158 LRRC patients were included, of whom 112 (71%) received IOERT and 46 (29%) received HDR-IORT. After multivariable analyses, the overall survival was not significantly different between the two IORT modalities. The local recurrence free survival was significantly longer in patients treated with HDR-IORT, both in LARC (p=0.041; HR 0.496; 95%CI 0.253-0.973) and LRRC (p=0.021; HR 0.567; 95%CI 0.349-0.920). In LARC patients, major postoperative complications were similar for both IORT modalities, whereas in LRRC patients, the incidence of major postoperative complications was higher after HDR-IORT.

Conclusion

This study showed a significantly better LRFS in favor of HDR-IORT in patients with an R1 resection for LARC or LRRC. Optimization of the IOERT technique seems warranted.

INTRODUCTION

Achievement of a resection with clear margins (R0 resection) is the most important goal in the treatment of locally advanced and locally recurrent rectal cancer (LARC and LRRC, respectively), as it offers the best prognosis in terms of recurrence-free and overall survival. Patients at risk for a resection without clear margins (R1 resection) are offered neoadjuvant treatment, consisting of external beam radiation therapy (EBRT) with a dose of 45 Gy to 50 Gy with concomitant chemotherapy, as this has been shown to be effective in local downstaging of the tumor and to increase the likelihood of achieving an R0 resection, thereby reducing the risk of local relapse.(1-2) In addition, in patients at risk for an R1 resection, multivisceral resections are usually necessary, requiring extensive expertise and thus centralization of care. Nevertheless, an R1 resection occurs in approximately 10% to 20% of patients with LARC and 40% of those with LRRC.(3-5) Preoperative radiation therapy with a dose of 45 Gy to 50 Gy cannot compensate for an R1 resection.6 A dose in excess of 60 Gy may be able to eradicate microscopic residual disease; however, administration of radiation therapy at a dose higher than 50 Gy is associated with excessive toxicity, because this level of exposure exceeds the normal-tissue tolerance, which prohibits increasing the EBRT dosage.(7-9)

Intraoperative radiation therapy (IORT), the delivery of a single boost of radiation therapy during surgery, has the ability to deliver a higher dose to the areas at highest risk for tumor involvement while at the same time allowing dose-limiting structures and organs such as the ureters and small intestine to be positioned outside the radiation field, thus mitigating the problem of increased toxicity resulting from the application of a higher dosage of radiation therapy. The biological equivalent of one single fraction IORT equals 1.5 to 2.5 times the dose delivered by conventional fractionation.8 Prior studies have suggested that use of IORT in patients with a positive microscopically circumferential resection margin reduces local recurrence rates.(10-12)

IORT can be delivered through different modalities, including intraoperative electron beam radiation therapy (IOERT) and high-dose-rate intraoperative brachytherapy (HDR-IORT), the former being the most frequently used based on the literature.(12, 13) The advantages of IOERT in relation to HDR-IORT include shorter set-up and treatment times and a more homogeneous radiation dose to be delivered throughout the tissue depth. An important limitation of IOERT, however, is that the applicators are poorly suited to curved areas or narrow spaces. In contrast, HDR-IORT is a more time-consuming procedure, but the use of flexible applicators allows for application to any curved surface. In addition, with HDR-IORT, it is possible to irradiate a larger area, and the steeper dose gradient between the target surface and the reference depth leads to a more concentrated dose to be delivered at the surface of the target area.(14)

This study aimed to compare the long-term oncological outcomes between patients who received either IOERT or HDR-IORT after an R1 resection for LARC or LRRC.

PATIENTS AND METHODS

Patients

All consecutive patients with LARC or LRRC who underwent a resection between 2000 and 2016 in the Catharina Hospital Eindhoven (CZE) or Erasmus MC Cancer Institute (EMC) were identified from a prospectively maintained database. We included all patients with an R1 resection after undergoing intentionally curative surgery in whom IORT was delivered by either IOERT or HDR-IORT. For the purpose of this study, in patients with LARC, an R1 resection was defined as a resection with involved or close margins (≤2 mm), as this margin was the cut-off value to deliver IORT based on a study by Nagtegaal et al.(15) In patients with LRRC, an R1 resection was defined as a resection with involved margins, in accordance with the literature.(16) Patients with peritoneal metastases, as well as patients who did not receive neoadjuvant radiation therapy, were excluded. The potential indication for IORT was determined during a meeting of a multidisciplinary tumor board, which included experienced surgeons, medical oncologists, radiation oncologists, and radiologists. The study was approved by both institutional local medical ethics committees (Medical research Ethics Committees United Nieuwegein, registration number W19.031 and Medical Ethics Review Committee Erasmus MC, registration number MEC-2017-449). Follow-up was completed until January 1, 2020.

Neoadjuvant treatment and surgical procedure

All patients received neoadjuvant radiation therapy, which was delivered in one of the two tertiary referral centers or in a referring hospital. In patients with LARC, neoadjuvant radiation therapy consisted of either short-course (25 Gy in 5 fractions of 5 Gy) or long-course (45-50.4 Gy in fractions of 1.8-2 Gy) EBRT. In patients with LRRC, neoadjuvant radiation therapy consisted of either long-course EBRT (45-50.4 Gy in fractions of 1.8-2 Gy) or reirradiation (30 Gy in fractions of 2 Gy). In case of long-course radiation therapy or reirradiation, concomitant capecitabine was administered (825 mg/m^2 twice daily on radiation therapy days). Induction chemotherapy, generally CAPOX (capecitabine, oxaliplatin) or FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin), was administered to a minority of patients before or after radiation therapy treatment. This was usually to treat and observe the biological behavior of synchronous metastases; induction chemotherapy was not considered the standard of care during the study period. After patients finished the neoadjuvant treatment course, pelvic magnetic resonance imaging was performed to assess the resectability.

The extent of pelvic surgery depended on the location of the tumor and the involvement of adjacent structures and was performed by experienced surgical oncologists. For specific reconstructive procedures, other specialists such as urologists or plastic surgeons were involved.

Intra-operative radiotherapy

At both referral centers, IORT was delivered in cases with clinically suspected narrow or involved margins or in cases with narrow or microscopically involved margins, based on assessment of frozen sections.

At the CZE, all patients who underwent surgery for LARC or LRRC were scheduled in an operating room with IORT facilities. The IORT was delivered by IOERT. In earlier years of the study, this was delivered using an Elekta SL-25 linear accelerator (Elekta Oncology Systems, Stockholm, Sweden).(17) From 2016 onward, IORT was delivered using a Mobetron 2000 linear accelerator (IntraOp Inc, Sunnyvale, California). Generally, the IORT dose was 10 Gy or 12.5 Gy. The dose was prescribed to the 90% isodose surface, generally ranging from 12 mm to 18 mm in depth, with energies ranging from 6 MeV to 8 MeV using a 30° to 45° beveled applicator of 5 cm to 7 cm in length. The rationale for the dosing strategy depended on the target area, the normal tissue at risk, and the anatomy of the patient.

At the EMC, all patients who underwent surgery for LARC or LRRC and in whom a resection margin of ≤2 mm was expected were planned in an operating room with IORT facilities. The IORT was delivered by high-dose-rate brachytherapy using a flexible intraoperative temple (i.e. the FIT procedure), which has been described previously.(18) In short, HDR-IORT was delivered using a flexible 5-mm-thick pad made of flexible silicon, with a dose of 10 Gy prescribed at a depth of 1 cm from the applicator surface. The size and shape were adjusted according to the surface of the area at risk.

Follow-up

Follow-up was performed according to the Dutch guidelines for colorectal cancer; carcinoembryonic antigen (CEA) measurements were performed 4 times a year during the first 2 years and twice a year during years 3 to 5. Ultrasonography of the liver was performed twice a year during the first 2 years and once a year thereafter. In case of an elevated CEA concentration or new ultrasonography findings, a thoracoabdominal computed tomography (CT) scan or a fluorodeoxyglucose (FDG) positron emission tomography (PET) / CT scan was performed. At the EMC, ultrasonography was replaced by thoracoabdominal CT scan for the majority of patients with LRRC from 2011 onward.

Study endpoints and statistics

Endpoints were overall survival (OS), local recurrence-free survival (LRFS), and the

incidence of major postoperative complications. Overall survival was calculated from the date of surgery until the date of death from any cause, or was censored at the last follow-up. Local recurrence-free survival was calculated from the date of surgery until the date local recurrence was detected by imaging or histology, or was censored at the last follow-up or death. Postoperative complications were graded according to the Clavien-Dindo classification.(19) Major complications were defined as a complication of grade 3 or greater.

Continuous data were reported as medians and interquartile ranges (IQRs) and categorical data as counts and percentages. Group comparisons were performed using Mann-Whitney U, $\chi 2$, or Fisher exact tests, as appropriate. Survival analyses were performed using the Kaplan-Meier method, and data were compared using log-rank tests. Two-sided P values <.05 were considered statistically significant. Cox proportional hazards modeling was performed for multivariable analysis using the stepwise backward selection option. In addition to the type of IORT, variables identified with a P value <.50 in the univariable analysis were included in the multivariable analysis. Statistical analyses were performed using IBM SPSS Statistics, version 25.0 (IBM Corp, Armonk, New York).

RESULTS

Locally advanced rectal cancer

In total, 1865 patients underwent a resection for LARC in one of the two tertiary referral centers between 2000 and 2016. An R1 resection was noted in 347 of 1865 patients, of whom 218 received IORT. Three patients were excluded from further analysis because of peritoneal metastases (2 patients) or for having received no neoadjuvant radiation therapy (1 patient). In 151 of the 215 included patients (70%), IORT was delivered by IOERT, whereas 64 patients (30%) received HDR-IORT. Patient, tumor, and treatment characteristics are summarized in Table 1. Most patients (73%) were diagnosed with a T4 tumor, and neoadjuvant treatment generally consisted of long-course radiation therapy (91% of patients). Only a minority of patients (16%) were diagnosed with synchronous metastases. Most patients (61%) underwent a multivisceral resection. The procedure time was significantly longer in patients who received HDR-IORT compared with IOERT (P <.001).

The HDR-IORT was delivered with a prescribed dose of 10 Gy in all patients, effectively leading to an average dose of ±17 Gy at the target surface. The median treated area was not known. The IOERT was delivered at a dose of 10 Gy at the 90% isodose surface in 130 patients (86%), a dose of 12.5 Gy in 20 patients (13%), and a dose of 15 Gy in 1 patient (1%). The median prescription depth (D90) was 14 mm (IQR, 12-15 mm), with a median treated area of 28 cm^2 (IQR, 27-32 cm^2).

Table 1. Patient, tumour and surgical characteristics in patients with locally advanced rectal cancer

		Total (N=215)	IOERT (N=151)	HDR-IORT (N=64)	P-value
		N (%)	N (%)	N (%)	
Gender	Female	64(30)	46(31)	18(28)	0.732
	Male	151(70)	105(70)	46(72)	
Age at resection	<70	156(73)	105(70)	51(80)	0.127
	≥70	59(27)	59(27)	13(20)	
Clinical tumour stage	cT3	57(27)	35(23)	22(34)	0.094
	cT4	157(73)	115(77)	42(66)	
Synchronous metastases	No	180(84)	129(85)	51(80)	0.297
	Yes	35(16)	22(15)	13(20)	
Neoadjuvant chemotherapy	No	196(91)	139(92)	57(89)	0.480
	Yes	19(9)	12(8)	7(11)	
Neoadjuvant radiotherapy	5x5 radiotherapy	20(9)	14(9)	6(9)	0.981
	(chemo)radiotherapy	195(91)	137(91)	58(91)	
Interval radiotherapy - surgery (weeks)	<8	27(15)	17(14)	10(16)	0.109
	8-12	86(47)	51(42)	35(56)	
	>12	72(39)	54(44)	18(29)	
Surgical procedure	LAR	46(21)	36(24)	10(16)	0.362
	APR	37(17)	24(16)	13(20)	
	Multivisceral resection	132(61)	91(60)	41(64)	
Procedure time (hour)	0-3	16(8)	16(11)	0(0)	<0.001
	3-5	90(43)	88(61)	2(3)	
	>5	102(49)	40(28)	62(97)	
Adjuvant therapy	No	189(88)	129(86)	60(94)	0.106
	Yes	25(12)	21(14)	4(6)	
Pathological tumour stage	pT1/2	4(2)	2(1)	2(3)	0.104
	pT3	128(60)	96(64)	32(50)	
	pT4	82(38)	52(35)	30(47)	
Pathological nodal stage	pN0	107(50)	74(49)	33(52)	0.918
	pN1	70(33)	50(33)	20(32)	
	pN2	36(17)	26(17)	10(16)	
Resection margin	0 mm	93(43)	64(42)	29(45)	0.844
	> 0 mm - ≤ 1 mm	73(34)	51(34)	22(34)	
	> 1 mm - ≤ 2 mm	49(23)	36(24)	13(20)	
Complications	Clavien-Dindo 0-II	140(71)	93(71)	47(73)	0.665
	Clavien-Dindo III-V	56(29)	39(30)	17(27)	

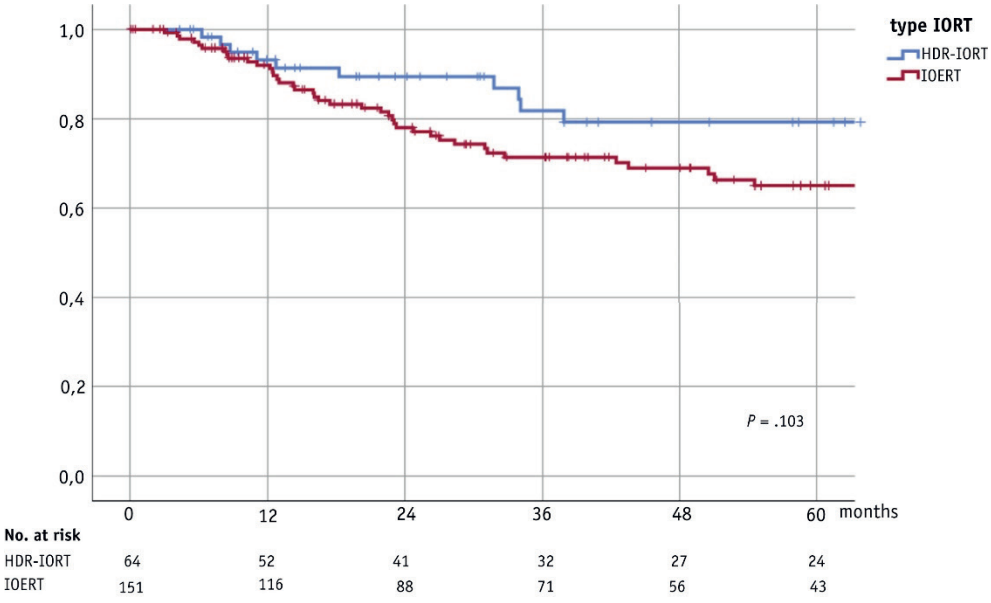
Missings not inluded in group comparison, percentages might not add up due to rounding

Abbriviations: APR: abdominoperineal resection; IOERT: intra-operative electron beam radiotherapy; HDR-IORT: high-dose-rate intra-operative brachytherapy; LAR: low anterior resection.

Locally advanced rectal cancer—survival outcomes

The median OS was 48 months (IQR, 19-111 months) for patients treated with HDR-IORT and 41 months (IQR, 21-137 months) for patients treated with IOERT. For patients who received HDR-IORT, the 3-year and 5-year OS rates were 61% and 47%, respectively. This was not significantly different compared with patients who received IOERT (3-year and 5-year OS rates, 58% and 40%, respectively; P = 0.989). Median LRFS was not reached. The 3-year and 5-year LRFS rates for patients who received HDR-IORT were 82% and 79%, respectively. For patients who received IOERT, these rates were 71% and 65%, respectively (P = 0.103; Figure 1).

Figure 1. Kaplan-Meier curve for local recurrence-free survival in patients with locally advanced rectal cancer.



Results of the univariable and multivariable analyses are shown in Table 2. After multivariable analysis, the IORT modality had no significant association with OS, whereas age, time between radiation therapy and surgery, pathologic tumor and lymph node stage (pT and pN, respectively), and resection margin did. For LRFS, multivariable analysis showed a significantly favorable LRFS in patients treated with HDR-IORT compared with those treated with IOERT (HR, 0.504; 95% CI, 0.254-0.999; P = 0.050). In addition, the time between radiation therapy and surgery, pT stage, and resection margin were significantly related to the development of a local recurrence.

Table 2. Multivariable analysis for overall and local recurrence free survival in LARC patients

	Overall Survival						Local recurrence					
Variable	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
Type IORT												
IOERT	1.00	Ref		1.00	Ref		1.00	Ref	0.110	1.00	Ref	
HDR-IORT	1.004	0.713-1.414	0.980	1.005	0.702-1.439	0.979	0.581	0.298-1.130	0.110	0.496	0.253-0.973	**0.041**
Age												
<70	1.00	Ref		1.00	Ref		1.00	Ref				
>70	1.437	1.021-2.023	**0.037**	1.984	1.384-2.844	**0.000**	0.581	0.283-1.191	0.138			
Gender												
Male	1.00	Ref					1.00	Ref				
Female	1.247	0.890-1.746	0.199				1.477	0.833-2.621	0.182			
cTstage												
T3	1.00	Ref					1.00	Ref				
T4	1.080	0.754-1.547	0.676				1.272	0.666-2.429	0.467			
Synchronous metastases												
No	1.00	Ref					1.00	Ref				
Yes	1.256	0.821-1.920	0.293				1.339	0.670-2.675	0.409			
Neoadjuvant chemotherapy												
No	1.00	Ref					1.00	Ref				
Yes	1.330	0.766-2.310	0.311				2.188	0.983-4.870	0.055			
Neoadjuvant radiotherapy												
5x5 radiotherapy	1.00	Ref					1.00	Ref				
(chemo)radiotherapy	0.677	0.397-1.155	0.152				0.555	0.236-1.305	0.177			
Time between RT and surgery												
<8 weeks	1.00	Ref					1.00	Ref				
8-12 weeks	0.949	0.580-1.553	0.835				2.164	0.643-7.285	0.212			
>12 weeks	1.434	0.857-2.397	0.170				3.176	0.938-10.756	0.063			
Type of surgery												
LAR	1.00	Ref					1.00	Ref				
APR	0.780	0.474-1.284	0.329				0.681	0.242-1.916	0.469			
Multivisceral resection	0.765	0.518-1.130	0.178				1.290	0.622-2.676	0.487			

Table 2. (continued)

	Overall Survival						Local recurrence					
Variable	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
Adjuvant therapy												
No	1.00	Ref					1.00	Ref				
Yes	1.014	0.620-1.658	0.957				1.526	0.717-3.249	0.273			
Procedure time (hours)												
0-3	1.00	Ref					1.00	Ref				
3-5	1.072	0.566-2.033	0.830				5.085	0.691-37.430	0.110			
>5	1.127	0.597-2.127	0.711				3.681	0.497-27.262	0.203			
pTstage												
T1-3	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
T4	2.077	1.509-2.859	**0.000**	2.046	1.461-2.866	**0.000**	2.765	1.589-4.812	**0.000**	2.482	1.387-4.444	**0.002**
pNstage												
N0	1.00	Ref		1.00	Ref		1.00	Ref				
N1	1.211	0.847-1.732	0.294	1.398	0.967-2.022	0.075	1.126	0.608-2.087	0.690			
N2	1.623	1.059-2.486	**0.026**	2.344	1.492-3.682	**0.000**	1.420	0.662-3.046	0.374			
Resection margin												
0 mm	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
>0 mm - ≤ 1 mm	0.626	0.439-0.891	**0.009**	0.575	0.393-0.842	**0.004**	0.542	0.295-0.995	**0.047**	0.629	0.332-1.191	0.154
> 1mm - ≤ 2 mm	0.489	0.316-0.758	**0.001**	0.496	0.314-0.784	**0.003**	0.286	0.119-0.689	**0.005**	0.359	0.146-0.883	**0.026**
Complications												
Clavien-Dindo 0-II	1.00	Ref					1.00	Ref				
Clavien-Dindo III-V	0.98	0.690-1.442	0.990				0.999	0.514-1.940	0.997			

Abbreviations: APR; abdominoperineal resection; HDR-IORT: high-dose-rate intraoperative brachytherapy; IOERT: intraoperative electron beam radiation therapy; IORT; intra-operative radiation therapy LAR; low anterior resection; RT; radiation therapy

Locally recurrent rectal cancer

In total, 587 patients underwent a resection for LRRC in one of the two tertiary referral centers between 2000 and 2016. Of these 587 patients, 196 had an R1 resection, of whom 161 received IORT. Three patients were excluded from further analysis; 1 patient had peritoneal metastases, and 2 patients did not receive neoadjuvant radiation therapy. Of the 158 patients receiving IORT, 112 (71%) received IOERT and 46 (29%) received HDR-IORT. Patient, tumor, and treatment characteristics are shown in Table 3. Patients who received HDR-IORT received neoadjuvant (chemo)radiation therapy instead of (chemo)reirradiation more often than patients who received IOERT (P = 0.001). The interval between the end of neoadjuvant radiation therapy and surgery was significantly shorter in patients who received HDR-IORT than in patients who received IOERT (P = 0.001), but the procedure time was significantly longer (P <0.001).

The HDR-IORT was delivered at a dose of 10 Gy in all patients, effectively leading to an average dose of ±17 Gy at the target surface. The median treated area was not known. The IOERT was delivered at a dose of 10 Gy at the 90% isodose surface in a majority of patients (67, 60%), and in 45 patients (40%) 12.5 Gy was delivered. The median prescription depth (D90) was 14 mm (IQR, 12-20 mm), with a median treated area of 32 cm^2 (IQR, 27-39 cm^2).

Table 3. Patient, tumour and surgical characteristics in patients with locally recurrent rectal cancer

		Total (N=158)	IOERT (N=112)	HDR-IORT (N=46)	P-value
		N (%)	N (%)	N (%)	
Gender	Female	54(34)	38(34)	16(35)	0.918
	Male	104(66)	74(66)	30(65)	
Age at resection	<70	122(77)	88(79)	34(74)	0.526
	≥70	36(23)	24(21)	12(26)	
cTumor stage primary tumour	cT1-2	28(18)	17(16)	11(24)	0.209
	cT3-4	128(82)	93(85)	35(76)	
cNodal stage primary tumour	cN0	76(49)	52(47)	24(52)	0.849
	cN1	50(32)	36(33)	14(30)	
	cN2	30(19)	22(20)	8(17)	
History metastases	Yes	21(14)	13(12)	8(17)	0.400
	No	131(86)	93(88)	38(83)	
Neoadjuvant treatment primary tumour	None	67(42)	39(35)	28(61)	0.008
	5x5 radiotherapy	48(30)	40(35)	8(17)	
	(chemo)radiotherapy	43(27)	33(30)	10(22)	
Surgical procedure primary tumour	Local excision	5(3)	3(3)	2(4)	0.670
	Sigmoid resection	15(10)	9(8)	6(13)	
	LAR	82(52)	60(54)	22(48)	
	APR	56(35)	40(36)	16(35)	
Synchronous metastases	Yes	21(13)	14(13)	7(15)	0.648
	No	137(87)	98(88)	39(85)	
Neoadjuvant chemotherapy recurrence	Yes	28(18)	22(20)	6(13)	0.324
	No	130(82)	90(80)	40(87)	
Neoadjuvant radiotherapy recurrence	5x5 radiotherapy	4(3)	1(1)	3(7)	0.001
	(chemo)radiotherapy	56(35)	32(29)	24(52)	
	(chemo)reirradiation	98(62)	79(71)	19(41)	
Interval radiotherapy - surgery (weeks)	<8	30(20)	13(13)	17(39)	0.001
	8-12	65(44)	52(50)	13(30)	
	>12	53(36)	39(38)	14(32)	
Surgical procedure	LAR	18(11)	11(10)	7(15)	0.112
	APR	15(10)	7(6)	8(17)	
	Multivisceral resection	108(68)	81(72)	27(58)	
	Non visceral resection	17(11)	13(12)	4(9)	
Procedure time (hours)	0-3	2(1)	2(2)	0(0)	<0.001
	3-5	28(19)	27(26)	1(2)	
	>5	120(80)	76(72)	44(98)	

Table 3. (continued)

Missings not inluded in group comparison, percentages might not add up due to rounding.
Abbreviations: IOERT: intra-operative electron beam radiotherapy; HDR-IORT: high-dose-rate intra-operative brachytherapy; LAR: low anterior resection; APR: abdominoperineal resection

Locally recurrent rectal cancer—survival outcomes

The median OS was 28 months (IQR, 17-43 months) for patients treated with HDR-IORT and 31 months (IQR, 12-52 months) for patients treated with IOERT. The 3-year and 5-year OS rates were 39% and 12%, respectively, for patients who received HDR-IORT, which was not significantly different compared with patients who received IOERT (3-year and 5-year OS rates of 44% and 18%, respectively; P = 0.747). The median LRFS was 19 months (IQR, 12-27 months) for patients treated with HDR-IORT and 14 months (IQR, 12-16 months) for patients treated with IOERT. The 3-year and 5-year LRFS rates for patients who received HDR-IORT were 38% and 34%, respectively. For patients who received IOERT, these rates were 29% and 19%, respectively (P = 0.139; Figure 2).

Figure 2. Kaplan-Meier curve for local recurrence-free survival in patients with locally recurrent rectal cancer

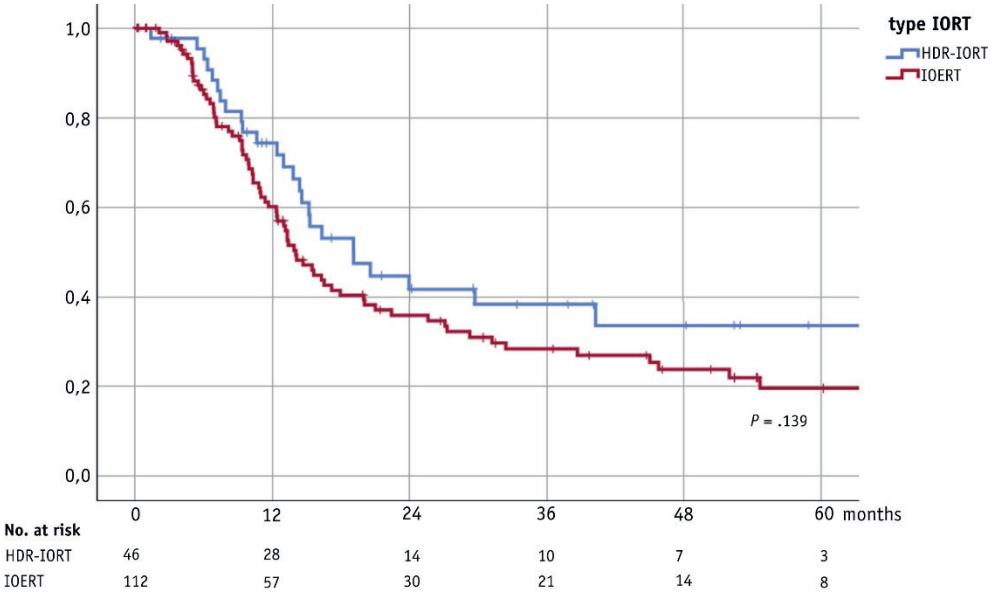


Table 4 shows the results of the univariable and multivariable analyses. As neoadjuvant radiation therapy for the primary tumor and the recurrent tumor were strongly correlated, only neoadjuvant radiation therapy for the primary tumor was included in the multivariable analysis. After multivariable analysis, the IORT modality had no significant association with OS, whereas age and N-stage of the primary tumor did. For LRFS, multivariable analysis revealed a significantly favorable LRFS in patients treated with HDR-IORT compared with patients treated with IOERT (HR, 0.567; 95% CI, 0.349-0.920; P = 0.021). In addition, the pT stage and pN stage of the primary tumor were significantly related to the development of a local recurrence.

Table 4. Uni- and multivariable analysis for overall and local recurrence free survival in LRRC patients

	Overall Survival						Local recurrence					
Variable	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
Type IORT												
IOERT	1.00	Ref			Ref		1.00	Ref			Ref	
HDR-IOBT	1.062	0.737-1.531	0.747	1.168	0.792-1.722	0.433	0.711	0.451-1.120	0.141	0.567	0.349-0.920	**0.021**
Age												
<70	1.00	Ref			Ref		1.00	Ref				
>70	1.753	1.191-2.581	**0.004**	1.780	1.207-2.626	**0.004**	1.476	0.916-2.379	0.110			
Gender												
Male	1.00	Ref					1.00	Ref				
Female	1.013	0.715-1.435	0.942				0.787	0.513-1.207	0.272			
cTstage primary tumor												
T3	1.00	Ref					1.00	Ref		)0	Ref	
T4	0.952	0.615-1.472	0.824				0.586	0.366-0.937	**0.026**	0.564	0.339-0.936	**0.027**
cNstage primary tumor												
N0	1.00	Ref			Ref		1.00	Ref		)0	Ref	
N1	1.335	0.906-1.967	0.144	1.312	0.891-1.934	0.169	0.908	0.567-1.456	0.690	0.986	0.602-1.616	0.955
N2	1.820	1.165-2.842	**0.008**	1.879	1.202-2.938	**0.006**	1.914	1.135-3.229	**0.015**	2.099	1.228-3.588	**0.007**
History metastases												
No	1.00	Ref					1.00	Ref				
Yes	1.542	0.954-2.492	0.077				1.070	0.569-2.012	0.834			
Neoadjuvant therapy primary tumor												
None	1.00	Ref			Ref		1.00	Ref		)0	Ref	
5x5 radiotherapy	1.346	0.904-2.003	0.143	1.306	0.863-1.978	0.207	1.666	1.035-2.682	**0.036**	1.445	0.866-2.411	0.158
(chemo)radiotherapy	1.594	1.046-2.428	**0.030**	1.440	0.921-2.251	0.110	1.932	1.183-3.153	**0.008**	1.521	0.888-2.604	0.127
Surgery primary tumor												
Local excision	1.00	Ref					1.00	Ref				
(Recto)sigmoid resection	1.087	0.354-3.343	0.884				0.404	0.096-1.694	0.215			
LAR	1.247	0.454-3.422	0.668				1.155	0.361-3.699	0.808			
APR	1.280	0.460-3.562	0.637				1.128	0.346-3.677	0.842			

Table 4. (continued)

	Overall Survival						Local recurrence					
Variable	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
Synchronous metastases												
No	1.00	Ref					1.00	Ref				
Yes	1.220	0.751-1.981	0.423				0.971	0.530-1.778	0.924			
Neoadjuvant chemotherapy												
No	1.00	Ref					1.00	Ref				
Yes	1.191	0.765-1.854	0.438				1.447	0.891-2.350	0.135			
Neoadjuvant radiotherapy												
5x5 radiotherapy	1.00	Ref					1.00	Ref				
(chemo)radiotherapy	1.139	0.354-3.666	0.828				0.539	0.164-1.769	0.308			
(chemo)reirradiadtion	1.512	0.475-4.815	0.484				0.922	0.288-2.950	0.891			
Time between RT and surgery												
<8 weeks	1.00	Ref					1.00	Ref		1.00	Ref	
8-12 weeks	1.120	0.705-1.780	0.631				1.556	0.865-2.798	0.140	0.974	0.500-1.898	
>12 weeks	1.399	0.860-2.276	0.176				1.890	1.029-3.478	**0.040**	1.236	0.628-2.433	
Type of surgery												
LAR	1.00	Ref					1.00	Ref				
APR	0.807	0.380-1.711	0.575				1.143	0.476-2.748	0.765			
Multivisceral resection	0.923	0.556-1.532	0.755				1.226	0.631-2.381	0.548			
Non visceral resection	1.000	0.509-1.963	1.000				0.875	0.355-2.155	0.771			
Procedure time (hours)												
0-3	1.00	Ref					1.00	Ref				
3-5	0.736	0.171-3.162	0.680				0.584	0.134-2.550	0.475			
>5	1.031	0.254-4.190	0.966				0.724	0.177-2.954	0.652			
Complications												
Clavien-Dindo 0-II	1.00	Ref					1.00	Ref				
Clavien-Dindo III-V	1.399	0.978-2.001	0.066				0.738	0.466-1.170	0.197			

Abbreviations: LRRC: locally recurrent rectal cancer; IOERT: intraoperative electron beam radiotherapy; HDR-IORT: high-dose-rate intraoperative brachytherapy; RT: radiotherapy; LAR: low anterior resection; APR: abdominoperineal resection

Complications

Of the 215 patients with LARC, data on postoperative complications were available in 196 cases (91%). Major complications were comparable between the two groups, as 30% of patients treated with IOERT and 27% of patients treated with HDR-IORT had at least 1 complication with a Clavien-Dindo grade ≥3 (P = .665). In patients who experienced a major complication, the most common were presacral abscess (27%), bleeding (11%), abdominal wound dehiscence with evisceration (11%), intraabdominal abscess (9%), perineal wound necrosis (5%), leakage of the ureter or bladder reconstruction (5%), anastomotic leakage (5%), and ureter stenosis (5%) (Supplementary Table 1). In-hospital mortality was observed in 2 of 151 patients (1%) in the IOERT group, whereas no in-hospital mortality was observed in the HDR-IORT group (P = 0.546).

Of the 158 patients with LRRC, data on postoperative complications were available in 157 cases (99%). In patients treated with HDR-IORT, a significantly greater number of major complications was observed compared with patients treated with IOERT (46% and 26%, respectively; P = .017). In patients who experienced a major complication, the most common were presacral abscess (26%), leakage of the ureter or bladder reconstruction (12%), abdominal wound dehiscence with evisceration (8%), and intraabdominal abscess (6%) (Supplementary Table 2). In-hospital mortality was observed in 4 of 112 patients (4%) in the IOERT group and in 1 of 46 patients (2%) in the HDR-IORT group (P > 0.999).

DISCUSSION

This retrospective study of data from two large tertiary referral centers showed a favorable LRFS for patients treated with HDR-IORT compared with those treated with IOERT after an R1 resection for LARC or LRRC. This difference suggests a dose-dependent efficacy of IORT, as HDR-IORT delivers a higher surface dose compared with IOERT. Moreover, the fact that one modality was more effective than the other indicates that IORT has a measurable effect on LRFS in R1 patients; to our knowledge, this has not been shown previously in a large comparative study.

Several published studies have assessed the feasibility and efficacy of administering IORT in patients with LARC and/or LRRC. The majority of these studies have focused on the use of IOERT and, to a lesser extent, HDR-IORT.(12) Only a few have reported on the use of both techniques, but to our knowledge, this is the first to compare the IOERT and HDR-IORT treatment modalities.(20, 21)

The difference in LRFS between HDR-IORT and IOERT observed in the current study may have been caused by differences in dose distributions between the two IORT modalities. HDR-IORT is delivered at a much more concentrated dose to the surface of the target area;

the estimated dose at the target surface was 170% of the prescribed 10 Gy dose at a 10-mm depth. IOERT delivers the radiation dose more homogeneously throughout the tissue depth, but as a consequence, it delivers a surface dose equal to the prescribed dose. Adjusting the IOERT procedure by increasing the surface dose with the use of a bolus and adapting the dose at a 10-mm depth to ensure it is equal to the HDR-IORT prescribed dose could result in a dose distribution that is more similar to that of HDR-IORT.

In addition, the size of the treated surface may also play a role in the observed difference in LRFS between both IORT modalities. Although we could not specify the irradiated area for HDR-IORT in this study, previous work has shown that the mean treated area is 73 cm^2 (range, 25-170 cm^2), which is 2 to 3 times larger than the area treated with IOERT.(22) Furthermore, IOERT applicators are poorly suited to curved areas such as the presacral and posterolateral area, in contrast to the flexible applicators used in HDR-IORT. However, we do not believe this played a role in the better dose delivery by HDR-IORT, as we corrected for the problems caused by the rigid applicators, such as minor airgaps and a limited diameter of the tube.

In the patients with LRRC, significant baseline differences between the two IORT modalities were observed regarding the neoadjuvant treatment and the time between EBRT and surgery. Previous work published by Holman et al showed that a waiting time shorter than 8 weeks, as was observed in the HDR-IORT group, resulted in better LRFS in patients with an R1 resection.(23, 24) This factor could also have played a role in the observed difference in LRFS between HDR-IORT and IOERT treatment groups in this study. However, in the multivariable analysis, we adjusted for these differences.

There was no observed difference in major postoperative complications between the two IORT modalities in patients with LARC. On the other hand, in patients with LRRC, HDR-IORT was associated with a significantly greater number of major postoperative complications compared with IOERT. Hypothetically, HDR-IORT induces more tissue damage and necrosis, owing to a higher surface dosage and a larger irradiated surface area compared with IOERT, which may increase the likelihood of postoperative complications. This hypothesis could not be explored further within this study, owing to the low frequency of each distinct complication event.

Another significant difference observed between the two groups was the duration of the procedure. As mentioned, HDR-IORT is a more time-consuming procedure to perform, because it requires individual treatment planning as well as a longer application time. Thus, the difference in the duration of the procedure is mainly the result of the IORT modality and not the extent of the surgery itself.

Despite the aforementioned difference in neoadjuvant treatment (which is a result of referral patterns rather than treatment strategies) and the time between EBRT and IORT in patients with LRRC, there were no baseline differences between the IOERT and HDR-IORT groups. Furthermore, both hospitals followed the same national guidelines regarding diagnostics and neoadjuvant treatment planning, and the preoperative, perioperative, and postoperative protocols, as well as the follow-up schedule, were similar between both hospitals. Moreover, most surgeons responsible for performing the procedures involved in this study worked at both hospitals and agreed that the case mix in both hospitals was similar. Hence, we feel that this study provides a valid comparison of the two IORT modalities.

IORT was not delivered to all patients with an R1 resection in our institutions. In patients with LARC, treatment with IORT was not delivered in cases of palliative resections or as a consequence of an incorrect clinical judgment of the resection margin status, false-negatives based on analysis of frozen sections, or technical problems encountered during surgery (eg, hemodynamic instability in the patient). In patients with LRRC, IORT was mainly omitted because of a high cumulative dose owing to prior (intraoperative) irradiation that did not allow an additional IORT boost. In addition, palliative resections and surgical technical problems (eg, hemodynamic instability in patients) were reasons to omit IORT.

With the evolving neoadjuvant treatment strategies, it remains important to bear in mind the possibility of delivering IORT. A neoadjuvant treatment strategy in which neoadjuvant radiation therapy is followed by consolidation chemotherapy as proposed in the Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial results in a longer interval between the radiation therapy and IORT compared with the so-called “total neoadjuvant treatment” strategies, in which neoadjuvant radiation therapy is preceded by induction chemotherapy; thus, a shorter interval between radiation therapy and IORT exists.(25, 26) Although a longer waiting time increases the chance of an R0 resection, a shorter interval seems to benefit the effect of IORT in case of an R1 resection (Table 2).(23, 24)

Owing to the retrospective nature of this study, there were some apparent shortcomings. However, as a result of the prospective maintenance of the database, very few data were missing: specifically, 2% and 1.6% of the values reported in Tables 2 and 4, respectively. Nonetheless, we could not specifically report on long-term complications associated with IORT. In particular, it would be of interest to compare complications such as plexopathy and peripheral neuropathy, which are known to be dose-dependent late toxicities associated with pelvic IORT, between the two modalities.(27) Furthermore, the patterns of

(re)recurrence (infield or outfield) were missing in 37% of patients with LARC and 24% of patients with LRRC, so no related conclusions could be drawn.

In conclusion, in this retrospective cohort study from two large tertiary referral centers, a significant difference in the efficacy of IORT modalities was observed in patients with an R1 resection for LARC or LRRC, in favor of HDR-IORT. Therefore, the CZE is currently in the process of adapting the IOERT procedure to improve outcomes, while limiting the toxicity, in patients with an R1 resection for LARC or LRRC.

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SUPPLEMENTS

Supplementary table 1. Type major postoperative complications LARC

	N (%)
Presacral abscess	15(27)
Abdominal wound dehiscence with evisceration	8(14)
Bleeding	6(11)
Intraabdominal abscess	5(9)
Leakage ureter/bladder/psoas hitch	3(5)
Perineal wound necrosis	3(5)
Anastomotic leakage	3(5)
Ureter stenosis	3(5)
Respiratory insufficiency	2(4)
Ileus	2(4)
Septic bleeding	2(4)
Peroperative hemorrhage	2(4)
Stoma necrosis	1(2)
Occlusion a. femoralis stent	1(2)
Reanimation (PEA)	1(2)
Relaparotomy to remove suture from uterus	1(2)
Wound abscess	1(2)
Blowout coecum due to oedema ostomy	1(2)

Some patients had ≥1 major complication

Supplementary table 2. Type major postoperative complications LRRC

	N (%)
Presacral abscess	13(26)
Leakage ureter/bladder	6(12)
Abdominal wound dehiscence with evisceration	4(8)
Intraabdominal abscess	3(6)
Bleeding	2(4)
Perineal wound necrosis	2(4)
Compartment syndrome	2(4)
Fistula	2(4)
Anastomotic leakage	2(4)
Peroperative hemorrhage	2(4)
Arrhythmia	2(4)
Hemodynamic instability	2(4)
Sepsis	2(4)
Stoma necrosis	1(2)
Lactate acidosis	1(2)
Acute tubular necrosis	1(2)
Decompensation	1(2)
Respiratory insufficiency	1(2)
Unknown	1(2)

CHAPTER 4

Locally recurrent rectal cancer: oncological outcomes of neoadjuvant chemoradiotherapy with or without induction chemotherapy

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ABSTRACT

Introduction

Treatment regimen for locally recurrent rectal cancer (LRRC) differs widely. In the Netherlands, neoadjuvant chemo(re-)irradiation (CRT) is standard of care in these patients, while some centres added induction chemotherapy (ICT) to the CRT as well. The aim of this study was to compare the results of two large tertiary referral centres with different neoadjuvant standards in the treatment of LRRC in the Netherlands and evaluate long-term oncological outcomes.

Methods

All patients who underwent a surgical resection for intended curable LRRC were retrospectively studied in Erasmus Medical Centre (EMC) or Catharina Hospital Eindhoven (CHE) between January 2014 and December 2020. The main outcomes studied were overall survival (OS), local re-recurrence free survival (LRFS), and metastasis free survival (MFS).

Results

In total, 191 patients were included in the study, 107 patients from CHE and 84 patients from EMC. In CHE, 78.5% of the patients were treated with ICT, compared to 2.4% in EMC. Both hospitals had similar rates of radical resections (p=0.678), while CHE had significantly more pathologic complete response (pCR) (p=0.031). The 5-year OS, LRFS and MFS were respectively 42%, 52.5%, and 37.1% in EMC versus 48.3%, 42.3% and 44.7% in CHE (p=0.325, p=0.410, p=0.205). When stratified for patient patients that received ICT, 14 patients (16.3%) had a pCR, compared to 11 patients without ICT (10.5%), p=0.237.

Conclusion

There were no significant differences in oncological outcomes between the hospitals. ICT did not result in more patients with a pCR, however CHE had significantly more patients with a pCR than EMC.

INTRODUCTION

In case of a surgical radical resection (R0 resection), locally recurrent rectal cancer (LRRC) has a 5-year overall survival rate of 48-58%, while an irradical resection (R1/2 resection) has a 5-year overall survival rate of only 10-18%.(1–3) The most common approach to achieve this R0 resection, is to administer chemoradiotherapy in the radiotherapy naïve patients before surgery, however, most patients with LRRC already received chemoradiotherapy for their primary tumour.(15,16) That results in a variety of treatment strategies that differs worldwide, which hampers comparison.

Some countries and centres focus on the extent of surgery without the use of chemo- or radiotherapy to accomplish the R0 resection.(4–7) Others do focus on neoadjuvant therapy, aiming for downstaging to facilitate R0 resections and a possibly less extensive approach to surgery.(8–10) In previously irradiated patients, the role of reirradiation in LRRC is still debated, as well as the addition of induction chemotherapy before neoadjuvant chemo(re)irradiation.(17–19) Whether successful downstaging truly enables less extensive surgery than upfront surgery for LRRC, whilst not compromising oncological outcomes, remains a matter of debate, with no clinical evidence proving superiority of either approach.(11–14)

In a previous study, two tertiary referral centres that followed different treatment strategies were compared. In one centre, upfront surgery was standard of care, whereas in the other, neoadjuvant long course chemoradiotherapy and chemo re-irradiation were standard of care.(20) This study showed that patients who received neoadjuvant long course chemoradiotherapy had significantly better oncological outcomes compared to those who had not. Upfront surgery resulted in the highest R0 resection rate, while overall survival in both hospitals was identical.

In this study, two Dutch tertiary referral centres were compared. Both centres consider long course chemoradiotherapy or chemo re-irradiation as standard treatment for LRRC, but one centre also treated their patients with additional induction chemotherapy as standard of care. The aim of this study was to evaluate long-term oncological outcomes in patients with locally recurrent rectal cancer, comparing the results of these two large tertiary referral centres with different neoadjuvant standards in the treatment of LRRC.

METHODS

Patients

All consecutive patients who underwent a surgical resection for intended curable LRRC were retrospectively enrolled in Erasmus Medical Centre (EMC) or Catharina Hospital Eindhoven (CHE) between January 2014 and December 2020. Patients from CHE before January 2016 were excluded, as induction chemotherapy (ICT) was not yet standard of care during that period and was only administered in a selection of patients. In EMC, patients were standardly treated with chemo(re)irradiation over the period from January 2014 till December 2020. Patients were excluded from analyses if they had a second or third recurrence, synchronous metastasis at time of recurrence, local excision of the primary tumour, or failure of watch and wait approach for the primary tumour that resulted in regrowth. Follow-up was completed until 24-11-2022.

Neoadjuvant treatment

In both hospitals, all patients received neoadjuvant treatment. In radiotherapy-naive patients, long course radiotherapy was delivered with a cumulative dose of 50-50.4Gy in fractions of 1.8 or 2Gy, mostly with concomitant capecitabine (825mg/m2 twice a day on radiotherapy days). In patients who previously received pelvic radiotherapy, radiotherapy was delivered with a cumulative dose of 30Gy in fractions of 2Gy, with an equivalent dose of concomitant capecitabine. In CHE, it was standard procedure to administer induction chemotherapy (ICT) prior to chemoradiotherapy. ICT generally consisted of three cycles of CAPOX (capecitabine and oxaliplatin) or four cycles of FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin). An additional course of chemotherapy, consisting of 1 cycle of CAPOX or 2 cycles of FOLFOX between chemoradiotherapy and surgery, was provided to patients with stable or responsive disease on ICT in case of acceptable tolerance.

Surgery

Surgery was performed 8–14 weeks after the last radiotherapy fraction. It generally consisted of an en-bloc resection of the tumour including involved pelvic organs and structures to achieve clear surgical margins. The procedures were categorized as followed: resection with re-anastomosis; abdominoperineal resection (APR); partial/total pelvic exenteration, defined as resection of the rectum, bladder, and prostate with vesicles or uterus with ovaries; and resection “not otherwise specified” (n.o.s.), defined as an extra-anatomical, soft tissue and/or bony resection. Surgery could be combined with intraoperative radiotherapy (IORT), delivered by intraoperative electron beam radiation therapy (IOERT) in CHE or high-dose-rate intraoperative brachytherapy (HDR-IORT) in EMC, at the discretion of the treating surgeon and radiation oncologist, at the area considered most at risk for an irradical resection aided by the results of frozen sections.

