Maaike
Verweij

REBALANCING TREATMENT OUTCOMES IN RECTAL CANCER

REBALANCING TREATMENT OUTCOMES IN RECTAL CANCER

Maaike Verweij

Rebalancing treatment outcomes in rectal cancer

ISBN: 978-94-6469-879-4
DOI: https://doi.org/10.33540/2232

Cover design and layout: © evelienjagtman.com
Printing: proefschriftmaken.nl

Publication of this thesis was financially supported by the departement of Radiation-Oncology of the University Medical Center Utrecht, Nationale Vereniging van Gastro-Enterologie, Therapeuticum Artemis Amersfoort, Castor EDC and Chipsoft.

REBALANCING TREATMENT OUTCOMES IN RECTAL CANCER

De balans vinden tussen uitkomsten van behandeling van endeldarmkanker
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 18 april 2024 des middags te 12.15 uur

door

Maria Elisabet Verweij
geboren op 10 april 1994
te Zaanstad

Promotoren
Prof. dr. Helena M. Verkooijen
Prof. dr. Martijn P. W. Intven

Copromotor
Dr. Wilhelmina M. U. van Grevenstein

Beoordelingscommissie
Prof. dr. Anne M. May
Prof. dr. I. Quintus Molenaar
Dr. Stella Mook
Prof. dr. Frank P. Vleggaar
Prof. dr. Johannes P. de Wilt

Contents

Chapter 5 (page 93)

Verweij, M. E., Gal, R., Burbach, J. P. M., Young-Afat, D. A., van der Velden, J. M., van der Graaf, R., May, A. M., Relton, C., Intven, M. P. W. & Verkooijen, H. M. **Most patients reported positively or neutrally of having served as controls in the trials within cohorts design.** Journal of Clinical Epidemiology. 2022; 148: 39-47. https://doi.org/10.1016/j.jclinepi.2022.04.015

Chapter 6 (page 113)

Verweij, M. E., Tanaka, M. D., Kensen, C. M., Heide, U. A. van der, Marijnen, C. A. M., Janssen, T., Vijlbrief, T., Grevenstein, W. M. U. van, Moons, L. M. G., Koopman, M., Lacle, M. M., Braat, M. N. G. J. A., Chalabi, M., Maas, M., Huibregtse, I. L., Snaebjornsson, P., Grotenhuis, B. A., Fijneman, R., Consten, E. C. J., Pronk, A., Smits, A. B., Heikens, J. T., Eijkelenkamp, H., Elias, S. G., Verkooijen, H. M., Schoenmakers, M. M. C., Meijer, G. J., Intven, M. P. W. & Peters, F. P. **Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial.** British Medical Journal Open. 2023; 13: e065010. https://doi.org/10.1136/BMJOPEN-2022-065010

Chapter 7 (page 137)

General discussion

Treatment strategy: future

Appendices (page 153)

Supplementary files

Nederlandse samenvatting in niet-medisch taalgebruik

Ontwerp van de omslag

List of publications

Dankwoord

About the author

Chapter 1

General introduction and thesis outline

General introduction

The rectum

The rectum is the most distal part of the large intestine. It connects the sigmoid colon to the anal canal. The primary function of the rectum is the storage of stools before defecation. Also, the rectum plays a role in the absorption of water and electrolytes [1,2]. From in- to outside, the rectum consists of a layer of mucosa, submucosa, circular and longitudinal smooth muscle. The rectum is surrounded by the mesorectal fat, which contains the neurovascular and lymphatic structures. The mesorectal fat is enveloped by the mesorectal fascia (MRF). Anteriorly, the mesorectum is attached to the vagina and cervix uteri in females and to the urinary bladder, prostate and seminal vesicles in males (Figure 1A-B). Distally, the mesorectum is attached to the sacrum. Alongside the mesorectum run the hypogastric nerve and inferior hypogastric plexus, which innervate the urinary bladder and genitals [3].

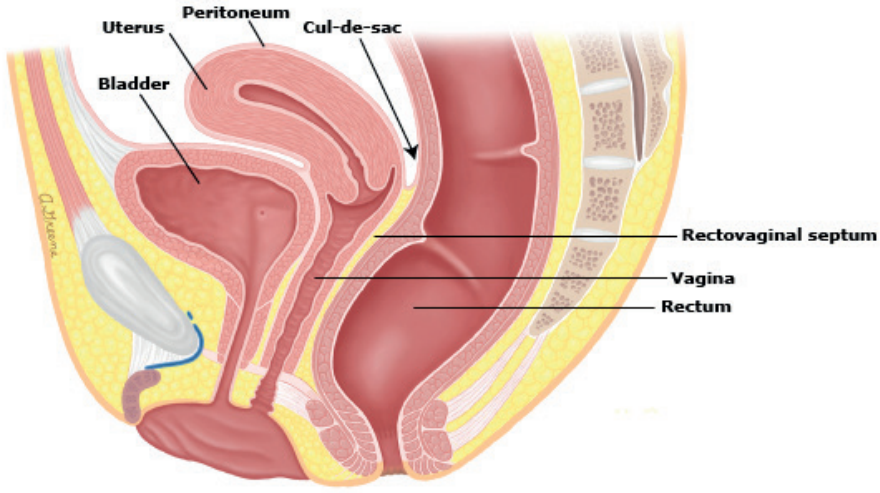
Rectal cancer

Each year, 12.000 patients in the Netherlands are diagnosed with colorectal cancer, of whom 3.200 rectal cancer [4]. Cancer arises when an accumulation of mutations makes a cell acquire the ability to proliferate excessively and invade other tissues [5,6]. Colorectal cancer most often arises from the (exocrine) glandular cells of the mucosa, which is called colorectal adenocarcinoma. Predisposing factors for colorectal cancer include male gender, higher age, inflammatory bowel disease, familial adenomatous polyposis, Lynch syndrome and familiar history of colorectal disease. Lifestyle factors that increase the risk of colorectal cancer include smoking, high alcohol intake, high body mass index, diabetes type II, low physical activity levels, low dietary fibre intake and high intake of red and processed meat [7,8].

Diagnosis and staging

A colorectal tumour may cause rectal bleeding, change in bowel habits, abdominal pain, unexplained weight loss or iron deficiency anaemia [9,10]. These symptoms can be an indication for a coloscopy. When a biopsy taken from a colorectal polyp during coloscopy shows malignant cells, colorectal cancer is diagnosed. About one third of Dutch colorectal cancer cases are identified following the national colorectal cancer screening programme, which offers a test for detecting occult blood in faeces to citizens between 55 and 75 years of age each two years [11].

A



B

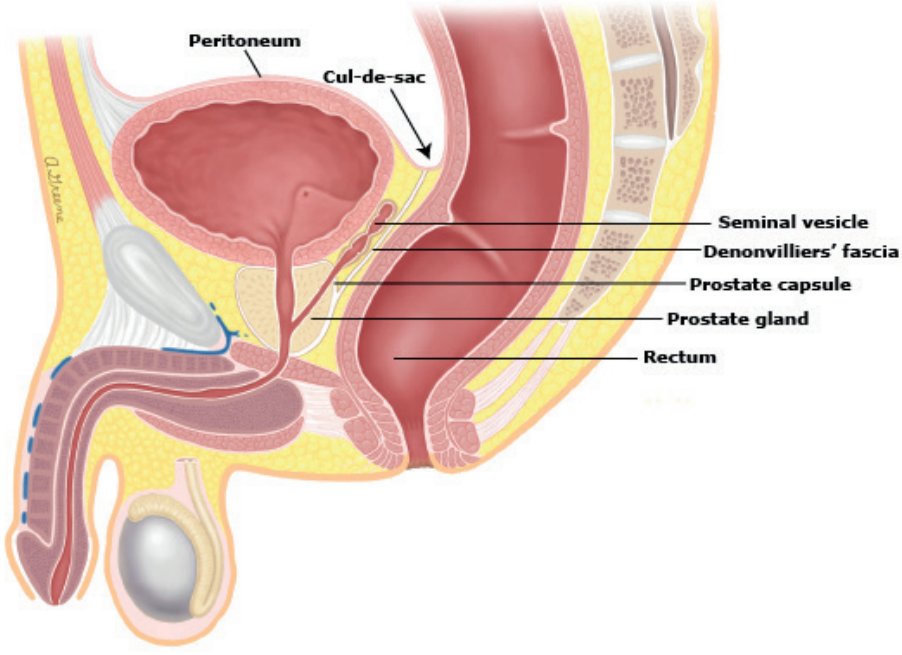


Figure 1A-B. Sagittal view of the pelvic anatomy in females (A) and in males (B) [2]

After diagnosis, the disease extension is evaluated using pelvic magnetic resonance imaging (MRI) and thoraco-abdominal computed tomography (CT). On sagittal MRI, a rectal tumour can be distinguished from a tumour in the sigmoid colon by the sigmoid take-off (Figure 2) [12]. The disease extension is described by the TNM staging, i.e., the extension of the tumour into the bowel wall (Tumour stage), the presence of suspicious locoregional lymph nodes (Nodal stage) and the presence of distant metastasis (Metastatic stage, Table 1). Locoregional lymph nodes are those in the mesorectum and the presacral, internal iliac and obturator spaces; metastasis to other lymph nodes are considered M1.

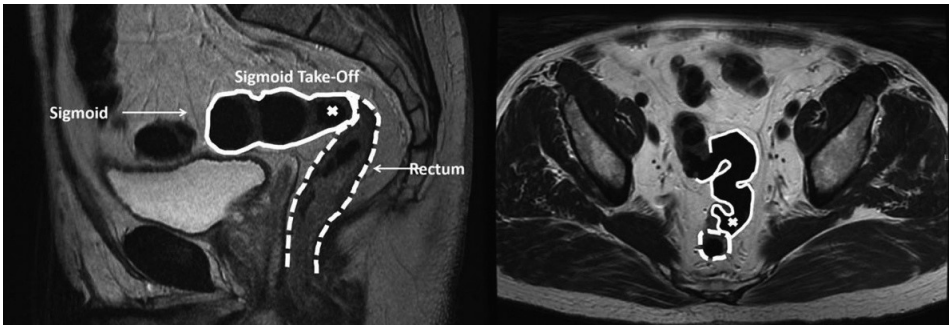


Figure 2. Sagittal (left) and transversal (right) pelvic MRI of a male displaying the sigmoid take-off (cross), the distinction between the sigmoid (solid outline) and the rectum (dashed outline). At the sigmoid take-off, the sigmoid sweeps away ventrally from the sacrum [12]

Table 1. Rectal cancer tumour, nodal, metastasis (TNM) staging according to the 8th edition of the American Joint Committee on Cancer and the Union for International Cancer Control

Tumour extension		**Nodal stage**		**Metastatic stage**	
Tis	Mucosa	N0	No suspicious lymph nodes	M0	No distant metastases
T1	Submucosa	N1	1-3 suspicious lymph nodes	M1	Distant metastases
T2	Muscularis propria	a	1 suspicious lymph node	a	Metastases to one organ without peritoneal metastases
T3	Mesorectal fat	b	2-3 suspicious lymph nodes	b	Metastases to two or more organs
a	< 1mm	c	Regional tumour deposits	c	Peritoneal metastasis with or without organ metastases
b	1-5 mm	N2			
c	5-15 mm	a	4–6 suspicious lymph nodes		
d	> 15 mm	b	> 6 suspicious lymph nodes		
T4	Structures outside the mesorectum				
a	Peritoneum				
b	Other organs				

The T3 subclassification is officially not part of the TNM staging, but it is reported here since it is used in the Netherlands to guide treatment decisions [13]. Abbreviations: is, in situ.

Treatment strategy

Past: what type of tumour does the patient have?

Traditionally, overall and disease-free survival were paramount in deciding the rectal cancer treatment strategy. A key predictor for overall and disease-free survival was the TNM stage [14]. Based on the TNM stage, tumours were categorised as early, intermediate risk or locally advanced. Increasingly intensive treatments were offered to patients of a higher risk category (Table 2). The cornerstone of this 'step-up' treatment of rectal cancer was surgery according to the principles of total mesorectal excision (TME). TME consists of 'en bloc' resection of the rectum and mesorectum, including the mesorectal lymph nodes, by sharp dissection along the mesorectal fascia [15]. TME was combined with neoadjuvant (chemo)radiotherapy in case of a higher risk tumour. Adjuvant chemotherapy was not used in the Netherlands because there was no overall survival (OS) benefit after adequate TME [16]. The standardisation of this multimodal treatment dramatically improved overall survival. In the Netherlands, the 5-year age-standardised survival increased from 70% in 1980 to 91% in 2012 for T1-2N0M0, 45% to 68% for T1-4N0M0 and 30% to 65% for T1-4N1-2M0, respectively [17,18].

Early rectal cancer

The risk of 5-year local recurrence after TME only for T1-3bNx rectal cancer was 1.7% in the MERCURY study [19]. Addition of neoadjuvant short course radiotherapy (SCRT, 25 Gy in 5 fractions) to TME for T1-3(MRF-)N0 resulted in less than 3% absolute risk reduction in the 10-year local recurrence rate in the Dutch TME trial. This effect was outweighed by an increase in risk of non-cancer related deaths [20]. cT1-3b(MRF-)N0M0 was thus considered early rectal cancer and standardly treated with direct TME.

Intermediate risk rectal cancer

Addition of neoadjuvant SCRT to TME resulted in improved 10-year local recurrence rates from 17% to 5% and an improved 10-year overall survival from 40% to 50% among patients with pTx(MRF-)N1-2 rectal cancer in the Dutch TME trial [21]. Comparison of neoadjuvant SCRT with neoadjuvant chemoradiation (CRT, 50Gy in 25 fractions with oral capecitabin as a radiosensitiser) showed lower acute toxicity rates (Grade 3-4: 3% vs. 18%) but more often involvement of the circumferential margin (13% vs. 4%) following SCRT for resectable cT3-4Nx rectal cancer in a

Polish randomised trial [22]. The same comparison in the randomised TROG trial including cT3Nx rectal cancer confirmed the lower acute toxicity rates (Grade 3-4: 2% vs. 27%) and decreased tumour downstaging (ypT0-2: 2% vs. 27%) following SCRT compared to CRT [23,24]. Both trials showed similar overall and disease-free survival at 4 and 5 years follow up, respectively [22,23]. Based on these results, cT3cd(MRF-)N0 and cT1-3(MRF-)N1 rectal cancer was considered intermediate risk and treated with neoadjuvant SCRT and TME.

Locally advanced rectal cancer

Involvement of the circumferential margin after TME is an important predictor for overall and disease-free survival [25]. For tumours that grow in or through the mesorectal fascia, tumour downstaging is imperative for a free circumferential margin. Since CRT showed more tumour downstaging than SCRT, CRT and TME was the standard treatment for locally advanced rectal cancer (T3[MRF+]-4Nx) [22,23]. Rather arbitrarily, tumours with four or more locoregional suspected lymph nodes (N2) were also classified and treated as locally advanced rectal cancer.

Table 2. Rectal cancer risk categories based on TNM stage and the recommended treatment strategy

TNM stage	Risk category	Treatment
T1-3bN0M0	Early	TME
T3cdN0M0 or T1-3(MRF-)N1M0	Intermediate risk	SCRT + TME
T3(MRF+)-4NxM0 TxN2M0	Locally advanced	CRT + TME

Abbreviations: TNM, tumour nodal metastasis stage; TME, total mesorectal excision; MRF; mesorectal fascia; SCRT, short course radiotherapy; CRT, chemoradiation.

Present: does the patient prefer treatment option A or B for the type of tumour (response)?

