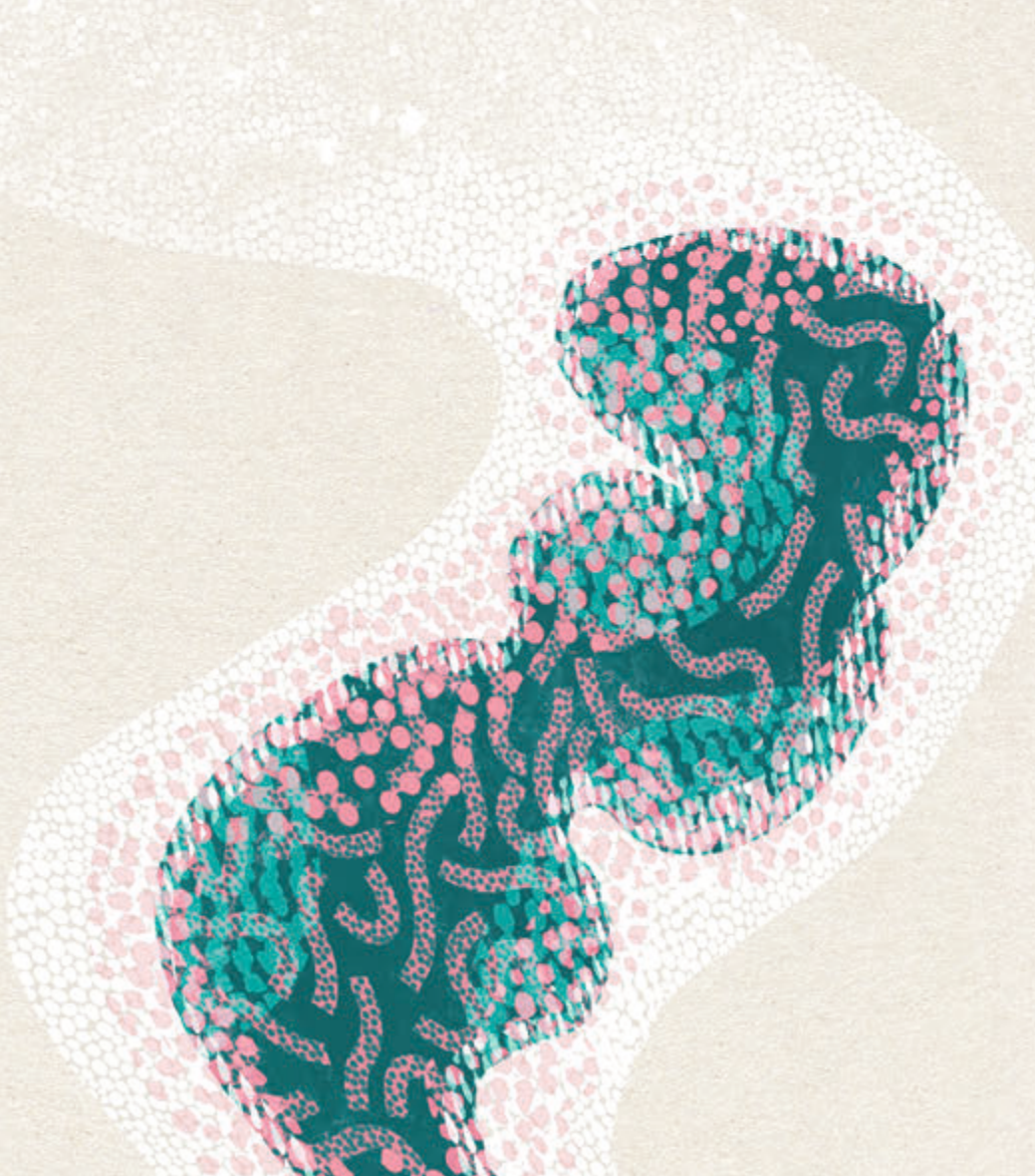
Watch-and-Wait in Rectal Cancer

WATCH-AND-WAIT IN RECTAL CANCER

response assessment and outcome

Marit E. van der Sande



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Watch-and-Wait in Rectal Cancer: response assessment and outcome

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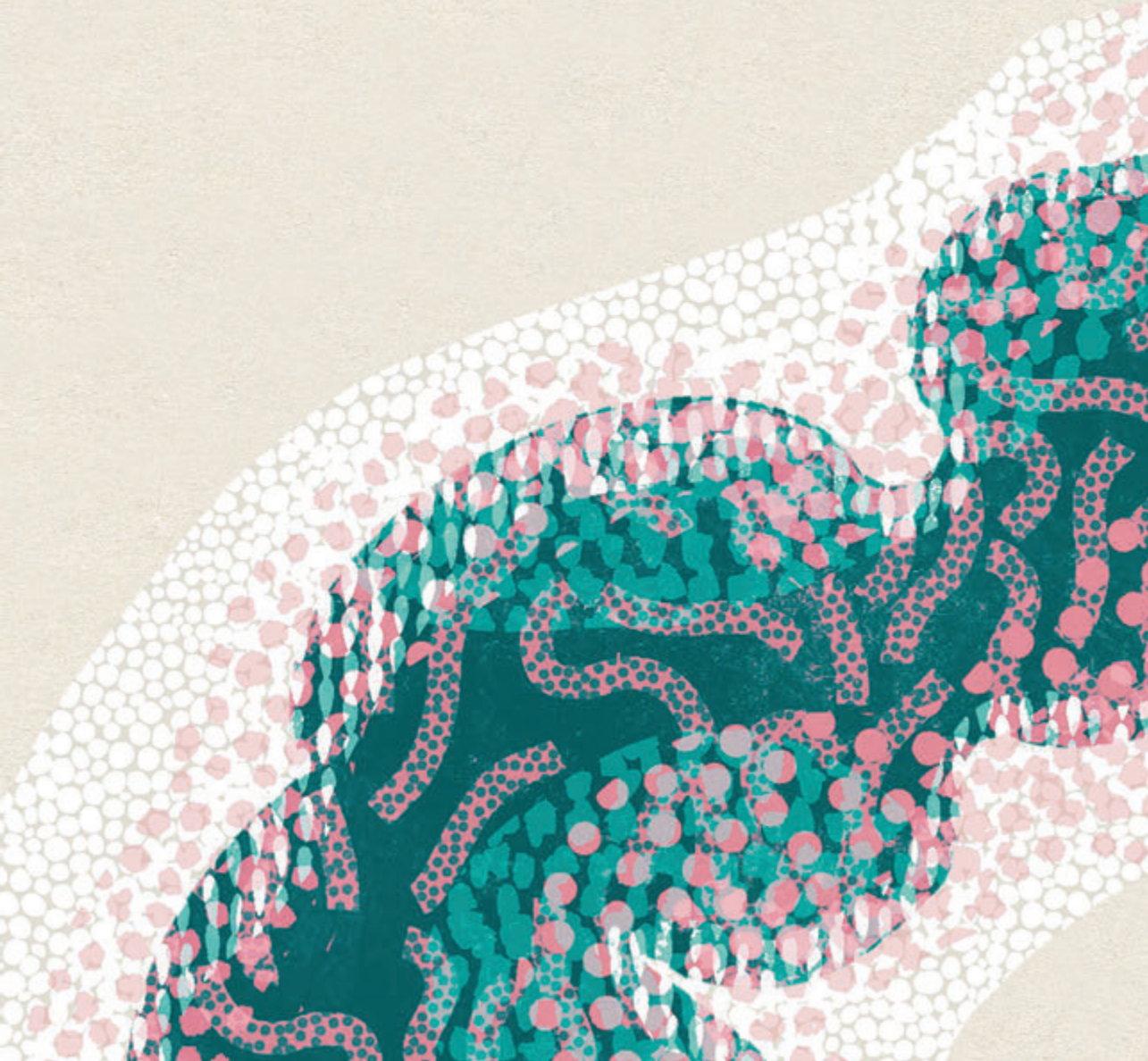

1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Every year approximately 14 000 people in the Netherlands are diagnosed with colorectal cancer. In one third of these people, the tumour is located in the rectum. The past decades rectal cancer treatment has been subject to many changes. One of the first major advances was the refinement of the surgical technique with standardized Total Mesorectal Excision (TME)[1], followed by improved staging, risk stratification and treatment planning with Magnetic Resonance Imaging (MRI), and the use of radiotherapy and chemoradiotherapy in a neoadjuvant setting[2-4]. All have contributed to substantial improvement in local control and survival in rectal cancer patients. Where local recurrence used to be the Achilles' heel after surgical treatment of rectal cancer with an incidence commonly reported up to 20–30%, rates are currently down to 5%[5, 6].

Unfortunately, this improved oncological outcome comes at a cost. TME, now the cornerstone in rectal cancer treatment, is associated with significant perioperative morbidity and mortality. The most common post-operative complications include infection, abscesses, postoperative ileus and anastomotic leakage[7, 8]. The overall mortality of rectal cancer surgery is around 2–3%, but mortality rates in patients over 80 years of age can increase up to 10–15%[9]. In the long-term, patients may also experience urinary, sexual and bowel dysfunction after TME, and may require a temporary or permanent stoma[10].

The increased awareness of both the short- and long-term morbidity of TME, along with the explicit wish of many patients to avoid a permanent stoma, forms the basis for an increasing interest in organ preservation alternatives to TME.

Risk stratification and standard treatment

Patients with rectal cancer are stratified into different risk profiles for local recurrence based on high resolution preoperative MRI[4]. Tumours can be identified as 'low risk', 'intermediate risk' or 'high risk' tumours, and these risk profiles guide treatment decisions. Low risk rectal cancer is treated with TME only. Current Dutch guidelines recommend preoperative short-course radiotherapy (25 Gy in 5 fractions) followed by TME as the first choice of treatment for patients with an intermediate risk tumour [Oncoline: National Guideline Colorectalcarcinoma 2019 (accessed July 13th, 2020)]. For patients with 'locally advanced' or 'high risk' rectal cancer, chemoradiotherapy (CRT) followed by surgery is the first choice of treatment. CRT regimens usually consist of 45-50 Gy in fractions of 1.8-2.0 Gy, combined with oral capecitabine 825-1000mg/m2 bid. Neoadjuvant CRT in locally advanced rectal cancer may lead to

downsizing and downstaging and thereby increase the resectability of the tumour, and has shown to provide better local control [3].

A paradigm shift

Patients with locally advanced rectal cancer who are treated with neoadjuvant CRT demonstrate a variable degree of response to treatment. While some patients do not show any response to CRT, around 15-20% have a pathologic complete response (pCR): an absence of any viable tumour cells in the resection specimen[11, 12]. Studies have shown that the degree of response to neoadjuvant treatment positively correlates with long-term oncological outcomes[13-15]. Patients with pCR have better local control, fewer distant recurrences and an improved overall survival (OS) compared to patients with no or a partial response. In a large pooled analysis of 14 series (n=3105), 5-year disease-free survival (DFS) was 83% in patients with pCR compared to 66% in non-pCR patients (HR=0.44, p<0.0001)[14]. Because of the excellent prognosis of patients with pCR the additional benefit of a radical resection to the overall and disease-free survival has been questioned in these patients, especially considering the risks that come with a surgical approach. Dr. Habr-Gama and collegues from Sao Paolo were the first to use this concept and proposed a non-operative management in patients with a clinical complete response (cCR). In 2004, they published their pioneering paper in which they followed 71 out of 265 patients with rectal cancer who had a cCR following CRT and were treated by observation alone[16]. Only 2 of the 71 patients had an endorectal recurrence during follow-up. The results also suggested that DFS and OS in patients managed non-operatively were similar to that of patients who had a pCR after surgery. The oncological and surgical community initially responded with skepticism and disbelief after the publication of these results, but soon it kindled the interest in organ preserving strategies in rectal cancer.

Organ preserving strategies in rectal cancer

Different organ preserving strategies have been explored in rectal cancer, including the watch-and-wait strategy for clinical complete responders. The watch-and-wait strategy refers to the non-operative approach described by dr. Habr-Gama et al. in which no immediate surgery is performed in patients with a complete response after neoadjuvant treatment. Patients enter a follow-up program with frequent monitoring aimed at an early detection of residual or recurrent disease, and surgery is performed only after residual or recurrent disease becomes apparent.

For patients with a near clinical complete response, additional strategies such as local excision, brachytherapy or contact radiotherapy have been proposed as an alternative to radical surgery.

Response assessment after chemoradiotherapy

One of the basic principles of organ preservation in rectal cancer is the assessment of tumour response after neoadjuvant treatment and to offer treatment tailored to the response. The gold standard for response assessment is the histological assessment of a resected specimen. However, to preoperatively assess which patients are suitable for organ preservation, a clinical response assessment has to be made. Different modalities can be used for response assessment. Generally, a combination of a physical exam with digital rectal examination (DRE), endoscopy with or without biopsies, and high-resolution imaging is used[17]. T2-weighted magnetic resonance imaging (MRI), positron emission tomography (PET) and endorectal ultrasound (EUS) can all show downsizing of the tumour, but accurate restaging is challenging due to therapy induced fibrosis, edema, inflammation and necrosis[18-20]. The addition of diffusion weighted imaging (DWI) to standard T2-weighted MRI can improve the performance of MRI for tumour restaging, because of a better differentiation between fibrosis and residual tumour[21, 22].

When to perform restaging is an issue of ongoing debate, but evidence suggests that a longer waiting interval may increase the response rate[23, 24]. Most organ preservation protocols schedule restaging after a waiting interval of ± 8 weeks.

There are currently no uniform criteria for a clinical complete response and inclusion criteria vary across organ preservation study protocols. The criteria used in the Netherlands are described in Table 1.

Most restaging strategies aim at minimizing the risk of missing residual tumour, to minimize the risk of undertreating patients. Mainly patients with a typical clinical complete response, that have whitening of the mucosa with teleangiectasia and mucosal integrity on endoscopy combined with absence of luminal and nodal disease on imaging, have been considered candidates for organ preservation[25, 26]. One of the downfalls of this selection strategy is that up to 30% of patients with a pathological complete response are not recognized at assessment due to overestimation of residual tumour[26, 27]. Optimization of the restaging process with regard to timing and criteria of the current restaging modalities may increase the number of patients that could benefit from organ preservation.

Table 1. Criteria for a clinical complete response after neoadjuvant therapy [from Martens et al. JNCI 2016, adjusted].

Modality	Criteria for clinical complete response	Criteria for clinical near-complete response*
DRE	No palpable tumour, when initially palpable with DRE	Small superficial soft irregularity
Endoscopy	No residual tumour and white scar	Small residual erythematous ulcer or irregular wall thickening
MRI	Standard T2-weighted MRI: Substantial downsizing with no residual tumour, or Residual fibrosis, or Residual wall thickening because of edema, and No suspicious lymph nodes Diffusion-weighted MRI: Low signal on high b-value (b800-b1000)	Standard T2-weighted MRI: Obvious downstaging with residual fibrosis but heterogeneous or irregular aspect and signal, or Obvious downstaging of lymph nodes but remaining node(s) 5mm Diffusion-weighted MRI: Small focal area of high signal on high b-value
Histopathology	Negative biopsies from scar (biopsy not mandatory)	Dysplastic changes

*Patients have a clinical near-complete response if they miss only one or two criteria of a clinical complete response but match the other criteria for a clinical near-complete response. DRE = digital rectal exam; MRI = magnetic resonance imaging.

Follow-up in watch-and-wait

Once selected for a watch-and-wait approach, patients enter a stringent follow-up program. Because the current restaging strategies after neoadjuvant treatment lack accuracy, adequate follow-up in patients undergoing watch-and-wait is essential to detect new growth of tumour cells, either at the primary tumour site, called 'local regrowth', or at distant sites. Early detection of local regrowth is important so that salvage surgery can still be performed timely without compromising oncological outcome. No uniform follow-up schedule has been established for a watch-and-wait approach and the follow-up schedules used in the current available studies are based on the opinions of experts rather than being evidence-based. Although there is little information on the value of MRI and endoscopy for the detection of local regrowth, most experts agree to perform surveillance with DRE, endoscopy and MRI[17]. The frequency of the examinations is often high in the first 2 years, with decreasing intensity thereafter. In the Netherlands the current follow-up schedule consists of 3-monthly endoscopy and MRI in the first year and 6-monthly thereafter[28]. Follow-up for distant metastases is performed with computed tomography (CT) imaging of the chest and liver and carcinoembryonic antigen (CEA) according to national guidelines, uniform to the follow-up for patients receiving radical surgery. Frequent

follow-up visits can be a burden for patients, physically and emotionally, so patients should be motivated to adhere to an intensive follow-up program.

Watch-and-wait for clinical complete responders

Following the results of Habr-Gama and colleagues, Maas et al. published their pilot study on 21 clinical complete responders undergoing a watch-and-wait strategy in 2011, showing only one endoluminal local recurrence and a 2-year DFS of 89% and an OS of 100%[14]. A later update on the Dutch series by Martens et al. included 100 patients, of whom 85 underwent a watch-and-wait policy and 15 a local excision, with a median follow-up of 41 months[28]. 3-year local regrowth-free survival, DFS and OS in the watch-and-wait group were 86%, 97% and 96%, respectively. The results from the ONCORE project showed that of the 129 patients managed by watch-and-wait after a clinical complete response to CRT (median follow-up 33 months), 34% had local regrowth and 88% of non-metastatic recurrence could be salvaged[29]. In the propensity score-matched analysis they found no significant difference in 3-year non regrowth-disease free survival (88% vs 78%, p=0.043) and overall survival (96% vs 87%, p=0.024) between the watch-and-wait group and the resection group. Many publications have followed confirming these initial observations, although no evidence exists from randomized controlled trials comparing watch-and-wait to standard treatment with surgery. Recent meta-analyses[30, 31], and the International Watch and Wait Database consortium[17] have provided results with more robust numbers, although they have also shown that the neoadjuvant therapy protocols, imaging strategies and follow-up protocols are very heterogeneous among the published data. Due to the relatively new nature of the strategy, long-term results are still lacking, especially on distant recurrences and outcomes after treatment of regrowth. These events may occur later than the 3 or 5-year follow-up that most studies have reported on.

Challenges in watch-and-wait

The body of evidence supporting the watch-and-wait strategy in complete responders continues to grow and is fueled by the increasing interest from the medical as well as the patient community. Despite the advances that have been made in the last decennium, the watch-and-wait strategy is not yet standard treatment for clinical complete responders. There are challenges that have yet to be faced and aspects of the watch-and-wait strategy that need further refinement. Some of the pressing questions of today regarding organ preservation in rectal cancer include:

- How can we increase the proportion of patients with a complete response to neoadjuvant treatment?
- How can we predict response to neoadjuvant treatment?
- How can we improve response assessment to neoadjuvant treatment?
- How can we best monitor patients undergoing organ preservation?
- What are the patient reported outcomes in patients undergoing organ preservation?
- What is the best treatment for patients who have tumour regrowth after organ preservation?

Aims of this thesis

The main aims of this thesis are: (1) to explore how to better select patients for organ preservation with the tools currently used; (2) to evaluate the quality of life and the functional outcomes in patients undergoing a watch-and-wait approach; (3) to explore the patients' perspective on organ preservation and rectal cancer treatment outcomes; and (4) to evaluate treatment and outcome of local regrowth after a watch-and-wait approach.

Thesis outline

This thesis is subdivided into three parts. **Part I** of this thesis focusses on response assessment after neoadjuvant treatment. In **chapter 2,** a cohort of patients with a pathological complete response after TME that were clinically suspect for residual tumour is presented. We evaluate whether there were distinct features on MRI and endoscopy that led to the false diagnosis of residual tumour at response assessment and will discuss the pitfalls on restaging MRI and endoscopy leading to these 'unrecognized' complete responders. **Chapter 3** assesses the accuracy of endoscopy and biopsies in restaging in a diagnostic study. Specifically, the predictive value of different endoscopic features that can be found at restaging is assessed.

Part II of this thesis focusses on patient reported and functional outcomes in organ preservation**.** In **chapter 4**, the results of a cross-sectional study on the long-term anorectal function, including questionnaires and anorectal manometry, in patients undergoing a watch-and-wait approach are reported. In addition, the influence of the dosimetric parameters of radiotherapy on the anorectal function is investigated. **Chapter 5** presents the results of a prospective multicenter study on the quality of life and functional outcomes, including bowel, urinary and sexual function, in rectal cancer patients undergoing a watch-and-wait approach. Outcomes in patients who are treated with additional local excision or total mesorectal excision after watch-and-wait and patients who do not require subsequent surgery are compared. In addition, the association between clinical parameters and QoL and functional outcome is

analyzed. In **chapter 6,** the results of a choice-based conjoint analysis are reported in which the importance of treatment outcomes for patients and physicians in locally advanced rectal cancer are analyzed and compared.

Part III of this thesis focusses on outcomes after local regrowth in patients undergoing a watch-and-wait approach. **Chapter 7** presents detailed outcome regarding the management, surgical and oncological outcome of patients with local regrowth from two prospective watch-and-wait cohorts.

In the general discussion in **chapter 8**, an overview of the findings presented in this thesis are discussed together with the future research perspectives of organ preservation in rectal cancer.

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PART I

RESPONSE ASSESSMENT AFTER NEOADJUVANT TREATMENT

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2

RESPONSE ASSESSMENT AFTER CHEMORADIOTHERAPY FOR RECTAL CANCER: WHY ARE WE MISSING COMPLETE RESPONSES WITH MRI AND ENDOSCOPY?

ABSTRACT

Purpose

To evaluate what features on restaging MRI and endoscopy led to a false clinical diagnosis of residual tumour in patients with a pathological complete response after rectal cancer surgery.

Methods

Patients with an 'unrecognized' complete response after (chemo)radiotherapy were selected in a tertiary referral centre for rectal cancer treatment. An 'unrecognized' complete response was defined as a clinical incomplete response at MRI and/or endoscopy with a pathological complete response of the primary tumour after surgery. The morphology of tumour bed and lymph nodes were evaluated on post-CRT T2-weighted MRI (T2-MRI) and diffusion weighted imaging (DWI). Post-CRT endoscopy images were evaluated for residual mucosal abnormalities. MRI and endoscopy features were correlated with histopathology.

Results

Thirty-six patients with an unrecognized complete response were included. Mucosal abnormalities were present at restaging endoscopy in 84%, mixed signal intensity on T2-MRI in 53%, an irregular aspect of the former tumour location on T2-MRI in 69%, diffusion restriction on DWI in 51% and suspicious lymph nodes in 25%.

Conclusions

Overstaging of residual tumour after (chemo)radiotherapy in rectal cancer is mainly due to residual mucosal abnormalities at endoscopy, mixed signal intensity or irregular fibrosis at T2-MRI, diffusion restriction at DWI and residual suspicious lymph nodes. Presence of these features is not definitely associated with residual tumour and in selected cases an extended waiting interval can be considered.

INTRODUCTION

Fifteen to twenty percent of patients with rectal cancer present with a pathological complete response (pCR) after chemoradiotherapy (CRT) and total mesorectal excision (TME)[1]. TME is associated with substantial morbidity and mortality and therefore the need for major surgery is questioned in good and complete responders. Moreover, it has raised interest in organ-preserving alternatives to major surgery, such as a local excision in near complete responders or a watch-and-wait policy in complete responders[2-6].

Selection of patients who may benefit from organ preservation requires an accurate identification of complete responders. Main tools for response assessment have included clinical assessment with digital rectal examination, endoscopy and biopsy, and imaging such as MRI and endorectal ultrasound[4,5,7]. However, when used individually, none of these techniques are able to accurately predict pCR after CRT, due to overestimation of residual tumour[8-10]. The combined use of these techniques increases the diagnostic accuracy[11]. It is currently recommended to combine digital rectal examination, endoscopy and MRI (including diffusion weighted imaging (DWI))[11]. This strategy is aimed at minimizing the risk of missing residual tumour and therefore minimizing the risk of undertreating patients. Mainly patients with a typical clinical complete response, fulfilling strict selection criteria that include whitening of the mucosa with teleangiectasia and mucosal integrity on endoscopy combined with absence of luminal and nodal disease on (DWI-)MRI, are considered for organ preservation[11,12]. However, due to these strict criteria up to 30% of the complete responders are not recognized at clinical response assessment, with the consequence that these patients undergo major surgery while organ preservation could be a possibility[11,13]. In order to reduce the number of unrecognized complete responders it is important to see what we can learn from these unrecognized complete responders. Specifically, we should evaluate whether there are distinct features on MRI and endoscopy that lead to the false diagnosis of residual tumour at response assessment, so that these pitfalls may be used as a teaching reference and to optimise the identification of complete responders in the future. Therefore, the aim of this study was to evaluate what features on restaging MRI and endoscopy led to a false diagnosis of residual tumour in patients with a pathological complete response after rectal cancer surgery.

PATIENTS AND METHODS

The need for informed patient consent was waived by the institutional ethics review board due to the retrospective nature of this study. This study was performed in a referral centre for organ preservation in rectal cancer (Maastricht University Medical Centre, Maastricht, the Netherlands), where restaging after neoadjuvant treatment was routinely performed. In our centre, all patients with a complete clinical response are offered organ preservation, and patients with an incomplete clinical response are offered standard treatment with resection. Criteria for a clinical complete response have been described previously[14]. However, some patients with an incomplete clinical response showed pathological complete response after resection, and could be considered 'unrecognized' clinical complete responses. These patients were included in the present retrospective study, providing they met the following inclusion criteria: (1) biopsy proven primary rectal cancer, (2) treatment with surgery after either a long course of CRT or a short course of radiotherapy (5x5Gy) followed by a prolonged waiting interval, between July 2006 and December 2015, (3) availability of restaging MRI (and endoscopic) examinations for response assessment after neoadjuvant treatment, and (4) complete response of the primary tumour at histopathology after surgery (ypT0). Referred patients had surgery in their primary hospital. Patients were excluded if they had surgery for persisting symptoms (e.g. obstructive stenosis).

Restaging MRI was routinely performed and available for all study patients. Until 2012, endoscopy was only performed upon indication (i.e. in case of a good response on imaging). From 2012 on, endoscopy was routinely performed as part of the response assessment in all patients.

Re-evaluation of MRI

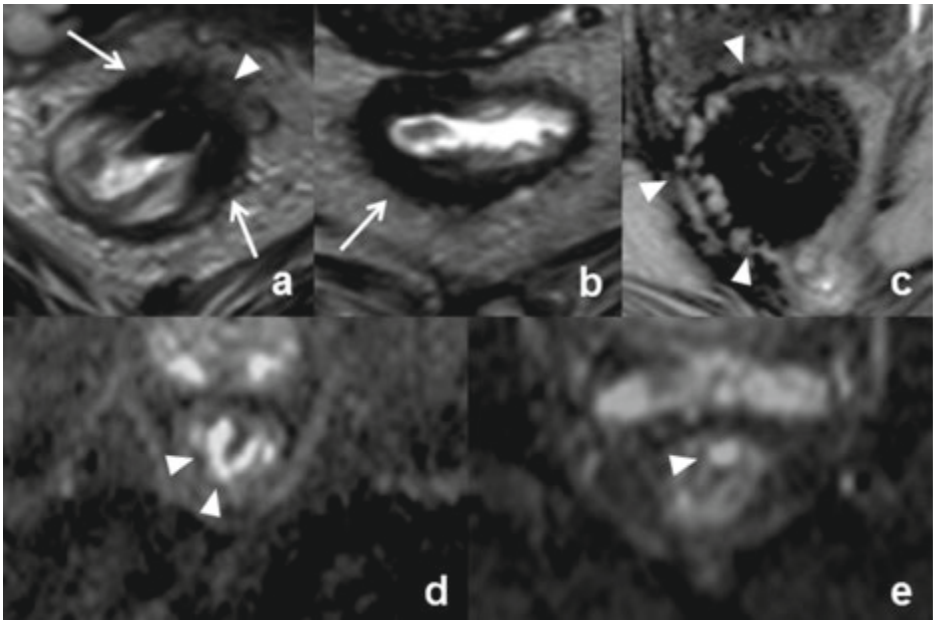
All MR imaging was performed with a 1.5T system (Intera (Achieva) or Ingenia, Philips Medical Systems, Best, The Netherlands) using a phased array body coil. Sequences included T2-weighted MRI and diffusion-weighted MRI. Detailed sequence parameters of the sequences used during the study period are provided in the Supplementary File 1. The primary staging MRIs performed before treatment were also at the reader's disposal. Images were analysed by a single expert radiologist (M.M.) with 8 years of experience in reading rectal cancer MRI. As this study aimed at identifying features leading to unrecognized complete response and not at assessing diagnostic performance to assess response, the reader was aware that all patients had a pathological complete response in the resected specimen.

The following features were evaluated on the restaging T2-weighted images: signal intensity of the tumour bed, pattern of fibrosis, presence of rectal wall oedema,

EMVI and lymph node morphology. The signal intensity of the tumour bed was scored to be either hypo-intense or consisting of mixed signal intensity. Pattern of fibrosis was scored as normalised rectal wall, minimal fibrosis, or regular/irregular full-thickness fibrosis[15]. Figure 1 shows examples of the MRI features that were evaluated. Lymph node morphology was assessed by evaluating the border, contour, the signal intensity heterogeneity of the nodes and the presence of fibrosis within the nodes. Examples of irregular nodes are shown in Figure 2.

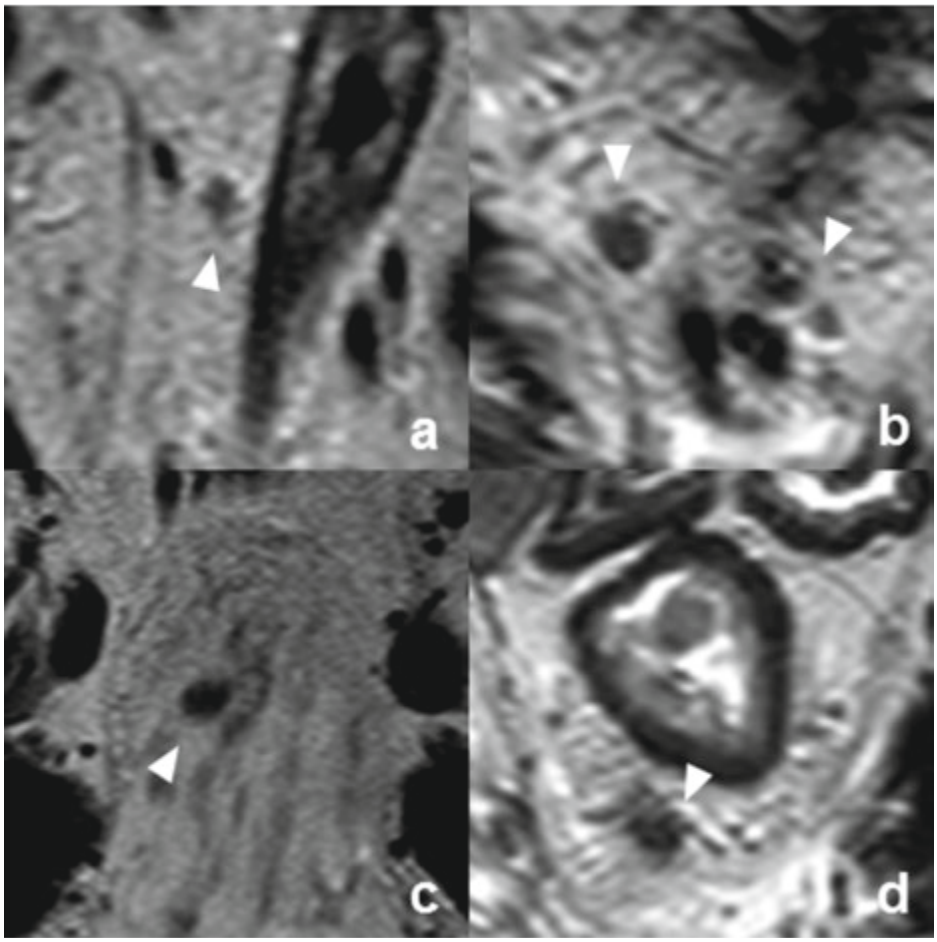
On restaging DWI-MRI, the presence and distribution (focal or diffuse) of diffusion restriction (high signal intensity on b1000 DW-images and corresponding low signal on the apparent diffusion coefficient maps) within the tumour bed were recorded.