Statistical analysis

Endpoints were overall survival (OS), local re-recurrence free survival (LRFS) and metastasis free survival (MFS). OS was calculated from the date of LRRC diagnosis until the date of death of any cause or was censored to the last follow-up date. LRFS and MFS were calculated from the date of LRRC diagnosis until the date local recurrence or metastasis were detected or were censored at the last follow-up or death. Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data as counts and percentages. Group comparisons were performed using the Chi-square test, Fisher exact tests or the Mann–Whitney U test, as appropriate. Survival analyses and cumulative incidences were calculated using the Kaplan–Meier method and comparisons were made using the log-rank test. Univariate Cox regression analysis was performed to calculate the association between overall survival and patient and tumour characteristics. Variables with a significance level of $p \leq 0.05$ in univariate analysis and clinically relevant variables were entered into the multivariate analysis. Two-sided p values of $p \leq 0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

Patient characteristics

In total, 191 patients were included in the study, 107 patients from CHE and 84 patients from EMC. The median follow-up period was 43 months [IQR 28-75 months], which was similar in both hospitals (p=0.368). Details regarding patient and treatment characteristics are shown in Table 1.

Table 1. Patient and treatment characteristics

Baseline		CHE N=107 (%)	EMC N=84 (%)	Overall N=191 (%)	*p*-value
Gender	Female	29 (27.1)	30 (35.7)	59 (30.9)	0.201
	Male	78 (72.9)	54 (64.3)	132 (69.1)	
Age	Mean (IQR)	66.8 (61-73)	66.9 (59-74)	66.6 (60-74)	0.632
Neoadjuvant chemotherapy primary	Yes	8 (7.5)	5 (6.1)	13 (6.9)	0.710
Neoadjuvant radiotherapy primary	Short course (25Gy)	23 (21.7)	14 (16.7)	37 (19.5)	0.013
	Long course (45-50Gy)	46 (43.6)	23 (27.4)	69 (36.3)	
Surgery primary	Sigmoidal resection	8 (7.5)	16 (19.0)	24 (12.6)	0.042
	TEM	3 (2.8)	4 (4.8)	7 (3.7)	
	LAR	63 (58.9)	39 (46.4)	102 (53.4)	
	APR	32 (29.9)	21 (25.0)	53 (27.7)	
	Other	1 (0.9)	4 (4.8)	5 (2.6)	
Adjuvant chemo primary	Yes	16 (15.1)	14 (17.7)	30 (16.2)	0.632
pTstage primary	0-2	26 (30.2)	27 (34.2)	53 (32.1)	0.588
	3-4	60 (69.8)	52 (65.8)	112 (67.9)	
pNstage primary	0	44 (53.0)	42 (51.9)	86 (52.4)	0.882
	+1	39 (47.0)	39 (48.1)	78 (47.6)	
pMstage primary	0	75 (83.3)	81 (100)	156 (91.2)	<0.001
	1	15 (16.7)	0	15 (8.8)	
Multifocal recurrence	Yes	17 (16.8)	11 (13.1)	28 (15.1)	0.480
Induction chemotherapy LRRC	Yes	84 (78.5)	2 (2.4)	86 (45.0)	<0.001
Neoadjuvant treatment LRRC	No radiotherapy at all	2 (1.9)	0	2 (1.0)	0.034
	(Chemo)radiotherapy (45-50Gy)	36 (33.6)	43 (51.2)	79 (41.4)	
	(Chemo)re-irradiation (30Gy)	69 (64.5)	40 (47.6)	109 (57.1)	
Surgery LRRC	Resection with re-anastomosis	14 (13.1)	19 (22.6)	33 (17.3)	0.012
	APE	49 (45.8)	28 (33.3)	77 (40.3)	
	Total pelvic exenteration	16 (15.0)	24 (28.6)	40 (20.9)	
	Tumour resection n.o.s.*	28 (26.2)	13 (15.5)	41 (21.5)	
Additional organs removed	Urinary bladder	19 (20.2)	28 (33.3)	47 (26.4)	0.047
	Prostate (males separately)	13 (19.7)	23 (42.6)	36 (30.0)	0.006
	Vagina (females separately)	14 (48.3)	10 (33.3)	24 (40.7)	0.243
	Uterus (females separately)	8 (27.6)	11 (36.7)	19 (32.2)	0.456
	Sacrum	32 (33.3)	14 (16.7)	46 (25.6)	0.011
IORT	Yes	87 (81.3)	45 (53.6)	132 (69.1)	<0.001
Pathologic complete response	Yes	19 (17.8)	6 (7.1)	25 (13.1)	0.031

Table 1. (continued)

Baseline		CHE N=107 (%)	EMC N=84 (%)	Overall N=191 (%)	*p*-value
Resection margin	R0	83 (77.6)	63 (75.0)	146 (76.4)	0.678
	R1/R2	24 (22.4)	21 (25.0)	45 (23.6)	
Postoperative complications ≤30 days	None	34 (31.8)	24 (27.9)	58 (30.1)	0.692
	Clavien-Dindo I-II	45 (42.5)	34 (40.5)	79 (41.6)	
	Clavien-Dindo III-V	27 (25.5)	26 (31.0)	53 (27.9)	

**Tumour resection n.o.s.= tumour resection not otherwise specified.*

Abbreviations: IORT: intra-operative radiation therapy. LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer

Type of neoadjuvant treatment for LRRC

Induction chemotherapy was administered in 86 patients in total, of which 84 patients (78.5%) in CHE and 2 patients (2.4%) in EMC. Most patients received chemo re-irradiation, 69 patients (64.5%) in CHE and 40 patients (47.6%) in EMC. Long course chemoradiotherapy was administered in 36 patients (33.6%) in CHE and 43 (51.2%) in EMC. The interval between diagnosis and surgery was 7.8 months (SD 3.1) for patients treated with ICT, compared with 5.5 months (SD 2.5) for patients treated without ICT.

Type of surgery for LRRC

In both hospitals, most patients underwent an APR, 49 patients (45.8%) in CHE and 28 patients (33.3%) in EMC. EMC performed more total pelvic exenterations (28.6% versus 15.0%), p=0.012, while in CHE more (partial) sacral bone resections were performed (33.3% versus 16.7%), p=0.011. IORT was administered in 87 patients (81.3%) in CHE and in 45 patients (53.6%) in EMC, p<0.001. There was no difference between the amount and severity of postoperative complications between the hospitals (p=0.692).

Both hospitals achieved similar rates of R0 resections, 83 patients (77.6%) in CHE and 63 patients (75.0%) in EMC, p=0.678. Pathological complete response rates (pCR) were 17.8% in CHE and 7.1% in EMC (p=0.031). When stratified for patient patients that received ICT, 14 patients (16.3%) had a pathologic complete response (pCR), compared to 11 patients without ICT (10.5%), p=0.237.

There were no significant differences in oncologic outcomes between the hospitals, as shown in Table 2 and Figure 1. In univariable Cox regression analysis, an R0 resection and a pCR were associated with an improved survival, while being female and having major postoperative complications (Clavien-Dindo III-V) were associated with impaired survival (p≤0.05). In the multivariable model, the association between an improved OS and an R0 remained, as well as having major postoperative complications and being female (p<0.001, p=0.020 and p=0.035 respectively). There were no significant differences in the

achievement of a pCR anymore, or between hospitals in the model (p=0.078 and p=0.915 respectively, as shown in Table 3. Within the group of patients with a R0 resection, the patients that had a pCR had a 5-year OS of 67.7%, compared to 50.1% in patients without a pCR (p=0.057), as shown in Figure 2.

Table 2. Survival of both hospitals from diagnosis of LRRC

Survival	Year	EMC (%)	CHE (%)	*p*-value
OS	1	91.7	96.2	0.325
	3	60.6	73.1	
	5	42.0	48.3	
Median OS	months (95%CI)	47.9 (36.5-61.2)	56.4 (35.9-76.9)	
LRFS	1	92.1	97.8	0.410
	3	64.3	54.4	
	5	52.5	42.3	
Median LRFS	months (95%CI)	68.7 (63.6-90.2)	46.5 (29.6-63.3)	
MFS	1	85.8	92.5	0.205
	3	47.9	52.5	
	5	37.1	44.7	
Median MFS	months (95%CI)	33.3 (20.7-45.9)	46.9 (35.1-58.7)	

Figure 1. Kaplan-Meier analysis of oncological outcomes in patients from CHE compared to EMC

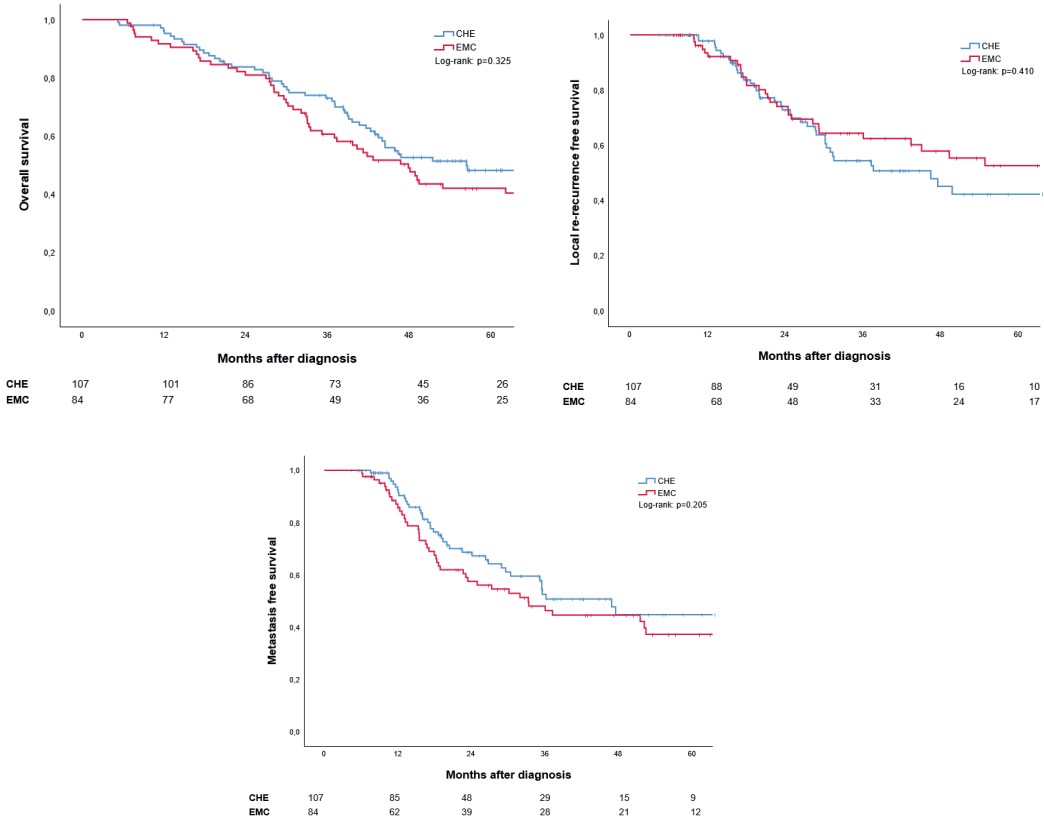
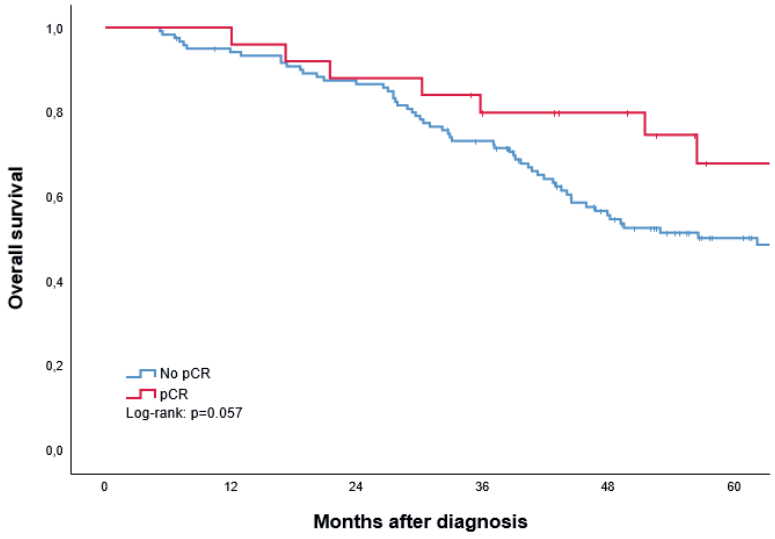


Figure 2. Kaplan-Meier analysis of the OS in patients with an R0 resection, stratified for pCR



pCR	25	25	22	18	16	9
No pCR	121	112	103	85	56	35

DISCUSSION

The aim of this study was to evaluate long-term oncological outcomes in patients with locally recurrent rectal cancer, comparing two Dutch tertiary referral centres with different local standards of care. CHE administered induction chemotherapy (ICT) prior to neoadjuvant chemoradiotherapy compared to chemoradiotherapy alone in the EMC. Most importantly, there were nog significant differences between the hospitals in oncological outcomes. However, there were significantly more patients from CHE with a pathologic complete response (pCR) than EMC, even though the sort of neoadjuvant treatment could not show a difference in pCR in this study. Achieving an R0 resection was associated with an improved overall survival in the multivariable Cox regression model.

Based on the latter, and based on our previous comparison with a centre in which upfront surgery was standard of care, one could argue that an R0 resection is the most efficient strategy, as neoadjuvant treatment appears of no advantage in respect to overall survival.(20) However, it is entirely reasonable to argue contrariwise, as upfront surgery also did not demonstrate to improve overall survival compared to neoadjuvant treatment, despite an increased R0 resection rate.(20–22) It seems unlikely that further escalation of surgical procedures would further improve oncological outcomes, as we are not able to change tumour biology. Moreover, the extensive surgical procedures result in a reduced

quality of life.(23–25) Therefore, there might be an advantage of neoadjuvant treatment in the attempt to deescalate the extent of the surgical procedures, without compromising oncological outcomes.

The achievement of a pCR was another important prognostic factor for survival in this study. A pCR could be achieved, due to a relatively benign tumour biology, with the addition of neoadjuvant treatment, regardless of the extent of surgery. In contrast to the achievement of an R0 resection, in which the extent of surgery is the main predictor, a pCR might be a true indicator of tumour biology. Therefore, the invalidating effects of extensive surgery could be prevented when a complete response is suspected before surgery, by a less radical surgical approach or even withdraw from surgery completely.

Tumour biology is probably one of the most important factors in the prediction of survival. The prolonged period of neoadjuvant treatment due to adding ICT, as done in CHE, might allow potential progression of the tumour and metastasis. With the combination of subsequent chemoradiotherapy, it allows for an even longer waiting period and a second evaluation, with the possibility to differentiate patients based on response. On the other hand, it could be stated that ICT could actually temporarily suppress the development of metastasis, and result in a delayed, but not prevented, development of metastasis. Nevertheless, in the follow up period of this study, the metastasis free survival was similar between the hospitals. Besides, toxicity grades of ICT seem manageable, and there was a similar number of postoperative complications between the hospitals.

The retrospective design of this study leads to certain limitations. As treatment with ICT was not standard in CHE between 2014 and 2016, patients within this period were excluded, even so, there could still be a minor selection bias due to the different selection of patients with curable intent in both hospitals due to the expected downstaging from the ICT. Besides, we have no data on patients that did not proceed to surgery. Data is lacking on the patients with progression of disease under neoadjuvant treatment, the patients that had a good response on treatment and were withdrawn from surgery, and the patients that choose a non-operative strategy. However, we do not think that this hampers comparison, as selection of patients for surgery is done according to the same standard of care methods in both hospitals. Another limitation of this study is the sample size, which is underpowered to perform adequate subgroup analyses in treatment varieties. Therefore, results of large prospective studies, focused on different treatment strategies is essential. Currently, two randomised controlled trials, the PelvEx II study and GRECCAR15, are recruiting patients to investigate the addition of ICT before chemoradiotherapy and the addition of chemoreirradiation in patients with LRRC.(26,27)

In conclusion, there were no significant differences in oncological outcomes between the hospitals. ICT did not result in more patients with a pCR, however CHE had significantly more patients with a pCR than EMC. The achievement of an R0 resection and a pCR were independently associated with improved survival. Focus on the response rate could be beneficial in the selection of patients.

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PART II

Morbidity of advanced rectal cancer

CHAPTER 5

Anterior Pelvic Exenteration

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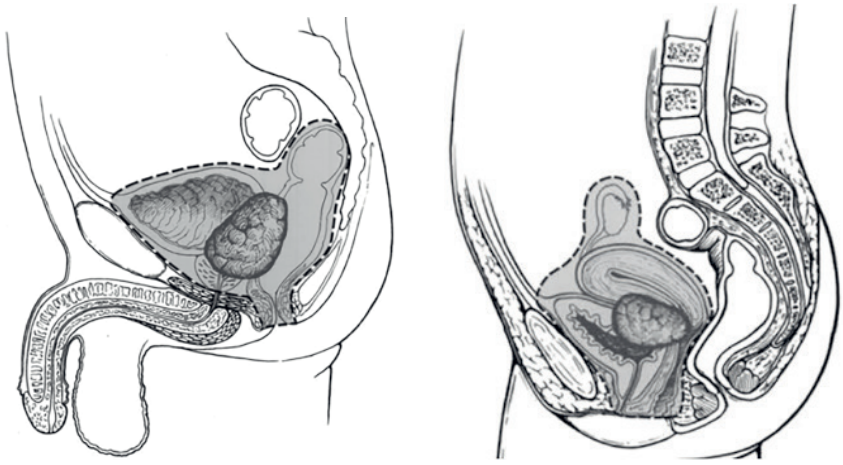
Background

In women, an anterior pelvic exenteration refers to removal of the bladder, uterus, and ovaries, leaving the rectum in situ; posterior pelvic exenteration refers to removal of the rec-tum, uterus, ovaries, and posterior vaginal wall. In men, an anterior exenteration means removal of the bladder, vesicles, and prostate, but this procedure is more commonly referred to as a cystoprostatectomy. A total pelvic exenteration includes complete excision of all pelvic organs including the bladder (+/− prostate/seminal vesicles) and rectum, and in women the uterus/ovaries and posterior vaginal wall (Figure 1). For selective resections of organs or structures that do not result in a formal anterior, posterior, or total pelvic exenteration, we use the term “modified exenteration.”

Diagnostics specific for Anterior Pelvic Exenteration

Before performing any extensive surgical procedures in the anterior pelvic area, diagnostic workup is imperative, both for surgical planning and eligibility. After diagnosis of the malignant disease, local status and distant metastasis need to be evaluated. One diagnostic modality that is eminently useful in patients with tumors in the anterior pelvic area is magnetic resonance imaging (MRI) with diffusion-weighted images. As it depicts tumor invasion in adjacent structures very accurately, feasibility of a successful complete resection can be evaluated. As urinary tract involvement is common in anterior pelvic malignancies, ureter obstruction and kidney function have to be evaluated carefully. The radioisotope renography, also known as the MAG3 scan, is especially helpful to detect any dysfunction in one of the kidneys. If one of the kidneys is not functioning properly, we usually choose to either ligate the ureter or remove the affected kidney. Re-anastomosing a kidney that has a little function may cause unnecessary complications such as anastomotic leakage and pyelonephritis.

Figure 1. Sagittal view of a total pelvic exenteration in the male (left) and anterior pelvic exenteration in the female (right).(23)



Surgical procedure

Traditionally, an anterior pelvic exenteration implies removal of the bladder, lower ureters, reproductive organs, draining lymph nodes, and pelvic peritoneum.(1) However, in clinical practice, the surgical procedure depends on the nature and the extent of the tumor. Anterior pelvic exenterations are performed by surgeon oncologists, gynecologists, and urologists. In case of limited ingrowth in other organs, a selective resection is sufficient. Resections of the ureter, uterus, and part of the bladder are examples of selective procedures that are routinely performed in specialized centers. More extensive tumors and locally recurrent malignancies often require formal anterior, posterior, or total pelvic exenterations. In this chapter, the different approaches for gynecological, urological, and rectal malignancies in the anterior pelvic area are described briefly. In addition, surgical procedures per involved organ in the anterior pelvic area are specified.

Anaesthesia and starting the procedure

Patients undergoing anterior pelvic exenterations are under general anesthesia and usually receive epidural anesthesia and are placed in the lithotomy position. Patients with advanced or recurrent pelvic cancer are generally not considered candidates for minimally invasive techniques, because tactile feedback is essential in achieving a radical resection. The procedure starts with a midline laparotomy. In our center, we routinely perform an omentoplasty, and therefore the midline incision may be advanced cranially further than strictly necessary for pelvic surgery. Since both locally advanced and locally recurrent

pelvic cancer is associated with a high incidence of systemic and peritoneal metastases, careful inspection of the whole abdomen is mandatory before continuing the procedure.

Urological approach

Anterior pelvic exenteration in urological cancers is often referred to as radical cystoprostectomy and is performed for muscle invasive bladder cancer and T4 prostate cancer. In men, the first step in this procedure is to mobilize and transect the distal ureters as described below. The space between the anterior rectum and posterior prostate may be entered by opening Denonvillier's fascia. The superior and inferior vesical artery are then identified and ligated respectively. To mobilize the bladder, seminal vesicles, and prostate, all tissue laterally from these structures has to be divided. The endopelvic fascia needs to be opened and the puboprostatic ligaments released. After ligation of the dorsal venous complex, the urethra is clipped and transected. By dividing the recto-urethralis muscles, the bladder, seminal vesicles, and prostate can be removed en bloc.

Gynaecological approach

In gynecological cancers, anterior pelvic exenteration includes removing the bladder, urethra, uterus, adnexa, and anterior vaginal wall. The posterior vaginal wall and rectum remain in situ. This procedure is mostly performed for malignancies of the cervix and anterior upper vagina. Anterior pelvic exenteration should only be performed if there is no tumor involvement in the space between the posterior vaginal wall and rectum. After mobilizing the bowel and entering the retroperitoneal space the distal ureters are transected. An incision in the pouch of Douglas is made to dissect the vaginal wall from the rectum. The broad and round ligaments and ovarian vessels are ligated and divided. The superior and inferior vesical arteries are identified and ligated, as are the uterine arteries and veins. The anterior and posterior vaginal wall may then be transected at the desired level. A more detailed description of the resection of the ureter, bladder, and vaginal wall is discussed below.

Rectal cancer

Locally advanced rectal cancer may invade the anterior pelvic organs such as the bladder and reproductive organs, especially in the case of locally recurrent rectal cancer in the pelvic area. In these cases, a total pelvic exenteration is performed.

Ureter dissection

The ureter is identified just above the level of the promontory and freed in a cranial and caudal direction, while preventing damage to the vasculature of the ureter itself. This is achieved by leaving the ureteral adventitia in place, rather than dissecting the ureter clean. Fibrosis and tumour are often difficult to differentiate during surgery and any fibrous tissue is considered tumour when performing radical resections. Transection of the ureter opens

up the lateral compartment of the pelvis and facilitates radical resection of disease in this compartment. Further resection of all tissues involved is performed, as identified by palpation, macroscopy and guided by preoperative MRI. When the bladder is not involved, the distal ureter may be cut and ligated, although leaving the ureter open rarely causes leakage from the bladder, because of the ureterovesical valve. The ureter may be reinserted in the bladder using the so called “psoas-hitch” technique. The bladder is mobilized on the contralateral and anterolateral side of the bladder. Ligation of the vesical artery and vein is usually not necessary. The bladder is incised transversely and fixed to the psoas muscle fascia just above the level of the anticipated anastomosis between ureter and bladder. The ureter is then inserted in the bladder through a small incision, spatulated and fixed with resorbable sutures. The transverse incision in the bladder is closed longitudinally, the single J catheter is led out through the bladder wall, the abdominal wall and skin. The single J splint is removed 10 days after surgery when no signs of anastomotic leakage are present on cystogram.

Lateral compartment in anterior pelvic exenterations

In case of involvement of the pelvic side wall, which occurs frequently in locally advanced and recurrent cancer, the internal iliac artery and vein may also be transected to facilitate more extensive resections up to the acetabulum. Reconstruction of the internal iliac artery and vein is generally not needed because of sufficient collateral blood supply. In seldom cases in which the external or common iliac vessels are involved, radical resection can sometimes be achieved by complete resection of the external or common iliac vessels.

In case of persistent lymph node metastases in the lateral compartment, a formal lymph node dissection of this area can be performed. The goal of lateral lymph node dissection is to resect all nodes in the pelvic side wall lateral from the internal iliac vessels after ligating these vessels while preserving the obturator nerve and sacral plexus. In some cases en bloc resection with these structures is necessary for full clearance of all suspect lateral lymph nodes.(2-4) This procedure is associated with increased urinary and sexual dysfunction, prolonged operation time and possible increased blood loss.(5, 6) However, in urological cancer, extensive pelvic lymph node dissection is recommended, not only to provide accurate staging and prognostic information, it might also be useful to identify patients eligible for adjuvant chemotherapy.(7-9) In rectal cancer, a recent meta-analysis showed no cancer specific advantages of extended lymphadenectomy, but there is evidence suggesting that patients with persistent lateral lymph nodes after neoadjuvant (chemo)radiotherapy may benefit from mesorectal excision with lateral lymph node dissection. (5, 10-12).

Partial cystectomy

Successful partial bladder resections are usually performed for radical resection of T4 sigmoid cancer, because these tumours may involve the more cranial aspect of the bladder. It is important to identify the orifices of both ureters to prevent obstruction of the ureter while closing the defect. It is also important to consider whether the size of the remaining bladder, combined with the anticipated function after neoadjuvant therapy, may result in a malfunctioning bladder. A urologist is often required to assist in decision making. When a small bladder remnant is unlikely to ever function properly a bladder resection and urinary diversion may be preferable. When partial resection is possible, we open the bladder cranially and choose the dissection planes on palpation and sight. We close the bladder with two layers of 3-0 slowly resorbable sutures. Lower tumours often involve the neck of the bladder and the orifices. Therefore, even small bladder wall resections at this level often result in a bladder remnant that is impossible to reconstruct in such a manner that both ureters can be reinserted into a functional remnant. Again, we advise to involve the urologist-oncologist in decision making. When partial resection is not feasible, a total pelvic exenteration is indicated.

Partial prostatectomy

In case of limited involvement of the prostate, without involvement of the urethra, a partial resection of the prostate may be attempted. It should be noted that the urethra is close to the posterior capsule of the prostate. We insert a large diameter silicone urinary catheter to palpate the urethra. Softer catheters are palpated less easily. Dissection of the capsule of the prostate should be performed through a perineal approach, usually as part of an abdominoperineal excision (APE) of the rectum. After performing the usual steps of an APE, we leave the anterior dissection as long as possible. We then identify the urethra by palpation of the silicone catheter and approach the capsule of the prostate caudally and laterally after lateral transection of the pelvic floor. The surgeon may now open the capsule of the prostate and include a layer of prostate in the resection specimen. Continuous palpation may clarify whether the tumour is resected completely and the surgeon can then return to the normal plane with or without including the seminal vesicles in the specimen. When complete removal of the seminal vesicles is performed, the surgeon should be aware that he is approaching the distal ureters from below. It is noteworthy that this type of resection often results in R2 resections, because the extra amount of tissue that can be resected is limited, palpation is difficult, especially in case of extensive fibrosis, and most surgeons are not accustomed to this dissection plane. Ideally, referral of these patients to a specialist centre, where conversion to a total pelvic exenteration can be performed as needed is advised. If prostate conserving surgery cannot be performed, which is common in case of more advanced tumours invading the prostate or locally recurrent disease in men, a prostatectomy should be performed. In some cases the urethra

cannot be re-anastomosed, as patients may have received a high dose radiotherapy, and this impairs proper healing of a vesico-urethral anastomosis. Therefore, a total pelvic exenteration is indicated in these cases.

Uterus and vaginal wall

Whereas in men, advanced malignancies may extend into bladder and prostate, in women, the uterus and posterior vaginal wall are the first to become involved in tumour extension. Tumour ingrowth into the body of the uterus is relatively rare, as the peritoneal reflection is located lower, at the level of the cervix. Tumour ingrowth at this level can easily be solved by en bloc resection of the uterus and adnexa, as is performed in gynaecological cancer. The ovarian vessels and ligaments are ligated and the uterus mobilized. This can be done by opening the peritoneum and dissecting the bladder form the anterior aspect of the uterus. The vaginal wall is identified and cleared to the caudal aspect of the cervix. The ureters are identified up to their insertion into the bladder or at least up to the point that they are no longer at risk. We then identify the vasculature at the level of the cervix, isolate and ligate it. When cutting of the many venous branches results in blood loss, it is imperative to be cautious with clamps, diathermy and energy devices, considering the proximity of the ureter. The vagina is opened anteriorly, below the palpated level of the cervix, using diathermy. The placement of clamps on the vaginal wall and lifting these facilitates separation of vagina and rectum. The rectum may be cut at the level desired. The vaginal wall may be closed with slowly absorbable sutures, taking care to not include the distal ureter.

Involvement of the cervix and posterior vaginal wall is more common. Findings on the preoperative MRI also guide decision making. The posterior wall is transected and the vaginal wall freed from the rectum. The lateral wall may be transected with diathermy, or an energy device. The defect in the vaginal wall may be large and when closed primarily, the remnant of the vagina may be small. This may be solved by performing some type of flap reconstruction. (e.g. Vertical Rectus Abdominis Myocutaneous Flap (VRAM Flap), in which case either skin, fascia or peritoneum may be used to replace the vaginal wall resected.(9) The alternative is to close the vagina primarily and refer the patient to the gynecologist for dilatation at an early stage. There are no data showing one technique is superior to the other. In case that the urethra is involved a total pelvic exenteration is indicated. In such cases, near complete removal of the vagina (colpectomy) is often unavoidable.

Urinary diversion (ileal conduit)

In anterior pelvic exenteration, the golden standard for urinary diversion is the ileal conduit. Although many variances exist, the best known technique is a Bricker

deviation.(13-15) In this procedure, a segment of the terminal ileum with a length of 12 to 18 centimetre is isolated at 10 centimetre from the valve of Bauhin on its mesentery. Usually, a hand sewed or stapled side-to-side anastomosis is performed to preserve continuation of the digestive tract. The mesentery window is closed with 3-0 absorbable sutures. The distal anastomosis of the ileum is then opened and the ileo-ureteral anastomosis can be constructed. The type of anastomosis performed (e.g. Bricker, Wallace) should be selected by the operating surgeon. The distal ileal loop is usually exteriorized through the lower right quadrant of the abdomen after bluntly dissecting the abdominal muscles and a circular excision in the skin is made.

Urinary diversion (colon conduit)

In some patients, the operator performs a colon conduit as urinary diversion, and is especially useful when the descending colon or sigmoid is transected during the procedure. The distal colon is cut leaving a segment of approximately 15-20 centimetre with an arterial pedicle. This may be the mesenteric inferior artery, the left colonic artery or in some cases, the left branch of the middle colic artery. After mobilization, both ureters may be anastomosed in exactly the same way as in Bricker's diversion. The urinary stoma often needs to be placed on the left side of the abdomen and after mobilization of the transverse colon, the stoma for stool is then placed on the right side of the abdomen. The advantage of this approach is that Bricker's diversion results in an extra ileo-ileostomy with a risk of complications such as leakage, whereas diversion with a colon conduit does not require an extra anastomosis.

When performing an ileal or colon conduit, small stents are placed in the ureters to ensure sufficient flow after surgery. The stents are fixed to the bowel wall with 4-0 quickly absorbable braided sutures and led out through the ostomy. If no complications occur, the stent are removed at day 9 and day 10 after surgery under antibiotic prophylaxis.

Mortality and morbidity

Anterior pelvic exenteration is a comprehensive surgical procedure with a high risk of complications, reinterventions and post-operative mortality.(16-20). However, due to improved surgical techniques, perioperative care and patient selection, there have been remarkable improvements in mortality and morbidity in the past decades.(18, 21, 22)

Morbidity

The overall morbidity rate after pelvic exenterative surgery is described within a range of 32-84%. The most important risk factor for perioperative morbidity is pre-operative pelvic irradiation.(17, 20, 23) Patients often experience general surgical complications such as (intraoperative) bleeding, wound infection, pneumonia and (pelvic or intra-abdominal) abscesses.(24) Perineal wound problems after exenterative surgery are also common:

besides wound infection and abscesses on the short term, perineal hernia or fistulas can occur on the long term.(23, 25) Muscle flap reconstructions may improve perineal wound outcome and pelvic floor dysfunction, but failure of perineal reconstructions often results in catastrophic wound problems.(26, 27)

Mortality

Perioperative 30-day mortality after pelvic exenteration is reported within a range of 0% - 25%.(28-32) A recent population based study described a mortality rate of 1.9% in women undergoing pelvic exenteration for gynaecologic malignancies.(32) Perioperative mortality after radical cystectomy for bladder cancer is reported between 1.2% and 3.2%.(33) For rectal cancer, a multicentre retrospective study reported a day mortality rates of 1.5% and 1.7% for locally advanced and locally recurrent rectal cancer respectively.(22)

Complications in anterior pelvic exenteration

Due to the more complex surgery which is performed in total pelvic exenterations, patients undergoing an anterior pelvic exenteration may experience less complications.(34) However, involvement of the urinary tract and the use of urinary diversions in anterior pelvic exenterations can lead to major problems.(35, 36) Short term complications of urinary diversion are leakage and obstruction of the urinary enteric anastomosis. Long term complications include urinary stenosis, fistula, stomal- and peristomal complications and upper urinary tract deterioration.(13) These complications can sometimes be managed conservatively but more often require reintervention by prolonged drainage, nephrostomy catheters or ureter re-implantation.(35-37) Other adverse events such as wound problems and gastro-intestinal complications also frequently occur in patients undergoing anterior pelvic exenteration.(17, 20, 23) Complications after anterior pelvic exenterations are listed in table 1.

Table 1. Complications after anterior pelvic exenteration

General
Haemorrhage
Wound infection
Intra-abdominal abscess
Pre-sacral abcess
Muscle flap necrosis
Pulmonary
Cerebrovascular
Cardiac
Delirium
Venous thrombosis
Urinary diversion related
Urinoma
Urosepsis
Metabolic acidosis
Anastomotic stricture
Obstruction
Fistula
Urinary tract infection
Acute renal failure
Hydronefrosis
Stomal and peristomal problems
Gastrointestinal
Ileus
Small bowel obstruction
Entericuteaneous fistula

Survival

Prognostic outcomes after the pelvic exenteration depend on the origin of the tumour.(16) For bladder cancer, five year survival rates after radical cystoprostatectomy have been reported between 60% to 67%. Main risk factors for recurrence and reduced bladder cancer specific survival are high tumour stage, lympho-vascular invasion and lymph node metastases.(38-41) In advanced and recurrent gynaecological malignancies, the five year overall survival rate after pelvic exenteration is around 50%.(42, 43) Five-year survival after pelvic exenteration for locally advanced recurrent rectal cancer is usually somewhere between 22% to 66%. For locally recurrent rectal cancer 5-year survival after pelvic exenteration is as low as 0% to 37%.(30, 44-46) Achievement of a clear resection margin is the most important predictive factor for survival in urological, gynaecological and rectal cancers.(16, 28, 29)

Quality of life following Anterior Pelvic Exenteration

Patients undergoing anterior pelvic exenteration are submitted to a major operation with a high complication rate, long hospital stay and an extensive rehabilitation process. This can have a huge impact on the quality of life. Patients often receive a permanent urostomy, colostomy, or both, which can be disabling in various ways.(47-49) However, patient-reported outcomes on quality of life usually improves after exenteration surgery and might even be comparable with those in general population in disease free patients.(50, 51)

Sexual dysfunction

Especially in younger women, anterior pelvic exenteration can greatly affect sexual function. Lubrication disorder and dyspareunia are common, especially when parts of the vaginal wall are resected.(52, 53) Due to this, women often experience a lack of sexual desire after pelvic surgery and only a small number of women is sexually active in the post-operative period.(52)

Men may experience erectile or ejaculatory dysfunction due to resection of the prostate and vesicles or due to damage to the neurovascular bundle supplying the genitalia.(54) A small number of men who were sexually active before cystoprostatectomy are still potent after surgery. Higher chances of remaining potency after surgery can be achieved when a nerve sparing operation is performed.(39, 54, 55) It is important to discuss expectations about sexual function after surgery with patients pre-operatively.(56)

Besides organic sexual dysfunction, both men and women report deterioration in body image and loss in sexual interest.(52-54) It is advisable to offer appropriate psychosexual counselling to patients and is particularly important in patients which are sexually active.(57, 58)

Urinary dysfunction

As in anterior pelvic exenteration the bladder is resected, most patients either end up with an ileal- or colon conduit or an orthotopic bladder.(13) Stoma related problems such as urinary leakage, odor, stomal- and peristomal complications and altered body image are considerable factors affecting patients' quality of life.(49) There is no stoma involvement in an orthotopic bladder and might have less effect on physical image compared to urinary conduits. However, patients with an orthotopic bladder frequently experience nocturnal incontinence and postoperative bladder retraining is needed.(59) For patients who receiver previous irradiation of the pelvic area an orthotopic bladder might not be the best option. An ileal- or colon conduit might then be preferred. Studies have shown that the quality of life of patients with an ileal conduit and orthotopic bladder are indifferend. Shared decision making and patient education seem to be the most important factors for postoperative satisfaction.(48, 60, 61)

General and mental health

General health is often affected as patients experience greater fatigue, anxiety and even depression, especially directly after surgery.(57, 58) Numerous other health problems such as pain, abdominal bloating, flatulence and voiding issues are common.(52) Some patients do not have the ability to return back to their profession occupation after surgery and have difficulties to proceed their social and leisure activities.(49)

Despite these changes and impairments, quality of life usually returns back to baseline within in a year. Therefore patients should not be denied exenterative surgery based on perceived poor quality of life.(51, 62, 63)

Summary Box
Anterior pelvic exenteration is a complex surgical procedure with considerable peri-operative morbidity and mortality rates, but it can be beneficial in a select group of patients.
Urinary diversion complications such as urinary fistula and pyelonephritis are frequent in anterior pelvic exenterations and can be life-threatening.
Achievement of a clear resection margin is the most important prognostic factor for overall survival.
Anterior pelvic exenteration has a major impact on physical and mental health. Adequate counseling is therefore recommended.

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CHAPTER 6

Relation between body composition and severe diarrhea in patients treated with preoperative chemoradiation with capecitabine for rectal cancer: a single-centre cohort study

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ABSTRACT

Introduction

Chemoradiation with capecitabine followed by surgery is standard care for locally advanced rectal cancer (LARC). Severe diarrhea is considered a dose-limiting toxicity of adding capecitabine to radiation therapy. The aim of this study was to describe the risk factors and the impact of body composition on severe diarrhea in patients with LARC during preoperative chemoradiation with capecitabine.

Methods

A single centre retrospective cohort study was conducted in a tertiary referral centre. All patients treated with preoperative chemoradiation with capecitabine for LARC from 2009 to 2015 were included. Patients with locally recurrent rectal cancer who received chemoradiation for the first time were included as well. Logistic regression analyses were performed to identify risk factors for severe diarrhea.

Results

A total of 746 patients were included. Median age was 64 years (interquartile range 57-71) and 477 patients (64%) were male. All patients received a radiation dosage of 25 × 2 Gy during a period of five weeks with either concomitant capecitabine administered on radiation days or continuously during radiotherapy. In this cohort 70 patients (9%) developed severe diarrhea. In multivariable logistic regression analyses female sex (OR: 4.42, 95% CI 2.54-7.91) and age ≥ 65 (OR: 3.25, 95% CI 1.85-5.87) were the only risk factors for severe diarrhea.

Conclusion

Female patients and patients aged sixty-five or older had an increased risk of developing severe diarrhea during preoperative chemoradiation therapy with capecitabine. No relation was found between body composition and severe diarrhea.

BACKGROUND

With approximately 4.500 of newly diagnosed cases per year in the Netherlands alone, rectal cancer is a common malignancy for both male and female.(1) Management of rectal cancer has rapidly changed due to the advent of new multimodality treatment modalities and has led to major improvements in oncologic outcomes.(2-4)

The golden standard for curative treatment of rectal cancer still consists of surgical resection. Herein, a radical resection ought to be achieved, as a circumferential resection margin (CRM) of ≤1 mm increases the risk of local recurrence.(5, 6) To improve the chance of a clear CRM, preoperative radiation therapy as neoadjuvant treatment is standard of care in patients with a high risk for local recurrence, including patients with locally advanced rectal cancer (LARC).(4) The addition of 5-fluorouracil (5-FU) to long course radiation therapy has shown to increase response rates.(7, 8) Disadvantages of continuous 5-FU infusion are the need of hospitalisation and complications related to central venous infusion. Both can lead to unwanted costs and a delay to surgery.(8)

Capecitabine is an orally administered prodrug and can be used as an alternative for continuous 5-FU infusion as effective radiosensitizer during radiation.(9, 10) Although capecitabine may reduce practical difficulties compared to continuous 5-FU infusion, acute toxicity during preoperative chemoradiation still remains a problem.(11) The most common adverse effects of capecitabine are diarrhea and palmar-plantar erythrodysesthesia syndrome. Acute toxicity during chemoradiation with concomitant capecitabine, most commonly being severe diarrhea, could lead to an interruption or cessation of preoperative treatment and is potentially life-threating. Furthermore, dehydration and/or significant limitations to the patients' self-care activities of daily living often results to the need of hospitalisation. Due to the great impact severe diarrhea has on both patient- and treatment outcomes, risk factors for should be identified and if possible corrected during the pre-treatment assessment.

Previous studies have identified low skeletal muscle mass as predictor for worse oncologic outcomes and toxicity during 5-FU based treatment in colorectal cancer patients.(12-15) However, the impact of body composition on toxicity during neoadjuvant chemoradiation with capecitabine has not yet been described. The objective of this study is to investigate possible risk factors for severe diarrhea in patients treated with neoadjuvant chemoradiation with capecitabine for rectal cancer.

METHODS

Patients

All consecutive patients with LARC treated with concomitant chemoradiation with capecitabine in the Erasmus MC Cancer Institute from January 2009 until July 2015 were retrospectively reviewed. Patients with locally recurrent rectal cancer (LRRC) who received chemoradiation for the first time were also included. Patient information, pre-treatment tumour characteristics and toxicity were obtained through patients' electronic medical records.

Treatment

All patients were treated with radiation therapy combined with capecitabine. Radiation therapy consisted of a radiation dose of 50 Gy delivered in 25 fractions of 2.0 Gy over a period of five weeks. In addition, a flat dose of 1500 mg capecitabine orally twice daily was administered starting on the first day of radiation therapy till the last day of radiation therapy. Before the 1st of December 2011 patients were treated with capecitabine taken only on radiation days, that was given on weekdays. After this date, the treatment regime changed to capecitabine prescribed seven days a week during radiation therapy due to a change in the guideline. Treatment toxicity was evaluated during several outpatient visits by radiation therapists and medical oncologists. Dihydropyrimidine dehydrogenase (DPD) testing before the administration of capecitabine was not performed during the study period.

Definitions

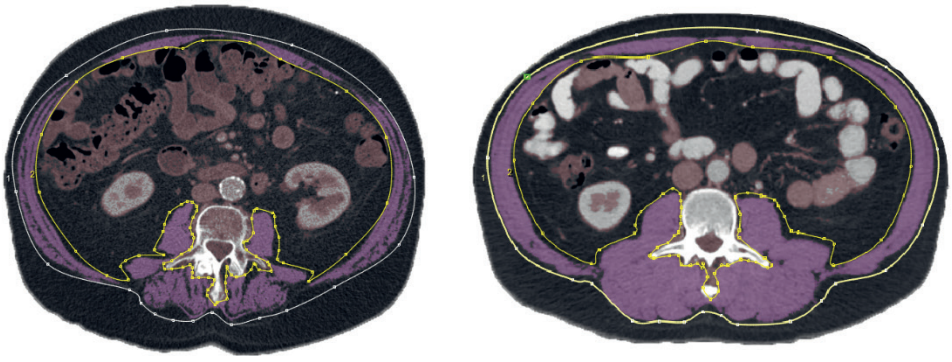
Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula before the start of preoperative treatment. Decreased kidney function was defined as an eGFR of <60 mL/min per 1.73 m2. Toxicity was scored according to the Common Terminology Criteria for Adverse events, version 4.0 (CTCAE v4.0). Herein, toxicity grade 3 was defined as either an increase of ≥7 stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared to baseline or limiting self-care activities of daily living (ADL). Toxicity events with grade 3 or higher were defined as severe diarrhea. Grade 1 and grade 2 diarrhea were defined as an increase of <4 stools and an increase of 4-6 stools over baseline, respectively.

Skeletal muscle mass assessment

Skeletal muscle mass was estimated on standard, routinely performed pre-radiation computed tomography (CT) scans of the abdomen. The total cross-sectional skeletal muscle area was measured at the third lumbar vertebra (L3) and adjusted for patients' body height squared to calculate the skeletal muscle index (SMI). International accepted

cut off values described by Martin et al were used to define low skeletal muscle mass.(16) Herein, low skeletal muscle mass was defined as SMI <53cm/m^2 in male patients with body mass index (BMI) ≥25 kg/m^2 and SMI <43cm/m^2 in male patients with BMI <25kg/m^2. Low skeletal muscle mass in female patients was defined as SMI <41cm/m2. In addition to skeletal muscle mass, skeletal muscle density at L3 was measured in Hounsfield units (HU). Low skeletal muscle density was defined as HU <33 in patients with BMI ≥25kg/m^2 and HU <41 in patients with BMI <25 kg/m^2. Muscle mass was measured with FatSeg, which is a validated developed software program to measure body composition on CT images.(17) An example of an abdominal CT scan at L3 level of a patient with sarcopenia and a patient with normal skeletal muscle mass and density is shown in Figure 1.

Figure 1. CT scans at the third lumbar vertebral level of a patient with sarcopenia (left) and a patient with normal skeletal muscle mass and density (right). The skeletal muscles are outlined.



Statistics

Continuous data were reported as median with interquartile ranges (IQR) and categorical data were reported as counts (percentage). Missing data were not included in descriptive statics. Univariate logistic regression analyses were used to identify possible risk factors for severe diarrhea. Variables with a p-value <0.1 were included in the multivariable analysis. Multivariable logistic regression with backward selection was then used to identify the most statistically relevant predictors for severe diarrhea. Variables of interest were sex, age, BMI, T-stage, N-stage, M-stage, skeletal muscle density, skeletal muscle mass and renal function. In the multivariable regression model with backward selection the significance level was set at a p-value <0.05. Frequency distribution of severe diarrhea for patients with LRRC and patients who received continuous chemoradiation therapy (after the 1st of December 2011) were analysed separately as possible risk groups for severe diarrhea by Pearson's chi-squared test. Also, the occurrence of severe diarrhea was

compared between female patients who underwent a hysterectomy in the past and female patients without a hysterectomy in the past. All analyses were performed using IBM Statistical Package for Social Sciences software (SPSS) version 25 and R version 3.6.1 (https://www.r-project.org/).

This study was approved by the medical ethics committee of the Erasmus MC (MEC-2016-262).

RESULTS

A total of 746 patients who received concomitant preoperative chemoradiation with capecitabine were included. Baseline characteristics and treatment details were summarized in Table 1. The median age was 64 years (IQR 57 – 71), 477 patients were male (64%) and 713 patients were treated for primary rectal cancer (96%). At baseline 325 patients had low skeletal muscle mass (51%), 278 patients had low skeletal muscle density (44%). Continuous dosing scheme of capecitabine was administered in 446 patients (60%). Decreased renal function was diagnosed in 51 patients (7%). In total, 70 patients (9%) experienced grade 3 to 5 diarrhea of whom 68 patients had grade 3, one patient had grade 4 and one patient had grade 5 diarrhea.

Table 1. Baseline characteristics and treatment details of rectal cancer patients treated with preoperative chemoradiation with capecitabine (n=746).

Sex	
Male	477 (64%)
Female	269 (35%)
Age (years)	64 (57 – 71)
T-stage	
2	33 (5%)
3	539 (76%)
4	134 (19%)
N-stage	
0	102 (14%)
1	265 (37%)
2	346 (49%)
M-stage	
0	659 (90%)
1	74 (10%)
Primary rectal cancer	713 (96%)
Recurrent rectal cancer	33 (4%)
BMI (kg/m^2)	25.8 (23.5 – 28.7)
Skeletal muscle mass	
Normal	306 (49%)
Low	324 (51%)
Skeletal muscle density	
Normal	353 (56%)
Low	278 (44%)
Capecitabine dosing scheme	
Weekdays only	300 (40%)
Continuous	446 (60%)
Renal function	
eGFR < 60 ml/min/1,73 m^2	51 (7%)
eGFR >= 60 ml/min/1,73 m^2	694 (93%)
Diarrhea	
No diarrhea	543 (73%)
Grade 1	90 (12%)
Grade 2	43 (6%)
Grade 3	68 (9%)
Grade 4	1 (0%)
Grade 5	1 (0%)

Percentages might not add up due to rounding.