In parallel with the improved overall survival, quality of life after rectal cancer treatment has become an important treatment outcome. The multimodal treatment significantly impairs quality of life. Rectal cancer survivors often suffer from fatigue, weight loss, abdominal pain, buttock pain, decreased body image, bowel dysfunction, urinary dysfunction and sexual dysfunction [26-29]. Some patients are willing to 'trade' some survival time for preserving quality of life after rectal cancer treatment [30]. The TNM stage no longer is the only determinant for the rectal cancer treatment. Patient preference is increasingly taken into account.

In this context, the founding of the watch-and-wait (WW) strategy or organ preservation has been a major development. Since patients who show a pathological complete response (pCR, i.e. no residual living tumour cells on pathological examination, ypT0N0) after neoadjuvant treatment and surgery have excellent survival, it was proposed to manage patients who reach a clinical complete response (cCR, no residual tumour on digital rectal examination, endoscopy and pelvic MRI, ycT0N0) after neoadjuvant treatment with active surveillance instead of surgery [31,32]. The WW strategy has quickly gained popularity. The international WW database showed that 5-year overall survival among patients managed with WW in case of cCR is comparable to the 5-year overall survival among patients who show pCR after TME (85% and 88%, respectively) [33,34]. WW is associated with superior quality of life and less bowel, urinary and sexual dysfunction than TME [35-38]. However, the WW strategy comes with a 25% risk of local tumour regrowth, which has to be managed by delayed TME. Among patients with a local tumour regrowth, the risk of distant metastasis is higher than among patients with a sustained cCR (18% vs. 5% at a median follow up time of 3.3 years) [33]. Patient preference studies demonstrated that, despite these risks, the majority of patients would prefer WW strategy over surgical management [39,40]. Following the traditional TNM-based standard treatments (Table 2), only locally advanced rectal cancer patients treated with CRT have some chance of becoming eligible for WW. New treatment options have emerged, wherein the possibility of organ preservation puts new weight on the balance.

Early rectal cancer

In pT1N0M0 rectal cancer without any risk factors, the risk of locoregional recurrence is 0.7% and local excision only is standard of care [41]. In pT1N0M0 with one or more risk factors, local excision followed by completion TME used to be standard of care. However, it is possible to leave out the completion TME and enter WW after local excision only. Local excision only offers a decreased postoperative complication rate and improved functional outcomes, but comes at the price of an increased risk of locoregional recurrence compared to completion TME [42,43]. The risk of locoregional recurrence depends on several risk factors, including poor histological differentiation, submucosal invasion, lymphatic or vascular invasion, tumour budding and an involved resection margin [44]. Presently, the choice between local excision and TME is discussed with patients with pT1N0M0 with risk factors. For patients with pT2-3bN0M0 rectal cancer, local excision only results in a ≥ 29% local recurrence rate so direct TME still is the standard treatment [45].

Intermediate risk rectal cancer

SCRT with a prolonged interval to surgery (4-8 weeks, SCRT-delay) has been introduced as an alternative to the traditional scheme of SCRT and surgery within one week (SCRT-direct surgery) by the Stockholm III trial. SCRT-delay improved the pCR rate from 0.3% to 10% and reduced the postoperative complication rate from 53% to 41% compared to SCRT-direct surgery [46,47]. In other words, there should be an approximate 10% chance of organ preservation when a response evaluation is scheduled several weeks after completion of radiotherapy during SCRT-delay. On the downside, SCRT-delay was associated with a 7% risk of hospital admission due to acute radiation-induced toxicity during the interval between radiotherapy and surgery. Overall and disease-free survival between groups were similar. The Dutch treatment guideline advises to propose both strategies to intermediate risk rectal cancer patients.

Addition of neoadjuvant SCRT to TME resulted in a decreased local recurrence rate in the Dutch TME trial. This came at the price of an increased risk of postoperative complications (48% vs 41%) and a higher risk of bowel and sexual dysfunction following SCRT [47-49]. The possibility of leaving out neoadjuvant SCRT should be mentioned when counselling intermediate risk rectal cancer patients.

Locally advanced rectal cancer

The probability of a complete response increases from 11% to 16% when the response evaluation is performed at more than 8 weeks following completion of CRT [51]. In patients who are motivated for organ preservation, it can be considered to delay the response evaluation.

SCRT combined with neoadjuvant systemic therapy resulted in a higher pCR rate (28% vs 14%) at the expense of more acute Grade ≥3 toxicity (48% vs. 25%) compared to neoadjuvant CRT for locally advanced rectal cancer in the RAPIDO trial. Postoperative complications, quality of life and bowel function were similar between groups, though more neurotoxicity Grade 1-2 occurred in the experimental arm. Furthermore, 5-year overall survival was similar. The 5-year local recurrence was higher in the experimental arm (10% vs. 6%) and the 5-year distant metastasis rate was lower (23% vs. 30%). Taking all these factors into consideration, the RAPIDO schedule can be used as alternative neoadjuvant treatment to CRT in locally advanced rectal cancer patients.

SCRT comes with less acute toxicity but also less tumour downstaging than CRT [22,23]. Quality of life after SCRT and CRT is largely similar [52,53]. In elderly or frail locally advanced rectal cancer patients and in patients with N2 as only 'locally advanced' characteristic, it is a possibility to swap CRT for SCRT as neoadjuvant treatment.

Thesis outline

Risks and benefits of short course radiotherapy with prolonged interval to surgery

In order to counsel intermediate risk rectal cancer patients on the choice between short course radiotherapy with immediate surgery versus short course radiotherapy with prolonged interval to surgery, information on risks and benefits of both treatment strategies is needed. **Chapter 2** provides detailed information on the toxicity during short course radiotherapy with prolonged interval to surgery. **Chapter 3** aims to confirm the advantage in the postoperative complication and pathological complete response rate following SCRT with a prolonged interval compared to direct surgery, that was demonstrated by the Stockholm III trial, in a Dutch nationwide database.

Radiotherapy dose-escalation for improving organ preservation rates

The majority of patients would prefer organ preservation over surgical management, but only a small proportion of patients reaches a cCR after standard neoadjuvant treatments. The randomised RECTAL-BOOST trial aimed to increase the proportion of pCR by administering dose-escalated CRT for locally advanced rectal cancer. In **chapter 4** the 2-year follow-up data on quality of life and oncological outcomes of participants to the RECTAL-BOOST trial are analysed. The RECTAL-BOOST trial followed the trials within cohorts (TwiCs) design. The experience of control patients with this trial design is evaluated in **chapter 5. Chapter 6** describes the protocol of the preRADAR trial, wherein SCRT will be dose-escalated for intermediate risk rectal cancer using the new technique of magnetic resonance-guided radiotherapy.

References

1 *The ASCRS Textbook of Colon and Rectal Surgery*. Springer New York 2011. https://doi.org/10.1007/978-1-4419-1584-9

2 Radical resection of rectal cancer - UpToDate. https://www.uptodate.com/contents/radical-resection-of-rectal-cancer?search=rectum&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H87588311 (accessed 30 August 2022)

3 Clausen N, Wolloscheck T, Konerding MA. How to optimize autonomic nerve preservation in total mesorectal excision: Clinical topography and morphology of pelvic nerves and fasciae. *World J Surg*. 2008;32:1768–75.

4 Cijfers darmkanker. https://iknl.nl/kankersoorten/darmkanker/registratie (accessed 21 March 2023)

5 Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science (1979)*. 2017;355:1330–4.

6 Van Engeland M, Derks S, Smits KM, *et al*. Colorectal cancer epigenetics: Complex simplicity. *Journal of Clinical Oncology*. 2011;29:1382–91.

7 Glynne-Jones R, Wyrwicz L, Tiret E, *et al*. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017;28:iv22–40.

8 Huxley RR, Ansary-Moghaddam A, Clifton P, *et al*. The impact of dietary and lifestyle risk factors on risk of colorectal cancer: A quantitative overview of the epidemiological evidence. *Int J Cancer*. 2009;125:171–80.

9 Thompson MR, O'Leary DP, Flashman K, *et al*. Clinical assessment to determine the risk of bowel cancer using Symptoms, Age, Mass and Iron deficiency anaemia (SAMI). *British Journal of Surgery*. 2017;104:1393–404.

10 Hamilton W, Round A, Sharp D, *et al*. Clinical features of colorectal cancer before diagnosis: A population-based case-control study. *Br J Cancer*. 2005;93:399–405.

11 Breekveldt ECH, Lansdorp-Vogelaar I, Toes-Zoutendijk E, *et al*. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. *Lancet Gastroenterol Hepatol*. 2022;7:60–8.

12 D'Souza N, de Neree tot Babberich MPM, D'Hoore A, *et al*. Definition of the rectum: An International, expert-based Delphi consensus. Ann Surg. 2019;270:955–9. https://doi.org/10.1097/SLA.0000000000003251

13 Siddiqui MRS, Simillis C, Bhoday J, *et al*. A meta-analysis assessing the survival implications of subclassifying T3 rectal tumours. *Eur J Cancer*. 2018;104:47–61.

14 Gunderson LL, Sargent DJ, Tepper JE, *et al*. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: A pooled analysis. *Journal of Clinical Oncology*. 2004;22:1785–96.

15 Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *British Journal of Surgery*. 1982;69:613–6.

16 Breugom AJ, Swets M, Bosset JF, *et al*. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: A systematic review and meta-analysis of individual patient data. *Lancet Oncol*. 2015;16:200–7.
17 Lemmens V, Steenbergen L van, Janssen-Heijnen M, *et al*. Trends in colorectal cancer in the south of the Netherlands 19752007: Rectal cancer survival levels with colon cancer survival. *Acta Oncol (Madr)*. 2010;49:784–96.
18 Brouwer NPM, Bos ACRK, Lemmens VEPP, *et al*. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. *Int J Cancer*. 2018;143:2758–66.
19 Taylor FGM, Quirke P, Heald RJ, *et al*. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: A prospective, multicenter, European study. *Ann Surg*. 2011;253:711–9.
20 Van Gijn W, Marijnen CA, Nagtegaal ID, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12:575–82.
21 Van Gijn W, Marijnen CA, Nagtegaal ID, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12:575–82.
22 Bujko K, Nowacki MP, Nasierowska-Guttmejer A, *et al*. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *British Journal of Surgery*. 2006;93:1215–23.
23 Ngan SY, Burmeister B, Fisher RJ, *et al*. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group Trial 01.04. *Journal of Clinical Oncology*. 2012;30:3827–33.
24 Ansari N, Solomon MJ, Fisher RJ, *et al*. Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum. *Ann Surg*. 2017;265:882–8.
25 Hall NR, Finan PJ, Al-Jaberi T, *et al*. Circumferential margin involvement after mesorectal excision of rectal cancer with curative intent: Predictor of survival but not local recurrence? *Dis Colon Rectum*. 1998;41:979–83.
26 Engel J, Kerr J, Schlesinger-Raab A, *et al*. Quality of Life in Rectal Cancer Patients. *Ann Surg*. 2003;238:203–13.
27 Maguire B, Clancy C, Connelly TM, *et al*. Quality of life meta-analysis following coloanal anastomosis versus abdominoperineal resection for low rectal cancer. *Colorectal Disease*. 2022;24:811–20.
28 Bryant CLC, Lunniss PJ, Knowles CH, *et al*. Anterior resection syndrome. Lancet Oncol. 2012;13:e403–8. https://doi.org/10.1016/S1470-2045(12)70236-X
29 Lange MM, van De Velde CJH. Urinary and sexual dysfunction after rectal cancer treatment. Nat Rev Urol. 2011;8:51–7. https://doi.org/10.1038/nrurol.2010.206

30 van der Valk MJM, van der Sande ME, Toebes RE, *et al.* Importance of patient reported and clinical outcomes for patients with locally advanced rectal cancer and their treating physicians. Do clinicians know what patients want? *European Journal of Surgical Oncology*. Published Online First: 15 April 2020. doi: 10.1016/j.ejso.2020.04.014

31 Habr-Gama A, Perez RO, Nadalin W, *et al.* Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: Long-term results. *Annals of Surgery*. Lippincott, Williams, and Wilkins 2004:711–8. https://doi.org/10.1097/01.sla.0000141194.27992.32

32 Maas M, Nelemans PJ, Valentini V, *et al.* Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. *Lancet Oncol*. 2010;11:835–44.

33 van der Valk MJM, Hilling DE, Bastiaannet E, *et al.* Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *The Lancet*. 2018;391:2537–45.

34 Maas M, Nelemans PJ, Valentini V, *et al.* Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. *Lancet Oncol*. 2010;11:835–44.

35 Hupkens BJP, Martens MH, Stoot JH, *et al.* Quality of Life in Rectal Cancer Patients After Chemoradiation. *Dis Colon Rectum*. 2017;60:1032–40.

36 Dizdarevic E, Frøstrup Hansen T, Pløen J, *et al.* Long-Term Patient-Reported Outcomes After High-Dose Chemoradiation Therapy for Nonsurgical Management of Distal Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2020;106:556–63.

37 Stijns RCH, De Graaf EJR, Punt CJA, *et al.* Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: The CARTS Study. *JAMA Surg*. 2019;154:47–54.

38 Bach SP, Gilbert A, Brock K, *et al.* Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. *Lancet Gastroenterol Hepatol*. 2021;6:92–105.

39 Couwenberg AM, Intven MPW, Burbach JPM, *et al.* Utility scores and preferences for surgical and organ-sparing approaches for treatment of intermediate and high-risk rectal cancer. *Dis Colon Rectum*. 2018;61:911–9.

40 Gani C, Gani N, Zschaeck S, *et al.* Organ preservation in rectal cancer: The patients' perspective. *Front Oncol*. 2019;9:318.

41 Dekkers N, Dang H, van der Kraan J, *et al.* Risk of recurrence after local resection of T1 rectal cancer: a meta-analysis with meta-regression. *Surg Endosc*. 2022;1:3.

42 Lu J-Y, Lin G-L, Qiu H-Z, *et al.* Comparison of Transanal Endoscopic Microsurgery and Total Mesorectal Excision in the Treatment of T1 Rectal Cancer: A Meta-Analysis. *PLoS One*. 2015;10:e0141427.

43 Doornebosch PG, Tollenaar RAEM, Gosselink MP, *et al*. Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer. *Colorectal Disease*. 2007;9:553–8.
44 Bosch S, Teerenstra S, De Wilt JW, *et al*. Predicting lymph node metastasis in pT1 colorectal cancer: A systematic review of risk factors providing rationale for therapy decisions. *Endoscopy*. 2013;45:827–34.
45 van Oostendorp SE, Smits LJH, Vroom Y, *et al*. Local recurrence after local excision of early rectal cancer: a meta-analysis of completion TME, adjuvant (chemo)radiation, or no additional treatment. British Journal of Surgery. 2020. https://doi.org/10.1002/bjs.12040
46 Erlandsson J, Holm T, Pettersson D, *et al*. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol*. 2017;18:336–46.
47 Erlandsson J, Lörinc E, Ahlberg M, *et al*. Tumour regression after radiotherapy for rectal cancer – Results from the randomised Stockholm III trial. *Radiotherapy and Oncology*. 2019;135:178–86.
48 Marijnen CAM, Kapiteijn E, van de Velde CJH, *et al*. Acute Side Effects and Complications After Short-Term Preoperative Radiotherapy Combined With Total Mesorectal Excision in Primary Rectal Cancer: Report of a Multicenter Randomized Trial. *Journal of Clinical Oncology*. 2002;20:817–25.
49 Peeters KCMJ, van de Velde CJH, Leer JWH, *et al*. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients - A Dutch Colorectal Cancer Group Study. *Journal of Clinical Oncology*. 2005;23:6199–206.
50 Marijnen CAM, van de Velde CJH, Putter H, *et al*. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial. *Journal of Clinical Oncology*. 2005;23:1847–58.
51 Ryan J, O'Sullivan DP, Kelly ME, *et al*. Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer. British Journal of Surgery. 2019;106:1298–310. https://doi.org/10.1002/bjs.11220
52 Pietrzak L, Bujko K, Nowacki MP, *et al*. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial. *Radiotherapy and Oncology*. 2007;84:217–25.
53 Wiltink LM, Nout RA, van der Voort van Zyp JRN, *et al*. Long-Term Health-Related Quality of Life in Patients With Rectal Cancer After Preoperative Short-Course and Long-Course (Chemo) Radiotherapy. *Clin Colorectal Cancer*. 2016;15:e93–9.