Figure 1. Examples of main pitfalls in restaging MRI in ypT0 patients leading to overstaging of residual tumour.



Mixed signal intensity (white arrowhead) within an area of fibrosis (arrows) (a), thick fibrosis in (b) and irregular fibrosis (white arrowheads) in (c) at T2-weighted MRI; massive diffusion restriction (d) and focal diffusion restriction (e) at DWI-MRI.

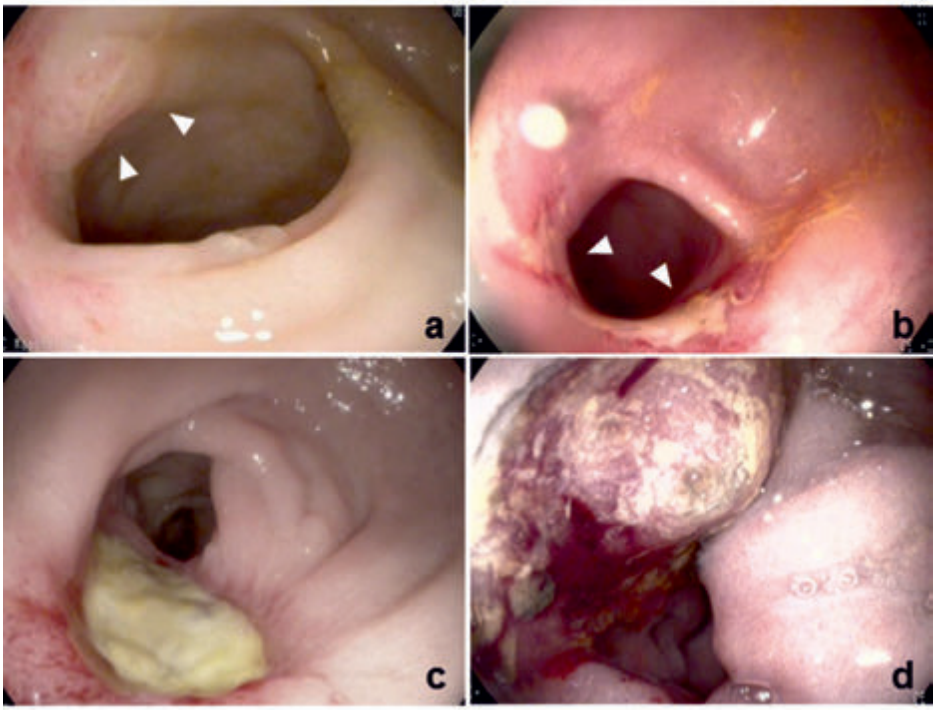
Figure 2. Irregular nodes in yN0 patients (a+b) and in yN+ (c+d) patients.



Re-evaluation of endoscopic images

Endoscopy with a flexible endoscope was performed after a phosphate enema, by one of six surgeons who were specialized in endoscopic response assessment. The digitally stored endoscopy images (white light images only) were re-evaluated for this study by a single experienced surgeon (G.B.) with 12 years of experience in restaging endoscopy. The presence of a white scar, a flat ulcer, a deep ulcer with irregular borders, polypoid tissue or gross tumour mass was scored. Examples of these endoscopic findings are shown in Figure 3. If biopsies were taken at the time of endoscopy, results were also provided to the reader and taken into account during scoring. Similarly to MRI, the reader was aware that all patients had a pathological complete response in the resected specimen.

Figure 3. Examples of mucosal abnormalities at restaging endoscopy in ypT0 patients.



A red scar with an adenomatous nodule (white arrowheads) (a), a scar with residual flat mucosal ulceration (b), deep mucosal ulceration with fibrinous tissue (c) and gross residual mass (d). All patients had ypT0 at histopathology after rectal cancer surgery.

Correlation with histopathology

Surgical specimens were assessed according to international guidelines[16]. The histopathology reports of the surgical specimens were reviewed to correlate histopathology features with MRI and endoscopic features. The presence of the following histopathologic features were scored: dysplasia, inflammation, fibrous tissue, acellular mucin, ulceration or calcifications. Examples of these histopathological findings can be found in the Supplementary file 2.

Statistical analysis

Statistical analyses were performed with SPSS Statistics 22 (IBM, Armonk, NY). Baseline data were collected for all patients and included age, sex, baseline clinical staging, neoadjuvant therapy, type of surgical procedure and histopathological staging. Descriptive statistics were calculated for the baseline characteristics and MRI, endoscopic and histopathologic features.

RESULTS

Study population

Thirty-nine rectal cancer patients with pathological complete response of the primary tumour (ypT0) after surgery were considered for inclusion. Three patients were excluded because they had an indication for surgery irrespective of the clinical response of the tumour for the following reasons: stenosis, incontinence and rectal stent. In total, 36 patients were included (24 men, 12 women; mean age at diagnosis 64 ± 13 years, for details see Table 1). Of the 36 patients, 8 patients had nodal metastases at histopathology (7 ypN1, 1 ypN2). These patients are separately described on their lymph node assessment below. The median interval from completion of (chemo)radiotherapy to response assessment was 8 weeks (IQR 8-17 weeks). Median interval from response assessment to resection was 28 days (IQR 15-36 days). Twenty (56%) patients underwent low anterior resection, 13 (36%) patients had an abdominoperineal resection and 3 (8%) patients had a full-thickness local excision. The 3 patients with local excision all had a disease-free follow-up of > 3 years, and are therefore considered to be ypT0N0.

T2-weighted MRI

Overall, in 26 (78%) patients features of residual luminal tumour were present on the restaging T2-weighted MRI. Mixed signal intensity was present in 19 (53%) patients. Full-thickness or irregularly shaped fibrosis was seen in 25 (69%) patients. EMVI was recorded in 3 (8%) of the patients and oedema in 17 (47%) patients.

Diffusion-weighted MRI

In 33 out of 36 patients a DWI sequence was available. Sixteen (49%) patients showed no residual diffusion restriction. In the remaining 17 patients, either focal diffusion restriction (n=14, 42%) or diffuse diffusion restriction (n=3, 9%) was found at re-evaluation.

Endoscopy

Restaging endoscopy was performed in 19 (53%) of the 36 patients. Only 3 patients (16%) presented with a flat scar without mucosal abnormalities. Polypoid tissue was present in 4 (21%) patients, a flat ulcer in 5 (26%) patients, an ulcer with irregular borders in 6 (32%) patients and gross residual tumour was present in 1 (5%) patient. Biopsies were taken in 10 patients. In 4 patients, this led to a suspected residual tumour: 3 patients showed high grade dysplasia and one biopsy adenocarcinoma, while in the resection specimen no adenocarcinoma was found in any of these patients.

Table 1. Patient characteristics (n=36)

Characteristic	Number of patients
Sex	
Male	24 (67%)
Female	12 (33%)
Mean age, in years (SD)	64 (13)
cT stage	
T1-2	7 (19%)
T3ab	14 (39%)
T3cd	9 (25%)
T4	6 (17%)
cN stage	
N0	6 (17%)
N1	8 (22%)
N2	22 (61%)
Neoadjuvant therapy	
CRT (50.0-50.4Gy)	34 (94%)
Short course RT + waiting interval (25Gy)	2 (6%)
Surgical procedure	
LAR	20 (56%)
APR	13 (36%)
FTLE	3 (8%)
Median CRT-restaging interval, in weeks (IQR)	8 (8-17)
Median restaging-resection interval, in days (IQR)	27 (15-36)

Abbreviations: CRT=chemoradiotherapy, RT=radiotherapy, LAR= low anterior resection, APR=abdominoperineal resection, FTLE=full thickness local excision, IQR=interquartile range.

Lymph nodes

In the 28 patients with ypT0N0, suspected residual mesorectal nodal metastasis was present in 7 (25%) patients, these nodes showed fibrosis and/or a spiculated border. In the 8 patients with ypT0N+, 5 (71%) patients also showed a fibrotic appearance or spiculated border of their nodes.

One of the patients with ypT0N0 showed a suspicious extramesorectal node in the right obturator area at MRI and underwent a TME resection with removal of the lateral node. The lateral node was negative on histology.

Correlation of imaging and endoscopy features with histopathology

Correlations between histopathology findings and MRI and endoscopic features are presented in Tables 2 and 3. All patients had a pathological complete response of the

Table 2. Frequency of histological features per MRI feature (n=36)

		Mixed T2-weighted signal		Full thickness/ irregular fibrosis		Diffusion restriction		Oedema		EMVI	
	Total	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Dysplasia	6	4 (23.5)	2 (10.5)	2 (18.2)	4 (16.0)	3 (18.8)	3 (17.6)	5 (27.8)	1 (5.9)	6 (18.2)	- (0.0)
Fibrous tissue	30	11 (64.7)	19 (100.0)	7 (63.6)	23 (92.0)	11 (68.8)	16 (94.1)	14 (77.8)	15 (88.2)	27 (81.8)	3 (100.0)
Inflammation	18	5 (29.4)	13 (68.4)	3 (27.3)	15 (60.0)	6 (37.5)	11 (64.7)	7 (38.9)	11 (64.7)	16 (48.5)	2 (66.7)
Acellular mucin	5	1 (5.9)	4 (21.1)	2 (18.2)	3 (12.0)	1 (6.3)	4 (23.5)	1 (5.6)	4 (23.5)	3 (9.1)	2 (66.7)
Ulceration	19	5 (29.4)	14 (73.7)	3 (27.3)	16 (64.0)	6 (37.5)	13 (76.5)	6 (33.3)	12 (70.6)	17 (51.5)	2 (66.7)
Dystrophic calcifications	5	2 (11.8)	3 (15.8)	- (0.0)	5 (20.0)	1 (6.3)	3 (17.6)	1 (5.6)	4 (23.5)	5 (15.2)	- (0.0)

Abbreviations: DWI=diffusion weighted imaging; EVMI=extramural venous invasion.
Numbers between parentheses are percentages.

Table 3. Frequency of histological features per endoscopic finding (n=19)

		Scar		Flat ulcer		Ulcer with irregular border		Polypoid tissue		Residual tumour	
	Total	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Dysplasia	4	4 (25.0)	- (0.0)	3 (21.4)	1 (20.0)	3 (23.1)	1 (16.7)	3 (20.0)	1 (25.0)	3 (16.7)	1 (100.0)
Fibrous tissue	17	15 (93.8)	2 (66.7)	12 (85.7)	5 (100.0)	12 (92.3)	5 (83.3)	13 (86.7)	4 (100.0)	16 (88.9)	1 (100.0)
Inflammation	8	7 (43.8)	1 (33.3)	5 (35.7)	3 (60.0)	4 (30.8)	4 (66.7)	8 (53.3)	- (0.0)	8 (44.4)	- (0.0)
Acellular mucin	2	2 (12.5)	- (0.0)	1 (7.1)	1 (20.0)	1 (7.7)	1 (16.7)	2 (13.3)	- (0.0)	2 (11.1)	- (0.0)
Ulceration	10	9 (56.3)	1 (33.3)	6 (42.9)	4 (80.0)	5 (38.5)	5 (83.3)	10 (66.7)	- (0.0)	10 (55.6)	- (0.0)
Dystrophic calcifications	4	4 (25.0)	- (0.0)	3 (21.4)	1 (20.0)	2 (15.4)	2 (33.3)	3 (20.0)	1 (25.0)	4 (22.2)	- (0.0)

Numbers between parentheses are percentages.

primary tumour (ypT0) and in six (19%) specimens foci of low- or high grade dysplasia at the former tumour location were found. Histopathology reports describe fibrosis in 30 (83%) patients, ulceration in 19 (53%) patients and inflammation in 18 (50%) patients. Acellular mucin was present in 5 (14%) surgical specimens and dystrophic calcifications were seen in 5 (14%) specimens. Fibrous tissue was more frequently found in patient with mixed signal intensity on T2-weighted MRI than in patients with homogeneous signal (100% vs. 65%). Microscopic ulceration was also found more frequently in patients with mixed T2-weighted signal (74% vs. 29%) and in patients with a high signal on the DWI-MRI (77% vs. 38%), see Table 2. Presence of acellular mucin or calcifications did not differ between patients with and without signs of residual disease on MRI. Dysplasia was found more frequently in patients with clinically suspected residual tumour at endoscopy than in patients without suspected residual tumour (100% vs. 17%).

DISCUSSION

The selection of patients with a complete response for organ preservation remains a challenge, with overstaging of residual tumour being the main source of error. This can lead to not recognizing patients with a complete response, who subsequently have a major resection of the rectum while they could have been treated with organ preservation. The goal of this study was to evaluate what features on restaging MRI and endoscopy led to a false diagnosis of residual tumour in these unrecognized complete responses. Overall, the commonest pitfalls were mucosal abnormalities on endoscopy, mixed signal or irregular aspect on T2-weighted MRI and a residual high signal on DWI-MRI. Overstaging of nodes was another important pitfall. For some of the pitfalls on MRI and endoscopy a potential substrate was found when reviewing histopathology.

Mucosal abnormalities such as an ulcer or polypoid tissue were present in the majority (88%) of the unrecognized complete responders at restaging endoscopy. These findings are in line with the study by Nahas et al[13]., who showed that 89% of the patients with an unexpected pCR after TME resection showed gross mucosal abnormalities at restaging endoscopy. Two other studies showed that in 61-74% of the patients downstaged to ypT0, macroscopic residual mucosal abnormalities were found in the surgical specimen[17,18]. Routine biopsies have been advocated to distinguish residual tumour from healing mucosa or residual adenoma. However, because of sampling errors there is a substantial risk for false negative biopsies[19]. In the present study there is even a false positive finding: one patient had adenocarcinoma in the biopsy taken at restaging endoscopy while having a pCR at resection only two weeks later.

Similar to endoscopy, T2-weighted MRI tends to overestimate the presence of residual tumour, mainly because of the presence of residual wall thickening at the former tumour location[9]. If this residual wall thickening shows a dark homogeneous fibrotic aspect, experienced radiologists will generally be able to identify this as a complete response. However, when the residual lesion shows a mixed signal, radiologists will interpret this as a sign of residual tumour. Although mixed signal is most often associated with residual tumour, this is not always the case. In patients with a pathological complete response this heterogeneous wall thickening is probably a mixture of fibrosis and oedema in the healing phase of the bowel wall, that in due time will proceed to full thickness homogeneous dark fibrosis. The addition of diffusion-weighted imaging to standard T2-weighted imaging can help to differentiate between scar tissue and residual tumour, as areas with residual diffusion restriction are suspicious for residual tumour[20]. A meta-analysis on the assessment of response to CRT in rectal cancer patients showed that the addition of DWI results in a significantly improved sensitivity from 50% with standard T2-weighted sequences to 84% with DWI[9]. In the present study approximately half of the unrecognized complete responders showed residual (focal) diffusion signal abnormalities. Probably, this can be explained by interpretation errors caused by persisting T2 signal from the rectal wall which is not entirely suppressed at DWI. Due to the small size of these foci, evaluation on the quantitative ADC map is difficult and leads to failure in recognizing these areas as T2 shine through[21]. Histological reactive changes, e.g. an ulcer, may cause a false high signal leading to interpretation errors. Similar interpretation pitfalls have been reported for DWI-MRI after transanal endoscopic microsurgery[22,23].

Another reason for not recognizing a complete response was the erroneous interpretation of a residual node as malignant. A common feature in overstaged nodes was the presence of border irregularity, a feature that is also found in many malignant nodes. While in primary staging the accuracy for nodal staging improves by the addition of morphological criteria to size criteria[24,25], for nodal response assessment after neoadjuvant treatment the use of morphological criteria can be confusing as both normal and metastatic nodes can show abnormal nodal morphology[26,27]. With a complete response in the primary tumour, there is a low a-priori risk of about 3-5% for residual nodal disease[1]. Therefore, in order to avoid needless surgery, it is worth considering (in patients with a clinical complete response in the primary tumour) to observe small residual irregular nodes for an additional period, especially when the nodes have decreased in size.

In many centres, organ preservation is only considered if a patient presents with a typical clinical complete response: a white scar with absence of mucosal abnormalities on endoscopy and no signs of residual luminal and nodal disease on MRI. The results

of this study show that patients with mixed T2 signal, residual diffusion restriction, mucosal abnormalities or irregular nodes do not necessarily have residual disease. In selected patients an extended waiting interval can be considered to provide a more convincing picture on whether or not there is a complete response. In our current clinical practice we have implemented an extended waiting interval in patients who show a 'near-CR' at first response assessment 8-10 weeks after neoadjuvant treatment, to allow for further regression to a complete response[28]. How many and what combinations of the abovementioned equivocal features allow for safe extension of the waiting interval remains unclear. The more of these features are present, the less likely it seems a patient is going to have a complete response. This should be further evaluated. Our study has some limitations. First, during the long study period the response evaluation strategy after (chemo)radiotherapy gradually changed, which led to missing endoscopy images in the early patients. Second, the time between response assessment and resection was rather long in some patients, so it is possible that patients did not have a pathological complete response during response assessment, but developed a complete response during the interval to surgery and thus were actually not overstaged. Third, histopathology reports were used to compare imaging findings with histological findings. By using standard clinical reports rather than doing a reassessment of histopathology it is possible that histological reactive changes were not always reported when present. Last, as we only included patients with a pathological complete response of the primary tumour and did not have a control group, we cannot draw conclusions about the incidence of the discussed features on patients with true residual tumour, which would provide insight into the prevalence of these features and their clinical impact.

CONCLUSION

Overstaging of residual tumour after CRT is mainly caused by the presence of residual mucosal abnormalities at endoscopy, mixed signal or irregular fibrosis at T2-weighted MRI, focal diffusion restriction at diffusion- weighted MRI and residual irregular nodes. Knowledge of these pitfalls can help clinicians to improve the selection of complete responders. In patients with a very good clinical response, the abovementioned features should not be regarded as unequivocal signs of residual tumour and an extended waiting interval followed by a reassessment can be considered to provide a more convincing picture of the presence of a complete response. Advances in imaging techniques, endoscopy and tumour markers will in the future hopefully overcome the challenges in response assessment.

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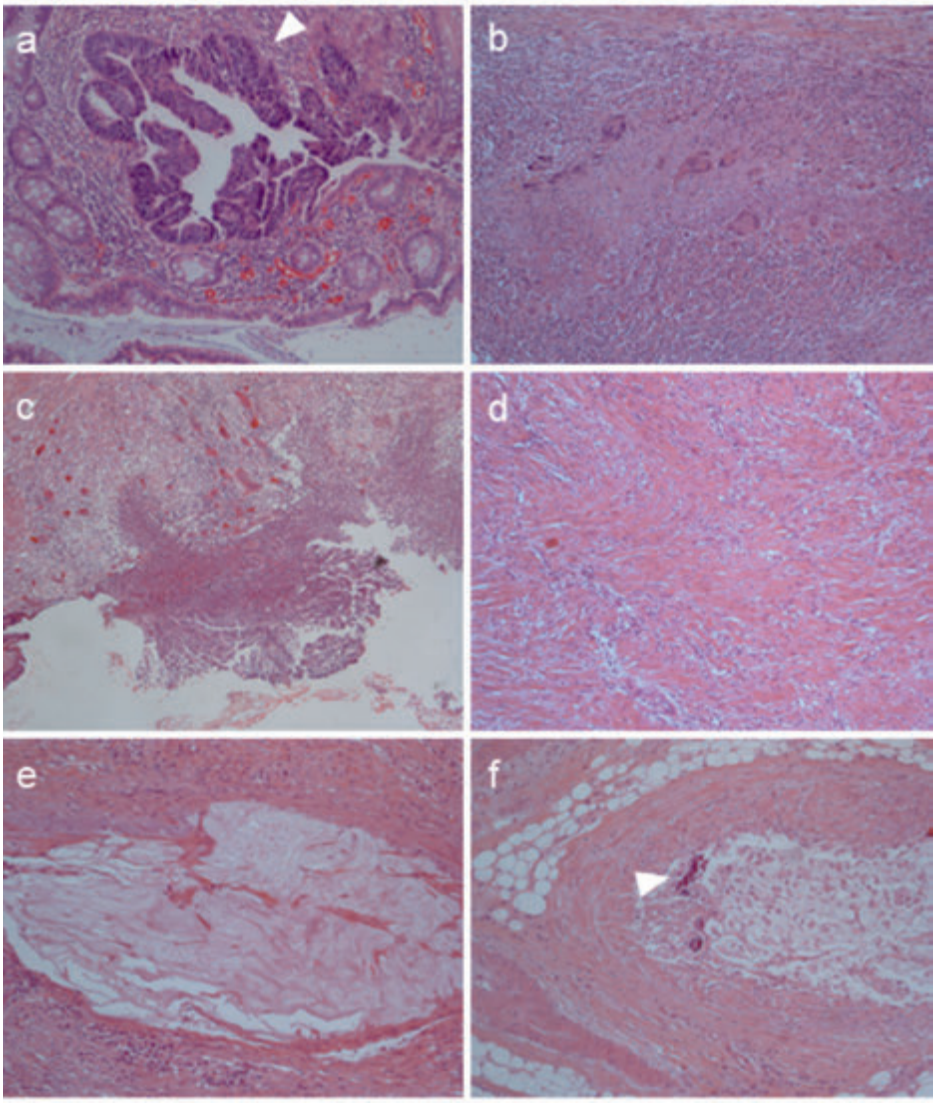
APPENDIX A. SUPPLEMENTARY FILES

Supplementary file 1. MRI sequence parameters

	T2-weighted FSE	Diffusion-weighted MRI sequences		
		DWIBS	DWI-SPIR	DWI-SPAIR
Repetition time	8456-9558	4808-4829	4971	4172-5241
Echo time	130-150	70	70	68-70
Number of slices	22-30	50	24	20-24
Slice thickness (mm)	3-5	5	5	5
FOV (mm)	200	440	320	320
Acquired in plane resolution (mm x mm)	0.78 x 1.14	2.50 x 3.11-3.18	1.82 x 2.31	1.82 x 2.27
Sensitivity encoding factor	-	1.9-2	1.9	1.9
Echotrain length	25	1	1	1
Number of signal averages	2-6	4	5	5
Acquisiotion time (min:sec)	4:37-6:30	10:37-12:20	05:33	05:51-06:44
Echo planar imaging (EPI) factor	-	53-55	55	61
b-values	-	0, (100), 500, 1000	0, 500, 1000	0, (25, 50, 100 500,1000)
Fatsuppression technique	-	STIR	SPIR	SPAIR

Abbreviations: FSE= Fast spin echo, FOV= Field of View, STIR = Short TI Inversion Recovery, SPIR = Spectral Presaturation with Inversion Recovery, SPAIR = Spectral Attenuated Inversion Recovery.

Supplementary File 2. Histopathological changes after chemoradiation in complete responders.



Focus of high grade dysplasia (a); granulomatous inflammation (b); active inflammation (c); 'stormiform' fibrosis (d); acellular mucin lake (e); dystrophic calcification within vessel (f).

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3

PREDICTIVE VALUE OF ENDOSCOPIC FEATURES FOR A COMPLETE RESPONSE TO NEOADJUVANT CHEMORADIOTHERAPY FOR RECTAL CANCER

ABSTRACT

Objective and Background

Watch-and-wait approach in rectal cancer relies on the identification of a clinical complete response (CR) after neoadjuvant (chemo)radiotherapy. This is mainly performed by rectal examination, magnetic resonance imaging, and endoscopy. Endoscopy has been less well studied, and the objective of the study is to assess the diagnostic value of endoscopy and the predictive value of endoscopic features for the identification of CR.

Patients and Methods

A total of 161 patients with primary rectal cancer undergoing flexible sigmoidoscopy for response assessment after neoadjuvant (chemo)radiotherapy between January 2012 and December 2015 at a single institution were evaluated retrospectively. Three independent readers scored endoscopic features and a confidence level score for a CR. Diagnostic performance of endoscopy and positive predictive value (PPV) of endoscopic features for a CR were calculated. If available, biopsy results were revealed to the reader and a change in confidence level was noted. Reference standard was histology after surgery, or long-term outcome in a watch-and-wait policy.

Results

Median time to endoscopy was 9 (interquartile range 8–12) weeks. Area under the receiver operator characteristic curve, sensitivity, specificity, PPV, and negative predictive value for a CR were 0.80 to 0.84, 72% to 94%, 61% to 85%, 63% to 78% and 80% to 89%, respectively. A flat scar was the most predictive feature of a CR (PPV 70%–80%). The PPV of small flat ulcers and large flat ulcers were 40% to 50% and 29% to 33%, respectively. The addition of biopsy results led to a significant change in confidence level score in 4% to 13% of patients.

Conclusions

More than 70% of the patients with a luminal CR after neoadjuvant treatment for rectal cancer can be identified by endoscopy at ±9 weeks. Together with findings on digital rectal examination (DRE) and magnetic resonance imaging, specific endoscopic features can be used to select patients for an extended observation period to select for organ preservation.

INTRODUCTION

The introduction of the total mesorectal excision (TME), preoperative radiotherapy, and chemoradiotherapy (CRT) in the treatment of rectal cancer have led to a marked improvement in the local recurrence rates[1–3]. The current focus in rectal cancer management has therefore shifted from improving oncological outcomes toward reducing the surgical morbidity and the adverse effects on functional outcome. A watch-and-wait approach, that is, no immediate surgery and close surveillance, could potentially avoid the risk for postoperative complications and significantly benefit quality of life in patients with a complete response (CR) to neoadjuvant treatment[4,5].

Although recent publications have shown promising outcomes with a low oncological risk[6,7], a few challenges remain to be overcome before widespread implementation of the watch-and-wait approach for rectal cancer can take place in clinical practice. One of these challenges is improving the selection of patients with rectal cancer who are candidates for a watch-and-wait approach, for which accurate methods for tumor response assessment after neoadjuvant treatment are needed. Recommended modalities for tumor response assessment include imaging with magnetic resonance imaging (MRI) and clinical assessment with digital rectal examination, endoscopy, and biopsies[6,8]. Response assessment with MRI is performed by T2- weighted and diffusion weighted imaging, and this combination yields a reasonable diagnostic accuracy for detection of a CR. The overall endoscopic and clinical assessment has been shown to be more accurate than MRI in 1 study, albeit with the same limitation of a relatively low sensitivity for the detection of a CR[9]. One of the reasons for this is that patients with a pathological CR may show residual ulcers or irregularities at restaging after the recommended 8- to 12-week interval from neoadjuvant treatment, instead of the white scar which is typically associated with a clinical CR[10,11]. In these cases, MRI will usually show ambiguous abnormalities (e.g., heterogeneous fibrosis or small focal diffusion restriction), which does not really help in clinical decision making. To solve this problem, the observation interval is increasingly extended with a second restaging after another 6 to 12 weeks in patients with a near clinical CR, to allow for further regression[12]. It is, however, unclear which group of patients will benefit from such an extended interval. Possibly, distinct features on endoscopy can be used to define groups of patients that may benefit from an extended interval or inclusion of a watch-and- wait policy. Therefore, the aims of this study were to assess the overall diagnostic accuracy of endoscopy for response assessment and to assess the predictive value for a CR of various endoscopic features.

MATERIALS AND METHODS

Study population

This study was performed in a single center in which restaging endoscopy was routinely done after neoadjuvant treatment for rectal cancer to assess the luminal tumor response.

All consecutive patients with primary rectal cancer who received neoadjuvant treatment between January 2012 and December 2015 were identified. Inclusion criteria were (1) primary rectal cancer; (2) neoadjuvant treatment with short-course radiotherapy or long-course CRT, both followed by a waiting interval to allow for downsizing; (3) restaging endoscopy within 6 to 16 weeks after the

end of neoadjuvant treatment; and (4) interval of less than 8 weeks between endoscopy and surgery. Exclusion criteria consisted of (1) unresectable rectal cancer, (2) absence of stored endoscopy images, and (3) insufficient endoscopy image quality (e.g., view impaired by residual stool, poor photo resolution, unclear location of remnant). After restaging, patients either underwent rectal cancer surgery or were enrolled in a watch-and-wait program as part of a prospective cohort study (registered on clinicaltrials.gov: NCT00939666 and NCT02278653). Follow-up data of more than 2 years were available for all patients undergoing a watch-and-wait approach. This study was approved by the Committee on Medical Research Ethics and informed consent was waived due to the retrospective nature of this study.

Endoscopic Assessment

All patients underwent flexible sigmoidoscopy (EPK-i video processor, Pentax Medical Netherlands, Uithoorn, The Netherlands) 6 to 16 weeks after the completion of neoadjuvant treatment for luminal response assessment. Pre-examination bowel cleansing was done with a rectal phosphate enema. Only white light imaging was used and images were digitally stored. Biopsies during endoscopy were not standard clinical routine, but were taken only at the endoscopists' judgment.

Endoscopic Image Evaluation

All restaging endoscopic images were retrospectively and independently evaluated by 3 readers. R1 (G.L.B.) is a gastrointestinal surgeon with 13 years of experience in assessing restaging endoscopy. R2 (J.M.) is a gastrointestinal surgeon with 4 years of experience in assessing restaging endoscopy. R3 (M.E.L.) is a gastroenterologist with 3 years of experience in assessing restaging endoscopy and 14 years of experience in diagnostic colonoscopy. Colonoscopy images of the primary tumor before

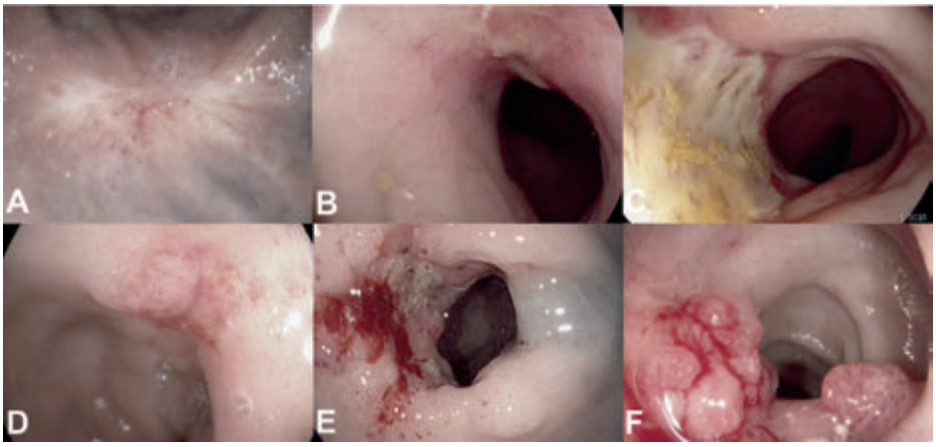
neoadjuvant treatment were not at the readers' disposal. The readers were blinded to each other's results and to the patients' outcomes.

The readers were asked to score the presence of the following endoscopic features, and to assign the most predominant endoscopic feature of each patient's endoscopic images:

1. a flat scar
2. a small flat ulcer (<1 cm)
3. a large flat ulcer
4. ulcer with an irregular border
5. an adenomatous mass
6. tumorous mass.

The endoscopic features are presented in Figure 1.

Figure 1. Endoscopic features at response assessment.



(A) Flat scar, (B) small flat ulcer <1 cm, (C) large flat ulcer, (D) adenomatous mass, (E) ulcer with an irregular border, (F) tumorous mass.