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate.

Logistic regression analyses

Results of logistic regression analyses were reported in Table 2, Table 3 and Table 4. Risk factors which were associated with severe diarrhea in univariate logistic regression analysis were female sex (odds ratio (OR): 3.63, 95% confidence interval (CI): 2.19 – 6.15), age ≥65 (OR: 3.06, 95% CI: 1.82 – 5.33), BMI (OR: 0.95, 95% CI: 0.88 – 1.00), decreased kidney function (OR: 2.57, 95% CI: 1.17 – 5.22) and low skeletal muscle mass (OR: 1.68, 95% CI: 0.99 – 2.93). In the multivariable logistic regression analysis with backwards selection only female sex (OR: 4.42, 95% CI: 2.54 – 7.91) and age ≥65 (OR: 3.25, 95% CI: 1.85 – 5.87) remained associated with severe diarrhea.

Table 2. Univariate regression analyses for severe diarrhea

	OR (95% CI)	P-value
Sex		
Male	Ref	
Female	3.63 (2.19 – 6.15)	<0.001
Age		
< 65 years	Ref	
≥ 65 years	3.06 (1.82 – 5.33)	<0.001
BMI (kg/m^2)		
	0.95 (0.88 – 1.00)	0.073
T-stage		
T2	Ref	
T3	1.00 (0.34 – 4.28)	1.000
T4	1.07 (0.32 – 4.90)	0.915
N-stage		
N0	Ref	
N1	1.27 (0.60 – 2.94)	0.551
N2	0.87 (0.41 – 2.03)	0.739
M-stage		
M0	Ref	
M1	0.38 (0.09 – 1.06)	0.108
Skeletal muscle mass		
Normal	Ref	
Low	1.68 (0.99 – 2.93)	0.059
Skeletal muscle density		
Normal	Ref	
Low	1.21 (0.72 – 2.05)	0.470
Renal function		
eGFR < 60 ml/min/1,73 m^2	Ref	
eGFR ≥ 60 ml/min/1,73 m^2	2.57 (1.17 – 5.22)	0.012

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate

Table 3. Multivariable logistic regression analysis for severe diarrhea

	Adjusted OR (95% CI)	P-value
Sex		
Male	Ref	
Female	4.41 (2.51 – 7.98)	<0.001
Age		
< 65 years	Ref	
≥ 65 years	3.03 (1.70 – 5.55)	<0.001
BMI (kg/m2)		
	0.95 (0.89 – 1.01)	0.132
Skeletal muscle		
Normal	Ref	
Low	1.16 (0.64 – 2.14)	0.632
Renal function		
eGFR < 60 ml/min/1,73 m^2	Ref	
eGFR ≥ 60 ml/min/1,73 m^2	2.07 (0.85 – 4.67)	0.090

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate

Table 4. Multivariable logistic regression analyses (after backwards selection) for severe diarrhea

	Adjusted OR (95% CI)	P-value
Sex		
Male	Ref	
Female	4.42 (2.54 – 7.91)	<0.001
Age		
< 65 years	Ref	
≥ 65 years	3.25 (1.85 – 5.87)	<0.001

Risk groups

Predesignated risk groups were analysed separately. One specific patient group that was especially at risk for severe diarrhea consisted of female patients with a hysterectomy before chemoradiation. The occurrence of severe diarrhea in 40 hysterectomy patients was significantly higher compared to 221 female patients who did not had this procedure in the past (n=14 (35.0%) vs. n=31 (14.1%), p=0.003). Five of 38 patients with LRRC (15.6%) developed severe diarrhea compared to 64 of 713 (9.1%) patients with primary cancer (p=0.391). Continuous dosing scheme of capecitabine was administered in 446 patients and no difference was found in the occurrence of severe diarrhea compared to the 300 patients treated with capecitabine on radiation days only (n=47 (10.5%) vs. n=23 (7.7%), p=0.234).

DISCUSSION

In this retrospective single centre cohort study identifying risk factors for developing severe diarrhea during preoperative chemoradiation with capecitabine female patients and patients older than the age of sixty-five were most at risk for developing severe diarrhea (resp. unadjusted OR: 3.63, 95% CI: 2.19 – 6.15 and 3.06, 95% CI: 1.82 – 5.33). No relation between body composition and severe diarrhea was found after adjusting for sex, age and renal function.

Female sex was associated with an increased risk of severe diarrhea in both univariate and multivariable analysis, and females were over four times more likely to develop severe diarrhea than males. This finding is in line with previous studies reporting a both greater incidence as severity of toxicity in females treated with 5-FU based chemotherapy.(15, 18, 19) It is hypothesized that females experience more toxicity during 5-FU treatment due to variation in pharmacological metabolism such as levels of dihydropyrimidine dehydrogenase and thymidylate synthase.(15, 20) However, the prevalence of DPD deficiency is estimated to be only 0.1-2.8% in the whole population, and could therefore not explain the large proportion of patients (9.4%) experiencing severe diarrhea.(21, 22) In addition, neutropenia, that is commonly associated with DPD deficiency, was only found in

9 patients (1.2%) in our study. This suggests that other, considerably more important, factors have contributed to the increased occurrence of severe diarrhea in female patients.

Alternatively, differences in the pelvic anatomy between females and males may explain the higher rate of diarrhea in female patients. The fact that females have a larger and broader pelvis than males makes it likely that more small bowel volume is located in the pelvic area, and thus within the radiation field. It is well recognized that there is an important causal relation between the volume of small bowel irradiated and the development of diarrhea.(23-25) One finding in this present study that supports this hypothesis is that female patients with a hysterectomy in the past have a greater risk of developing diarrhea compared to female patients without hysterectomy (35.0% vs. 14.1%, p=0.003). As more free space is left behind in the lower pelvic area after hysterectomy, it is plausible that more descended bowel is irradiated, hereby increasing the risk of receiving a toxic dosage. Although the dose-volume relationship between diarrhea and irradiated bowel volume is broadly established in literature, the role of female pelvic anatomy has not clearly been emphasised in these studies.(23, 26-28) Finally, differences between sexes in the experience of symptoms might also play a role in the (subjective) reporting of toxicity scores but fail to explain objective toxicity outcome measures such as the higher incidence of leukocytopenia among females found in other studies.(15)

To investigate the impact of body composition, low skeletal muscle mass, low skeletal muscle density and BMI were analysed as possible risk factors for severe diarrhea. Low skeletal muscle mass and low BMI were both predictors for severe diarrhea, but this correlation was not statically significant after adjusting for sex, age and renal function. In further analysis, low skeletal muscle mass was significantly more common in female patients compared to male patients (61% vs 47%, p=0.003). The association between low skeletal muscle mass and severe diarrhea might therefore be confounded by sex. In the current study, patients with low skeletal muscle density had no increased risk for severe diarrhea compared to patients with normal skeletal muscle density.

The incidence of severe diarrhea in the current study is comparable to several other studies describing an incidence of 4.2%-10.2%.(9-11, 29-31) In the study of Swellengrebel et al. patients were treated with continuous dosing of capecitabine and 10.2% patients developed severe diarrhea. The authors discussed the option of only prescribing capecitabine on days of radiation to optimize tolerability. In this study, patients treated before first of December 2011 received capecitabine only on radiation days, and patients after this date were treated with continuous dosing. Although statistical difference was not reached, the occurrence of severe diarrhea was more common in patients treated with

continuous dosing compared to patients treated with capecitabine on radiation days (10.5% vs. 7.7%, p=0.234).

In the current study, female patients and patients aged sixty-five or older were evidently more at risk for severe diarrhea. The remaining question of this research is how to translate these results into practice. One could argue that these specific patient groups should be offered an altered dosage of capecitabine or a different radiation scheme, for example short course radiation with a longer waiting period. A downsize of this strategy is the possibility of undertreatment of these patients, potentially resulting in less tumour downgrading and thus a higher risk of an irradical resection margin.(4) Another possible solution for diminishing toxicity rates during chemoradiation with capecitabine is the use prehabilitation programs. Promising results of the benefits of prehabilitation and exercise programs for rectal cancer patients undergoing chemoradiation treatment are emerging.(32-34) Targeting treatment on subgroups which have most advantage from it will eventually make prehabilitation programs more sufficient and cost-effective. However, whether prehabilitation actually reduces the risk of severe diarrhea in these patients is uncertain. Ongoing trials will hopefully give more insight in the optimisation of (personalized) prehabilitation for rectal cancer patients undergoing preoperative chemoradiation.(33, 35, 36)

This retrospective cohort study from a single centre has several limitations. First, no dose-volume analyses of irradiated bowel were performed in this study. Secondly, DPD testing was not standard of care during the study period in the Netherlands and was therefore not conducted in our population. Patients with a (partial) DPD deficiency treated with 5-FU have an increased risk of developing toxicity.(37) Nowadays, prospective DPD screening and implicating DPD genotype-based dose reductions have resulted in a safer chemoradiation treatment regime.(38) Toxicity rates of chemoradiation in rectal cancer patients treated present day are therefore probably lower compared to patients in our population. It should also be acknowledged that presumed lower DPD activity in females may have contributed to the higher incidence of severe diarrhea in female patients found in this current study.(39) Another limitation of this study is the lack of follow-up data. Surgery and post-operative treatment were usually performed in referral hospitals. Important patient outcomes such as surgical complications and long-term oncologic survival were therefore not investigated.

In conclusion, this study demonstrates that female patients and patients aged sixty-five or older are especially at risk for severe diarrhea during preoperative chemoradiation therapy with capecitabine. Due to the retrospective nature of this study, no comprehensive explanation for the higher toxicities rates among these patients could be determined.

These findings however suggest that high risk patients should be treated with caution and that alternative neoadjuvant treatment methods might be considered. In the future, high risk patients could, for example, be followed-up more frequently, scheduled with treatment breaks or administered with an adjusted dosage of radiosensitizer (e.g., capecitabine).

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CHAPTER 7

The impact of nutritional status and body composition on postoperative outcomes after pelvic exenteration for locally advanced and locally recurrent rectal cancer

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ABSTRACT

Introduction

Pelvic exenteration for locally advanced (LARC) and locally recurrent rectal cancer (LRRC) provides radical resection and local control but is affected by considerable morbidity. The aim of this study is to determine risk factors, including nutritional status and body composition, for postoperative morbidity and survival after pelvic exenteration in patients with LARC or LRRC.

Methods

Patients with LARC or LRRC who underwent total or posterior pelvic exenteration in a tertiary referral centre from 2003 to 2018 were retrospectively analysed. Nutritional status was assessed using the Malnutrition Universal Screening Tool (MUST). Body composition was estimated using standard of care preoperative CT scans of the abdomen. Logistic regression analyses were performed to identify risk factors for Clavien-Dindo complication grades ≥ III. Risk factors for impaired overall survival were calculated using Cox proportional hazards analysis.

Results

In total, 227 patients who underwent total (n=111) or posterior (n=116) pelvic exenteration were analysed. Major complications (Clavien-Dindo grade ≥ III) occurred in 82 patients (36%). High risk of malnutrition (MUST score ≥ 2) was the only risk factor for major complications (odds ratio: 3.99; 95% confidence interval (CI): 1.76 – 9.02) in multivariable analysis. Mean follow-up was 44.6 months. LRRC and lymphovascular invasion were independent risk factors for impaired overall survival (respective hazard ratios: 1.61; 95% CI: 1.04 – 2.48 and 2.20; 95% CI: 1.38 – 3.51).

Conclusion

High risk of malnutrition by MUST is a strong risk factor for major complications in patients with LARC or LRRC undergoing exenteration surgery.

INTRODUCTION

Worldwide, rectal cancer is one of the most commonly diagnosed cancer(1, 2). Approximately 10% of rectal cancer patients present with locally advanced rectal cancer (LARC) (3, 4). Despite improvements in the multimodality treatment of primary rectal cancer, 4-8% develop locally recurrent rectal cancer (LRRC) after total mesorectal excision (TME) (5-7). A radical resection remains the cornerstone of curative treatment for primary and locally recurrent rectal cancer(8-10). Most patients with LARC and LRRC are treated with neoadjuvant chemoradiotherapy (NACRT) followed by surgical resection. Achieving radical resection of LARC and LRCC is especially challenging when adjacent pelvic organs are involved. In some patients, a partial resection of the adjacent organ is sufficient for a radical resection, but often a multivisceral anatomical resection is needed (i.e. a total or posterior pelvic exenteration (TPE; PPE)). TPE and PPE are major procedures and are associated with significant morbidity and (in-hospital) mortality. Previous studies showed that the 30-day morbidity and hospital mortality rates after exenteration surgery for rectal cancer are higher compared with TME-surgery (69% and 3% versus 21% and 0.6%, respectively) (10-17).

Malnutrition and an altered body composition are known predictive factors for postoperative complications and impaired survival in patients with colorectal cancer (CRC) (18-26). Nutritional status and body composition as risk factors in patients with LARC or LRRC undergoing exenteration surgery have only scarcely been described. Taken into account the high proportion of patients that are exposed to severe surgery-related complications, risk factors for perioperative morbidity should be identified and if possible corrected during the preoperative assessment of these patients.

The aim of this study was to identify prognostic parameters for postoperative morbidity, mortality and survival in patients with LARC or LRRC undergoing pelvic exenteration surgery.

METHODS

Patients

In this retrospective cohort study, patients with LARC or LRCC who underwent curative TPE or PPE between January 2003 and December 2018 a tertiary referral centre in the Netherlands, were identified from a prospectively maintained database. Patient information was retrospectively extracted from medical records. Survival data were recorded from the municipal register.

All patients with LARC or LRCC were discussed in a multidisciplinary tumour board for advanced colorectal cancers comprising dedicated surgical, medical- and radiation oncologists and radiologists. LARC was defined as rectal adenocarcinoma diagnosed as cT4, mesorectal fascia involvement, N2 disease and/or suspicious extramesorectal lymph nodes and was based on MRI. LRRC was defined as recurrent rectal cancer within the pelvis, diagnosed either by MRI or histology. Patients were referred to a dietitian in case of suspected malnutrition at the discretion of the treating physician.

Neoadjuvant therapy usually consisted of long course radiation therapy (either 25x2Gy for LARC/LRRC or 15x2Gy for LRRC if previously irradiated) with concomitant capecitabine (2dd1500mg). Restaging with CT-thorax/abdomen and MRI of the pelvis was performed two months after the last treatment date. When curative treatment was still deemed feasible (i.e. resectable and no extensive distant metastases), patients were planned for surgery. All patients included in this study were surgically treated and followed up in the Erasmus MC Cancer Institute. TPE was defined as a complete resection of the rectum (with or without the anal canal), bladder and (partial) posterior vaginal wall/uterus/adnexa (in women) or the prostate/seminal vesicles (in men). PPE was defined as a resection of the rectum, posterior vaginal wall/uterus/adnexa without the removal of the bladder.

The study was approved by the Erasmus MC local medical ethics committee (MEC 2020-0104).

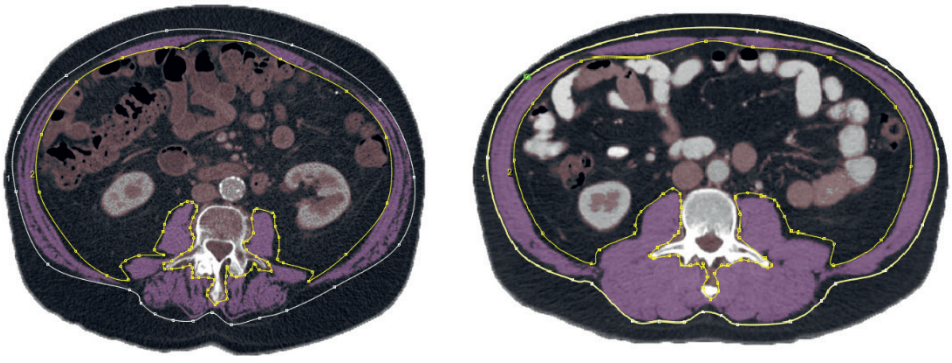
Variables and measurements

Data collection included patients' demographics (age, sex), treatment and disease characteristics. Body mass index (BMI) was divided into low (< 20 kg/m2), normal (20 – 25 kg/m2) and high BMI (≥ 25 kg/m2). Weight loss was expressed as a percentage by calculating the difference between patients' weight prior to neoadjuvant chemoradiotherapy (NACRT) and prior to surgery (((weightNACRT – weightsurgery)/weightNACRT) * 100%) and was categorised into >5% weight loss and <5% weight loss (or muscle gain). Nutritional status prior to surgery was assessed using the Malnutrition Universal Screening Tool (MUST), a screening tool to identify adults who are malnourished or at risk of malnutrition by extracting three determinants from patient records: unplanned weight loss, BMI and no nutritional intake for > 5 days (27). Risk of malnutrition by MUST was categorised into three groups: score of 0 (no risk), 1 (medium risk) and ≥ 2 (high risk). The Charlson Comorbidity Index (CCI) was calculated and categorised by using the 75th percentile as cut-off point. Albumin levels were determined after chemoradiation. Hypoalbuminemia was defined as serum albumin level < 35 g/L. The severity of complications was ranked according to the Clavien-Dindo Classification (28).

Body composition measurement

The patient's body composition was estimated by three muscle-related variables: skeletal muscle mass (SMM), muscle wasting and skeletal muscle density (SMD), which were obtained from routinely performed pre- and post-radiation CT-scans of the abdomen. Low skeletal muscle mass was defined as a low skeletal muscle index (SMI) using sex-specific cut-off points as previously described in a large non-metastatic colorectal cancer patients population (29).The SMI was estimated by measuring the total cross-sectional skeletal muscle area at the level of the third lumbar vertebra (L3) on CT-scans with an in-house developed program (FatSeg) and was adjusted for patients' body height (30). Muscle loss was expressed by calculating the difference between the SMI before NACRT and the SMI prior to surgery (((SMINACRT – SMIsurgery) /SMINACRT) * 100%). Muscle wasting was defined as more than the 75th percentile of muscle loss (compared to the other patients within this study). SMD was expressed in the average count of Hounsfield units (HU) within the measured skeletal muscle mass. Low SMD was defined using HU cut-off points (22), as shown in Figure 1.

Figure 1. Examples of abdominal CT-scans at the level of the third lumbar vertebra from patients with different types of body composition. Left is a patient with low skeletal mass and density, right is a patient with normal skeletal mass and density.



Outcomes of interest.

The primary outcome of interest was Clavien-Dindo complication grade ≥ III within 30 days after the date of surgery. Secondary outcome was overall survival.

Statistical analyses

Continuous data were reported as median (interquartile ranges (IQR)) and categorical data were reported as count (percentage). The Mann Whitney U test was used for comparison of continuous data and the $\chi 2$ test for categorical data. Logistic regression analyses were carried out to identify possible risk factors for major complications. Univariate analyses were performed of the independent variables. Age, gender and variables with a significance level of $p < 0.10$ were included in multivariable analysis. BMI and weight loss were not included in the multivariable analysis because these variables were already determinants of the MUST. Overall survival was calculated from the date of surgery until the date of last follow-up or death and estimated for variables using the Kaplan-Meier method and compared by the log-rank test. Adjusted risk factors for overall survival were calculated using multivariable Cox proportional hazards analysis. Variables with p-values < 0.10 in the univariate analysis were included in multivariable analysis. Statistical analyses were performed using IBM SPSS statistics version 25.0.0.1 and R version 4.0.2. The level of statistical significance was $p < 0.05$.

RESULTS

In total, 227 patients were included. Baseline characteristics of all patients are listed in Table 1. On average, patients lost a median of 1.5kg (IQR: -5kg; 0.2kg) of total body weight during neoadjuvant treatmen. Patients lost a median of 0.48% (IQR: -5.82%; 3.88%) of skeletal muscle mass during neoadjuvant treatment. Muscle wasting was present in 38 patients with more than 5.82% of skeletal muscle mass loss (> 75th percentile). A total of 58 patients were referred to a dietitian. MUST was scored in 208 patients, and 32 patients (15%) had MUST score ≥ 2. Of the patients with MUST score ≥ 2, 15 (47%) were referred to a dietitian. Major complications were more prevalent in patients with MUST score ≥ 2 compared to patients with MUST < 2 (26% vs. 9%; $p = 0.004$).

Table 1. Baseline characteristics of patients with Clavien-Dindo Classification grade < III and grade ≥ III complications

	Total (n = 227)	Grade < III (n = 145)	Grade ≥ III (n = 82)	P-value
Gender - n (%)				0.180
Male	92 (41%)	54 (37%)	38 (46%)	
Female	135 (60%)	91 (63%)	44 (54%)	
Age, years -median (IQR)	64 (55-71)	64 (56 – 71)	65 (55 – 70)	0.740
Age, years - n (%)				
< 70	154 (68%)	95 (66%)	59 (72%)	0.319
≥70	73 (32%)	50 (35%)	23 (28%)	
ASA-score - n (%)				0.753
1	51 (25%)	32 (24%)	19 (26%)	
2	124 (61%)	78 (60%)	46 (62%)	
3	30 (15%)	21 (16%)	9 (12%)	
BMI (kg/m^2) - n (%)				0.059
Low (< 20)	31 (14%)	16 (11%)	15 (19%)	
Normal (20-25)	91 (41%)	60 (42%)	31 (39%)	
High (>25)	100 (45%)	66 (46%)	34 (43%)	
Weight loss - n (%)				0.065
< 5%	149 (73%)	101 (79%)	48 (64%)	
5 – 10%	33 (16%)	16 (13%)	17 (23%)	
> 10%	21 (10%)	11 (9%)	10 (13%)	
MUST - n (%)				**0.004**
Low risk (0)	139 (67%)	96 (73%)	43 (57%)	
Medium risk (1)	37 (18%)	24 (18%)	13 (17%)	
High risk (≥ 2)	32 (15%)	12 (9%)	20 (26%)	
Charlson comorbidity index - n (%)				0.397
< 5	168 (74%)	110 (76%)	58 (71%)	
≥ 5	59 (26%)	35 (24%)	24 (29%)	
Hypoalbuminemia - n (%)	31 (22%)	18 (21%)	13 (25%)	0.621
Skeletal muscle mass - n (%)				0.331
Normal	71 (36%)	49 (39%)	22 (32%)	
Low skeletal muscle mass	124 (64%)	77 (61%)	47 (68%)	
Muscle wasting - n (%)	38 (25%)	25 (26%)	13 (24%)	0.845
Skeletal muscle density - n (%)				0.286
Normal	83 (43%)	58 (46%)	26 (38%)	
Low	111 (57%)	68 (54%)	43 (62%)	
Neoadjuvant therapy - n (%)				0.266
None	10 (4%)	6 (4%)	4 (5%)	
Chemoradiation	171 (75%)	109 (75%)	62 (76%)	
Radiotherapy alone	44 (19%)	30 (21%)	14 (17%)	
Chemotherapy alone	2 (1%)	0 (0%)	2 (2%)	
Tumour type - n (%)				0.061
LARC	148 (65%)	101 (70%)	47 (57%)	
LRRC	79 (35%)	44 (30%)	35 (43%)	
Distant metastasis at presentation - n (%)	35 (15%)	23 (16%)	12 (15%)	0.806
Pelvic exenteration - n (%)				0.103
Posterior	116 (51%)	80 (55%)	36 (44%)	
Total	111 (49%)	65 (45%)	46 (56%)	
(Lympho)vascular invasion - n (%)	39 (19%)	22 (25%)	17 (14%)	0.200
Radical resection (R0)- n (%)	179 (79%)	121 (83%)	58 (71%)	**0.024**

Percentages may not total 100% due to rounding.

Abbreviations: BMI: Body mass index; MUST: Malnutrition Universal Screening Tool; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer.

Postoperative complications

In total, 171 patients (75%) developed complications, of whom 89 patients (39%) had minor complications (grade I-II). Eighty-two patients (36%) had major complications (grade ≥ III) with of whom 11 patients died within thirty days postoperatively (5%; grade V). Readmission within 90 days occurred in 58 patients (26%) and 5 patients died during readmission (9%). The results of logistic regression analyses are listed in Table 2. Low BMI, weight loss (5-10%), MUST score ≥ 2 and LRRC (vs. LARC) were associated with major complications in univariate analysis (OR: 2.11; 95% CI: 0.96 – 4.64, OR: 2.2; 95% CI: 1.04 – 4.80, OR: 3.72; 95% CI: 1.67 – 8.29 and OR: 1.71; 95% CI: 0.97 – 3.00, respectively). In multivariable logistic regression analysis only MUST score ≥ 2 was associated with major complications (OR: 3.99; 95% CI: 1.76 – 9.02).

Table 2. Uni- and multivariable logistic regression analyses for major complications (grade ≥ III)

		Major complications (grade ≥ III)			
		UVA		MVA[†]	
		OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Gender					
	Male	1 (reference)			
	Female	0.69 (0.40 – 1.19)	0.181	0.81 (0.44 – 1.47)	0.481
Age		1.00 (0.98 – 1.02)	0.889	1.00 (0.97 – 1.02)	0.790
BMI		2.11 (0.96 – 4.64)	0.063	NA*	
	Normal (20-25)	1 (reference)			
	Low (<20)	1.81 (0.79 – 4.17)	0.158		
	High (>25)	1.00 (0.55 – 1.82)	0.992		
Weight loss					
	< 5%	1 (reference)		NA*	
	5 – 10%	2.24 (1.04 – 4.80)	**0.039**		
	> 10%	1.91 (0.76 – 4.81)	0.168		
MUST					
	Low risk (0)	1 (reference)		1 (reference)	
	Medium risk (1)	1.21 (0.56 – 2.60)	0.626	1.22 (0.56 – 2.63)	0.618
	High risk (≥ 2)	3.72 (1.67 – 8.29)	**0.001**	3.99 (1.76 – 9.03)	**0.001**
Charlson comorbidity index ≥ 5		1.30 (0.71 – 2.39)	0.398		
Hypoalbuminemia		1.23 (0.54 – 2.77)	0.621		
Low skeletal muscle mass		1.36 (0.73 – 2.53)	0.332		
Muscle wasting		0.93 (0.43 – 2.00)	0.845		
Low skeletal muscle density		1.39 (0.76 – 2.53)	0.287		
Disease status					
	LARC	1 (reference)			
	LRRC	1.71 (0.97 – 3.00)	0.062	1.58 (0.85 – 2.95)	0.148
Pelvic exenteration					
	Posterior	1 (reference)			
	Total	1.57 (0.91 – 2.72)	0.104		

**Already included in the MUST. [†]19 cases not included in multivariable analyses due to missing values.*
Abbreviations: BMI: Body mass index; MUST: Malnutrition Universal Screening Tool; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer

Overall survival

Mean follow-up was 44.6 months. The median overall survival for all included patients after exenteration was 51.3 months (95% CI: 42.4 – 70.0 months). Patients with low SMD had impaired overall survival compared with patients with normal SMD (5-year OS rates: 37% and 53%, p = 0.045). The outcomes of the Cox proportional hazards analysis are listed in Table 3. Independent risk factors for impaired overall survival were LRRC (vs. LARC; HR: 1.61; 95% CI: 1.04 – 2.48) and lymphovascular invasion (HR: 2.20; 95% CI: 1.38 – 3.51). Overall survival curves of patients with LARC vs LRRS and patients with vs without lymphovascular invasion are depicted in Figure 2. No significant association was found between age, low SMD or distant metastasis at presentation and survival in the multivariable analysis.

Figure 2. Overall survival of A) patients with locally advanced vs. locally recurrent rectal cancer and B) patients with- and without lymphovascular invasion

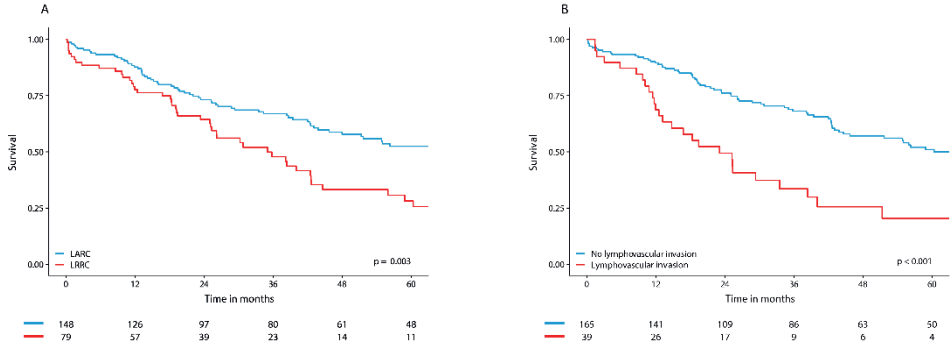


Table 3. Uni- and multivariable Cox proportional hazard analysis for overall survival

	Univariate HR (95% CI)	P-value	Multivariable HR (95% CI)[†]	P-value
Female gender	0.82 (0.58 – 1.18)	0.285		
Age	1.02 (1.00 – 1.04)	0.022	1.02 (1.00 – 1.04)	0.142
MUST score ≥ 2	1.30 (0.81 – 2.08)	0.277		
Low skeletal muscle mass	1.29 (0.86 – 1.94)	0.217		
Muscle wasting	1.40 (0.87 – 2.24)	0.169		
Low skeletal muscle density	1.49 (1.00 – 2.20)	0.050	1.36 (0.88 – 2.12)	0.172
LRRC (vs. LARC)	1.70 (1.18 – 2.45)	0.004	1.61 (1.04 – 2.48)	0.032
Distant metastasis at presentation	2.00 (1.26 – 3.17)	0.003	1.43 (0.81 – 2.52)	0.213
(Lympho)vascular invasion	2.47 (1.61 – 3.79)	< 0.001	2.20 (1.38 – 3.51)	0.001
Radical resection	0.80 (0.53 – 1.21)	0.289		

[†]52 cases not included in multivariable analyses due to missing values.
Abbreviations: BMI: Body mass index; MUST: Malnutrition Universal Screening Tool; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer.

DISCUSSION

In this retrospective cohort study, 82 patients (36%) with LARC or LRRC undergoing exenteration surgery developed major complications. Nutritional status by MUST was a strong predictive factor for major complications. Patients with a preoperative high risk of malnutrition (MUST score ≥ 2) had a fourfold increased risk of developing major complications as compared with patients with a low-medium risk. LRRC and lymphovascular invasion are widely accepted as poor prognostic factors and were the only two independent prognostic factors for impaired survival in this cohort (31-33).

The major complication rates after pelvic exenteration in this study are in line with previous studies, reporting thirty-day major morbidity and mortality rates of 25 – 44% and 0 – 25% (10-16), and are considerably higher compared with non-exenterative CRC surgery (17). The MUST score has been established as predictor for impaired outcome in colorectal cancer surgery,(34) but has not been investigated in patients undergoing pelvic exenteration. Morbidity was more frequently observed in patients with higher MUST scores, but this did not seem to influence survival. The finding that BMI was no predictor for major complications was consistent with previous results in CRC surgery (35). Although technically TPE is a more extensive procedure compared with PPE, TPE was not associated with more major complications. Furthermore, major complications were significantly not more common in patients with LRRC, despite the fact that these patients had undergone former oncologic treatment. This finding appears to be in line with a larger series describing similar complication rates in LARC and LRRC patients undergoing pelvic exenteration (36).

Of the investigated body composition variables, patients with low SMD had impaired overall survival compared to patients with normal SMD, but SMD was not independently associated with survival in the multivariable analysis. Muscle wasting, which has been associated with disease-free survival but not with overall survival in LARC patients undergoing neoadjuvant treatment,(37) was neither associated with major complications nor overall survival in this study. Gender, age, weight loss, CCI, hypoalbuminemia, distant metastasis at presentation and radical resection were no predictive factors for morbidity and survival, but have been described in larger studies including colorectal patients.(10, 11, 14, 21, 24, 38, 39)

This study has several limitations. First, it was a retrospective study with a selected group of patients from a single centre. Its retrospective nature caused missing information in some patient records (e.g. CT-scans, serum level albumin and weight loss). Serum albumin was not routinely determined at one fixed time preoperatively, which resulted in a wide time variation. In this line, some potential confounders could not be corrected for (e.g.

preoperative dietitian involvement, nutritional support). Low skeletal muscle mass was estimated by radiological muscle quality and quantity only, and was not confirmed or further investigated (e.g. by the determination of muscle strength or physical performance) (40). It should be noted that selection bias by eligibility screening for major pelvic surgery might have influenced the outcomes in this study. For example, elderly patients were only treated when considered exceptionally fit for their age, whilst younger patients with unfavourable tumour characteristics might have been more easily considered candidate for exenteration surgery.

This study provides important and useful insights for predicting complications and survival in patients with LARC and LRRC and future potential for preoperative optimisation strategies, for example prehabilitation (41-46). Findings of this study may contribute to a more accurate preoperative risk assessment in the future for patients with LARC or LRRC undergoing pelvic exenteration surgery. It merits future research whether preoperative intervention of a dietitian and nutritional support in patients with a high MUST score diminishes major complication rates in patients undergoing pelvic exenteration. In this cohort not even half of the patients with high risk of malnutrition (47%) had been referred to a dietitian for preoperative nutritional support. This may leave room for improvement given the finding that a high MUST score proved such a strong independent predictor for major complications this study. The MUST score is very easily applicable and repeatable in daily clinical practice, which is an advantage over measures such as body composition. A more accurate risk assessment may help optimising patients' physical status preoperatively to improve postoperative outcomes by identifying potential targets for prehabilitation (34, 38, 47).

Prehabilitation is a process to enhance and optimise the patient's functional capacity before surgery. The program consists of a combination of optimising nutrition, exercising and restricting risk factors, usually in the setting of a multidisciplinary team of medical specialists, dietitians and physiotherapists. There is growing evidence for improvement of postoperative outcomes in colorectal cancer patients by administering a prehabilitation program during neoadjuvant treatment (41-46). A meta-analysis showed that even nutritional-only prehabilitation decreased the length of hospital stay by two days (46). The first international multicentre study investigating multimodal prehabilitation for patients undergoing colorectal cancer surgery is still ongoing (48).

This study demonstrates that high risk of malnutrition (MUST score ≥ 2) is a strong risk factor for major morbidity and mortality within 30 days in patients with LARC or LRRC undergoing exenteration surgery. Prehabilitation with nutritional support for patients at

high risk of malnutrition might improve perioperative outcomes, whilst identification of other prehabilitation targets merits additional research.

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CHAPTER 8

Omentoplasty in patients undergoing abdominoperineal resection after long-course chemoradiation for locally advanced and locally recurrent rectal cancer: a comparative single-institution cohort study

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ABSTRACT

Introduction

Omentoplasty is a commonly performed procedure after abdominoperineal resection for rectal cancer, but its effectiveness to reduce pelviperineal complications is not firmly established. We aimed to assess the impact of omentoplasty on short-term pelviperineal complications and postoperative outcomes following long-course (chemo)radiotherapy and abdominoperineal resection in patients with locally advanced and locally recurrent rectal cancer.

Methods

All patients with locally advanced and locally recurrent rectal cancer undergoing abdominoperineal resection after neoadjuvant (chemo)radiation in a tertiary referral centre between 2008 and 2020 were retrospectively reviewed. Multivariable logistic and linear regression analyses were performed to examine the association between omentoplasty and pelviperineal complications, duration of nasogastric tube drainage and length of hospital stay.

Results

A total of 245 patients were analysed. Pelviperineal complications occurred in 151 patients (50%) overall, and in 125 (51%) and 26 (43%) of patients with or without omentoplasty. Independent predictors of pelviperineal complications in multivariable analyses were smoking (OR 2.68, 95% CI 1.46 – 4.94) and high BMI (OR 1.68, 95% CI 1.00 – 2.83), but not omentoplasty (OR 1.36, 95% CI 0.77-2.40). Mean duration of nasogastric tube drainage was longer after omentoplasty (6 vs. 4 days). Patients undergoing omentoplasty had a significantly longer hospital stay (14 vs. 10 days), and omentoplasty remained associated with a prolonged hospital stay after adjusting for confounding (β-coefficient 3.05, 95% CI 0.05-5.74).

Conclusion

Omentoplasty was not associated with a reduced risk of the occurrence of short-term pelviperineal complications after abdominoperineal resection in patients undergoing long-course (chemo)radiotherapy. Furthermore, in patients undergoing omentoplasty a prolonged duration of nasogastric tube drainage and hospital stay was observed.

INTRODUCTION

Surgical resection after neoadjuvant chemoradiotherapy is standard treatment for locally advanced and locally recurrent rectal cancer (resp. LARC; LRRC).(1, 2) In cases where anal sphincter preservation is not an option, an abdominoperineal resection (APR) is performed. Due to the creation of a perineal wound and a large pelvic cavity, the risk of complications after APR is one of the highest in colorectal surgery.(3) The incidence of perineal wound complications after APR, including dehiscence, necrosis, infection, fistula and pelviperineal abscess, is reported to be as high as 47%.(4) Neoadjuvant radiotherapy increases the risk of wound problems.(4, 5) Various techniques have been proposed to reduce pelviperineal complications, such as the use of negative pressure therapy, musculocutaneous flaps or biomesh.(6-9)

Theoretically, the omentum might also promote wound healing due to its angiogenic and immune activities.(10) Omentoplasty is a procedure in which the greater omentum is pediculised on one of the two gastro-epiploic arteries and subsequently used for filling of the pelvic cavity. However, omentoplasty can result in prolonged postoperative ileus and there have been conflicting results about the effectiveness of omentoplasty to reduce pelviperineal complications.(11, 12) A recent meta-analysis showed no benefit of omentoplasty after APR and even suggested the increased risk of perineal hernias on the long term.(11) A retrospective cohort study also revealed a higher rate of perineal hernia after omentoplasty.(13)

Interpretation of literature is complicated by heterogeneity of included patients and interventions. Most series have mainly included patients with primary resectable rectal cancer with different neoadjuvant schedules. Patients treated with long-course (chemo)radiotherapy for locally advanced and locally recurrent rectal cancer are commonly underrepresented in these studies and therefore the role of omentoplasty in this specific patient population has yet to be evaluated. The aim of this single-institution comparative cohort study is to evaluate the effect of omentoplasty on pelviperineal complications, duration of nasogastric tube drainage and hospital stay in patients undergoing long-course (chemo)radiotherapy and APR for LARC or LRRC.

METHODS

Patients who underwent an APR in a tertiary referral centre were retrospectively identified from a prospectively maintained database. The main end point was overall pelviperineal complications until the end of follow-up with a minimum of 30 days postoperatively. The secondary end points were duration of nasogastric tube drainage and length of stay.

Patients

All consecutive patients who underwent an APR for rectal adenocarcinoma after neoadjuvant long-course (re-)irradiation with concomitant capecitabine for locally advanced or locally recurrent rectal adenocarcinoma from 2008 until 2020 were included. Data collection was performed by reviewing patient records by two independent researchers and discrepancies were corrected by consensus. The data extracted from patient records included baseline characteristics, operative details, details about hospital stay and postoperative complications.

Treatment

Chemoradiotherapy consisted of neoadjuvant long-course radiotherapy (25 x 2Gy), with the addition of capecitabine as radiosensitiser for patients with LARC and LRRC patients who were radiotherapy-naïve.(14) Previously irradiated LRRC patients were treated with adjusted dose long-course re-irradiation with capecitabine (15 x 2Gy).(15) Type of surgery was defined as intersphincteric or standard APR, with or without additional resection. Additional resection was categorised as extended (urinary tract resection, posterior exenteration and/or sacral resection) or limited (not extended, including partial prostate resection, posterior vaginectomy and coccygectomy). When deemed necessary by the treating surgeon, patients were proactively planned for flap reconstructions, which were performed by dedicated plastic surgeons. Intraoperative radiation therapy (IORT) was performed in case of suspicion of involved resection margins, either clinically or based on assessment of frozen sections.(16) Omentoplasty was performed by four surgeons treating rectal cancer in our institute, and the decision to create an omentoplasty was based on individual patient- and surgical characteristics. Omentoplasty was performed in a consistent way throughout the duration of the study. The omentum was pedicled on either the right or the left gastroepiploic artery, based on the preference of the surgeon.

Pelviperineal wound problems were scored as they were described in patient records. Dehiscence was defined as any open wound, not further specified in minor or major, since measurements were not systematically reported. Treatment of large perineal wound defects consisted of vacuum-assisted closure (VAC) therapy or drainage and/or

debridement in the operating room, and this policy was consistent over the study period. Perineal wound infection was defined as reported in case files or in case of pus evacuation, thus including perineal abscess. The documentation of a presacral abscess was based on radiology reports of CT-abdomen imaging. Presacral abscess drainage was performed under CT guidance or in the operating room. Perineal fistulas were scored if wound problems persisted for over one year postoperative. Time of wound healing was scored when complete wound healing was reported in the hospital or outpatient clinical record.

No fixed postoperative protocol was followed and treatment decisions such as NGS removal were at the discretion of the senior surgeons on a daily basis. Generally, during the first two postoperative days, patients had no oral intake and nutritional support was provided by enteral feeding for at least three days (Bengmark). After day two, enteral nutritional support was abated based on resuming oral intake from day three onwards. Following clamping of the gastric decompression tube, gastric retention was observed during the day. The tube was removed if gastric retention was less than 250 mL per day. Follow-up at our outpatient clinic was typically after 1, 3, 6, 9 and 12 months postoperative.

Statistics

Statistical analysis was performed using SPSS 21st edition (Armonk, NY: IBM Corp.). Descriptive statistics are displayed as absolute numbers with percentages or means with standard deviations (SD). For comparative analysis of categorical variables, Chi square test was performed. All continuous variables were non-normally distributed following Kolmogorov-Smirnov and Shapiro-Wilk analysis. For analysis of continuous variables, Mann-Whitney-U tests were performed. A multiple logistic regression was performed for the categorical outcome variable 'pelviperineal complications' and independent variables were included into the model if a p value of <0.1 in simple logistic regression was found. Analysis of the continuous variable 'length of stay' and 'duration of nasogastric tube drainage' was performed by multiple linear regression, using backward elimination. Results are reported as odds ratio (OR) and adjusted odds ratio (aOR) or as regression coefficient, with 95%-confidence intervals (CI). All p-values were two-sided. Statistical significance was set at $p < 0.05$.

The study was approved by the Erasmus MC local medical ethics committee (MEC 2020-0104).

RESULTS

Baseline characteristics and operative details

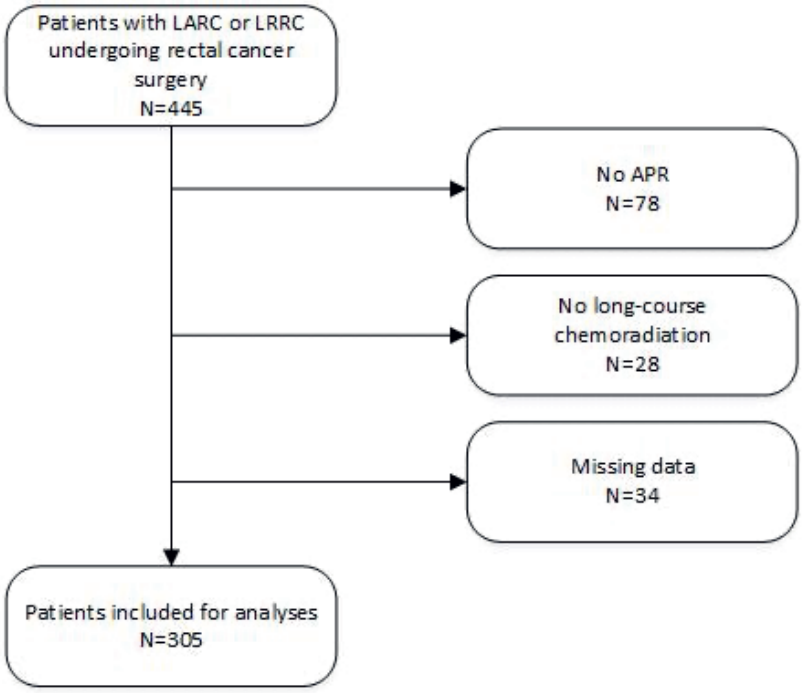
In total 445 patients were evaluated of which 305 patients were included for analyses (as shown in the flowchart in Figure 1). Baseline characteristics are demonstrated in Table 1. Ninety-nine patients (33%) were female. The mean age was 63 years and the mean BMI 26 kg/m2. Most patients (n=223, 73%) underwent an APR for LARC and the remaining 82 patients (27%) had LRRC. Omentoplasty was performed in 245 patients (80%). IORT was performed in 75 patients (25%). In 51 patients (17%) a total pelvic exenteration was performed, and 34 patients (11%) underwent a posterior pelvic exenteration. An ileal conduit described by Bricker was performed in 39 patients (13%), and a colon conduit was created in 12 patients (4%). For perineal wound closure, muscle flap reconstruction was performed in 55 patients (18%) and bio-mesh was used in 8 patients (3%). Of the 55 patients whom had a muscle flap reconstruction, 44 patients (80%) also had omentoplasty. In total 43 vertical rectus abdominis myocutaneous (VRAM), 9 gluteus and 3 gracilis reconstructions were performed.

Table 1. Baseline characteristics, treatment- and post-operative details of patients undergoing abdominoperineal resection (APR) for locally advanced and locally recurrent rectal cancer

		Total N = 305 (100%)	Omentoplasty N = 245 (80%)	No omentoplasty N = 60 (20%)
Gender	Female	99 (33%)	77 (31%)	22 (37%)
	Male	206 (67%)	168 (69%)	38 (63%)
Age (years)	Mean (SD)	63 (± 11.6)	62 (± 11.4)	65 (± 11.8)
BMI (kg/m2)	Mean (SD)	26 (± 4.3)	26 (± 4.1)	27 (± 4.8)
ASA classification	ASA 1	78 (26%)	63 (26%)	15 (25%)
	ASA 2	167 (55%)	137 (56%)	30 (50%)
	ASA 3	53 (17%)	40 (16.3%)	13 (22%)
	ASA 4	1 (0%)	0 (0%)	1 (2%)
Smoking	No	229 (75%)	187 (76%)	42 (70%)
	Yes	68 (22%)	56 (23%)	12 (20%)
Comorbidity	Respiratory	37 (12%)	28 (11%)	9 (15%)
	Cardiac	82 (27%)	56 (23%)	26 (43%)
	Diabetes	40 (13%)	23 (9%)	17 (28%)
Tumour type	LARC	223 (73%)	177 (72%)	46 (77%)
	LRRC	82 (27%)	68 (28%)	14 (23%)
Neoadjuvant therapy	Chemoradiation	296 (97%)	237 (97%)	59 (98%)
	Radiotherapy alone	9 (3%)	8 (3%)	1 (2%)
Operative details				
Type of surgery	iAPR	25 (8%)	15 (6%)	10 (17%)
	APR	280 (92%)	230 (94%)	50 (83%)
Operative approach	Open	289 (94%)	239 (98%)	50 (83%)
	Laparoscopic	11 (4%)	6 (2%)	5 (8%)
	Robot-assisted	5 (2%)	0 (0%)	5 (8%)
Additional resection	None	103 (34%)	75 (31%)	28 (47%)
	Limited	108 (35%)	88 (36%)	20 (33%)
	Extended	94 (31%)	82 (33%)	12 (20%)
IORT	Yes	75 (25%)	67 (27%)	8 (13%)
	No	230 (75%)	178(73%)	52 (87%)
Perineal closure	Primarily	217 (71%)	179 (73%)	38 (63%)
	Muscle flap	55 (18%)	44 (18%)	11 (18%)
	Biomesh	8 (3%)	7 (3%)	1 (2%)
Operative time (minutes)	Mean (SD)	396 (± 149.7)	416 (± 148.8)	307 (± 118.9)
Blood loss (mL)	Mean (SD)	1874 (± 1793)	2020 (± 1831)	1320 (± 1533)

Data presented as n (%) unless otherwise indicated. Data were not available for all patients.
Abbriviations: (i)APR: (intersphincteric) abdominoperineal resection; IORT: intraoperative radiation therapy; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer.