Chapter 2

Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer

Maaike E. Verweij, Sieske Hoendervangers, Charlotte M. von Hebel, Apollo Pronk, Anandi H. W. Schiphorst, Esther C. J. Consten, Anke B. Smits, Joost T. Heikens, Emiel G. G. Verdaasdonk, Tom Rozema, Helena M. Verkooijen, Wilhelmina M. U. van Grevenstein and Martijn P. W. Intven

Colorectal Disease. 2023; 25: 24-30.

Abstract

Aim

A prolonged interval (>4 weeks) between short-course radiotherapy (25 Gy in five fractions, SCRT-delay) and total mesorectal excision for rectal cancer has been associated with a decreased postoperative complication rate and offers the possibility of organ preservation in the case of a complete tumour response. This prospective cohort study systematically evaluated patient-reported bowel dysfunction and physician-reported radiation-induced toxicity for 8 weeks following SCRT-delay.

Methods

Patients who were referred for SCRT-delay for intermediate risk, oligometastatic or locally advanced rectal cancer were included. Repeated measurements were done for patient-reported bowel dysfunction (measured by the low anterior resection syndrome [LARS] questionnaire and categorized as no, minor or major LARS) and physician-reported radiation-induced toxicity (according to Common Terminology Criteria for Adverse Events version 4.0) before start of treatment (baseline), at completion of SCRT and 1, 2, 3, 4, 6 and 8 weeks thereafter.

Results

Fifty-one patients were included; 31 (61%) were men and the median age was 67 years (range 44-91). Patient-reported bowel dysfunction and physician-reported radiation-induced toxicity peaked at weeks 1-2 after completion of SCRT and gradually declined thereafter. Major LARS was reported by 44 patients (92%) at some time during SCRT-delay. Grade 3 radiation-induced toxicity was reported in 17 patients (33%) and concerned predominantly diarrhoea. No Grade 4-5 radiation-induced toxicity occurred.

Conclusion

During SCRT-delay, almost every patient experiences temporary mild-moderate radiation-induced toxicity and major LARS, but life-threatening toxicity is rare. SCRT-delay is a safe alternative to SCRT-direct surgery that should be proposed when counselling rectal cancer patients on neoadjuvant strategies.

Introduction

Preoperative short-course radiotherapy (SCRT, 25 Gy in five fractions) and long-course chemoradiation (CRT, 50 Gy in 25 fractions combined with a radiosensitizer) are two common neoadjuvant regimens for the treatment of rectal cancer [1,2]. An interval of more than 8 weeks between CRT and total mesorectal excision (TME) for locally advanced rectal cancer has been known to improve tumour downstaging without compromising the postoperative complication rate [3]. In contrast, the recommended interval between SCRT and TME for intermediate risk rectal cancer used to be less than 1 week (SCRT-direct surgery), conforming with the treatment schedules of the Swedish Rectal Cancer and Dutch TME trials [4,5]. SCRT with a prolonged interval to TME (4 weeks or more, SCRT-delay) was reserved for patients with locally advanced rectal cancer who were too frail to receive CRT [1].

Recently, SCRT-delay has become a treatment option for a broader range of rectal cancer stages. The randomized Stockholm III trial showed that SCRT-delay results in a significant reduction of postoperative complications (41% vs. 53%, $P = 0.001$) and an improved pathological complete response rate (10% vs. 0.3%, $P < 0.001$) compared to SCRT-direct surgery for resectable rectal cancer [6,7]. The Dutch M1 trial demonstrated that SCRT-delay and neoadjuvant chemotherapy results in good overall survival (median 3.8 years) for oligometastatic (M1) rectal cancer [8]. Furthermore, the randomized RAPIDO trial showed that SCRT-delay and neoadjuvant chemotherapy results in decreased disease-related treatment failure rate (24% vs. 30%, $P = 0.019$) compared to standard CRT and TME in patients with locally advanced rectal cancer [9].

A drawback of SCRT-delay is the occurrence of radiation-induced toxicity during the interval. Information on the course of the side effects would be useful for patient counselling on neoadjuvant treatment strategies. This prospective cohort study structurally evaluated patient-reported bowel dysfunction and physician-reported radiation-induced toxicity during the 8 weeks following SCRT-delay for rectal cancer.

Methods

Patients and treatment

Patients were included between December 2018 and June 2021 in the University Medical Centre Utrecht and between July 2020 and June 2021 in the Jeroen Bosch Hospital. Patients were eligible if they were referred for SCRT-delay (defined as an interval of at least 4 weeks between completion of SCRT and TME) for either intermediate risk rectal cancer (T1-3[distance to the mesorectal fascia >1 mm (MRF−)]N1M0 or T3cd[MRF−]N0M0), locally advanced rectal cancer and contraindication for CRT (T3-4[distance to the mesorectal fascia ≤1 mm (MRF+)]NxM0 or TxN2M0) or oligometastatic disease (M1) [10]. Exclusion criteria were inadequate command of the Dutch language, severe cognitive disorder or treatment with palliative intent. All patients provided informed consent for the current study and were asked for informed consent for the Dutch Prospective Colorectal Cancer cohort (PLCRC) [11]. PLCRC is a nationwide cohort study wherein data of adult colorectal patients are collected. The medical ethics committee of the University Medical Centre Utrecht approved PLCRC and waived the current study for ethical review. Clinical data were collected from the electronic medical files and within the PLCRC.

Treatment strategy was decided in a multidisciplinary team meeting. SCRT consisted of 25 Gy in five fractions on consecutive working days. Target volumes were the mesorectum, presacral lymph nodes, internal iliac lymph nodes and, in locally advanced rectal cancer, the obturator region [12]. Radiotherapy was administered on either a magnetic resonance guided linear accelerator (MR-Linac) or a conventional Linac. Planning target volume margins used for the mesorectum and elective lymph node regions were 10 and 8 mm on a conventional accelerator and 4-6 and 4 mm on the MR-Linac, respectively [13]. Treatment was delivered using a volumetric modulated arc therapy technique on the conventional accelerator or an online adapted MRI-guided intensity modulated radiotherapy technique on the MR-Linac. Patients with oligometastatic disease received additional treatment (i.e., neoadjuvant chemotherapy and/or liver surgery) after SCRT. Surgery according to the principles of TME was performed at the referral hospitals.

Endpoints

Bowel dysfunction and radiation-induced toxicity were measured before the start of radiotherapy, at completion of SCRT and at 1, 2, 3, 4, 6 and 8 weeks thereafter. Patients were censored at the time of TME when TME was performed before 8 weeks after completion of SCRT. Bowel dysfunction was measured by the low anterior resection syndrome (LARS) score questionnaire and recorded in a paper or online diary [14]. The LARS score questionnaire consists of five questions on 'incontinence for flatus', 'incontinence for liquid stools', 'frequency', 'clustering' and 'urgency'. These questions add up to a weighted sum that is categorized as no LARS (0-20), minor LARS (21-29) or major LARS (30-42). The LARS score questionnaire and its Dutch translation have been validated for measuring bowel dysfunction after low anterior resection (LAR) [15,16]. This short questionnaire was used because it is well suited for repeated measurements of bowel function. Radiation-induced toxicity was recorded during telephone consultations by a physician for diarrhoea, fatigue, cystitis, urinary incontinence and dermatitis according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [17]. In the case of missing toxicity, the CTCAE score were retrospectively retrieved from the electronic medical files (n=23 at baseline, n=8 at completion of SCRT and n=2 at 1 week after completion of SCRT). Non-prespecified complaints and additional treatments during SCRT-delay were retrieved from the electronic medical files and were censored at the start of chemotherapy when chemotherapy was administered within 8 weeks following completion of SCRT.

Statistical methods

Baseline characteristics were described as number (proportion) or median (range or interquartile range [IQR]). The LARS score questionnaire was processed according to its manual [14]. The LARS score questionnaires and radiation-induced toxicity measurements were reported as number (proportion) of patients per category or Grade per week.

In order to personalize information for future patients about the severity of bowel dysfunction they may expect during SCRT-delay, the course of LARS was described for several subgroups: neoadjuvant treatment (radiotherapy only vs. radiotherapy and chemotherapy), clinical tumour stage (cT2 vs. cT3[MRF−] vs. cT3[MRF+]-4), tumour location (distal [lower border of the tumour 0-3 cm from

anorectal junction on sagittal MRI] vs. midrectal [3-6 cm] vs. proximal [≥6 cm]), age (40-60 vs. 60-80 vs. 80+ years), gender (male vs. female) and LARS score at baseline (no or minor LARS vs. major LARS).

Results

Fifty-one patients including 31 men (61%) were enrolled (Table 1). The median age was 67 years (range 44-91). The indication for SCRT-delay was intermediate risk rectal cancer in 32 patients (63%), locally advanced rectal cancer and frailty in five patients (10%) and oligometastatic disease in 14 patients (28%). Ten out of 14 patients with oligometastatic disease (71%) were treated with chemotherapy at 14 days after completion of SCRT (median, IQR 12-18) and seven patients with oligometastatic disease (50%) had liver surgery at 157 days (median, IQR 56-180) after completion of SCRT. Of all patients, TME was performed in 40 patients (78%) at 72 days (median, IQR 53-102) after completion of SCRT. Four patients (7.8%) did not undergo TME due to disease progression and three patients (5.9%) declined or were judged unfit to undergo TME (Supplementary File 1). Four patients (7.8%) with a (rectal) clinical complete response entered a watch and wait follow-up programme.

Table 1. Patient, tumour and treatment characteristics of 51 rectal cancer patients treated with short-course radiotherapy and prolonged interval to surgery

	N (%)
Male gender	31 (61)
Age in years (median [range])	67 [44, 91]
CCI (%)	
0	33 (65)
1-2	11 (22)
3+	7 (14)
Ostomy before start of treatment	3 (5.9)
Clinical tumour stage	
cT2	9 (18)
cT3	38 (75)
cT4	4 (7.8)
Involvement of mesorectal fascia (≤ 1 mm, MRF+)	11 (22)

Table 1. Continued

	N (%)
Clinical nodal stage	
cN0	7 (14)
cN1	37 (73)
cN2	7 (14)
Clinical metastasis stage = M1	14 (28)
Tumour location [A]	
Distal (0-3 cm)	15 (31)
Midrectal (3-6 cm)	15 (31)
Proximal (6+ cm)	21 (41)
Indication for SCRT	
Intermediate risk rectal cancer [B]	32 (63)
Locally advanced rectal cancer	5 (9.8)
cM1 rectal cancer	14 (28)
Treatment on MR-Linac	26 (51)
Definitive treatment	
TME	40 (78)
Watch & wait [C]	4 (7.8)
No TME due to distant disease progression	4 (7.8)
No TME due to patient being unfit for surgery	3 (5.9)
Days between completion of SCRT and TME (median [IQR])	72 [53, 102]
Subgroup of cM1 patients (n=14)	**N (%)**
Chemotherapy during interval	10 (71)
Days between completion of SCRT and start of chemotherapy (median [IQR])	14 [12, 18]
Liver surgery	7 (50)
Days between completion of SCRT and liver surgery (median [IQR])	157 [56, 180]

A: Measured as distance between lower border of the tumour and anorectal junction on sagittal MRI. B: Rectal cancer stage 1-3(MRF−)N1M0 or T3c-d(MRF−)N0M0 according to the Dutch guideline. C: One patient entered watch and wait after a transanal minimal invasive surgical (TAMIS) procedure without residual tumour cells on pathology. Abbreviations: CCI, Charlson Comorbidity Index (calculated excluding patient age and the rectal tumour); MRF, mesorectal fascia; SCRT, short-course radiotherapy; MR-Linac, magnetic resonance guided linear accelerator; TME, total mesorectal excision; IQR, interquartile range.

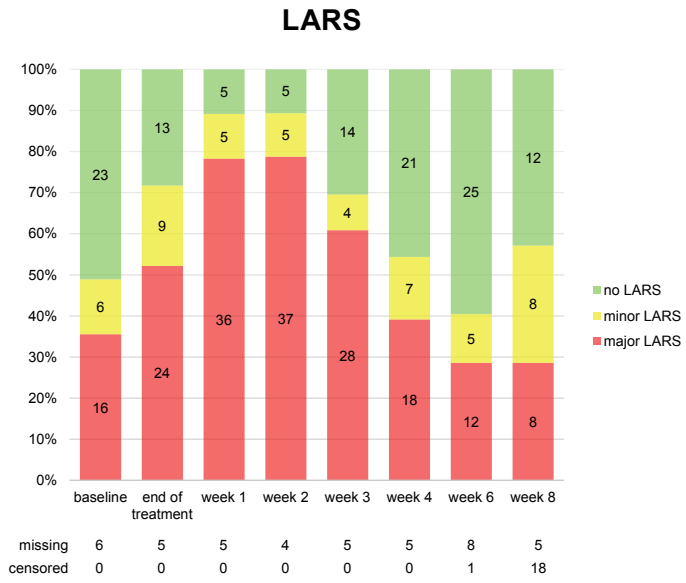
Both patient-reported bowel dysfunction and physician-reported radiation-induced toxicity peaked at 1-2 weeks after completion of SCRT and gradually declined thereafter (Figure 1A-F and Supplementary File 2A-E). As an exception, the LARS score component 'incontinence for flatus' and physician-reported urine incontinence did not show a clear pattern.

At its peak incidence, major LARS was reported by 37 patients (79%). As for the components of the LARS score questionnaire, clustering of stools that occurred at least once a week was reported by up to 41 patients (85%), urge at least once a week by 37 (79%), incontinence for flatus at least once a week by 26 (57%), defaecation frequency of more than seven times a day by 17 (35%) and incontinence for liquid stools at least once a week by 13 patients (27%). In total, 44 patients (92%) reported major LARS at some time during SCRT-delay.

At its peak incidence, radiation-induced diarrhoea was observed in 36 patients (77%), fatigue in 29 (63%), cystitis in 19 (41%), dermatitis in eight (17%) and urine incontinence in four (8.0%). In total, radiation-induced toxicity Grade 3 diarrhoea occurred in 16 patients (31%) and one patient (2.0%) had Grade 3 fatigue. In one patient, TME was moved up to 4 weeks after completion of SCRT due to persisting Grade 3 diarrhoea. No Grade 4-5 radiation-induced toxicity occurred.

Outside the prespecified toxicities, 42 (82%) patients reported rectal haemorrhage, 21 (41%) rectal or anal pain, 19 (37%) incontinence for solid stools, 17 (33%) abdominal pain, 14 (27%) constipation, 14 (27%) anorexia/nausea, nine (18%) urinary tract obstruction and two (3.8%) neuropathic buttock pain during SCRT-delay and before the start of chemotherapy (additional treatments during SCRT-delay are reported in Supplementary File 3).