The readers were also asked to score the likelihood of a CR based on the endoscopic images, using a confidence level score (1 definitely residual tumor, 2 probably residual tumor, 3 possibly residual tumor/possibly CR, 4 probably CR, 5 definitely CR). In case biopsies were taken at restaging endoscopy, the results were shared with the readers after their first visual evaluation and they were asked again to give a confidence level for a CR based on the images and biopsy results together. A change in confidence level score based on biopsy results was noted.

Reference Standard

The histopathological staging of the surgical resection specimen served as the reference standard in patients undergoing surgery. The surgical specimens were assessed according to the method of Quirke and Dixon[13], and response was described using the TNM staging classification. Because this study focused on the luminal response assessment, N (nodal) stage was not included and only T (tumor) stage was used as a reference standard for a CR. A ypT0 was considered a CR, a ypT1– 4 was considered residual tumor. In patients undergoing a watch-and-wait policy, a sustained CR of more than 2 years, without evidence of luminal regrowth, was considered a CR. This period for a sustained CR was chosen as the vast majority of local regrowth appear within the first 2 years of follow-up and are rarely encountered after this period[6,14].

Statistical Analyses

Statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corporation, Armonk, NY) and STATA version 11 (StataCorp LLC, TX). Nominal data are presented as absolute frequencies and percentages. Continuous data are presented as median numbers with interquartile range (IQR). Receiver operating characteristic (ROC) curves were plotted for each reader to assess the diagnostic value of endoscopy for the detection a CR. Cut-off for the confidence was set between confidence levels 3 and 4, which was decided before the start of the study. CR was the positive outcome measure. The area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value with 95% confidence intervals (CIs) were calculated for each reader. PPVs for a CR were calculated for each endoscopic feature. AUCs were compared by the method of Hanley and McNeil[15]. Quadratic weighted kappa was calculated to assess the interobserver agreement between readers for the confidence level of a CR. Cohen kappa was calculated to assess the interobserver agreement for the categorization of endoscopic features (0–0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 substantial; 0.81–1 excellent agreement).

RESULTS

Patients

Three hundred thirteen patients with rectal cancer treated with CRT or short-course radiotherapy with a waiting interval between January 2012 and December 2015 were identified, of whom 203 met the inclusion criteria. Figure 2 presents the patient flowchart. Of these 203 patients, we excluded 42 patients for the following reasons:

absence of stored endoscopy images (n 10), insufficient endoscopic image quality (n 23), no surgery or follow-up (n 6), and follow-up in watch-and-wait less than 2 years (n 3). A total of 161 patients, of whom 104 (65%) men, were included in the analysis. Median age was 65 (IQR 57–73) years. Baseline patient characteristics are shown in Table 1.

Sigmoidoscopy was performed after a median 9 (IQR 8– 12) weeks after the last day of neoadjuvant radiotherapy. Eighty-seven (54%) patients subsequently underwent rectal surgery, of whom 80 patients underwent TME and 7 patients underwent local excision with transanal endoscopic microsurgery. Fourteen (16%) of the 87 patients undergoing rectal surgery had ypT0 and 73 (84%) patients had residual luminal tumor (ypT1–4) at pathologic assessment. One out of 9 patients with luminal CR after TME had a pathological positive lymph node (ypT0N1), but was considered a luminal CR for this study. Seventy-four (47%) patients underwent a watch-and-wait policy, of which 19 (26%) experienced a luminal regrowth after a median follow-up time of 6 (IQR 4–18) months. Fifty-five (74%) patients remained without luminal regrowth, with a median follow- up time of 45 (IQR 34–53) months. In the patients undergoing rectal surgery, surgery was performed a median of 18 (IQR 15–35) days after the sigmoidoscopy.

Figure 2. Flowchart of patient inclusion.

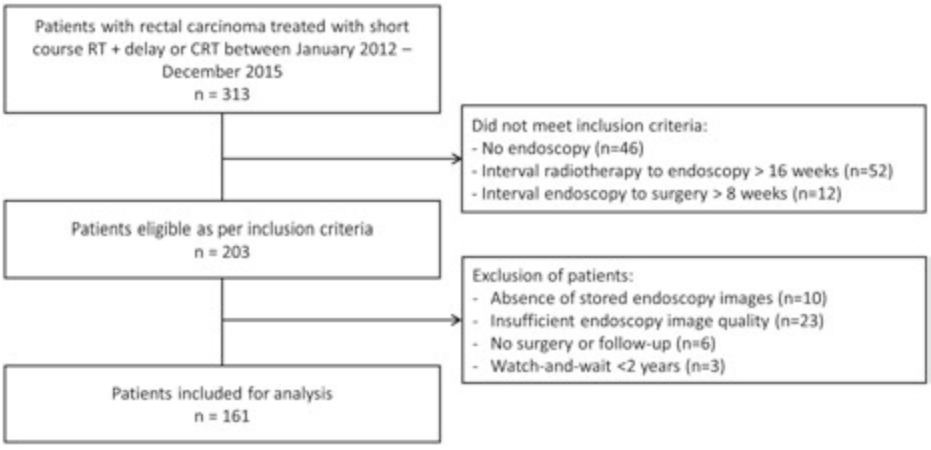


Table 1. Patients with Rectal Cancer and Treatment Characteristics

	All (n=161)	Non-CR (n=92)	CR (n=69)	*P*
Sex, n (%)				0.849
Male	104 (64.6)	60 (65.2)	44 (63.8)	
Female	57 (35.4)	32 (34.8)	25 (36.2)	
Age, median (IQR), yr	64 (57–73)	64 (57–73)	64 (57–72)	
Clinical T-stage, n (%)				0.337
cT1–2	35 (21.7)	17 (18.5)	18 (26.1)	
cT3	118 (73.3)	69 (75.0)	49 (71.0)	
cT4	8 (5.0)	6 (6.5)	2 (2.9)	
Clinical N-stage, n (%)				0.027
cN0	41 (25.5)	24 (26.1)	17 (24.6)	
cN1	46 (28.6)	19 (20.7)	27 (39.1)	
cN2	74 (46.0)	49 (53.3)	25 (36.2)	
Neoadjuvant treatment, n (%)				0.001
Long course CRT	145 (90.1)	77 (83.7)	68 (98.6)	
Short course RT interval	16 (9.9)	15 (16.3)	1 (1.4)	
Type of treatment, n (%)				<0.001
Surgery	87 (54.0)	73 (79.3)	14 (20.3)	
Watch-and-wait	74 (46.0)	19 (20.7)	55 (79.7)	
Interval RT to endoscopy, median (IQR), weeks	9 (8–12)	8 (8–10)	10 (8–13)	0.001
Interval endoscopy to surgery, median (IQR), days*	18 (15–35)	18 (13–30)	34 (15–44)	0.055

*patients undergoing surgery. RT indicates radiotherapy.

Diagnostic Accuracy of Endoscopy

Endoscopy was accurate in predicting the response in 126 (78%), 118 (73%), and 129 (80%) of 161 patients for R1, R2, and R3, respectively. The ROC curves for the prediction of CR of all 3 readers are presented in Figure 3. The AUCs for the prediction of CR were 0.84 (95% CI: 0.77–0.90), 0.80 (95% CI: 0.73–0.87), and 0.84 (95% CI: 0.78– 0.91) for R1, R2, and R3, respectively. Table 2 shows all diagnostic accuracy parameters.

Figure 3. AUC for the prediction of complete response (n=161).

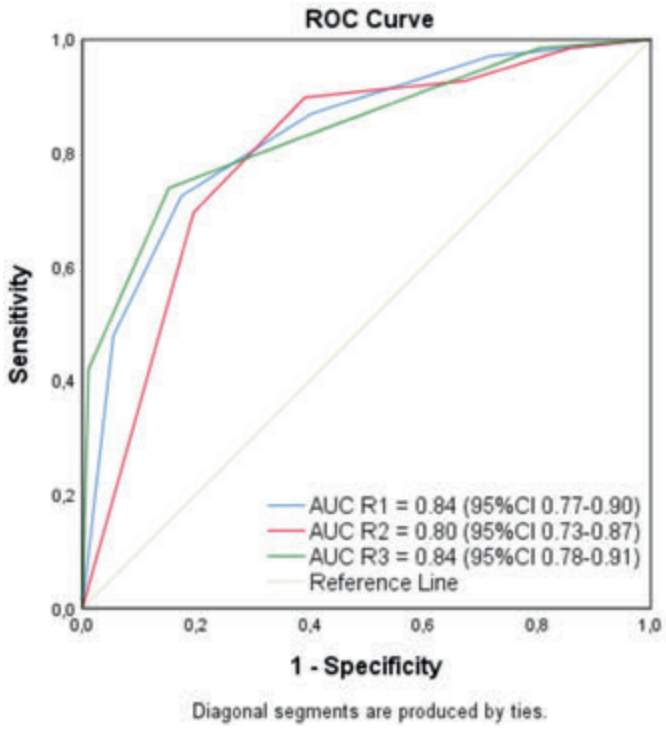


Table 2. Diagnostic Accuracy of Endoscopy Using a Confidence Level Score for the Prediction of a Complete Response.

	Reader 1	Reader 2	Reader 3
Sensitivity	72 (50/69)	90 (62/69)	74 (51/69)
95% CI	62–83	83–97	64–84
Specificity	83 (76/92)	61 (56/92)	85 (78/92)
95% CI	75–90	51–71	77–92
PPV	76 (50/66)	63 (62/98)	78 (51/65)
95% CI	65–86	54–73	68–88
NPV	80 (76/95)	89 (56/63)	81 (78/96)
95% CI	72–88	81–97	73–89
AUC	0.84	0.80	0.84
95% CI	0.77–0.90	0.73–0.87	0.78–0.91

Numbers are percentages. Absolute numbers are given within parentheses. CI indicates confidence interval; PVV, positive predictive value; NPV, negative predictive value; AUC, area under the ROC curve.

Endoscopic Features

The distribution of endoscopic features was significantly different between patients with and without a CR for each reader (P < 0.001). In patients with a CR, 64% to 77% had a flat scar, 6% to 12% a small flat ulcer, 6% to 10% a large flat ulcer, 1% to 7% an ulcer with an irregular border, 4% an adenomatous mass, and 4% to 6% gross residual mass. In contrast, patients without CR showed a flat scar in 12% to 25%, small flat ulcer in 7% to 11%, a large flat ulcer in 11% to 15%, an ulcer with an irregular border in 19% to 30%, an adenomatous mass in 7% to 20%, and gross residual mass in 19% to 28%.

Table 3 provides the PPV for a CR per endoscopic feature. A flat scar was most predictive of a CR: 70% to 80% of patients had a CR. Small flat ulcers and large flat ulcers were predictive of a CR in 40% to 50% and 29% to 33%, respectively.

Table 3. Predictive Value for a Complete Response of Endoscopic Features

	Reader 1	Reader 2	Reader 3
Flat scar			
PPV for CR	77 (44/57)	70 (53/76)	80 (45/56)
95% CI	66–88	59–80	70–91
Small flat ulcer			
PPV for CR	50 (7/14)	40 (4/10)	44 (8/18)
95% CI	24–76	9–70	21–67
Large flat ulcer			
PPV for CR	33 (5/15)	29 (4/14)	33 (7/21)
95% CI	9–57	5–52	13–54
Irregular ulcer			
PPV for CR	15 (5/33)	15 (3/20)	4 (1/27)
95% CI	3–27	0–31	0–11
Adenoma			
PPV for CR	27 (3/11)	14 (3/21)	33 (3/9)
95% CI	1–54	0–29	3–64
Tumor mass			
PPV for CR	13 (4/30)	11 (2/19)	14 (4/29)
95% CI	1–26	0–24	1–26

Numbers are percentages. Absolute numbers are given within parentheses. CI indicates confidence interval.

Biopsies

Biopsies were taken in 55 of 161 patients (34%). Biopsy histology showed no (pre) malignant features in 34 (62%) patients, low-grade dysplasia in 6 (11%) patients, high-

grade dysplasia in 7 (13%) patients, and adenocarcinoma in 8 (15%) patients. Thirty out of 55 patients with a biopsy had residual tumor after resection or a watch-and-wait policy, of whom 7 (23%) patients had a biopsy positive for adenocarcinoma.

After the biopsy results were revealed to the readers, the confidence level for a CR changed in 15 (27%), 18 (33%), and 13(24%) out of 55 patients for R1, R2, and R3, respectively. In 4 (7%), 7 (13%), and 2 (4%) patients the confidence level changed from residual tumor to CR or vice versa (for details see Supplementary Table 1). The AUCs did not significantly change for the 3 readers for sigmoidoscopy with biopsy results compared to sigmoidoscopy without biopsy results in these 55 patients (data shown in Supplementary Fig. 1).

Interobserver Agreement

Table 4 shows the interobserver agreement between the 3 readers for both confidence level and endoscopic features. The readers showed substantial agreement in the confidence level for a CR (k0.62– 0.76). Lower agreement was shown when the readers assigned the individual endoscopic features, with moderate to substantial agreement (k0.47– 0.64).

Table 4. Interobserver Agreement of 3 Readers on Endoscopy for the Assignment of a Confidence Level or Endoscopic Feature.

	Reader 1 – Reader 2	Reader 1 – Reader 3	Reader 2 – Reader 3
Confidence Level*	0.67 (0.59–0.76)	0.76 (0.70–0.83)	0.62 (0.52–0.72)
Features#	0.54 (0.45–0.62)	0.64 (0.55–0.72)	0.47 (0.39–0.56)

*Kappa values with quadratic weighting.

#Cohen kappa values.

DISCUSSION

In the present study the overall judgment of the endoscopy reader of a definite or probable CR identified 72% to 90% of the patients with a luminal CR (sensitivity). Of those assessed as definite or probable complete responders, 63% to 78% truly had a pathological CR or were free of regrowth in a watch-and-wait approach (PPV). The present study also showed that although the majority of patients with a CR presented with the typical flat scar, 23% to 36% showed other endoscopic features at response assessment. The PPV for a CR was highest in patients with a flat scar (70%–80%), and was 40% to 50% in patients with a small flat ulcer. Large flat ulcers,

ulcers with an irregular border, or residual adenomatous or tumorous masses were more consistent with residual tumor, as we found lower predictive values for a CR in these patients.

There are relatively few studies that have assessed the accuracy of endoscopic findings to identify pCR. One early study investigating the utility of proctoscopy for response assessment reported disappointing results with poor accuracy, identifying only 50% of complete responders and with 25% residual tumor in those thought to be CR.16 In another study, flattening of the marginal tumor swelling and re-epithelialization of ulceration was assessed on endoscopic images to predict pCR[17].

The sensitivity of these findings to predict a pCR was 69% to 87%, but specificity was only 39% to 74%. In both studies response assessment was, however, performed within 6 weeks after CRT. In a 2015 article by our group, clinical assessment with endoscopy and DRE was more accurate than MRI alone for identification of a CR, with a sensitivity of 53% and specificity of 97%[9]. Residual tumor was rarely missed with endoscopy and DRE, at the expense of a lower sensitivity to detect CR compared to the present study. This demonstrates that the readers in the present study have adopted a selection strategy aimed at identifying more responders, accepting a higher rate of false positive CRs (22%– 37%), a change of strategy that is discussed below.

Habr-Gama et al[11], the pioneers of watch-and-wait, have previously described the frequently observed endoscopic features in complete responders: whitening of the mucosa with telangiectasia and absence of any mucosal, superficial or deep ulceration, any palpable nodule, or stenosis. Many organ preservation trials have adopted these criteria for a clinical CR. In a recent study only 27% of the patients with a pCR, however, fulfilled these criteria at preoperative restaging[18]. Accordingly, previous studies have shown that when the mucosa was assessed after resection, only 25% to 39% of patients with pCR showed mucosal integrity or white scarring[19–21]. In our study, 64% to 77% of patients with CR had a flat scar as the predominant endoscopic feature, whereas 23% to 36% of the complete responders had other endoscopic presentations. The original Habr-Gama criteria for a clinical CR represent a very strict approach for the selection of patients for a watch-and-wait policy, yet evidently underestimate the tumor response. When exclusively patients with a flat scar without any mucosal abnormalities are considered for organ preservation, many patients with a good (and possibly complete) response will be managed by radical surgery, losing the opportunity for organ preservation. Widening the inclusion criteria for a watch- and-wait policy, for example, including patients with a residual ulcer, will lead to identifying more patients with a CR. Of course, this will also lead to an increased number of patients with residual tumor or local regrowth during follow-up.

This strategy can also be interpreted as extending the observation interval to give tumors with a very good response the opportunity to regress further, and to decide later whether or not to proceed with a resection[12]. In the present study half of the patients with a small flat ulcer had either a pCR after resection or a sustained CR during watch-and-wait, and an extended observation interval could have identified these patients. On the contrary, in patients who showed a residual large ulcer, ulcer with an irregular border, adenomatous mass, or gross tumorous mass at endoscopy lower predictive values for a CR were found and direct surgery seems justified.

Although the present study evaluated response assessment after neoadjuvant treatment with endoscopy only, in clinical practice the response assessment and the decision-making process also relies on important additional information of the digital rectal examination and MRI[6,9]. MRI provides information on both the response of the primary tumor (with morphologic patterns and MRI tumor regression grading) and on nodal response[22]. Recent guidelines recommend MRI to be routinely performed in every patient after CRT[8,23]. Additional considerations in decision making are the distance of the tumor to the sphincter, and how the patient values sphincter and organ preservation. The present study was not focused on this clinical decision-making process, but rather on the value of the different features of the endoscopic response. It is, however, clear that this information should be combined with MRI findings, as 1 study showed that this combination yielded the highest accuracy with an AUC under the ROC curve of 0.89[9]. Further research should define the chances of a CR for the different combinations of findings on different assessment techniques.

The interobserver agreement for the presence of the endoscopic features and the confidence level scores for a CR were moderate to substantial between the 3 readers. Two of the readers (R1 and R3) work at the same hospital and perform restaging with continuous feedback to each other and had substantial agreement in confidence levels for CR prediction. The agreement between R2 and the 2 other readers was lower, because R2 showed a more liberal approach with higher confidence levels. This resulted in a sensitivity of more than 90%, but with a higher false positive rate of 37%.

The added value of biopsies is questionable. Interestingly, in our study the addition of biopsies almost never changed the readers' confidence level of response. The AUC for endoscopy with biopsies was not statistically different from the AUC of endoscopy alone. This may have been caused by a lack of confidence in biopsy results from the readers, as previous reports have shown that negative biopsies often represent sampling errors and are therefore of limited clinical use for ruling out residual tumor[24,25]. This is supported by our results that showed false negative biopsy results in 50% of the patients.

Advanced endoscopy technologies such as the narrow-spectrum technologies and autofluorescence imaging are an expanding field of research and may improve the mucosal, structural, and microvascular visualization of the rectal wall[26]. This may help in the differentiation between ongoing response or residual tumor after neoadjuvant treatment in rectal cancer. These technologies have, however, yet to be explored in the setting of restaging assessment. Several limitations of this study should be addressed. This was a retrospective study and the readers only evaluated the static endoscopic images taken by other endoscopists; video was not available. We therefore excluded all patients in whom the readers felt the images were of insufficient quality to make a prediction, potentially leading to selection bias. Also, this study was performed in a referral center for organ preservation. Patients with a good response mostly established on MRI were referred to our center for full response assessment, leading to a high a priori chance of a CR in this study. This has an influence on the positive and negative predictive values. In the current study, nodal involvement was disregarded as endoscopy only assesses the luminal response and not nodal response, whereas in clinical practice nodal involvement and other MRI findings will obviously have influence on the treatment. Last, the range of the intervals between neoadjuvant treatment and endoscopy, and between endoscopy and surgery might also have influenced our results, although the AUCs were not significantly different between patients with an interval shorter or longer than the median interval to endoscopy and to surgery, as shown in Supplementary Tables 2 and 3.

CONCLUSION

In conclusion, our study demonstrates that more than 70% of the patients with a luminal CR after neoadjuvant treatment for rectal cancer can be identified by endoscopy. Although the majority of patients with a CR presented with the typical flat scar, one third showed other endoscopic features at response assessment. When a small flat ulcer was seen 40% to 50% went on to have a CR, and these patients may be selected for an extended observation interval. For patients with large flat ulcers, ulcers with an irregular border or residual adenomatous or tumorous masses, predictive values for a CR were low and direct surgery is justified. When combined with the findings of clinical examination and restaging MRI, this information can be of value when discussing the treatment option of organ preservation with patients who have a good response to chemoradiation.

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APPENDIX A. SUPPLEMENTARY FILES

Supplementary Table 1. Significant changes in confidence level scores for a complete response after the addition of biopsy results (n=55).

	No significant change	CR to residual tumour	Residual tumour to CR	Total
Reader 1				
Negative biopsy, *n*	43	0	4	47
Positive biopsy, *n*	8	0	0	8
Total, *n*	51	0	4	55
Reader 2				
Negative biopsy, *n*	41	2	4	47
Positive biopsy, *n*	7	1	0	8
Total, *n*	48	3	4	55
Reader 3				
Negative biopsy, *n*	46	0	1	47
Positive biopsy, *n*	7	1	0	8
Total, *n*	53	1	1	55

Residual tumour = confidence level 1-3
Complete response (CR) = confidence level 4-5

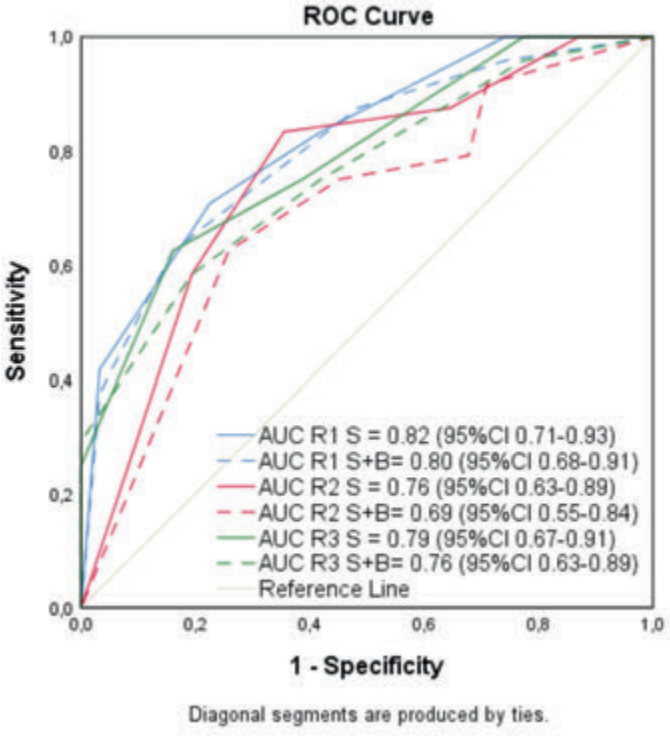
Supplementary Table 2. Area under the ROC-curve (AUC) of endoscopy within groups according to time interval to endoscopy.

	Interval <8.7 weeks (n=80)	Interval ≥ 8.7 weeks (n=81)	*p* value
Reader 1	0.85 (95%CI 0.75-0.94)	0.80 (95%CI 0.71-0.90)	0.510
Reader 2	0.83 (95%CI 0.73-0.93)	0.74 (95%CI 0.64-0.84)	0.223
Reader 3	0.79 (95%CI 0.68-0.89)	0.87 (95%CI 0.80-0.95)	0.201

Supplementary Table 3. Area under the ROC-curve (AUC) of endoscopy within groups according to time interval to surgery.

	Interval <18 days (n=40)	Interval ≥ 18 days (n=45)	*p* value
Reader 1	0.81 (95%CI 0.58-1.00)	0.71 (95%CI 0.53-0.89)	0.505
Reader 2	0.64 (95%CI 0.34-0.94)	0.70 (95%CI 0.51-0.90)	0.725
Reader 3	0.85 (95%CI 0.63-1.00)	0.63 (95%CI 0.45-0.81)	0.142

Supplementary Figure 1. Area under the ROC-curve (AUC) for the prediction of complete response of sigmoidoscopy without (S) or with (S+B) biopsy (n = 55).



PART II

PATIENT REPORTED AND FUNCTIONAL OUTCOMES

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IMPACT OF RADIOTHERAPY ON ANORECTAL FUNCTION IN PATIENTS WITH RECTAL CANCER FOLLOWING A WATCH AND WAIT PROGRAMME

ABSTRACT

Background and purpose

To assess the long-term anorectal function in rectal cancer patients following a watch-and-wait policy after chemoradiotherapy and to investigate the dose–volume effects of radiotherapy on the anorectal function.

Methods and materials

Thirty-three patients with primary rectal cancer who were treated with chemoradiotherapy and a watch-and-wait policy with minimum follow-up of 2 years were included. We assessed the anorectal function using anorectal manometry and patient reported outcomes (Vaizey and LARS-score). Dose–volume histograms were calculated for the rectum and anal sphincter complex, and associations between the dose–volume parameters and anorectal function were assessed.

Results

Dmean to the rectum and anal sphincter complex was 50.5 Gy and 44.7 Gy, respectively. After a median follow-up of 38 (range 23–116) months, 33.3% of the patients reported major LARS. Mean LARS score was 23.4 ± 11.3 and mean Vaizey score was 4.3 ± 4.1. The most frequent complaints were clustering of defaecation and faecal urgency. Trends towards a higher Vaizey and LARS score after higher anal sphincter complex dose were observed, although these associations were not statistically significant.

Conclusions

This is the first study to investigate the late dose-volume effects of radiotherapy specifically on the anorectal function in rectal cancer patients. One-third of the patients had major LARS and the most frequent reported complaints were clustering and faecal urgency. Additionally, we observed trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose. However, this should be evaluated on a larger scale. Future efforts to minimise the dose to the sphincters could possibly reduce the impact of radiotherapy on the anorectal function.

INTRODUCTION

The standard of care for patients with locally advanced or distal rectal cancer is neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision (TME). CRT leads to downsizing and downstaging of the tumour in most patients, it may increase the opportunity for sphincter-saving surgery and CRT decreases the risk for local recurrence[1]. However, treatment with neoadjuvant CRT and TME can adversely affect bladder, sexual, and anorectal function in the long term[2]. In patients who achieve a complete response to neoadjuvant CRT, a watch-and-wait policy can be considered to avoid the related morbidity and mortality of TME[3-5].

The main goal of a watch-and-wait policy is an anticipated improved functional outcome and quality of life, while maintaining a good oncological outcome. While there is growing evidence supporting the oncological safety, the quality of life and functional outcomes after a watch-and-wait policy remain less explored. In a previous report we showed that quality of life after a watch-and-wait policy was better than after CRT and TME[6]. Nonetheless, the anorectal function was impaired in the watch-and-wait group, with one third of the patients reporting major bowel dysfunction. This comes as no surprise as irradiation of the rectum is known to cause injury to the rectal wall and related autonomic nerves resulting in impaired long-term functional outcome[7]. Because of the proximity of the anal canal to the tumour, the anal sphincter muscles are often also in the high-dose field of radiation in patients with low rectal cancer. However, very limited data are available on the relationship between radiotherapy dose and anorectal dysfunction in rectal cancer patients. Particularly in rectal cancer patients in whom no resection is performed after CRT, e.g. in patients following a watch-and-wait policy, the effects of chemoradiotherapy alone on functional outcomes can be assessed. In this study we assessed the long-term anorectal function in rectal cancer patients following a watch-and-wait policy, using the Vaizey score, LARS (Low Anterior Resection Syndrome) score and anorectal manometry. Additionally, we explored the associations between the radiotherapy dosimetric parameters of the rectum and anal sphincter complex and the anorectal function outcomes.

METHODS AND MATERIAL

Study population

Patients with primary rectal cancer and a complete response after CRT who were treated according to a watch-and-wait policy in our institute between January 2009 and April 2015 and who had a minimum follow-up of two years were included in this

cross-sectional study. Follow-up of two years was chosen so long-term effects, which at that time are expected to have reached a plateau phase, could be measured. All patients were part of a prospective cohort study on the watch-and-wait policy (clinicaltrials.gov NCT00939666) and a part was also included in a previous report on quality of life[6]. The inclusion criteria for a watch-and-wait policy in rectal cancer have been described previously[4,8]. Exclusion criteria for the present study were salvage therapy for recurrent disease or having a colostomy. Ethics committee approval was obtained for sending out questionnaires and patients gave a separate informed consent for a manometric evaluation of the anorectal function during routine follow-up.

Chemoradiotherapy

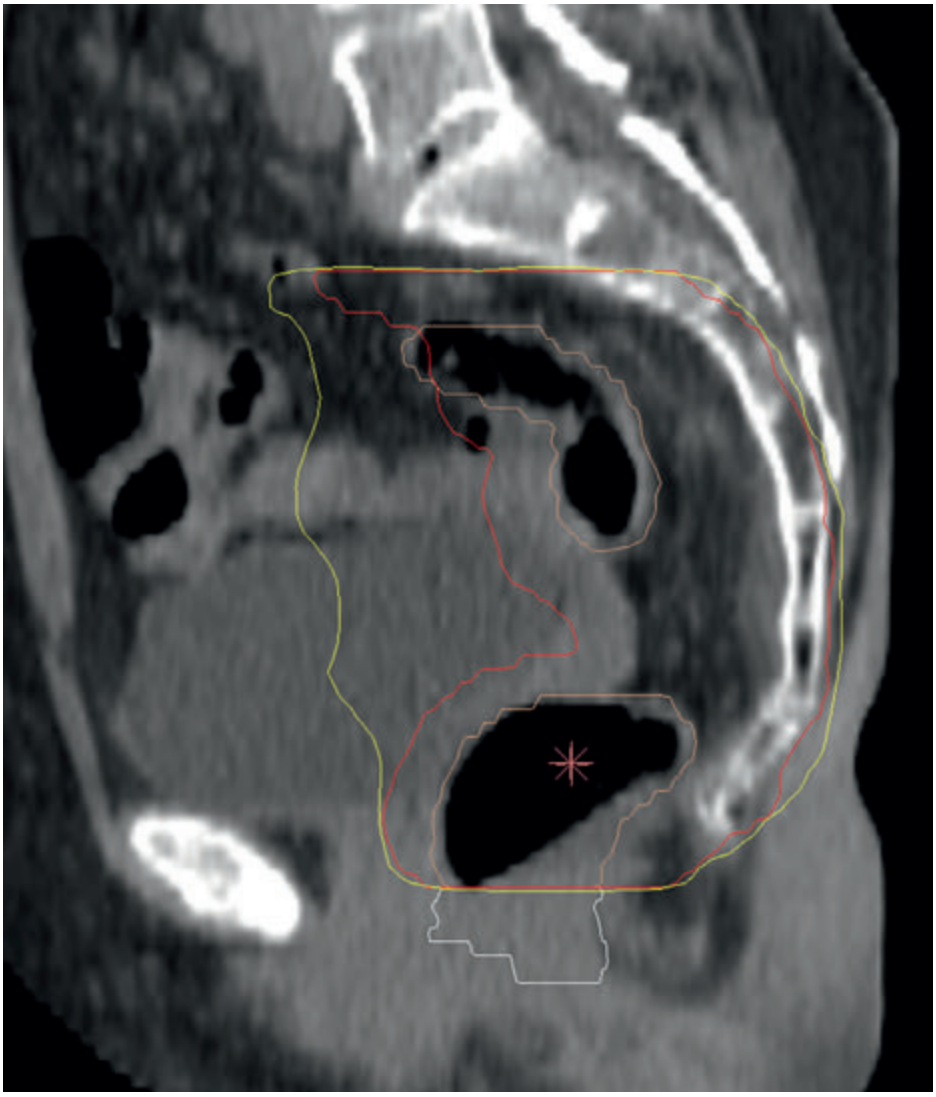
All patients were treated with chemoradiotherapy. 3D-conformal or intensity-modulated radiotherapy consisted of 50.4Gy, with daily fractions of 1.8Gy on weekdays. Dose specification occurred according to ICRU 50/62. The clinical target volume (CTV) included the gross tumour volume, the mesorectum, presacral and internal iliac node regions, and in case of distal node positive tumours the obturator fossa. A symmetric PTV margin of 1 cm was applied. No dose limitations were used for the anal sphincter complex during initial treatment planning. Radiotherapy was combined with 825 mg/m2/day capecitabine bid, seven days a week.