Figure 1. Flowchart of patient selection



Pelviperineal complications

Postoperative outcomes are shown in Table 2. Overall, 151 (50%) patients developed a pelviperineal wound problem. The majority of pelviperineal complications were wound dehiscence (n=125, 41%). In 27 patients (9%) a perineal abscess was opened. For the treatment of large perineal wound defects, 11 patients (4%) had VAC therapy and 16 patients (5%) had drainage and/or debridement in the operating room. Deeper, presacral abscesses were objectified on imaging and subsequently treated in 19 patients (6%). Fistulas were present in 31 patients (10%) after one year of follow-up. Of the 31 patients with fistula, 4 patients (13%) had an enterocutaneous fistula (all in the omentoplasty group). Perineal wound healing was achieved in 178 patients (58%) after 1 week. After 30 days 175 patients (57%) had complete wound healing. Seventy-three patients (24%) patients had persistent perineal wound problems at six months after surgery. Patients undergoing omentoplasty developed pelviperineal complications in a comparable proportion than those without omentoplasty (151 patients (51%) vs. 26 patients (43%), p = 0.282).

Table 2. Baseline post-operative outcomes of patients undergoing abdominoperineal resection (APR) for locally advanced and locally recurrent rectal cancer

Postoperative outcome		Total N = 305 (100%)	Omentoplasty N = 245 (80%)	No omentoplasty N = 60 (20%)
Nasogastric tube	Yes	272 (89%)	239 (98%)	33 (55%)
	No	33 (11%)	6 (2%)	27 (45%)
Nasogastric tube duration, days	Mean (SD)	6 (± 4.3)	6 (± 4.5)	4 (± 2.1)
Nasogastric tube reinsertion	Yes	35 (12%)	26 (11%)	9 (15%)
	No	265 (87%)	215 (88%)	50 (83%)
Length of stay, days	Mean (SD)	13 (± 9.8)	14 (± 10.4)	10 (± 6)
Postoperative complications	Overall	205 (67%)	179 (73%)	26 (43%)
	Pneumonia	27 (9%)	25 (10%)	2 (3%)
	Urinary tract infection	22 (7%)	19 (8%)	3 (5%)
	Sepsis	24 (8%)	23 (9%)	1 (2%)
	Cardiac	25 (8%)	22 (9%)	3 (5%)
Pelviperineal wound problem	All	151 (50%)	125 (51%))	26 (43%)
	Dehiscence	125 (41%)	107 (44%)	18 (30%)
	Wound infection	83 (27%)	72 (29%)	11 (18%)
	Perineal abscess	27 (9%)	25 (10%)	2 (3%)
	Presacral abscess	19 (6%)	15 (6%)	4 (7%)
	Fistula	31 (10%)	28 (11%)	3 (5%)
	Necrosis	25 (8%)	21 (9%)	4 (7%)
Relaparotomy	Yes	34 (11%)	31 (13%)	3 (5%)
Dindo classification	Dindo 1-2	125 (41%)	109 (45%)	16 (27%)
	Dindo 3-4	72 (24%)	63 (26%)	9 (15%)
	Dindo 5	7 (2%)	6 (2.4%)	1 (2%)
Perineal wound healed	After 7 days	178 (58%)	137 (56%)	41 (68%)
	After 30 days	175 (57%)	138 (56%)	37 (62%)
	After 180 days	232 (76%)	185 (76%)	47 (78%)

Data presented as n (%) unless otherwise noted. Data were not available for all patients.

Abbreviations: APR: abdominoperineal resection; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer.

Multiple logistic regression modelling was used to determine independent associations between omentoplasty, other covariates and overall pelviperineal complications (Table 3). Omentoplasty was not significantly associated with pelviperineal complications (OR 1.437; 95% CI 0.752-2.746), and neither a predictor for the occurrence of presacral abscess in univariable and multivariable analyses (OR 0.913; 95% CI 0.292-2.858 and aOR 0.613; 95% CI 0.179-2.105, respectively). Independent predictors of pelviperineal complications were high BMI (aOR 1.681; 95% CI 1.00-2.83) and smoking (aOR 2.681; 95% CI 1.547-4.936). Extended additional resection was significantly associated with pelviperineal complications in univariable analysis (OR 2.133; 95% CI 1.207-3.768), but didn't reach significance after multivariable analysis (aOR 1.719; 95% CI 0.891-3.315).

Table 3. Uni- and multivariable analyses for the occurrence of pelviperineal complications in patients undergoing abdominoperineal resection (APR) for locally advanced and locally recurrent rectal cancer

		Pelviperineal complications			
		Univariable analysis		Multivariable analysis	
		OR (95% CI)	p-value	aOR (95% CI)	p-value
Gender	Male	1 (reference)		1 (reference)	
	Female	1,126 (0,697 - 1,819)	0.627	0,731 (0,420-1,271)	0.267
Age		0,998 (0,978 - 1,017)	0.810	0,992 (0,971-1,015)	0.502
BMI	Normal (20-25)	1 (reference)		1 (reference)	
	Low (<20)	1,469 (0,503 – 4,296)	0.482	1,762 (0,485-6,401)	0.389
	High (>25)	**1,494 (0,936 - 2,385)**	**0.092**	**1,682 (0,999 -2,832)**	**0.050**
Smoking	No	1 (reference)		1 (reference)	
	Yes	**2,031 (1,163 - 3,546)**	**0.013**	**2,681 (1,457-4,936)**	**0.002**
Comorbidities	Respiratory	1,393 (0,697-2,786)	0.348		
	Cardiac	**1,645 (0,986-2,745)**	**0.057**	1,541 (0,791-3,004)	0.204
	Diabetes	1,448 (0,740 - 2,834)	0.280		
ASA classification	Class 1-2	1 (reference)		1 (reference)	
	Class 3-4	**1,947 (1,063 - 3,567)**	**0.031**	1,290 (0,597-2,788)	0.518
Omentoplasty	No	1 (reference)		1 (reference)	
	Yes	1,362 (0,771 - 2,406)	0.272	1,437 (0,752-2,746)	0.272
IORT	No	1 (reference)			
	Yes	1,518 (0,897 - 2,568)	0.120		
Additional resection	None	1 (reference)		1 (reference)	
	Limited	1,569 (0,909 - 2,709)	0.106	1,473 (0,822-2,638)	0.193
	Extended	**2,133 (1,207 - 3,768)**	**0.009**	1,719 (0,891-3,315)	0.106
Tumor type	LARC	1 (reference)		1 (reference)	
	LRRC	**1,761 (1,053 - 2,945)**	**0.031**	1,565 (0,864-2,833)	0.139
Perineal closure	Primarily	1 (reference)			
	Muscle flap	1,189 (0,657 - 2,153)	0.568		
	Biomesh	0,594 (0,139 - 2,549)	0.484		

Abbrevations: aOR = adjusted OR; APR: abdominoperineal resection; IORT: intraoperative radiation therapy; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer.

Overall complications

Overall complications after APR occurred in 205 patients (67%). Seven patients died in the first 30 postoperative days, resulting in a mortality rate of 2%. One hundred and five patients (41%) developed mild or moderate complications, while 72 patients (24%) had severe complications (Clavien Dindo class III or IV).

Duration of gastric tube

In total 272 patients (89%) had a nasogastric tube postoperatively. The mean duration of a nasogastric tube drainage after APR was 6 +/- 3 days. In 35 patients (12%), the gastric tube had to be replaced after removal. The variables significantly associated with longer nasogastric tube drainage were smoking (β-coefficient 1.36; 95% CI 0.18-2.54), omentoplasty (β-coefficient 1.97, 95% CI 0.35-3.59), and extended resection (β-coefficient 1.66; 95% CI 0.57-2.74) (Table 4).

Table 4. Linear regression analyses for duration of nasogastric tube drainage in patients undergoing abdominoperineal resection (APR) for locally advanced and locally recurrent rectal cancer

Factor	**Duration of gastric tube**	
	β-coefficient (95% Confidence Interval)	p-value
Comorbidity (cardiac)	1.140 (-0.050; 2.330)	0.060
Smoking (yes)	1.359 (0 .176; 2.542)	0.025
Omentoplasty (yes)	1.968 (0 .346; 3.589)	0.018
Extended organ resection (yes)	1.657 (0.573; 2.740)	0.003

Length of stay

Patients in this study were found to have a mean length of stay of 13 days. The relationship between patient demographics, operative details and hospital stay is shown in Table 5. After multiple linear regression analysis of these covariates, using backward deletion method, the influence of each individual factor could be estimated by its regression coefficient (Table 6). After adjusting for the covariates, an independent association was observed between omentoplasty and longer hospital stay (β-coefficient 3.05; 95% CI 0.05-5.74). Also female gender, smoking, respiratory comorbidities, ASA class III-IV, IORT and LRRC were associated with an increased length of stay.

Table 5. Length of stay in patients undergoing abdominoperineal resection (APR) for locally advanced and locally recurrent rectal cancer

Length of stay		Mean (SD)	Median (IQR)	p-value
Gender	Female	14.8 (± 12.3)	10 (7)	0.066
	Male	12 (± 8.4)	9 (5)	
BMI	Normal (20-25)	12.7 (± 9.6)	10 (6)	0.724
	Low (<20)	13.2 (± 12.6)	10 (4)	0.951
	High (>25)	13.1 (± 9.9)	9.5 (8)	0.715
Smoking	No	12.3 (± 8.1)	10 (6)	0.415
	Yes	15 (± 14.2)	10 (7)	
Comorbidity	**Respiratory**	**18.6 (± 16.6)**	**14 (7)**	**0.001**
	Cardiac	**14.5 (± 11.3)**	**11 (8)**	**0.038**
	Diabetes	11.9 (± 5.5)	9.5 (8)	0.557
ASA classification	ASA 1-2	11.9 (± 8.7)	9 (6)	
	ASA 3-4	**16.3 (± 11.7)**	**11 (10)**	**0.002**
Omentoplasty	**Yes**	**13.5 (± 10.5)**	**10 (7)**	**0.001**
	No	10.2 (± 6.1)	8 (5)	
IORT	**Yes**	**17.0 (± 13.6)**	**11.5 (9)**	**<0.001**
	No	11.5 (± 7.9)	9 (6)	
Additional resection	None	10.5 (± 8.8)	8 (3)	
	Limited	11.5 (± 6.2)	9 (6)	0.658
	Extended	**17.0 (± 12.8)**	**12 (8)**	**<0.001**
Tumor type	LARC	11.3 (± 7.6)	9 (5)	
	LRRC	**17.3 (± 13.4)**	**12 (10)**	**< 0.001**
Perineal closure	**Primarily**	**12.7 (± 10.2)**	**9 (7)**	**0.017**
	Muscle flap	**14.5 (± 9.8)**	**12 (6)**	**0.001**
	Biomesh	13.3 (± 12.5)	8.5 (3)	0.658

Abbreviations APR: abdominoperineal resection; IORT: intraoperative radiation therapy; IQR: interquatile range; LARC: locally advanced rectal cancer; LRRC: locally recurrent rectal cancer.

Table 6. Linear regression analyses for a prolonged length of stay in patients undergoing abdominoperineal resection (APR) for locally advanced and locally recurrent rectal cancer

Factor	**Length of stay**	
	β-coefficient (95% Confidence Interval)	p-vale
Gender (male)	-2.768 (-4.985; -0.551)	0.015
Comorbidity (respiratory)	4.159 (0.851; 7.468)	0.014
Smoking (yes)	3.395 (0.919; 5.872)	0.007
ASA 3 or 4 (vs ASA 1 or 2)	3.254 (0.407; 6.101)	0.025
Omentoplasty (yes)	3.053 (0.053; 5.736)	0.026
IORT (yes)	3.793 (1.2; 6.5)	0.006
LRRC (vs LARC)	4.209 (1.568; 6.850)	0.002

DISCUSSION

This is the first retrospective comparative cohort study evaluating the effect of omentoplasty in patients who underwent long-course neoadjuvant (chemo)radiotherapy and APR for locally advanced and locally recurrent rectal cancer. In this series of patients with large and irradiated pelvic cavities, omentoplasty was not associated with a lower risk of pelviperineal complications. Furthermore, patients undergoing omentoplasty had a longer duration of nasogastric tube drainage and hospital stay.

Results of this study suggest that performing an omentoplasty alone does not make up for the other risks that might cause pelvic or perineal wound problems. No reduced risk of the occurrence of pelviperineal complication was observed in patients in whom an omentoplasty was performed (OR 1.36, 95% CI 0.77-2.40) and is in line with other studies reporting on pelviperineal outcomes in patients undergoing omentoplasty after different radiation schemes and APR for rectal cancer.(11, 17) The majority of pelviperineal complications found in this study were superficial wound problems and dehiscence, whilst only a minority of patients developed deep infections such as a presacral abscess (6%). Since omentoplasty is intended to fill the pelvic cavity, it is expected to have little beneficial effect on perineal wound healing. However, omentoplasty was also not associated with a lower incidence of presacral abscesses in both univariable and multivariable analysis. Although results of this study show that pelvic complications were similar in patients with and without omentoplasty, some studies suggest that an omentoplasty increases the risk of perineal hernia.(11, 13)

Several factors may play a role in the relatively high rate of perineal complications in the patients treated with an omentoplasty (51% compared to 43% in patients without omentoplasty). First, the mobilisation of the greater omentum might jeopardise its vascularisation, leaving a (partially) devascularised omentum in the neo-pelvis.(18, 19) A partially devascularised, necrotic omentum could be a source of infection, balancing out the potential benefit of an omentoplasty. Finally, imbalance regarding the extent of APR might have contributed to the higher pelviperineal complication rate after omentoplasty. Patients who underwent an omentoplasty had a longer hospital stay (14 vs. 10 days) and longer duration of nasogastric tube drainage (6 vs. 4 days) compared to patients without an omentoplasty. Gastroparesis after omentoplasty might be related to devascularisation of the greater curvature of the stomach by altered function of the cells of Cajal, which play an important role in the gastric peristalsis.20 The increased length of stay for patient that underwent omentoplasty could easily be explained by longer nasogastric tube drainage. However, these findings should be interpreted with caution due to the relatively small

number of patients, especially in the group that did not undergo omentoplasty. In addition, residual confounding (e.g., the extent of the surgery) might still play a role in the observed associations with gastroparesis and longer hospital stay in this study. Few studies have evaluated the post-operative occurrence of gastroparesis after omentoplasty. One study have found a trend towards a delayed gastric functioning and prolonged need of a nasogastric tube in patients undergoing omentoplasty.(20) In addition, a higher incidence of post-operative ileus was reported after omentoplasty.

The effect of long-term radiation on the quality of pelvic tissue in patients receiving long-course radiation therapy with or without concomitant chemotherapy has not yet been investigated. Although oncological outcomes of patients treated with long-course and short-course radiation are similar, some randomised studies show lower acute toxicity rates and moreover better perineal wound healing after short course radiation.(21, 22) This study shows that perineal wound problems occurred in 50% of this population with intensive neoadjuvant and subsequent surgical treatment for locally advanced and locally recurrent rectal cancer and is comparable with other studies.(9, 11) It should be noted however that perineal wound problems is strongly dependent on patient population, treatment intensity, definition and study type.

To achieve improved wound healing after APR, the use of other techniques, such as myocutaneous flaps and biological mesh, might be considered. There are currently no published randomised controlled trials comparing muscle flaps with primary closure or biological mesh repair of perineal defects after APR. Meta-analysis of cohort series shows that the use of myocutaneous flaps reduces perineal wound infections and major complications when compared with primary closure. However, substantial flap-related morbidity has been reported, including longer operating time, deep surgical site infections, wound dehiscence, enterocutaneous fistula and reoperation.(23) An ongoing RCT (NEAPE) is assessing physical performance and wound healing in patients who undergo biological mesh vs. muscle flap closure after extended APR.(24) The BIOPEX study concluded that biological mesh closure does not reduce perineal wound complications when compared with primary closure.(9) The ongoing BIOPEX-2 study is examining perineal wound healing after a small transposition flap from the adjacent perineal skin and subcutaneous fat vs primary closure.(25) Future research will guide us in choosing the optimal surgical approach for wound closure in APR.

Limitations of this cohort study were related to its single-centre retrospective design. Some imbalances between the baseline characteristics and operative details of the omentoplasty and no omentoplasty group were unavoidable. Although confounding

factors such as the extent of additional resection, primary versus recurrent disease and IORT were included in the multivariable analyses, other non-included confounders could have influenced the results and some bias by indication might have remained. There was no way to control the influence of the surgeon's decision to perform an omentoplasty. A common reason for not performing an omentoplasty was the absence of an adequate greater omentum. Unfortunately, this was not adequately documented. It is also important to note that the potential benefit of omentoplasty might have been underestimated due to a risk of allocation bias (no omentoplasty in low risk patients). Secondly, there was a risk of reporting bias. Particularly the reporting of pelviperineal complications is subject to the interpretations of the examiner and the way of reporting. For this reason, both large and small wound defects were grouped together as dehiscence. Lastly, there was no evaluation of the occurrence of postoperative perineal hernia, due to the lack of reporting or follow-up imaging being performed at the referring centre.

In summary, results of former studies show no advantages of performing an omentoplasty during APR. The results of this study further support these findings for patients undergoing APR after long-course neoadjuvant (chemo)radiotherapy. Furthermore, a prolonged hospital stay and longer nasogastric tube drainage were observed in the omentoplasty group. Until today, there is no evidence that an omentoplasty has any added value in terms of post-operative complication risks or oncologic safety. Based on current evidence, including this study, performing omentoplasty during APR should be discouraged.

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PART III

Management of stage IV disease

CHAPTER 9

Treatment of locally advanced rectal cancer and synchronous liver metastases: multi-centre comparison between two treatment strategies

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ABSTRACT

Introduction

Patients with locally advanced rectal cancer and synchronous liver metastases can be treated with a liver first approach (LFA; systemic chemotherapy, local treatment of liver metastases and subsequent (chemo)radiotherapy and rectal surgery) or M1-schedule (M1; short-course pelvic radiotherapy (5x5Gy), systemic chemotherapy and subsequent local treatment of tumour sites). The aim of this study was to compare outcomes of both treatment strategies.

Methods

This was a multicentre comparative cohort study including consecutive patients with locally advanced rectal cancer and potentially resectable liver metastases who were treated with LFA (1 centre) or M1 (8 centres) between 2004 and 2018. Main outcomes were overall survival and progression-free survival.

Results

From a total of 330 patients, 260 patients with locally advanced rectal cancer were included. Seventy-two of 96 patients (75%) completed LFA and 133 of 164 patients (81%) completed M1 (p=0.245). If completed, duration was 44.0 weeks for LFA (IQR 39.5 – 49.9) and 35.9 weeks for M1 (IQR 29.5 - 42.6, p<0.001). For the overall population, 3-year overall survival was 58.0% (95% CI: 48.7% - 69.3%) after LFA and 60.6% (95% CI: 53.1% - 69.2%) after M1 (p=0.209). Corresponding three-year progression-free survival was 22.6% (95% CI: 15.1% - 33.9%) and 24.4% (95% CI: 18.2% - 32.6%, p=0.652), respectively. Complete response of the primary tumour (either clinically or pathologically) was observed in 6 patients (9%) after LFA, and 15 patients (12%) following M1 (p=0.624).

Conclusion

The LFA and M1-schedule resulted in similar oncological outcomes in patients with locally advanced rectal cancer and synchronous liver metastases.

INTRODUCTION

Fifteen percent of all rectal cancer patients presents with synchronous liver metastases.(1, 2) The management of locally advanced rectal cancer has been optimized during the last decades, with neoadjuvant (chemo)radiotherapy and (beyond) total mesorectal excision (TME) surgery, and most recently the introduction of total neoadjuvant treatment using modern systemic therapy.(3-5) For patients with synchronous liver metastases, the optimal treatment strategy is less clear with high variability among institutions worldwide.(6) Whilst systemic treatment plays an important role to control metastatic disease, (chemo)radiotherapy can improve local control of the primary tumour.(4, 7-9)

In the Netherlands, two specific treatment sequences have mainly been used for treating patients with locally advanced rectal cancer and synchronous liver metastases: the “liver first approach” (LFA) and the “M1-schedule” (M1).(10-13)

The LFA consists of induction systemic chemotherapy, subsequent local treatment of the liver metastases, followed by long-course (chemo-)radiotherapy and resection of the primary tumour. Since survival is determined by metastatic disease, the rationale behind the liver first strategy is to only treat the rectal tumour when control of synchronous liver metastases is established. Radiotherapy and primary tumour resection can be avoided in patients with disease progression or deterioration of the clinical condition during the first phase of the schedule.(14)

M1 starts with pre-operative short-course pelvic radiotherapy (5 x 5 Gy), followed by systemic therapy and subsequent surgical treatment of both liver and rectum (either simultaneous, liver first or primary tumour first).(15) The advantage of starting with short-course radiotherapy is the immediate downstaging effect on the primary tumour whilst still retaining a minimal delay in the initiation of systemic therapy and a sufficient interval from radiotherapy to resection of the primary tumour. This strategy has shown to be safe and effective, and with excellent local control, good pathological response rates and the opportunity of organ preservation.(16-18)

The primary aim of this study was to compare long-term oncological outcomes between the LFA and the M1-schedule, and secondarily to evaluate treatment completion and duration as well as morbidity.

METHODS

This was a multicentre comparative cohort study in nine tertiary referral centres in the Netherlands, including patients with locally advanced rectal cancer and synchronous liver metastases with or without limited extrahepatic disease (potentially) amenable to local treatment. The Erasmus MC Cancer Institute exclusively used LFA in the period between January 2004 until December 2018, and the other eight Dutch centres applied the M1-schedule between January 2010 (initiation of M1-schedule) until December 2018. Patients with progressive disease or clinical deterioration before any local treatment was performed, were not included in this study.

Locally advanced rectal cancer was defined as a tumour with at least one of the following characteristics: tumour >5 cm; mesorectal fascia (MRF) ingrowth or ingrowth in adjacent organ on MRI (T4); N+ tumour, i.e. at least one lymph node >8 mm or 4 lymph nodes >5 mm on CT scan or magnetic resonance imaging (MRI).(10, 12) All patients were discussed in a multidisciplinary team (MDT) of liver- and colorectal surgeons, radiologists, radiation oncologists and medical oncologists before start of treatment and for response evaluation and re-staging in between treatment modalities. Patient-, tumour-, and treatment data were retrospectively obtained from electronic patient files.

Liver first approach

In the Erasmus MC Cancer Institute, eligible patients were treated with the liver first approach.(10) Patients were first treated with systemic chemotherapy with or without bevacizumab and radiological tumour response was assessed after three cycles. If no disease-progression was observed, local treatment of the liver metastases was performed, sometimes preceded by some additional cycles of systemic therapy. Subsequent long-course radiotherapy was started, which consisted of 25 x 1.8-2 Gy with or without concomitant capecitabine.(19) Rectal surgery was planned after restaging with a thoracic- and abdominal CT scan and pelvic MRI, even when (near) complete response was observed. Eligible patients were planned for surgery 8-12 weeks after completion of neoadjuvant (chemo)radiotherapy.

M1-schedule

Eight centres in the Netherlands have been using the M1-schedule since 2010.(15) In this schedule, treatment started with short course radiotherapy, 5 x 5 Gy, followed by 3-6 cycles of systemic treatment, mostly consisting of doublet chemotherapy with or without bevacizumab. Subsequent local treatment of both tumour locations was planned after restaging with a thoracic- and abdominal CT scan and pelvic MRI. Sequence of local

treatments differed, and either liver first, primary first or a synchronous resection was performed at the discretion of the treating MDT.

Outcomes

Main outcomes were overall survival (OS) and progression-free survival (PFS), independent of treatment completion. Other outcomes were clinical- and pathological complete response rates of the primary tumour, schedule completion rate, schedule duration, and complications. OS, PFS, and schedule duration were measured from the date of diagnosis of the liver metastases. The schedule was considered complete after resection of both tumour locations. Completion of the schedule was also considered to be achieved in case of a combination of surgery and a complete clinical response.

Progression was defined as either progression or recurrence of the local-, hepatic- or extrahepatic disease. Clinical complete response after neoadjuvant treatment of the primary tumour was achieved if pelvic MRI and/or endoscopy revealed no residual/recurrent local disease during three consecutive follow-up visits. Pathological complete response of the primary tumour was achieved when no vital tumour cells were found in the specimen. Complications were scored using the Clavien-Dindo (CD) surgical complication score. Only severe complications (≥ grade 3) were reported.(20)

Statistics

Continuous data were presented as medians and interquartile ranges (IQR). Categorical data were presented as numbers and percentages. Groups were compared using Chi-squared and Mann Whiney U test. Schedule duration and total length of stay were (separately) reported for patients who completed the schedule as well as for patients who did not complete the schedule. Missing or unknown categories were not included in statistical analyses. Kaplan Meier method was used to calculate OS and PFS. These were compared using the log-rank test. A P-value less than 0.05 was considered statistically significant. Statistical analyses were performed using R version 4.1.1 (http://www.r-project.org).

The study was approved by the medical ethics committees.

RESULTS

Of 330 patients identified, 70 patients who did not fulfil the definition of LARC were excluded (Figure 1). Ninety-six patients (37%) were treated according to the liver first approach, and 164 patients (63%) followed the M1-schedule. Baseline characteristics are listed in Table 1 and treatment details in Table 2. The median number of liver metastases at diagnosis was higher in patients treated with LFA (3.0 (IQR: 2.0 - 5.0)) compared to patients treated with M1 (2.0 (IQR: 1.0 - 4.0), p=0.011). The completion rate was 72 of the 96 (75%) in the LFA group and 133 of the 164 (81%) in the M1 group (p=0.245).
In LFA, all 96 patients had liver surgery. After liver surgery, 8 patients (8%) did not start with chemoradiation: 3 patients had progression, 2 patients died, and 3 patients had sufficient response to chemotherapy alone to allow for surgery without subsequent radiotherapy. Sixteen patients (17%) had progression during or after chemoradiation. Primary tumour resection was performed in 74 patients (77%) treated with LFA. Two of those patients did not complete the schedule due to unresectable liver progression during surgery.

Table 1. Baseline characteristics

		LFA (n=96)	M1 (n=164)	p-value
Age (median [IQR])		62.6 [56.3, 67.8]	61.6 [55.4, 68.7]	0.646
Gender (%)	Male	67 (70%)	116 (71%)	0.873
	Female	29 (30%)	48 (29%)	
Comorbidity (%)		54 (56%)	85 (52%)	0.490
cT-stage (%)	T2	1 (1%)	4 (2%)	0.175
	T3	57 (63%)	119 (73%)	
	T4	32 (36%)	41 (25%)	
cN-stage (%)	N0	4 (5%)	12 (7%)	0.709
	N1	22 (28%)	50 (31%)	
	N2	52 (67%)	101 (62%)	
LM distribution (%)	Unilobar	42 (44%)	89 (54%)	0.102
	Bilobar	54 (56%)	75 (46%)	
LM number at diagnosis (median [IQR])		3.0 [2.0, 5.0]	2.0 [1.0, 4.0]	0.011
LM diameter of largest lesion at diagnosis (median [IQR])		2.8 [2.0, 4.4]	2.8 [2.0, 4.2]	0.941
Extrahepatic disease at diagnosis (%)		13 (14%)	32 (20%)	0.219

Abbreviations: IQR – interquartile range. LFA – liver first approach. LM – liver metastases. M1 – M1-schedule.

Figure 1. Flowchart selection criteria

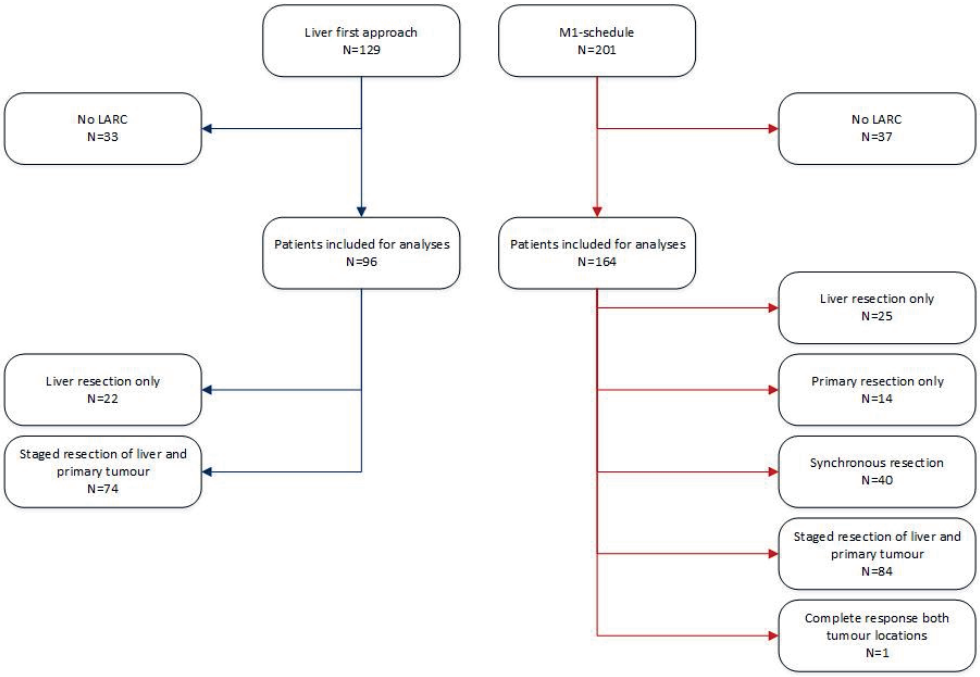


Table 2. Treatment details

		LFA (n=96)	M1 (n=164)	p-value
Completion (%)	No	24 (25%)	31 (19%)	0.245
	Yes	72 (75%)	133 (81%)	
Stomy before/during scheme (%)	No	78 (82%)	117 (74%)	0.140
	Yes	17 (18%)	41 (26%)	
Moment of colostomy (%)	No colostomy	39 (42%)	76 (49%)	0.016
	Before schedule	8 (9%)	31 (20%)	
	During schedule	9 (10%)	10 (6%)	
	At primary resection	37 (40%)	39 (25%)	
Permanent colostomy at the end of treatment (%)	No colostomy	39 (42%)	76 (49%)	0.299
	Colostomy	54 (58%)	80 (51%)	
Number of systemic chemotherapy cycles (median [IQR])		4.0 [3.0, 5.0]	6.0 [3.0, 6.0]	0.001
Bevacizumab added to systemic therapy (%)		24 (25%)	110 (68%)	<0.001
LM surgery type (%)	Hemihepatectomy	22 (23%)	34 (23%)	0.008
	Segment/wedge resection	33 (34%)	65 (44%)	
	Ablation	5 (5%)	19 (13%)	
	Combined resection and ablation	36 (38%)	29 (20%)	
	*No LM resection**	*0*	*10*	
	*Missing**	*0*	*7*	
LM surgery resection margins (%)	R0	83 (86%)	106 (76%)	0.214
	R1	8 (9%)	18 (13%)	
	R2	0 (0%)	2 (1%)	
	Ablation	5 (5%)	13 (9%)	
	*No LM resection**	*0*	*10*	
	*Missing**	*0*	*15*	
LM pathological complete response (%)	CR	10 (12%)	18 (17%)	0.357
	No CR	73 (88%)	89 (83%)	
	*Ablation**	*5*	*13*	
	*No LM resection**	*0*	*10*	
	*Missing**	*8*	*34*	
Rectal radiological response (%)	Complete response	1 (2%)	9 (7%)	0.006
	Partial response	48 (81%)	122 (90%)	
	Progression of disease	4 (7%)	1 (1%)	
	Stable disease	6 (10%)	4 (3%)	
	*Missing**	*12*	*1*	
	No MRI made	*25*	*27*	
Rectal surgery type (%)	APR	20 (27%)	37 (26%)	0.005
	Exenteration	8 (11%)	2 (1%)	
	Hartmann	0 (0%)	8 (6%)	
	LAR	45 (62%)	89 (63%)	
	Local excision	0 (0%)	1 (1%)	
	*No primary resection**	*22*	*26*	
	*Missing**	*1*	*1*	
Rectal surgery resection margins (%)	R0	62 (91%)	111 (87%)	0.427
	R1	6 (9%)	16 (13%)	
	*No primary resection**	*22*	*26*	
	*Missing**	*6*	*11*	

Table 2. (continued)

		LFA (n=96)	M1 (n=164)	p-value
Rectal pathological complete response (%)	No complete response	59 (91%)	113 (88%)	0.266
	Pathological complete response	6 (9%)	10 (8%)	
	Clinical complete response	0 (0%)	5 (4%)	
	*No primary resection**	*22*	*21*	
	*Missing**	*9*	*15*	
Overall treatment duration (median [IQR])		40.6 [31.1, 47.2]	34.9 [28.1, 41.8]	0.008
Treatment duration if scheme completed (median [IQR])		44.0 [39.5, 49.9]	35.9 [29.5, 42.6]	<0.001
Total length of stay if scheme completed (mean (SD))		18.8 (8.9)	18.0 (11.8)	0.686

** Not included in percentages*

Abbreviations: APR: abdominoperineal resection; IQR: interquartile range; LFA: liver first approach; LAR: low anterior resection; LM: liver metastases; M1: M1-schedule; SD: standard deviation.

In the M1 group, simultaneous resection of both tumour sites was performed in 40 patients (24%), and staged resection in 84 patients (51%). Thirty-nine patients (24%) only had liver- or rectal surgery, of whom 25 had liver surgery first and 14 rectal surgery first. The remaining patient had complete radiological response of both tumour sites and had no surgery. Ten of 39 patients did not undergo surgery of the primary tumour or metastases because of a complete response of either the rectum (n=5) or the liver (n=5), and incomplete local treatment was due to disease progression in the other 29 patients. Two patients had surgery of both tumour sites but did not complete the schedule due to incomplete liver resection.

Treatment details and complications

Treatment details are described in Table 2, and complication details in Table 3. Median number of neoadjuvant systemic chemotherapy cycles was 4.0 (IQR: 3.0 - 5.0) in LFA and 6.0 (IQR: 3.0 - 6.0) in M1 (p=0.001). Bevacizumab was added to the chemotherapeutic regimen in 24 patients (25%) in LFA and 110 patients (68%) in M1 (p<0.001). Major complications (CD grade ≥ 3) related to local treatment of the liver were observed in 4 LFA patients (4%) versus 16 patients (15%) in M1 (p=0.010). The complication rate after simultaneous resection of forty patients treated M1 (33%), was higher compared to 16% complications in staged resections added up in LFA (4% liver resection and 12% rectal resection). The mean total length of hospital stay for patients that completed the schedule was 18.8 (standard deviation (SD): 8.9) for LFA and 18.0 (SD: 11.8) for M1. For patients that completed the schedule, median duration was 44.0 weeks (IQR: 39.5 - 49.9) in LFA and 35.9 weeks (IQR: 29.5 - 42.6) in M1 (p<0.001).

Table 3a. Complications according to the Clavien-Dindo classification and hospital stay after simultaneous resection

		M1 (n=40)
Hospital stay (median [IQR])		11.5 [9.2, 20.2]
Simultaneous resection complications (%)	None	14 (36%)
	Grade 1	3 (8%)
	Grade 2	9 (23%)
	Grade 3	9 (23%)
	Grade 4	3 (8%)
	Grade 5	1 (3%)
	*Missing**	*1*
Major complications (%)	Yes	13 (33%)

** Not included in percentages*

Table 3b. Complications according to the Clavien-Dindo classification and hospital stay after liver treatment

		LFA (n=96)	M1 (n=124)	p-value
Hospital stay (median [IQR])		6.5 [5.0, 8.0]	7.0 [5.0, 10.0]	0.468
Liver resection complications (%)	None	73 (78%)	67 (64%)	0.232
	Grade 1	6 (6%)	7 (7%)	
	Grade 2	11 (12%)	15 (14%)	
	Grade 3	2 (2%)	9 (9%)	
	Grade 4	1 (1%)	4 (4%)	
	Grade 5	1 (1%)	3 (3%)	
	*Missing**	*2*	*4*	
	No resection†*	*0*	*15*	
Major complications (%)		4 (4%)	16 (15%)	0.010

** Not included in percentages*

† Patients with complete response of both tumour sites (n=1) and patients with primary resection only (n=14)

Table 3c. Complications according to the Clavien-Dindo classification and hospital stay after primary resection

		LFA (n=96)	M1 (n=124)	p-value
Hospital stay (median [IQR])		9.0 [8.0, 11.8]	9.0 [7.0, 13.8]	0.481
Primary resection complications (%)	None	45 (62%)	42 (49%)	0.073
	Grade 1	2 (3%)	10 (12%)	
	Grade 2	17 (23%)	15 (18%)	
	Grade 3	6 (8%)	15 (18%)	
	Grade 4	3 (4%)	3 (4%)	
	Grade 5	0 (0%)	0 (0%)	
	*Missing**	*1*	*13*	
	No resection†*	*22*	*26*	
Major complications (%)	Yes	9 (12%)	18 (21%)	0.141

** Not included in percentages*

† Patients with complete response of both tumour sites (n=1) and patients with liver resection only (n=25)

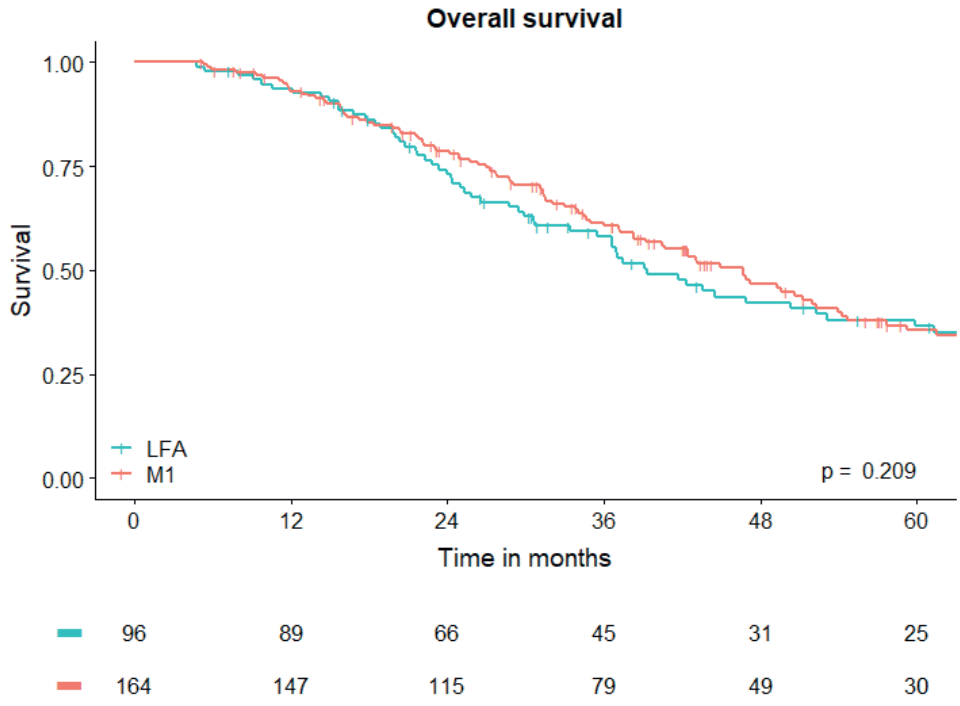
Complete response

Pathological complete response of the liver metastases was found in 10 patients (12%) treated with LFA and 18 patients (17%) treated with M1 (p=0.357). In M1, 5 patients had no liver surgery because a clinical complete response after chemotherapy was observed, either during surgery or on imaging. Complete responses (either clinical or pathological) of the primary tumour were observed in 6 patients (9%) in the LFA group and 15 patients (12%) in the M1 group (p=0.624). Radiological complete response of the primary tumour on the first MRI after radiotherapy was found in 1 patient (2%) in the LFA group and in 9 patients (7%) in the M1 group (p=0.152). A watch-and-wait strategy for the primary tumour was initiated in 10 patients in the M1-schedule, of whom 5 patients had a sustained clinical complete response (i.e. no residue and/or recurrence in follow-up moments) and no surgery of the primary tumour was performed. One patient with a clinical complete response at first evaluation did not have any follow-up moments. Four patients still had surgery due to regrowth, of whom 1 had Transanal Minimally Invasive Surgery (TAMIS). Pathological complete response in the resected specimen of the primary tumour was found in 6 patients (9%) treated with LFA and in 10 patients (8%) treated with M1 (p=0.797).

Survival

The median follow-up time for survivors was 43.7 months, and did not differ between patients treated with LFA and M1 (p=0.927). Median overall survival was 43.1 months (95% CI: 38.2 - 51.2 months), and median progression-free survival was 15.6 months (95% CI: 14.6 - 17.7 months). Overall- and progression-free survival are shown in Figures 2 and 3. Three-year OS was 58.0% (95% confidence interval (CI): 48.7% - 69.3%) after LFA and 60.6% in after M1 (95% CI: 53.1% - 69.2%) (log rank test: p=0.209). Three-year PFS was 22.6% (95% CI: 15.1% - 33.9%) in LFA and 24.4% (95% CI: 18.2% - 32.6%) for the M1 schedule (log rank test: p=0.575). At the end of follow-up, the number of patients with local recurrence in the pelvis after completion of the schedule was 5 (6.9%) in LFA and 13 (9.8%) in M1 (p=0.494).

Figure 2. Overall survival of patients treated with the liver first approach (LFA) and the M1-schedule



DISCUSSION

This multicentre retrospective cohort study compared two accepted treatment schedules for patients with potentially curable locally advanced rectal cancer and synchronous liver metastases in the Netherlands. Overall- and progression-free survival were similar after either treatment. Also complete response- and local recurrence rates were comparable. A similar proportion of patients completed the whole treatment schedule (75% LFA and 81% M1), with an absolute 8 weeks shorter duration in the M1 group. Major complications after liver surgery more often occurred in patients treated with M1 schedule.

Several systematic reviews and meta-analyses compared different treatment sequences on surgical-, oncological- and survival outcomes in patients with colorectal cancer and synchronous liver metastases.(21-24) In these studies, comparable survival outcomes were usually found for simultaneous surgery, liver first or primary first approach. The M1-schedule has not yet been compared to any other schedule. The current study suggests that the M1-schedule is comparable to the liver first approach in terms of survival.

Response rates after comparable neoadjuvant treatment schedules have already been investigated in randomised controlled trials that compared short-course radiotherapy followed by waiting or systemic chemotherapy to long-course (chemo)radiotherapy in non-metastatic rectal cancer.(25, 26) The Stockholm III trial showed a pathological complete response rate after short-course radiotherapy with delay of 11.8%.(27) The Polish II trial found a pathological complete response rate of 16% in patients with short-course radiotherapy followed by 3 cycles of FOLFOX4, compared to 12% in patients treated with (chemo)radiotherapy (p=0.17).(26)

The complete response rates (either clinical or pathological) observed in this study were 9-12% after both treatment schedules, and is lower compared with the complete response rates found in recent total neoadjuvant treatment trials.(5, 28-30) For example, the RAPIDO trial observed a pathological complete response rate of 28% in patients treated with short-course radiotherapy followed by systemic chemotherapy, compared to 14% in patients treated with long-course chemoradiation (p<0.001).(28) However, it has been suggested that in the RAPIDO trial, patients with larger tumours might not undergo the same downstaging effects after the experimental total neoadjuvant treatment as smaller, earlier-stage tumours.(31) In addition, previously reported complete response outcomes of the M1-schedule in stage IV rectal cancer patients that also included non-locally advanced tumours, are 26%, which is considerably higher compared to the response rates observed in this study.(15) This implies that the beneficial downstaging effect of short-course radiation and consolidation chemotherapy on the primary tumour is more pronounced in rectal cancer patients with T2 or T3 tumours compared to patients with larger, locally advanced, rectal tumours with synchronous liver metastases. Thus, the relatively small proportion of complete responders after LFA and M1 is likely to be explained by more aggressive biological disease behaviour. As recent data indicate that the watch-and-wait approach is safe in stage IV rectal cancer with (near-) complete response, future research should focus on optimal selection of patients that can be treated with organ preservation.(32) Such strategies are especially of interest in these patients as prognosis is mainly determined by their metastases.

Major complications after liver surgery were more frequently observed in the M1-schedule (15% versus 4%), and the major complication rate after simultaneous resection in M1 was relatively high (33% (for comparison: complications after staged resections in LFA were after 4% liver resection and 12 after rectal resection). It should be noted that, besides differences in treatment sequence, other factors such as case-mix (e.g., preoperative chemotherapeutic regimen) could also play an important role in morbidity outcomes. At the end of both treatment schedules, the proportion of patients with a permanent stoma

was similar. The median duration of the completed M1-schedule was 8 weeks shorter than LFA, this was approximately the same as the difference in treatment duration of the radiation schedules (one week of short-course radiotherapy in M1 versus five weeks of long-course (chemo-)radiotherapy plus a waiting period in LFA). There were no differences in length of total hospital stay.

Cost efficiency of both treatment schedules is expected to be equal, however, no formal economic evaluation was performed. More cycles of chemotherapy were administered in patients treated with M1. During neoadjuvant radiotherapy, short-course radiation in M1 consists of less hospital visits compared to long-course chemoradiation, but it should be taken into consideration that chemoradiation and rectal surgery was spared in eight patients in LFA due to disease progression in the first phase of the schedule, hereby saving costs and unnecessary treatment. Generally, local therapy for the primary rectal tumour can safely be omitted in case of disease progression, and in only ten percent of those patients, palliative rectal resection is required.(14)

Both the M1-schedule and LFA have advantages and disadvantages, and one of the two schedules can be more beneficial for an individual patient over the other. For example, in patients with symptomatic rectal cancer such as bleeding and obstructive symptoms, short-course radiotherapy can be administered to obtain durable local control, and may reduce the risk of an emergency stoma compared to the downstaging effects of systemic chemotherapy only.(14, 33) Additionally, the interval after short-course radiotherapy can efficiently be used to treat the liver with systemic chemotherapy and surgery, whilst observing the local behaviour of the primary tumour when a (near) complete response is found. However, patients with progressive metastatic disease during the first phase of the schedule, may not benefit from downstaging the primary tumour, and radiotherapy can cause both morbidity and futile costs. Therefore, LFA might be more convenient in patients with more extensive liver metastases at the moment of diagnosis, in which the chance of completion of the full schedule is expected to be lower. In addition, the LFA might be preferred in patients with locally advanced tumours who are planned for procedures associated with severe morbidity, such as exenterative surgery or intraoperative radiation therapy (IORT). In the LFA, resection of the primary tumour is only considered when control of all other disease sites is achieved, and a longer treatment period may provide time to evaluate disease behaviour. A downside of LFA is that a simultaneous resection of both tumour sites is not possible, which can be a valuable treatment option in selected patients with stage IV disease.

This was a retrospective analysis with several limitations. First, only patients without progressive disease or clinical deterioration before any surgery was performed were selected. Although the proportion of patients with disease progression during neoadjuvant treatment is likely to be equal in both treatment schedules, some selection bias was unavoidable and (oncologic) survival outcomes found in this study are likely to be better than in daily practice on an intention to treat basis. Second, some patients were referred back to the referring hospital before finishing treatment. Final (surgical) treatment and follow-up was then performed by the referring hospitals. Despite retrieving this data as adequately as possible by contacting hospitals and general practitioners, some surgical and follow-up information was missing. Differences in the local guidelines and MDT decisions of the included hospitals influenced the results of this study. For example, no organ preservation methods were used for LFA, even when a radiological complete response was found, and therefore the number of patients with a rectum preservation treatment could not be compared. Also, the number of patients included in this study was relatively low and baseline differences existed between the two treatment groups. For instance, the variation in the inclusion periods in both schedules might have affected outcomes found in this study. Finally, toxicity of the neoadjuvant treatment was not evaluated in this study due to the risk of selection bias, as patients who had clinical deterioration due to toxicity before surgery was performed, were not included in this study.