A



B

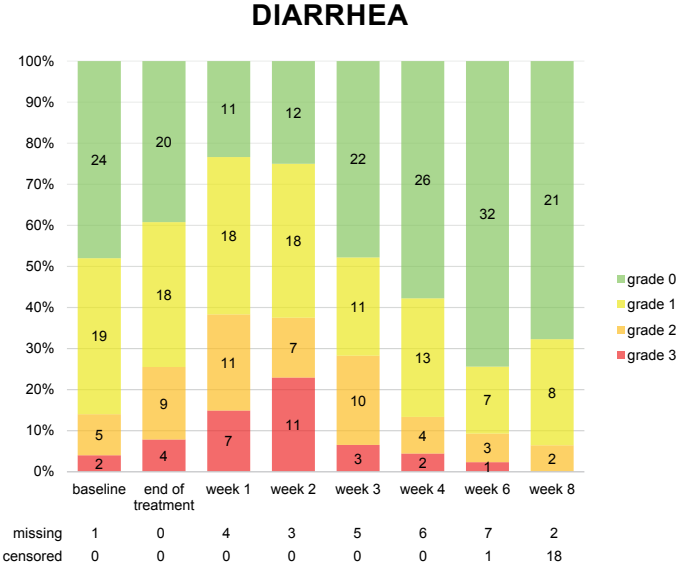
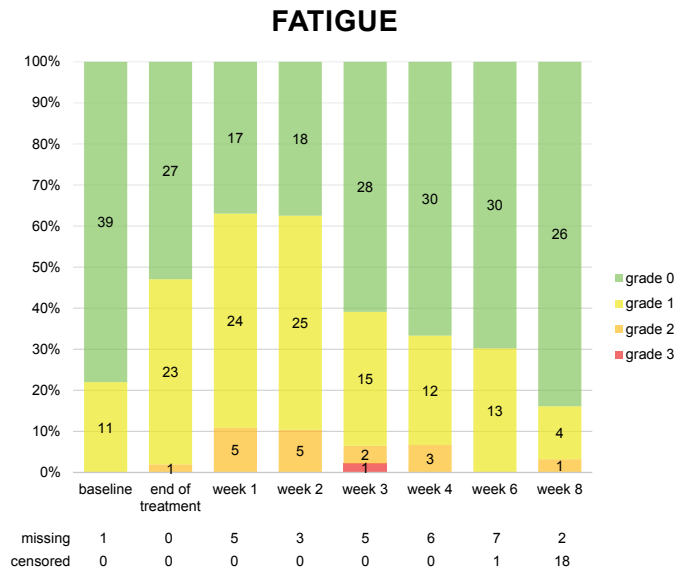


Figure 1A-F. Patient-reported bowel dysfunction measured by the low anterior resection syndrome (LARS) score and physician-reported radiation-induced toxicity according to CTCAE during short-course radiotherapy and prolonged interval to surgery (SCRT-delay) for rectal cancer (n=51). Patients were censored at the time of TME when TME was scheduled within 8 weeks after completion of SCRT.

C



D

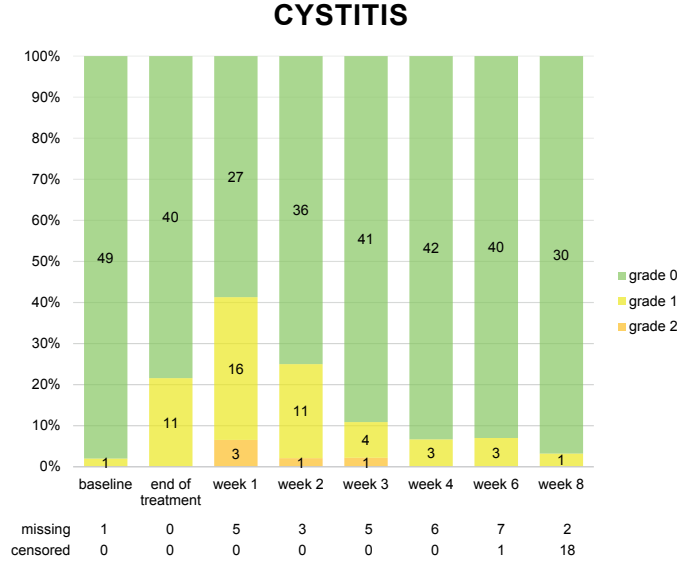
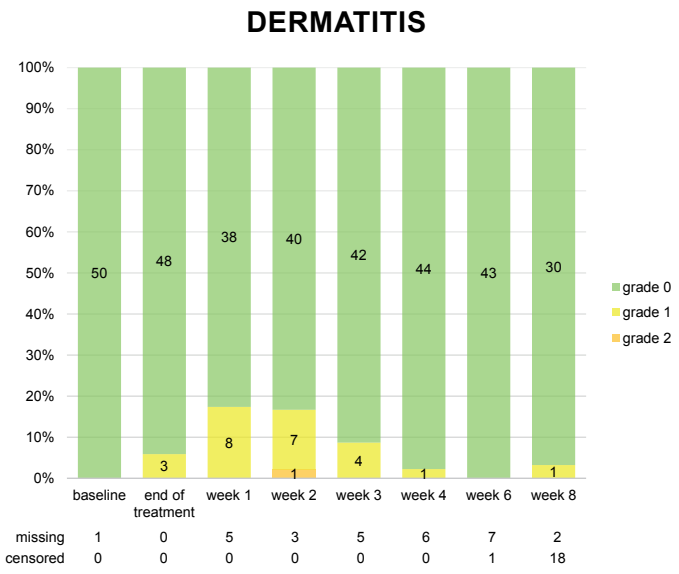


Figure 1A-F. Continued

E



F

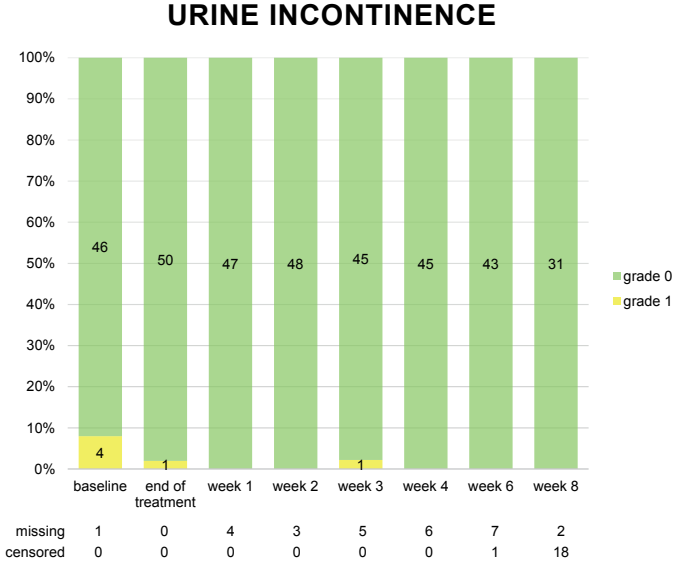


Figure 1A-F. Continued

Subgroup analysis showed that the vast majority of patients treated with neoadjuvant chemotherapy continued to report major LARS at weeks 3 and 4 after completion of SCRT, while the incidence of major LARS already declined in patients treated with radiotherapy only (Supplementary File 4A-E). The majority of patients with cT3(MRF+)-4 continued to report major LARS throughout follow-up, and they consistently reported more major LARS than patients with cT3(MRF-) or cT2. Patients with proximal, midrectal or distal tumours reported similar levels of major LARS. Patients aged 80 years or older consistently reported more major LARS than patients of 60-80 years, who reported more major LARS than patients of 40-60 years. Female patients consistently reported more major LARS than men. Most patients with major LARS at baseline continued to report major LARS throughout follow-up.

Discussion

During SCRT-delay for rectal cancer, patient-reported major LARS and physician-reported radiation-induced toxicity Grades 1-2 were highly prevalent at 1-2 weeks after completion of SCRT and gradually declined thereafter. Radiation-induced toxicity Grade 3 occurred in total in 33% of patients and consisted predominantly of diarrhoea. No Grade 4-5 radiation-induced toxicity occurred. Patients treated with neoadjuvant chemotherapy, with a higher clinical tumour stage, older age, female gender and major LARS at baseline reported more major LARS during SCRT-delay. Patients reported more major LARS than physicians reported Grade 3 radiation-induced diarrhoea.

This is the first study that provides a detailed insight into the course of radiation-induced toxicity during SCRT-delay. Previous studies have only reported on cumulative toxicity incidences following SCRT-delay. A 2014 meta-analysis by Bujko et al. reported that radiation-induced toxicity occurred in 27-41% of patients during SCRT-delay, of whom 2-5% had Grade ≥3 toxicity [18]. In the Stockholm III trial, 7% (n=23) of patients treated with SCRT-delay were admitted to the hospital due to radiation-induced toxicity [6]. In our study, no Grade 4-5 toxicity occurred and in only one patient TME was moved up due to persisting Grade 3 toxicity. Advances in radiotherapy techniques since the start of the Stockholm III trial, that included patients between 1998 and 2013, might explain the lower toxicity rates in

our cohort. In contrast, no Grade 3-4 radiation-induced toxicity occurred during SCRT-delay and before the start of chemotherapy in the M1 trial. Administration of chemotherapy was delayed in seven (14%) patients due to Grade 2 radiation toxicity at 2 weeks after completion of SCRT [19]. The relatively favourable toxicity results of the M1 trial might be explained by their young and fit study population (median age 59 [range 33-75] and Eastern Cooperative Oncology Group 0 or 1). Our study shows that, using current radiotherapy techniques in an all-comer population, almost every patient experiences temporary mild-moderate radiation-induced toxicity during SCRT-delay, but life-threatening radiation-induced toxicity is rare. Combining our results with the lower risk of postoperative complications and the increased probability of organ preservation, SCRT-delay should be preferred over SCRT-direct surgery in most rectal cancer patients [6,7]. SCRT-direct surgery could still be considered for patients with no interest in organ preservation and/or a high risk of radiation-induced toxicity following SCRT-delay.

Neoadjuvant chemotherapy, higher clinical tumour stage, older age, female gender and major LARS at baseline were associated with major LARS during SCRT-delay. Previous studies found a distal tumour, female gender and a younger age to be predictive of the LARS score at one or more years after anterior resection [14,20]. However, the relation between younger age and bowel dysfunction might have been biased by the selection of patients for anterior resection. Anorectal function decreases with age and is worse in women than in men, especially after (vaginal) childbirth [21,22]. It is therefore plausible that older and female patients are more susceptible to major LARS following radiotherapy for rectal cancer. Tumours of a higher stage or at a more distal location exert more pressure on the anorectal complex and on the rectal ampulla, so more major LARS was expected in those subgroups. A high clinical tumour stage was strongly associated with the occurrence of major LARS, but tumour location was not associated with LARS. Chemotherapy was associated with a slower recovery of LARS after SCRT. These risk factors should be considered when counselling patients on LARS during SCRT-delay.

Patient-reported LARS and physician-reported radiation-induced diarrhoea showed similar patterns, but a considerable proportion of patients reported major LARS when physicians reported diarrhoea Grade 0, 1 or 2. This difference is probably due to the extensiveness of the LARS score questionnaire compared to diarrhoea

according to the CTCAE grading system [14]. When interpreting the LARS score, it should be acknowledged that major LARS has a prevalence of 15% in a reference population [23,24]. Also, it is well known that physicians consistently report lower frequency and severity of toxicity than patients do in direct reports [25]. Our study once again shows the importance of collecting patient-reported outcomes for measuring the impact of a treatment.

The LARS score questionnaire has been validated for measuring bowel dysfunction after LAR [14-16,26]. Here, the LARS score questionnaire was used to measure bowel dysfunction following radiotherapy for rectal cancer, an indication for which it has not been specifically validated. That the LARS score questionnaire does not cover all radiation-induced bowel symptoms is illustrated by the high prevalence of rectal haemorrhage (82%), rectal pain (41%) and incontinence for solid stools (37%) in our study. However, major LARS has been correlated with poor quality of life in a reference population, indicating that the LARS score questionnaire is of value outside of the LAR population [23]. Other studies have used the LARS score questionnaire in patients who had not been treated with LAR, that is, patients on a watch-and-wait strategy [27-29]. Future research could focus on the development and validation of a simple questionnaire like the LARS score questionnaire for measuring bowel dysfunction following radio(chemo) therapy for rectal cancer.

In this study, toxicity was only recorded for diarrhoea, fatigue, cystitis, urine incontinence and dermatitis during 8 weeks following completion of SCRT. Adverse events during the remaining duration of chemotherapy were not recorded. Because of these choices, it was unfortunately not possible to compare our results to trials that reported the cumulative incidence of toxicity of SCRT-delay and neoadjuvant chemotherapy together (such as the RAPIDO trial).

Missing values for physician-reported radiation toxicity and non-prespecified complaints were retrospectively retrieved from the electrical medical files. Their prevalence might be underestimated due to underreporting.

Conclusion

During SCRT-delay, almost every patient experiences temporary mild-moderate radiation-induced toxicity and major LARS, but life-threatening toxicity is rare. Neoadjuvant chemotherapy, higher clinical tumour stage, older age, female gender and major LARS are risk factors for major LARS during SCRT-delay. SCRT-delay is a safe alternative to SCRT-direct surgery that should be proposed when counselling rectal cancer patients on neoadjuvant treatment strategies.

References

1. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv22-40. https://doi.org/10.1093/annonc/mdx224
2. National Institute for Health and Care Excellence. Colorectal Cancer NICE Guideline. 2020. www.nice.org.uk/guidance/ng151. Accessed September 17, 2022.
3. Ryan J, O'Sullivan DP, Kelly ME, et al. Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer. Br J Surg. 2019;106(10):1298-310. https://doi.org/10.1002/bjs.11220
4. Påhlman L. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980-7. https:// doi.org/10.1056/NEJM199704033361402
5. Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638-46. https://doi.org/10.1056/NEJMoa010580
6. Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol. 2017;18(3):336-46. https://doi.org/10.1016/S1470-2045(17)30086-4
7. Erlandsson J, Lörinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B, et al. Tumour regression after radiotherapy for rectal cancer—results from the randomised Stockholm III trial. Radiother Oncol. 2019;135:178-86. https://doi.org/10.1016/j. radonc.2019.03.016
8. Bisschop C, van Dijk TH, Beukema JC, Jansen RLH, Gelderblom H, de Jong KP, et al. Short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical treatment in primary stage IV rectal cancer: long-term results of a phase II study. Ann Surg Oncol. 2017;24(9):2632-8. https://doi.org/10.1245/s10434-017-5897-0
9. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EMK, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2020;22(1):29-42. https:// doi.org/10.1016/S1470-2045(20)30555-6
10. Primaire behandeling rectumcarcinoom - Richtlijn - Richtlijnendatabase. https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/primaire_behandeling_rectumcarcinoom_ bij_crc.html. Published 2019. Accessed March 24, 2022.
11. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncol. 2016;55(11):1273-80. https:// doi.org/10.1080/0284186X.2016.1189094