Organ delineation and dose calculations

The rectum and anal sphincter complex were manually delineated on the axial CT images (3 mm slice thickness) of the original radiotherapy planning CT scans, using FocalTM treatment planning system (XiO, Elekta AB, Stockholm, Sweden). Organ contours were defined according to the Pelvic Normal Tissue contouring guidelines by the Radiation Therapy Oncology Group (RTOG)[9]. The rectum was defined as a solid organ including the rectal contents from the lowest slice with a rectal lumen to the rectosigmoid flexure where the rectum moves ventrally and loses its round shape. The anal sphincter complex (internal and external sphincter muscle) circumference was delineated as a solid organ from anal verge to the anorectal border. All delineations were performed by one investigator (M.S.) and confirmed by a radiation oncologist specialised in rectal cancer treatment (M.B.). Examples of these delineations are shown in Fig. 1.

Dose–volume histograms (DVH) were calculated with the original treatment plans and were used to measure the radiation dosimetric coverage of the rectum and anal sphincter complex for each patient. The maximum and mean doses were calculated (Dmax and Dmean), as well as the relative volumes receiving a dose of 30–50 Gy or more (V30 Gy-V50 Gy).

Figure 1. Delineation of anal sphincter complex (white) and rectum (orange) on CT scan.



Manometry

Anorectal function was assessed using manometry at one of the routine follow-up outpatient visits. Anorectal manometry was performed with the patient in the left lateral position with knees and hips bent to 90°. Patients did not receive bowel preparation[10]. A four-channel catheter (Mui Scientific, Mississauga, Canada) with a water perfusion system connected to an electronic polygraph (Synectics Medical, Stockholm, Sweden) was used for the investigation. A 7 cm inflatable balloon was

incorporated at the top of the catheter. The catheter was calibrated outside the patient at study level before introduction. A stationary technique was used and mean anal resting pressure (MRP) and squeeze anal pressures (MRP) were measured[11]. These parameters were calculated as the average of the four radial measuring points. For rectal capacity, first rectal sensation (FS), volume at first urge to defaecate (FUTD) and maximum tolerable volume (MTV) were measured during stepwise balloon inflation. Manometry examinations were performed by two investigators (M.S. and B.H.).

Questionnaires

Anorectal function was also evaluated using two validated scores sent out as questionnaires: the Vaizey score and LARS score. The Vaizey score was used to assess faecal incontinence[12]. Patients were asked to evaluate their defaecation pattern in the last four weeks, including questions regarding consistency of stool loss, frequency and its effect on lifestyle. Results are reported on a continuous scale from 0 to 24. Faecal incontinence is defined as a score 12 points.

The Dutch version of the LARS score was used to evaluate bowel dysfunction[13]. It consists of five questions regarding incontinence for flatus and liquid stool, frequency, clustering and urgency. The range of this score is 0–42 and outcome categories are no LARS (score 0–20), minor LARS (score 21–29) and major LARS (score 30–42).

Statistical analysis

SPSS v22.0 (SPSS Inc, Chicago, IL) was used for statistical analyses. Stochastic regression imputation was used to impute incomplete variables to prevent a loss of statistical precision and to decrease the likelihood of bias. Multiple regression was used to quantify preliminary associations between the dose–volume parameters and the manometry and questionnaire scores and was adjusted for sex, tumour height and age. A two-tailed p value ≤0.05 was considered significant in all analyses.

RESULTS

Patient characteristics and dosimetric data

Thirty-three patients with a median age of 68 (range 38–85) years, of whom 21 male (64%), were included in this study. Patients' demographics are shown in Table 1. Median time from end of CRT to anorectal function assessment was 38 (range 23–117) months. Twenty-three patients (70%) had low rectal cancer (5 cm from anorectal junction), 10 patients had mid-high rectal cancer. Mean (±SD) distance from distal border of tumour to anorectal junction was 3.9 (±3.0) cm. The radiation dose–volume

data are shown in Table 2. The mean (±SD) Dmean and mean V50 Gy to the rectum were ± 1.3 Gy and 90.1 ± 19.4%, respectively. The mean (±SD) Dmean to the anal sphincter complex was 44.7 ± 9.7 Gy, whereas the V50 Gy was 47.1% ± 37.9%, meaning that on average 47% of the anal sphincter volume had a planned dose of ≤50 Gy.

Table 1. Patients' demographics (n = 33).

Characteristics	
Sex	
Male	21 (63.6%)
Female	12 (36.4%)
Median age, in years (range)	67.5 (38–85)
Median follow-up, in months (range)	38.4 (23–117)
cT stage	
cT2	8 (24.2%)
cT3	24 (72.8%)
cT4	1 (3.0%)
cN stage	
cN0	8 (24.2%)
cN1	12 (36.4%)
cN2	13 (39.4%)
Tumour height	
≤5 cm	23 (69.7%)
>5 cm	10 (30.3%)

Table 2. Radiation dose-volume data.

	Anal sphincter complex	Rectum
Volume (cm^3)	14.9 ± 4.7	98.0 ± 27.7
D_{max} (Gy)	47 ± 11	52.0 ± 1.1
D_{mean} (Gy)	44.7 ± 9.7	50.5 ± 1.3
V_{30} Gy (%)	85.4 ± 25.3	99.2 ± 2.7
V_{35} Gy (%)	85.0 ± 25.6	98.8 ± 2.8
V_{40} Gy (%)	81.3 ± 27.2	99.1 ± 2.7
V_{45} Gy (%)	80.3 ± 28.4	99.0 ± 3.1
V_{50} Gy (%)	47.1 ± 37.9	90.1 ± 19.4

Abbreviations: Dmax = Maximal dose, Dmean = Mean dose, V30 Gy-V50 Gy = percentage of volume receiving >30 to >50 Gy.

Manometry

Overall, the mean MRP was 30 ± 12 mmHg and mean MSP was 104 ± 41 mmHg. Mean volume at first sensation (FS) was 47 ± 26 mL, 88 ± 28 mL at first urge to defaecate (FUTD), and 136 ± 36 mL at maximum threshold (MTV), see Table 3.

Table 3. Results of anorectal manometry.

	***n* = 33**
MRP, mean (SD) mmHg	30 (12)
MSP, mean (SD), mmHg	104 (41)
FS, mean (SD), mL	47 (26)
FUTD, mean (SD), mL	88 (28)
MTV, mean (SD), mL	136 (36)

Abbreviations: MRP = mean resting pressure, MSP = mean squeeze pressure, FS = volume to first sensation, FUTD = volume to first urge to defecate, MTV = maximum tolerable volume.

Questionnaire outcomes

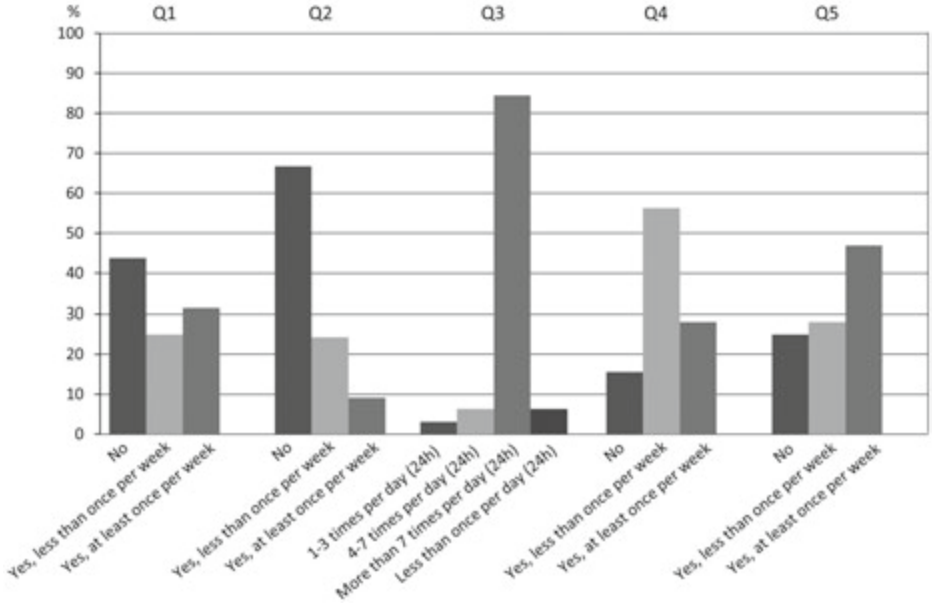
The mean Vaizey score was 4.3 ± 4.1. Two (6%) patients had faecal incontinence, based on the Vaizey score (>12 points). The results for all items on the Vaizey score are presented in Table 4. Of the 33 patients, 15 (46%) patients reported a lack of the ability to defer defaecation for 15 minutes. One (3%) patient reported the use of pads/plugs, and one (3.0%) other patient reported the use of constipating agents.

Table 4. Vaizey score items (n=33).

	Never	**Rarely**	**Sometimes**	**Weekly**	**Daily**
Incontinence for solid stool, *n* (%)	28 (85)	– (0)	4 (12)	– (0)	1 (3)
Incontinence for liquid stool, *n* (%)	21 (64)	7 (21)	4 (12)	1 (3)	– (0)
Incontinence for gas, *n* (%)	13 (40)	11 (33)	5 (15)	1 (3)	3 (9)
Alterations in lifestyle, *n* (%)	27 (81)	3 (10)	2 (6)	– (0)	1 (3)
	No	**Yes**			
Need to wear a pad/plug, *n* (%)	32 (97)	1 (3)			
Use of constipating agents, *n* (%)	32 (97)	1 (3)			
Unable to defer defaecation for 15 min, *n* (%)	17 (54)	15 (46)			

The mean LARS score was 23.4 ± 11.3. Twelve (36%) patients had no LARS (score 0–20), 10 (30%) patients had minor LARS (score 21–29) and 11 (33%) patients had major LARS (score 30–39). The most reported complaint in the LARS questionnaire was clustering, with nine (27%) patients reporting clustering at least once a week and 18 patients (55%) less than once a week. Urge incontinence for faeces at least once a week was reported by 15 (46%) patients and less than once a week by 9 (27%) patients. Occasions of uncontrollable flatus at least once a week were reported in 10 (30%) patients, less than one a week in 8 (24%) patients. Complaints of frequency or accidental leakage of stools were less often reported, see Figure 2.

Figure 2. LARS score; answers per question.



Q1: Do you ever have occasions when you cannot control your flatus?
Q2: Do you ever have any accidental leakage of liquid stool?
Q3: How often do you open your bowel?
Q4: Do you ever have to open your bowels again within one hour of the last bowel opening?
Q5: Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

Correlation of dosimetric data to anorectal function

There weren't any statistically significant associations between dose parameters and the LARS or Vaizey score. However, we did observe a trend towards higher Vaizey scores after higher Dmax (b=0.341, p=0.211), V30 Gy (b=0.374, p=0.095), V35 Gy (b=0.343, p=0.126) and V40 Gy (b=0.381, p=0.109) of the anal sphincter complex. Additionally, a trend towards higher LARS scores after higher Dmean of the anal sphincter complex (b=0.362, p=0.122) was observed. Regarding the rectal dose, regression analysis showed trends towards higher Vaizey scores after higher V35 Gy (b=0.353, p=0.066) and V40 Gy (b=0.309, p=0.117), although not statistically significant. The results of all regression analyses are presented in the Supplementary files.

For all dosimetric parameters of the anal sphincter complex, except V50 Gy, higher doses were associated with higher squeeze pressure (MSP). No associations were found between the dosimetric parameters and resting pressure (MRP) or anorectal sensory function (FS, FUTD, MTV).

DISCUSSION

This study assessed the long-term anorectal function and the association between the anorectal function and the radiotherapy dose parameters in rectal cancer patients following a watch-and- wait policy. One-third of the patients has major LARS after a minimal follow-up of two years. The most frequent complaints were clustering of defaecation and faecal urgency. Additionally, we observed trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose.

To date, there have been few studies that assessed the anorectal function in rectal cancer patients treated according to a watch- and-wait policy after CRT. In our previous study by Hupkens et al.[6], the long-term quality of life and functional outcomes were compared between 41 watch-and-wait patients and 41 patients treated with CRT and TME. In that study, 36% of the watch-and-wait policy patients experienced major LARS, compared to 67% of the patients who underwent CRT followed by TME. This showed that although bowel function was generally better after a watch-and-wait policy, there were patients with significant functional impairment after CRT alone.

Habr-Gama et al. on the other hand concluded that the consequences of radiotherapy on the anorectal function may be minimal[14]. The anorectal function of patients undergoing watch-and-wait after CRT to was compared to the function of patients treated with full-thickness local excision after CRT. Fifty-four watch-and-wait patients were assessed with anorectal manometry and validated questionnaires and most outcomes were considered to be within the normal range. However, the Fecal Incontinence Quality of Life (FIQL) Scale and the Vaizey score were used, which both emphasise on faecal incontinence. Although faecal incontinence is a common issue, bowel dysfunction after rectal cancer treatment is more complex and may also involve frequent bowel movements and complaints of clustering and faecal urgency[15]. The scores used in the study of Habr-Gama et al. may not have been sensitive enough to detect these complaints adequately and may therefore have underestimated the adverse effects of radiotherapy.

Despite an absence of baseline anorectal function information in the present study, it is likely that neoadjuvant chemotherapy contributed to the observed bowel dysfunction in this study population as it is well known that neoadjuvant radiotherapy is a risk factor for anorectal dysfunction after TME[16–18]. In other pelvic malignancies, however, it is better established what the effects of stand-alone radiotherapy are on bowel functioning. In anal cancer, approximately

43-54% of the patients report faecal incontinence after radiation treatment[19–21]. In prostate cancer patients, faecal incontinence is reported in up to 57% and bowel urgency in 34%[22,23].

Faecal continence is a complex system and multiple components fundamental to continence are suggested to be involved in the pathogenesis of radiotherapy induced anorectal dysfunction. Some studies suggest that radiotherapy negatively affects innervation of the anorectum, including the pudendal nerve, the myenteric plexus, and the lumbosacral plexus.[24–26] Furthermore, radiotherapy can induce structural morphologic alterations, such as collagen depositions in the internal and external anal sphincter[25,27], and fibrosis of the rectal wall[28]. This can compromise sphincter tone, sphincter contractibility, and anorectal sensitivity. Although we did not find an association between higher planned radiotherapy dose to the anal sphincter complex and lower anal pressures, we did observe low mean anal resting pressures and anal squeeze pressures after CRT in the present study when compared to normal values from literature[29]. This is in accordance with other studies showing reduced anal sphincter tone and squeeze pressures after pelvic irradiation[30–32]. Decreased anal pressures have been related to complaints of urgency and incontinence specifically[33,34]. In prostate cancer, decreased sensory thresholds for defaecation urge have also been reported after irradiation, while in the present study these were in the normal range[30,35].

While there were no significant associations between the dose parameters and questionnaire outcomes, the results suggest that higher Vaizey and LARS score were associated with a higher Dmean and Dmax of the anal sphincter complex, and a higher LARS score with higher Dmean of the rectum. One other study in rectal cancer survivors, treated with CRT and TME, investigated the relationship between radiation dose and anorectal function[36]. They showed that the volume of the anal sphincters receiving >20 Gy was predictive of poor sphincter control as measured on the Wexner scale. In prostate cancer survivors, it has repeatedly been shown that dosimetric parameters of the anal sphincter and rectum are associated with late gastrointestinal toxicity and patient reported outcomes[37–39]. Moreover, the dose to different anatomic substrates have been correlated to different symptoms[33,40]. These studies[33,37–40] suggest that the anorectal region should be avoided whenever possible during radiation treatment planning for prostate cancer. Delineation guidelines and dose constraints for the anal sphincter complex could also facilitate sphincter sparing radiotherapy in rectal cancer, and thereby possibly reduce the impact on functional outcomes.

The following limitations should be taken into consideration when interpreting the results of the present study. Our analyses are based on a relatively small group

of patients. As a result, we observed several associations that may be of clinical relevance, but lacked the statistical power to draw firm conclusions. Furthermore, we had no baseline information about the anorectal function, and it remains unclear whether the reported symptoms were present before the diagnosis of rectal cancer and treatment with CRT. However, when baseline measurements are taken in rectal cancer patients, these measurements are likely to be influenced by the rectal tumour and may not represent normal anorectal functioning. In the absence of questionnaires that have been validated specifically for patients undergoing a watch-and-wait policy, we used the LARS score to assess bowel dysfunction.

Despite these limitations, this is the first study to explore the specific dose-volume effects of chemoradiation alone in rectal cancer patients on the long-term anorectal function. Our results may provide support in the rationale for sphincter sparing radiotherapy, however the relation between the dosimetric parameters and the long-term anorectal function in chemoradiation for rectal cancer should be evaluated on a larger scale. Especially with the current interest in radiotherapy to achieve organ preservation in rectal cancer, insights into functional deterioration after radiotherapy are needed, as well as insights into the specific mechanisms that are affected. With these insights, further improvements in radiotherapy delivery could be aided, as to maximise the effect on the tumour while minimising the detrimental impact on the anorectal function.

CONCLUSION

In conclusion, it is often difficult to differentiate between the radiation and surgery induced damage in rectal cancer patients treated with chemoradiotherapy. This study in rectal cancer patients followed in a watch-and-wait programme is the first study to investigate the dose-volume effects of radiotherapy specifically on the anorectal function in rectal cancer patients. One third of the patients reported major LARS after a minimal follow-up of two years. The most frequent complaints were clustering of defaecation and faecal urgency. Additionally, we observed trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose. However, this should be evaluated on a larger scale. Future efforts to minimise the dose to the sphincters could possibly reduce the impact of radiotherapy on the anorectal function.

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APPENDIX A: SUPPLEMENTARY FILES.

Supplementary table. Multiple regression analyses of influence of dosimetric parameters on anorectal manometry outcomes, Vaizey and LARS score.

	Anorectal manometry										Questionnaires			
	MRP		MSP		FS		FUTD		MTV		Vaizey		LARS	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Anal sphincter complex														
D_{max}	-0.260	0.149	0.371	0.064	0.143	0.447	0.160	0.437	0.228	0.262	0.341	0.098	0.211	0.314
D_{mean}	-0.001	0.996	0.362	0.113	-0.006	0.979	-0.055	0.813	-0.045	0.845	0.276	0.242	0.362	0.122
V_{30Gy}	0.018	0.927	0.444	0.040	0.207	0.309	0.190	0.395	0.208	0.348	0.374	0.095	0.189	0.407
V_{35Gy}	0.055	0.781	0.475	0.027	0.203	0.319	0.215	0.332	0.242	0.271	0.343	0.126	0.180	0.429
V_{40Gy}	0.111	0.599	0.521	0.022	0.004	0.985	-0.023	0.922	0.081	0.733	0.381	0.109	0.209	0.388
V_{45Gy}	0.191	0.365	0.493	0.031	-0.028	0.898	-0.021	0.930	0.095	0.688	0.285	0.235	0.069	0.778
V_{50Gy}	0.060	0.766	0.134	0.554	0.009	0.966	-0.024	0.917	-0.080	0.724	0.182	0.428	0.215	0.350
Rectum														
D_{max}	-0.255	0.217	0.417	0.037	0.089	0.639	0.108	0.601	0.164	0.423	0.291	0.162	0.238	0.257
D_{mean}	-0.128	0.491	-0.240	0.245	-0.053	0.782	-0.135	0.518	-0.265	0.197	0.047	0.827	0.236	0.264
V_{30Gy}	-0.142	0.400	0.026	0.224	0.064	0.707	0.091	0.625	0.087	0.639	0.240	0.206	0.188	0.314
V_{35Gy}	-0.086	0.618	0.257	0.179	0.160	0.366	0.180	0.351	0.309	0.102	0.244	0.212	-0.092	0.642
V_{40Gy}	-0.064	0.709	0.292	0.124	0.213	0.224	0.215	0.261	0.317	0.091	0.353	0.066	-0.032	0.872
V_{45Gy}	-0.076	0.664	0.342	0.075	0.190	0.291	0.204	0.297	0.309	0.108	0.309	0.117	0.002	0.991
V_{50Gy}	-0.164	0.339	0.297	0.118	0.214	0.223	0.255	0.181	0.254	0.181	0.200	0.309	0.191	0.332

Results are corrected for sex, tumour height and age.

Abbreviations: MRP = resting pressure, MSP = squeeze pressure, FS = volume to first sensation, FUTD = volume to first urge to defecate, MTV = maximum tolerable volume, LARS = Low Anterior Resection Syndrome score.

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5

LONG-TERM QUALITY OF LIFE AND FUNCTIONAL OUTCOME OF RECTAL CANCER PATIENTS FOLLOWING A WATCH-AND-WAIT APPROACH: A PROSPECTIVE COHORT STUDY

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IMPORTANCE OF PATIENT REPORTED AND CLINICAL OUTCOMES FOR PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER AND THEIR TREATING PHYSICIANS. DO CLINICIANS KNOW WHAT PATIENTS WANT?

ABSTRACT

Introduction

Several factors are included in decision making for treatment of patients with locally advanced rectal cancer, including a trade-off between risks and gains of both clinical and functional outcomes. However, it is largely unknown which outcomes are most important to patients and whether this differs between patients and clinicians.

Methods

Both clinicians and patients treated for locally advanced rectal cancer were invited to fill out an online questionnaire, including a choice-based conjoint experiment. Participants were presented 14 comparisons of two hypothetical case presentations, characterized by different treatments and outcomes of care (6 attributes) and were asked to select the case with the best outcome at that moment. Hierarchical Bayes Estimation was used to calculate the relative importance (RI) of each of the six attributes.

Results

In total, 94 patients and 128 clinicians completed the questionnaire. For patients, avoiding surgery with permanent stoma was most important (RI 24.4, 95%CI 21.88–26.87) and a 2-year difference in disease-free survival was least important (RI 5.6, 95%CI 4.9–6.2%). Clinicians assigned highest importance to avoiding severe and daily worries about cancer recurrence (RI 30.7, 95%CI 29.1–32.4), while this was ranked 4th by patients (RI 17.9, 95%CI 16.5–19.4, $p < 0.001$).

Conclusion

When confronted with different outcomes within one case description, patients find the duration of disease-free survival the least important. In addition, considerable differences were found between the importance assigned by patients and clinicians to clinical and functional outcomes, most notably in avoiding surgery with permanent stoma and worries about recurrence.

INTRODUCTION

The standard of care for patients with high-risk rectal cancer includes preoperative chemoradiotherapy and surgery. Several factors have contributed to major improvements in local recurrence rates and survival in the last decades, resulting in increased attention for long-term functional and patient reported outcomes. Unfortunately, treatment for rectal cancer is still associated with considerable morbidity, including a temporary or definitive colostomy, fecal incontinence, urinary incontinence and sexual dysfunction[1,2]. For patients without detectable residual tumour after neoadjuvant chemoradiotherapy, a 'clinical complete response', watch and wait (W&W) is increasingly adopted as a treatment option[3]. The benefits of W&W are clear, as patients potentially avoid the risk of surgical morbidity, and the oncological risks of W&W seem to be very small for strictly selected clinical complete responders[4]. Several studies are now focusing on achieving organ preservation in more patients by increasing complete response rates. This can be done either by intensifying neoadjuvant therapy[5]; expanding the waiting period between radiotherapy and surgery[6]; or adding preoperative (chemo)radiotherapy in patients with less advanced tumours[7,8] However, for patients who still require surgery these approaches may lead to inferior outcomes, because the risk of complications and morbidity is higher in patients who have received preoperative (chemo)radiotherapy and surgery compared to patients undergoing surgery alone. In addition, some patients still prefer surgery above frequent surveillance and the risk of tumour regrowth, even if the oncological outcome is equal[9]. It is therefore essential to know the patients' preferences when deciding on the best approach for an individual patient. However, little is known about the reasoning leading to treatment choices; which outcomes are considered most important by patients? Both clinical outcomes like survival and patient reported outcomes on worries about cancer recurrence or fecal, urinary or sexual dysfunction will undoubtedly play a role to a certain extent. In the present study, we aim to examine the tradeoffs between different clinical and patient reported outcomes by patients, and the extent to which clinicians value the same outcomes.

MATERIALS AND METHODS

Study design

A questionnaire study was conducted containing a choice-based conjoint experiment among patients and clinicians. Patients were eligible if they had completed curative treatment for locally advanced rectal cancer with long course chemoradiotherapy

or a comparable long-course neoadjuvant treatment schedule between 6 and 18 months before inclusion. This period was chosen to balance between emotional burden for patients still undergoing treatment and recall bias if treatment was longer ago. Patients who had surgery (any type) were eligible as well as W&W patients. Other inclusion criteria for patients were: age >18 years, good command of Dutch language and no signs of residual or recurrent disease. Patients from six participating institutions were invited, including three general hospitals, two academic hospitals and one tertiary referral center. All participating hospitals have expertise in surgical treatment for rectal cancer and W&W strategies. Patients were invited to fill out an online questionnaire via mail, and in case of no response after 2 weeks, they received a one-time reminder by telephone. The questionnaires were filled out anonymously and the researchers did not collect any personal data from the hospital records.

Clinicians directly involved in the decision making and treatment of patients with rectal cancer were invited to participate, including surgeons, gastroenterologists, radiation oncologist and medical oncologists. Clinicians were approached by e-mail via their professional association and scientific conferences. No personal reminders were sent. The questionnaires were filled out anonymously. This study was approved by the Medical Ethics committee of the Netherlands Cancer Institute, Amsterdam (METC18.939), and by the board of directors of all six participating institutions. Patients nor clinicians received any compensation for participation.

Questionnaire

An online questionnaire was developed using Sawtooth Software SSI Web 8.2.4 (Sequim, WA, www.sawtooths oftware.com), following a similar design as a previous study among breast cancer patients[10]. The first part of the questionnaire consisted of general questions about the respondent. For patients, this included general questions on their age, family situation and the type of received treatment. For clinicians, this included general questions about their age, position and experience. In the second part, we asked all participants to rank seven different aspects of the treatment for rectal cancer from most important to least important to them (1 being the most important and 7 the least important): “to live longer” (disease-free survival, DFS); “to have no colostomy”; “to have no surgery”; ““to have no fecal incontinence”, “to have no urinary incontinency”, “to have no sexual dysfunction”; “to have no worries about cancer recurrence”.

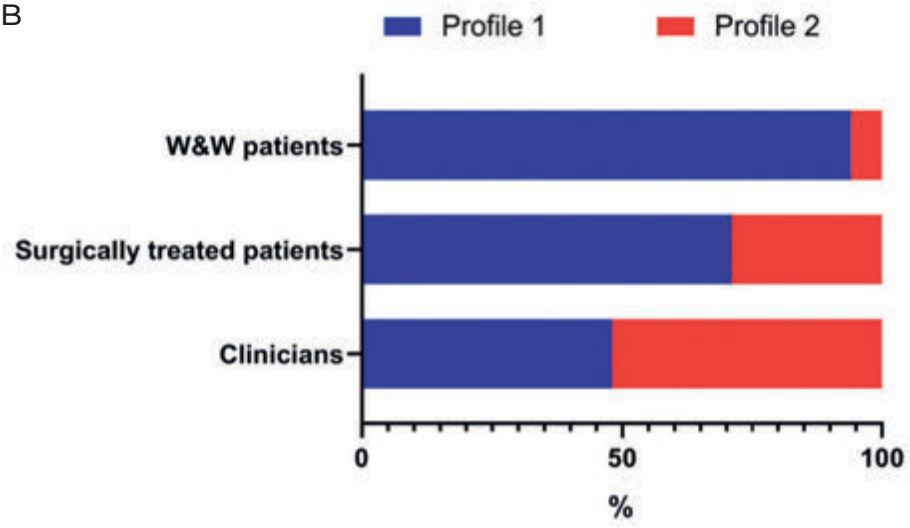
The third part of the questionnaire included the choice-based conjoint (CBC) experiment, consisting of 14 tasks to compare the treatment outcomes of two hypothetical case descriptions. An example of such a task is displayed as Fig. 1A. Participants were asked to choose which of two cases had, in their opinion, the

Figure 1. A) Example CBC task presented to all participants and response of patients (W&W and patients who had surgery, and clinicians) B) Response of W&W patients, patients who underwent surgery and clinicians.

A

	Profile 1	Profile 2
Disease free survival	7 years	9 years
Type of treatment after chemoradiotherapy	Watch-and-wait	Surgery with definitive colostomy
Fecal incontinence	Incidental unintended loss of stools or mucus. Wearing a pad	No fecal incontinence
Urinary dysfunction	No urinary dysfunction	Impaired sense of urgency, toilet use at fixed times
Sexual dysfunction	No sexual dysfunction	Male: retrograde ejaculation Female: vaginal dryness
Worries about cancer recurrence	Weekly difficulty sleeping due to worries about cancer recurrence	No worries about cancer recurrence

B



best outcome of rectal cancer treatment. Each profile was characterized by six attributes containing both treatment given for rectal cancer and possible outcomes, where each attribute could vary from the worst to best possible outcome across 3 or 4 levels. (e.g. between no complaints and severe complaints, see Table 1). We chose to limit the experiment to six attributes, as participants are known to switch to simplification strategies to deal with the difficulty of a comparison when faced with too much information in a choice experiment[11]. Relevant attributes were selected based on literature regarding adverse outcomes known to influence long-term influence on quality of life. Subsequently, relevant levels for each attribute were decided after consultation with clinical experts. Tasks with impossible or clinically irrelevant combinations of attributes within one profile were prohibited. The questionnaire was pilot tested among professionals and patients for language and inconsistencies. Eventually ten versions of the questionnaire were generated, including 12 random tasks and two 'fixed' tasks that were identical in all versions. These versions were randomly distributed over all respondents. The order of attributes was also randomized across respondents, to prevent biased importance for the first mentioned attribute. We used the exact same hypothetical case profiles for patients and medical professionals, with only textual modifications from layman's language to medical terminology. All case descriptions were presented in the third person to prevent hindsight bias in patients.

Statistical analysis

Only participants who completed the entire questionnaire were included for analysis. Descriptive analyses were used to describe the characteristics of respondents. First, we assessed the mean ranking of the participants prior to the CBC experiment, including the percentage of participants who put the attribute at that rank as a measure of consensus between participants. Subsequently, Hierarchical Bayes estimation was used to calculate the importance of each attribute based on all answers given by the respondent within one questionnaire, expressed as the mean utility (standard deviation) and relative importance (RI +95% confidence interval). For each attribute, the RI is calculated using the maximum difference in utilities within that attribute relative to the total across all attributes, which is set to 100[12]. In other words, a higher RI of one attribute reflects that on average more participants assign a stronger preference for the best compared to the worst level of this specific outcome. The RI assigned to an attribute by patients versus clinicians were compared using an independent t-test. If the confidence intervals were not overlapping and the p-value was <0.01, this was considered a statistically significant difference. The Root likelihood (RLH) indicates the goodness of the fit of the total model, where the best possible RLH is 1.0, and the worse possible is the 'null RLH' expected by chance,

Table 1. Attributes, levels and explanation for patients.