In conclusion, the liver first approach and the M1-schedule are both safe and effective treatment modalities for the treatment of patients with locally advanced rectal cancer and synchronous liver metastases with curative intent. No differences were found in overall survival and progression-free survival.

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CHAPTER 10

Treatment of colorectal lung metastases: a two centres retrospective study

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ABSTRACT

Introduction

Clear guidelines for management of colorectal lung metastases (LM) are not available. Treatment modalities include surgery, thermal ablation, stereotactic radiotherapy (SABR), and systemic therapy. This study aimed to provide insight in the treatment strategies and efficacy of local and systemic therapy in patients with LM eligible for (potentially) curative treatment.

Methods

This was a retrospective study of patients discussed at multidisciplinary team meetings in two tertiary referral centres in 2018. Patients treated with local or systemic therapy for ≤5 LM and ≤5 resectable peritoneal, lymph node, or hepatic metastases were eligible. Patients with previously treated LM were excluded. Patient and tumour characteristics were compared between treatment groups. Treatment strategies were compared between centres and survival data between treatment groups, local treatment modalities, and treating centres.

Results

Ninety-two patients (median 2 LM, range 1-5) were included. Seventy-one (77%) patients underwent local treatment (17 surgery, 13 ablation, 38 radiotherapy, 3 combination of local treatments) and 21 (23%) with systemic therapy alone. The latter group more frequently had extra pulmonary metastases (81.0% vs 26.8%, $p<0.001$) and synchronous presentation of LM (23.8% vs 7.0%, $p=0.045$). Choice of local versus systemic therapy and time to start first treatment after LM diagnosis (median 109 days, IQR 44-240 vs 116 days, IQR 53-168) were comparable between centres. Three-year survival rates did not differ between treatment groups, local treatment modalities, or treating centres.

Conclusion

Treatment strategies and oncological outcomes were similar between centres. Survival outcomes were comparable between locally and systemically treated patients.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, with almost 2 million new patients each year.(1) The lung is the second most common organ for distant spread. Lung metastases (LM) are diagnosed synchronously in 4-17% of patients, of whom 31-40% only have lung metastases.(2-5) In patients with stage IV CRC incidence rates are higher, 37% and 23% for synchronous and metachronous LM, respectively.(3) These rates are probably even higher than reported as thoracic imaging is not always performed. The debate on the best approach and timing of treatment in patients with lung metastases who are eligible for potentially curative treatment is ongoing. Distinctive evidence is not available.(6-10)

Local treatment of LM is advocated in selected patients with a limited number of LMs, to achieve long-term survival.(6, 8, 9) Surgery and less invasive local therapy modalities such as percutaneous thermal ablation and stereotactic body radiotherapy (SABR) are currently of interest.(11-16) The benefit of one of these local treatment modalities over another, over systemic therapy, or even over conservative treatment is not evident. The only non-inferiority randomised controlled trial, PulMiCC, investigating the benefit of local treatment over active monitoring terminated early due to slow accrual.(17) This trial would never have met its statistical endpoint as the estimated 5 year overall survival of the first 33 patients in the active monitoring group was 29% instead of the 5% previously reported and used for trial design. Although some retrospective studies claimed benefit of surgery over other treatment options, selection bias was likely present.(18-20) Studies regarding LM treatment are generally retrospective, single-centre, not CRC specific, and/or compare two therapies at maximum.(21-26) The question whether or not local treatment of lung metastases improves survival and which local treatment modality is best, remains unanswered. Currently, patients' and treating physicians' preference is still leading.
The aim of this multicentre study was to provide more insight in the different treatment strategies for patients with colorectal LM amenable for potentially curative treatment. Patients who were treated with systemic therapy alone and those who underwent local treatment were compared. Also, local procedures (surgery, thermal ablation, and SABR) were analysed separately.

METHODS

Patients

Consecutive patients with CRC discussed during multidisciplinary team meetings (MDTs) in the Erasmus MC and Netherlands Cancer Institute were reviewed for the presence of LM in 2018 to assure long-term follow-up after treatment start. Both centres are tertiary care referral centres for treatment of CRC in the Netherlands. All MDTs at which CRC patients were discussed (e.g. dedicated CRC, metastatic CRC, lung, liver, and HIPEC MDTs) were screened. The MDT was attended by a surgeon, radiologist, interventional radiologist, radiation oncologist, medical oncologist, and a nurse practitioner. Included patients had limited colorectal LM and were considered for curative LM directed treatment. Patients with ≤5 LM and ≤5 (resectable) peritoneal deposits or clinically pathological lymph nodes or hepatic metastases were eligible. Patients were excluded if no follow-up data were available, when they did not receive LM directed therapy in the MDT centre, if they had previously received LM directed therapy, if the patient refrained from treatment, and when patients had a second primary tumour requiring treatment or with a significant effect on survival. Pathological confirmation of LM preceding treatment was not required. The study was approved by the Netherlands Cancer Institute ethics review board for both centres (NCI IRBd20-046, EMC MEC-2020-0104).

Data collection

Patient characteristics and tumour and treatment details were collected from the electronic patient medical files. Patient characteristics included age at LM diagnosis, sex, comorbidity, and pulmonary symptoms. Comorbidity was determined using the updated Charlson Comorbidity Index (uCCI).(27) Tumour data included date of diagnosis CRC, indeterminate lung nodules (ILN) and LM, primary tumour location, TNM-stage, moment of LM diagnosis (synchronous or metachronous), unilateral or bilateral distribution of LM, in situ extra pulmonary metastases at LM diagnosis, histological confirmation LM, the number and size of LM both at diagnosis and at start treatment, date of pulmonary recurrence, and the date of extra pulmonary disease progression. Lung lesions were documented as ILN or LM as mentioned in radiologist's reports or MDT. Radiologist reports described ILN as dubious lung nodules, indeterminate lung nodules or lung nodules requiring follow-up. ILN were considered true LM in case of growth, occurrence of new suspicious lung lesions, and when histopathology was obtained. Lung nodules on imaging were also considered LM when documented as such in the radiology or MDT report, and when the patient was informed about pulmonary metastases. The diagnosis of lung metastases was considered synchronous when detected on first chest imaging and within a maximum 6 months after diagnosis of the primary tumour. Treatment details included

type of local treatment per LM, use of systemic therapy and dates, surgical approach and resection type, SABR schedule, completion rates, and complications after local therapy. Major complications were collected for up to 90 days post-treatment and were evaluated according to the Clavien-Dindo surgical complication score for surgical resection and thermal ablation.(28) The Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) was used for SABR.(29) Major complications were defined as ≥grade 3 complications and scored per procedure.

Treatment

The choice of (local) treatment was determined in the MDTs. Surgical resection was performed by (cardio)thoracic surgeons using video-assisted thoracic surgery (VATS) or thoracotomy. Percutaneous thermal ablation was performed by microwave ablation (Emprint™, Medtronic and the new introduced NeuWave™, Johnson&Johnson) or the newly introduced cryoablation system (Visual ice™, Boston Scientific). The treating radiation and medical oncologist determined the SABR and systemic therapy schedules, respectively, according to national and local guidelines.

Outcomes

Patient- and tumour characteristics were compared between patients receiving systemic therapy only and patients receiving local treatment for their LM. To provide insight in the treatment strategies per patient a swimmersplot was generated. This included the time to LM diagnosis, time to first (local) treatment, time to first disease progression, and time to survival or last follow-up moment including survival status. Time of diagnosis ILN to LM and time of LM diagnosis to treatment was compared between treating centres. Local treatment details, completion, and major complications were described. Incomplete treatment was defined as a pathological confirmed irradical resection and as residual tumour in the treated area on first post procedural chest CT after thermal ablation. Incomplete treatment in SABR-treated lesions was not documented, as the occurrence of radiation-induced fibrosis is very common. All regrowth in SABR-treated area was considered pulmonary disease progression. Progression free survival (PFS) and overall survival (OS) rates of patients treated with systemic therapy only and patients who underwent local treatment were compared. PFS and OS were stratified by type of local treatment. PFS was defined as the time from start first treatment to first disease progression, or last follow-up appointment. Growth of concurrent in situ tumour sites before their indicated treatment were not considered disease progression when treatment strategies were not altered. Overall survival (OS) was defined from the date of LM diagnosis until the date of death or the date of last contact.

Statistics

The cohorts were described using descriptive statistics. Missing or inconclusive values were not included in analyses. Group comparisons were tested using Chi-square and the Fishers' exact test was used in case one cell had <10 events. Differences of nonparametric unpaired variables were performed using the Student's t test for normally distributed data and the Mann Whitney U test for not normally distributed data. The Kaplan-Meier method was used to analyse the time to event data (time of ILN diagnosis to LM diagnosis, time of LM diagnosis to start treatment, PFS, and OS) and groups comparison was tested using the Log-rank test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS® for Windows, version 25.0 (IBM Corp. Armonk, New York, USA) and R® version 3.6.1 (https://www.r-project.org/).

RESULTS

Patients

Ninety-two of 1417 CRC patients discussed in the MDTs were included (figure 1). Fifty-four patients (51%) did not have thoracic imaging before LM diagnosis. Thirty-two (63%) of the patients with prior thoracic imaging had ILN which turned out to be LM. Seventy-one patients (77%) received local treatment with or without systemic therapy and 21 patients (23%) received systemic therapy only. Of the locally treated patients 17 (24%) underwent surgery, 13 (18%) underwent thermal ablation, 38 (54%) were treated with SABR and 3 (4%) patients received a combination of local treatment modalities. Combined treatments included 2 patients with surgery and SABR and 1 patient with ablation and SABR. Patient and tumour characteristics of the systemic therapy only and locally treated patients are shown in Table 1. Ablations were performed in one centre only. The choice for local treatment or systemic therapy only did not differ between centres. The median number of lung metastases at diagnoses was 2 (IQR 1-2). The median size of the largest lung metastasis at start treatment was 11 mm (IQR 9-16 mm). Extra pulmonary metastases were more often present in the systemic therapy only group (81.0% vs 26.8%, p<0.001). Baseline characteristics per treatment modality of the locally treated patients are shown in supplementary table 1.

Table 1. Baseline characteristics of all patients with limited colorectal lung metastases

	Systemic treatment (n=21)		*Local treatment (n=71)*		*p-value*
Treating centre					0.749
1	10	47.6%	31	43.7%	
2	11	52.4%	40	56.3%	
Age at time LM, years					0.503
Median (IQR)	62	(52-70)	65	(55-72)	
Sex					0.799
Male	14	66.7%	43	60.6%	
Female	7	33.3%	28	39.4%	
Site primary tumour					0.892
Right sided colon	2	9.5%	9	12.7%	
Left sided colon	7	33.3%	25	35.2%	
Rectum	12	57.1%	37	52.1%	
T-stage[a]					1.000
T0-2	3	15.0%	12	17.6%	
T3-4	17	85.0%	56	82.4%	
Unknown*	1		3		
N-stage[a]					1.000
N0	7	36.8%	25	36.8%	
N1-2	12	63.2%	43	63.2%	
Unknown*	2		3		
Comorbidity					0.499
None (uCCI 0)	13	61.9%	52	73.2%	
Mild (uCCI 1-2)	8	38.1%	15	21.1%	
Severe (uCCI >2)	0	0.0%	4	5.6%	
Pulmonary complaints					1.000
No	11	91.7%	40	88.9%	
Yes	1	8.3%	5	11.1%	
Unknown*	9		26		
Indeterminate lung lesions before LM					0.719
No	3	27.3%	13	39.4%	
Yes	8	72.7%	20	60.6%	
No prior thoracic imaging*	10		38		
Presentation LM					**0.045**
Synchronous	5	23.8%	5	7.0%	
Metachronous	16	76.2%	66	93.0%	
Number LM (diagnosis)					0.326
Single	7	33.3%	33	46.5%	
Multiple	14	66.7%	38	53.5%	
Distribution LM (diagnosis)					0.605
Unilateral	15	71.4%	44	62.0%	
Bilateral	6	28.6%	27	38.0%	
Extra pulmonary metastases at LM diagnosis					**<0.001**
No	4	19.0%	52	73.2%	
Yes	17	81.0%	19	26.8%	
Number LM (start treatment)					0.311
Single	6	28.6%	31	43.7%	
Multiple	15	71.4%	40	56.3%	
Size largest LM (start treatment)					0.178
<20 mm	18	94.7%	54	80.6%	
>20 mm	1	5.3%	13	19.4%	
Unknown*	2		4		

Table 1. (continued)

	Systemic treatment (n=21)		*Local treatment (n=71)*		*p-value*
Histological confirmation LM before treatment					0.194
No	12	100%	49	83.1%	
Yes	0	0%	10	16.9%	
Unknown*	9		12		
Pretreatment systemic therapy	NA				NA
No			56	78.9%	
Yes			15	21.1%	

[a] pathological stage or in case of pretreatment or unknown pathological stage clinical stage (if higher stage)

** not included in statistical analysis*

Abbriviations: LM: lung metastasis; NA; not applicable; uCCI: updated Charlson Comorbidity Index

Figure 1. Patient selection

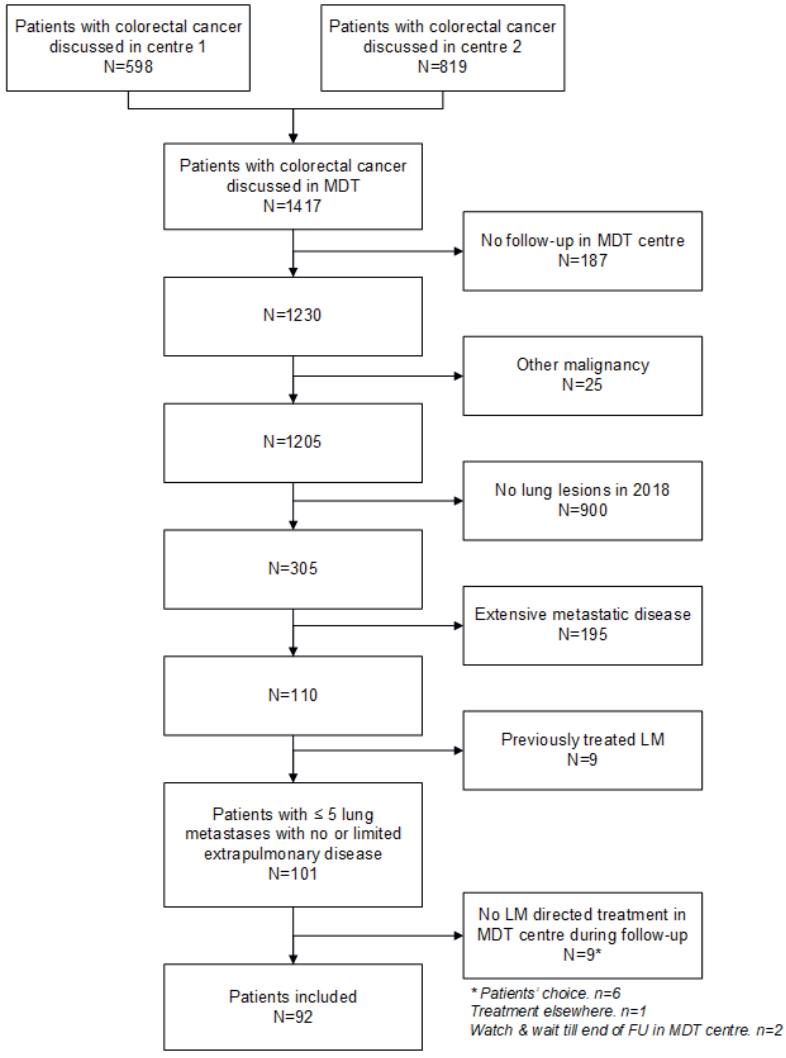
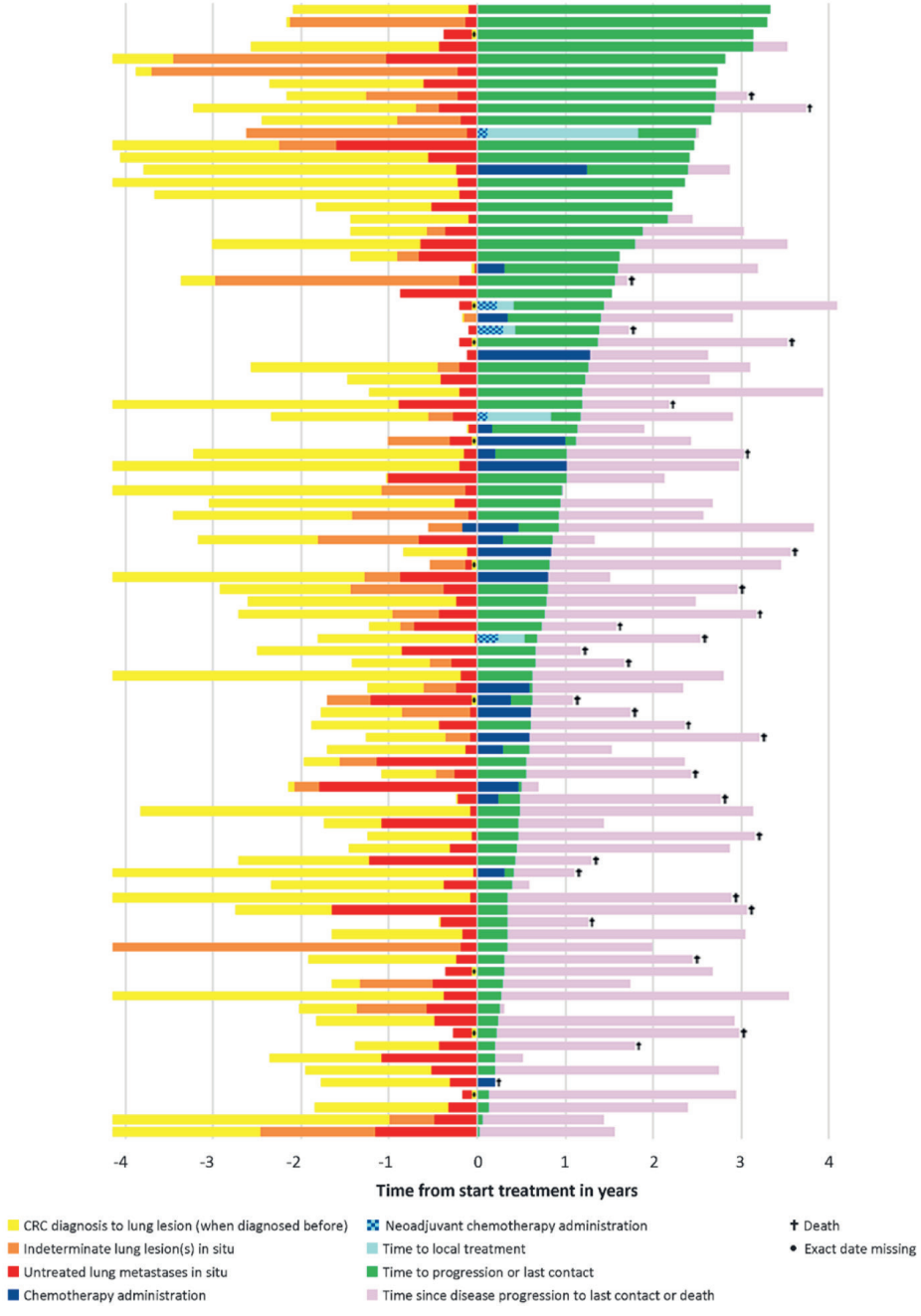


Figure 2. Course of disease per patient



Treatment

The course of disease, including progression of ILN to LM, start and duration of systemic therapy, moment of first local treatment, and occurrence of disease progression and death for each patient are shown in figure 2. Median time of ILN to LM diagnosis was 191 days (IQR 95-400). Median time of LM diagnosis to start systemic therapy only or first local treatment was 92 days (IQR 55-188) with a maximum of 652 days. In 10 patients (11%) local or systemic therapy was started only after additional LM appeared. Time of diagnosis ILN to diagnosis LM (median 296 days, IQR 87-397 vs 144 days, IQR 159-386) and time of LM diagnosis to start treatment (median 109 days, IQR 44-240 vs 116 days, IQR 53-168) did not differ between centres (p=0.250 and p=0.675, respectively).

Most patients received one local procedure (n=59, 64%). Ten patients (11%) had two procedures and two patients (2%) had three procedures. Up to five LM were treated in one procedure. Fifteen patients had received systemic therapy before local treatment (21 %), mostly before SABR. In total, 85 local procedures were performed including 20 (24%) resections, 20 (24%) thermal ablations, and 45 (52.9%) SABR. The number of LM treated in one procedure ranged from 1-3, 1-4, and 1-5 per procedure for surgery, thermal ablation, and SABR, respectively. Three of the 20 (15%) surgical procedures were thoracotomies and the remainder were VATS resections. Two lobectomies (10%) were performed. Other patients underwent lung sparing resections and the extent of surgery was missing for 2 procedures. Most commonly used SABR schedules were 3 fractions of 17 Gy (23 patients, 55%), 3 fractions of 18 Gy and 5 fractions of 11 Gy were used in 5 procedures each (12%). SABR schedules were missing for 3 procedures. Major complications were observed after 1 thermal ablation procedures (5%), 2 SABR procedures (5%), and none after surgery. All complications were grade 3 complications. The patient who underwent thermal ablation required percutaneous drainage the next day for pneumothorax. The SBRT patients had a RTOG grade 3 pneumonia. Incomplete treatment was observed after 1 thermal ablation and the residue was successfully re-ablated. Forty-four locally treated patients (62%) had pulmonary recurrences during follow-up and the pulmonary recurrence rate did not differ between local treatment groups (39% surgery vs. 64% thermal ablation vs. 72% SABR, p=0.058). Median time from start treatment to pulmonary recurrence was 283 days (IQR 150-424).

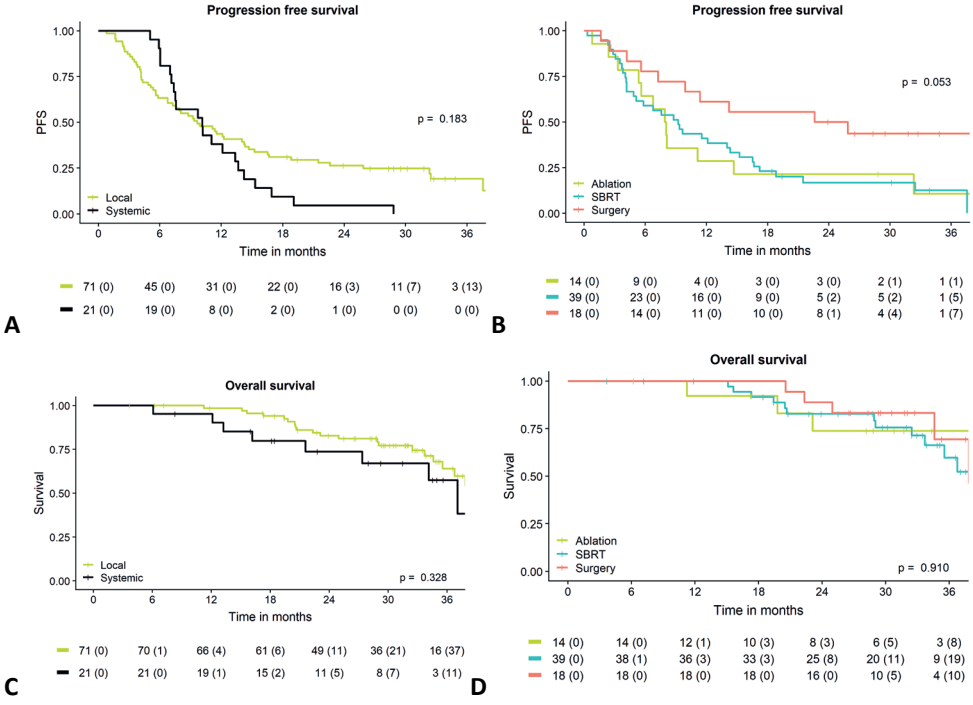
Survival

Seventy-seven patients (83.7%) had intra- and/or extra- pulmonary disease progression during follow-up. Median PFS was 9.8 months (95% CI: 7.6 months - 13.4 months). Three-year PFS in all patients was 14.6% (95% CI: 8.3% - 25.5%). PFS at 3 years was 0% in patients treated with systemic chemotherapy compared to 19.3% (11.1% - 33.0%) in patients

treated with local therapies (long rank: p=0.183, Figure 3A). PFS did not differ between centres (p=0.663). Of the patients with local strategies, patients treated with surgery had the highest 3-year PFS rates of 43.8% (95% CI: 25.7% – 74.4%), compared to 10.1% for thermal ablation (95% CI: 1.9% – 59.3%), and 12.6% for SABR (95% CI: 5.9% – 31.2%) (Figure 3B, p=0.053).

At last contact, 23 patients (25.0%) were disease-free at median follow-up of 32.6 months, 39 patients (42.4%) were alive with disease and 30 patients (32.6%) had died. Median follow-up time did not differ between groups (p=0.143). None of the patients in the systemic therapy only group had a complete response to therapy and therefore nobody was disease-free at last contact. Median time from lung diagnosis to last follow-up appointment for survivors was 32.4 months and did not differ between the systemic only and locally treated groups (35.6 months vs. 32.1 months respectively, p=0.189). Median OS was 42.3 months (95% CI: 36.8 months – not reached). The 3-year OS rate of all patients was 62.2% (95% CI: 50.5% – 76.7%) and did not differ between centres (p=0.780). Three-year OS rates were 57.5% (95% CI: 36.7% – 90.0%) in patients treated with systemic therapy only compared to 64.0% (95% CI: 50.7% – 80.7%) in patients treated with local therapy (Figure 3C, p=0.328). Three-year survival rates were 69.4% for surgery (95% CI: 45.9% – 100%), 73.8% for thermal ablation (95% CI: 52.2% – 100%), and 59.7% for SABR (95% CI: 42.6% – 83.8%, Figure 3D, p=0.910).

Figure 3. Survival of patients with limited lung metastases stratified per treatment modality



DISCUSSION

Studies comparing local to systemic or no treatment are scarce and hampered by selection bias, reserving local treatment options for fit patients with “good” prognostic factors and “less aggressive” tumours. A recent observational study of 512 patients reported 5-year survival rates of electively operated and non-operated patients of 47% and 22% respectively.(20) Kim et al. showed a difference in the 3-year overall survival rate in favour of local treatment, 78% after metastasectomy compared to 36% for patients receiving systemic therapy and/or best supportive care.(30) Omission of resection was, among other parameters, negatively associated with overall survival. Although terminated early due to low accrual, the randomised controlled PulMiCC trial did not report any difference in overall survival in patients treated with local treatment compared to systemic therapy or watchful waiting.(31)

Pulmonary recurrence and overall survival rates were not different between patients treated with surgery, thermal ablation, or SABR. Studies reporting outcomes of single local modalities showed five-year overall survival rates of 40%-83%.(12, 13, 16, 32-34) Studies comparing local modalities show conflicting results regarding survival. Lodeweges et al. found no difference in 5-year survival rate after surgery or SABR (81% vs 83%, respectively), however some of these patients did have metastases from non-CRC origin, which could have influenced results.(22) Other studies choose surgery over radiation therapy due to favourable (local) progression-free survival rates.(21, 35) Two reviews have suggested that surgery should be preferred over radiation and ablation.(10, 36) These differences in oncologic outcomes could be explained by patient selection, preserving surgery only for the fittest patients, and physician’s preference. All these data combined may indicate that the choice of treatment for limited lung metastases does hardly affect overall survival in metastatic CRC.

On procedural level, incomplete treatment and major morbidity rates were low. No major complications were reported after surgery even though it is the most invasive treatment. Underreporting of complications in patients treated with metastasectomy may be considered, which is also found in other studies when comparing invasive to minimal and less-invasive procedures, especially when drain placement and hospitalisation are not part of the less invasive procedure.(36) Pneumothorax frequently occurs after surgery or ablation, but can be managed expectantly most often. Morbidity rates after SABR are overall limited.(16) This sample size is insufficient to draw any conclusions regarding superiority of one treatment over another in respect to major morbidity. Arguments other than complication rates and long-term survival probability become relevant if safety and survival are similar. Endpoints of future studies should include quality of life, recovery

time, time without any therapy, time without disease in situ, re-treatment rate, treatment costs, and residual pulmonary function. Metastasectomy can have negative effects on respiratory function and quality of life. (17, 37) Although no studies have compared these outcomes with thermal ablation and SABR for colorectal lung metastases, those less invasive modalities may have less impact on lung capacity and quality of life.(11, 38) On the other hand, long-term pulmonary toxicity is also seen after SABR and ablation, and should therefore be administered with care in particular in patients with pre-existent (restrictive) lung disease.

Baseline characteristics, including extra pulmonary disease load, of patient groups who underwent local and systemic therapy for limited metastatic CRC are highly relevant for interpretation of outcome. The number of patients was low. Preference for a specific treatment due to other patient-, centre-, or tumour factors cannot be nullified when interpreting these results. It is remarkable, however, that no inter-hospital variation in survival outcomes was observed. The use of chemotherapy in the locally treated group as initial treatment is another limitation. Potential selection bias here is important. Good responders to initial treatment with chemotherapy are likely elected for local consolidation therapy despite not being considered eligible for local treatment at first, leaving non-responders in the systemic only group.

In conclusion, survival rates were comparable in patients with colorectal cancer and limited lung metastases treated with local therapy or systemic therapy alone. Surgery, thermal ablation, and SABR as local treatment modalities of lung metastases seem equally effective. Patient selection is important when deciding on the most appropriate treatment for patients with colorectal lung metastases. Patients' and treating physicians' preference of treatment modality can be leading without apparent negative consequences for patients that fit this studies inclusion criteria. Although local treatment might not improve survival, it can still be a valuable treatment option to delay systemic treatment. Future studies should focus on patient specific outcomes, such as quality of life and time without treatment or hospital visits, and treatment costs.

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SUPPLEMENTARIES

Supplementary table 1. Baseline characteristics locally treated patients with limited colorectal lung metastases

	Surgery		Ablation		SABR	
	18		14		39	
Treating centre						
1	8	44.4%	0	0.0%	23	59.0%
2	10	55.6%	14	100.0%	16	41.0%
Age at time LM, years						
Median (IQR)	63	(53-71)	57	(48-65)	67	(58-72)
Sex						
Male	14	77.8%	10	71.4%	19	48.7%
Female	4	22.2%	4	28.6%	20	51.3%
Site primary tumour						
Right sided colon	4	22.2%	1	7.1%	4	10.3%
Left sided colon	7	38.9%	5	35.7%	13	33.3%
Rectum	7	38.9%	8	57.1%	22	56.4%
T-stage[a]						
T0-2	3	17.6%	3	21.4%	6	16.2%
T3-4	14	82.4%	11	78.6%	31	83.8%
Unknown*	1		0		2	
N-stage[a]						
N0	7	41.2%	4	28.6%	14	37.8%
N1-2	10	58.8%	10	71.4%	23	62.2%
Unknown*	1		0		2	
Comorbidity						
None (uCCI 0)	14	77.8%	11	78.6%	27	69.2%
Mild (uCCI 1-2)	4	22.2%	2	14.3%	9	23.1%
Severe (uCCI >2)	0	0%	1	7.1%	3	7.7%
Pulmonary complaints						
No	9	90.0%	13	92.9%	18	85.7%
Yes	1	10.0%	1	7.1%	3	14.3%
Missing*	8		0		18	
Indeterminate lung lesions before LM						
No	4	57.1%	5	41.7%	4	28.6%
Yes	3	42.9%	7	58.3%	10	71.4%
No prior thoracic imaging*	11		2		25	
Presentation LM						
Synchronous	0	0%	1	7.1%	4	10.3%
Metachronous	18	100%	13	92.9%	35	89.7%
Number LM (diagnosis)						
Single	10	55.6%	6	42.9%	17	43.6%
Multiple	8	44.4%	8	57.1%	22	56.4%
Distribution LM (diagnosis)						
Unilateral	13	72.2%	7	50.0%	24	61.5%
Bilateral	5	27.8%	7	50.0%	15	38.5%
Extra pulmonary metastases at LM diagnosis						
No	17	94.4%	8	57.1%	27	69.2%
Yes	1	5.6%	6	42.9%	12	30.8%

Supplementary table 1 (continued)

	Surgery		Ablation		SABR	
Number LM (start treatment)						
Single	9	50.0%	6	42.9%	16	41.0%
Multiple	9	50.0%	8	57.1%	23	59.0%
Size largest LM (start treatment)						
<20 mm	11	64.7%	12	85.7%	31	86.1%
>20 mm	6	35.3%	2	14.3%	5	13.9%
Unknown*	1		0		3	
Histological confirmation LM before treatment						
No	11	68.8%	9	100%	29	85.3%
Yes	5	31.3%	0	0%	5	14.7%
Unknown*	2		5		5	
Pretreatment systemic therapy						
No	17	94.4%	13	92.9%	26	66.7%
Yes	1	5.6%	1	7.1%	13	33.3%

[a] pathological stage or in case of pretreatment or unknown pathological stage clinical stage (if higher stage)

** not included in statistical analysis*

Abbreviations: LM = lung metastases. uCCI = updated Charlson Comorbidity Index

Supplementary figure 1. Course of disease per patient stratified per treating centre

CHAPTER 11

The clinical relevance of indeterminate lung nodules in patients with locally recurrent rectal cancer

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ABSTRACT

Introduction

To evaluate the clinical relevance of indeterminate lung nodules (ILN) in patients with locally recurrent rectal cancer (LRRC) treated in a tertiary referral centre.

Methods

All patients with LRRC diagnosed between 2000 and 2017 were retrospectively reviewed. Reports of staging chest CT-scans were evaluated for ILN. Patients with distant metastases including lung metastases at time of LRRC diagnosis were excluded. Overall (OS), progression-free survival (PFS) and the cumulative incidence of lung metastases were compared between patients with and without ILN.

Results

In total 556 patients with LRRC were treated during the study period. In the 243 patients eligible for analysis, 68 (28%) had ILN at LRRC diagnosis. Median OS was 37 months for both the patients with and without ILN (p=0.37). Median PFS was 14 months for the patients with ILN and 16 months for patients without ILN (p=0.80). After correction for potential confounding, ILN present at LRRC diagnosis was not associated with impaired OS or PFS (adjusted hazards ratio [95% confidence interval]: 0.81 [0.54-1.22] and 1.09 [0.75-1.59]). The 5-year cumulative incidence of lung metastases was 31% in patients with ILN and 28% in patients without ILN (p=0.19).

Conclusion

Our study shows that ILN are present in roughly a quarter of patients with LRRC. No differences in OS, PFS, or the cumulative incidence of lung metastases were found between patients with and without ILN at LRRC diagnosis. These results suggest that ILN are of little to no clinical relevance in patients with LRRC.

INTRODUCTION

Indeterminate lung nodules (ILN) are encountered commonly on chest computed tomographic (CT) in colorectal cancer (CRC) patients and can be difficult to distinguish from small lung metastases.(1) Management of ILN in CRC patients is challenging, especially when found at presentation. When these ILN are misdiagnosed as lung metastases, patients could be staged incorrectly. This could lead to patients being incorrectly precluded from potentially curative therapy. On the other hand, high morbidity of curative intended treatment might be spared if lung metastatic lesions are recognized in an early stage on chest CT and treatment strategy can be changed accordingly.

Currently only general recommendations for ILN are available, such as the Fleischner criteria.(2) Patients with a known malignancy are excluded from these guidelines, as ILN are more likely to be cancer-related compared to the general population. Several studies have investigated ILN in patients with colorectal cancer (CRC), locally advanced rectal cancer (LARC), and metastatic CRC, with reported incidences ranging from 9-39%.(1, 3-6) The incidence of ILN in patients with locally recurrent rectal cancer (LRRC) has so far not been described. Furthermore, little is known of the clinical relevance of ILN in CRC patients, and especially in patients with LRRC.

Approximately 4-10% of rectal cancer patients will develop local recurrence after surgery for primary rectal cancer.(7-10) Curative intended treatment for LRRC can be offered in a selected group of patients, but surgery is challenging and associated with high morbidity and mortality.(11-14) Whereas in isolated LRRC surgical resection may improve survival, this may not be the case for patients with extensive metastatic disease.(15, 16) A staging chest (CT) scan is therefore standard of care to evaluate the presence of lung metastases in the Netherlands, when curative treatment is considered, but may introduce difficulties in clinical decision making when ILN's are found. Whether or not LRRC patients with ILN should be precluded for curative treatment and if these ILN are indicative for future lung metastases is yet unknown.

The aim of the current study is therefore to evaluate the clinical relevance of ILN in patients with LRRC. Patients without distant metastases at time of LRRC diagnosis were analysed to compare prognostic factors in patients with and without ILN.

METHODS

Patient selection and data

All consecutive LRRC patients discussed in the multidisciplinary tumour board (MDT) of the Erasmus MC Cancer Institute, Rotterdam, the Netherlands, between January 2000 and December 2017 were retrospectively reviewed. LRRC was defined as locally recurrent disease in the pelvic area after previous resection of histologically confirmed rectal cancer. Diagnosis of LRRC had to be confirmed by either a biopsy or a combination of imaging and raised serum carcinoembryonic antigen (CEA) levels. Patients with absent staging CT and/or patients with distant metastases at LRRC diagnosis, including lung, were excluded. Patient demographics, clinicopathological disease characteristics and outcome measures were obtained by review of hospital medical records, from referral hospitals and from general practitioners.

This study was approved by the medical ethics committee of Erasmus MC (MEC-2020-0104).

Treatment strategy

All patients with suspected LRRC were discussed in the MDT consisting of dedicated surgical oncologists, medical oncologists, radiation oncologists and radiologists to establish optimal treatment strategy. Patients with LRRC were generally considered candidates for curatively intended treatment in case of absent extensive distant metastatic disease, when considered resectable on MRI, and if judged fit for major surgery. When treated with curative intention, patients with LRRC generally received neoadjuvant long-course radiotherapy (44.6-52Gy), with or without the addition of capecitabine as radiosensitizer.(17) Previously irradiated LRRC patients were treated with short-course re-irradiation (27-30Gy).(18) After neoadjuvant treatment, patients were restaged by chest and abdominal CT and MRI 4-6 weeks after finishing neoadjuvant treatment to evaluate tumour response and distant metastases and discussed in the MDT.(19) Depending on the findings patients either continued with curatively intended surgical resection, or in case of progressive disease treatment was altered to a non-surgical strategy. Palliative treatment strategies consisted of radiotherapy, systemic chemotherapy, diversion colostomy, any combination of these three and best supportive care. In case of curative intended resection, postoperative surveillance was scheduled every three to six months and consisted of outpatient visits, serial blood CEA assessments and medical imaging by chest- and abdominal CT and/or abdominal MRI.

Indeterminate lung nodules and lung metastases

Staging chest CT was defined as a chest CT made before any treatment and within 3 months of diagnosis of LRRC at either the referring hospital or at the Erasmus MC Cancer Institute. Chest CT scans from the referring hospitals were always reassessed by a dedicated radiologist from our centre. No consensus in the definition of ILN has been established.(1) In the current study, all intrapulmonal lesions of which the nature could not be determined on chest CT by a dedicated radiologist were considered as ILN. Reports from radiologists were retrospectively evaluated by the investigator. All inconclusive lesions in which the radiologist could not confirm whether its nature was benign or malignant were classified as ILN. Lung lesions smaller than 1 cm or calcified lesions were more likely to be considered benign. Round and vascular characteristics were more likely to be classified as malignant. In principal, ILN found at the moment of LRRC diagnosis were left in situ until progression to metastases was observed. Similarly to ILN, lesions were classified as lung metastases based on the reports from dedicated radiologists.

Outcomes

Short- and long-term oncological outcomes were compared between patients with and without ILN at diagnosis of LRRC. Short-term outcomes of interest were number of patients eligible for curative intended treatment, number of patients with disease progression due to lung metastases at response evaluation after neoadjuvant treatment and the number of patients actually undergoing surgical resection of LRRC. Overall (OS), progression-free survival (PFS) and the cumulative incidence of lung metastasis were analysed to determine long-term oncological outcomes. OS was defined as the time from diagnosis of LRRC to death or date of last follow-up. PFS was defined as the time from diagnosis of LRRC to date of disease progression or death, whichever came first. Analyses on long term oncological outcomes were performed in surgically treated patients separately. For the analyses in the surgically treated patients, survival was estimated from date of surgical resection of LRRC.

Statistics

Continuous data were presented as medians and interquartile ranges (IQR). Categorical data were presented as absolute numbers and percentages. Between group comparisons were performed using the Chi-squared for categorical data and the Mann Whitney U test for non-parametric continuous data. OS and PFS were estimated by the method of Kaplan-Meier and compared using the log-rank test. Survival estimates were reported as median and as 5-year survival rates with corresponding 95% confidence interval (CI). Uni- and multi-variable Cox proportional hazards regression models were fitted for OS and PFS to

identify possible predictors and to correct for potential confounding. Results from the proportional hazards regression analyses were reported as Hazard Ratio (HR) with corresponding 95%CI. Cumulative incidence functions of time from diagnosis of LRRC to diagnosis of lung metastases were estimated by a Fine and Gray competing risk model and compared by Gray's test.(20) Herein the competing risk was defined as death without prior diagnosis of lung metastases, since deceased patients in whom lung metastases had not been diagnosed prior to death are no longer at risk for developing lung metastases. The cumulative incidence function as described by Scrucca et al. (2007) was used to estimate 95%CI of the cumulative incidence function.(21) Statistical significance level was set at an α of 0.05. Statistical analyses were performed using IBM SPSS Statistics version 25.0.0.1 and R version 3.6.1 (http://www.r-project.org).

RESULTS

Between January 2000 and December 2017 a total of 556 patients diagnosed with LRRC were discussed in the MDT of the Erasmus MC Cancer Institute. Distant metastases at LRRC diagnosis were found in 191 patients (34%) and were excluded for further analysis in this study. Forty-six patients had lung metastases, 64 had liver metastasis and 25 patients had both. Metastases elsewhere were found in 56 patients. Within the 365 patients with isolated LRRC a staging chest CT performed within three months of diagnosis of LRRC was available in 243 patients (67%). Reasons for absent staging chest CT were; no curative treatment options based on pelvic imaging alone in 37 patients (30%), staging chest CT performed after (start of) neo-adjuvant treatment in 42 patients (34%), and other types of thoracic imaging including thoracic X-ray in 18 patients (18%) and Positron-Emission Tomography (PET) in 17 patients (14%). From seventeen patients with PET, four patients had ILN in which one had 18F-fluorodeoxyglucose (FDG) uptake. In the 243 patients included for analysis ILN were found in 68 patients (28%) and in the remaining 175 patients (72%) no lung nodules were described. The median follow-up for survivors was 81 months (IQR 42-131 months). During follow up 199 patients had disease progression and 170 patients died.

Table 1. Patient and treatment details

		Patients with ILN at diagnosis LRRC (n=68)	Patients without ILN at diagnosis LRRC (n=175)	P-value
Gender (%)	male	44 (65)	111 (63)	0.852
	female	24 (35)	64 (37)	
Age at primary resection, years (median [IQR])		65.5 [57.8, 73.2]	67.0 [59.5, 73.0]	0.817
Primary details				
T stage (%)	T1-T2	16 (24)	34 (21)	0.670
	T3-T4	52 (76)	128 (79)	
N stage (%)	N0	27 (41)	76 (50)	0.233
	N1-N2	39 (59)	77 (50)	
Neoadjuvant radiotherapy primary (%)		40 (59)	68 (39)	0.005*
Radical resection (%)		48 (86)	147 (92)	0.180
Differentiation primary (%)	Good	4 (9)	11 (9)	0.612
	Moderate	34 (79)	93 (78)	
	Poor	5 (12)	15 (13)	
DFI, months (median [IQR])		23.0 [15.5, 39.5]	24.0 [12.0, 40.5]	0.621
LRRC treatment details				
LRRC treatment intention (%)	Curative	54 (79)	135 (77)	0.703
	Palliative	14 (21)	40 (23)	
Altered treatment after restaging (%)		14 (21)	21 (12)	0.086
Resection (%)		40 (59)	114 (65)	0.359
Follow-up details				
Second chest CT (%)		59 (87)	125 (72)	0.014*
Time to second chest CT, weeks (median [IQR])		14.5 [12.0, 20.5]	19.0 [14.0, 42.0]	0.005**

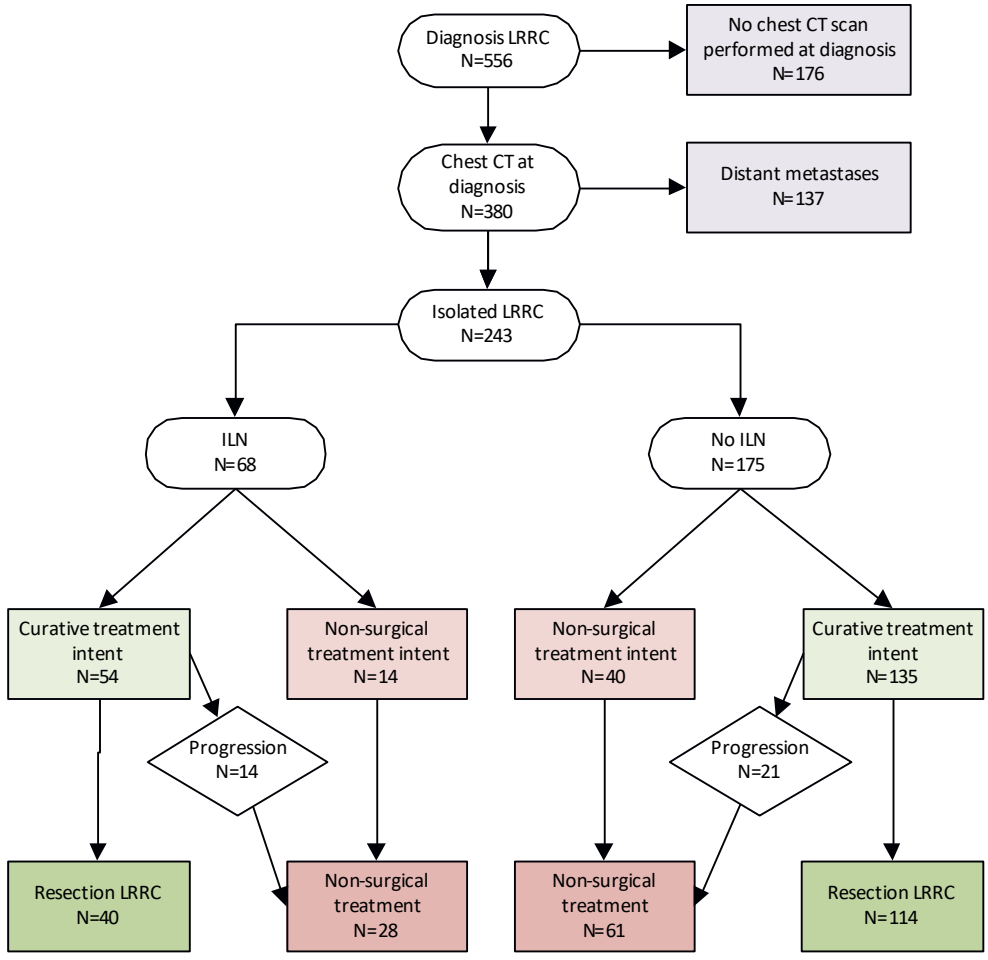
**Chi squared test. **Mann Whitney U test. Missing values were not included in group comparison. Percentages might not add up due to rounding.*

Abbreviations: DFI: disease-free interval between resection of primary rectal cancer and diagnosis of LRRC; ILN: indeterminate lung nodules; IQR: interquartile range; LRRC: locally recurrent rectal cancer.