12. Valentini V, Gambacorta MA, Barbaro B, Chiloiro G, Coco C, das P, et al. International consensus guidelines on clinical target volume delineation in rectal cancer. Radiother Oncol. 2016;120(2):195- 201. https://doi.org/10.1016/j.radonc.2016.07.017
13. Intven MPW, Otterloo SR, Mook S, et al. Online adaptive MR-guided radiotherapy for rectal cancer; feasibility of the workflow on a 1.5T MR-linac; clinical implementation and initial experience. Radiother Oncol. 2020;154:172-8. https://doi.org/10.1016/j.radonc.2020.09.024
14. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg. 2012;255(5):922-8. https://doi.org/10.1097/SLA.0b013 e31824f1c21
15. Juul T, Ahlberg M, Biondo S, Emmertsen KJ, Espin E, Jimenez LM, et al. International validation of the low anterior resection syndrome score. Ann Surg. 2014;259(4):728-34. https://doi.org/10.1097/ SLA.0b013e31828fac0b
16. Hupkens BJP, Breukink SO, C Olde Reuver Of Briel, et al. Dutch validation of the low anterior resection syndrome score. Colorectal Dis. 2018;20(10):881-7. https://doi.org/10.1111/codi.14228
17. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009. http://www.meddr amsso.com. Accessed May 2, 2022.
18. Bujko K, Partycki M, Pietrzak L. Neoadjuvant radiotherapy (5 × 5 Gy): immediate versus delayed surgery. Recent Results Cancer Res. 2014;203:171-87. https://doi.org/10.1007/978-3-319-08060-4_12
19. van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol. 2013;24(7):1762-9. https:// doi.org/10.1093/annonc/mdt124
20. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynne-Jones R, Branagan G, et al. Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. Gut. 2018;67(4):688-96. https://doi.org/10.1136/gutjnl-2016-312695
21. Gundling F, Seidl H, Scalercio N, Schmidt T, Schepp W, Pehl C. Influence of gender and age on anorectal function: normal values from anorectal manometry in a large Caucasian population. Digestion. 2010;81(4):207-13. https://doi.org/10.1159/00025 8662
22. Jameson JS, Chia YW, Kamm MA, Speakman CTM, Chye YH, Henry MM. Effect of age, sex and parity on anorectal function. Br J Surg. 1994;81(11):1689-92. https://doi.org/10.1002/bjs.1800811143
23. van Heinsbergen M, Van der Heijden JAG, Stassen LP, et al. The low anterior resection syndrome in a reference population: prevalence and predictive factors in the Netherlands. Colorectal Dis. 2020;22(1):46-52. https://doi.org/10.1111/codi.14790
24. Juul T, Elfeki H, Christensen P, Laurberg S, Emmertsen KJ, Bager P. Normative data for the low anterior resection syndrome score (LARS score). Ann Surg. 2019;269(6):1124-8. https://doi. org/10.1097/SLA.0000000000002750

25. Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nat Rev Clin Oncol. 2016;13(5):319-25. https://doi.org/10.1038/nrcli nonc.2015.222
26. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg. 2013;100(10):1377-87. https://doi.org/10.1002/bjs.9223
27. Hupkens BJP, Martens MH, Stoot JH, Berbee M, Melenhorst J, Beets-Tan RG, et al. Quality of life in rectal cancer patients after chemoradiation. Dis Colon Rectum. 2017;60(10):1032-40. https:// doi.org/10.1097/DCR.0000000000000862
28. Haak HE, Maas M, Lambregts DMJ, Beets-Tan RGH, Beets GL, Melenhorst J, et al. Is watch and wait a safe and effective way to treat rectal cancer in older patients? Eur J Surg Oncol. 2020;46(3):358-62. https://doi.org/10.1016/j.ejso.2020.01.005
29. Custers P, van der Sande M, Grotenhuis B, Peters F, van Kuijk S, Breukink S, et al. Quality of life and functional outcome of rectal cancer patients following a watch-and-wait approach. Eur J Surg Oncol. 2022;48(2):e35. https://doi.org/10.1016/j.ejso.2021.12.441

Chapter 3

Timing of rectal cancer surgery after short-course radiotherapy: national database study

Maaike E. Verweij, Jolien Franzen, Wilhelmina M. U. van Grevenstein, Helena M. Verkooijen and Martijn P. W. Intven

British Journal of Surgery. 2023; 110, 839-845

Abstract

Aim

Previous randomized trials found that a prolonged interval between short-course radiotherapy (SCRT, 25 Gy in 5 fractions) and surgery for rectal cancer (4-8 weeks, SCRT-delay) results in a lower postoperative complication rate and a higher pathological complete response (pCR) rate than SCRT and surgery within a week (SCRT-direct surgery). This study sought to confirm these results in a Dutch national database.

Methods

Patients with intermediate risk rectal cancer (T3[without involvement of the mesorectal fascia (MRF-)]N0M0 and T1-3[MRF-]N1M0) treated with either SCRT-delay (4-12 weeks) or SCRT-direct surgery in 2018-2021 were selected from a Dutch national colorectal cancer database. Confounders were adjusted for using inverse probability of treatment weighting (IPTW). The primary endpoint was the 90-day postoperative complication rate. Secondary endpoints included the pCR rate. Endpoints were compared using log-binomial and Poisson regression.

Results

Some 664 patients were included in the SCRT-direct surgery and 238 in the SCRT-delay group. After IPTW, the 90-day postoperative complication rate was comparable after SCRT-direct surgery and SCRT-delay (40.1% versus 42.3%; risk ratio [RR] 1.1, 95% confidence interval [CI] 0.9 to 1.3). A pCR occurred more often after SCRT-delay than SCRT-direct surgery (10.7% versus 0.4%; RR 39, 95% CI 11 to 139).

Conclusion

There was no difference in surgical complication rates between SCRT-delay and SCRT-direct, but SCRT-delay was associated with more patients having a pCR. SCRT-delay with scheduling of a response evaluation is recommended for patients who are interested in watch & wait strategy. SCRT-direct surgery still seems a good option for patients who prefer surgical management.

Introduction

Total mesorectal excision (TME) preceded by short-course radiotherapy (SCRT, 25 Gy in 5 fractions) has been the recommended treatment strategy for intermediate risk rectal cancer (T1-3[without involvement of the mesorectal fascia (MRF-)]N1M0 and T3cd[MRF-]N0-1M0) in the Netherlands for over 20 years [1]. Addition of neoadjuvant SCRT to surgery reduced local recurrence rates in the randomized Swedish rectal cancer and Dutch TME trials [2,3]. Rather arbitrarily, these trials used a maximum interval of 1 week between completion of SCRT and surgery (SCRT-direct surgery). This short interval remained the standard, backed up by negative results for a slightly longer interval; a retrospective study demonstrated an increased risk of postoperative complications when the time between the start of SCRT and TME exceeded 13 days [4]. Subgroup analysis of the Dutch TME trial also showed an increased risk of 1-year overall mortality in older patients operated within 4-7 days of completion of SCRT compared with 1-3 days [5].

More recently, SCRT with a prolonged interval to surgery (4-8 weeks, SCRT-delay) came into focus as a more tolerable neoadjuvant strategy than chemoradiation (50 Gy in 25 fractions combined with a radiosensitizer) for frail patients with locally advanced rectal cancer [6,7]. The optimal timing of surgery after SCRT was again open to debate. Prospective studies followed, showing acceptable toxicity and improved tumour downstaging after SCRT-delay [8-10]. Randomized evidence in favour of SCRT-delay came from the Stockholm III trial, which showed a lower 30-day postoperative complication rate (40.6% versus 52.7%; $P = 0.001$) and a higher pathological complete response (pCR) rate (10.4% versus 0.3%; $P < 0.001$) than after SCRT-direct surgery, at the expense of more acute radiation-induced toxicity Grade 3-4 (6.5% versus 0.3%; $P < 0.001$) [11,12]. The lower postoperative complication rate in the SCRT-delay group was for a large part accounted for by a lower rate of surgical complications (surgical-site infection, deep infection, anastomotic leak, postoperative bleeding, stoma-related complications, wound dehiscence, or other surgical complication). Since publication of the Stockholm III trial, the Dutch treatment guideline has advised discussion of both SCRT-direct surgery and SCRT-delay with patients who have intermediate risk rectal cancer (shared decision-making) [1]. The present study sought to confirm the results of the Stockholm III trial in the Dutch national

database using the target trial framework [13]. The 90-day postoperative complication rate was compared between SCRT-direct surgery and SCRT-delay in an inverse probability of treatment weighted (IPTW) analysis.

Methods

The goal of this study was to evaluate 90-day postoperative complication rates after SCRT-delay versus SCRT-direct surgery for rectal cancer. As the study aimed to answer a causal question using observational data, it was designed according to the target trial framework (Table 1) [13].

Patients

Patients who were treated for intermediate risk rectal cancer (lower border of the tumour below the sigmoid take-off and cT3[MRF-]N0M0 or cT1-3[MRF-]N1M0 stage) with SCRT and surgery during 2018-2021 in the Netherlands were included [1,14]. Exclusion criteria were recurrent rectal cancer, neoadjuvant chemotherapy, resection not by partial mesorectal excision or TME (for example, local excision, sigmoid resection, proctocolectomy), or TME preceded by local excision. Patients were selected for the SCRT-direct surgery group if the maximum interval between completion of radiotherapy and surgery was 1 week (0-7 days), and for the SCRT-delay group if the interval was 4-12 weeks (28-84 days). This study used a broader interval for SCRT-delay than the Stockholm III trial because some centres in the Netherlands perform response evaluation and surgery at 10-12 weeks after completion of SCRT, in line with the STAR-TREC study [15].

Anonymized data were provided by the Dutch Colorectal Audit (DCRA). The DCRA is a mandatory registration that collects patient, tumour, treatment, and surgical and pathological outcome data for all patients who are treated surgically for colorectal cancer in the Netherlands [16]. Several methods are in place to ensure data validity in the DCRA, as described elsewhere [16]. Comparison of the DCRA with the Dutch National Cancer Registry showed a case completeness rate of 94% and good correspondence in data (for example, anastomotic leakage rates were 10.4% and 8.7% respectively) [17]. The clinical audit board of the DCRA approved the research proposal of the present study. No further ethical review was required under Dutch law.

Table 1. Summary of the protocol of the ideal trial evaluating the effect of short-course radiotherapy and surgery within a week versus a prolonged interval to surgery on the 90-day postoperative complication rate (target trial), emulated using observational data

Protocol component	**Description**
Eligibility criteria	Patients with intermediate risk rectal cancer (lower border of tumour below sigmoid take-off and cT3cd[MRF-]N0M0 or cT1-3[MRF-]N1M0 stage) with indication for SCRT and surgery during 2018-2021 in the Netherlands
Treatment strategies	A: SCRT followed by TME within 1 week (SCRT-direct surgery) B: SCRT followed by TME within 4-12 weeks (SCRT-delay)
Assignment procedures	Random assignment to treatment A or B
Follow-up time	Starts at randomization and ends at 90 days after discharge from hospital, death or loss to follow-up
Primary endpoint	90-day postoperative complication rate
Secondary endpoints	pCR Complications requiring reintervention Organ failure requiring admission to ICU Postoperative death Anastomotic leakage Surgical-site infection Abscess not at anastomosis Duration of hospital stay Unplanned readmission within 90 days of initial discharge from hospital
Type of analysis	Intention-to-treat

Abbreviations: TNM, tumour nodal metastasis stage; MRF, mesorectal fascia; SCRT, short-course radiotherapy; TME, total mesorectal excision; pCR, pathological complete response; ICU, intensive care unit.

Outcomes

The primary outcome was the 90-day postoperative complication rate, defined as the occurrence of any complication within 90 days after surgery or during the primary hospital stay. Secondary outcomes were the pCR rate (ypT0N0), 90-day complications requiring reintervention (Clavien-Dindo III), organ failure requiring admission to ICU (Clavien-Dindo IV), death (Clavien-Dindo V), anastomotic leakage, surgical-site infection, abscess not at the anastomosis, duration of hospital stay (number of days

between surgery and hospital discharge), and unplanned readmission within 90 days of initial discharge from the hospital. Anastomotic leakage was defined by the presence of intra-abdominal fluid or abscess at the anastomosis requiring treatment. This outcome was evaluated only in patients in whom an anastomosis was created.

Statistical analysis

Missing values in baseline patient, tumour, and treatment characteristics were assumed to be missing at random and were imputed using single imputation (Supplementary Files 2-4) [18]. Confounders were selected based on clinical knowledge. Sex, age, BMI category, history of bowel resection, ostomy before start of treatment, preoperative anaemia, preoperative bowel obstruction, ASA fitness Grade, Charlson Comorbidity Index, clinical tumour category, clinical nodal status, tumour location, surgical approach, and type of resection were considered to be confounders (Supplementary File 3). Confounding was adjusted for using IPTW [19]. IPTW assigns a weight to each patient, which is calculated as the inverse of the predicted probability of receiving the treatment that was actually received, given the distribution of confounders. Through weighting, a pseudopopulation is created that is well balanced in terms of confounders. This process mimics the exchangeability of groups after random treatment assignment (Table 1). Baseline differences between groups before and after weighting were expressed as the standardized mean difference (SMD), calculated as the mean difference between groups divided by the pooled standard deviation [20]. An SMD of 0.10 or less was considered to indicate well balanced groups [20].

Outcomes were compared between groups using binomial regression for dichotomous outcomes and Poisson regression for count outcomes, both with log link and a robust standard error [21,22]. $P < 0.050$ was considered significant. Analyses were repeated with the SCRT-delay group restricted to an interval of 4-8 weeks (28-56 days), so that the present results could be compared directly with those of the Stockholm III trial. Analyses were repeated in the complete-case population to explore the impact of missing data.

The minimal detectable difference was calculated to see whether the sample size was sufficient to confirm the difference in postoperative complication rate (12% absolute difference) that was demonstrated by the Stockholm III trial. Given the present sample size, a postoperative complication rate of 41%, an α of 5%, power of 80%, and a

two-sided alternative hypothesis, this study could detect a difference of 11% or more. Analyses were done using R version 4.2.0, and packages mice, ipw, survey, sandwich, and EnvStats (R Foundation for Statistical Computing, Vienna, Austria) [23-25].

Results

Of 7391 patients in the Netherlands who had surgery for cT1-3 primary rectal cancer during the study interval, 664 were included in the SCRT-direct surgery group and 238 in the SCRT-delay group (Supplementary File 1).

Before imputation and IPTW, patients in the SCRT-direct surgery group were younger (median 67 [interquartile range (IQR) 58-74) versus 68 [IQR 60-77] years), had a lower ASA Grade (Grade I-II: 80.9% versus 72.7%), and more often underwent (L)AR without ostomy (40.6% versus 27.7%). They less often had APR (16.9% versus 21.4%), (L)AR with permanent ostomy (16.4% versus 22.3%) or (L)AR with deviating ostomy (26.1% versus 28.6%) than patients in the SCRT-delay group (Table 2). After imputation and IPTW, baseline characteristics were well balanced.

Before IPTW, 90-day postoperative complications developed in 265 patients (39.9%) in the SCRT-direct surgery group and in 101 (42.4%) in the SCRT-delay group (risk ratio [RR] 1.1, 95% confidence interval [CI] 0.9 to 1.3; P = 0.492) (Table 3). Anastomotic leakage occurred in 71 (16.1%) and 24 (17.9%) respectively (RR 1.1, 95% CI 0.7 to 1.7; P = 0.627). Similarly, other postoperative complications and duration of hospital stay were comparable between groups. Two patients (0.3%) in the SCRT-direct surgery group and 26 (11.0%) in the SCRT-delay group had a pCR (RR 36, 95% CI 8.7 to 152; P < 0.001).

After IPTW, 90-day postoperative complications were registered in 266.2 patients (40.1%) in the SCRT-direct surgery group and 100.6 (42.3%) in the SCRT-delay group (RR 1.1, 95% CI 0.9 to 1.3; P = 0.614). Anastomotic leakage developed in 69.2 (16.3%) and 28.0 (18.3%) respectively (RR 1.1, 95% CI 0.7 to 1.9; P = 0.667). Other postoperative outcomes remained similar between groups. A pCR occurred in 2.8 patients (0.4%) in the SCRT-direct surgery group and 25.5 (10.7%) in the SCRT-delay group (RR 39, 95% CI 11 to 139; P < 0.001).