Attribute	Levels	Description
Disease-free survival	1. 7 years 2. 8 years 3. 9 years	The years a patient is alive without any signs of cancer recurrence.
Type of treatment	1. TME with permanent colostomy 2. TME with temporary colostomy 3. TME without colostomy 4. Watch and wait	After neoadjuvant chemoradiotherapy, there are several therapeutic options. The options included in this questionnaire were: surgery with a permanent stoma; surgery with temporary stoma; or surgery without a stoma. The fourth option is to "watch and wait". This is an option for patients in whom the tumour and lymph nodes are completely resolved after neoadjuvant therapy. Instead of surgery, active surveillance is then performed with frequent endoscopy, MRI and clinical examinations, because there is a chance that the tumour regrows, in which case surgery has to be performed anyway.
Fecal incontinence	1. Severe complaints 2. Mild complaints 3. No complaints	Weekly unintended loss of stools after which change of clothes is required Incidental loss of mucus or stool, wearing a pad No complaints of fecal incontinence
Urinary dysfunction	1. Severe complaints 2. Mild complaints 3. No complaints	Urinary incontinence, or self-catherization necessary Impaired sense of urgency, toilet use at fixed times No complaints of urinary dysfunction
Sexual dysfunction	1. Severe complaints 2. Mild complaints 3. No complaints	Impotence (male) or pain during intercourse (female) Retrograde ejaculation; semen enters the bladder instead of emerging through the penis during orgasm (male) or vaginal dryness (female) No complaints of sexual dysfunction
Worry about cancer recurrence	1. Severe, daily worries 2. Mild worries 3. No worries	Daily difficulty sleeping due to worries about cancer recurrence Weekly difficulty sleeping due to worries about cancer recurrence No complaints of worries about cancer recurrence

The questionnaire was conducted in Dutch; attributes, levels and the descriptions are translated into English for the purpose of this report.
Abbrevations: TME; total mesorectal excision.

calculated as 1/the number of alternatives (0.5 in the current study). A higher RLH thus indicates higher consistency of the respondent throughout the questionnaire. To investigate differences in the priorities of patients who underwent different treatment, a subgroup-analysis was performed comparing between preferences for patients with a colostomy, patients without a colostomy and W&W patients (who did not undergo surgery). A second subgroup analysis was performed among physicians, based on their clinical specialty. All analyses were performed in Sawtooth Lighthouse Studio Version 9.6.1 and SPSS statistics 25.

RESULTS

Participants

In total, 174 patients were invited from 6 participating institutes, of whom 102 (59%) patients responded and eventually 94 (54%) patients completed the questionnaire. Mean age was 62 years and 43% of patients were female (Table 2). 55% of patients underwent surgical resection according to TME principle, 7% underwent transanal endoscopic microsurgery (TEM) and 37% were enrolled in a W&W program. Out of 176 clinicians who responded to the invitation, 128 (72%) completed the questionnaire. Most respondents were surgeons (n=71), followed by radiation oncologists (n=24), medical oncologists (n =17) and gastroenterologists (n=16). No significant differences in characteristics were found between the participants who completed the questionnaire and those who did not complete the questionnaire (Supplementary Table A).

Direct ranking exercise

IN the direct ranking exercise prior to the CBC experiment, most patients (80%) as well as clinicians (64%) ranked “to live longer” as the most important outcome in the ranking exercise, followed by having “no worries about cancer recurrence” (Table 3). Patients ranked the attribute “to have no surgery” considerably higher (5th) than clinicians, of whom 51% ranked this as the least important outcome. The subgroup analysis showed some differences in preferences between patients who underwent different treatment (supplementary Table B): W&W patients especially ranked “to have no colostomy” and “to have no surgery” higher than patients who underwent surgery and have a colostomy themselves. Correspondingly, patients with a colostomy ranked having “no fecal incontinence” as more important than W&W patients and patients without a colostomy, who have a higher risk to have experienced postoperative fecal incontinence themselves. Between clinicians with a different specialty, no major differences were found.

Table 2. Respondent characteristics.

Patients	n= 94	Clinicians	n=128
Age, mean (SD)	61 (9)	**Age, mean (SD)**	49 (10)
Sex		**Sex**	
Female	40 (42.6)	Female	50 (39.1)
Male	54 (57.4)	Male	78 (60.9)
Marital status		**Specialty**	
Married	69 (73.4)	Surgeon	71 (55.5)
Unmarried	12 (12.8)	Gastroenterologist	16 (12.5)
Single	6 (6.4)	Radiation oncologist	24 (18.8)
Widowed	3 (3.2)	Medical oncologist	17 (13.3)
Divorced	4 (4.3)		
Surgical approach		**Current position**	
Open TME	25 (26.6)	Senior staff	106 (82.8)
Laparoscopic TME	27 (28.7)	Fellow	8 (6.3)
TEM	7 (7.4)	Resident in training	14 (10.9)
No surgery (W&W)	35 (37.2)		
Colostomy		**Years of experience**	
Permanent colostomy	28 (29.8)	< 5 years	13 (10.2)
Temporary colostomy	4 (4.3)	5-10 years	27 (21.1)
Temporary colostomy, reversed	13 (13.8)	11-20-years	49 (38.3)
None	49 (52.1)	> 20 years	39 (30.5)
		Hospital of employment	
		Academic hospital	33 (25.8)
		General hospital	86 (67.2)
		Tertiary referral hospital	9 (7.0)

Data are presented as n (%) unless indicated otherwise.
Abbreviations: TME = total mesorectal excision, W&W = watch and wait, SD = standard deviation.

Table 3. Mean ranking by patients and clinicians prior to choice-based conjoint experiment.

Ranking	Patients (n = 94)	Clinicians (n = 128)
1	To live longer (80%)	To live longer (64%)
2	No worries about cancer recurrence (48%)	No worries about cancer recurrence (39%)
3	No colostomy (34%)	No fecal incontinence (37%)
4	No faecal incontinence (27%)	No colostomy (17%)
5	No surgery needed (18%)	No urinary dysfunction (29%)
6	No urinary dysfunction (31%)	No sexual dysfunction (27%)
7	No sexual dysfunction (44%)	No surgery needed (51%)

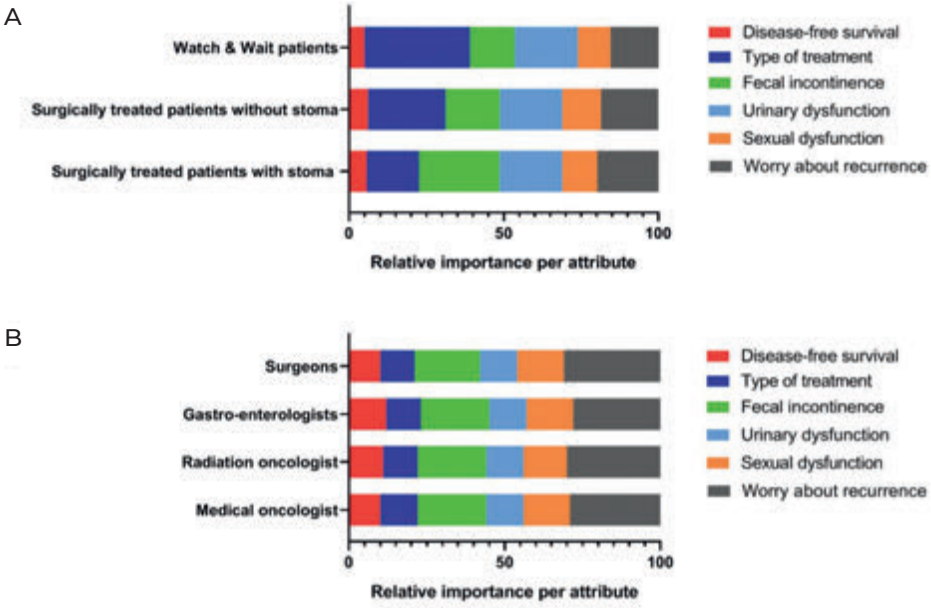
Mean ranking of the attributes, with the percentage of patients/clinicians who put the attribute at that rank in parentheses

Choice-based conjoint experiment

In the choice-based conjoint experiment, participants were asked to choose which hypothetical patient had the best outcome of treatment for rectal cancer in their opinion. Figure 1A shows one of the fixed tasks presented to all respondents. Notably, most patients preferred the first profile (Figure 1B), independent of the (surgical or non-surgical) treatment they had received, whereas the opinion of clinicians was evenly distributed (48% chose profile 1 versus 52% for profile 2).

The mean utility and relative importance of the attributes in relation to each other are reported in Table 4. For patients, in contrast to the results of the direct ranking exercise prior to the choice-based experiment, a difference of 2 years in DFS was considered least important (RI 5.59, 95%CI 4.94–6.23) and type of treatment was on average 4 times more important (RI 24.38, 95%CI 21.88–26.87), with particularly strongly negative utility for TME with permanent colostomy. The subgroup analysis showed that DFS was considered least important, independent of the surgical treatment received by patients (Figure 2A). On average, fecal incontinence and urinary incontinence were equally important (Table 4, RI 20.48 95%CI 18.65–22.32 and RI 20.36, 95%CI 18.93– 21.80). However, as shown in Figure 2A, surgically treated

Figure 2. Subgroup analysis.



A) Relative importance of patients per group based on the type of treatment. B) Relative importance of clinicians based on clinical specialty

Table 4. Overall utility and relative importance for patients and clinicians.

		Patients (n = 94)			Clinicians (n = 128)			
RLH	Mean (range)	0.86 (0.62-0.95)			0.85 (0.61-0.94)			
Attributes	**Levels**	**Mean overall utility per level (SD)**		**Overall RI (95% CI)**	**Mean overall utility per level (SD)**		**Overall RI (95% CI)**	**p-value**
Disease-free survival	7 years	- 4.73	16.58	5.59 (4.94-6.23)	-19.59	32.44	10.30 (9.00-11.60)	< 0.001*
	8 years	- 4.25	9.84		-1.90	18.18		
	9 years	8.89	17.90		21.50	30.32		
Type of treatment	TME with perm. colostomy	-82.61	47.10	24.38 (21.88-26.87)	-31.98	15.83	10.85 (10.12-11.57)	< 0.001*
	TME with temp. colostomy	13.78	20.77		0.74	18.34		
	TME without colostomy	28.11	29.43		15.23	17.63		
	Watch and wait	40.74	48.09		16.01	22.03		
Fecal incontinence	Severe complaints	-66.83	43.36	20.48 (18.65-22.32)	-73.44	23.45	21.40 (20.39-22.41)	< 0.001
	Mild complaints	18.17	25.91		19.02	17.42		
	No complaints	48.66	22.74		54.42	14.03		
Urinary dysfunction	Severe complaints	-71.35	28.21	20.36 (18.93-21.80)	-40.28	14.71	11.95 (11.28-12.61)	< 0.001*
	Mild complaints	24.46	14.96		11.63	13.40		
	No complaints	46.88	22.37		28.66	12.33		
Sexual dysfunction	Severe complaints	-27.51	13.49	11.25 (10.34-12.16)	-40.32	15.71	14.79 (14.11-15.46)	< 0.001*
	Mild complaints	-8.60	15.07		-6.68	11.69		
	No complaints	36.11	17.53		46.99	13.64		
Worry about cancer recurrence	Severe. daily worries	-57.90	27.43	17.94 (16.49-19.40)	-106.25	34.20	30.72 (29.08-32.35)	< 0.001*
	Mild worries	14.37	23.28		31.01	21.17		
	No worries	43.54	23.90		75.25	28.97		

Independent t-tests were used to compare the relative importance in the patient and clinicians group. A p-value <0.01 and non-overlapping confidence intervals indicates a statistically significant difference (*)

Abbreviations: RLH = root likelihood, SD = standard deviation, RI = relative importance.

patients assigned higher importance to not having any fecal incontinence than W&W patients, whereas urinary dysfunction was similarly important in all subgroups. For W&W patients, the type of treatment was considered more important (i.e. avoiding surgery with a permanent colostomy), whereas patients who had a colostomy assigned higher importance to avoiding fecal incontinence.

For clinicians, the CBC-experiment showed they considered DFS and the type of treatment least important (RI 10.30, 95%CI 9.00–11.60 and RI 10.85, 95%CI 10.12–11.57 respectively). Not having to worry about cancer recurrence was considered the most important attribute by clinicians. The subgroup analysis comparing clinicians of different specialties showed that their opinions were remarkably consistent, despite the small sample size (Figure 2B). There were considerable differences in the preferences between patients and clinicians. The importance of DFS and worries about cancer recurrence were statistically significantly lower in patients compared to clinicians, whereas the importance of the type of treatment and urinary incontinence were statistically significant higher in patients than in clinicians (Table 4, all $p < 0.001$).

DISCUSSION

In this study, patients on average ranked “to live longer” as the most important outcome in the direct ranking exercise. Surprisingly, this turned out to be the least important outcome in the conjoint analysis when simultaneously confronted with multiple other outcomes, showing that patients are not willing to accept inferior functional outcome against all costs to have one or two years longer survival. Patients valued the attribute “the type of treatment” at least 4 times more important than DFS, whereas clinicians evaluated these attributes equally and least important. Figure 1 clearly illustrates the disagreement in preferences of patients and clinicians. It was hypothesized that participants would be 50-50 divided on this task given to all participants, which turned out to be true only for clinicians, whereas 80% of all patients preferred the first profile. In addition, patients considered “worries about cancer” far less important than clinicians but assigned higher importance to urinary dysfunction. Undoubtedly, the choices patients make are motivated by the treatment they have undergone and toxicity they have experienced (Figure 2A).

As there are various treatment approaches available, shared decision making (SDM) is essential to choose the best strategy for an individual patient. However, in clinical practice this is not always easily executed, mainly due to lack of time and differences in understanding between patients and clinicians[13]. A study examining SDM for preoperative radiotherapy in rectal cancer patients reported that in 46% of

the audio-taped pretreatment consultations the patients' values and preferences were not discussed at all[14]. In only half of the consultations patients expressed their values at their own initiative. Most frequently mentioned values were related to sexual dysfunction and fecal incontinence. However, the presence of a colostomy and W&W as a treatment option were not included in this study. The present study indicates that after undergoing treatment, sexual dysfunction may be considerably less important compared to other attributes.

Focusing on patient preferences for organ preserving strategies, three previous studies examined the preferences for a specific rectal cancer treatment. One study included patient interviews and a questionnaire among clinicians, and reported that the preference of patients for W&W was stronger than physicians expected. On average, patients were willing to accept a 20% risk of regrowth and a 20% decrease in overall survival to achieve organ preservation, while 38% still preferred surgical treatment even if survival was equal[15]. Similar to our results, clinicians in this study underestimated the value that patients place on functional outcomes and quality of life compared to survival. A recent study reported that a considerable proportion of patients (51%) place W&W as their first preferred treatment, while in 39% of patients W&W was the least preferred treatment[16]. Consistently, a recent study reported that 16% of the included patients could not imagine to ever choose for W&W[9]. In the last study, almost half of all patients (45%) would not accept a potentially more toxic chemoradiotherapy regimen in order to increase the chances of a clinical complete response. All studies conclude that there is large variety in patient preferences, including patients who would accept an oncological risk (if there is any) for better functional outcomes, and patients who reject the idea of W&W even if all outcomes are exactly similar.

In the present study, we chose to examine the relative importance of different treatment outcomes to give a more comprehensive overview of patient preferences, rather than a strict comparison between different treatment options. Unexpectedly, all groups of patients appear to prioritize functional outcomes over one or two years longer DFS. The subgroup analysis showed that patients considered the adverse outcomes associated with the treatment they received as being less important, which can be explained by cognitive dissonance: patients cope with their decisions and post-treatment morbidity, whether this is a colostomy or fecal incontinence.

CBC experiments are used to examine the importance of attributes relative to each other. The results provide understanding of the factors that determine the preference and decisions of a patient. As patients are forced to make a tradeoff with each task, this method provides more information than simply asking participants to rank

attributes. Illustrative are our results regarding DFS, which was considered the most important in the simple ranking exercise yet turned out to be the least important in the CBC experiment when simultaneously confronted with other treatment outcomes. Evidently, patients want to live as long as possible, but not at the expense of inferior functional or patient reported outcomes.

A limitation of this design is that the RI of an attributes depends on the choice and definitions of the levels per attribute. For example, the RI of "worries about cancer recurrence" was high in clinicians, and some clinicians responded that "daily worries about cancer recurrence" rarely occurs in daily practice. Although the levels were determined in collaboration with clinical experts, it is possible that the RI is overestimated due to the extremity of this level. Nonetheless, the same definitions were used in the patient questionnaire, and patients considered this less important. Other possible explanations for the high importance clinicians assigned to the attribute worries about cancer recurrence compared to patients, could be that there are limited therapeutic options for a physician to improve this; or that patients with a history of cancer have presumably learnt to deal with this more than the average physician. This study is also limited by the relatively small sample size and heterogeneity of the study groups. On the other hand, the broad inclusion criteria have enabled a comprehensive overview of patient priorities. The study is susceptible for response bias, and no clinical information of non-respondents was available due to Dutch privacy legislation. However, the attrition rate for patients was low (8 out of 102). As it was possible to broadly invite clinicians anonymously via professional associations, the study population of professionals was considerably larger than the patient group. It is possible that this has influenced our results. It was also noticed that the response of surgeons was higher than clinicians of other specialties. In the Netherlands, surgeons are usually responsible for pretreatment consultations with patients. This may be the reason that the study attracted more surgeons, as they are frequently confronted with dilemmas of shared decision making. However, we showed that the opinion of clinicians with different specialties are considerably similar. Moreover, it is possible that the clinicians who responded to the questionnaire were predominantly W&W minded (selective response). However, even if this is true, W&W minded clinicians appear to overestimate the importance of DFS compared to all patients. Despite these limitations, the results indicate that patients can have completely different values than clinicians expect.

CONCLUSION

Shared decision making can be a true challenge, as clinicians and patients per definition speak a different language. A patient will be confronted with these considerations only once in their lifetime; while clinicians take their experience of ten - maybe hundreds - of cases before into account. Yet, with multiple treatment options available, a choice needs to be made. Results from the current study may help to clarify the differences in perspectives between patients and clinicians.

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SUPPLEMENTARY FILES

Table A. Baseline characteristics of clinicians who filled out the questionnaire complete versus incomplete.

Clinicians	Completes (n=128)	Incomplete (n=48)	P-value
Age, mean (SD)	49 (10)	47 (10)	0.61
Sex			0.85
Female	50 (39.1)	18 (37.5)	
Male	78 (60.9)	30 (62.5)	
Specialty			0.30
Surgeon	71 (55.5)	25 (52.1)	
Gastroenterologist	16 (12.5)	7 (14.6)	
Radiation oncologist	24 (18.8)	5 (10.4)	
Medical oncologist	17 (13.3)	11 (22.9)	
Current position			0.46
Senior staff	106 (82.8)	40 (83.3)	
Fellow	8 (6.3)	1 (2.1)	
Resident in training	14 (10.9)	7 (14.6)	
Years of experience			0.72
< 5 years	13 (10.2)	7 (14.6)	
5-10 years	27 (21.1)	12 (25.0)	
11-20-years	49 (38.3)	15 (31.3)	
>20 years	39 (30.5)	14 (29.2)	
Hospital of employment			0.57
Academic hospital	33 (25.8)	10 (20.8)	
General hospital	86 (67.2)	36 (75.0)	
Tertiary referral hospital	9 (7.0)	2 (4.2)	

Data are presented as n (%) unless indicated otherwise.

Table B. Subgroup analysis - Mean ranking of patients (n=94)

Ranking	Surgically treated patients with colostomy (n=45)	Surgically treated patients without colostomy (n=14)	W&W (n=35)
1	To live longer	To live longer	To live longer
2	No worries about cancer recurrence	No worries about cancer recurrence	No colostomy
3	No faecal incontinence	No colostomy	No worries about cancer recurrence
4	No colostomy	No faecal incontinence	No surgery needed
5	No urinary dysfunction	No urinary dysfunction	No faecal incontinence
6	No sexual dysfunction	No sexual dysfunction	No urinary dysfunction
7	No surgery needed	No surgery needed	No sexual dysfunction

PART III

OUTCOMES AFTER LOCAL REGROWTH

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7

MANAGEMENT AND OUTCOME OF LOCAL REGROWTHS IN A WATCH-AND-WAIT PROSPECTIVE COHORT FOR COMPLETE RESPONSES IN RECTAL CANCER

ABSTRACT

Objective

To evaluate the management and oncological outcomes of rectal cancer patients with local regrowth in a watch-and-wait (W&W) program.

Background

Approximately 15%–30% of patients with a clinical complete response after (chemo) radiotherapy who undergo a W&W policy will experience a local regrowth. The risks of these local regrowths have not yet been fully established and main concerns include high postoperative morbidity, requirement of advanced surgery, and pelvic recurrence after regrowth treatment.

Methods

All patients with a local regrowth after an initial W&W approach between January 2005 and March 2018 were retrospectively identified from cohorts of rectal cancer patients with a clinical complete response after (chemo) radiotherapy. Type and outcome of regrowth treatment were assessed. Oncological outcome was assessed using Kaplan-Meier estimates.

Results

Eighty-nine out of 385 patients developed a local regrowth after a median of 9 (interquartile range 7–14) months. Median follow-up time was 28 (interquartile range 19–41) months. Eighty-four (94%) patients underwent surgical treatment of the local regrowth: total mesorectal excision was performed in 58 out of 84 (69%) patients and local excision was performed in 26 (31%) patients. The 2-year local recurrence-free rate, distant metastasis-free rate, disease-free survival, and overall survival in the patients undergoing surgical treatment were 97.8%, 91.8%, 90.3% and 98.4%, respectively.

Conclusion

The vast majority (97%) of patients with regrowth after a W&W policy were able to undergo treatment with curative intent for local regrowth. Uncontrolled pelvic disease was very rare.

INTRODUCTION

In rectal cancer treatment there is a growing interest in organ-preserving strategies such as a local excision and a watch-and-wait (W&W) approach after (chemo) radiotherapy. The rationale is the potential avoidance of postoperative complications and long-term functional side effects of total mesorectal excision (TME), the standard of surgical treatment of rectal cancer. Patients undergoing TME may experience major surgical complications such as anastomotic leakage and perioperative mortality, especially in the frail elderly[1]. In the long-term, a substantial number of patients will also experience urinary or sexual dysfunction, and many patients will have a permanent colostomy or a disturbed bowel function, severely affecting their quality of life[2–7].

After the landmark publication on the W&W approach in patients with a clinical complete response (cCR) to neoadjuvant chemoradiotherapy (CRT) by Habr-Gama and colleagues in 2004[8], other series have confirmed the feasibility of the approach and the relative safety[9,10]. The assessment of a cCR is usually performed with a combination of digital rectal examination (DRE), flexible endoscopy and magnetic resonance imaging (MRI)[11]. Although the experience and the accuracy with these selection techniques is increasing, there is currently no assessment technique that allows 100% accuracy to detect small foci of residual viable cancer cells. This will inevitably lead to a number of local regrowths in any W&W program. The reported incidence varies between 15% and 30% of patients[12–14]. The clinical risks of these local regrowths have not yet been fully established and there is concern that they: (a) might be technically more difficult to operate; (b) may lead to a higher postoperative morbidity; (c) may require ''beyond TME'' surgery due to increased invasiveness; (d) and finally, could convey a worse oncologic outcome, especially higher risk of distant metastasis, than if resected without the delay of W&W. Another concern is that further pelvic recurrence after regrowth treatment can lead to unsalvageable disease with major suffering. Therefore, the aim of this study was to provide data on the management and oncological outcomes of patients with local regrowth in a W&W program.

METHODS

All patients with a suspected local regrowth after an initial W&W approach between January 2005 and April 2018 were retrospectively identified from 2 prospectively collected W&W cohorts: a single-center cohort from the Champalimaud Foundation (Lisbon, Portugal), and the Dutch W&W series. The Dutch series is a series of patients

from 15 hospitals who initially referred their patients to the Maastricht University Medical Center and Netherlands Cancer Institute, and now run their own W&W program in a network structure, coordinated by the Netherlands Cancer Institute.

Inclusion criteria for this study were (1) primary rectal cancer without distant metastasis, (2) neoadjuvant treatment with either CRT or short-course radiotherapy with long interval, (3) a near- complete or complete clinical response to neoadjuvant treatment, (4) clinical surveillance under a W&W protocol, (5) suspected local regrowth.

The study was approved by the Institutional Review Board Committee.

Response assessment

Response assessment after neoadjuvant treatment was performed between 6 and 12 weeks after the end of treatment with DRE, endoscopy, and MRI. Patients with a cCR or near-complete response were eligible for a W&W treatment in both series. A cCR was defined as a combination of: (1) no residual tumor felt on DRE, (2) a white scar and/or telangiectasia of the mucosa at endoscopy, (3) low signal intensity at the original tumor site on T2-weighted MRI (T2W- MRI) and absence of diffusion restriction on diffusion weighted-MRI (DW-MRI), and (4) homogeneous signal intensity within the remaining lymph node(s), with a regular contour.

A near-complete response was defined as: (1) minor soft mucosa abnormality/irregularity felt on DRE, (2) superficial ulceration and/or mild persisting erythema of the scar, (3) intermediate/low residual signal on T2W-MRI and/or small foci of diffusion restriction on DW-MRI, or (4) obvious downstaging of lymph nodes but remaining node(s) 5 mm[9]. In case of a clinical complete or near-complete response, W&W was offered as an alternative to standard treatment with TME. Patients were informed comprehensively about the W&W approach and its risks, and the definitive decision for a W&W approach was made in a shared-decision process, highly involving the patients' treatment preferences.

W&W and Diagnosis of Regrowth

Follow-up assessments in the W&W surveillance protocol included DRE, MRI, and sigmoidoscopy every 3 months in the first year, and every 6 months thereafter up to 5 years after inclusion. Additional standard rectal cancer follow-up according to local guidelines included imaging of the chest and liver, carcinoembryonic antigen measurements, and out-patient clinic visits for a period of 5 years.

Signs of luminal regrowth were defined as new mucosal abnormalities on endoscopy, often supported by an isointense mass or wall thickening of the fibrotic scar on T2W-MRI or new focal high signal spots on DW-MRI. Signs of intra-mural regrowth were defined as new mass with intermediate signal intensity or wall thickening of the

fibrotic scar on T2W-MRI first, with possible changes on endoscopy later. Histological confirmation of regrowth was generally obtained for a suspected luminal or intramural regrowth. Signs of nodal regrowth included lymph node enlargement or change in contour features on consecutive MRI.

Treatment of Local Regrowth

The decision on when and how to treat a suspected or confirmed local regrowth again involved the patients' preferences. Often patients preferred to wait until unequivocal histological proof of disease or progression of disease at imaging was present. Full staging with sigmoidoscopy, MRI, carcinoembryonic antigen measurements and imaging of the liver and chest was performed to assess the extent and distant spread of the tumor. Although TME resection was the preferred standard treatment option for resectable local regrowth, local excision was discussed as an alternative treatment option in patients with limited tumor extent and a strong preference for a continued effort to preserve the rectum. Treatment for local regrowth was performed either in the referring hospital or in the W&W expert hospital, according to the patients' preference.

Variables and Outcome Measures

Baseline characteristics included age, sex, American Society of Anesthesiologists classification, tumor distance from anorectal junction on MRI, neoadjuvant treatment and induction chemotherapy. The following operative variables were collected: type of intervention, surgical approach, operating time, estimated blood loss, diverting ileostomy, or permanent colostomy. Postoperative out- comes included: length of hospital stay, surgical morbidity (Clavien Dindo grade ≤ 2)[15] and in-hospital mortality. Histopathological outcomes included Tumor Node Metastasis (TNM) staging (according to the American Joint Committee on Cancer, 7th edition), number of harvested and positive lymph nodes, and resection margin involvement.

Oncological outcomes included: local recurrence-free rate, defined as absence of pelvic recurrence after surgery for regrowth; disease-free survival, defined as absence of untreated regrowth, pelvic recurrence after regrowth treatment, distant metastasis or death from any cause; distant metastasis-free rate, defined as absence of distant metastasis; and overall survival, defined as death from any cause.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics (version 22.0, Inc., Chicago, IL). Quantitative data were expressed as median with interquartile range. Categorical data were reported as the number of patients with percentages. Local recurrence-free rate, disease-free survival, distant metastasis-free rate, and overall

survival were estimated with Kaplan-Meier. Time to event was calculated from the date of primary rectal cancer diagnosis for all outcomes, unless specified otherwise.

RESULTS

Eighty-nine of the 385 patients with near-complete or complete clinical response treated according to a W&W policy had local regrowth and were included in this analysis. Seventy percent were male and median age at primary diagnosis of rectal cancer was 64 (range 31–82) years. Neoadjuvant treatment at time of primary diagnosis consisted of CRT in 83 (93%) patients and short-course radiotherapy with a long interval in 6 (7%) patients. Median follow- up was 28 [interquartile range (IQR) 19–41] months. Median time from end of neoadjuvant radiotherapy to local regrowth diagnosis was 9 (IQR 7–14) months. All patients' baseline characteristics are listed in Table 1 and are shown separately for the 2 cohorts in Supplemental File 1.

Table 1. Baseline Characteristics of Patients With Local Regrowth After a Watch-and-wait Approach.

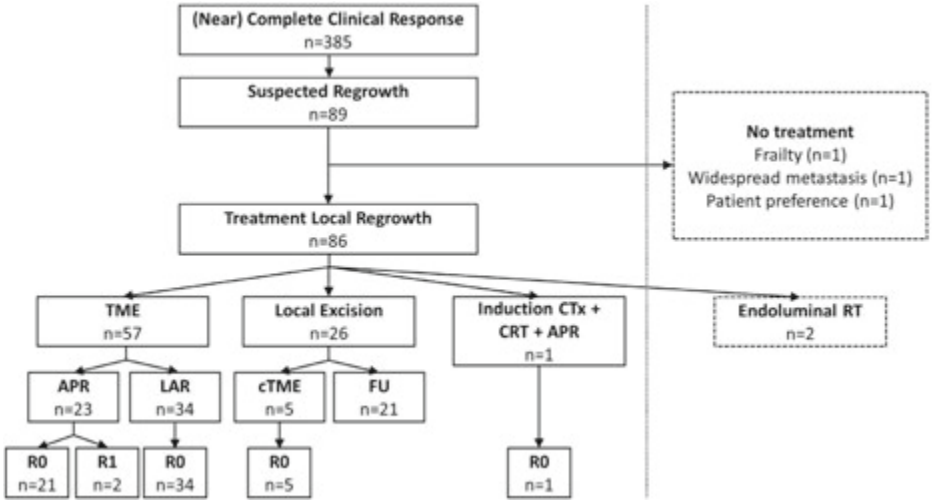
	N=89
Age, median (range), years	64 (31-82)
Male, No. (%)	62 (70)
Distance to anorectal junction, median (IQR), cm	2.5 (0-5.0)
ASA classification, No. (%)	
I	16 (18)
II	46 (52)
III	9 (10)
NA	18 (20)
Clinical T stage, No. (%)	
mrT2	12 (14)
mrT3	66 (74)
mrT4	11 (12)
Clinical N stage, No. (%)	
mrN0	28 (32)
mrN1	26 (29)
mrN2	35 (39)
Neoadjuvant treatment, No. (%)	
Chemoradiotherapy	83 (93)
Short course RT + interval	6 (7)
Consolidation chemotherapy, No. (%)	19 (21)
Time to regrowth*, median (IQR), months	9 (7-14)

*Calculated from last day of radiotherapy.
Abbreviations: ASA, American Society of Anesthesiologists; NA, not available; RT, radiotherapy

Treatment of Local Regrowth

Of the 89 patients with local regrowth, 84 (94%) patients underwent surgical treatment of the local regrowth. TME was performed in 58 out of 84 (69%) patients, of which 34 (40%) patients underwent low anterior resection (LAR) and 23 (27%) patients underwent abdominoperineal resection (APR) (Figure 1). One patient received induction chemotherapy and CRT followed by APR. Local excision was performed in 26 (31%) patients, 5 of whom underwent completion TME (1 LAR and 4 APR) because of ypT2 at histology (Table 2). Two patients opted for local treatment with endoluminal radiotherapy: 1 patient received 70 Gy with brachytherapy and 1 patient received 60 Gy with contact radiotherapy. Three patients did not undergo any treatment because of: patient preference (n=1); presence of widespread distant metastasis (n=1); and progressive dementia (n=1).