Short-term oncological outcomes

Baseline characteristics and treatment details of the 68 patients with and 175 patients without ILN were reported in table 1. No difference in baseline characteristics were observed between patients with and without ILN, apart from patients with ILN more frequently received neoadjuvant radiotherapy as part of their treatment for primary rectal cancer (59% versus 39%, p<0.01). Concerning follow-up, a second chest-CT was performed more often (87% versus 72%, p=0.01) and sooner (median 15 versus 19 weeks, p<0.01) in the patients with ILN (table 1). Figure 1 depicts a flow diagram of the study population and the treatment course of the patients with and without ILN. Curative intended treatment at the moment of diagnosis LRRC was initially advised in both groups evenly (79% for ILN versus 77% without ILN, p=0.70). Treatment strategy was altered solely due to the diagnosis of lung metastases in 2 of 14 patients (14%) with ILN and in 2 of 21 patients (10%) without ILN (p=0.66). Forty patients (59%) with ILN completed curatively intended resection of LRRC compared to 114 patients (65%) without ILN (p=0.36).

Figure 1. Flowchart of patients with and without ILN at diagnosis LRRC



Long-term oncological outcomes

Median OS was 37 months with a 5-year OS (95% CI) of 31% (21-47%) in patients with ILN compared to 37 months and 28% (22-37%) in patients without ILN (p=0.37, figure 2A). Similarly to OS, median PFS was 14 months with a 5-year PFS (95%CI) of 17% (12-24%) in patients with ILN compared to 16 months and 22% (14-35%) in patients without ILN (p=0.80, figure 2B). After correction for potential confounding the significant predictors for death were age at diagnosis of LRRC, node positive primary tumour and non-surgical treatment (table 2A). The only predictor for disease progression after correction for potential confounding was non-surgical treatment (table 2B). The presence of ILN at diagnosis of LRRC was neither associated with additional risk for death (adjusted HR[95%CI]: 0.81 [0.54-1.22], p=0.32, table 2A) nor for disease progression (adjusted HR[95%CI]: 1.09 [0.75-1.59], p=0.66, table 2B). The results of the competing risk analysis evaluating the cumulative incidence of lung metastases over time were reported in figure 3. The 5-year (95% CI) cumulative incidence of lung metastasis in patients with ILN was 31% (21-43%) compared to 28% (21-35%) in patients without ILN (p=0.19, figure 3).

Figure 2. Flowchart of patients with and without ILN at diagnosis LRRC

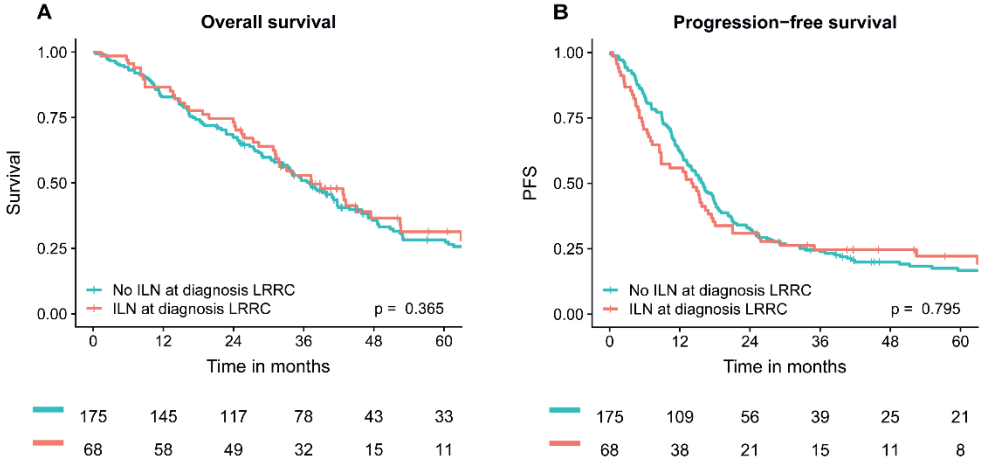


Table 2A. Cox proportional hazard model for survival

	HR uv (95% CI)	p (uv)	HR mv [95% CI]	p (mv)
Age at diagnosis LRRC	1.024 [1.009-1.040]	0.002	1.027 [1.010-1.046]	0.003
T stage T3-T4	1.290 [0.862-1.929]	0.216	1.180 [0.742-1.876]	0.484
N stage N1-N2	1.044 [0.757-1.440]	0.792	1.434 [1.007-2.040]	0.045
Radiotherapy primary	0.888 [0.654-1.207]	0.449	0.732 [0.511-1.049]	0.089
Irradical resection primary	1.461 [0.870-2.453]	0.152	1.371 [0.773-2.433]	0.281
ILN at diagnosis LRRC	0.852 [0.601-1.207]	0.366	0.812 [0.541-1.219]	0.315
Non-surgical treatment	3.788 [2.741-5.235]	<0.001	3.597 [2.472-5.236]	<0.001

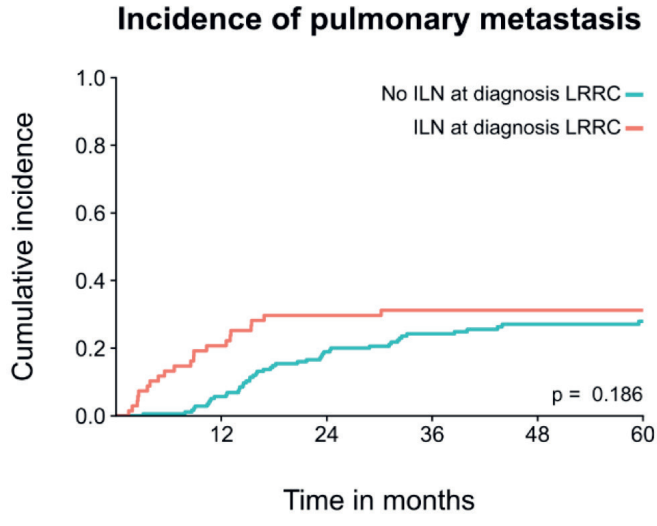
HR: hazard radio. uv: univariate analysis. mv: multivariate analysis. p: p-value. CI: confidence interval. ILN: indeterminate lung nodules. LRRC: locally recurrent rectal cancer.

Table 2B. Cox proportional hazard model for progression

	HR uv [95% CI]	p (uv)	HR mv [95% CI]	p (mv)
Age at diagnosis LRRC	1.015 [1.001-1.029]	0.032	1.007 [0.992-1.023]	0.379
T stage T3-T4	1.240 [0.862-1.784]	0.246	1.262 [0.815-1.954]	0.297
N stage N1-N2	1.002 [0.746-1.344]	0.992	1.152 [0.831-1.598]	0.395
Radiotherapy primary	1.051 [0.795-1.391]	0.726	0.814 [0.584-1.133]	0.222
Irradical resection primary	1.357 [0.833-2.210]	0.221	1.122 [0.663-1.897]	0.669
ILN at diagnosis LRRC	1.043 [0.762-1.429]	0.793	1.087 [0.746-1.586]	0.663
Non-surgical treatment	4.224 [3.138-5.686]	<0.001	3.597 [2.528-5.120]	<0.001

HR: hazard radio. uv: univariate analysis. mv: multivariate analysis. p: p-value. CI: confidence interval. ILN: indeterminate lung nodules. LRRC: locally recurrent rectal cancer.

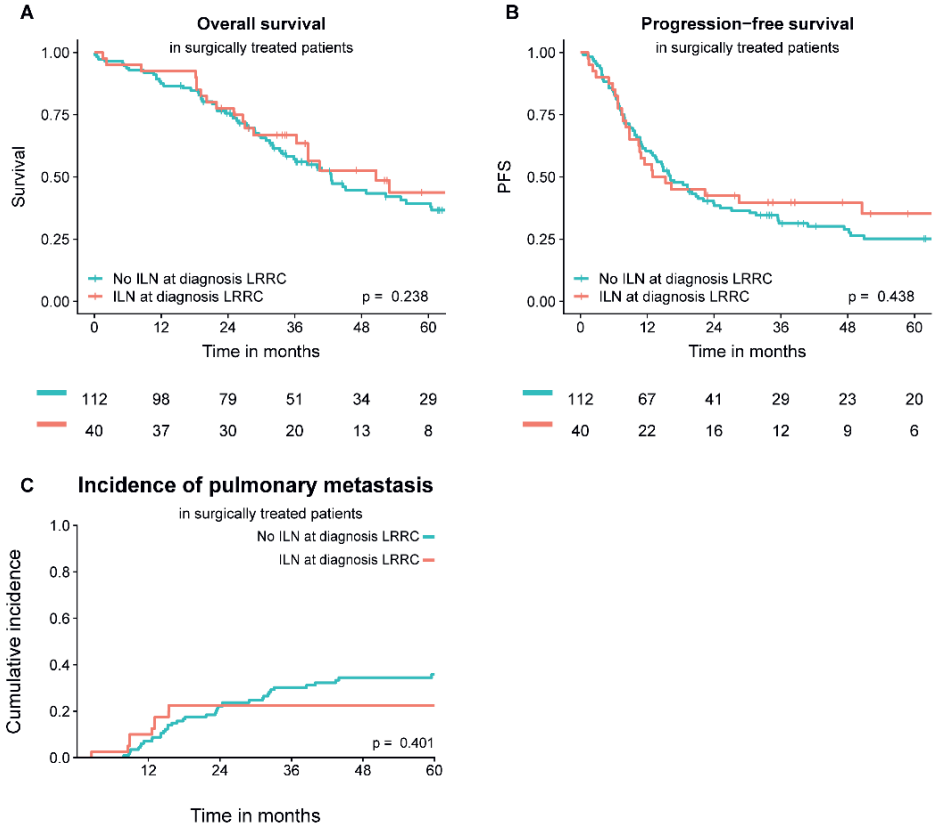
Figure 3. The cumulative incidence of pulmonary metastasis in patients with and without indeterminate lung nodules (ILN) at diagnosis of locally recurrent rectal cancer (LRRC)



Surgically treated patients

In 152 patients actually undergoing surgical resection of LRRC, 40 (26%) had ILN (figure 1). No differences in OS or PFS were observed between patients with and without ILN actually undergoing resection of LRRC. Median and 5-year (95%CI) OS was 51 months and 44% (29-66%) in patients with ILN and 42 months and 39% (30-51%) in patients without ILN (p=0.24, figure 4A). Median and 5-year (95%CI) PFS for surgically treated patients with ILN was 14 months and 35% (23-55%) versus 16 months and 25% (18-35%) for the surgically treated patients without ILN (p=0.44, figure 4B). No difference was seen in the 5-year (95% CI) cumulative incidence of lung metastases, which was 23% (11-37%) versus 36% (27%-45%) in surgically treated patients with and without ILN (p=0.40, figure 4C).

Figure 4. Overall survival, progression-free survival and cumulative incidence of pulmonary metastasis in surgically treated patients with and without indeterminate lung nodules (ILN) at diagnosis of locally recurrent rectal cancer (LRRC)



DISCUSSION

This study shows that ILN were present in 28% of the patients with isolated LRRC in our tertiary referral centre. No differences in OS or PFS were found between patients with and without ILN. Furthermore, the five-year cumulative incidence of lung metastases did not differ between patients with and without ILN, although they did appear to be detected earlier (figure 3). The early detection could partly be explained by the median time to follow-up chest CT, which was found to be significantly shorter in patients with ILN. Therefore, this apparent "earlier detection" could just be the result of earlier imaging during the follow-up of these patients and the clinician's decision to follow-up on those ILN detected at LRRC presentation.

At the moment of isolated LRRC diagnosis, patients with and without ILN were both offered curative intended treatment evenly. In 14 patients with ILN curative intended treatment was terminated due to progressive disease during neo-adjuvant treatment. In two of these fourteen patients (14%) this decision was based solely on the diagnoses of lung metastases. Therefore, the decision to alter treatment from curative to palliative after neoadjuvant therapy was seldom based on the presence or progression of the ILN itself. Similarly, in the patients without ILN, treatment was also altered in two of twenty-one patients (10%) solely due to the diagnosis of lung metastases after neoadjuvant treatment.

Given the absent difference in survival and the equal incidence of lung metastasis between patients with and without ILN, plus the fact that treatment was rarely altered due to the diagnosis of lung metastases after neoadjuvant treatment, these results suggest that the presence of ILN in patients with LRRC is of little clinical relevance. These ILN are therefore not more indicative of future lung metastases compared to patients with no ILN observed. Although ILN might be of little clinical relevance in the treatment of LRRC, a staging chest CT remains recommended to identify lung metastasis, as the NCCN Clinical Practice Guidelines in Oncology for rectal cancer suggest.(22) In LRRC, curative intended surgery may not be feasible if (an abundance of) lung metastases are found and palliative treatment should be considered as an alternative.(23) As few data is available regarding best treatment of lung metastases in patients with LRRC, the MDT remains the golden standard to assess the appropriate treatment options for each individual patient.(24, 25)

To our best knowledge, no studies have reported the incidence of ILN in patients diagnosed with LRRC, no data is available on oncological outcomes in these patients, and no guidelines have been established managing this specific patient group. In this current study, the incidence of ILN at diagnosis in isolated LRRC patients was 28%. Several other

studies have investigated ILN in CRC, LARC and metastatic CRC(1, 3-6, 26). A large systematic review on the prevalence of ILN in CRC patients determined the incidence to be 9%.(1) This rate is considerably lower than the 28% of our study. This review however only included studies with patients suitable for curative resection, whereas in our study we also included patients undergoing palliative treatment. Another study investigated the clinical relevance of ILN in patients undergoing partial hepatectomy for CRC liver metastases. Similar to our study, no differences in DFS and OS were observed between patients with and without ILN. Half of the patients with ILN did however develop lung metastases. Unfortunately, the frequency of lung metastases in the patients without ILN was not reported which makes it impossible to determine whether or not the patients with ILN were actually at higher risk for developing lung metastases.(5) In our study we did compare the cumulative incidence of lung metastases in patients with and without ILN and did not find a difference.

PET is of limited additional value in distinguishing lung metastases and ILN.(27, 28) A positive uptake makes a malignancy more likely, but most subcentimetre lung lesions will either be not detected on PET or have a risk of being false-negative.(29, 30) In our centre, PET is not routinely performed. Seventeen patients in this study did however undergo PET in their referring hospital. ILN were found in four of these patients at LRRC diagnosis, in three of whom no FDG uptake was detected. In one patient we did see FDG uptake, but our MDT determined the lesion to be more suspicious for infection and no change in treatment strategy was made. In our series, although PET was only performed in a small proportion of patients, it was of no added value in distinguishing ILN from metastases.

This study describes a relatively large series of not only surgically, but also palliatively treated patients with LRRC. Several limitations should however be noted which mostly relate to the selected patient population and the retrospective nature of the study. A staging chest CT prior to start of treatment was only available in 67% of the eligible patients. This might be explained by the fact that some of these patients were only referred to our centre for palliative radiotherapy and therefore did not undergo complete diagnostic workup. Due to this selection bias, the incidence of ILN and cumulative incidence of lung metastases reported in the current study could very well be an underestimation. Especially when considering the limited follow-up of palliatively treated patients, as most of these patients received treatment in their referring hospitals and follow-up chest CT scans are not routinely performed in palliatively treated patients. No accepted definition of ILN was available. CT scans were reported by different radiologists and some patients had a CT scan prior to the diagnosis LRRC, introducing difficulty in consistently defining lung lesions as benign, ILN or lung metastases. Finally, it should be

noted that over the study period of seventeen years the quality of chest CT-scans has improved. The usage of thinner slices in recent years may have influenced the sensitivity of identifying lung nodules in LRRC patients.

In conclusion, indeterminate lung nodules are common in patients diagnosed with locally recurrent rectal cancer. No differences in overall survival, progression-free survival, nor the cumulative incidence of lung metastases were found between patients with and without ILN at diagnosis of LRRC. These results suggest that indeterminate lung nodules are of little to no clinical relevance in patients with LRRC. Curative treatment should therefore never be withheld based solely on the presence of indeterminate lung nodules.

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CHAPTER 12

Locally recurrent rectal cancer and metastases: is there still a chance for cure?

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ABSTRACT

Introduction

Patients with locally recurrent rectal cancer (LRRC) generally have poor prognosis, especially those who have (a history of) metastases. The aim of this study was to investigate the impact of metastases on oncological outcomes in LRRC patients undergoing curative treatment.

Methods

Consecutive patients with surgically treated LRRC between 2005 to 2019 in two tertiary referral hospitals were retrospectively analysed. Oncological survival of patients without metastases were compared with outcomes of patients with metastases synchronous with the primary tumour, patients with metastases in the primary-recurrence interval, and patients with synchronous LRRC metastases.

Results

A total of 535 LRRC patients were analysed, of whom 398 (74%) had no (history of) metastases, 22 (4%) had synchronous metastases with the primary tumour, 44 (8%) had metachronous metastases, and 71 (13%) had synchronous LRRC metastases. Patients with synchronous LRRC metastases had worse survival compared to patients without metastases (adjusted hazard ratio: 1.56 (95% confidence interval: 1.15 - 2.12), whilst survival of patients with synchronous primary metastases and metachronous metastases of the primary tumour was similar as those patients who had no metastases. In LRRC patients who had metastases in primary-recurrence interval, patients with early metachronous metastases had better disease-free survival as patients with late metachronous metastases (3-year disease-free survival rate 22%, 95% confidence interval: 8% - 58%, p=0.039).

Conclusion

LRRC patients with synchronous metastases undergoing curative surgery have relatively poor prognosis. However, LRRC patients with a history of metastases diagnosed nearby the primary tumour have comparable (oncological) survival as LRRC patients without metastases.

INTRODUCTION

Locally recurrent rectal cancer (LRRC) occurs in 6-10% of patients who are curatively treated for primary rectal cancer.(1-3) LRRC significantly impacts quality of life and has poor prognosis, but can be cured in selected cases.(4-6) Curative treatment for LRRC, consisting of neoadjuvant treatment and surgery, is associated with considerable morbidity.(7-9) Due to previous radiation and surgery, resection of LRRC is technically challenging and unlike primary rectal cancer, local recurrences frequently present with ingrowth in adjacent organs such as the bladder and reproductive organs, making multivisceral resections necessary. Generally, treatment with curative intent is only considered when a radical resection of the pelvic recurrence, along with possible resectable metastatic disease, can be obtained.(10, 11).

Over the last decades, novel treatment approaches such as preoperative (chemo-)radiotherapy and total mesorectal excision (TME) for primary rectal cancer have reduced local recurrence rates, but that also means that the biological behaviour of the tumours that do recur is different.(12-14) Nowadays, patients tend to have more synchronous distant metastases with LRRC, with a reported incidence of 36%-74%.(12, 15, 16) Due to the poor prognosis of these patients, treatment for patients with synchronous metastases is usually with palliative intent, aiming at delaying progression of disease and prolonging survival. Uncertainty remains whether long-term disease-free survival with curative intended treatment can be achieved in at least some of these patients, and how these patients should be selected. For example, it has been suggested that the presence of indeterminate lung nodules in LRRC does not influence outcomes, and that these patients should not be excluded from surgery based on the presence of these lesions alone.(17)

In primary rectal cancer, different treatment strategies for the local treatment of (synchronous) metastases have been established and include metastectomy, cytoreductive surgery, stereotactic radiation and microwave ablation, mostly in combination with systemic therapy . Local treatment of colorectal oligometastatic disease is the standard of care when possible, however, this strategy has not been shown to be indisputable superior to non-local interventions in randomized controlled trials.(18-24) Evidence that these modalities can improve outcomes for LRRC with synchronous metastases is also limited, but some small retrospective series have demonstrated good outcomes in selected patients with LRRC and locally treated distant metastases.(25, 26)

A recent retrospective cohort study demonstrated that LRRC patients with a history of curatively treated metastases have similar oncological outcomes compared to patients

without metastases, implying that curative treatment should not be excluded solely based on formerly diagnosed metastases.(27) Conversely, patients who present with synchronous metastases along with the pelvic recurrence have a poor prognosis. These findings suggest that the moment of metastases could impact LRRC patients' prognosis, and it might be of interest to further explore the metastatic history of curatively treated LRRC patients.

The aim of this study is to investigate the impact of metastases and its timing on oncological outcomes in patients with locally recurrent rectal cancer undergoing curative treatment.

METHODS

Patients

All consecutive patients with surgically treated LRRC between 2005 to 2019 in two tertiary referral hospitals, Catharina Hospital (CHE) and Erasmus MC Cancer Institute (EMC), were retrospectively analysed. Patients treated for local re-recurrence were excluded. LRRC was defined as local recurrence in the pelvic area after curative treatment of rectal adenocarcinoma. Diagnosis of LRRC had to be confirmed by either a biopsy or a combination of imaging and raised serum carcinoembryonic antigen (CEA) levels. All patients were discussed in a dedicated LRRC multidisciplinary team (MDT), including expert surgeons, radiologists, radiation oncologists and medical oncologists. Patient demographics, clinicopathological disease characteristics and outcome measures were obtained by review of hospital medical records, from referral hospitals and from general practitioners. This study was approved by the medical ethics committee of EMC (MEC-2020-0104) and CHE (AW21.067/W21.178).

Treatment strategy

At the discretion of the MDT, the most preferable treatment strategy was discussed for each individual patient. In general, curative treatment was considered, when a radical resection of the LRRC and local treatment for all metastases was considered feasible, taking anticipated downstaging by neoadjuvant therapy into account. Palliative treatment (either chemotherapy, radiation therapy, a combination of both, or best supportive of care) was advised in patients with extensive or incurable metastases and/or irresectable pelvic recurrences. Curative treatment in radiotherapy naïve patients included neoadjuvant radiotherapy (44.6–52Gy), usually with the addition of capecitabine as radiosensitiser.(28) Treatment of choice of previously irradiated LRRC patients was (chemo)re-irradiation up to 30Gy.(29) In CHE, induction chemotherapy was administrated before radiation therapy in a part of the patients since 2012. After (chemo)radiation

and/or induction chemotherapy restaging with thoracic- and abdominal (PET-)CT and pelvic MRI was performed, after which patients were re-discussed in the MDT to assess the treatment response and development of de novo metastases. Depending on the findings patients either continued with curatively intended surgical resection, or in case of progressive disease, treatment was with palliative intent, which did not include palliative resection.

Surgery consisted of low anterior resection (LAR) or abdominoperineal resection (APR), usually combined with an additional resection, extra-anatomical resection of the local recurrence, or multivisceral resection. Multivisceral resection was defined as tumour resection with addition of any other pelvic organ such as the bladder, uterus, vagina, ovaries, prostate, or vesicles. Intraoperative radiotherapy (IORT) was administered in case of clinically suspected or frozen section proven positive margins.

Treatment strategies for patients with synchronous metastases were determined based on the location and extent of the distant metastases. Surgery, radiofrequency ablation, stereotactic radiation, chemotherapy, or a combination were used to treat liver metastases. Lung metastases were treated with metastasectomy or stereotactic radiotherapy, with or without the use of chemotherapy. Metastases were treated before LRRC treatment, between neoadjuvant therapy and surgery, or after the surgical resection of the LRRC. Peritoneal metastases were treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) concurrently with LRRC resection. Usually, inguinal or para-aortic lymph node metastases were resected during LRRC surgery. Follow-up was conducted according to the Dutch colorectal cancer guidelines, and consisted of CEA measurements and thoracic- and abdominal CT imaging. Depending on patient preference, follow-up was done at the referral centre or the referring hospital.

Outcomes

Oncological outcomes were compared between patients with LRRC in combination with different metastatic patterns. Patients were categorized in four groups: 1) LRRC patients without (history of) metastases; 2) LRRC patients after curatively treated primary rectal cancer with synchronous metastases; 3) LRRC patients with a history of metachronous metastases, diagnosed between the primary rectal cancer and the local recurrence; and 4) LRRC patients with synchronous metastases diagnosed simultaneous with the local recurrence. Patients with both a history of metastases and synchronous metastases at the moment of LRRC were categorised as having “synchronous LRRC metastases”. Patients with both synchronous metastases with the primary rectal cancer and metachronous metastases between primary and LRRC were categorised as having “metachronous

metastases". Overall survival (OS) was defined as the time between the date of LRRC surgery and the date of death or last follow up. Disease-free survival (DFS) was defined as the time from LRRC surgery to the date of disease recurrence or death, whichever came first. Local recurrence-free survival (LRFS) and metastases-free survival (MFS) were defined as the time between the date of LRRC surgery and the date of local re-recurrence or last follow-up, and the date of diagnosis of distant metastases or last follow-up, respectively.

Statistics

Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data were reported as count (percentage). Group and individual comparisons were made using the Chi-square or Mann-Whitney-U-test as appropriate. Survival rates were calculated by the method of Kaplan-Meier and compared with the log-rank test. The Cox regression method was used for univariable and multivariable survival analyses. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 28.0.0.0 and R version 4.2.1 (http://www.r-project.org).

RESULTS

Of the 616 curatively treated cases of LRRC in the two referral centres, 535 individual patients who were diagnosed with a first local recurrence were analysed (71 patients with a local re-recurrence were excluded). The majority (n=398, 74%) of patients had no (history of) metastases. A total of 22 patients (4%) had synchronous metastases with the primary tumour, 44 patients (8%) had metachronous metastases and 71 patients (13%) had synchronous LRRC metastases. Eight patients with synchronous LRRC metastases also had metachronous metastases (and were analysed in the synchronous LRRC group). Five patients with metachronous metastases also had primary synchronous metastases (and were analysed in the metachronous metastases group). One patient had metastases at all three time points. Baseline characteristics were shown in Table 1 and details about the LRRC and the subsequent treatment in Table 2. An overview of metastases and corresponding treatment details is provided in Table 3.

Table 1. Baseline characteristics

		No metastases (n=398)	Synchronous metastases primary (n=22)	Metachronous metastases (n=44)	Synchronous metastases LRRC (n=71)	p-value
Age (median [IQR])		65.9 [59.0, 72.6]	61.6 [55.2, 69.5]	64.3 [58.5, 69.4]	63.8 [58.5, 70.1]	0.074
Sex (%)	Male	260 (65.3%)	14 (63.6%)	28 (63.6%)	44 (62.0%)	0.954
	Female	138 (34.7%)	8 (36.4%)	16 (36.4%)	27 (38.0%)	
ASA score (%)	1	47 (12.8%)	1 (5.6%)	2 (5.0%)	4 (6.1%)	0.556
	2	267 (72.6%)	13 (72.2%)	29 (72.5%)	48 (72.7%)	
	3	53 (14.4%)	4 (22.2%)	9 (22.5%)	14 (21.2%)	
	4	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Induction chemotherapy primary (%)	Yes	8 (2.0%)	5 (22.7%)	3 (6.8%)	4 (5.6%)	<0.001
	No	388 (98.0%)	17 (77.3%)	41 (93.2%)	67 (94.4%)	
(y)pT stage primary (%)	0	2 (0.9%)	1 (5.3%)	0 (0.0%)	1 (1.4%)	0.030
	1	15 (6.4%)	0 (0.0%)	1 (2.3%)	2 (2.8%)	
	2	48 (20.5%)	1 (5.3%)	6 (14.0%)	5 (7.0%)	
	3	131 (56.0%)	11 (57.9%)	32 (74.4%)	46 (64.8%)	
	4	38 (16.2%)	6 (31.6%)	4 (9.3%)	17 (23.9%)	
(y)pN stage primary (%)	0	126 (53.6%)	7 (36.8%)	11 (25.6%)	35 (49.3%)	0.008
	1	70 (29.8%)	9 (47.4%)	16 (37.2%)	19 (26.8%)	
	2	39 (16.6%)	3 (15.8%)	16 (37.2%)	17 (23.9%)	
M stage primary (%)	0	393 (100.0%)	0 (0.0%)	39 (88.6%)	69 (97.2%)	<0.001
	1	0 (0.0%)	22 (100.0%)	5 (11.4%)	2 (2.8%)	
Neoadjuvant radiation scheme primary (%)	None	190 (47.9%)	10 (45.5%)	10 (22.7%)	33 (46.5%)	0.001
	Chemoradiation	100 (25.2%)	9 (40.9%)	17 (38.6%)	25 (35.2%)	
	Short-course (25Gy)	100 (25.2%)	1 (4.5%)	13 (29.5%)	12 (16.9%)	
	Long-course (44-60Gy)	7 (1.8%)	2 (9.1%)	4 (9.1%)	1 (1.4%)	
Type of surgery primary (%)	APR	99 (27.2%)	5 (22.7%)	18 (41.9%)	22 (31.9%)	0.306
	LAR	200 (54.9%)	14 (63.6%)	20 (46.5%)	34 (49.3%)	
	Sigmoid	59 (16.2%)	2 (9.1%)	5 (11.6%)	13 (18.8%)	
	Exenteration	4 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	W&W	2 (0.5%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	

Table 1. (continued)

		No metastases (n=398)	**Synchronous metastases primary (n=22)**	**Metachronous metastases (n=44)**	**Synchronous metastases LRRC (n=71)**	p-value
Resection margin primary (%)	R0	156 (78.4%)	9 (90.0%)	18 (78.3%)	29 (65.9%)	0.588
	R1	41 (20.6%)	1 (10.0%)	5 (21.7%)	14 (31.8%)	
	R2	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	
Adjuvant chemotherapy primary (%)	Yes	65 (16.6%)	6 (28.6%)	15 (34.1%)	9 (12.7%)	0.011
	No	326 (83.4%)	15 (71.4%)	29 (65.9%)	62 (87.3%)	
Interval primary - LRRC (median [IQR])		23.3 [12.3, 41.7]	18.6 [10.7, 34.6]	36.0 [22.5, 57.7]	20.7 [12.0, 40.5]	0.002

Abbreviations: APR - abdominoperineal resection. ASA - American Society of Anesthesiologists. IQR - interquartile range. LAR - low anterior resection. LRRC – locally recurrent rectal cancer. W&W – watch and wait.

Table 2. LRRC and treatment details

		No metastases (n=398)	**Synchronous metastases primary (n=22)**	**Metachronous metastases (n=44)**	**Synchronous metastases LRRC (n=71)**	p-value
Multifocality (%)	Yes	36 (9.7%)	2 (9.1%)	11 (25.0%)	19 (27.1%)	<0.001
	No	334 (90.3%)	20 (90.9%)	33 (75.0%)	51 (72.9%)	
Induction CTx LRRC (%)	Yes	98 (24.6%)	5 (22.7%)	19 (43.2%)	40 (56.3%)	<0.001
	No	300 (75.4%)	17 (77.3%)	25 (56.8%)	31 (43.7%)	
Differentiation (%)	Adenocarcinoma	305 (87.4%)	19 (90.5%)	33 (86.8%)	67 (98.5%)	0.218
	Mucinous carcinoma	34 (9.7%)	1 (4.8%)	4 (10.5%)	1 (1.5%)	
	Complete response	10 (2.9%)	1 (4.8%)	1 (2.6%)	0 (0.0%)	
Radiation scheme LRRC (%)	None	5 (3.3%)	1 (4.8%)	1 (2.4%)	4 (6.1%)	0.036
	(Chemo)radiation (50Gy)	82 (54.7%)	11 (52.4%)	11 (26.8%)	24 (36.4%)	
	(Chemo)irradiation (30Gy)	62 (41.3%)	9 (42.9%)	29 (70.7%)	36 (54.5%)	
	Short-course radiation (25Gy)	1 (0.7%)	0 (0.0%)	0 (0.0%)	2 (3.0%)	
Type of surgery LRRC (%)	APR*	140 (35.6%)	9 (40.9%)	22 (50.0%)	22 (31.0%)	0.510
	LAR*	91 (23.2%)	5 (22.7%)	5 (11.4%)	18 (25.4%)	
	Extra-anatomical resection of the local recurrence	18 (4.6%)	1 (4.5%)	1 (2.3%)	3 (4.2%)	
	Posterior exenteration	14 (3.6%)	2 (9.1%)	2 (4.5%)	6 (8.5%)	
	Total exenteration	130 (33.1%)	5 (22.7%)	14 (31.8%)	22 (31.0%)	
IORT (%)	Yes	288 (72.4%)	15 (68.2%)	32 (72.7%)	52 (73.2%)	0.974
	No	110 (27.6%)	7 (31.8%)	12 (27.3%)	19 (26.8%)	
Complications (%)	Clavien-Dindo 0-2	290 (72.9%)	16 (72.7%)	27 (61.4%)	48 (67.6%)	0.378
	Clavien-Dindo 3-5	108 (27.1%)	6 (27.3%)	17 (38.6%)	23 (32.4%)	
Resection margin LRRC (%)	R0	269 (67.6%)	18 (81.8%)	28 (65.1%)	42 (60.0%)	0.386
	R1	126 (31.7%)	4 (18.2%)	14 (32.6%)	26 (37.1%)	
	R2	3 (0.8%)	0 (0.0%)	1 (2.3%)	2 (2.9%)	

Table 2. (continued)

** Usually combined with an additional resection*

Abbreviations: APR: abdominoperineal resection; IORT; intraoperative radiotherapy; IQR: interquartile range; LAR: low anterior resection; LRRC: locally recurrent rectal cancer.

Table 3. Metastases details

		Synchronous primary (n=29)	Metachronous (n=52)	Synchronous LRRC (n=71)
Location	Liver	20 (69%)	32 (62%)	22 (31%)
	Lung	3 (10%)	14 (27%)	20 (28%)
	Peritoneal	3 (10%)	2 (4%)	10 (14%)
	Lymph nodes	2 (7%)	0 (0%)	14 (20%)
	Other	0 (0%)	4 (8%)	3 (4%)
	More than one location	1 (3%)	0 (0%)	2 (3%)
Solitary/multiple	Solitary	13 (45%)	28 (54%)	28 (39%)
	Multiple	16 (55%)	24 (56%)	43 (61%)
Treatment	Chemotherapy (CTx)	3 (10%)	2 (4%)	9 (13%)
	Radiotherapy	0 (0%)	2 (4%)	8 (12%)
	RFA	2 (7%)	1 (2%)	0 (0%)
	Metastectomy	14 (48%)	34 (65%)	31 (44%)
	CTx + metastectomy	7 (24%)	7 (14%)	17 (24%)
	No treatment (W&W)	0 (0%)	0 (0%)	2 (3%)
	Combination	3 (10%)	6 (15%)	4 (6%)
Timing metastases treatment	Before primary/LRRC treatment	13 (45%)	NA	37 (52%)
	During primary/LRRC treatment	5 (17%)	NA	29 (40%)
	After primary/LRRC treatment	11 (38%)	NA	3 (4%)
	Untreated	0 (0%)	NA	2 (3%)

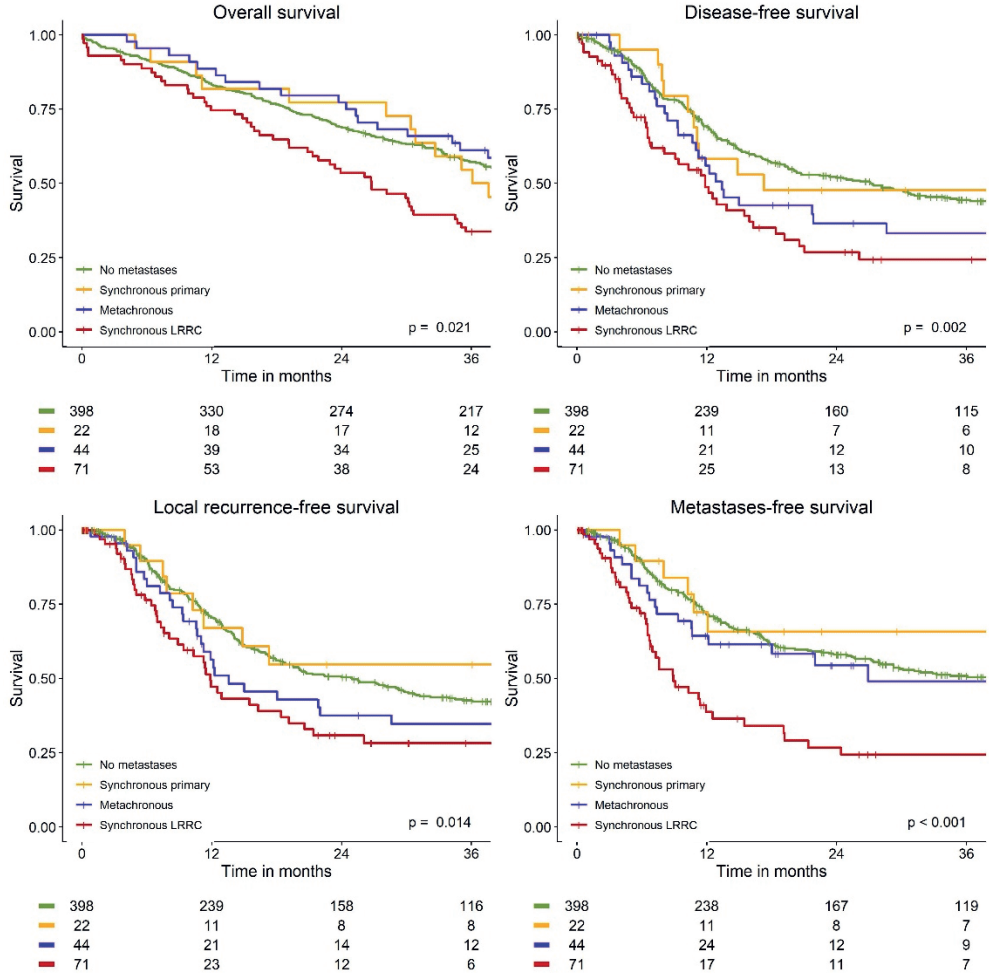
**The numbers do not correspond with groups because some patients had both primary synchronous metastases, metachronous metastases and/or synchronous metastases with LRRC.*

Abbreviations: CTx – chemotherapy. LRRC – locally recurrent rectal cancer. W&W – watch and wait.

Oncological outcomes

Median survival in the cohort was 40 months (95% confidence interval (CI): 36.1 – 45.0 months). Survival outcomes are shown in Figure 1. The 3-year OS rate was 57% (95% CI: 53% - 62%) in patients without metastases, 55% (95% CI: 37% - 80%) in patients with primary synchronous metastases, 61% (95% CI: 48% - 77%) in patients with primary metachronous metastases, and 34% (95% CI: 24% - 47%) in patients synchronous metastases LRRC (long rank p=0.021). Disease-free survival, local recurrence-free survival and metastasis-free survival was poorest in patients with synchronous metastases with the local recurrence (resp. 3-year survival rates: 24%, 28% and 24%), and best in patients synchronous metastases only with the primary tumour (resp. 3-year survival rates: 48%, 55% and 66%).

Figure 1. Oncological outcomes in surgically treated LRRC patients with or without a history of or present metastases



Univariable and multivariable survival analyses

Results of the Cox (proportional hazards) regression analyses is shown in Table 4. In univariable and multivariable analyses, age, neoadjuvant chemoradiation for the primary tumour, synchronous metastases with the LRRC, IORT, multifocality, multivisceral resection of LRRC, and R1- and R2 resections were all associated with poor survival. The most important factor for impaired survival was a R0 resection (OR: 2.00 (95% CI: 1.58 - 2.55) and OR: 3.43 (95% CI: 1.39 - 8.51) for R1- and R2 resection respectively). Patients with LRRC and synchronous metastases had impaired survival compared to patients without metastases. Primary synchronous metastases and metachronous metastases did not influence survival.

Table 4. Cox (proportional hazards) regression analyses

	Univariate HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Age	**1.02 (1.01 – 1.04)**	**<0.001**	**1.03 (1.02 – 1.05)**	**<0.001**
Female sex	1.07 (0.86 – 1.31)	0.559	1.07 (0.84 - 1.35)	0.594
T-stage (T3-4)	1.02 (0.76 – 1.38)	0.889		
N-stage (N1-2)	1.09 (0.85 – 1.40)	0.476		
Radiation primary tumour				
Preoperative chemoradiation primary (vs. no radiation)	**1.45 (1.14 - 1.85)**	**0.003**	**1.34 (1.01 - 1.76)**	**0.040**
Long-course radiation primary (vs. no preoperative radiation)	1.53 (0.85 - 2.76)	0.154	1.65 (0.85 - 3.22)	0.140
Short-course radiation primary (vs. no preoperative radiation)	1.28 (0.99 - 1.64)	0.058	1.05 (0.78 - 1.42)	0.732
Metastases				
Synchronous metastases primary (vs. no metastases)	1.07 (0.73 - 1.56)	0.731	0.93 (0.62 - 1.41)	0.746
Metachronous metastases (vs. no metastases)	0.91 (0.54 - 1.53)	0.725	1.16 (0.67 - 2.02)	0.603
Synchronous metastases LRRC (vs. no metastases)	**1.56 (1.17 - 2.07)**	**0.002**	**1.56 (1.15 - 2.12)**	**0.005**
Induction chemotherapy LRRC	1.09 (0.87 - 1.36)	0.449		
IORT	**1.28 (1.01 - 1.62)**	**0.039**	**1.24 (0.95 - 1.62)**	**0.118**
Multifocality	**1.47 (1.09 - 1.98)**	**0.012**	**1.46 (1.05 - 2.02)**	**0.024**
Multivisceral resection	**1.41 (1.14 - 1.73)**	**0.001**	**1.34 (1.06 - 1.69)**	**0.014**
R1 resection (vs R0)	**1.98 (1.61 - 2.44)**	**<0.001**	**2.00 (1.58 - 2.55)**	**<0.001**
R2 resection (vs R0)	**3.63 (1.61 - 8.18)**	**0.002**	**3.43 (1.39 - 8.51)**	**0.008**

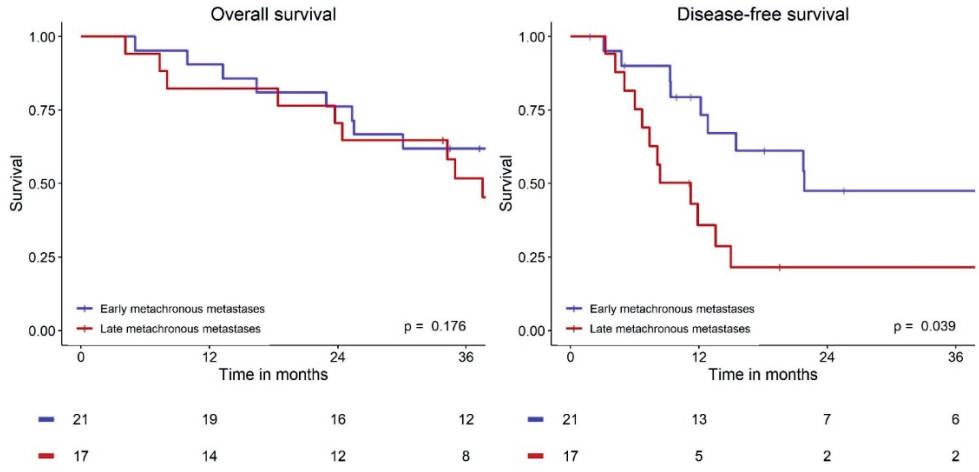
Abbreviations: IORT: intraoperative radiotherapy; LRRC: locally recurrent rectal cancer.

Subgroup analyses

A hypothesis-driven subgroup survival analysis was performed to determine the impact of the moment of metastases in the primary-recurrence interval in 52 patients with metachronous metastases. Herein, patients who were diagnosed with metastases within one year after primary rectal cancer surgery (n=21) were compared with those who had metastases within one year before diagnosis of LRRC (n=17) (early metachronous versus late metachronous). Patients who were categorised in both groups were excluded (n=6). Another six patients with metachronous metastases but who did not had any metastases within one year after primary rectal cancer and within one year before diagnosis of LRRC were also not included in this analysis. In two patients the time of metastases diagnosis was missing.

In the subgroup analysis, overall survival between patients with early and late metachronous metastases did not differ, but an improved disease-free survival was observed in patients with early metachronous metastases (3-year disease-free survival rate 48%, 95% CI: 29% - 79%) versus those with late metachronous metastases (3-year disease-free survival rate 22%, 95% CI: 8% - 58%)(log rank p=0.039).

Figure 2. Overall- and disease-free survival of LRRC patients with early and late metachronous metastases in primary-recurrence interval



DISCUSSION

The aim of this retrospective cohort study was to investigate the oncological outcomes of surgically treated LRRC patients with a history or present metastases. Results demonstrate that the moment of diagnosis of metastases has significant impact on prognosis, wherein patients with metastases diagnosed nearby the primary tumour have better oncological outcomes as compared to those who have metastases shortly prior to, or synchronous with, LRRC. In multivariable analysis, synchronous metastases diagnosed with LRRC was an independent risk factor for poor survival.

In this study, 14% of patients who were eligible for surgery for their local recurrence also had distant metastases. Obviously, this is much lower than the approximate 40% synchronous distant metastases rate in the entire LRRC population encountered in daily practice.(12, 16, 30-32) Most LRRC patients diagnosed with concomitant metastases will not undergo curative intended treatment, and previously published data from one of the participating institutes demonstrate that the reason not to initiate curative treatment is mainly due to metastatic disease (58%).(15) Unfortunately, the occurrence of LRRC is associated with (extensive) distant metastases and poor prognosis.(12) For example, it was shown from data from the Dutch TME trial that 74% of the twenty-three LRRC patients in the preoperative radiotherapy plus TME group developed distant metastases, most of them with a short interval between local recurrence to metastatic disease (median 0.9 months, 95% CI: 0.3 to 1.5 months).(12) Thus, the 14% of LRRC patients with synchronous metastases included in this study, should be considered as selection of patients in whom the biological behaviour is considered to be relatively good by treating physicians.

Disease-free survival of patients with metastases synchronous to the primary tumour and patients with metachronous metastases was similar to patients without metastases, which may be explained by the selection process. It is reasonable to suggest that patients with a history of metastases and unfavourable disease characteristics will have developed extensive (untreatable) metastases before presenting with LRRC. Contrarily, a long disease-free interval before the diagnosis of LRRC might be suggestive for disease with less metastatic potential. This also explains that patients with early metachronous metastases of the primary tumour have better outcomes in terms of recurrences compared to patients with late metachronous metastases of the primary tumour (3-year DFS: 48% vs 22%, p=0.039).

In previously reported results of a single centre study by Voogt et al, patients with metastases synchronous to the primary tumour and patients with metachronous metastases were analysed as a single group.(27) In this current study, we found that these

patients have comparable oncological outcomes, but that in patients with metachronous metastases, the timing of diagnosis in the primary-recurrence interval is associated with disease-free survival after LRRC treatment. As demonstrated by Voogt et al, patients with synchronous metastases with LRRC have worse prognosis compared to patients without metastases or only a history of metastases. In order to improve patient selection for curative treatment in patients with synchronous metastases and LRRC, administration of induction chemotherapy may be of added value in discriminating patients into risk groups based on disease behaviour. Patients who achieve sufficient response whilst on treatment are likely to be better candidates for curative treatment. On the other hand, patients with disease progression during systemic treatment most likely have an extremely poor prognosis, and palliative treatment that focusses on comfort and quality of death is usually superior to surgery.(15)

Limitations of this study are mainly associated with the retrospective design, and the relatively small sample sizes of patients included in the compared groups. Generally, both hospitals share the same case-mix and adhere to the same guidelines and follow-up schedules, but some differences in LRRC management, such as the use of induction chemotherapy in CHE, should be acknowledged. Also, only patients who underwent curative intended surgery for LRRC were included in this study, so patients in whom palliative treatment was started (often because of metastatic disease), or those who started curative treatment but did not get surgery (usually because of progressive disease) were excluded. Therefore, it is important to mention that the analysed patients were highly selected, and that LRRC patients encountered in daily practice on an intention-to-treat basis, have much higher chances of having unfavourable disease characteristics (e.g. extensive metastatic disease) compared to those in this study. Despite these limitations, we consider the study population, derived from a prospectively maintained database, an accurate reflection of the surgically treated LRRC population.