Table 2. Patient, tumour, and treatment characteristics of patients with intermediate risk rectal cancer who had short-course radiotherapy and surgery within a week versus a prolonged interval (4-12 weeks) to surgery, before and after single imputation and inverse probability of treatment weighting

	Before SI and IPTW		
	SCRT-direct surgery (n=664)	**SCRT-delay (n=238)**	**SMD**
Sex ratio (F : M)	234 : 432	85 : 153	0.010
Age (years) median (IQR)	67 (58-74)	68 (60-77)	0.175
BMI (kg/m^2)			0.127
Underweight (< 18.5)	10 (1.5)	4 (1.7)	
Normal weight (18.5-24.9)	237 (36.5)	100 (42.6)	
Overweight (25.0-29.9)	279 (43.0)	92 (39.1)	
Obese (≥ 30.0)	123 (19.0)	39 (16.6)	
History of bowel resection	11 (1.7)	1 (0.4)	0.122
Ostomy before start of treatment	11 (1.7)	6 (2.5)	0.061
Preoperative anaemia [a]	41 (6.2)	16 (6.7)	0.022
Preoperative bowel obstruction [b]	9 (1.4)	3 (1.3)	0.006
ASA fitness Grade			0.255
I	120 (18.1)	27 (11.3)	
II	417 (62.8)	146 (61.3)	
III	123 (18.5)	61 (25.6)	
IV	4 (0.6)	4 (1.7)	
CCI score			0.131
0	277 (58.7)	124 (58.8)	
1	107 (22.7)	40 (19.0)	
2	55 (11.7)	32 (15.2)	
3	24 (5.1)	10 (4.7)	
4-7	9 (1.9)	5 (2.4)	
Clinical tumour category			0.224
cT1	14 (2.1)	1 (0.4)	
cT2	135 (20.3)	40 (16.8)	
cT3ab	209 (31.5)	94 (39.5)	
cT3x	148 (22.3)	48 (20.2)	
cT3cd	158 (23.8)	55 (23.1)	
Clinical nodal category = cN1	538 (81.3)	195 (82.3)	0.026

Before SI and IPTW	After SI and IPTW		
Missing	**SCRT-direct surgery (n=664)**	**SCRT-delay (n=238)**	**SMD**
0 (0)	233.9 : 432.1	83.9 : 153.6	0.002
3 (0.3)	68 (59-75)	66 (59-75)	0.001
18 (2.0)			0.027
	10.5 (1.6)	3.9 (1.6)	
	254.9 (38.4)	91.2 (38.4)	
	277.6 (41.8)	96.9 (40.8)	
	121.0 (18.2)	45.6 (19.2)	
0 (0)	8.9 (1.3)	3.4 (1.4)	0.008
5 (0.6)	11.7 (1.8)	3.4 (1.5)	0.025
0 (0)	42.9 (6.5)	16.1 (6.8)	0.013
11 (1.2)	11.3 (1.7)	3.6 (1.5)	0.013
0 (0)			0.040
	107.6 (16.2)	35.6 (15.0)	
	415.5 (62.6)	152.9 (64.4)	
	135.2 (20.4)	47.0 (19.8)	
	5.7 (0.9)	2.1 (0.9)	
219 (24)			0.022
	391.0 (58.9)	140.7 (59.3)	
	136.0 (20.5)	48.8 (20.5)	
	84.1 (12.7)	30.3 (12.8)	
	37.6 (5.7)	12.8 (5.4)	
	15.2 (2.3)	4.8 (2.0)	
0 (0)			0.020
	11 (1.7)	3.6 (1.5)	
	129.3 (19.5)	46.6 (19.6)	
	223.0 (33.6)	78.4 (33.0)	
	144.4 (21.8)	53.0 (22.3)	
	156.2 (23.5)	55.9 (23.5)	
3 (0.3)	542.9 (81.8)	195.4 (82.3)	0.014

Table 2. Continued

	Before SI and IPTW		
	SCRT-direct surgery (n=664)	**SCRT-delay (n=238)**	**SMD**
Tumour location [c]			0.073
Distal (0-3 cm)	155 (25.4)	62 (27.8)	
Midrectal (3-6 cm)	208 (34.1)	69 (30.9)	
Proximal (≥ 6 cm)	247 (40.5)	92 (41.3)	
Surgical approach			0.115
Laparotomy	15 (2.3)	2 (0.9)	
Laparoscopy	390 (60.0)	137 (60.6)	
TaTME	73 (11.2)	25 (11.1)	
Robot-assisted laparoscopy	172 (26.5)	62 (27.4)	
Type of resection			0.289
Extralevator APR	32 (4.8)	12 (5.0)	
Conventional APR	80 (12.1)	39 (16.4)	
(L)AR with permanent ostomy	108 (16.4)	53 (22.3)	
(L)AR with deviating ostomy	172 (26.1)	68 (28.6)	
(L)AR without ostomy	268 (40.6)	66 (27.7)	

Values are n (%) unless otherwise indicated. Differences between groups are expressed as the standardized mean difference (SMD), calculated as the difference between group means divided by the pooled standard deviation. A: Haemoglobin below 7 mmol/l in men and below 6.5mmol/l in women. B: Admission to hospital or endoscopic intervention for obstructive symptoms.

Sensitivity analyses with the interval between completion of radiotherapy and surgery in the SCRT-delay group restricted to 4-8 weeks and complete-case analysis showed similar results (Supplementary Files 5-9).

Before SI and IPTW	After SI and IPTW		
Missing	**SCRT-direct surgery (n=664)**	**SCRT-delay (n=238)**	**SMD**
69 (7.6)			0.073
	166.6 (25.1)	59.3 (25.0)	
	233.7 (35.2)	76.3 (32.1)	
	263.7 (39.7)	101.9 (42.9)	
26 (2.9)			0.044
	12.5 (1.9)	4.1 (1.7)	
	400.6 (60.3)	146.6 (62)	
	71.9 (10.8)	22.8 (9.6)	
	179.0 (27.0)	64.0 (27.0)	
4 (0.4)			0.030
	31.8 (4.8)	11.4 (4.8)	
	90.7 (14)	31.6 (13.3)	
	118.2 (17.8)	41.6 (17.5)	
	178.2 (26.8)	66.8 (28.1)	
	245.1 (36.9)	86.1 (36.3)	

C: Distance between lower border of tumour and anorectal junction on sagittal MRI. Abbreviations: SI, single imputation; IPTW, inverse probability of treatment weighting; SCRT, short-course radiotherapy; ASA, American Society of Anaesthesiologists; CCI, Charlson Comorbidity Index; TaTME, transanal total mesorectal excision; APR, abdominoperineal resection; (L)AR, (low) anterior resection.

Table 3. Ninety-day postoperative complication and pCR rates after short-course radiotherapy and surgery within a week (SCRT-direct surgery) versus a prolonged interval (4-12 weeks, SCRT-delay) to surgery, before and after inverse probability of treatment weighting

	SCRT-direct surgery (n=664)	SCRT-delay (n=238)	Risk ratio (95% CI)	P
Before IPTW				
Complication (any)	265 (39.9)	101 (42.4)	1.1 (0.9, 1.3)	0.492
Anastomotic leakage [a]	71 (16.1)	24 (17.9)	1.1 (0.7, 1.7)	0.627
Abscess	46 (6.9)	21 (8.8)	1.3 (0.8, 2.1)	0.338
Surgical-site infection	23 (3.5)	11 (4.6)	1.3 (0.7, 2.7)	0.421
Reintervention	119 (17.9)	47 (19.7)	1.1 (0.8, 1.5)	0.531
Admission to ICU	54 (8.5)	14 (6.2)	0.7 (0.4, 1.3)	0.285
Death	4 (0.6)	4 (1.7)	2.8 (0.7, 11)	0.140
Duration of hospital stay (days), median (IQR) [b]	5 (4-9)	5 (4-8)	1.0 (0.8, 1.1)	0.589
Readmission to hospital	137 (20.9)	41 (17.7)	0.8 (0.6, 1.2)	0.290
pCR	2 (0.3)	26 (11.0)	36 (8.7, 152)	< 0.001
After IPTW				
Complication (any)	266.2 (40.1)	100.6 (42.3)	1.1 (0.9, 1.3)	0.614
Anastomotic leakage [a]	69.2 (16.3)	28.0 (18.3)	1.1 (0.7, 1.9)	0.667
Abscess	46.3 (7.0)	21.3 (9.0)	1.3 (0.7, 2.4)	0.419
Surgical-site infection	23.3 (3.5)	10.7 (4.5)	1.3 (0.6, 2.7)	0.499
Reintervention	118.9 (17.9)	50.7 (21.3)	1.2 (0.8, 1.7)	0.345
Admission to ICU	56.1 (8.8)	12.0 (5.4)	0.6 (0.4, 1.1)	0.093
Death	4.0 (0.6)	3.1 (1.3)	2.2 (0.6, 7.9)	0.229
Duration of hospital stay (days), median (IQR) [b]	5 (4-9)	5 (4-8)	1.0 (0.1, 7.1)	0.974
Readmission to hospital	138.1 (21.1)	41.8 (18.0)	0.9 (0.6, 1.2)	0.408
pCR	2.8 (0.4)	25.5 (10.7)	39 (11, 139)	< 0.001

Outcomes were compared between groups using binomial regression for dichotomous outcomes and Poisson regression for count outcomes, both with log link and a robust standard error. Values are expressed as n (%) unless stated otherwise. A: Anastomotic leakage was evaluated only among 440 patients in the short-course radiotherapy (SCRT)-direct surgery and 134 in the SCRT-delay group in the unweighted population, corresponding to 423 and 153 patients respectively in the weighted population) in whom an anastomosis was created. B: Calculated as number of days between surgery and day of discharge. Abbreviations: SCRT, short course radiotherapy; CI, confidence interval; IPTW, inverse probability of treatment weighting; ICU, intensive care unit; IQR, interquartile range; pCR, pathological complete response.

Discussion

In this study using Dutch nationwide real-world data, the 90-day postoperative complication rate was similar after SCRT-direct surgery and SCRT-delay. The pCR rate was significantly higher in the SCRT-delay group.

This study did not confirm the 12% decrease in postoperative complication rate after SCRT-delay compared with SCRT-direct surgery that was demonstrated in the Stockholm III trial, despite a sufficient sample size. This result was consistent when SCRT-delay was restricted to a 4-8-week interval. The difference between the present results and those of the Stockholm III trial might be explained by improvements in radiotherapy technique since the start of the Stockholm III trial. The Stockholm III trial recruited patients between 1998 and 2013 [11]. During the largest part of the study, radiotherapy was administered with a three- or four-beam box technique [26]. Nowadays, intensity modulated radiotherapy is the standard of care, which has better precision and results in a lower dose to healthy tissues than the three- or four-beam box technique [27-29]. The authors believe that contemporary radiotherapy techniques increase the risk of postoperative complications to a lesser extent than the technique used in the Stockholm III trial, diminishing the effect of the interval between SCRT and TME on the postoperative complication rate.

The increased probability of a pCR after a prolonged interval between SCRT and TME has been reported consistently in literature [30,31]. Similarly, a prolonged interval between chemoradiation (50 Gy in 25 fractions combined with a radiosensitizer) and TME for rectal cancer is associated with an improved pCR rate [32]. Patients who showed a pCR could in theory have been managed by watch-and-wait strategy instead of TME [33]. This strategy avoids the morbidity of surgery, and has been associated with improved quality of life and less bowel, urinary, and sexual dysfunction [34-36]. To evaluate eligibility for watch and wait, a response evaluation in patients treated with SCRT-delay has been proposed. The appropriate timing, sensitivity/specificity of the response evaluation, and oncological safety of the watch-and-wait strategy after SCRT are a focus for future research. SCRT-delay and a response evaluation should be offered to patients who are interested in watch and wait.

A substantial proportion of patients with rectal cancer are not interested in a watch-and-wait strategy [37,38]. Based on the present data, prolonging the interval to surgery does not confer any advantages in terms of postoperative complications in this group. In the Stockholm III trial, 6.5% of patients in the SCRT-delay group were admitted to the hospital owing to acute radiation-induced toxicity [11]. Again, it is likely that this number overestimates the toxicity rate of current clinical practice because of the older radiotherapy techniques used in the Stockholm III trial. A recent prospective cohort study showed no unplanned hospital admissions resulting from radiation-induced toxicity after SCRT-delay, but one in three patients experienced temporary Grade III (severe and disabling but not life-threatening) acute radiation-induced toxicity during the interval [39]. Therefore, SCRT-direct surgery still seems a good option for patients who prefer surgical management.

There are several explanations for the relationship between timing of surgery and the risk of postoperative complications. First, inflammation of the irradiated tissues might impair surgery. Radiation-induced toxicity peaks during weeks 1 and 2 after completion of SCRT and gradually recovers thereafter [39]. This peak may reflect the least favourable time frame for performing surgery, which is in line with older studies that showed increased morbidity when SCRT-direct surgery was slightly delayed [4,5]. In addition, radiotherapy is known to trigger the immune system at a systemic level [40]. Some studies have suggested that preoperative radiotherapy impairs the immune response to surgery, which could be measured by a decreased postoperative leucocyte count or a decreased postoperative-to-preoperative leucocyte ratio [41-43]. The SCRT-delay group in the Stockholm III trial had a significantly higher postoperative-to-preoperative leucocyte ratio than the SCRT-direct surgery group, implying that the immune response had recovered by 4-8 weeks after SCRT [43]. Another theory is that a prolonged interval increases the risk of pelvic fibrosis. In a non-randomized non-blinded trial, surgeons scored a higher level of fibrosis in the group that had an 11-week compared with a 6-week interval between chemoradiotherapy and TME [44]. However, this difference did not translate into an increased postoperative complication rate. Finally, a prolonged interval offers the opportunity to improve patient fitness and nutritional status before surgery. Such prehabilitation programmes reduce duration of hospital stay and postoperative complication rates [45,46]. SCRT-delay combined with a prehabilitation programme might be a good strategy for frail patients.

This study comes with limitations. In some centres in the Netherlands, it is already standard of care to schedule a response evaluation after SCRT-delay and then offer a watch-and-wait strategy in patients with a clinical complete response. Patients managed according to a watch-and-wait strategy were not registered in the DCRA during the study period. The pCR rate in this study will therefore be an underestimation of the real organ-preserving potential of SCRT-delay. The DCRA does not include an explicit definition of postoperative complications. Generally, postoperative complications are defined as 'any deviation from the normal postoperative course' [47]. Differences in the interpretation of this definition may have affected the postoperative complication rate in the present study. Despite the data validation mechanisms that ensure the validity of the DCRA, registry studies like this remain prone to misclassification [16,17,48,49]. This limitation may have led to some effect dilution towards the null. There will always be some residual confounding in non-randomized studies. Because traditionally SCRT-delay was offered to frail patients, residual confounding in the present study will probably disfavour the postoperative complication rate in the SCRT-delay group. Outcomes after rectal cancer surgery differ between hospitals in the Netherlands, and preferences for SCRT-delay or SCRT-direct surgery probably also differ between hospitals [50]. Hence, the hospital of treatment should be considered a confounding factor. This confounder was not corrected for as it did not seem feasible to combine a mixed-effects model with imputation and IPTW. This study had a sufficient sample size to detect a difference of 11% in the 90-day postoperative complication rate between groups. There was no indication of a difference (there was a non-significant absolute risk reduction of 2% in favour of the SCRT-direct surgery group). Nonetheless, it still is possible that the interval between SCRT and TME had a modest effect on the postoperative complication rate that was not detected.

Conclusion

The 90-day postoperative complication rate following SCRT-direct surgery and SCRT-delay was similar in Dutch nationwide real-world data. SCRT-delay was associated with a significantly higher probability of a complete response. The authors recommend SCRT-delay with scheduling of a response evaluation for patients who are interested in watch & wait strategy. SCRT-direct surgery still seems a good option for patients who prefer surgical management.