Figure 1. Flowchart of patient treatment.



APR indicates abdominoperineal resection; CRT, chemoradiotherapy; cTME, completion total mesorectal excision; CTx, chemotherapy; RT, radiotherapy; FU, follow-up; LAR, low anterior resection; TME, total mesorectal excision.

Table 2. Regrowth treatment and histopathological outcome.

	N=86
Time to treatment, median (IQR), months*	12 (9-15)
Type of regrowth treatment, No. (%)	
TME	
Low anterior resection	34 (40)
Abdominoperineal resection	23 (27)
Local excision	
Local excision only	21 (24)
Completion TME	5 (6)
Endoluminal radiotherapy	2 (2)
Induction CTx, CRT and TME	1 (1)
Operative approach TME, No. (%)	
Open	9 (14)
Laparoscopic	45 (71)
Robotic	7 (11)
NA	2 (3)
Conversion, No (%)	1 (2)
ypT stage TME, No. (%)	
T0	6 (10)
T1	6 (10)
T2	32 (51)
T3	17 (27)
T4	2 (3)
ypT stage Local excision, No. (%)	
T0	5 (19)
T1	4 (15)
T2	15 (58)
T3	1 (4)
Tx	1 (4)
ypN stage TME, No. (%)	
N0	52 (83)
N1	9 (14)
N2	2 (3)
Resection margin TME, No. (%)	
R0	61/63 (97)
R1	2/63 (3)

*Calculated from last day of radiotherapy. Abbreviations: TME, total mesorectal excision; CTx, chemotherapy; CRT, chemoradiotherapy; NA, not available.

Perioperative and Postoperative Outcomes

Table 3 provides the perioperative details. Intraoperative complications were rare, in 1 patient a ureteral injury occurred. Severe postoperative complications (Clavien Dindo grade 3) were present in 9 (10%) patients, all after TME. Two patients underwent endoscopic decompression for a pseudo obstruction, 1 patient an ileostomy revision

for a stenosis, and 1 patient underwent an early ileostomy closure within the same admission for a high output stoma. Two patients had intra-abdominal abscesses for which surgical drainage was required. One patient had an anastomotic leak for which a relaparotomy was performed, and 1 patient had an incarcerated trocar hernia requiring resection of a small bowel segment. One elderly frail patient died of a postoperative severe pneumonia.

Table 3. Perioperative details

Operating time, median (IQR), minutes†	
TME	232 (200-270)
Local excision	80 (40-100)
Blood loss, median (IQR), mL‡	
TME	100 (25-300)
Local excision	0 (0-15)
Intraoperative complications, No. (%)	
None	80 (93)
Ureteral injury	1 (1)
NA	5 (6)
Length of hospital stay, median (IQR), days	
TME	8 (5-13)
Local excision	2 (1-3)
Clavien-Dindo grade, No. (%)	
II	14 (17)
IIIa	2 (2)
IIIb	6 (7)
IV	0 (-)
V	1 (1)

† Operating time data available in 64 patients.
‡ Blood loss data available in 57 patients.
Abbreviations: IQR, interquartile range; NA, not available; TME, total mesorectal excision.

Histology results

Of the 84 patients undergoing surgical treatment of regrowth, 66 (73%) had luminal regrowth only in the resected specimen. Nine (11%) patients had both luminal and nodal regrowth and 2 (2%) patients had nodal metastases only. Luminal regrowth was most often confined to the bowel wall (Table 2).

In 9 (11%) of the patients with suspected regrowth undergoing surgery, no tumor was found at histology and was misdiagnosed as regrowth. In 2 of these patients there was adenomatous tissue with low grade (n 1) or high-grade dysplasia (n 1). The R0 rate after TME was 97%, with 1 involved margin and 1 close margin.

Of the 5 patients undergoing completion TME after local excision, 4 (80%) had no additional tumor at histology and 1 patient showed a ypT2.

Oncological Outcomes

The 2-year local recurrence-free rate in the 84 patients undergoing surgical treatment of regrowth was 97.8% [95% confidence interval (CI): 0.85–1.00] (Figure 2). Four out of 84 patients had a local recurrence. Two patients had a local recurrence after a local excision. One patient was salvaged with completion APR and 1 with LAR. The remaining 19 patients treated only with local excision remained free of recurrence during a median follow-up of 20 (IQR 13–29) months. Two patients had a local recurrence after APR, but did not undergo salvage treatment because of widespread metastatic disease (n=1) and local progression under chemotherapy (n=1). The details of the 4 patients with local recurrence are shown in Table 4, along with the details of the 2 patients who had insufficient local control of the regrowth with intraluminal radiotherapy.

Figure 2. Kaplan-Meier analyses of local recurrence-free rate, distant metastasis-free rate, disease-free survival and overall survival from date of diagnosis, with 95% confidence interval.

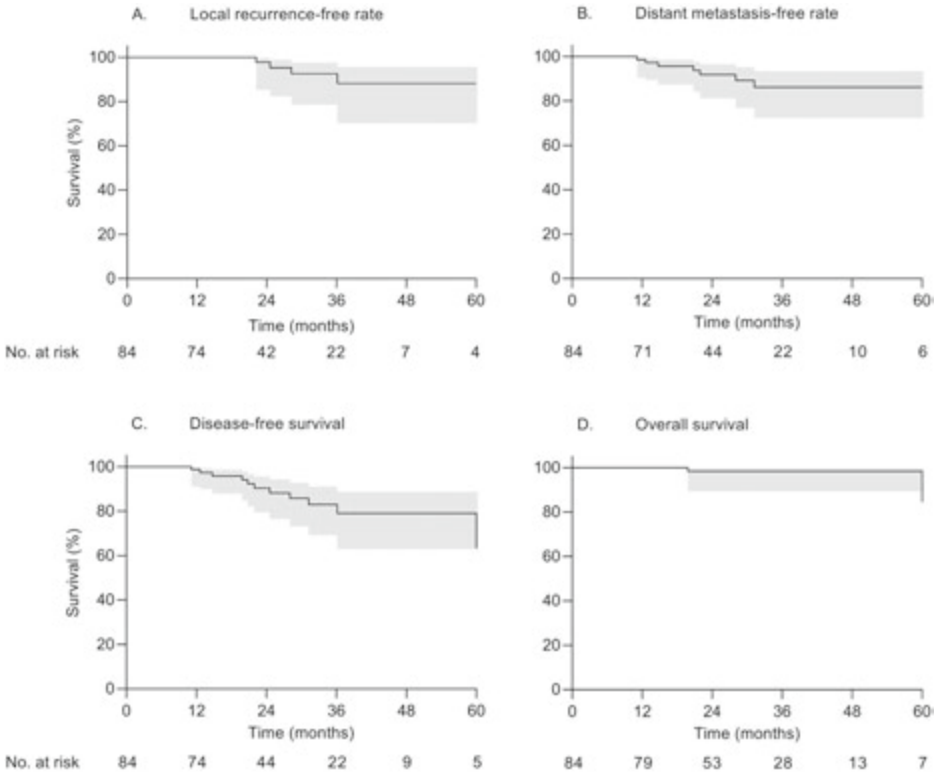


Table 4. Overview of patients with local recurrence after regrowth treatment.

Patient	Gender	Age, years	Clinical tumor stage	Distance from ARJ, cm	Neoadjuvant treatment	Time to regrowth (from RT), months	Type of regrowth	Initial treatment for regrowth	Time to recurrence, months	Type of recurrence	Treatment of recurrence	Salvaged
1	F	48	cT3N1	7	CRT	8	Luminal	TEM (ypT1)	17	Luminal	TEM (ypT3) and completion APR (no tumor)	Yes
2	M	63	cT3N0	5.5	CRT + CAPOX	24	Luminal	TEM (ypT2)	9	Luminal	Lap LAR (ypT2N0)	Yes
3	M	76	cT3N2	5	CRT	7	Luminal	Lap APR (ypT3N0 R1)	11	Pelvic + widespread metastases	Palliative chemotherapy	No
4	M	69	cT4N0	2.5	CRT	11	Luminal	Lap LAR (ypT2N0)	12	Para-aortic lymph nodes	Palliative chemotherapy	No
5	M	43	cT4N2	0	ScRT + CAPOX	5	Luminal	Contact RT (60Gy)	4	Luminal	TEM (ypT3 R1) and completion APR (ypT3N0).	Ongoing (pelvic re-recurrence)
6	M	55	cT3N1	2	CRT	16	Luminal	Brachy RT (70Gy)	5	Luminal	Lap APR (ypT3N0 R1)	Ongoing (pelvic re-recurrence)

Abbreviations: ARJ, anorectal junction; RT, radiotherapy; CRT, chemoradiotherapy; TEM, transanal endoscopic microsurgery; APR, abdominoperineal excision; CAPOX, capecitabine/oxaliplatin; ScRT, short course radiotherapy; Gy, Gray; LAR, low anterior resection.

Two-year distant metastasis-free rate was 91.8% (95% CI: 0.81– 0.97) (Figure 2). Seven out of the 84 patients developed distant metastases (synchronous with regrowth n=2, after regrowth n=5). Two-year disease-free survival and overall survival were 90.3% (95% CI: 0.80–0.96) and 98.4% (95% CI: 0.89–1.00), respectively. Overall survival of the total W&W cohort (n=385) is shown in the Supplemental File 2.

DISCUSSION

In the present study the vast majority of patients (97%) with regrowth after a W&W policy were able to undergo a curative treatment for local regrowth. Our data suggests that the initial primary surgery treatment options for rectal cancer are almost always available in patients with local regrowth. Additionally, organ-preservation after local regrowth was still possible in selected patients. Furthermore, there seems to be no increased risk of surgical complications after the delayed surgical treatment.

When offering W&W to rectal cancer patients, the possibility of local regrowth and its consequences should always be discussed. In our cohort, 89 of 385 patients experienced local regrowth and had an indication to undergo further treatment of their rectal cancer. In the present study we were able to treat 97% of local regrowths, which is in line with the previously reported Sao Paulo series, where salvage therapy was possible in 93% of the patients[16]. In an individual participant data meta-analysis, which includes the Sao Paulo data and a part of the data of the presented study, the proportion of regrowth patients undergoing salvage therapy was 89%[17]. The pooled proportion of patients undergoing salvage therapy in the meta-analysis of Dossa and colleagues was 95%[12]. Reasons for not undergoing treatment of local regrowth can be diverse: patient frailty and/or patient refusal to accept rectal amputation or major abdominal surgery, or widespread or unresectable distant dissemination. None of the regrowths in the present study were considered technically unresectable, although 1 patient did require induction chemotherapy and chemoradiation to downsize a presacral regrowth.

Uncontrolled pelvic disease can be highly troublesome for the patient and should be avoided as much as possible. In the current series there were overall 6 of 89 patients with a local regrowth who did not achieve local disease control, translating to 1.6% for the original cohort of W&W patients. This includes the 3 patients who did not undergo treatment for local regrowth because of frailty, widespread metastatic disease or explicit wish of the patient. Additionally, there were 2 patients who refused the proposed TME surgery, received intraluminal radiotherapy, later

required salvage TME, and are currently undergoing further treatment for a second local recurrence. Depending on whether or not to include these patients, the failure of local control varies between 0.3% and 1.6%. This is consistent with the 1% risk of locally unsalvageable disease estimated in the International Watch and Wait Database study[14]. Additionally, one has to keep in mind that even with a pathological complete response, a rectal resection is not an absolute safeguard for local control, as evidenced by the 2.8% local recurrence rate in this group of patients in the meta-analysis by Maas et al[18]. To keep the number of uncontrolled pelvic recurrences low in a W&W strategy, it is essential to have a tight follow-up program, with close surveillance especially in the first 2 years. Although the exact schedule is not yet clear, it is generally agreed that follow-up should at least include DRE, flexible endoscopy and MRI.

Since the start of the W&W program, our protocol has been to proceed with the initially planned surgery when a local regrowth is detected. The standard procedure is to offer these patients a TME, either a LAR or a rectal amputation as initially planned. Distal tumors can require a rectal amputation, and many patients who entered the W&W program because of the chance to avoid a permanent colostomy will still be keen to explore alternatives, and will enquire about a local excision. In the present study a local excision was performed in 30% of the patients, and whereas about two-thirds of them had an adverse histology (ypT2) after local excision, only few patients agreed to completion TME. Interestingly, 4 out of 5 patients showed no additional luminal or nodal tumor after completion TME. Furthermore, we observed only 2 recurrences in the rest of the local excision patients after a median follow-up of 20 months. This outcome is better than expected for ypT2 patients, and a similar observation was made in the GRECCAR 2 study of local excision after chemoradiation[19]. However, the GRECCAR 2 study generally included smaller tumors and we remain cautious in extrapolating this to patients with more advanced tumors. Again, it comes down to shared decision making, and how much risk the patient is willing to take to avoid major surgery, a permanent colostomy or major low anterior resection syndrome.

There is a concern that delayed surgery can be more difficult with more complications because of the increased fibrosis. Some observational studies suggest no differences whereas the only randomized trial, the French GRECCAR 6 study, showed a higher morbidity rate in surgery after 11 versus 7 weeks, mostly due to an increased risk of medical complications[20,21]. In the present study patients were operated after a median interval of 12 months after the radiotherapy. Although the study was not designed to assess surgical difficulty and there was no comparative group, the low rate of serious complications (Clavien-Dindo >III of 10%) with only a single anastomotic

leak, the standard operative time of 232 minutes and a low conversion rate of 2% suggest that if anything, the increased risk is rather low.

A highly important issue that is beyond the scope of this study is whether or not persistent tumor or regrowth can be the origin of distant metastases. It has been shown in the large International Watch and Wait Database study that patients with a regrowth also have higher chance of metastatic disease than patients without a regrowth: 18% versus 5%[14]. In the present study the

2-year metastatic disease rate in patients with local regrowth was 8.2%. It remains unclear whether this risk is entirely related to the inherent higher metastatic risk in incomplete responders when compared to complete responders, or whether a part of this risk is related to the omission of immediate TME surgery after CRT. This is an important question, and difficult to answer with certainty without randomized data.

The main strengths of the present study include the large number of patients undergoing W&W included by combining 2 study cohorts, the detailed data on regrowth treatment and the comprehensive information on the morbidity of regrowth surgery in rectal cancer patients. This study also has its limitations. First, despite the prospective design of the W&W cohort studies, some perioperative details for this study were retrospectively collected and were therefore not available for all patients. Second, this study had an intermediate follow-up duration and more events may occur with an extended follow-up. It is therefore of great importance to continue a close follow-up after regrowth treatment. Last, this study was performed in a network of centers experienced in organ-preservation treatment in rectal cancer. The results of the present study therefore should be interpreted with care, as the study was performed in a highly controlled setting.

CONCLUSION

In conclusion, almost all patients (97%) with regrowth after a W&W policy for rectal cancer were able to undergo treatment with curative intent for local regrowth. Uncontrolled pelvic disease after W&W was very rare. Our data also suggests that the initial primary surgery treatment options for rectal cancer are generally still available in patients with local regrowth and even organ-preserving treatment for regrowth is possible in selected patients.

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SUPPLEMENTARY FILES

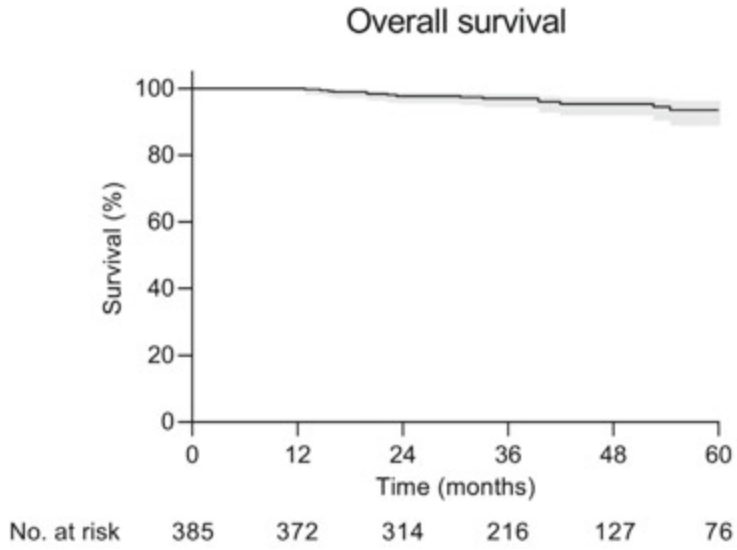
Supplemental File 1. Baseline characteristics per cohort.

	All patients n=89	Dutch cohort n=72	Lisbon Cohort n=17	*p*-value
Age, median (range), years	64 (31-82)	65 (57-70)	61 (54-69)	0.440
Male, No. (%)	62 (70)	51 (82)	11 (65)	0.621
Distance to anorectal junction, median (IQR), cm	2.5 (0-5.0)	2.8 (0-5.0)	4.0 (2.0-6.0)	0.093
ASA classification, No. (%)				-
I	16 (18)	13 (18)	3 (18)	
II	46 (52)	37 (51)	9 (53)	
III	9 (10)	4 (6)	5 (29)	
NA	18 (20)	18 (25)	-	
Clinical T stage, No. (%)				-
mrT2	12 (14)	10 (14)	2 (12)	
mrT3	66 (74)	52 (72)	14 (82)	
mrT4	11 (12)	10 (14)	1 (6)	
Clinical N stage, No. (%)				-
mrN0	28 (32)	26 (36)	2 (12)	
mrN1	26 (29)	18 (25)	8 (47)	
mrN2	35 (39)	28 (39)	7 (41)	
Neoadjuvant treatment, No. (%)				0.358
Chemoradiotherapy	83 (93)	68 (94)	15 (88)	
Short course RT + interval	6 (7)	4 (6)	2 (12)	
Consolidation chemotherapy, No. (%)	18 (20)	7 (10)	11 (65)	0.000
Time to regrowth*, median (IQR), months	9 (7-14)	9 (7-13)	14 (9-18)	0.032

*Calculated from last day of radiotherapy.

Abbreviations: ASA, American Society of Anesthesiologists; NA, not available; RT, radiotherapy

Supplemental File 2. Kaplan-Meier analysis of overall survival in patients with near complete or complete clinical response treated according to a W&W policy (n=385), with 95% confidence interval.



The overall survival in patients with near complete or complete clinical response treated according to a W&W policy was 97.7% (95% CI: 95.5-98.9) at 2 years, and 93.5% (95% CI: 88.7-96.3) at 5 years.

APPENDIX

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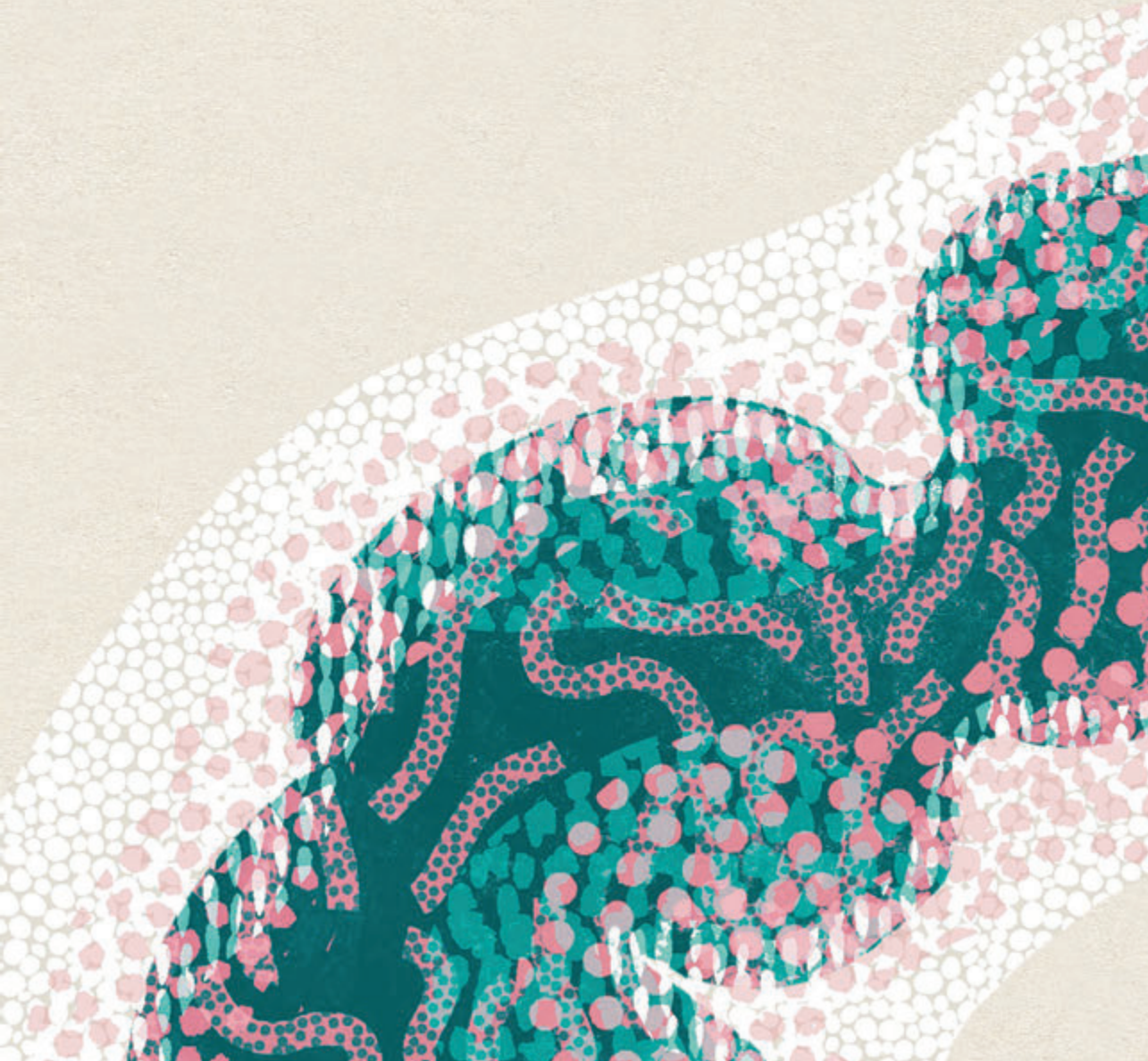

8

GENERAL DISCUSSION

GENERAL DISCUSSION

The management of patients with rectal cancer is evolving rapidly. A radical resection along the 'holy plane' by total mesorectal excision (TME) has been considered the cornerstone of curative treatment in rectal cancer[1]. Although local control following TME has been excellent, TME is a major abdominal procedure with a high risk of postoperative morbidity and many patients experience poor functional outcome with negative effects on quality of life (QoL)[2]. Therefore, a shift in the management of rectal cancer towards less radical approaches, including the watch-and-wait approach (W&W) has taken place in an effort to reduce the adverse effects of treatment and preserve QoL. While radical surgery will remain necessary in a large group of patients with rectal cancer, there is also an increasing role for neoadjuvant strategies with the aim of achieving a complete response and entering subsequent organ preservation programs.

Although there are many encouraging reports on the W&W approach[3–8], several areas of uncertainty currently limit the applicability of the approach outside of study protocols and implementation into daily clinical practice. In this thesis, we addressed some of these areas of uncertainty and aimed to provide valuable insights for further development and to ultimately facilitate implementation of organ preservation into routine clinical practice.

Response assessment

Evaluation of tumour regression after neoadjuvant treatment is an essential step in assessing the eligibility of a patient for organ preservation. Unfortunately, at present the accuracy of diagnostic tools to assess response to neoadjuvant treatment is limited and is considered to be one of the main challenges in organ preservation. Even using a multimodality approach with digital rectal examination, endoscopy, T2-weighted MRI (T2W-MRI) and diffusion-weighted imaging (DWI), 30% of the pathological complete responses (pCR) may not be recognized due to overstaging of residual tumour[9], leading to major surgery in patients who could have been treated successfully with organ preservation.

A clear definition for a clinical complete response (cCR) on endoscopy was presented by Habr-Gama et al.[10]. It was proposed that a cCR encompasses whitening of the mucosa with teleangiectasia and mucosal integrity on endoscopy, and only then patients should be considered for a W&W approach. Patients that have any deep or superficial ulcer, any palpable nodule, or any significant stenosis were considered to have an incomplete response. However, in chapter 2 the most common errors in failure to recognize a complete response included residual mucosal abnormalities

on endoscopy, along with full thickness or irregular shaped fibrosis and mixed signal intensity on T2W-MRI, and focal diffusion restriction on DWI. Histology showed reactive changes to CRT such as fibrosis, inflammation and ulceration in the majority of the specimens of the unrecognized complete responders. This is in line with other studies that looked at surgical specimens and showed that 61-74% of patients with a pCR have macroscopical mucosal abnormalities[11,12]. The definition of a cCR by Habr-Gama et al. was therefore too cautious, aiming to prevent W&W in patients with potentially residual tumour rather than to identify patients with potentially a complete response. In terms of diagnostic accuracy this definition was aiming at a high specificity for the detection of complete response, at the expense of a low sensitivity. This was demonstrated in a study by Nahas et al., which had a sensitivity of only 27% for the detection of ypT0 using these endoscopic criteria, and a very high specificity of 96% [13].

Respecting the wishes of many patients to avoid major surgery whenever possible, many centres who practice organ preservation have shifted the selection criteria for a W&W approach to a less conservative strategy. Patients who show a very good response without the typical features of a complete response are allowed a longer observation period. This response is often labelled as a 'near cCR', and can be based on equivocal findings on endoscopic as well as on MRI[4,8]. This response category is not yet well defined and still covers a broad spectrum of responses. In chapter 3 we provided an indication of the positive predictive value (PPV) for a complete response for different endoscopic features which adds to the understanding of patients with a near cCR; a small flat ulcer for example had a PPV for a complete response of 40-50%. Thus, after careful selection, extending the observation period could increase the number of patients who are eligible for organ preservation[14]. In a cohort study, 62% of the patients with a near cCR at first evaluation who were included in a watch-and-wait approach, met the criteria for a cCR at a second evaluation three months later[4]. A local excision of a near cCR could also provide histological information on the exact tumour regression, with the added value of being therapeutic in very small remnants. There is some concern about the morbidity and functional outcome; up to 50% of major LARS has been reported after local excision after radiotherapy[15–17]. Another local treatment option for patients with a near complete response could include contact X-ray brachytherapy. The Dutch phase II feasibility OPAXX trial (NL75896.031.20) will further define the role of additional contact X-ray brachytherapy versus extending the waiting interval and/or local excision in patients with a near cCR. Further refinement of the near CR category will also help stratify patients into the different treatment options. In addition, more robust response assessments methods

are needed. However, we also have to accept that no prediction is a 100% accurate and some uncertainty is and will remain an inherent part of organ preservation.

Quality of life

Over the past two decades quality of life (QoL) is increasingly regarded as a key patient outcome in rectal cancer treatment, as many patients experience substantial morbidity and long-term sequelae after standard treatment. The primary goal of organ preservation is therefore to minimize these negative effects of treatment. With a growing number of treatment options for patients with rectal cancer, making treatment decisions for the individual patient is an increasingly difficult task. The first step is a good understanding of all treatment options, including the potential risks and benefits, by both the clinician and the patient. This will often require additional counseling by the clinician. In chapter 5 we provided important information on long-term QoL and functional outcomes of rectal cancer patients following a W&W approach, which can be used for counseling. The next step is to balance the potential risks and benefits according to the preference and wishes of the patient. This requires elucidating the relative value of the different outcome measures for a given patient. The conjoint-base choice experiment in chapter 6 showed that there are situations where patients prioritize functional outcomes and avoiding a stoma over one or two years of extra disease-free survival. The fact that some patients are not willing to maximize survival at the expense of functional outcomes and quality of life is often underestimated by clinicians[18]. Another difference between patients and clinicians demonstrated by the conjoint-base choice experiment was that patients showed a much stronger strong aversion to surgery with a definitive colostomy than clinicians. There is however a large variation in patient preferences, and there are also patients who reject W&W even if survival is equal[18–20]. Eliciting patient preferences is therefore important, as each patient will have their own preferences and may balance survival against QoL outcomes differently. Clinicians should also be aware of their own preferences and not let these interfere with the assessment of the preferences and decision of the patient.

For counseling and decision making in LARC it is especially valuable to know how W&W compares to the standard treatment with radical resection after CRT. In comparison with studies in literature on QoL after standard treatment, our W&W cohort in chapter 5 scored better on almost all subscales regarding general QoL on the majority of cancer-specific QoL, including the subscales on gastrointestinal problems[21,22]. Although randomized data is not available, few studies have compared W&W to patients undergoing CRT and TME and showed QoL and functional outcome results in favor of W&W[23,24]. An important advantage for W&W is reflected by the

percentage of patients who experience major LARS, which in this thesis was shown to be 25-33% in patients treated with W&W, while it can be as high as 66% after standard treatment[25–27].

While our results confirm the anticipated benefits in QoL, it also shows that patients who undergo a W&W approach experience some degree of bowel, sexual and urinary dysfunction after treatment with (chemo)radiotherapy. In chapter 4 we observed a trend towards worse long-term anorectal function after a higher radiotherapy dose to the anal sphincter complex. Our study was performed in a small sized cohort and this should be explored further. In other malignancies reduced anal sphincter tone and squeeze pressures have been observed after pelvic irradiation and were correlated with complaints of urgency and incontinence specifically[28–30]. Possibly, radiotherapy dose delivery could be optimized with new techniques such as MR guided radiotherapy, offering better anatomical visualization and adaptive workflows. This could maximize the effect on the tumour while sparing surrounding tissues and thereby minimize the harmful effects of radiotherapy on functional outcomes.

A randomized comparison of QoL and functional outcome after W&W with outcomes after TME only would shed a light on whether organ preservation could also be favourable in patients with early stage rectal cancer. To give an indication, 35% of patients experience major LARS after TME only[26,31] and this thesis showed 25-33% after W&W in LARC. The STAR-TREC trial, although only partially randomized, will provide valuable information regarding the risks and benefits of different treatment strategies in patients with early stage rectal cancer[32].

Tumour regrowth

One of the concerns in W&W is that a regrowth is no longer resectable, that it requires more extensive surgery, or that it leads to further local recurrence with uncontrolled pelvic disease. In current literature, a wide variation of the incidence of local regrowth is reported due to heterogeneous baseline characteristics and inclusion criteria in studies, but large meta-analyses and pooled data demonstrate local regrowth rates of approximately 25%[7,8,33]. In Chapter 7 we showed most patients with local regrowth were amenable for deferred surgery with R0 margins. This is in line with other reports [7,8,34]. Uncontrolled pelvic disease after watch-and-wait is a rare event. In the series reported in this thesis the risk was estimated at 0.3-1.6% for the complete cohort of W&W patients, comparable to the estimate of 1% of locally unsalvageable disease reported by the International Watch and Wait Database consortium[8]. One also has to keep in mind that even with a pCR a rectal resection is not an absolute safeguard against local recurrence, as evidenced by the 2.8% local recurrence rate in patients with pCR after surgery in the meta-analysis by Maas et al.[35].

In some patients with a local regrowth, a local excision is still possible as an organ preservation alternative to a TME. However, two-thirds showed an adverse histology after local excision, most often a ypT2 status, where a completion TME is advised because of an increased risk of residual disease and local recurrence[36,37]. However, many patients who opted for a local excision in order to avoid major surgery decline a completion TME, and prefer to accept a slightly elevated risk for recurrence, provided they are closely followed with MRI and endoscopy.