In conclusion, there is a chance of cure in patients with locally recurrent rectal cancer, who have or have had metastases. Especially patients with metastases diagnosed synchronously of shortly after the primary tumour have outcomes similar to patients without metastases. In these patients, treatment with curative intent should not be withheld on the basis of the history of metastatic disease. In patients with metastases diagnosed shortly prior to, or synchronous with LRRC, curative treatment should be carefully considered, as these patients tend to have a relatively poor oncological outcome. In patients with LRRC and synchronous metastases, initiating treatment with systemic chemotherapy may provide an opportunity to further observe disease behaviour and select those patient who are likely to benefit from curative treatment.

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CHAPTER 13

Circulating tumour DNA as biomarker for rectal cancer: A systematic review and meta-analysis

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ABSTRACT

Introduction

Circulating tumour DNA (ctDNA) has been established as a promising (prognostic) biomarker with the potential to personalise treatment in cancer patients. The objective of this systematic review is to provide an overview of the current literature and the future perspectives of ctDNA in non-metastatic rectal cancer.

Methods

A comprehensive search for studies published prior to the 4th of October 2022 was conducted in Embase, Medline, Cochrane, Google scholar, and Web of Science. Only peer-reviewed original articles and ongoing clinical trials investigating the association between ctDNA and oncological outcomes in non-metastatic rectal cancer patients were included. Meta-analyses were performed to pool hazard ratios (HR) for recurrence-free survival (RFS).

Results

A total of 291 unique records were screened, of which 261 were original publications and 30 ongoing trials. Nineteen original publications were reviewed and discussed, of which seven provided sufficient data for meta-analyses on the association between the presence of post-treatment ctDNA and RFS. Results of the meta-analyses demonstrated that ctDNA analysis can be used to stratify patients into very high and low risk groups for recurrence, especially when detected after neoadjuvant treatment (HR for RFS: 9.3 [4.6 – 18.8]) and after surgery (HR for RFS: 15.5 [8.2 – 29.3]). Studies investigated different types of assays and used various techniques for the detection and quantification of ctDNA.

Conclusion

This literature overview and meta-analyses provide evidence for the strong association between ctDNA and recurrent disease. Future research should focus on the feasibility of ctDNA-guided treatment and follow-up strategies in rectal cancer. A blueprint for agreed-upon timing, preprocessing, and assay techniques is needed to empower adaptation of ctDNA into daily practice.

INTRODUCTION

Rectal cancer is a worldwide cause of cancer-related mortality, with a global incidence of approximately 732,200 new cases per year.(1) The introduction of combined neoadjuvant (chemo)radiotherapy and total mesorectal excision (TME) has significantly reduced the local recurrence rate, though distant recurrence rates remain around 30%.(2) Recurrences are likely to derive from residual locoregional disease after surgery or subclinical metastatic disease (minimal residual disease).(3) These micrometastases are undetectable by the currently used imaging techniques. Carcinoembryonic antigen (CEA) is a widely accepted tumour marker in the follow-up of colorectal cancer, but is imperfect due to the limited accuracy of this test to detect recurrence, mostly owing to its high rate of false positive results.(4, 5) Consequently, there is an urgent need for novel techniques to detect minimal residual disease after standard treatment, in order to identify those patients who are at high risk for recurrent disease. Classification of these patients would enable a 'tailored' postoperative treatment approach, in which patients could be stratified into groups who may benefit from additional treatment or, otherwise, less intensive surveillance.

Circulating tumour DNA (ctDNA) is a component of the total amount of cell-free DNA (cfDNA), and it presumed that this ctDNA is shed into the bloodstream by necrotising cancer cells. Measurement of ctDNA in peripheral blood samples has been established as a promising biomarker, with the potential to optimise tailored treatment in cancer patients.(6-8) In recent years, ctDNA has been investigated in various cancer types and settings, and is considered to be an important diagnostic tool for the detection of minimal residual disease after surgery. The potential clinical utility of ctDNA has already been established in certain fields. In stage II colon cancer, ctDNA-guided treatment resulted in a reduction in the number of patients receiving adjuvant therapy when compared to conventional stratification methods, whilst not altering the risk of recurrence.(9) For rectal cancer, research establishing the true clinical value of ctDNA-guided treatment has yet to be conducted. In addition, there is still a lack of consensus whether the use of adjuvant chemotherapy is justified in rectal cancer patients, and postoperative treatment regimens differ per country.(10, 11)

During curative treatment of rectal cancer, there are several methods and time points when ctDNA could be measured in peripheral blood samples. At diagnosis and before any treatment, the amount of ctDNA could be associated with the extent of the disease. During or after neoadjuvant treatment, changes in the level ctDNA could be associated with response or progression. Finally, the presence of ctDNA after surgery is an indication of minimal residual disease. The conceivable added value of ctDNA in rectal cancer is its

potential application as a guide for therapy selection. Herein, patients who are stratified as high-risk for recurrence could, for example, be treated with adjuvant systemic therapy, while patients without detectable ctDNA after neoadjuvant treatment and surgery might be suitable for less intensive follow-up regimes.

In literature, several methods have been described to analyse the presence of ctDNA in peripheral blood samples, with different recommendations regarding pre-analytical conditions.(12-14) In rectal cancer, two main ctDNA detection techniques are measuring the absolute number of cfDNA or identifying tumour-specific somatic mutations.(15) These mutations are usually detected using polymerase chain reaction (PCR) or next-generation sequencing (NGS). Although PCR is a viable option to detect a small number of already known somatic mutations, the main advantage of NGS is the possibility to interrogate multiple genes at once, and it does not necessarily require prior knowledge of a specific mutation profile. Both techniques could either be applied to the unique mutations of the patient's tumour (i.e., tumour-informed with specific panel) or to a universal panel of genes commonly mutated in (colorectal) cancer patients (i.e., tumour-agnostic). Finally, a universal panel could be used that is evaluated by the patients' tumour tissue (i.e., tumour-informed with predefined panel). Given the heterogeneity in measurement techniques of ctDNA, a summary of the applied techniques in previous studies may provide insight in suitable approaches for specific purposes.

The aim of this literature review is to provide an overview of the current evidence and ongoing trials in the field of ctDNA in non-metastatic rectal cancer.

METHODS

This systematic review and meta-analyses were conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analysis). A comprehensive search was performed in five databases (Embase, Medline, Cochrane, Web of Science and Google Scholar), including potential studies published prior to the 4th of October 2022. Only English-written, peer-reviewed clinical studies that investigated the association between ctDNA and oncologic outcomes in non-metastatic rectal cancer patients were included. Non-original articles (i.e. review articles and meta-analyses) and case reports were excluded. The complete search term performed on the 4th of October 2022 is shown in Supplementary 1.

Study selection and quality assessment

Screening of the articles was performed by two independent authors (JR, LW) and disagreement was resolved through joint assessment and in collaboration with a third reviewer (NB). Quality assurance was performed by two individual reviewers (JR, LW) according to the Quality In Prognosis Studies tool (QUIPS).(16) Three categories of risk of bias were considered as the outcome of the QUIPS tool, being low, moderate and high risk of bias. The outcomes of the quality assessment using the QUIPS tool were visualised using the Risk-of-bias VISualization (robvis) tool. (17) In case of disagreement, joint evaluation was performed, and a third reviewer (SW) was approached when deemed necessary. Study characteristics like study design, sample size and specifications about the ctDNA assessment (collection time points, target, assay type, quantification method, whether the technique was NSG or PCR based and whether it was tumour informed) were collected.

Meta-analyses

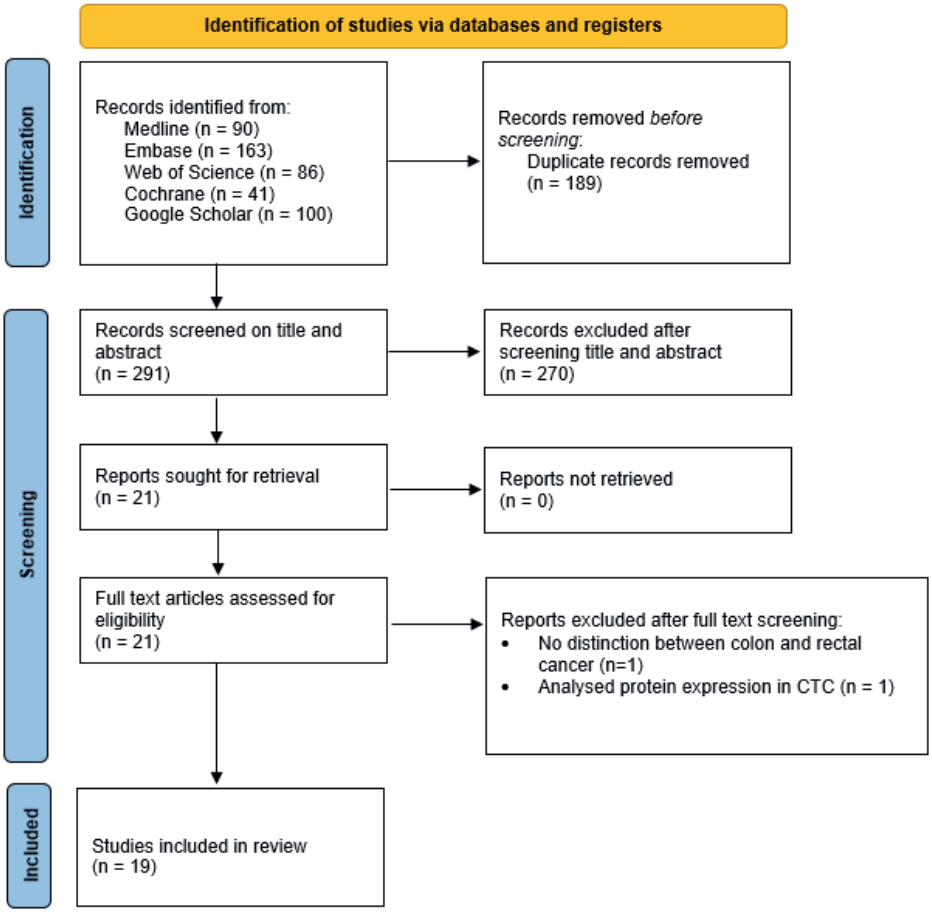
Meta-analyses were performed using the generic inverse-variance method using a random-effects model. Herein, only studies that reported hazard ratios with either confidence intervals or p-values, for recurrence-free survival (RFS) or disease-free survival (DFS) were included. Studies that did not report appropriate or sufficient data for the pooled analysis were separately discussed. Outcomes of interest included: hazard ratios (HR), 95% confidence intervals (CI), I2 values for heterogeneity, and p-values, in which a value <0.05 was considered statistically significant. Meta-analyses and figures were established from Review Manager (RevMan) version 5.4.1, The Cochrane Collaboration, 2020.

RESULTS

A total of 480 records were retrieved by the systematic search, of which 189 were duplicates, 261 were original publications and 30 were ongoing trials (Figure 1). All 291 unique studies and trials were screened for eligibility, after which 270 publications were excluded by reading title and abstract. Reasons for exclusion were reports of conference abstracts, case reports, (systematic) reviews, studies that did not include patients with rectal cancer, and studies that had not investigated clinical outcomes. The full text of twenty-one studies was assessed, of which two additional studies were excluded due to a lack of distinction between colon and rectal cancer, and due to an analysis of circulating tumour cells, which was ineligible for the current meta-analysis. A total of nineteen studies is discussed in this literature review, of which seven were included in the meta-analysis. For each included study a quality assurance was performed according to the QUIPS tool, as

shown in Supplementary 2. Study characteristics, including outcome measures and the number of patients, are reported in table 1.
Nine out of nineteen (47%) included studies were considered high risk of bias, six (32%) received a low risk of bias score, and four studies (22%) a moderate risk of bias. High risk of bias was mostly due to bias in prognostic factor measurement and attrition, as depicted in the graph in Supplementary 3. ctDNA measurement techniques varied greatly among included studies. Most frequently used quantification methods were digital droplet PCR (ddPCR), real time PCR (qRT-PCR) and next generation sequencing (NGS). Five studies designed their panel based on the unique tumour and patient (tumour informed – tumour specific). Four studies applied a tumour informed predefined panel, and ten adopted a tumour agnostic approach. Liu et al. investigated multiple ctDNA techniques.(18) All studies in this review only included patients with locally advanced rectal cancer (LARC). No eligible studies were found that included non-LARC patients.

Figure 1. PRISMA flowchart



Original articles

All included studies were either prospective or retrospective cohort studies. A total of 1598 patients undergoing treatment for LARC were included, with sample sizes ranging from 25 to 159 patients. The methods for ctDNA analyses (assay type, quantification method, tumour-informed or -agnostic) are described in Table 1. Twelve studies (63%) used a mutation-specific panel, of which nine were tumour-informed. Seven other studies measured total cfDNA concentration. Nine studies quantified ctDNA with a PCR-based technique. NGS was the chosen technique in eight studies, and another two studies used the direct fluorescent assay (dFA). Time points at which ctDNA was measured varied, and are reported from baseline (defined as before the start of any treatment) up until last follow-up after definite treatment. Additional details regarding plasma isolation, cfDNA isolation, and pre-processing conditions can be found in Supplementary 4.

Table 1. Summary of ctDNA analyses methods

First author	PMID	Year	Assay type	NGS PCR	Tumour informed	Time points (s)	Patients	Outcome (binary)
Zitt	19096128	2008	cfDNA concentration	PCR	Agnostic	BL, post-CRT, end treatment	26	Treatment response
Agostini	21416156	2011	cfDNA concentration	PCR	Agnostic	BL, post-CRT	67	Treatment response
Sun	24378613	2014	cfDNA concentration	PCR	Agnostic	BL, post-CRT	34	Treatment response
Boysen	29110585	2017	cfDNA concentration	PCR	Agnostic	Post-CRT	75	Both
Liu	35306340	2017	Mutation-specific panel	NGS	Both	During and post-NAT	82	Long-term (oncologic) survival
Sclafani	29362371	2017	Mutation-specific panel	PCR	Agnostic	BL	97	Both
Schou	29253083	2018	cfDNA concentration	dFA	Agnostic	BL, after induction chemotherapy, after CRT, serial samples 5 years after surgery	123	Long-term (oncologic) survival
Tie	29420226	2019	Mutation-specific panel	NGS	Informed	BL, post-CRT, post-surgery	159	Long-term (oncologic) survival
Appelt	31569168	2020	cfDNA concentration	PCR	Agnostic	BL	146	Both
Guo	32997420	2020	Mutation-specific panel	NGS	Agnostic	BL	194	Treatment response
Khakoo	31852830	2020	Mutation-specific panel	PCR	Informed	BL, mid CRT, post-CRT, after surgery	47	Both
Murahashi	32565539	2020	Mutation-specific panel	NGS	Agnostic	BL, post-NAT, post-surgery	85	Both
Pazdirek	32793464	2020	Mutation-specific panel	PCR	Agnostic	BL, during CRTx	36	Long-term (oncologic) survival
Zhou	33046514	2020	Mutation-specific panel	NGS	Informed	BL, during CRT, presurgery, and postsurgery	106	Long-term (oncologic) survival
McDuff	34250394	2021	Mutation-specific panel	PCR	Informed	BL, preoperatively, and postoperatively	29	Both
Wang	34464382	2021	Mutation-specific panel	NGS	Agnostic	BL, during nCRT, and after surgery	119	Both
Vidal	33727257	2021	Mutation-specific panel	NGS	Agnostic	BL, post-NAT	72	Both
Roesel	35837093	2022	Mutation-specific panel	NGS	Agnostic	T0, Tend, T4, T7, Top, TIMV, Tpost-op	25	Treatment response
Truelsen	35733829	2022	cfDNA concentration	dFA	Agnostic	BL, mid therapy and at end of therapy	76	Treatment response

Abbreviations: BL: baseline; cfDNA: cell-free DNA; CRT: chemoradiotherapy; dFA: direct fluorescence assay; LARC: locally advanced rectal cancer; NAT: neoadjuvant treatment; NSG: next generation sequencing; PCR: polymerase chain reaction.

ctDNA and treatment outcomes in rectal cancer (cfDNA concentration studies)
The earliest study in the systematic search reporting clinical outcomes, published in 2008, investigated changes in cfDNA levels before and after neoadjuvant chemoradiation in patients with LARC using quantitative real-time polymerase chain reaction (qRT-PCR).(19) No association was found between baseline cfDNA levels and tumour response, but the study showed that patients who responded to chemoradiation had a decrease in cfDNA levels (median 2.2 ng/mL), whereas in patients without response, cfDNA levels significantly increased (median 5.1 ng/mL) (P = 0.006). The authors concluded that cfDNA concentration could be used for therapy monitoring in patients with rectal cancer undergoing preoperative chemoradiation, and these findings were repeatedly confirmed in several other exploratory studies.(20-23)

ctDNA and long-term oncologic survival outcomes in rectal cancer (cfDNA concentration studies)
Besides the use of cfDNA for response outcomes, cfDNA was investigated as predictor for long-term (oncological) outcomes as well. In 2017, Boysen et al. were the first to find an association between the level of pre-surgery cfDNA and the risk of recurrence after surgery.(22) In this study including 75 patients with LARC, the level of cfDNA was quantified by ddPCR and expressed as copy number of beta 2 microglobulin. The median levels of cfDNA for patients with recurrent disease were 13,000 copies/mL compared to 5200 copies/mL for non-recurrent patients (p = 0.08).

In line with this, Schou et al. demonstrated, in a study with 123 participants, that patients with baseline cfDNA levels above the 75th quartile measured by a direct fluorescent assay, had a higher risk of local or distant recurrence and shorter time to recurrence compared with patients with plasma cfDNA below the 75th percentile (HR = 2.48, 95% CI: 1.3–4.8, P = 0.007).(24) The same applied to DFS (HR = 2.43, 95% CI: 1.27–4.7, P = 0.015). In a subgroup analysis with 71 patients who received induction chemotherapy (capecitabine and oxaliplatin (CAPOX)) before chemoradiation, the prognostic impact of plasma levels of cfDNA remained significant for time to recurrence and DFS. In multivariate analysis, a high cfDNA level was significantly associated with time to progression and DFS. During follow-up, the association remained significant regardless of time point for sample analysis.

Finally, Appelt et al. found that fractional abundance of hypermethylation of the neuropeptide Y gene in cfDNA (meth-cfDNA), could be used as baseline prognostic marker as well.(25) They showed in 146 LARC patients that meth-cfDNA, determined by quantitative PCR on baseline, was associated with a significantly worse overall survival

(adjusted HR: 2.08, 95% CI: 1.23-1.51) and distant metastases rate (55% vs. 72% at 5 y, p=0.01).

ctDNA and long-term oncologic survival outcomes in rectal cancer (mutation-specific assay studies)

While multiple studies described the prognostic value of cfDNA concentrations, an important downside is that these assays lack the ability to discriminate between cfDNA from healthy cells and cfDNA directly derived from the tumour (ctDNA). Especially in the context of MRD detection, there is a need for tests with high specificity.

Therefore, in recent years, more and more studies utilising techniques that can specifically detect ctDNA have increasingly been described. The largest study conducted so far by Tie et al., including 159 patients with LARC, has demonstrated that ctDNA status could be used to classify groups as very high and low risk for recurrence.(26) Somatic mutations in individual patient's tumours were identified via massively parallel sequencing of 15 genes commonly mutated in colorectal cancer, after which personalised assays were designed to quantify ctDNA in plasma samples. Prior to neoadjuvant (chemo)radiotherapy 122 (77%) patients had detectable ctDNA. After surgery, 19 patients (12%) had detectable ctDNA of which 58% recurred during follow-up (median 24 months). In contrast, recurrence occurred in only 8.6% of the patients without detectable ctDNA (HR 13, 95% CI 5.5-31, p<0.001). The prognostic value of detectable ctDNA for recurrence was even stronger in patients with a high pathological stage (ypT3-4 and ypN1-2), demonstrated by recurrence rates up to 89% after 2 years in patients with detectable ctDNA after surgery combined with pathologically staged lymph node metastases. This study also showed that the predictive value of ctDNA was strong when measured after treatment. No difference in RFS was observed between patients with detectable ctDNA and those without detectable ctDNA before treatment (HR 1.1; 95% CI: 0.42 - 3.0). However, for the post-treatment measurements, the Kaplan-Meier estimates of RFS at 3 years were 50% (95% CI: 28% - 88%) and 85% (95% CI: 79% - 93%) for the postchemoradiation ctDNA-positive and ctDNA-negative groups respectively, and 33% (95% CI: 16% - 72%) and 87% (95% CI: 79% - 95%) for the postoperative ctDNA-positive and ctDNA-negative groups. This study also demonstrated that postoperative CEA (≥5.0 ng/ml) was also a predictor for recurrence (adjusted HR 5.1, 95% CI: 1.3 - 18), but that in patients with normal CEA, postoperative detectable ctDNA remained associated with a high risk of recurrence (HR 8.8, 95% CI 3.2 to 24; P<0.001).

Another prospective multicentre study also investigated the predictive value of ctDNA analysed by targeted NGS at different time points before and during treatment in 106 LARC patients undergoing chemoradiation.(27) Mutations in cfDNA were only called as somatic

mutations if these mutations were also present in the primary tumour, which was also subjected to targeted NGS. ctDNA was detected in 75% of patients at baseline, 16% during chemoradiation, 11% before surgery, and 7% after surgery. Again, detectable ctDNA after surgery was the strongest predictive factor for distant metastasis (HR 25.30, 95% CI 1.475-434.0), compared to one cycle after the initiation of chemoradiation (HR 6.635, 95% CI: 1.240-35.50), and 7 weeks after chemoradiation (before surgery) (HR 19.82, 95% CI: 2.029-193.7). However, these subgroup analyses were underpowered (only 6 patients had detectable ctDNA in the postoperative ctDNA group).

Khakoo et al. investigated the role of ctDNA by tracking up to three somatic variants that were found in tumour tissue in plasma using ddPCR in patients with LARC. They showed that all three patients with detectable ctDNA after surgery had recurrent disease compared with none of the 20 patients with undetectable ctDNA (P = 0.001).(28) Similar results were found in a study conducted by McDuff et al. In this study, NGS was used to identify mutations in the primary tumour, and mutation-specific ddPCR were used to assess mutation fraction in ctDNA. The study found that all four LARC patients with detectable postoperative ctDNA recurred (positive predictive value = 100%), whereas only two of 15 patients with undetectable ctDNA recurred (negative predictive value: 87%).(29) The hazard ratio for RFS at a median follow-up of 20 month was 12 in patients with detectable postoperative ctDNA (P = 0.007). Another study of 119 LARC patients demonstrated that post-operative ctDNA testing with a tumour-agnostic customised NGS panel targeting 422 cancer-related genes, in combination with a high-risk pathological feature (perineural invasion, tumour deposits, vascular invasion, and lymph node metastasis), was able to predict the recurrence of all six patients that were analysed in this risk group (HR 90, 95% CI: 17 – 479 compared to undetectable ctDNA and no high risk features).(30)

Another prospective cohort study conducted by Murahashi et al. used NGS on a cfDNA panel with 14 target genes to investigate the association of ctDNA on preoperative treatment response and postoperative recurrence in 85 LARC patients.(31) A significant association was found between changes in ctDNA before and after neoadjuvant treatment (≥80% change in cfDNA versus < 80% change in cfDNA) and pathological complete response (OR 8.5; 95% CI: 1.4–163). In addition, the rate of recurrent disease was significantly higher in patients with high levels of postoperative ctDNA (≥0.5%) than in those with low levels of ctDNA (<0.5%) (HR 17.1, 95% CI: 1.0-282). In this study, postoperative CEA (≥5.0 ng/ml) was also independently associated with recurrence (adjusted HR: 6.9, 95% CI 1.6–29), and all four patients that had a combination of detectable ctDNA and CEA had disease relapse (HR: 34, 95% CI: 0.4 - 2631).

The phase II GEMCAD 1402 study, including 72 patients with LARC undergoing total neoadjuvant treatment (fluorouracil, leucovorin, and oxaliplatin with or without aflibercept, followed by chemoradiation and surgery), also evaluated ctDNA as biomarker to predict tumour response and survival outcome.(32) ctDNA was detectable using a tumour-agnostic CRC-specific NGS assay (Guardant reveal) integrating somatic mutations and epigenomic signatures in 83% of patients at baseline and in 15% following total neoadjuvant treatment (pre-surgery). Baseline ctDNA detection was not associated with poor survival outcomes, but detectable ctDNA just before surgery (after total neoadjuvant treatment) was significantly associated with systemic recurrence, shorter DFS (HR, 4; P = 0.033), and shorter overall survival (HR, 23; P < 0.0001). The predictive value of detectable ctDNA after surgery was not investigated in this study.

Finally, an exploratory study by Liu et al. analysed three different ctDNA techniques in LARC patients in samples taken after neoadjuvant treatment.(18) The three ctDNA assays were: 1. a tumour-informed personalized assay, 2. a tumour-agnostic targeted assay of genes frequently mutated in CRC, and 3. a copy number alteration-based approach. All three investigated techniques were associated with a poor RFS. The personalised assay targeting tumour-informed mutations was significantly associated with an increased risk of recurrence (HR = 27.38; log-rank P < 0.0001), the universal panel of genes frequently mutated in colorectal cancer (HR = 5.18; log-rank P = 0.00086), and the low depth sequencing for copy number alterations (CNAs) analysis showed a compromised performance in predicting recurrence (HR = 9.24; log-rank P = 0.00017). Of note, this study was not powered to detect differences between the three assays.

Alternative cfDNA and ctDNA techniques

Alternative methods to enable the use of cfDNA in clinical practice have been described as well. Guo et al. analysed gene promoter coverage in cfDNA of 20 patients with LARC (both 10 patients with- and without pathological complete response), in order to predict tumour expression status and subsequently patients' response to chemoradiation.(33) Thus, this study did not investigate mutations (ctDNA), but determined the relative coverage of gene promoter regions in the cfDNA. In a letter to the editor, they propose a classifier of promoters with differential coverage between cfDNA of patients with and without pathological complete response, and validated the use of this prediction technique in 194 LARC patients. The classifier resulted in an AUC of 0.89 (0.83-0.94) to discriminate patients with and without pathological response, but no external validation of this classifier was performed.

Sclafani et al. used ctDNA to assess KRAS/BRAF mutations in baseline blood samples from 114 patients with LARC, and compared these to mutations in tumour tissue.(34) Notably, in 26 patients the ctDNA analysis revealed a KRAS mutation that was not previously found in tumour tissue using standard PCR-based techniques. However, a more sensitive technique (ddPCR) and additional analysis of a different tissue section revealed that 22 of these 26 "newly" detected plasma mutations were already detectable in the tumour in hindsight. In this study, no association between the presence of KRAS/BRAF in ctDNA and clinical outcomes was found.

Meta-analyses

The association between recurrence-free survival and: 1) the presence of ctDNA after neoadjuvant treatment (chemoradiation with or without systemic treatment), 2) the presence of ctDNA after curative intent surgery were investigated in meta-analyses. Results are summarised in figure 2 and figure 3. The pooled hazard ratio for ctDNA presence after neoadjuvant treatment was 9.26 (95% CI: 4.56 – 18.84) compared to those patients who were without detectable ctDNA after neoadjuvant treatment. After surgery, patients with detectable ctDNA had increased risk for recurrence, compared to patients without detectable ctDNA (HR 15.54, 95% CI: 8.23 – 29.34).

Figure 2. Meta-analysis of the association between recurrence-free survival and the presence of ctDNA after neoadjuvant treatment (chemoradiation with or without systemic treatment)

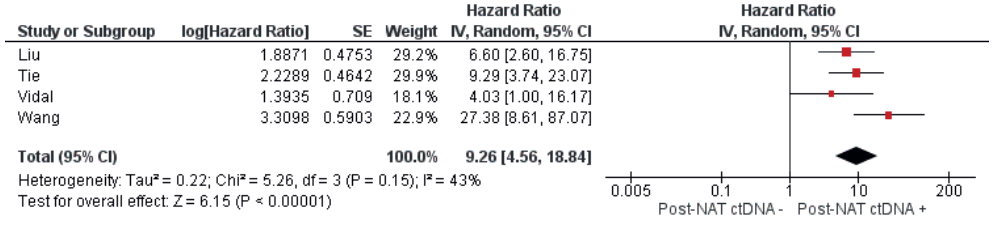
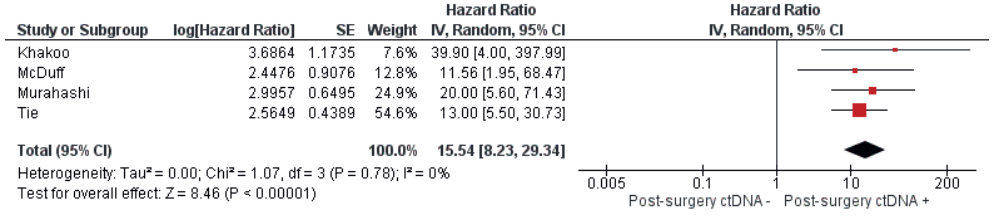


Figure 3. Meta-analysis of the association between recurrence-free survival and the presence of ctDNA after curative intent surgery



Ongoing ctDNA trials in rectal cancer

Two interventional trials were found in the systematic search investigating the use of ctDNA in patients with rectal cancer, being the DYNAMIC-RECTAL trial (ACTRN12617001560381) and the SYNCOPE study (NCT04842006). The aim of the DYNAMIC-RECTAL trial was to randomise 408 patients to either a ctDNA-informed arm and a standard of care arm.(35) In the ctDNA-informed arm, patients would receive adjuvant chemotherapy if ctDNA was detected, or a not detected in the presence of a high-risk tumour (based on the standard pathology risk assessment of the tumour). In the standard of care arm, the decision regarding adjuvant chemotherapy was based on the standard pathology risk assessment of the tumour. Recruitment of this study terminated early, as accrual slowed down due to the COVID-19 pandemic and the total neoadjuvant treatment approach in this population was adopted. Therefore, the target number could not be reached within the planned recruitment period.

The SYNCOPE study randomises 93 rectal cancer patients into a group of patients that will be treated with novel precision methods, being ctDNA and organoid-guided adjuvant therapy, and a group of patients that will undergo conventional treatment strategy. Primary outcomes are RFS and the number of patients with detectable ctDNA in the postoperative sample of patients in the conventional treatment arm who are not assigned to chemotherapy.

DISCUSSION

The aim of this literature review was to provide an overview of the current evidence and ongoing trials in the field of ctDNA in non-metastatic rectal cancer. Studies have consistently shown the strong association between detectable ctDNA after treatment and unfavourable prognosis. It can be concluded from these results that ctDNA analysis from peripheral blood samples, especially detected after surgery with curative intent, stratifies patients into two groups: one with a very high risk for recurrence, another with a low risk for recurrence. Thus far, there are no rectal cancer trials published, that have investigated ctDNA-guided adjuvant treatment in a randomised setting.

Based on our systematic search, this systematic review is the first to pool long-term oncological survival outcomes in a meta-analysis. A systematic review by Boyson et al. included nine single arm studies with a total of 615 patients undergoing chemoradiation for rectal cancer and investigated the relation between ctDNA and clinical outcomes.(15) Eight of the nine studies showed some degree of correlation between ctDNA and either response to chemoradiation, risk of recurrence or disease-free survival. A second

systematic review also included nine studies and investigated the association between clinical outcomes and ctDNA at different time points (at diagnosis, after chemoradiation, and after surgery).(36) No association was found between treatment response and ctDNA status at baseline. Studies reporting the prognostic impact of ctDNA after chemoradiation and before surgery showed varying results. All five studies reporting outcomes of detectable ctDNA postoperative and clinical outcomes, found an association between ctDNA positivity after surgery and worse survival. This review demonstrated that post-operative ctDNA is the most predictive prognostic factor of all investigated time points. A third systematic review investigating different ctDNA measurement techniques on predictive and prognostic outcomes in LARC patients, concluded that detection of ctDNA at different time points of treatment was consistently associated with worse prognosis, but that the ideal method and timing for the liquid biopsy still needed to be defined.(37)

Although all studies found a positive correlation between ctDNA and treatment and oncological outcomes, various methods to analyse ctDNA were used, including those with quantitative (e.g. absolute cfDNA concentration) and qualitative (tumour-specific somatic mutations) measurements. Articles that utilized quantitative analyses were generally published between 2008-2018, and were considered relatively inferior because quantitative tests do not have the ability to discriminate tumour DNA from physiological circulating DNA from non-cancerous cells. More recent studies often used qualitative techniques that are able to specifically detect tumour-specific cfDNA. These mutation-specific analyses are nowadays considered as technique of choice, and are acceptable in terms of costs.(38) Differences in qualitative analyses exist as well, as was shown as shown by Liu et al.(18) This study revealed that minor differences in the sensitivity of ctDNA are observed when different gene panels and techniques for ctDNA quantification are used, in which a personalised assay targeting tumour-informed mutations was suggested to yield the best performance. However, tumour-informed assays are more expensive and labour-intensive as they require sequencing of the tumour and subsequent design of tumour-specific assays. This can be challenging, especially in a setting where the turnaround time for clinical decision-making needs to be short and will be accompanied by higher costs. A tumour-agnostic method is likely to have a faster turnaround time, as it is easier to conduct, and is accompanied by lower costs. Currently, well-powered studies in a real-world setting comparing all assays with regard to its sensitivity, specificity and turnaround time are lacking.

Another controversy in ctDNA analysis is the optimal timing of measurement to detect MRD after surgery, as it has been suggested that an abundance of surgery-induced cfDNA fragments could hamper the detection of ctDNA from the tumour.(39) In a study by

Hendriksen et al., it was shown that cfDNA levels in patients with colorectal cancer were increased by threefold during the first week after surgery (median 3.6-fold increase, mean: 4.0, 95% CI 2.90–5.37, P = 0.0005), and slowly decreased over the next 3 weeks. Notably, it was assumed that in five of the eight patients, ctDNA was falsely measured as being negative, as these patients were ctDNA positive in all other measurements in which ctDNA surgery-induced cfDNA fragments were not increased. Therefore, to maximize sensitivity of the measurement, one could argue to only measure ctDNA at least four weeks after surgery. On the other hand, when the results of the ctDNA analyses have clinical consequences, e.g. ctDNA-based adjuvant therapy, results ought to be known within the timeframe that consolidation treatment will still be sufficient. Typically, most ctDNA assays are accompanied by an additional four weeks turnover time from blood withdrawal to definite results,(40) so the typical timeframe of a maximum of 8 or 12 weeks from surgery to start with adjuvant treatment could be endangered when delaying the ctDNA result too long.(41-43) A balance between test sensitivity, and considerations regarding turnaround times inherent to different methods, should be considered for each clinical implication and setting.

Precision biomarkers to predict postoperative outcomes, such as ctDNA, could contribute to the ongoing debate whether additional treatment should be considered after rectal cancer surgery. The role of adjuvant systemic treatment in rectal cancer has not been established globally; practice differs between Europe and the USA, and between European countries as well. In the Netherlands, adjuvant chemotherapy is not recommended for any stage.(44) There are only a few randomised controlled trials on adjuvant chemotherapy for rectal cancer available, which yielded conflicting results.(45) The fact that the benefit of adjuvant chemotherapy has not yet been demonstrated, is likely related to a dilution effect, and it might very well be true that a subgroup of patients will benefit from additional treatment. Therefore, it would certainly be of interest to explore whether high-risk patients based on ctDNA detected in postoperative peripheral blood samples might benefit from adjuvant treatment. A trial randomising patients with detectable ctDNA into an adjuvant treatment group and a follow-up group is warranted. Such a trial should be able to answer the important question whether ctDNA-guided adjuvant treatment is beneficial in rectal cancer.

Another potential opportunity of ctDNA-guided treatment is the ability to tailor follow-up strategies based on patients' individual risk of recurrence. As intensive follow-up does not appear to improve overall and cancer-specific survival and quality of life in colorectal cancer, there seems to be an incentive to reduce surveillance after curative surgery.(44, 46, 47) Studies have demonstrated that ctDNA outperforms CEA in (colo)rectal cancer patients

to detect relapsing disease.(5, 26, 27, 48) Therefore, ctDNA-based risk prediction for recurrence may very well be an excellent biomarker to stratify patients without detectable DNA into a less intensive and decentralised surveillance programme in the home environment or even earlier discharge of standard follow-up. This could eventually improve health-related quality of life, cause a reduction in health-related and societal costs as well as anxiety in cancer patients, without compromising oncological outcomes. Further research would be needed to investigate whether this ctDNA-guided follow-up approach is feasible in rectal cancer.

Finally, novel technical advances highlight the promise of several tumour-agnostic ways to detect ctDNA (i.e. without prior tissue-based information) in the future. For example, recent results highlight the merit of circulating cell free (cf)DNA methylation analyses for both detection and classification of many cancer types, including colorectal cancer.(49-52) Next to methylation profiling, recently discovered “fragmentomics” also shows great promise for the sensitive detection of cancer using cfDNA.(53-55) Both cfDNA methylation profiling and fragmentomics capture information from a much broader spectrum of the circulating tumour genome, theoretically enabling a higher analytical sensitivity for the detection of minute traces of ctDNA in case of MRD. Supporting this notion, combining features from different molecular levels was shown to have complementary value for MRD detection in colorectal cancer.(56)

In conclusion, in rectal cancer patients treated with neoadjuvant treatment and surgery, a very strong association was found between post-treatment detectable ctDNA and recurrent disease as well as overall survival. Randomised controlled trials are needed to investigate whether this ctDNA-informed risk classification could be used during clinical decision making for the purpose of patient-tailored treatment.

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SUPPLEMENTARIES

Supplementary 1. Search terms

The following search was performed on the 4th of October 2022:

Embase

('rectum cancer'/exp OR 'rectum carcinoma'/de OR 'rectum resection'/exp OR 'rectum tumor'/exp OR (((rectum OR rectal) NEAR/3 (cancer OR carcinom* OR tumor* OR tumour* OR neoplas* OR adenocarcinom* OR resect* OR unresect* OR excision*)) OR proctectom* OR LARC):ab,ti,kw) AND ('circulating tumor DNA'/de OR 'DNA determination'/mj/de OR 'circulating free DNA'/de OR (((free* OR circulat*) NEAR/3 (DNA*)) OR ctDNA* OR ct-DNA* OR cfDNA OR cf-DNA*):ab,ti,kw) NOT ([Conference Abstract]/lim OR [Conference Review]/lim)*

Medline

(exp Rectal Neoplasms/ OR exp Proctectomy/ OR (((rectum OR rectal) ADJ3 (cancer OR carcinom* OR tumor* OR tumour* OR neoplas* OR adenocarcinom* OR resect* OR excision*)) OR proctectom* OR LARC).ab,ti,kf.) AND (Circulating Tumor DNA/ OR *Sequence Analysis, DNA/ OR Cell-Free Nucleic Acids/ OR (((circulat* OR free*) ADJ3 (DNA*)) OR ctDNA* OR ct-DNA* OR cfDNA OR cf-DNA*).ab,ti,kf.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.*

Cochrane

((((rectum OR rectal) NEAR/3 (cancer OR carcinom* OR tumor* OR tumour* OR neoplas* OR adenocarcinom* OR resect* OR excision*)) OR proctectom*):ab,ti,kw) AND ((((circulat* OR free*) NEAR/3 (DNA*)) OR ctDNA* OR ct-DNA* OR cfDNA OR cf-DNA*):ab,ti,kw) NOT "conference abstract":pt*

Web of Science

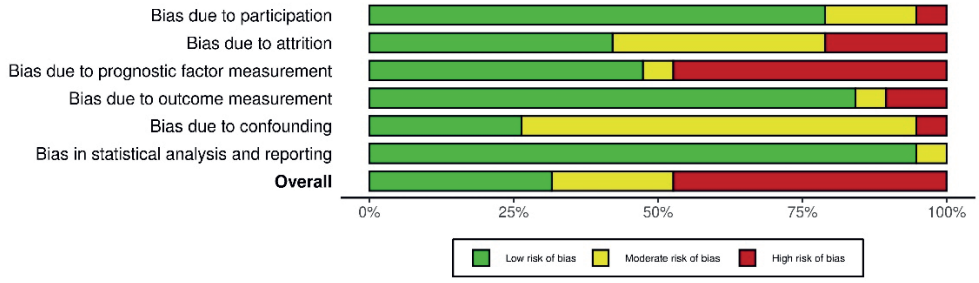
TS=(((((rectum OR rectal) NEAR/2 (cancer OR carcinom* OR tumor* OR tumour* OR neoplas* OR adenocarcinom* OR resect* OR excision*)) OR proctectom*)) AND ((((circulat* OR free*) NEAR/2 (DNA*)) OR ctDNA* OR ct-DNA* OR cfDNA OR cf-DNA*))) NOT DT=(Meeting Abstract OR Meeting Summary)*

Google Scholar

"rectum|rectal
cancer|carcinoma|tumor|tumour|neoplasm|adenocarcinoma|resection|excision"|proctectomy
"circulating|ct|cf DNA"|"cell free DNA"|ctDNA|cfDNA|"circulating tumor|tumour DNA"|"cell free tumor|tumour DNA"
'rectum|rectal
cancer|carcinoma|tumor|tumour|neoplasm|adenocarcinoma|resection|excision'|proctectomy
'circulating|ct|cf DNA'|'cell free DNA'|ctDNA|cfDNA|'circulating tumor|tumour DNA'|'cell free tumor|tumour DNA'

Supplementary 2. Quality Assessment QUIPS tool

Supplementary 3. Reasons of bias QUIPS tool



Supplementary 4. Detailed overview of ctDNA analyses methods (see next page)

Author, year	Assay type	Target / assay	Tumour informed	Tube type	Plasma isolation	cfDNA isolation	Preprocessing	NSG / PCR	Risk of Bias
Zitt et al. 2008	cfDNA concentration	cfDNA concentration (185 gene)	Agnostic	EDTA	2x3000rpm, within 2 hours	qiaAMP	Not optimal	PCR	High
Agostini et al. 2011	cfDNA concentration	cfDNA (Alu 247, Alu 115 repeat, and Alu 247/115 ratio (cfDNA integrity index))	Agnostic	EDTA	1x3000g, within 4 hours	qiaAMP	Not optimal	PCR	High
Sun et al. 2014	Multiple	cfDNA concentration, KRAS mutation and O6-methylguanine-DNA methyltransferase promoter methylation status of cfDNA	Agnostic	Unknown	Unknown	qiaAMP	Unknown	PCR	High
Boysen et al. 2017	cfDNA concentration	cfDNA concentration (beta-2 microglobulin)	Agnostic	EDTA	1x 30g, time unknown	qiaAMP	Not optimal	PCR	High
Liu et al. 2017	Mutation-specific panel	Personalised assay targeting tumour-informed mutations, universal panel of genes frequently mutated in colorectal cancer, and low depth sequencing for copy number alterations	Both	EDTA	1x 4000g + 1x12000g, within 2 hours	Apostle MiniMax cfDNA isolation kit	optimal	NGS	Low
Sclafani et al. 2017	Mutation-specific panel	KRAS/BRAF mutations	Tumour informed (predefined panel)	Unknown	Unknown	Unknown	Unknown	PCR	High
Schou et al. 2018	cfDNA concentration	cfDNA concentration	Agnostic	Citrate	1x2000g, within 2 hours	None	Not optimal	dFA	High
Tie et al. 2019	Mutation-specific panel	Personalised assays	Tumour informed (tumour specific)	EDTA	1x1200g + 1x1800g, time unknown	qiaAMP	Not optimal	NGS	Low
Appelt et al. 2020	cfDNA concentration	Meth-ctDNA	Agnostic	Serum	Serum	qiaSymphony	Serum is not optimal for cfDNA analyses	PCR	High
Guo et al. 2020	Promoter genes	Promoter profiling of cfDNA	Agnostic	Unknown	Unknown	qiaAMP	Unknown	NGS	High
Khakoo et al. 2020	Mutation-specific panel	Personalised assays based on six oncogenes	Tumour informed (tumour specific)	Streck	2x1600g	qiaAMP	Not optimal	PCR	Low
Murahashi et al. 2020	Mutation-specific panel	cfDNA panel covering 14 genes with over 240 hotspots.	Agnostic	EDTA	1x1600g + 1x16000g, time unknown	MagMAX	Unknown	NGS	Moderate
Pazdirek et al. 2020	Mutation-specific panel	Panel of six selected oncogenes	Tumour informed (predefined panel)	Unknown	Unknown	Nucleospin plasma XS kit	Unknown	PCR	Moderate
Zhou et al. 2020	Mutation-specific panel	Personalised assays	Tumour informed (tumour specific)	EDTA	1x2500g + 1x16000g, within 3 hours	qiaAMP	Optimal	NGS	Low
McDuff et al. 2021	Mutation-specific panel	Personalised assays determined by NGS	Tumour informed (tumour specific)	Streck	1x1600g + 1x3000g	qiaAMP	Optimal	PCR	Moderate
Vidal et al. 2021	Mutation-specific panel	Somatic mutations and epigenomic signatures	Agnostic	EDTA	1x3200 rpm, within 3 hours	Unknown	Not optimal	NGS	Moderate
Wang et al. 2021	Mutation-specific panel	422 cancer-related genes	Tumour informed (predefined panel)	EDTA	1x1800g, within 2 hours	Nucleospin plasma XS kit	Not optimal	NGS	Low
Roesel et al. 2022	Mutation-specific panel	Oncomine panel	Tumour informed (predefined panel)	Streck	unknown	MagMAX	Unknown	NGS	Low
Truelsen et al. 2022	cfDNA concentration	Median cfDNA	Agnostic	EDTA	1x1200g, within 1 hours	None	Not optimal	dFA	High

cfDNA: cell-free DNA. ctDNA: circulating tumour DNA. . dFA: direct fluorescence assay NSG: next generation sequencing. PCR: polymerase chain reaction

DISCUSSION AND SUMMARY

CHAPTER 14

Discussion and future perspectives

The aim of this thesis is to further improve the multimodality treatment of the more advanced stages of rectal cancer. Management of advanced rectal cancer continues to change rapidly with the advent of new chemo- and radiotherapy treatment strategies in the perioperative setting. Although results appear promising, they should be validated in "real-world" patients. The focus of this thesis lies on patients with advanced rectal cancer who were treated in tertiary referral centres in the Netherlands, and provides new insights in oncological outcomes, morbidity, treatment and patient selection of both conventional and modern treatment approaches.