References

1. Richtlijn–Richtlijnendatabase. Primaire behandeling rectumcarcinoom. https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/primaire_behandeling_rectumcarcinoom_ bij_crc.html (accessed 24 March 2022)
2. Wedish S, Ectal R, Ancer C, Rial T. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980-987
3. Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-646
4. Hartley A, Giridharan S, Gray L, Billingham L, Ismail T, Geh JI. Retrospective study of acute toxicity following short-course preoperative radiotherapy. Br J Surg 2002;89:889-895
5. Van Den Broek CBM, Vermeer TA, Bastiaannet E, Rutten HJT, Van De Velde CJH, Marijnen CAM. Impact of the interval between short-course radiotherapy and surgery on outcomes of rectal cancer patients. Eur J Cancer 2013;49:3131-3139
6. Radu C, Berglund Å, Påhlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer–a retrospective study. Radiother Oncol 2008;87:343-349
7. Hatfield P, Hingorani M, Radhakrishna G, Cooper R, Melcher A, Crellin A et al. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Radiother Oncol 2009;92:210-214
8. Faria S, Kopek N, Hijal T, Liberman S, Charlebois P, Stein B et al. Phase II trial of short-course radiotherapy followed by delayed surgery for locoregionally advanced rectal cancer. Color Dis 2014;16:066-070
9. Beppu N, Matsubara N, Noda M, Yamano T, Kakuno A, Doi H et al. Short-course radiotherapy with delayed surgery versus conventional chemoradiotherapy: a comparison of the short- and long-term outcomes in patients with T3 rectal cancer. Surgery 2015;158:225-235
10. Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer-treatment results at 5-year follow-up. Langenbecks Arch Surg 2012;397:801-807
11. Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017;18:336-346
12. Erlandsson J, Lörinc E, Ahlberg M, Pettersson D, Holm T, Glimelius B et al. Tumour regression after radiotherapy for rectal cancer–results from the randomised Stockholm III trial. Radiother Oncol 2019;135:178-186
13. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol 2016; 183:758-764

14. D'Souza N, de Neree tot Babberich MPM, D'Hoore A, Tiret E, Xynos E, Beets-Tan RGH et al. Definition of the rectum: an international, expert-based Delphi consensus. Ann Surg 2019; 270:955-959
15. Rombouts AJM, Al-Najami I, Abbott NL, Appelt A, Baatrup G, Bach S et al. Can we Save the rectum by watchful waiting or Trans Anal microsurgery following (chemo) Radiotherapy versus Total mesorectal excision for early REctal Cancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. BMJ Open 2017;7:e019474
16. Van Leersum NJ, Snijders HS, Henneman D, Kolfschoten NE, Gooiker GA, ten Berge MG et al. The Dutch surgical colorectal audit. Eur J Surg Oncol 2013;39:1063-1070
17. DICA. Jaarrapportage 2011. https://dica.nl/jaarrapportage-2013/ archief/DICA%20 Jaarrapportage%202011.pdf
18. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;339:157-160
19. Austin PC. The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. Stat Med 2010;29:2137-2148
20. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Communications in Statistics–Simulation and Computation 2009;38:1228-1234
21. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661-3679
22. Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RHH. Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 2012; 184:895-899
23. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1-67
24. van der Wal WM, Geskus RB. Ipw: an R package for inverse probability weighting. J Stat Softw 2011;43:2-23
25. Zeileis A, Köll S, Graham N. Various versatile variances: an object-oriented implementation of clustered covariances in R. J Stat Softw 2020;95:1-36
26. Pettersson D, Cedermark B, Holm T, Radu C, Påhlman L, Glimelius B et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010;97:580-587
27. Urbano MTG, Henrys AJ, Adams EJ, Adams EJ, Norman AR, Bedford JL et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. Int J Radiat Oncol Biol Phys 2006;65: 907-916
28. Arbea L, Ramos LI, Martínez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (IMRT) versus 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications. Radiat Oncol 2010;5:17

29. Wee CW, Kang HC, Wu HG, Chie EK, Choi N, Park JM et al. Intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy in rectal cancer treated with neoadjuvant concurrent chemoradiation: a meta-analysis and pooled-analysis of acute toxicity. Jpn J Clin Oncol 2018;48: 458-466
30. Bujko K, Partycki M, Pietrzak L. Neoadjuvant radiotherapy (5×5 Gy): immediate versus delayed surgery. Recent Results Cancer Res 2014;203:171-187
31. Wu H, Fang C, Huang L, Fan C, Wang C, Yang L et al. Short-course radiotherapy with immediate or delayed surgery in rectal cancer: a meta-analysis. Int J Surg 2018;56:195-202
32. Ryan J, O'Sullivan DP, Kelly ME, Syed AZ, Neary PC, O'Connell PR et al. Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer. Br J Surg 2019;106:1298-1310
33. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-718
34. Hupkens BJP, Martens MH, Stoot JH, Berbee M, Melenhorst J, Beets-Tan RG et al. Quality of life in rectal cancer patients after chemoradiation. Dis Colon Rectum 2017;60:1032-1040
35. Quezada-Diaz FF, Smith JJ, Jimenez-Rodriguez RM, Nash GM, Guillem JG, Weiser MR et al. Patient-reported bowel function in patients with rectal cancer managed by a watch-and-wait strategy after neoadjuvant therapy: a case-control study. Dis Colon Rectum 2020;63:897-902
36. Bach SP, Gilbert A, Brock K, Korsgen S, Geh I, Hill J et al. Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. Lancet Gastroenterol Hepatol 2021;6:92-105
37. Couwenberg AM, Intven MPW, Burbach JPM, Emaus MJ, Van Grevenstein WMU, Verkooijen HM. Utility scores and preferences for surgical and organ-sparing approaches for treatment of intermediate and high-risk rectal cancer. Dis Colon Rectum 2018;61:911-919
38. Gani C, Gani N, Zschaeck S, Eberle F, Schaeffeler N, Hehr T et al. Organ preservation in rectal cancer: the patients' perspective. Front Oncol 2019;9:318
39. Verweij ME, Hoendervangers S, von Hebel CM, Pronk A, Schiphorst AHW, Consten ECJ et al. Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer. Colorectal Dis 2023;25:24-30
40. Formenti SC, Demaria S. Systemic effects of local radiotherapy. Lancet Oncol 2009;10:718-726
41. Fokstuen T, Holm T, Glimelius B. Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. Radiother Oncol 2009;93:293-297

42. Hartley A, Giridharan S, Srihari N, McConkey C, Geh JI. Impaired postoperative neutrophil leucocytosis and acute complications following short course preoperative radiotherapy for operable rectal cancer. Eur J Surg Oncol 2003;29:155-157
43. Pettersson D, Glimelius B, Iversen H, Johansson H, Holm T, Martling A. Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III trial. Br J Surg 2013;100:969-975
44. Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011;254: 97-102
45. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N et al. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. Gastroenterology 2018;155:391-410.e4
46. Daniels SL, Lee MJ, George J, Kerr K, Moug S, Wilson TR et al. Prehabilitation in elective abdominal cancer surgery in older patients: systematic review and meta-analysis. BJS Open 2020; 4:1022-1041
47. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213
48. Rutegård M, Kverneng Hultberg D, Angenete E, Lydrup ML. Substantial underreporting of anastomotic leakage after anterior resection for rectal cancer in the Swedish Colorectal Cancer Registry. Acta Oncol 2017;56:1741-1745
49. Gunnarsson U, Seligsohn E, Jestin P, Påhlman L. Registration and validity of surgical complications in colorectal cancer surgery. Br J Surg 2003;90:454-459
50. Henneman D, Snijders HS, Fiocco M, van Leersum NJ, Kolfschoten NE, Wiggers T et al. Hospital variation in failure to rescue after colorectal cancer surgery: results of the Dutch Surgical Colorectal Audit. Ann Surg Oncol 2013;20:2117-2123

Chapter 4

Impact of dose-escalated chemoradiation on quality of life in patients with locally advanced rectal cancer: 2-year follow-up of the randomized RECTAL-BOOST trial

Maaike E. Verweij, Sieske Hoendervangers, Alice M. Couwenberg, J. P. Maarten Burbach, Maaike Berbee, Jeroen Buijsen, Jeanine Roodhart, Onne Reerink, Apollo Pronk, Esther C. J. Consten, Anke B. Smits, Joost T. Heikens, Wilhelmina M. U. van Grevenstein, Martijn P. W. Intven and Helena M. Verkooijen

International Journal of Radiation Oncology, Biology and Physics. 2022; 112, 694–703

Abstract

Aim

Dose-escalated chemoradiation (CRT) for locally advanced rectal cancer did not result in higher complete response rates but initiated more tumour regression in the randomized RECTAL-BOOST trial (Clinicaltrials.gov NCT01951521). This study compared patient reported outcomes between patients who received dose-escalated CRT (5x3 Gy boost + CRT) or standard CRT for 2 years after randomization.

Methods

Patients with locally advanced rectal cancer who were participating in the RECTAL-BOOST trial filled out European Organisation for Research and Treatment of Cancer QLQ-C30 and CR29 questionnaires on quality of life (QoL) and symptoms at baseline, 3, 6, 12, 18, and 24 months after start of treatment. Between-group differences in functional QoL domains were estimated using a linear mixed-effects model and expressed as effect size (ES). Symptom scores were compared using Mann-Whitney U test.

Results

Patients treated with dose-escalated CRT (boost group, n=51) experienced a significantly stronger decline in global health at 3 and 6 months (ES −0.4 and ES −0.4), physical functioning at 6 months (ES −1.1), role functioning at 3 and 6 months (ES −0.8 and ES −0.6), and social functioning at 6 months (ES −0.6), compared with patients treated with standard CRT (control group, n=64). The boost group reported significantly more fatigue at 3 and 6 months (83% vs 66% respectively 89% vs 76%), pain at 3 and 6 months (67% vs 36% respectively 80% vs 44%), and diarrhoea at 3 months (45% vs 29%) compared with the control group. From 12 months onwards, QoL and symptoms were similar between groups, apart from more blood/mucus in stool in the boost group.

Conclusion

In patients with locally advanced rectal cancer, dose-escalated CRT resulted in a transient deterioration in global health, physical, role, and social functioning and more pain, fatigue and diarrhoea at 3 and 6 months after start of treatment compared with standard CRT. From 12 months onwards, the effect of dose-escalated CRT on QoL largely resolved.

Introduction

Locally advanced rectal cancer (LARC) is treated with chemoradiation (CRT) followed by total mesorectal excision (TME) [1,2]. Neoadjuvant CRT, which entails radiation therapy of 50 Gy in 25 fractions with concurrent fluoropyrimidine-based chemotherapy, is administered to facilitate surgery with a clear resection margin and to reduce the risk of local recurrence [3]. This multimodality approach results in 10-year overall survival of approximately 60% [4,5], but is also associated with impaired quality of life (QoL) and side effects including bowel dysfunction, urinary incontinence, sexual complaints, and stoma-related problems [6-10]. QoL and functional outcomes might be improved by rectum-sparing treatments, such as local excision and active surveillance (also known as the watch-and-wait [WW] strategy) [11-14]. A WW strategy is feasible in patients with a clinical complete response (cCR) after neoadjuvant treatment.

The randomized RECTAL-BOOST trial investigated whether an additional 15 Gy radiation therapy boost before CRT (boost group) could improve the pathological complete response (pCR) rate compared with standard CRT (control group) in LARC [15]. The trial did not result in a difference in complete response (36% vs 38%, P = .86), but did show significantly more tumour regression (Mandard 1-2) in the boost group compared with the control group (69% vs 45%, P = .02) [16]. Based on this finding, dose-escalated CRT may become a neoadjuvant strategy enabling rectum-sparing treatment in selected rectal cancer patients.

After treatment with dose-escalated CRT, a substantial proportion of patients will experience additional toxicity without achieving cCR. Therefore, the probability of organ preservation needs to be weighed against the effect on QoL. Primary analysis of the RECTAL-BOOST trial showed a significantly lower QoL summary score in the boost group at 3 months after randomization (mean difference [MD] −7.5, 95% confidence interval [CI], −12.1 to −3.0) and comparable scores at 6 and 12 months (MD −3.6, 95% CI, −8.3 to 1.0 respectively MD −0.6, 95% CI, −5.6 to 4.4) [16]. The current study further investigates the effect of dose-escalated CRT versus standard CRT on different QoL domains, symptoms, and functional outcome. Patient-reported outcomes (PROs) and disease-free survival (DFS) of LARC patients are compared for the first 2 years after the RECTAL-BOOST trial.

Methods

Patients and treatment

The design of the RECTAL-BOOST trial (Clinicaltrials.gov NCT01951521) has been described in detail [15]. In short, the RECTAL-BOOST trial was a nonblinded, phase II randomized controlled trial performed within a prospective cohort of colorectal cancer patients (Dutch Prospective Colorectal Cancer cohort, PLCRC), according to the Trials within Cohorts (TwiCs) design [17,18]. The RECTAL-BOOST trial was performed in the UMC Utrecht and the Maastro/MUMC+. The institutional review board of the UMC Utrecht approved PLCRC and the RECTAL-BOOST trial. Cohort participants with locally advanced tumours within 10 cm from the anorectal junction and a World Health Organization performance status 0 to 2, who consented to fill out questionnaires and who provided broad consent to randomization to future intervention studies, were eligible. Exclusion criteria were presence of inflammatory bowel disease, prior pelvic radiation therapy, contraindication for magnetic resonance imaging or capecitabine, pregnancy within the last year, and inadequate command of the Dutch language. Patients were allocated to either standard treatment, that is, either CRT that involved 50 Gy in 25 fractions of 2 Gy with concurrent capecitabine 825 mg/m2 twice daily for 5 or 7 days per week (control group) or dose-escalated CRT including a radiation boost to the tumour of 15 Gy in 5 fractions of 3 Gy without concurrent chemotherapy in the week before the start of CRT (boost group) [15,16]. TME was performed at 12 weeks after completion of CRT. Several patients who achieved cCR entered active surveillance. Baseline patient, tumour, and treatment characteristics were collected within PLCRC.

Patient-reported outcomes

Patients filled out questionnaires before start of neoadjuvant therapy (baseline) and at 3, 6, 12, 18, and 24 months after start of treatment. Questionnaires were provided online or on paper and collected within the Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) platform [19]. QoL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) core and colorectal cancer specific QoL questionnaires (EORTC QLQ-C30 and QLQ-CR29) [20,21]. EORTC QLQ-C30 includes a global health score, five functional domains (physical, role, emotional, cognitive, and social functioning), and nine cancer-related symptoms [20]. The EORTC QLQ-

CR29 contains colorectal cancer-specific domains and symptoms [21]. Bowel function was measured with the low anterior resection syndrome (LARS) score in patients without an ostomy at the moment of sending the questionnaire (i.e., patients after LAR with restored bowel continuity or on WW) [22]. The LARS score contains five questions regarding incontinence for flatus, incontinence for liquid stools, stool frequency, re-evacuation, and urgency.

Oncological outcomes

Disease recurrence and survival were obtained from the electronic patient records and the municipality registry up to October 2020. Events for DFS included no resection of the tumour due to progression or the patient being unfit for surgery, macroscopic nonradical resection (R2) of the tumour, locoregional recurrence after radical resection of the primary tumour, distant metastatic disease, second primary cancer, or death, whichever came first. A local regrowth during WW strategy that was manageable with curative salvage operation (R0 or R1) did not count as an event for DFS [23].