There is a concern that deferred surgery may be more difficult with more complications. The only randomized trial regarding this question, the GRECCAR 6 trial, showed a higher morbidity rate for surgery after 11 versus 7 weeks[38]. Although our study was not designed to assess surgical difficulty, when we compare the operative details from our series to data from large clinical trials[39,40], it suggests that the increased risk for surgical complications or an irradical resection when deferring surgery is low. In addition, Nasir et al. showed similar R0 rates, anastomotic leak rates, Clavien-Dindo grades and 30-day morbidity and re-admission rates for patients who underwent deferred surgery as for patients who underwent TME for persistent disease after CRT[41].

FUTURE PERSPECTIVES

Implementation of watch-and-wait for locally advanced rectal cancer

Ideally, new treatments are evaluated in a randomized controlled manner before implementation into daily clinical practice. In the field of W&W this would be very challenging, as experience has learned that in a trial with arms that are perceived highly different with regard to quality of life, patients have strong preferences and object to randomization. While RCT data is absent, there currently is a strong body of evidence for W&W in patients with initial LARC, including high volume data from meta-analyses and the International Watch and Wait Database (IWWD) registry[7,8]. It shows the strategy is safe, yields good oncological results and benefits QoL. In addition, the implementation of a W&W strategy into clinical practice has the potential to improve the number of quality-adjusted life years (QALY's) and reduce health care costs[42,43].

Some concerns remain regarding the risk of distant metastases (DM) in patients with persisting disease or local regrowth, which may withhold implementation of the strategy. While the proportion of patients developing distant metastases in W&W appears to be low in the total group, a few studies showed a clear difference in the incidence of DM in patients with a local regrowth compared to patients without a local regrowth[4,5,8,44], questioning whether deferring surgery in patients

who apparently had residual tumour and developed a local regrowth leads to an increased risk for developing DM or that this is due to unfavorable tumour biology at baseline. This is a very important question, but difficult to answer with certainty without randomized data.

Another criticism on the W&W evidence is that it mainly comes from expertise centers and that the results may not be reproducible in other centers. The effectiveness and safety of organ preservation strategies is undoubtedly related to the quality of restaging assessments, patient selection and experience of the clinician. Therefore, experience with the assessment of rectal MRI and endoscopy should be ensured in centers interested in implementing organ preservation, with preferably high volumes of rectal cancer patients to build expertise. Structured reporting templates for MRI and endoscopic response assessment could assist less experienced readers with the interpretation of these examinations[45,46]. In the Netherlands, the W&W strategy for patients with LARC has been implemented in 15 hospitals in cooperation with our team at the Netherlands Cancer Institute, a tertiary referral center for W&W, in the recent years. We provided standardized protocols for assessment and follow-up, with training for radiologists, endoscopists and surgeons, along with a second reading of the examinations of patients with a cCR or near cCR. The second reading initially resulted in discrepancies between the participating and tertiary centers often, emphasizing the need for experienced readers or the opportunity to consult them when starting out. Data on all W&W patients are collected prospectively within our prospective multicenter study and are currently being analyzed, providing feedback on our implementation strategy. This strategy could then be adopted by other centers interested to implement organ preservation in rectal cancer. However, to maintain high volumes and high quality of care, organ preservation should best be offered in dedicated centers.

Advances in response prediction and assessment

As previously stated more robust methods to determine the clinical response to neoadjuvant therapy are needed to better stratify patients into those who can be treated with an organ preservation strategy or W&W, and those who require surgery. Quantitative approaches to assess clinical response to neoadjuvant treatment are being investigated; initially in functional imaging including DWI with apparent diffusion coefficient (ADC) and dynamic contrast enhanced (DCE) or 'perfusion' MRI, but more recently with a focus on radiomics. In radiomics, a large number of imaging features are extracted from MRI or CT that, with advanced automated quantitative imaging algorithms, can be used to build an image-based tumour phenotype with prognostic and predictive value. While very promising, most of the radiomics studies

have small sample sizes and standardization for replication and external validation on a larger scale is required[47,48]. Therefore, these signatures should be further analyzed to determine their clinical usefulness.

A recent study on artificial intelligence (AI) in endoscopy also showed the feasibility of deep learning methods on endoscopic images for response assessment in rectal cancer[49]. Future research with large datasets and high-resolution imaging could further explore the diagnostic performance of AI in restaging endoscopy. Other advanced endoscopy technologies such as the narrow-spectrum technologies and autofluorescence imaging are also an expanding field of research and may improve the mucosal, structural, and microvascular visualization of the rectal wall[50]. This may help in the differentiation between ongoing response or residual tumour after neoadjuvant treatment. These technologies have, however, yet to be explored in the setting of restaging.

Current treatment decisions for organ preservation in LARC are based on the response to neoadjuvant treatment. In the future, rectal cancer treatment will likely also include a prediction of response to neoadjuvant treatment that will that lead to a more precise and personalized treatment. Prediction of little to no response could identify patients who should go straight to surgery and thereby avoid unnecessary delays and exposure to ineffective yet detrimental treatments. Prediction of a good response may on the other hand select patients for neoadjuvant treatment with the aim of organ preservation. Currently, many clinical features, blood biomarkers, molecular markers and imaging markers are investigated for response prediction, but are not ready for clinical application. Furthermore, there are high expectations for the use of AI to integrate multiple data streams, such as clinical, molecular and imaging data, to form prediction models that can ultimately support clinical decision making[51].

Radiotherapy for non locally advanced rectal cancer with the aim of organ preservation

Since the introduction of population-based screening in 2014, colorectal cancers are more often detected at an earlier disease stage and the percentage of patients that present with less advanced stages of rectal cancer will increase[52]. While there is no survival benefit in patients with early stage rectal cancer receiving pre-operative radiotherapy[53], patients with lower cT stage and small tumour size have a higher probability of achieving a pCR after neoadjuvant treatment[35,54]. This has sparked an interest in its application in early stage rectal cancer again with the intention of organ preservation. CRT followed by transanal local excision in small cT2 and cT3 tumours is oncologically safe in good responders, but the multiple treatments can give rise to cumulative toxicities, particularly in patients who still need to undergo completion TME after local excision[55,56]. More acceptable toxicity rates with high

organ preservation rates were seen in the TREC study, comparing short-course radiotherapy followed by transanal endoscopic microsurgery versus TME surgery alone in early stage (cT1-2N0M0) rectal cancer, with a maximum diameter of 30 mm)[57]. The ongoing international STAR-TREC trial (NCT02945566) is a phase 2/3 trial with a partially randomized patient preference design that compares radical surgery, organ preservation with short-course radiotherapy, and organ preservation with CRT in patients with early stage (cT1-3bN0M0) rectal cancer, with a more selective use of local excision and applying watch-and-wait were possible in the organ preservation arms[32]. This trial will give us data on whether a CRT or short-course radiotherapy strategy is superior in terms of achieving organ preservation and if there are acceptable rates of organ preservation and treatment related toxicity, among other outcomes.

Strategies to enhance the likelihood of a favourable response

Increasing the response rate after neoadjuvant treatment, and thereby increasing the number of patients that could benefit from organ preservation, has been a primary focus of many clinical trials. Different intensification strategies have been investigated, e.g. radiotherapy dose-escalation, multiagent chemoradiotherapies or additional chemotherapy before or after CRT [total neoadjuvant treatment (TNT)].

A meta-analysis demonstrated that radiotherapy dose escalation is a good strategy to increase pCR rates[58]. However, relatively high doses (>60Gy) are necessary to establish this[59]. This raises concerns for increased toxicity. In that light, the delivery of high-precision and adaptive boosts using MR-guided radiotherapy is a very promising technique[60]. Endorectal brachytherapy also offers the advantage of delivery of higher doses of RT to the rectal tumour, while minimizing exposure to the sphincters and other organs at risk due to a steep dose gradient. Contact X-ray brachytherapy can deliver even higher doses to the mural rectal tumour (up to 90Gy/3 fractions) and has been highly effective in patients with early rectal cancer or in combination with external beam radiotherapy in inoperable or high surgical risk patients[61,62]. The feasibility of contact X-ray brachytherapy as a boost to CRT is the subject of the ongoing international OPERA trial for cT2, cT3a-b tumours (NCT02505750), and of the ongoing Dutch OPAXX trial for locally advanced tumours with a near cCR (NL75896.031.20).

A novel approach in the management of rectal cancer is total neoadjuvant therapy (TNT), where additional chemotherapy is given either before (induction) or after (consolidation) (chemo)radiotherapy. While primarily aimed at reducing micrometastases early in the course of the disease and thereby potentially prevent distant recurrence, TNT has also shown great potential in downstaging of the primary tumour and increasing pCR rates[63,64]. The RAPIDO trial and PRODIGE 23 trial - two

randomized phase 3 trials comparing TNT to standard neoadjuvant CRT in locally advanced rectal cancer – consistently reported a pCR rate of 28% despite different investigational TNT regimens; twice the rate of pCR after standard CRT[65,66]. A higher pCR rate after TNT could translate into a higher number of patients eligible for organ preservation, as was demonstrated by the preliminary results of the OPRA trial[67]. Although it included a slightly more favourable patient group than the RAPIDO trial, the OPRA trial showed organ preservation was achieved in about half of the patients. Notably, up-front CRT followed by consolidation chemotherapy resulted in a higher organ preservation rate compared to induction chemotherapy followed by CRT (58% vs. 43%). Consolidation chemotherapy was also proposed as the preferred TNT sequence for organ preservation in a recent publication by the German Rectal Cancer Study Group[68], as it resulted in higher pCR rate without compromising disease-free survival, toxicity, QoL, or stool incontinence in their randomized phase 2 trial.

Another strategy being investigated as sequential therapy after radiotherapy are immune checkpoint inhibitors. Primary analysis of a phase I/II study investigating CRT, nivolumab monotherapy and subsequent surgery in patients with MSS LARC showed a pCR rate of 30%, suggesting the potential for future use of immunotherapy in rectal cancer and warranting further research[69]. A small ongoing trial in the Netherlands Cancer Institute is currently testing 5x5Gy with a subsequent short course of bevacizumab and atezolizumab for intermediate risk and low risk distal rectal cancer (NCT04017455).

Concluding remarks

Organ preservation in rectal cancer has come a long way since the initial publication of Habr-Gama et al. on the watch-and-wait approach. In this thesis we presented prognostic value of restaging endoscopy, patient preferences and detailed outcomes regarding QoL, functional outcome and regrowth after a watch-and-wait approach in patients with rectal cancer, providing valuable information for patient counseling, treatment decision making and future research. There are still many challenges in organ preservation and in the coming years further research will focus on finding tools for more robust response prediction and assessment, increasing the number of patients with a clinical complete response, the optimal timing and type of treatment for near clinical complete responders and the effectiveness of organ preservation strategies in early stage rectal cancer. Despite the challenges ahead, it has become very clear that some rectal cancer patients can be cured with neoadjuvant therapy alone and radical surgery is no longer necessary in all patients. With the ongoing efforts of all disciplines involved, including surgery, medical oncology, radiation oncology, radiology, basic science, and artificial intelligence, it is undeniable that organ preservation will be offered to many future rectal cancer patients.

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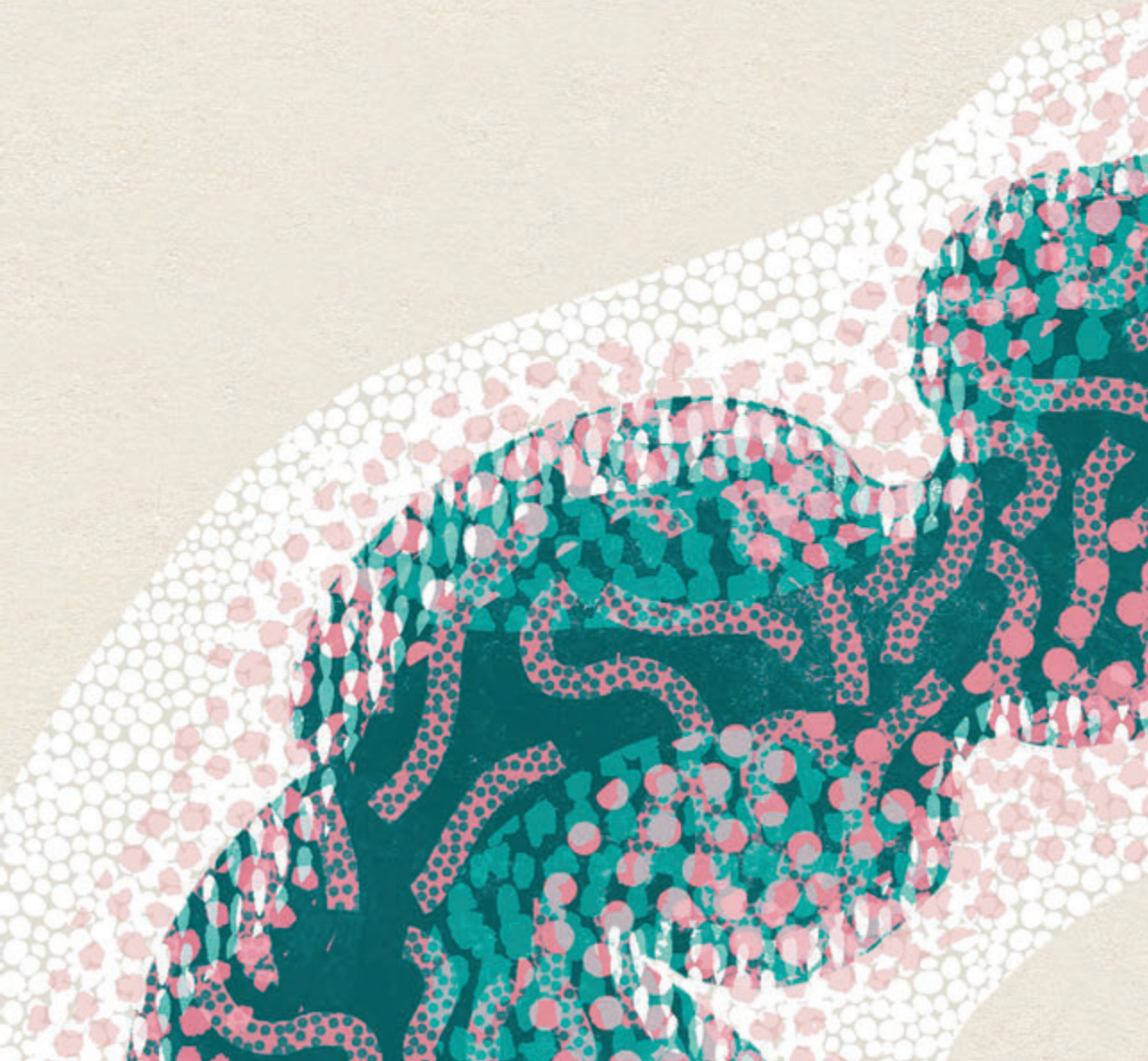
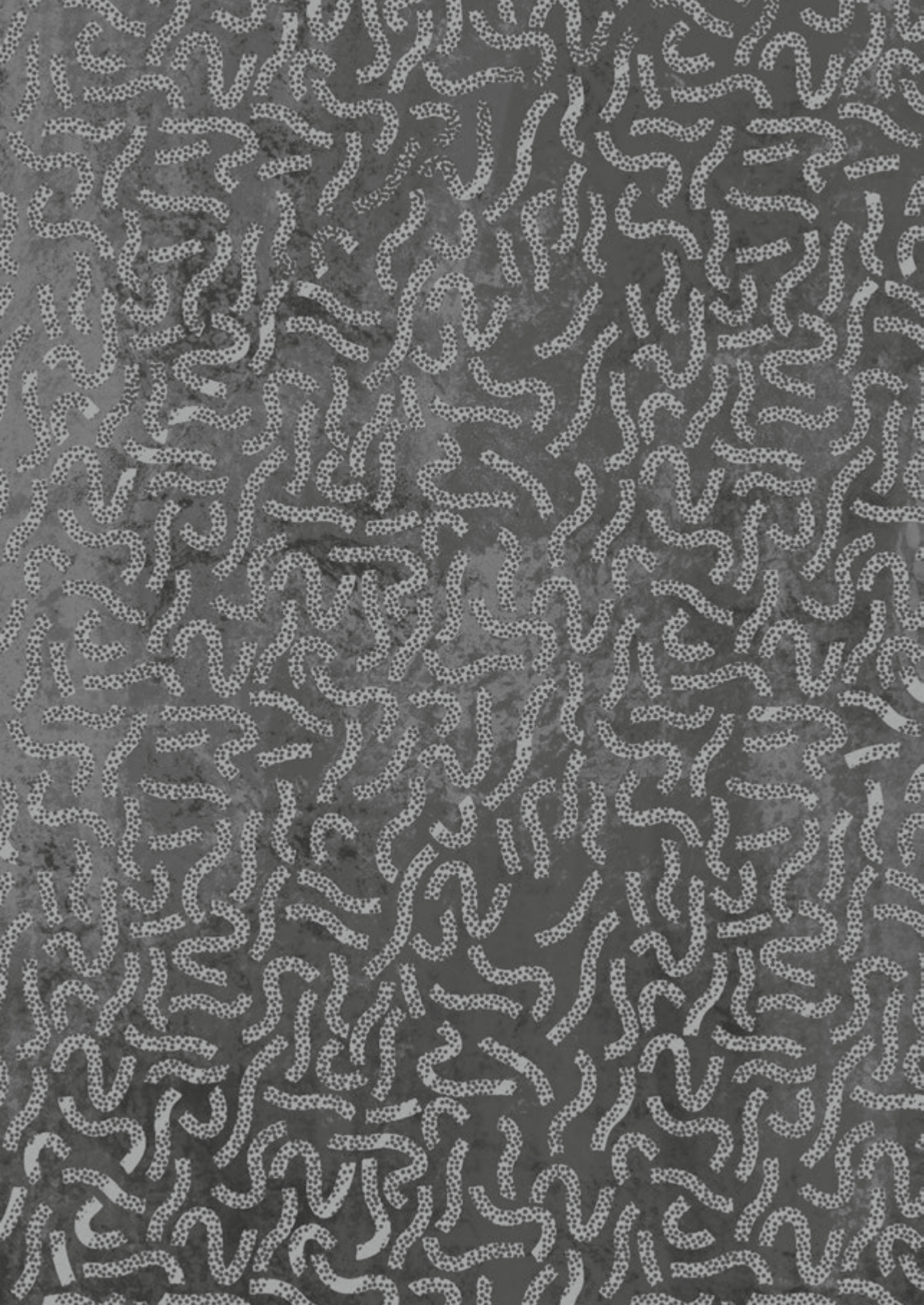


SUMMARY
NEDERLANDSE SAMENVATTING
IMPACT PARAGRAPH
LIST OF PUBLICATIONS
CURRICULUM VITAE



SUMMARY

For rectal cancer patients with a clinical complete response following neoadjuvant treatment the Watch-and-Wait approach (W&W) has emerged as an organ sparing alternative to total mesorectal excision (TME). The W&W approach, with no immediate surgery and close surveillance, could potentially avoid the risk for postoperative complications and significantly benefit quality of life (QoL) in rectal cancer patients. Although there are many encouraging reports on the W&W approach, several areas of uncertainty currently limit the applicability of the approach outside of study protocols and implementation into daily clinical practice. In this thesis, we aimed to explore how to better select patients for organ preservation, to explore the patients' perspective on organ preservation and rectal cancer treatment, and to investigate outcomes in watch-and-wait regarding QoL and regrowth.

Part I - Response assessment after neoadjuvant treatment

One of the basic principles of organ preservation is the assessment of the tumor response to neoadjuvant therapy and to offer treatment tailored to the response. In this part of the thesis we focused on how to improve response assessment, as accuracy for restating is low and potentially eligible patients for a watch-and-wait approach are missed using clinical examination, endoscopy and MRI. In chapter 2 we evaluated a cohort of 36 patients with a pathological complete response (pCR) that were clinically suspect for residual tumour. In these "unrecognized" complete responders we aimed to find distinct features on restaging endoscopy, T2-weighted MRI and diffusion weighted imaging (DWI) that may have led to the false diagnosis of residual tumour at response. On re-evaluation of the restaging endoscopy images, only 16% of the patients presented with a flat scar while 84% of the patients had mucosal abnormalities, not consistent with a clinical complete response. On MRI, an irregular aspect of the former tumour location was seen in 69% of patients, mixed signal intensity in 53%, and diffusion restriction on DWI in 51%. A quarter of the patients also showed suspicious lymph nodes, which might have been the reason for performing a rectal resection. For some of these pitfalls on MRI and endoscopy, histological reactive changes to chemoradiotherapy (CRT), e.g. fibrosis or microscopic ulceration, were found as a substrate when reviewing histopathology reports. Clinicians should be aware of these pitfalls on endoscopy and MRI, when selection patients for organ preservation. In patients with a very good clinical response otherwise, the abovementioned features should not be regarded as unequivocal signs of residual tumour and an extended waiting interval followed by a reassessment can be considered to provide a more convincing picture of the response.

Because the majority of patients with an unrecognized CR showed mucosal abnormalities we aimed to assess the accuracy of restaging endoscopy in a diagnostic study in chapter 3. The endoscopic images of 161 consecutive rectal cancer patients, who underwent CRT followed by either rectal resection or a watch-and-wait approach, were assessed by three independent readers who scored which endoscopic feature was present and what the confidence level for a luminal complete response (CR) was. The median time to endoscopy was 9 (interquartile range 8–12) weeks. We found that endoscopy had a moderate accuracy for the prediction of a complete response, with an AUC of 0.80 to 0.84 for the three readers. The readers identified 72% to 90% of the patients with a luminal CR and of those assessed as definite or probable complete responders, 63% to 78% truly had a pCR or were free of regrowth in a watch-and-wait approach. Providing the readers with biopsy results did not improve the accuracy in the prediction of a CR.

This study also showed that although the majority of patients with a CR presented with the typical flat scar, some showed other endoscopic features at response assessment. The positive predictive value (PPV) for a CR was highest in patients with a flat scar (70%–80%), and was 40% to 50% in patients with a small flat ulcer. Large flat ulcers, ulcers with an irregular border, or residual adenomatous or tumorous masses were more consistent with residual tumor as we found lower predictive values for a CR in these patients. These findings, in combination with the findings of clinical examination and restaging MRI, can be of value when discussing the treatment option of organ preservation. We concluded that patients who show a small flat ulcer, in addition to patients who have the typical flat scar, may be selected for an extended observation interval.

Part II - Patient reported and functional outcomes

The main goal of a watch-and-wait policy is an anticipated improved functional outcome and quality of life, while maintaining a good oncological outcome. While there is growing evidence supporting the oncological safety, the quality of life and functional outcomes after a watch-and-wait policy remain less explored. In chapter 4 we presented a cross-sectional study on the long-term anorectal function in patients with locally advanced rectal cancer undergoing a watch-and-wait approach and investigated the influence of the dosimetric parameters of radiotherapy on the anorectal function. We identified all watch-and-wait patients between 2009-2015 from a one institute who had > 2 years of follow-up and assessed the long-term anorectal function using the Low Anterior Resection Syndrome (LARS) score, Vaizey score and anorectal manometry. The radiotherapy dose was assessed by calculating the radiotherapy dose-volume histogram parameters of the rectum

and anal sphincter complex in each patient. Thirty-three patients were included in the analysis, with a median follow-up of 37 months. One-third of the patients reported major LARS. The most frequent complaints were clustering of defaecation and faecal urgency. Although there were some trends towards worse long-term anorectal function after higher anal sphincter complex radiotherapy dose, we observed no significant associations between the radiotherapy dose parameters to the rectum and anal sphincters and the LARS or Vaizey score. In addition, we observed no association between the dosimetric parameters and resting pressure (MRP) or anorectal sensory function (first sensation (FS), first urge to defecate (FUTD), and maximal tolerable volume (MTV)), although the observed mean anal resting pressures and anal squeeze pressures were low compared to values mentioned in literature. Despite the limitations of the study (small cohort, cross-sectional study, questionnaires not validated in watch-and-wait), this was the first study to explore the specific effects of (chemo)radiation in W&W patients on the anorectal function. It should be evaluated on a larger scale, especially with the current interest in radiotherapy to achieve organ preservation in rectal cancer. Further insights into the specific mechanisms of anorectal dysfunction after CRT can help form strategies to minimize the impact on anorectal function.

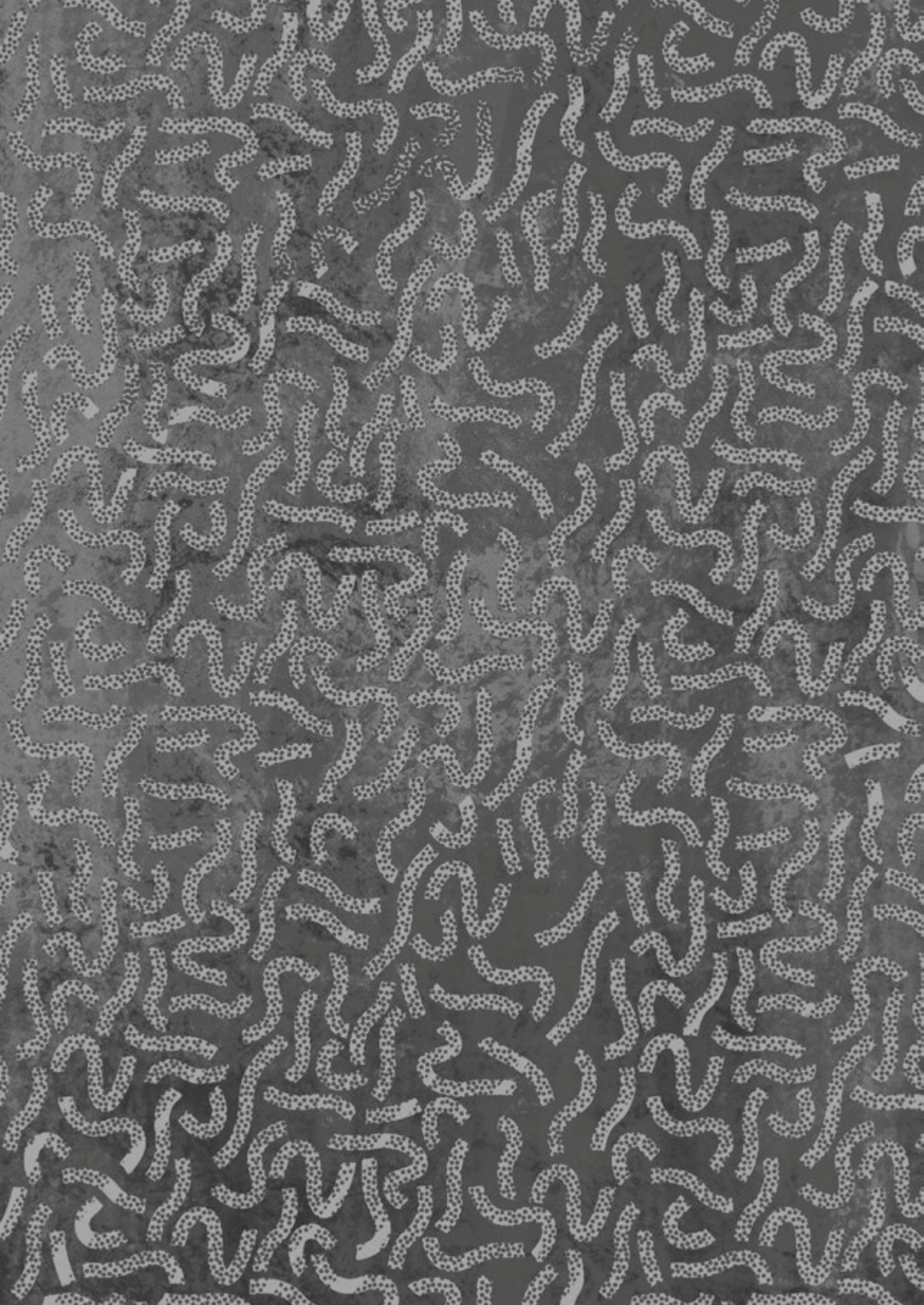
In chapter 5 we presented the results of our prospective study on quality of life and functional outcome of rectal cancer patients following a W&W approach. A total of 300 non-metastasized rectal cancer patients who were prospectively included in the Dutch Watch-and-Wait registry had a minimum follow-up of 24 months by April 2021, of whom 287 patients were included for analysis on QoL and functional outcome including bowel, urinary, and sexual function. At the time of inclusion in the registry, 153 patients (53%) had a cCR, 125 patients (43%) a near cCR, and 9 patients (3%) an incomplete response. At 24 months of follow-up, 227 patients (79%) were still followed by W&W, 18 patients (6%) were treated with additional local excision (LE), and 42 patients (15%) with TME for either regrowth or suspicion of residual tumour. The W&W group reported good QoL, with limited variation over time. Major LARS was seen in about 25% of patients at all time-points. Male patients reported severe erectile dysfunction and moderate urinary dysfunction in 31% and 19% at 24 months. The sexual satisfaction and overall sexual function of female patients decreased during follow-up. Patients treated with LE had comparable QoL scores with the W&W group, but reported more major LARS (56%) at 24 months. Patients who underwent TME scored worse on several QoL subscales compared to the W&W group. Linear regression indicated that women had a worse outcome on several QoL subscales and a higher mean LARS score at 24 months. Higher age at inclusion was particularly associated with more urinary and sexual dysfunction in men at 24 months.

With a growing number of treatment options for patients with rectal cancer, making the right treatment decision for the individual patient is an increasingly difficult task for patients and multidisciplinary teams. It requires a good understanding of all treatment options, including the potential risks and benefits of each strategy. This study shows important information that can be used to counsel patients on what to expect following W&W.

In chapter 6 we presented the results of a conjoint-based choice experiment, in which we examined the tradeoffs between different clinical and patient reported outcomes that rectal cancer patients and physicians who are involved in treatment of rectal cancer patients make. In a direct ranking experiment, both patients and clinicians considered disease-free survival to be the most important outcome in rectal cancer treatment. However, the conjoint-based choice experiment showed disease-free survival was least important for patients, as they valued type of treatment (W&W, surgical resection with or without a temporary or definitive colostomy), faecal incontinence, urinary and sexual functioning and worries about cancer recurrence to be more important when simultaneously confronted with multiple outcomes. Avoiding surgery with permanent stoma was the most important outcome for patients, while clinicians assigned highest importance to avoiding severe and daily worries about cancer recurrence. We concluded that patients do value DFS high, but not at the cost of functional outcomes after treatment.

Part III - Outcomes after local regrowth

In chapter 7 we described the management and oncological outcomes of patients with local regrowth in two watch-and-wait cohorts. Approximately 15%–30% of patients with a clinical complete response after (chemo) radiotherapy who undergo a W&W policy will experience a local regrowth. The risks of these local regrowths have not yet been fully established and main concerns include high postoperative morbidity, requirement of advanced surgery, and pelvic recurrence after regrowth treatment. We identified 89 patients with a local regrowth from a cohort of 385 rectal cancer patients with a clinical complete response after (chemo) radiotherapy undergoing a W&W approach between 2005 and 2018. We found that almost all patients (97%) with local regrowth after a W&W policy were able to undergo treatment with curative intent for their regrowth. The majority (94%) underwent a surgical treatment of the local regrowth: total mesorectal excision was performed in 69% of patients and local excision in 31%. There seemed to be no increased risk of surgical complications after the delayed surgical treatment. We concluded that uncontrolled pelvic disease after W&W was very rare. A highly important question that is still unanswered is whether or not regrowth can be the origin of distant metastases.