PART I – ONCOLOGICAL OUTCOMES OF ADVANCED RECTAL CANCER

Current treatment strategies and outcomes for LARC

The current standard treatment to achieve cure for both locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) is chemoradiation followed by radical tumour resection, and has been established since approximately two decades.(1) Prior to that, management of patients with LARC consisted of upfront resection, followed by adjuvant radiotherapy and chemotherapy. In 2004, the German CAO/ARO/AIO-94 trial demonstrated that preoperative instead of postoperative chemoradiation resulted in better compliance, reduced toxicity and improved local control, after which adjuvant radiation was abandoned.(2) In around 10-15% of patients treated with preoperative chemoradiation alone, all vital tumour cells are eradicated, and surgical resection can often be safely omitted. Patients with such response may be treated with an active surveillance approach, which is commonly referred to as the 'watch and wait' strategy.(3) With current practice, five-year overall survival rates after curative intended treatment for LARC range from 31% - 77%.(4, 5) Local recurrences and distant metastases after optimal treatment occur in about 5-10% and 27-34% of patients respectively.(4, 6, 7)

Alternative treatment strategies for LARC

Total neoadjuvant therapy, consisting of systemic chemotherapy and (chemo-)radiotherapy before and/or after surgery, is increasingly utilised in patients with LARC, and has been investigated in this thesis. The potential value of the addition of systemic chemotherapy in the neoadjuvant setting is twofold. First, the administration of systemic chemotherapy could eradicate micro-metastases, and may subsequently reduce distant metastases.(8) Second, a longer and more intensified neoadjuvant treatment period could enlarge the chance of a complete response, enabling the watch and wait strategy in more patients. However, the treatment burden of increased toxicity from systemic treatment, plus the extensive follow-up after a possible clinical complete response, should be considered before adopting total neoadjuvant treatment as standard of care. For example, an older

patient who is willing to accept a stomy over an active surveillance programme with frequent hospital visits, might achieve much better quality of life after standard treatment with (chemo-)radiotherapy and surgery.
Trials investigating total neoadjuvant treatment, e.g. CAO/ARO/AIO-12, OPRA trial, PRODIGE 23, RAPDIO, all demonstrate a limited benefit in disease-free survival, but fail to show improvement in overall survival.(8-11) Notably, these trials consistently report a complete response rate of around 28%. A recent retrospective analysis conducted by Voogt et al. found that patients with LARC treated with CAPOX or FOLFOX prior to chemoradiation and surgery had a pathological complete response rate of 14%, and another 16% completed a successful watch and wait strategy.(12) Taken into account all available evidence, intensified preoperative treatment consisting of systemic therapy and chemoradiation might be justified in at least a subgroup of patients. Which patients benefit most from additional chemotherapy is still an unanswered question. In the RAPIDO trial, a reduced number of metastases was found during follow-up in the experimental group, without an effect on overall survival. The study also showed that large (T4) tumours did not seem to undergo the same local downstaging effects after total neoadjuvant treatment compared to smaller (T3 and T2) tumours.(8) In Chapter 10 of this thesis, we demonstrated that patients with LARC and synchronous liver metastases had much lower complete responses after combination treatment, as compared to previous reported outcomes of non-LARC stage IV patients undergoing identical treatment.(13)

In this thesis and in collaboration with Catharina Hospital Eindhoven, an alternative method for patient selection who might benefit from escalation treatment was introduced for high-risk LARC. In a comparative cohort study conducted in two referral centres, the role of induction chemotherapy in addition to chemoradiation was assessed in LARC patients with high-risk features on MRI, being the presence of ingrowth in the mesorectal fascia, grade 4 extramural venous invasion (EMVI), extensive lateral lymph node metastases or tumour deposits (MEND-it criteria). The addition of induction chemotherapy to standard chemoradiation improved complete response rates in patients that were selected for surgery, and even a prolonged survival was observed in these patients. This survival advantage could, however, be explained by the fact that patients with progressive disease during chemotherapy were not included in the survival analyses. It should therefore be noted that the good outcomes after induction chemotherapy might be related to a better selection for surgery, rather than the induction treatment itself. Nevertheless, major surgery could have been spared in patients with progressive disease during neoadjuvant treatment. As the prognosis of these patients is mainly determined by metastases, it is unlikely that they would not have benefitted from primary tumour

resection. Long-term outcomes of retrospective series, but also prospective studies should provide more clarity on the role of induction chemotherapy in high-risk LARC. The MEND-IT trial (NCT04838496), a phase II prospective trial investigating the role of FOLFOXIRI in high-risk LARC patients, is currently recruiting in the Netherlands.

Conclusively, it is unlikely that future research will provide definite answers or a one-size-fits-all treatment for LARC. 'Tailored' treatment approaches based on individual risk factors and distinct tumour biology subtypes will, in all probability, be used more frequently to treat patients with LARC in the future. Future research, for example on novel (genomic) biomarkers and organoids, might be able to better identify those patients that benefit from certain neoadjuvant treatment regimes. Better prediction of outcomes will hopefully also pave the way for methods to de-escalate treatment, as it has been suggested at least a proportion of patients with advanced rectal cancer is overtreated with current treatment strategies.(14) For example, patients with tumours that are radiotherapy-resistant might be better off with upfront resection (and without neoadjuvant radiation therapy). Consequently, late adverse effects of neoadjuvant treatment can be avoided, improving the long-term functional outcomes in a subgroup of patients. These personalised treatment options also enable physicians to take specific needs and wishes from individual patients into consideration. This will eventually improve shared decision-making and quality of life.(15)

Adjuvant chemotherapy for LARC

The debate on whether adjuvant chemotherapy is warranted in patients with LARC is ongoing. In several European countries and the United States, postoperative chemotherapy is standard of care for stage II-III rectal cancer, whilst in the Netherlands, adjuvant treatment is not recommended.(16) Some trials, as well as a Cochrane systematic review, reported beneficial effects of systemic adjuvant chemotherapy after surgery on both overall survival (hazard ratio (HR): 0.83, 95% confidence intervals (CI): 0.76 – 0.91) and disease-free survival (HR 0.75, 95% CI: 0.68 – 0.83).(17, 18) This review, however, has the important shortcoming that the included trials were conducted before total mesorectal excision (TME) surgery was fully incorporated, and findings could therefore not be extrapolated to current practice. Two recent meta-analyses that included the pooled analyses of patients who were mainly treated with preoperative radiotherapy and TME surgery, showed no benefit in overall survival, disease-free survival or distant recurrences.(19, 20)

Although the value of adjuvant chemotherapy, if any, is not well established in literature, this does not mean that a subgroup of rectal cancer patients does not benefit from postoperative treatment. For example, the meta-analysis from Breugom et al. has demonstrated that a subgroup of patients with tumours located higher up in the rectum, had less distant metastases after chemotherapy (HR 0.61, 95% CI 0.40 – 0.94) compared to the control group that underwent standard follow-up.(19) It should however be acknowledged that trials included in this analysis were conducted before the new definition of the rectum was established,(21) and that some of the patients included might have been incorrectly staged colon cancers patients with tumours located in the lower sigmoid. A benefit in survival has not been demonstrated, even in the subgroup. In addition, recurrence-free survival does not necessarily correlate with overall survival.(22) The conclusion that can be drawn from the available literature is that the number needed to treat for a relevant reduction of recurrences and overall survival in patients with rectal cancer is relatively high. Precision biomarkers that predict oncological outcomes after surgery, such as circulating tumour DNA (ctDNA), could contribute to the ongoing debate whether or not additional treatment should be considered after rectal cancer surgery.

Circulating tumour DNA (ctDNA)

CtDNA from peripheral blood samples is considered an important diagnostic tool for the detection of minimal residual disease after surgery.(23-25) In recent years, ctDNA has been investigated in various cancer types and settings, and has the potential to optimise personalised medicine in oncology. For example, data from a recent trial in stage II colon cancer demonstrated that a ctDNA-guided treatment approach can reduce the number of patients receiving adjuvant therapy whilst not altering the risk of recurrence.(26) In this thesis, it was demonstrated in a systematic review that ctDNA after surgery is a very strong predictor for recurrent disease in rectal cancer (hazard ratio for recurrence-free survival: 15.5 [8.2 – 29.3]). It would certainly be of interest to explore whether high-risk patients based on detected ctDNA in postoperative peripheral blood samples might benefit from adjuvant treatment. A trial randomising patients with detectable ctDNA into an adjuvant treatment group and a follow-up group is warranted. Such a trial should be able to answer the important question whether ctDNA-guided adjuvant treatment is feasible in rectal cancer.

Current treatment strategies and outcomes in LRRC

Although major improvements have been made in the management of primary rectal cancer, including TME surgery, preoperative radiotherapy and more accurate staging methods, LRRC still occurs in 5-10% of patients after curative treatment of rectal cancer.(2,

6, 27, 28) Before these improvements, local recurrence rates up to 20% - 40% were considered inevitable.(29, 30) Besides changes in incidence, differences in tumour behaviour of recurrent disease have been observed in the past decades as well.(31, 32). More local recurrences occur in patients who were treated with radiation and TME surgery. Relapsing tumours after previous radiation tend to exhibit aggressive biological behaviour, in accordance with their insensitivity to radiotherapy. LRRC results in poor prognosis and has significant impact on quality of life.(33-35) About half of patients with LRRC cannot be cured, and the foremost goal of treatment is to achieve control of the debilitating disease manifestations such as pain, bleeding, fistula and tenesmus.(36) With adequate palliative (chemo)radiotherapy, symptoms can be managed with a duration of 6–9 months, with an overall response rate of 75%.(37, 38)

LRRC patients without extensive metastases and resectable local disease can be treated with curative intent. Because LRRC develops in the surgical resection planes of the TME, LRRC by definition involves structures that are located outside the mesorectum. This makes surgical resection of LRRC technically challenging. External beam radiotherapy prior to surgery plays an important role in local downstaging of LRRC.(39) Retrospective series, dating from the early 2000s, have shown that (re)irradiation with long-course radiation therapy and concomitant radiosensitiser to induce tumour shrinkage is safe and feasible, and has been established as standard treatment prior to surgery in the Netherlands.(40-43). Optimal tumour response can be achieved when a higher dose radiation is given, but can only safely be administered up to 45-50 Gy in radionaïve patients, and up to 30 Gy in patients who had been treated with (chemo)radiation for primary rectal cancer. A dose exceeding 60 Gy is associated with intolerable toxicity of the dose-limiting structures such as the small intestine and bladder. Intraoperative radiation therapy (IORT) delivers a single boost of radiation during surgery, commonly 10 Gy, with the biological equivalent equal to 1.5 to 2.5 times the dose of the conventional fractionation.(44) In patients at risk for an irradical resection after preoperative (chemo)radiation, IORT has the ability to deliver a high dose of radiation to areas at risk for tumour involvement.(42, 45-47)

Two commonly used methods for IORT are high-dose-rate brachytherapy (HDR-IORT) or intraoperative electron beam radiotherapy (IOERT).(45, 48) The former uses a flexible template that is formed in concordance with the intrapelvic areas that are suspect for tumour residual, and delivery takes about two hours. The administration of IOERT is completed more quickly. Retrospective data discussed in this thesis suggest that in LARC and LRRC patients with an R1 resection, longer local recurrence-free survival is achieved with HDR-IORT. This may be explained by the fact that HDR-IORT has a flexible applicator,

and is therefore able to administer a relatively high surface dosage to narrow areas. Consequently, more tumour cells may be eradicated, but theoretically, more normal tissue will be damaged as well. This is in line with the increase in postoperative complications seen in HDR-IORT patients, especially in LRRC. Another explanation for the higher efficacy of HDR-IORT may lie in the higher surface dose that is delivered by HDR-IORT as compared to IORT. In Catharina Hospital, the application of IORT was modulated as to match HDR-IORT with regard to the radiotherapy dose delivered at the surface.

Radical LRRC resection and long-term survival is only reserved for a selection of patients with relatively favourable tumour characteristics, as the majority of patients with LRRC have extensive local disease or distant metastases. Due to the high risk of morbidity after LRRC resection, extensive surgery should only be performed when a radical intrapelvic resection is feasible after potential downstaging, and not as a palliative treatment.(49) Although this strategy is generally accepted in the Netherlands, alternative strategies to achieve curation are used in institutes abroad. Extensive upfront resection with the goal to achieve a radical resection, including the removal of half of the pelvis and leg (hemipelvectomy), is not uncommon in European countries. It goes without saying that with more extensive surgery more R0 resections could be achieved, but at the cost of higher morbidity and more complications. Although a R0 resection is commonly associated with improved survival, achieving one with boundless surgery does not necessarily translate to better outcomes, as was shown in a recent comparative analysis in which one of the two hospitals used more extensive surgery than the other.(50) Despite the higher R0 rate in the hospital that used more extensive surgery, survival was comparable. This implies that disease biology is much more important for prognosis than the achievement of radicality itself. In the Netherlands, five-year overall survival outcomes of 48% - 60% can be achieved after adequate treatment of (re)irradiation and microscopic radical resection.(49, 51, 52) Relapse rates are higher compared to primary rectal cancer; chances of remittent disease, either local or distant, are reported up to 70 - 85%.(51, 53, 54) In this thesis, we analysed a large cohort of 447 LRRC patients who underwent surgical and non-surgical treatment options. In the surgically treated patients, we found that in patients in whom a R0 resection was achieved, the 5-year overall survival was 51%, compared to 34% for R1-resections and 10% for R2-resections. Surprisingly, comparable overall survival was found in patients who underwent a R2-resection compared to optimally treated non-surgical patients.

One strategy to improve LRRC resectability and long-term outcomes that has been of interest since some years, is the addition of induction chemotherapy to standard

chemoradiation and surgery.(55) It has been hypothesised that preoperative oxaliplatin-based chemotherapy could eradicate occult metastatic disease, thus improve metastases-free survival. Another advantage of initiating treatment with systemic chemotherapy, is the possibility to longer observe disease behaviour prior to extensive surgery. Given the relatively poor relapse- and survival rates after LRRC resection, one could argue that, currently, too many patients are getting the benefit of the doubt for curative-intended surgery. Unfortunately, some LRRC patients experience disease recurrence very shortly after curative treatment, sometimes when having hardly recovered from the major surgery and the related complications they underwent. With this "disease-observing" strategy, major procedures could be reserved only for patients who have good treatment response to induction chemotherapy and chemoradiation, and surgery could be spared in case of progressive disease. In patients who develop distant metastases or local growth during neoadjuvant treatment, palliative treatment is probably a more appropriate treatment option.

Although conclusive evidence is yet to be acquired, some comparative studies provide some promising results regarding the use of induction chemotherapy for LRRC. First, a retrospective cohort study by van Zoggel et al. demonstrated an improved pathological complete response rate in patients who received induction chemotherapy, but failed to show an improvement of R0 resection rate (55% versus 49%, p=0.506).(56) Second, Voogt et al. demonstrated in a large cohort of 132 patients that a pathological response rate of 17% can be achieved with induction chemotherapy, and that in patients with a pathological complete response excellent 3-year survival rates of 92% are found. The PelvEx II study (NCT04389086) is the first randomised study to compare induction chemotherapy followed by chemo(re)irradiation and surgery with chemo(re)irradiation and surgery alone in LRRC patients without metastases. Although the primary aim of this trial is to improve the R0 resection rate, outcomes of this study may also demonstrate a clinically relevant reduction of distant metastases due to the elimination of occult micro-metastases with chemotherapy. Results of this study are awaited.

PART II – MORBIDITY OF ADVANCED RECTAL CANCER

The boundaries of treatment options for patients with advanced rectal cancer have changed in the past decades, which resulted in more local treatment of distant metastases, more pelvic exenteration surgery and advanced reconstructive methods. Although perioperative methods have also improved over the years, which reduced the morbidity and mortality rates, postoperative complications still occur in up to 60% of patients.(5, 57, 58) In addition, preoperative chemoradiation, especially combined with

systemic chemotherapy, entails considerable toxicity and treatment-related complications, and severe complications are reported up to 4% – 10%.(59-62) Complications and hospital admission can lead to unwanted costs and delay in surgery, as well as it may deteriorate patients' clinical condition, making an unfavourable postoperative outcome even more likely.(60)

An optimal balance between aggressive treatment against potentially lethal disease on the one hand, versus ensuring acceptable risks and quality of life on the other hand, should be made for each individual patient.(63) Factors to be considered are underlying medical conditions, previous rectal cancer treatment (e.g., radiation therapy, surgery), concomitant medication, and lifestyle factors. Prior to surgery, patients have the tendency to decrease their daily activities with a negative effect on physical and mental fitness, which increases the risk of severe complications. In this thesis, we found that patients who are frail (patients with older age, low skeletal muscle index and poor nutrition status) are especially high at risk for complications during chemoradiation and after surgery. Whether these very frail patients should be eligible for major curative-intended procedures in the first place, is a complex dilemma for physicians and patients. During and after treatment, numerous (permanent) physical and mental health problems are expected and can include pain, bloating, flatulence, voiding issues, and anxiety.(64) Some patients will have such debilitating complaints that they will not return to their daily life, occupation, and leisure activities. For adequate expectation management, all possibilities including those with poor outcomes, should be discussed with patients. During counselling, it is also important to mention the non-surgical options for advanced rectal cancer. Although curation will not be achieved with palliative options, management to ease pain and other symptoms could be valuable for patients, as well as it may improve the quality of death. As previously discussed in this thesis, LRRC patients who are treated with adequate palliation (combined radiotherapy and chemotherapy) can achieve a median survival of 22 months. This is comparable with patients who undergo a macroscopically irradical resection.

Prehabilitation

Besides adequate counselling, a promising innovation to reduce treatment-related morbidity is discussed in this thesis. Last years, there is an increasing interest in methods that address patients' modifiable risk factors prior to surgery.(65) This is called prehabilitation. The rationale behind prehabilitation is that by improving functional capacity and preoperative risk factors, better recovery and a reduction in complications can be achieved. Prehabilitation might partially overcome the current dilemma of exposing frail advanced rectal cancer patients to potentially life-threatening complications.

Multimodal prehabilitation is based on five principles:

1. Supervised training programme on strength and endurance
2. Optimisation of nutritional status and supplementation of protein and vitamins
3. Cessation of smoking and lifestyle changes
4. Mental support and optimal patient information
5. Patient blood management: correcting preoperative anaemia and hyperglycaemia

Two randomised studies have been performed that investigated the role of prehabilitation in patients who were at high risk of complications, and underwent large abdominal surgery.(66, 67) Barberan-Garcia and colleagues found that patients who participated in a prehabilitation programme were less likely to have postoperative complications (31% versus 62%, p=0.001), and stayed in the hospital shorter (8 days vs 13 days, p=0.078).(66) A Dutch trial conducted by van Berkel et al., also found a significant difference in complications rates in favour of the prehabilitation group (43% versus 72%, p=0.001).(67) The results of a large international randomised trial investigating the effects of a multimodal prehabilitation programme in patients with colorectal cancer in the Netherlands are underway.(68)

Despite the emerging positive evidence from randomised controlled trials, there is still a lack of studies investigating prehabilitation programmes in daily practice. It is very conceivable that patients participating in prehabilitation trials, are those who are open for lifestyle interventions to begin with. This could lead to a considerable selection bias, and the expected positive results of prehabilitation might be disappointing when implemented in daily care. In addition, the beneficial effects of prehabilitation have mainly been established in selected patients who did not receive neoadjuvant treatment. Patients who are treated with longer and more intensified preoperative treatment regimens, such as long-course chemoradiation for advanced rectal cancer, are underreported in trials. During long-course chemoradiation, patients have the tendency to decrease their daily activities with a negative effect on physical and mental fitness.(69) Patient who deteriorate during neoadjuvant treatment, however, are more at risk for perioperative complications and have impaired disease-free survival.(70, 71) These adverse outcomes can possibly be prevented with prehabilitation, and the feasibility of multimodal prehabilitation in advanced rectal cancer patients is an interesting topic for future research.

Lack of compliance is another difficulty that hinders the implementation of prehabilitation programmes in practice, and is particularly relevant for rectal cancer patients undergoing long-course chemoradiation. Recent data from a tertiary-care hospital reveal that in real-

life practice, the completion rate of a supervised exercise training prehabilitation programme is only 34%.(72) Compliance of prehabilitation programmes in patients undergoing neoadjuvant treatment should be evaluated further, and methods to increase this compliance need to be explored. These could for example be at-home training or additional support with smartphone applications. Better understanding of hindering factors to comply will be valuable for further implementation of prehabilitation programmes, and this eventually will improve the clinical utility of prehabilitation in daily practice. This is beneficial especially for frail rectal cancer patients who undergo chemoradiation and major surgery, as these patients are likely to gain most from preoperative optimisation.

PART III – MANAGEMENT OF STAGE IV RECTAL CANCER

Treatment of stage IV rectal cancer remains a challenge. For long, management of patients with distant metastases had only the goal to prolong life, but not cure. Since the mid-1990s, more patients with resectable metastases are treated with surgery with the potential to achieve long-term survival, or even disease-free survival.(73) Moreover, by the means of modern chemotherapeutic agents, ablation and radiation methods, minimal invasive strategies for metastases are now available, enabling curative intended treatment for more patients. With these advances, selected patients, especially those who have limited lung- or liver metastases, have increasingly better chances of favourable outcomes.

Local treatment of stage IV disease

Local therapy is usually the treatment of choice for patients with limited resectable colorectal lung- or liver metastases. However, whether the resection of metastases actually improves survival is still uncertain, as current evidence is mainly based on non-randomised observational data.(73) Large case series and population studies in colorectal cancer patients usually observe an advantage in survival after local treatment,(74, 75) but these outcomes may also just be the result of the selection of patients with more favourable disease.(76) Three randomised controlled trials provide at least some information on the additional value of local treatment of metastases.(77-79)

First, the phase II CLOCC trial investigated the use of local treatment in addition to systemic treatment in colorectal cancer patients with unresectable liver metastases, and found prolonged survival (HR 0.58, 95% CI 0.38 – 0.88) in patients who were treated in the intervention arm.(77) Second, the SABR-COMET phase II trial also demonstrated better progression-free and overall survival in patients with limited metastases who were treated with SBRT, compared to patients receiving palliative treatment alone.(80) An important

limitation of both the CLOCC and the SABR-COMET trials, is that an important imbalance of baseline characteristics was found (e.g., the number of metastases and primary cancer type), favouring the intervention arms. Most recently, the PulMiCC trial compared the survival of 46 patients who underwent surgery versus 47 patients who underwent active surveillance as treatment for colorectal lung metastases.(79) Although full accrual was not reached due to poor recruitment, this study revealed a surprisingly well 5-year survival of 30% (15-46%) in patients in the active surveillance group, which was considerably higher than 5-year survival of <5% that was generally assumed.

The results of the available literature combined, suggest that local treatment might have a positive influence on oncological outcomes of selected patients with metastasised colorectal cancer. Moreover, better local control can enable a delay in the initiation of systematic (palliative) chemotherapy, thus postponing the toxic side effects of these treatment regimes. On the other hand, local treatment therapies are associated with morbidity and costs as well. The potential harms and benefits of local treatment for patients with stage IV rectal cancer should therefore be discussed in a multidisciplinary team, but also with patients for adequate expectation management.

Synchronous liver metastases

In this thesis, we especially focus on LARC patients with synchronous liver metastases. Synchronous liver metastases are present in approximately 15% of rectal cancer patients, half of them being eligible for curative treatment.(81, 82) What should be the optimal treatment strategy for possible curation is a subject to debate. In the Netherlands, different strategies are used to treat patients with primary rectal cancer in combination with synchronous liver metastases; some advocate for a scheme that starts with systemic chemotherapy,(83) whilst others think that initiating treatment with radiotherapy on the rectum is optimal.(84) Both schemes have advantages and disadvantages. In this thesis, we found that patients with LARC and synchronous liver metastases treated with the liver first approach (LFA; systemic chemotherapy, local treatment of liver metastases and subsequent (chemo)radiotherapy and rectal surgery) and M1 (M1; short-course pelvic radiotherapy (5x5Gy), systemic chemotherapy and subsequent local treatment of tumour sites) have similar oncological outcomes. Interestingly enough, pathological complete response rates were only 9-12% after extensive neoadjuvant strategies consisting of both systemic treatment and local radiation in both schemes. This indicates that patients with LARC and liver metastases might have different tumour biology compared to the lower stages of rectal cancer without liver metastases. In lower staged patients, pathological

response rates are generally around 30% after combination treatment of chemotherapy and radiation therapy.(8, 85)

Lung metastases

After the liver, the lung is the second most common site of rectal cancer metastases. Synchronous lung metastases occur in 5% of all patients with rectal cancer, and about 7% will develop lung metastases after curative treatment. (86, 87) Lung metastases are usually an indication of advanced systemic disease, and are most commonly treated with systemic therapy. In selected patients with limited disease however, surgical metastasectomy can be considered as a potentially curative treatment option, in which 5-year survival rates of more than 50% can be achieved.(88, 89) Other – less invasive – local therapy modalities including stereotactic body radiotherapy (SBRT) and thermal ablation are also used as possible treatment options to achieve local control.(90) Currently, it is still unclear which patients with lung metastases, if any, benefit most from specific treatment strategies.(91, 92) In real-life practice, patients' and treating physicians' preference seems to be the leading factor in the decision for either treatment modality. In a retrospective cohort study included in this thesis, we investigated the role of different local treatment modalities in patients with limited pulmonary disease. In addition, the results were compared with patients treated with chemotherapy alone. Pulmonary recurrence rates and overall survival rates were comparable in patients treated with surgery, thermal ablation, or SABR, indicating that the choice of local treatment for limited lung metastases hardly affects outcomes.

Aspefic lung nodules

Aspecfic lung nodules are usually not considered clinically relevant in the treatment of the primary tumour due to the low a-priori risk of being malignant.(93) In this thesis, the role of indeterminate lung nodules (ILN) in patients with LRRC was investigated, and we found that ILN did not affect outcomes; patients with LRRC and ILN did not even have an increased risk for lung metastases or impaired disease-free survival. The decision for curative or palliative treatment was hardly ever based on the presence of ILN, and no difference was found in overall survival. Two systematic reviews on the clinical relevance of ILN in colorectal cancer had the same result, and concluded that the presence of ILN should not influence management strategies.(94, 95)

FUTURE PERSPECTIVES

Management of advanced rectal cancer is constantly evolving, and will probably do so in the coming years. In particular, personalised medicine based on certain risk profiles is gaining more popularity, and future research will likely focus on better stratification methods for optimal management of patients with rectal cancer. Some of these methods are already described in this thesis, for example the use of the MEND-it criteria as selection method for the administration of total neoadjuvant treatment. Other innovative technologic and therapeutic advancements that might contribute to the search of better tailored treatment strategies are currently on their way making it into clinical practice.

Immune checkpoint inhibitors have been on the rise for some years now, and will probably have an important role in improving organ preservation rates in rectal cancer patients with mismatch repair deficiency (MMR-D) in the future. In the setting of metastatic colorectal cancer, programmed death 1 (PD-1) inhibitors such as pembrolizumab and nivolumab are already established as viable first-line treatment options.(96, 97) In addition, immunotherapy administered prior to surgery in early-stage colon cancer has shown to be highly effective for tumour downstaging, especially in MMR-D tumours.(98) In locally advanced rectal cancer, data is more scarce since MMR-D is present in a much smaller proportion as compared to colon cancer (in rectal cancer, MMR-D is present in about 5% of patients).(99, 100) Nevertheless, a recent phase 2 study showed that 12 patients with locally advanced rectal cancer and MMR-D who were treated with PD-1, all had a sustained complete response.(101) At the moment of publication, all patients had a follow-up length of 6 months as a minimum, and most importantly, chemoradiotherapy and surgery was omitted in all patients. Although these results are very hopeful, long-term outcomes of this study are necessary to assess whether PD-1 blockade therapy can achieve sustained complete responses in the long-term. Even more importantly, the advent of PD-1 inhibitors might pave the way for other effective mutation-specific- or immunomodulatory treatment options for rectal cancer.

Another promising emergence in clinical oncology is the use of artificial intelligence, and more specifically deep-learning. Deep-learning models have the ability to predict outcomes based on previously “learned” correlations and connections, and become more accurate as they process more data. The usefulness of deep-learning in oncology has already been proved in various cancer types.(102, 103) In the fields of rectal cancer, many opportunities are yet to be explored and include, amongst others, the accurate determination of prognosis, improving diagnosis accuracy, and predicting treatment responses.

For example, deep-learning could be of interest in better understanding and predicting the nature of aspecific lesions encountered on diagnostic imaging. As discussed in Chapter 14 of this thesis, indeterminate lung nodules are commonly encountered during the diagnostic work-up of rectal cancer. In multidisciplinary team meetings, these nodules form a diagnostic dilemma, as radiologists often have difficulties in describing these lesions as either benign or malignant. In addition, the impact on prognosis is uncertain, as lung metastases seem to behave differently as compared to liver metastases, with a more indolent disease activity.(104) Currently, it is still unclear which patients with lung nodules benefit most from specific treatment strategies such as active surveillance, local pulmonary treatment or systemic therapy.(91, 92) Consequently, deep-learning on CT images in order to better predict the nature and outcomes of these nodules has the potential to enrich the armamentarium of rectal cancer management. Several studies have shown promising results regarding the use of artificial intelligence for the detection and malignancy prediction of pulmonary lesions on imaging.(105, 106) It is very conceivable that in the future, computer-aided diagnosis (CAD) will be used in clinical practice, and is already in use in some centres for the detection of pulmonary metastases on chest radiography.(107)

Deep-learning models have been proven to be useful in other diagnostic domains as well. For example, deep-learning models applied to whole-slide images of resection specimens already outperform current clinical staging factors in colorectal cancer prognosis.(108) Furthermore, a small study has demonstrated that deep-learning is able to predict neoadjuvant treatment response on pre-treatment biopsies.(109) Accurate pre-treatment prediction of complete response to chemoradiation would provide valuable insights into multiple aspects. First, it would provide patients with better insight into their treatment course and likelihood of organ and function preservation. Second, the pre-treatment identification of poor responders would allow future personalised treatment by the adaptation of currently investigated alternative preoperative regimens such as total neoadjuvant treatment. Third, histology-based predictions after clinical complete response could even further stratify patients in those who will experience local regrowth and those who will achieve a sustained complete response. This enables caregivers and patients the opportunity to adhere to personalised treatment and surveillance strategies, based on the risk for local regrowth. Further evaluation of deep-learning methods to predict (neoadjuvant) treatment response is warranted.

In short, the rapid technological advances and emerging evidence of accurately predicting deep-learning models are currently paving the way for a smarter use of healthcare, and are likely to improve outcomes of rectal cancer patients in the near future.

CONCLUSIONS

The aim of this thesis was to investigate the multimodality treatment of the more advanced stages of rectal cancer, and to validate commonly used as well as novel treatment methods in real-life patients. In conclusion, we found that the addition of induction chemotherapy in LRRC seems to be safe, and results in good outcomes in selected patients. Treatment morbidity of advanced rectal cancer is considerable, and especially forms a problem in patients who are older, have a low skeletal muscle index and have poor nutrition status. These patients tend to have more severe complications during their treatment course, and should be followed-up with care.

More local options are now available for the treatment of stage IV rectal cancer, but whether the resection of lung- or liver metastases actually improves survival is uncertain. For lung metastases, local control can be achieved by surgery, thermal ablation and SBRT, without apparent negative consequences for opting for each modality. Management options for stage IV rectal cancer should be discussed in a multidisciplinary team. Individual patients' risk factors and preferences should also be taken into account when composing a treatment plan for these patients. The current impetus to individualise treatment will further improve the now established multidisciplinary management of advanced rectal cancer. Future research identifying novel (digital) biomarkers as well as optimal 'tailored' treatment approaches should therefore continue.

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CHAPTER 15

Summary

Rectal cancer is a worldwide cause of cancer-related mortality with increasing incidence.(1) Although marked improvements have been made in rectal cancer management, which have significantly improved oncologic outcomes, the disease burden remains high up until today. A main contributor to this burden is so-called *advanced rectal cancer*. Advanced rectal cancer comprises locally advanced rectal cancer, rectal cancer that recurs in the pelvic area, and stage IV rectal cancer. Curative treatment of these diseases is a major challenge, and may endanger the balance between acceptable oncological- and functional outcomes. Novel treatment strategies for patients with advanced disease, such as chemoradiation and pelvic exenteration surgery, have improved oncological survival rates, but come with a price. Treatment-related morbidity and even mortality, as well significant loss of quality and standard of living, are the devastating consequences that patients have to accept for a chance to live. The objective of this thesis is to provide the multimodality management of rectal cancer with novel insights and innovative treatment methods, and focuses on patients with rectal cancer that is beyond the margins of the disease.

PART I: ONCOLOGICAL OUTCOMES OF ADVANCED RECTAL CANCER

The principal aim of rectal cancer management is to achieve long-term oncological survival, without overtreating patients who do not benefit from aggressive treatment. In Chapter 2, it was demonstrated that resection margin is an important factor for survival after surgery for locally recurrent rectal cancer (LRRC). In addition, the overall survival of patients who underwent a macroscopically irradical resection was worse compared to patients who were treated non-surgically with alternatives such as radiotherapy, chemotherapy and best supportive care. In Chapter 3, two different methods to administer intraoperative radiation therapy (IORT) were investigated, being IOERT and HDR-IORT. HDR-IORT was associated with a lower local recurrence rate after R1 resection, but more postoperative complications were observed as well. The role of induction chemotherapy in patients with LRRC was investigated in Chapter 4. No differences in complete response rate were found when induction chemotherapy was added to the current standard of care preoperative regimen consisting of chemoradiation.

PART II: MORBIDITY IN ADVANCED RECTAL CANCER

Morbidity during and after treatment of advanced rectal cancer remains a problem, and is associated with dysfunction of the intestinal tract, urinary system and reproductive organs. These can have devastating consequences for patients' quality of life.(2, 3) In Chapter 5, the impact on quality of life after anterior pelvic exenteration is described. We reviewed

common complications that occur after this major procedure, and found that urinary diversion complications, such as urinary fistula and pyelonephritis, are commonly encountered. Quality of life is decreased right after surgery, but slowly increases in the long-term. In Chapter 6 and Chapter 7, we found that sarcopenia, malnutrition, female sex, and age were risk factors for major complications in patients who underwent chemoradiation and pelvic exenterative surgery for advanced rectal cancer. Modifiable risk factors should therefore be addressed in the preoperative setting, and these chapters stimulate further research on prehabilitation in this specific population. Other ways to prevent complications in rectal cancer patients have been investiaged in this part as well. For example, it is commonly thought that the use of an omentoplasty to fill up the pelvic space after an abdominal perineal resection could reduce perineal complications. However, we demonstrated in Chapter 8 in a large cohort that omentoplasty did not reduce pelviperineal complications, and that patients undergoing omentoplasty had longer nasogastric tube duration and hospital stay.

Part III: MANAGEMENT OF STAGE IV DISEASE

Patients with stage IV rectal cancer are a heterogeneous population. For these patients, tailored treatment established in an experienced multidisciplinary team (MDT), is warranted. Curative treatment options are possible in some cases, but are usually associated with high toxicity and invasive interventions. In addition, stage IV rectal cancer patients not only have a wide variation in disease load and biological behaviour, tolerance for treatment and patients' physical condition also play a key role in choosing the most appropriate treatment strategy. In Chapter 9, two accepted treatment schedules for patients with potentially curable locally advanced rectal cancer and synchronous liver metastases were compared. Overall survival and progression-free survival were similar after either treatment. Also, complete response rates and local recurrence rates were comparable. Lung metastases often require different treatment strategies, as these have a more indolent disease behaviour and seldom lead to lethal consequences. In practice, lung metastases are treated with surgery, thermal ablation, stereotactic radiotherapy, and systemic therapy. In Chapter 10, we demonstrated that both overall survival and progression-free survival after treatment with each of these modalities are similar. Therefore, patients' and physicians' preference could play an important role in choosing one of these modalities. The impact of indeterminate lung nodules (Chapter 11) and distant metastases (Chapter 12) on long-term outcomes in surgically treated patient with LRRC is described in the last chapters of this thesis. Especially, patients with synchronous metastases diagnosed with their local recurrence have poor prognosis. On the other hand, selected LRRC patients with indeterminate lung nodules or a history of metastases have

similar outcomes compared to LRRC without (a history of) metastases. Finally, in Chapter 13, the role of postoperative circulating tumour DNA (ctDNA) as novel biomarker for rectal cancer was investigated in a systematic review. The presence of ctDNA after surgery was a strong predictor for both recurrence and survival in patients with locally advanced rectal cancer.

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CHAPTER 16

Dutch summary

Het rectumcarcinoom is een belangrijke oorzaak van de wereldwijde kanker-gerelateerde sterfte, en heeft een stijgende incidentie.(1) In 2020, werden er in Nederland ruim 4000 patiënten gediagnosticeerd met een rectumcarcinoom.(2) Gelukkig is de behandeling van het rectumcarcinoom de afgelopen jaren flink verbeterd. Toch blijft de ziektelast van rectumcarcinoom hoog. Dit is met name het geval bij rectumtumoren die de anatomische grenzen van de darm overschrijden, te weten: het lokaal gevorderd rectumcarcinoom, het lokaal terugkerend rectumcarcinoom en het stadium IV rectumcarcinoom. Voor patiënten met deze ziekten is het behalen van genezing nog steeds een grote uitdaging. Door de komst van nieuwe celdodende therapieën en chirurgische technieken komen behandelaren soms voor netelige keuzen te staan; namelijk die van streven naar goede oncologische overleving of behoud van kwaliteit van leven. Het doel van dit proefschrift is om de huidige zorg van het rectumcarcinoom te verbeteren middels nieuwe inzichten en behandelstrategieën, waarbij de ziekte met een vergevorderd stadium op de voorgrond staat.

DEEL 1: ONCOLOGISCHE UITKOMSTEN VAN HET UITGEBREID RECTUMCARCINOOM

Het voornamelijke doel van de behandeling van het rectumcarcinoom is om langdurige oncologische overleving te behalen, zonder patiënten onnodig zwaar te behandelen. In Hoofdstuk 2 van dit proefschrift werd een grote groep patiënten met een lokaal recidief rectumcarcinoom geanalyseerd die zowel chirurgisch als niet-chirurgisch werden behandeld. Een chirurgische behandeling waarbij een radicale resectie werd gehaald was de belangrijkste voorspeller voor een gunstige prognose. Patiënten die tijdens of na chirurgie een macroscopisch irradicale resectie bleken te hebben, hadden een vergelijkbare overleving met patiënten die behandeld werden met niet-chirurgische opties, zoals bestraling en/of chemotherapie. In hoofdstuk 3 werden twee veelgebruikte methoden om intra-operatieve radiotherapie toe te dienen onderzocht. In dit retrospectieve cohortonderzoek werd bij patiënten met een krappe (< 2mm) of microscopisch irradicale resectiemarge, lineaire versneller therapie (IOERT) vergeleken met hoge dosis-brachytherapie (HDR-IORT). Uit de resultaten bleek dat de patiënten die HDR-IORT hadden ondergaan, een langere recidiefvrije periode hadden, maar ook meer postoperatieve complicaties hadden, vergeleken met de patiënten die IOERT kregen. Het toevoegen van inductiechemotherapie bij de standaard voorbehandeling met chemoradiotherapie werd onderzocht bij patiënten met een lokaal recidief rectumcarcinoom in Hoofdstuk 4. Hoewel er een klein verschil leek te zijn in het aantal complete responses in de patiëntengroep die werd behandeld met inductiechemotherapie, was er géén duidelijk verschil in oncologische uitkomsten zoals overleving.

DEEL 2: MORBIDITEIT VAN HET UITGEBREID RECTUMCARCINOOM

Morbiditeit tijdens en na de behandeling van het uitgebreid rectumcarcinoom is een belangrijk probleem. Bepaalde complicaties van deze behandeling kunnen namelijk leiden tot ernstige disfunctie van het spijsverteringskanaal, urinesysteem en reproductieve organen. Schade aan deze orgaansystemen kan ernstige consequenties hebben op de kwaliteit van leven van patiënten.(3, 4) In Hoofdstuk 5 beschrijven we in een boekhoofdstuk in detail de chirurgische technieken, complicaties en de impact op kwaliteit van leven van een anterieure bekkenexenteratie, een ingreep die regelmatig wordt toegepast bij het uitgebreid rectumcarcinoom. In Hoofdstuk 6 en Hoofdstuk 7 onderzochten we risicofactoren voor het krijgen van ernstige complicaties bij de behandeling van het uitgebreid rectumcarcinoom. Hieruit bleek dat een lage spiermassa, een slechte voedingstoestand, vrouwelijk geslacht en leeftijd waren geassocieerd met belangrijke complicaties zoals ernstige diarree tijdens chemoradiatie en chirurgische complicaties na de operatie. Tot slot bespreken we in Hoofdstuk 8 de waarde van de omentumplastiek, een veelgebruikte chirurgische techniek die wordt toegepast om de kans op abcessen in het kleine bekken te verminderen. Uit de resultaten van ons retrospectieve cohortonderzoek bleek dat patiënten die een omentumplastiek ondergingen géén verminderde kans bleken te hebben op abcessen in het kleine bekken, ondanks correctie voor externe factoren. Wel hadden deze patiënten een langere ziekenhuisopname, waarvan een verlengde duur van de neusmaagsonde waarschijnlijk de oorzaak was.

DEEL 3: BEHANDELING VAN STADIUM IV RECTUMCARCINOOM

Het behalen van genezing bij patiënten met stadium IV rectumcarcinoom is vaak een uitdagende opgave, en helaas niet altijd mogelijk. In dit proefschrift onderzochten we verschillende behandelingen voor patiënten met stadium IV rectumcarcinoom, en beschreven we de invloed van afstandsmetastasen bij chirurgisch behandelde patiënten met een lokaal recidief rectumcarcinoom. In Hoofdstuk 9 werden twee verschillende behandelschema's (het zogenaamde "liver-first-schema" en het "M1-schema") voor patiënten met lokaal gevorderd rectumcarcinoom en levermetastasen retrospectief vergeleken. Uit de resultaten bleek dat gelijkwaardige oncologische uitkomsten werden gevonden bij het toepassen van beide schema's in deze populatie. In Hoofdstuk 10 werden verschillende behandelingen voor patiënten met beperkte longmetastasering geëvalueerd, en ook hier werden gelijke uitkomsten gevonden na behandeling met metastectomie, bestraling, ablatie, en chemotherapie. In de volgende hoofdstukken van dit proefschrift,

werd de impact van atypische longafwijkingen (Hoofdstuk 11) en afstandsmetastasen (Hoofdstuk 12) onderzocht bij patiënten die chirurgisch zijn behandeld voor een lokaal recidief rectumcarcinoom. Hieruit bleek dat patiënten met synchrone metastasen bij het lokaal recidief rectumcarcinoom een slechte prognose hadden, terwijl patiënten met atypische longafwijkingen of metastasen in de voorgeschiedenis vergelijkbare oncologische uitkomsten hadden als patiënten zonder metastasen. Het laatste hoofdstuk (Hoofdstuk 13) is een literatuuronderzoek naar de rol van postoperatief detecteerbaar circulerend tumor DNA (ctDNA) als mogelijke nieuwe biomarker voor patiënten die zijn geopereerd voor een rectumcarcinoom. Postoperatief detecteerbaar ctDNA bleek in een meta-analyse een sterke voorspeller te zijn voor het krijgen van een recidief na curatieve behandeling. Daarnaast hadden patiënten met postoperatief detecteerbaar ctDNA een slechtere overleving.

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APPENDICES

LIST OF PUBLICATIONS

IN THIS THESIS

J.A.W. Hagemans, **J.M. van Rees**, W J. Alberda, J. Rothbarth, J.J.M.E. Nuyttens, E. van Meerten, C. Verhoef, J.W.A. Burger. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. European Journey of Surgical Oncology.

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PHD PORTFOLIO

Name PhD student: J.M. van Rees

Erasmus MC Department: Surgical Oncology

Research Courses	**Year**	**EC**
Research integrity course	2020	0.3
Erasmus MC - eBROK	2020	1.5
ICH - Good Clinical Practice (GCP) E6 (R2)	2020	1.0
NIHES Biostatistics I [CK020]	2021	4.0
NIHES Biostatistics II [CK030]	2022	4.5
Other Courses		
Young Esser Masterclass – Basics of Hand & Wrist Injuries	2022	2.0
Advanced Trauma Life Support	2022	2.0
Oral Presentations		
Oral Presentation - OGC Research Meeting *KWF proposal REACT study*	2021	1.0
Oral Presentation - OGC Research Meeting *Prehabilitation for locally advanced rectal cancer and oesophageal cancer.*	2021	1.0
Oral Presentation – SJOCO *Artificial intelligence in medicine: methods, applications and implementation*	2022	1.0
DCCG Researchmiddag Werkgroep Systemische therapie *Adjuvant chemotherapy for prevention of recurrence in patients with detectable ctDNA after surgery in high-risk rectal cancer.*	2022	1.0
DCCG Researchmiddag Werkgroep Primaire tumorbehandeling *Adjuvant chemotherapy for prevention of recurrence in patients with detectable ctDNA after surgery in high-risk rectal cancer.*	2022	1.0
Expert Panel - Tweede Prehabilitatie Congres Eindhoven *Prehabilitatie voor alle patiënten? Middagsessie 2e prehabilitatiecongres - Rectumcarcinoom*	2022	2.0
Oral Presentation - ESSO41 *Treatment of colorectal lung metastases: a retrospective analysis*	2022	2.0
Oral Presentation - ESSO41 *Adjuvant chemotherapy for prevention of recurrence in patients with detectable ctDNA after surgery in high-risk rectal cancer.*	2022	2.0
Speaker - Patient organisation meeting *Deelname rondetafelgesprek publieksbijeenkomst Stichting Darmkanker*	2022	2.0
Oral Presentation – Chirurgendagen 2023 *Lokaal recidief rectumcarcinoom en metastasen op afstand: kans op curatie?*	2023	1.0
Conference Posters		
Poster Presentation - ESSO40 *The optimal treatment sequence for patients with stage IV rectal cancer and limited liver metastases: a nationwide comparison of two strategies.*	2022	1.0
Poster Presentation - ESSO41 *Omentoplasty in patients undergoing abdominoperineal resection after long-course chemoradiation for locally advanced and locally recurrent rectal cancer.*	2022	1.0

Conference Posters (continued)		
Poster Presentation - Tweede Prehabilitatie Congres Eindhoven *Prehabilitatie bij oncologische patiënten die intensieve voorbehandeling ondergaan: een multicenter protocol.*	2022	1.0
Conference abstracts		
Abstract Publication - NVvH Chirurgendagen 2020 *Intraoperatieve elektronenstraling versus intraoperatieve brachytherapie na een irradicale resectie van lokaal voortgeschreden en lokaal recidiverend rectum carcinoom*	2020	1.0
Abstract Publication - NVvH Chirurgendagen 2020 *De optimale behandelsequentie voor patiënten met een lokaal uitgebreid rectumcarcinoom en synchrone levermetastasering: een vergelijking van twee schema's in Nederland.*	2020	1.0
Teaching and Supervision		
Master student - Eva Visser	2020	2.0
Master student - Paul Harmsen	2021	2.0
Education for master students: colorectal cancer	2021	1.0
Grants and Awards		
Nederlandse Organisatie voor Wetenschappelijk Onderzoek "Incentive Grants for Women in STEM". *(co-author)* *Deep-learning applied to medical science: Intelligent prediction of response to rectal cancer treatment.*	2021	-
KWF CALL 2022 - Thema Smart Measurement Technology. *Predicting outcomes of lung nodules in colorectal cancer patients with smart measurement technology.*	2022	-
Interne Subsidieronde Erasmus MC "Nog efficiënter gebruik schaarse faciliteiten tijdens pandemieën" *Multimodale prehabilitatie bij patiënten met rectum- en slokdarmcarcinoom ter reductie van klinische ligdagen op de IC en verpleegafdeling na de operatie.*	2022	-
ESSO41 Best Clinical Trial Award. *Adjuvant chemotherapy for prevention of recurrence in patients with detectable ctDNA after surgery in high-risk rectal cancer.*	2022	-
Other		
Peer review of research articles in several scientific journals	2020-2022	4.0
Total EC		44.3

DANKWOORD

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ABOUT THE AUTHOR

Jan Maarten van Rees was born on April the 30th 1995 in Schiedam, the Netherlands. After graduation, he started medical school at the Medical Faculty of the Erasmus University Rotterdam.

Throughout his studies, Jan was especially attracted to (tropical) emergency- and surgical disciplines and did internships at the Emergency Department of Groote Schuur-Hospitaal in Kaapstad, South Africa and the Emergency Department of Acadamic Hosptial Paramaribo, Suriname (dr. van Kanten). His final clinical internship was at the Department of Surgery at IJsselland Ziekenhuis (dr. van Ruler), whereafter he decided to pursue his career towards surgery.

His interest in scientific research developed in his Bachelors, where he started doing observational research at the Department of Neurology. After his internship at the Deparment of Surgical Oncology at Daniel den Hoed, or "de Daniel", he decided to change research directions and applied as a student researcher at the Deparment of Surgical Oncology. Here, he enjoyed doing rectal cancer research under the supervision of prof. dr. C. Verhoef, whilst finishing his internships. After completing his Masters, he got the opportunity to extend his research at the Deparment of Surgical Oncology and started working as a full-time PhD-candidate for two years. During his research, he was keen to practice medicine and did out of office shifts at the general practitioner's centre of Maasstad Ziekenhuis Rotterdam.

In December 2022, he started working at Ikazia Ziekenhuis Rotterdam as a surgical resident not in training (ANIOS), where he is currently practicing his skills as a clinician under the supervision of dr. W.J. Vles and dr. P.T. den Hoed. Jan happily lives with his girlfriend Lissa Wullaert in Kralingen, Rotterdam.

A