NEDERLANDSE SAMENVATTING

Voor patiënten met een klinisch complete respons na een neoadjuvante behandeling is het watch-and-wait beleid (W&W) een alternatief voor een operatieve behandeling middels een totale mesorectale excisie (TME). Door W&W - een actieve surveillance – toe te passen, kan mogelijk het risico op postoperatieve complicaties vermeden worden en de kwaliteit van leven van patiënten met een rectumcarcinoom verbeteren. Ondanks het toenemende aantal onderzoeken naar W&W, wordt de toepassing van deze orgaansparende behandeling in de dagelijkse klinische praktijk beperkt door verschillende openstaande vraagstukken. De doelen van dit proefschrift zijn om (1) te onderzoeken hoe we de patiëntselectie voor orgaansparende behandeling kunnen verbeteren met de huidige technieken; (2) de patiënt gerapporteerde en functionele uitkomsten na een W&W beleid te evalueren; (3) het patiëntperspectief op orgaanpreservatie en de behandeling van het lokaal gevorderd rectumcarcinoom te onderzoeken, en (4) de behandeling en uitkomsten van een lokale teruggroei van tumor (regrowth) te evalueren.

Deel I - Responsevaluatie na neoadjuvante behandeling

Een van de basisprincipes van orgaanpreservatie is aanbieden van een behandeling op maat, afhankelijk van de tumorrespons op de neoadjuvante behandeling. Uit eerder onderzoek blijkt dat een groot deel van patiënten die in aanmerking kunnen komen voor W&W gemist worden bij de responsevaluatie. In hoofdstuk 2 worden de MRI- en endoscopiebeelden van een cohort van patiënten met een pathologische complete respons (pCR), die klinisch verdacht waren voor resttumor, opnieuw geëvalueerd. De uitkomsten laten zien dat slechts 16% van deze gemiste complete responders een vlak litteken, algemeen beschouwd als het typisch endoscopisch beeld van een klinisch complete respons, toonde bij de responsevaluatie. Daarentegen toonde 84% van dit cohort nog mucosale afwijkingen. Op MRI werd bij 69% van de patiënten een irregulier aspect van de rectumwand op de voormalige tumorlocatie gezien, toonde 53% een gemengde signaalintensiteit en 51% diffusierestrictie op DWI. Een kwart van de patiënten had tevens verdachte lymfeklieren op beeldvorming. Deze kenmerken op endoscopie, T2-gewogen MRI en diffusie-gewogen MRI hebben mogelijk geleid tot een foutieve diagnose van resttumor in deze gemiste complete responders. Voor enkele van deze kenmerken werden bij het beoordelen van histopathologie rapporten van de rectumresectie reactieve veranderingen door de chemoradiotherapie (CRT) gevonden als substraat, zoals fibrose of microscopische ulceratie. Artsen dienen bij het selecteren van patiënten voor een orgaansparende behandeling zich bewust te zijn dat deze kenmerken ook kunnen voorkomen bij patiënten met een complete respons. Als patiënten verder een zeer goede respons

vertonen, zal de aanwezigheid van een van de bovengenoemde kenmerken bij de responsevaluatie daarom niet moeten worden beschouwd als een onmiskenbaar teken van resttumor, maar zou een aanvullende observatieperiode gevolgd door een nieuwe responsevaluatie overwogen kunnen worden.

In hoofdstuk 3 wordt een onderzoek naar de accuratesse van restadiering middels endoscopie gepresenteerd. De endoscopische beelden van 161 opeenvolgende patiënten met een rectumcarcinoom die neoadjuvante CRT ondergingen gevolgd door een rectumresectie of een W&W beleid, werden beoordeeld door 3 onafhankelijke readers. De resultaten van het onderzoek laten zien dat endoscopie een redelijk tot goede accuratesse heeft voor het voorspellen van een CR, met een AUC van 0.80-0.84. Het uitvoeren van een biopt bij endoscopie verhoogde de accuratesse van endoscopie in het voorspellen van een CR niet. Dit onderzoek liet tevens zien dat de PVW voor een CR het hoogst was bij patiënten die een vlak litteken toonden. De PVW voor een CR was 40%-50% voor bij patiënten met een klein vlak ulcus. Grotere vlakke ulcera, ulcera met een irregulaire rand, of resterende adenomateuze of tumorachtige afwijkingen hadden lagere PVW en waren meer voorspellend voor de aanwezigheid van resttumor. Afgaande op deze resultaten kan er worden overwogen om patiënten met een klein vlak ulcus te selecteren voor extra observatieperiode gevolgd door een nieuwe responsevaluatie om een overtuigender beeld te krijgen van de tumorrespons en of de patiënt geschikt is voor een orgaansparende behandeling.

Deel II - Patiënt-gerapporteerde en functionele uitkomsten

Het belangrijkste doel van W&W zijn verbeterde functionele uitkomsten en kwaliteit van leven (QoL) na een behandeling van het rectumcarcinoom, met behoud van goede oncologische uitkomsten. In de cross-sectionele studie in hoofdstuk 4 wordt de anorectale functie beschreven van 33 patiënten na een mediane follow-up van 37 maanden. Ook werd de invloed van de dosimetrische parameters van de radiotherapie op de anorectale functie onderzocht. Een derde van de patiënten meldde ernstige Low Anterior Resection Syndrome (LARS) klachten. De meest voorkomende klachten waren clustering en fecale urgentie. Hoewel er enkele trends waren die wezen op een slechtere anorectale functie na een hogere bestralingsdosis op het anale sfinctercomplex, waren er geen significante correlaties tussen de dosimetrische parameters van de anus en rectum en de LARS- of Vaizey-score. Er werd geen correlatie gevonden tussen de dosimetrische parameters en de anorectale sensorische functies (first sensation (FS), first urge to defecate (FUTD), en maximal tolerable volume (MTV)). Ondanks de beperkingen van de studie (een klein cohort, cross-sectioneel onderzoek, vragenlijsten niet gevalideerd voor W&W),

was dit de eerste studie die de specifieke langetermijneffecten van radiotherapie op de anorectale functie onderzocht bij patiënten met een rectumcarcinoom. Met de huidige ontwikkelingen in de behandeling van het rectumcarcinoom, waarbij de toepassing van (chemo)radiotherapie of een additionele radiotherapie boost met de intentie om orgaansparend te behandelen wordt onderzoek, is het belangrijk om inzicht te krijgen in de specifieke effecten van radiotherapie of de anorectale functie. Dit zou kunnen helpen bij het vormen van strategieën, zoals een dosisreductie of het aanpassen van de bestralingsvelden, om de impact op de anorectale functie te minimaliseren.

Hoofdstuk 5 toont de resultaten van onze prospectieve studie naar de QoL en functionele uitkomsten na een W&W beleid bij patiënten met een rectumcarcinoom, waarin we 287 patiënten hebben geïncludeerd met een follow-up van 24 maanden. De W&W-groep rapporteerde een goede QoL, met beperkte variatie over de tijd. Ernstige LARS werd gezien bij circa 25% van de patiënten gedurende de follow-up. Ernstige erectiestoornissen en matige urinedysfunctie werden door respectievelijk 31% en 19% van de mannelijke patiënten gerapporteerd na een follow-up duur van 24 maanden. Voor vrouwelijke patiënten nam de totale score en de tevredenheidsscore van Female Sexual Function Index af gedurende de follow-up. Patiënten behandeld met LE hadden een vergelijkbare QoL met de W&W groep, maar rapporteerden wel een hogere LARS score (28.2 vs. 20.7) en vaker major LARS (55.6% vs. 25.1%) op 24 maanden. Patiënten die een TME ondergingen voor een regrowth of resttumor scoorden hadden een slechtere QoL dan de W&W groep. Door middel van lineaire regressieanalyse werd aangetoond dat vrouwen een slechtere uitkomst hadden op meerdere QoL subschalen en een hogere LARS-score hadden op 24 maanden. Een hogere leeftijd bij inclusie was met name geassocieerd met meer mictieklachten en seksuele dysfunctie bij mannen.
Met een groeiend aantal behandelopties voor patiënten met een rectumcarcinoom wordt het nemen van de juiste behandelkeuze voor de individuele patiënt een steeds moeilijkere taak voor patiënten en multidisciplinaire teams. Het vereist een goed begrip van alle behandelingsopties, inclusief de voordelen en mogelijke risico's. De informatie uit deze studie kan worden gebruikt om voor te lichten over de functionele uitkomsten na W&W.

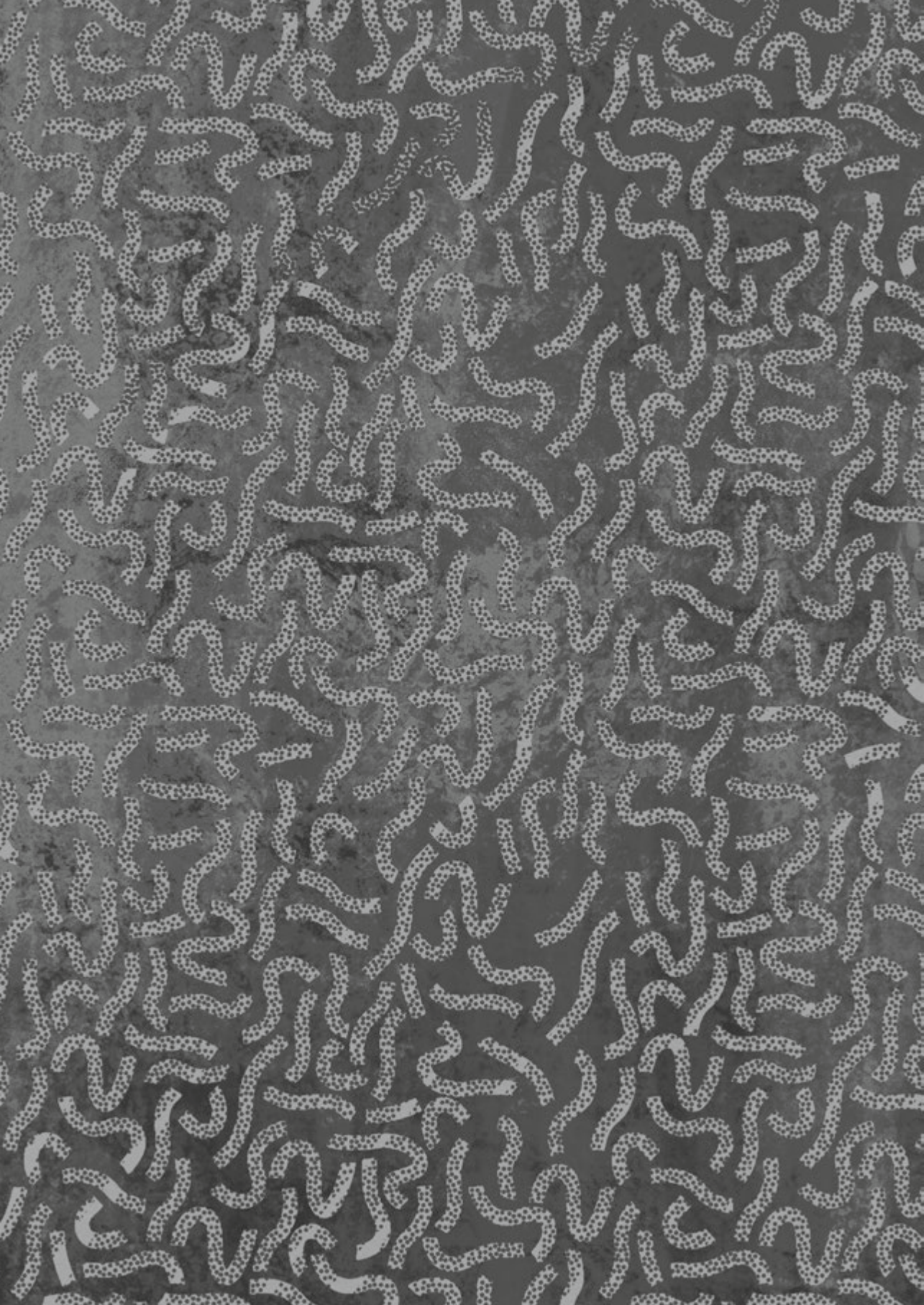
In hoofdstuk 6 presenteerden we de resultaten van een vragenlijstonderzoek met een keuze-experiment, waarin we de afwegingen voor verschillende behandeluitkomsten onderzochten bij patiënten en artsen. Wanneer werd gevraagd de verschillende uitkomsten te rangschikken, beschouwden zowel patiënten als artsen ziektevrije overleving als de belangrijkste uitkomst bij de behandeling van het rectumcarcinoom. Het keuze-experiment toonde echter aan

dat ziektevrije overleving het minst belangrijk was voor patiënten wanneer ze werden geconfronteerd met meerdere uitkomsten tegelijkertijd, en meer waarde werd gehecht aan andere uitkomsten zoals het type behandeling (W&W of operatie met of zonder stoma), fecale incontinentie, blaasfunctie, seksuele functie en zorgen over een recidief. Tevens waren er bij het keuze-experiment duidelijke verschillen tussen welke uitkomsten patiënten en welke artsen belangrijk vonden. Zo bleek dat artsen de meeste waarde hechtten aan de mate van zorgen over een recidief, maar het type behandeling de belangrijkste uitkomst was voor patiënten. We concludeerden dat patiënten ziektevrije overleving hoog waarderen, maar niet ten koste van functionele resultaten na behandeling.

Deel III - Uitkomsten na een lokale regrowth

Ongeveer 15%-30% van de patiënten met een klinisch complete respons na (chemo) radiotherapie die een W&W-beleid ondergaan zal een lokale regrowth krijgen. De risico's van deze regrowth zijn nog niet duidelijk en er zijn zorgen over hoge postoperatieve morbiditeit, de noodzaak tot uitgebreide chirurgische resectie of een locoregionaal recidief na regrowth behandeling.

In hoofdstuk 7 beschrijven we de behandeling en oncologische uitkomsten van patiënten met lokale regrowth afkomstig uit twee W&W cohorten. We identificeerden 89 patiënten met een regrowth en vonden dat 97% van hen een curatieve behandeling hadden ondergaan voor de regrowth. De meerderheid (94%) onderging een chirurgische behandeling; totale mesorectale excisie werd uitgevoerd bij 69% van de patiënten en een lokale excisie bij 31%. Er leek geen verhoogd risico te zijn op chirurgische complicaties te zijn na deze uitgestelde chirurgische behandelingen. We concludeerden dat irresectabele locoregionale recidieven na W&W zeldzaam waren. Een zeer belangrijke vraag welke tot op heden onbeantwoord blijft is of regrowth een hoger risico op afstandsmetastasen geeft.



IMPACT PARAGRAPH

Main aims and outcomes of this thesis

The main aims of this thesis are: (1) to explore how to better select patients for organ preservation with the tools currently used, (2) to investigate the quality of life and the functional outcomes in patients undergoing a watch-and-wait approach, (3) to explore the patients' perspective on organ preservation and rectal cancer treatment outcomes and (4) to evaluate treatment and outcome of local regrowth.

In Chapter 2 of this thesis we identified distinct features that may form pitfalls for clinicians in the assessment of tumor response with MRI and endoscopy. These included residual mucosal abnormalities on endoscopy, along with full thickness or irregular shaped fibrosis and mixed signal intensity on T2W-MRI, and focal diffusion restriction on DWI. These pitfalls may lead to an underestimation of patients that are eligible for organ preservation. In our diagnostic study in Chapter 3 we found that endoscopy had a moderate accuracy for the prediction of a complete response. While a white scar was most predictive of a complete response, we concluded that patients who show a small flat ulcer in the rectal mucosa surgery may also be selected for an extended observation interval. The results of Chapter 4 and 5 showed that watch-and-wait patients had good long-term quality of life, although bowel and sexual dysfunction were observed after treatment with (chemo)radiotherapy. Patients who did not have local regrowth had better quality of life and less bowel and sexual dysfunction compared to patients who had rectal surgery for local regrowth. The results of our studies can be used to counsel patients on the watch-and-wait approach and make informed treatment decisions on organ preservation. Making the right treatment decision for the individual patient is an increasingly difficult task for clinicians and patients. The results of Chapter 6 showed that patients and clinicians value treatment outcomes different and therefore have different treatment preferences. It showed that patients do value being free of cancer very high, but not at the cost of functional outcomes after treatment. The last part of this thesis, Chapter 7, showed that having a local regrowth did not compromise the outcome for patients undergoing a watch-and-wait approach. Almost all patients were still able to undergo treatment and there seemed to be no increased risk for complications after delaying the surgery.

Relevance

Colorectal cancer has a major impact on society, as it is a major cause of morbidity and mortality. In the Netherlands, it's the fourth most common type of cancer in men and women and approximately 4000 patients are newly diagnosed with rectal

cancer each year. The treatment of rectal cancer has tremendously evolved over the past decades and is moving towards a personalized approach for each rectal cancer patient. Organ preservation will play a major part in future treatment decisions, but it is still in a transitional phase. In 2020, the watch-and-wait approach has been included in the Dutch national guidelines on colorectal cancer as a treatment option that can be discussed with patients with a clinical complete response. While organ preservation should be performed in centers with a certain level of experience, clinicians in all colorectal multidisciplinary teams should be aware of organ preserving alternatives and should discuss these with the patient when a clinical complete response is encountered. This thesis gives clinicians more insight into the different MRI and endoscopic features that can be found at restaging and what they mean for the clinical prediction of treatment response. This could aid the standardization of the definitions of clinical complete and near clinical complete response and may be used in response-based decision algorithms. This thesis also provides valuable information on treatment outcomes regarding quality of life, functional outcome and regrowth after a watch-and-wait approach and on patient preferences. This can be used to counsel future patients on the watch-and-wait approach and to make better shared and informed treatment decisions.

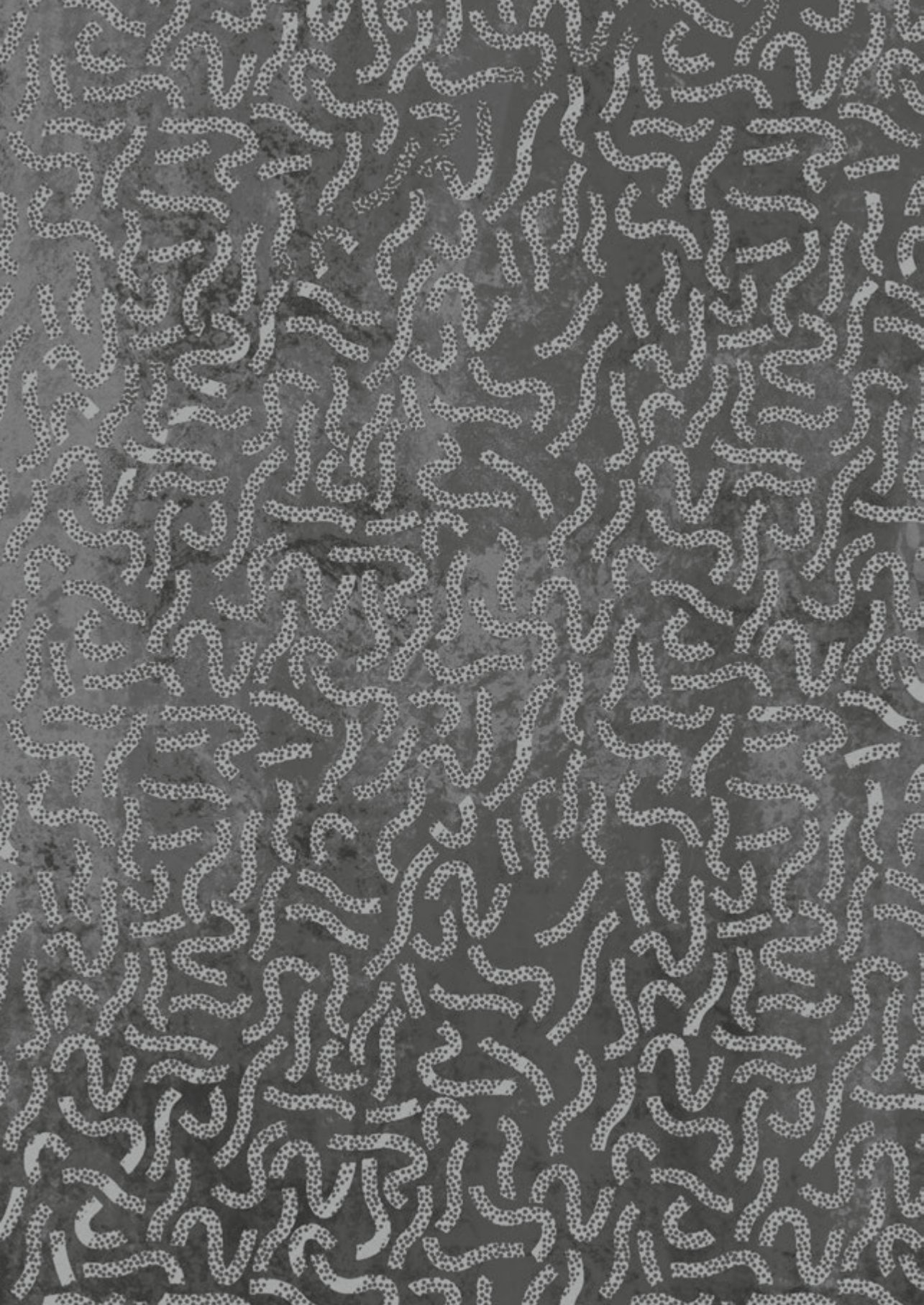
Target population

The results of this thesis are relevant for several target groups. The relevance for clinicians has been described above. Including organ preservation as a treatment option multidisciplinary team will also affect rectal cancer patients. The results of this thesis give a clear overview of patient outcomes that can be used to counsel patients on what to expect following a watch-and-wait approach, including when regrowth occurs. Patients can therefore be better informed with the results of this thesis. If surgery can be omitted, significantly less morbidity and better functional outcomes and quality of life are expected for these patients. While this thesis was mostly focused on patients with locally advanced rectal cancer who have an indication for treatment with (chemo)radiotherapy before surgery, organ preservation could potentially also benefit patients with other stages of rectal cancer. Ongoing studies such as the TESAR and STAR-TREC trial will show the of organ preservation in patients with early stage rectal cancer. This thesis is also relevant for other researchers, as the data on outcome provided in this thesis be used as reference standard in new organ preserving strategies.

Activities

The research presented in this thesis has been shared with the medical community in peer reviewed papers and at national and international conferences. Research

has also been shared among the Dutch Watch-and-Wait consortium, consisting of the participating clinicians of the prospective multicenter study on the watch-and-wait approach. Newsletters are shared and a watch-and-wait symposium has been organized at the Antoni van Leeuwenhoek for the consortium for training and updates on recent study results. Future meetings could continue to provide a platform for scientists and clinicians to share results and new ideas for organ preservation in rectal cancer. The data registry that was initially build for our multicenter study, now continues to serve as a registry for patients following a watch-and-wait approach in rectal cancer in the Netherlands, which can be a source of data for any future research.



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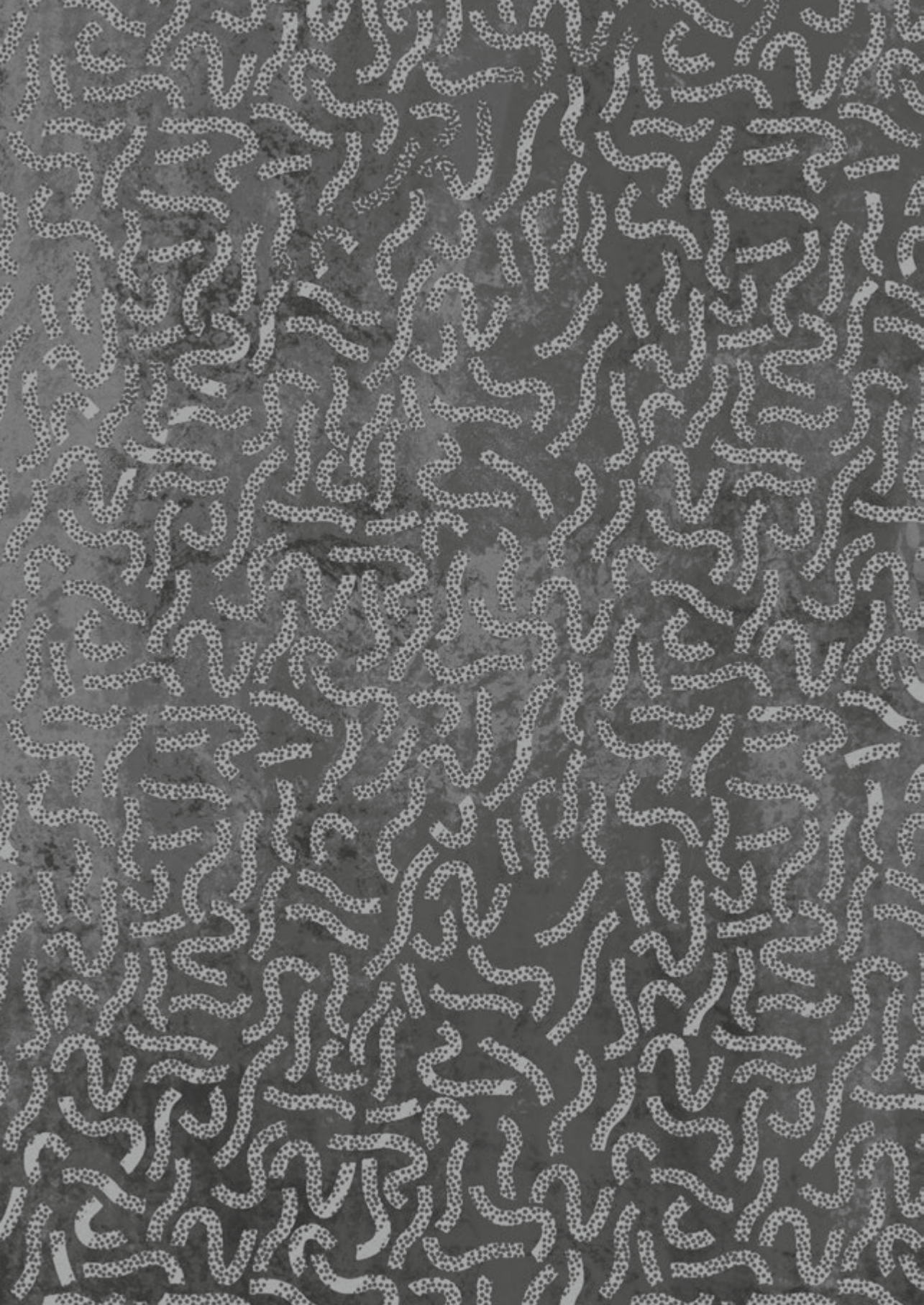

DANKWOORD

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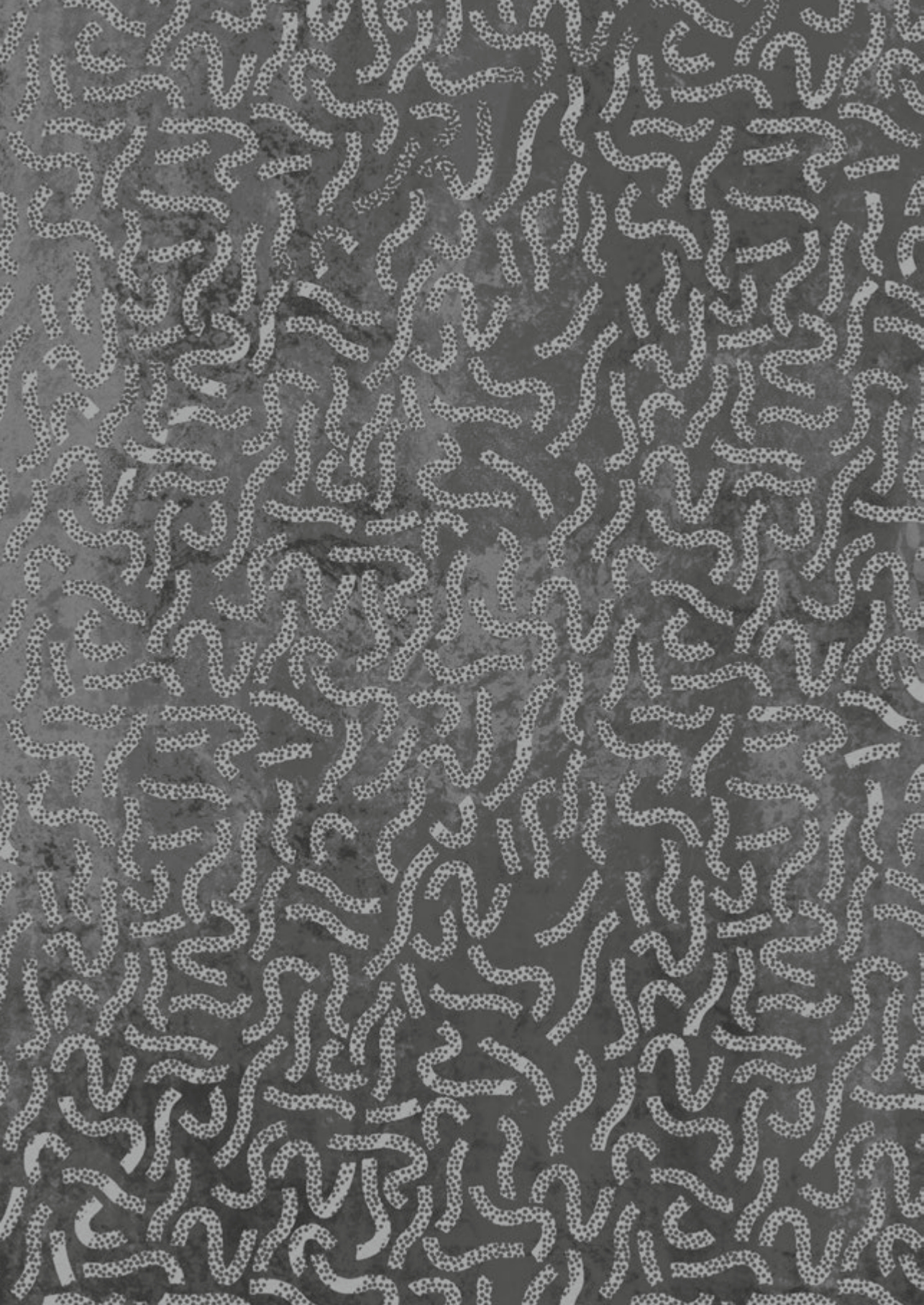

CURRICULUM VITAE

Marit Everine van der Sande was born on January 7, 1992, in Delft, the Netherlands. She received her secondary education at Dalton Den Haag in the Hague, where she also obtained an International Baccalaureate degree in English. In 2009, Marit moved to Maastricht to start her study in Medicine at Maastricht University. During her studies she went to Manipal, India, for a clinical internship in ENT and head and neck surgery. In her final year of Medicine, Marit participated in a research internship at the department of general surgery at Maastricht University Medical Centre. There, she started her research on the anorectal function in rectal cancer patients, under the supervision of dr. S.O. Breukink. For this research she received the Student Award from the Nederlandse Vereniging voor Gastroenterologie (Dutch Society of Gastroenterology).

After obtaining her medical degree in 2015, Marit continued her research in rectal cancer as a PhD candidate at the department of surgery at the Antoni van Leeuwenhoek (AvL) - Netherlands Cancer Institute in Amsterdam, under the supervision of prof. dr. G.L. Beets, dr. S.O. Breukink and dr. M. Maas. Marit coordinated a multicenter study on the watch-and-wait strategy in rectal cancer, which led to the implementation of this treatment strategy in > 15 hospitals in the Netherlands. She had the opportunity to present her research at national and international conferences.

After working as a researcher at the AvL, Marit started working as a resident (not in training); first in general surgery at the Flevoziekenhuis in Almere and at Gelre Ziekenhuizen in Apeldoorn, and currently in ophthalmology at Xpert Clinics in Zeist.