Statistical analysis

The QoL questionnaires were transformed into scores between 0 and 100 according to their manuals [21,24]. A high score on global health or functional domains represents a high level of functioning or a high QoL. A high score on symptom scales represents a high level of complaints. Only the QoL domains and symptoms that were expected to be affected by dose-escalated CRT were analysed. For the functional QoL domains, a linear mixed-effects model was applied with a random intercept, time (as factor), interaction between time and treatment, and an autoregressive covariance structure of the first order (assuming that the correlation systematically decreases with increasing distance between timepoints) [25]. The estimates of the time and treatment interaction were presented as MD between the treatment groups at each time point with 95% CI. The outcomes were interpreted with the standardized ES, calculated as the MD divided by the pooled standard deviation of the baseline score. ES was categorized into "no change" (ES < 0.2), "small change" (ES, 0.2 to 0.4), "moderate change" (ES, 0.5 to 0.7), and "considerable change" (ES ≥ 0.8) [26]. Symptom scores were presented as proportion of patients experiencing no (0), mild (1 to 49), moderate (50 to 99), or severe (100) level of complaints and as MD. Symptom scores were compared using the Mann-Whitney U test, because a mixed model was too complex for our

data. LARS questionnaires were processed to a weighted sum according to the manual, ranging from 0 to 42. This score is interpreted as "no LARS" (total score, 0-20), "minor LARS" (total score, 21-29), or "major LARS" (total score, 30-42). LARS scores were compared using Mann-Whitney U test [22]. Because the number of patients without a (temporary) ostomy at 3 and 6 months was low, LARS scores are presented at 12, 18, and 24 months after start of treatment. Overall survival and DFS times were calculated from start of radiation therapy. Survival probabilities were estimated with the Kaplan-Meier method and compared using log rank test.

Because dose-escalated CRT was expected to unfavourably affect QoL scores and symptoms, intention-to-treat analysis (i.e., including patients who did not undergo the boost intervention in the intervention arm) would dilute the real effect estimate. The effect of dose-escalated CRT on PROs was therefore evaluated in the per-protocol population, that is, among 64 patients in the control arm who received standard CRT and 51 (of 64 patients) in the intervention arm who accepted and received dose-escalated CRT. In two sensitivity analyses, the mixed-effects model was reapplied to (1) a selection of patients of the per-protocol population who were primarily treated with TME (i.e., excluding WW and palliative treatment) and (2) the intention-to-treat population. Survival data were analysed as intention-to-treat because patients who decline the intervention are, in general, more likely to have a worse baseline prognosis. For interpretation of QoL results, survival analyses were repeated in the per-protocol population.

The level of significance was set at $P < .05$. Analyses were performed using SPSS Statistics version 25 (IBM) and RStudio version 1.1.442 (RStudio, Inc.).

Results

Between September 2014 and July 2018, 128 patients were included in the RECTAL-BOOST trial. A total of 51 (80%) of 64 patients who were randomized to the intervention group accepted and received the boost intervention (Supplementary File 1). Thirteen patients refused the intervention and underwent standard CRT. Sixty-four patients were randomized to the control group, and all underwent standard CRT. Most patients were male in both the boost and the control group (75% and 74%, respectively) (Table 1). Median age was 64 and 62 years in the

boost and the control group, respectively. Most tumours were located within 3 cm of the anorectal angle in both the boost and the control group (53% and 57%, respectively). The boost group included less cT4 tumours than the control group (18% and 31%, respectively). Patients in the boost group more often underwent low anterior resection (LAR) than patients in the control group (41% and 33%, respectively). Twenty-two percent of patients in the boost group and 14% in the control group entered WW strategy after CRT. At 2 years, 14% (n=7) and 8% (n=5) respectively had a sustained cCR.

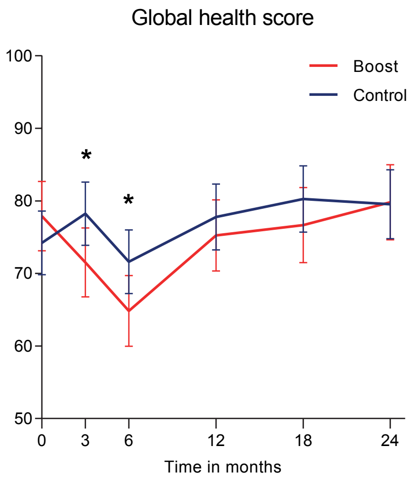
Response rates for the QLQ-C30 and QLQ-CR29 questionnaires were 92% versus 86% at baseline and 85% versus 74% at 24 months for the boost group and the control group, respectively (Supplementary File 2A-B). There was a larger decline in global health score, physical functioning, role functioning and social functioning in the boost group compared with the control group during the first year after start of treatment (Figure 1A-F). Based on a linear mixed-effects model, there was a significant between-group difference of small ES in global health at 3 and 6 months (ES −0.4 and ES −0.4, respectively), a considerable difference in physical functioning at 6 months (ES −1.1), a considerable and moderate difference in role functioning at 3 and 6 months (ES −0.8 and −0.6, respectively) and a moderate difference in social functioning at 6 months (ES −0.6) (Table 2). From 12 months onwards, there were no significant differences in functional QoL domains between groups. Sensitivity analysis of patients primarily treated with TME showed comparable results (Supplementary File 3). In the intention-to-treat population, there was a significant between-group difference of small ES in global health at 3 months (ES −0.4), a moderate difference in physical functioning at 6 months (ES −0.8) and a moderate difference in role functioning at 3 months (ES −0.7) (Supplementary File 4,5).

Table 1. Patient, tumour, and treatment characteristics of patients with locally advanced rectal cancer included in the per-protocol study population of the RECTAL-BOOST trial

	Boost group (n=51)	**Control group (n=64)**
Age in years	64 (26-75)	62 (37-80)
Sex = male	38 (74.5)	47 (73.4)
Tumour location [a]		
≤3.0 cm	27 (52.9)	36 (57.1)
3.1-5.0 cm	8 (15.7)	8 (12.7)
5.1-10.0cm	16 (31.4)	19 (30.2)
Clinical tumour stage		
cT2	2 (3.9)	5 (7.8)
cT3	40 (78.4)	39 (60.9)
cT4	9 (17.6)	20 (31.2)
Distance to the mesorectal fascia ≤1 mm	33 (64.6)	46 (71.9)
Clinical nodal stage		
cN0	5 (9.8)	9 (14.1)
cN1	12 (23.5)	17 (26.6)
cN2	34 (66.7)	38 (59.4)
Clinical oligometastatic disease = cM1	3 (5.9)	2 (3.1)
Tumour dose in Gy [b]	69.2 (54.1-71.3)	50 (49.4-51.5)
Treatment after chemoradiation		
Low anterior resection	21 (41.2)	21 (32.8)
Abdominoperineal resection	17 (33.3)	32 (50)
Watch-and-wait [c]	11 (21.6)	9 (14.1)
Palliative systemic treatment	2 (3.9)	2 (3.1)

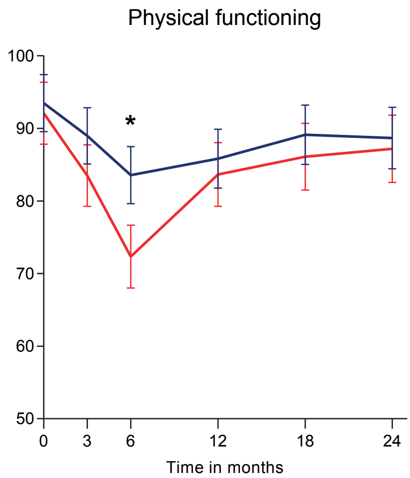
Data are presented in number (%) or median (range). A: Measured as the distance from the anorectal angle to the lower border of the tumour on sagittal magnetic resonance imaging. B: mean dose (D95) to the planned target volume of the tumour. C: Includes 1 patient in the boost group who entered watch-and-wait after local excision.

A



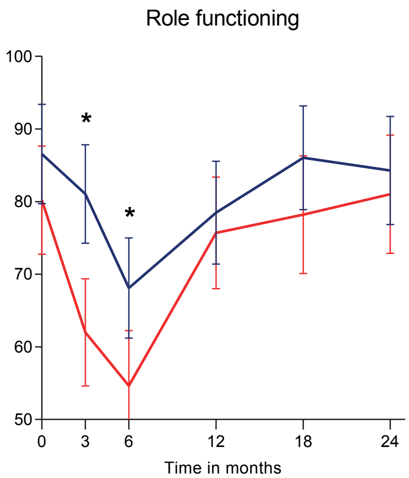
n	0	3	6	12	18	24
boost	47	48	45	44	39	39
control	55	56	55	51	50	46

B



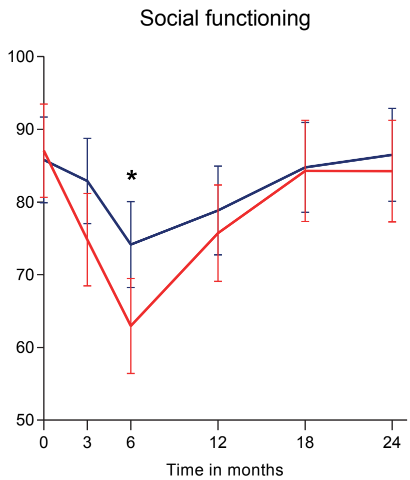
n	0	3	6	12	18	24
boost	47	48	45	44	39	39
control	55	56	55	51	50	46

C



n	0	3	6	12	18	24
boost	47	48	45	44	39	39
control	55	56	55	51	50	46

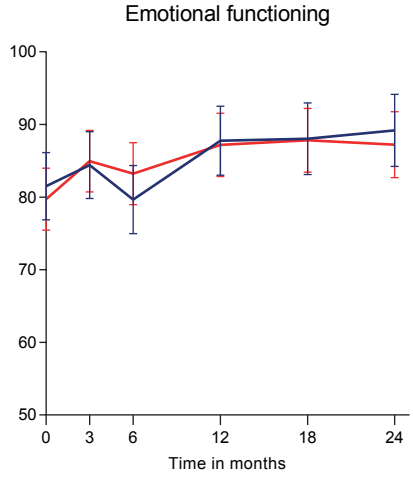
D



n	0	3	6	12	18	24
boost	47	48	45	44	39	39
control	55	56	55	51	50	46

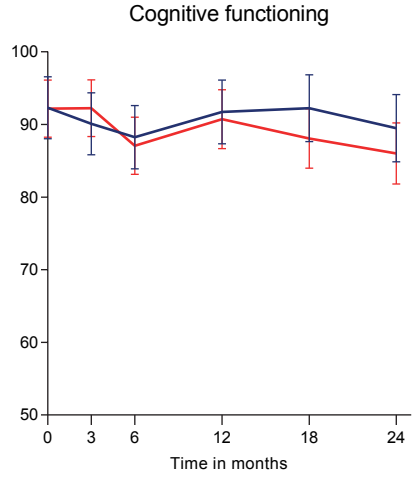
Figure 1A-F. QLQ-C30 functional quality-of-life domains measured at baseline and at 3, 6, 12, 18, and 24 months after start of treatment in patients treated with dose-escalated chemoradiation (boost group, red) and standard chemoradiation (control group, blue) in the per-protocol population. Scores are presented as means with 95% confidence interval. A higher score indicates better global health or better functioning. Significant between-group differences ($P < .05$), based on a linear mixed-effects model, are marked with an asterisk.

E



n	0	3	6	12	18	24
boost	47	48	45	44	39	39
control	55	56	55	51	50	46

F



n	0	3	6	12	18	24
boost	47	48	45	44	39	39
control	55	56	55	51	50	46

Figure 1A-F. Continued

The boost group reported significantly more often fatigue at 3 (83% vs 66%) and 6 months (89% vs 76%), pain at 3 (67% vs 36%) and 6 months (80% vs 44%), and diarrhoea at 3 months (45% vs 29%) compared with the control group. Blood or mucus in stool was more prevalent in the boost group at 6 months (42% vs 20%), 12 months (30% vs 14%), 18 months (23% vs 8%), and 24 months (28% vs 11%). There were no differences in terms of constipation, urinary frequency, or urinary incontinence (Figure 2A-G, Supplementary File 6).

Response rates for the LARS questionnaire in patients with bowel continuity at 12 and 24 months were 79% and 88% in the boost and 71% and 75% in the control group, respectively (Supplementary File 2C). Major LARS was reported by 57% in the boost group versus 56% in the control group at 12 months (P = .8), 68% versus 58% at 18 months (P = .9), and 61% versus 47% at 24 months after start of treatment (P = .5, Figure 3).

Table 2. Mean differences in EORTC QLQ-C30 functional quality-of-life domains between the boost and the control group (reference) over time in the per-protocol population. Mean differences were interpreted with the standardized effect size, calculated as the mean difference divided by the pooled standard deviation of the mean quality-of-life score per domain at baseline. Significant between-group differences (P < .05), based on a linear mixed-effects model, are bolded.

		Baseline	**3 months**				**6 months**			
		Mean (SD)	**MD**	**95% CI**	**ES**	**P**	**MD**	**95% CI**	**ES**	**P**
Global health	Control	74.1 (18.8)	Ref.				Ref.			
	Boost	78.0 (17.3)	−6.7	−13.0 to −0.4	−0.4	**.037**	−6.8	−13.2 to −0.3	−0.4	**.039**
Physical functioning	Control	93.2 (9.0)	Ref.				Ref.			
	Boost	92.8 (11.9)	−5.5	−11.1 to 0.2	−0.4	.058	−11.2	−17.0 to −5.5	−1.1	**.000**
Role functioning	Control	86.4 (20.1)	Ref.				Ref.			
	Boost	81.2 (25.2)	−19.0	−28.9 to −9.2	−0.8	**.000**	−13.5	−23.4 to −3.4	−0.6	**.009**
Social functioning	Control	85.2 (17.2)	Ref.				Ref.			
	Boost	88.3 (18.0)	−8.1	−16.6 to 0.4	−0.5	.062	−11.2	-19.8 to −2.6	−0.6	**.011**
Emotional functioning	Control	79.7 (18.3)	Ref.				Ref.			
	Boost	82.4 (17.7)	−0.5	−6.7 to 5.6	0.0	.862	−3.6	−9.8 to 2.6	−0.2	.259
Cognitive functioning	Control	92.4 (12.8)	Ref.				Ref.			
	Boost	93.3 (13.3)	−2.1	−7.8 to 3.5	−0.2	.457	1.2	−4.6 to 6.9	0.1	.691

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment for Cancer Quality of Life Core Questionnaire; SD, standard deviation; MD, mean difference; CI, confidence interval; ES, effect size; ref., reference.

	12 months				18 months				24 months			
MD	**95% CI**	**ES**	**P**	**MD**	**95% CI**	**ES**	**P**	**MD**	**95%CI**	**ES**	**P**
	Ref.				Ref.				Ref.		
−2.5	−9.1 to 4.0	−0.1	.450	−3.6	−10.3 to 3.1	−0.2	.295	0.3	−6.6 to 7.1	0.0	.935
	Ref.				Ref.				Ref.		
−2.2	−8.0 to 3.7	−0.2	.461	−3.0	−9.0 to 3.0	−0.3	.326	−1.5	−7.6 to 4.6	−0.1	.631
	Ref.				Ref.				Ref.		
−2.8	−13.0 to 7.4	−0.1	.591	−7.8	−18.4 to 2.7	−0.3	.145	−3.3	−14.0 to 7.5	−0.1	.550
	Ref.				Ref.				Ref.		
−3.1	-11.9 to 5.7	−0.2	.488	−0.5	−9.5 to 8.6	0.0	.919	−2.2	−11.4 to 7.0	−0.1	.637
	Ref.				Ref.				Ref.		
0.6	−5.7 to 6.9	0.0	.853	0.2	−6.3 to 6.7	0.0	.952	2.0	−4.6 to 8.5	0.1	.557
	Ref.				Ref.				Ref.		
1.0	−4.9 to 6.8	0.1	.740	4.2	−1.8 to 10.2	0.3	.171	3.5	−2.6 to 9.6	0.3	.263

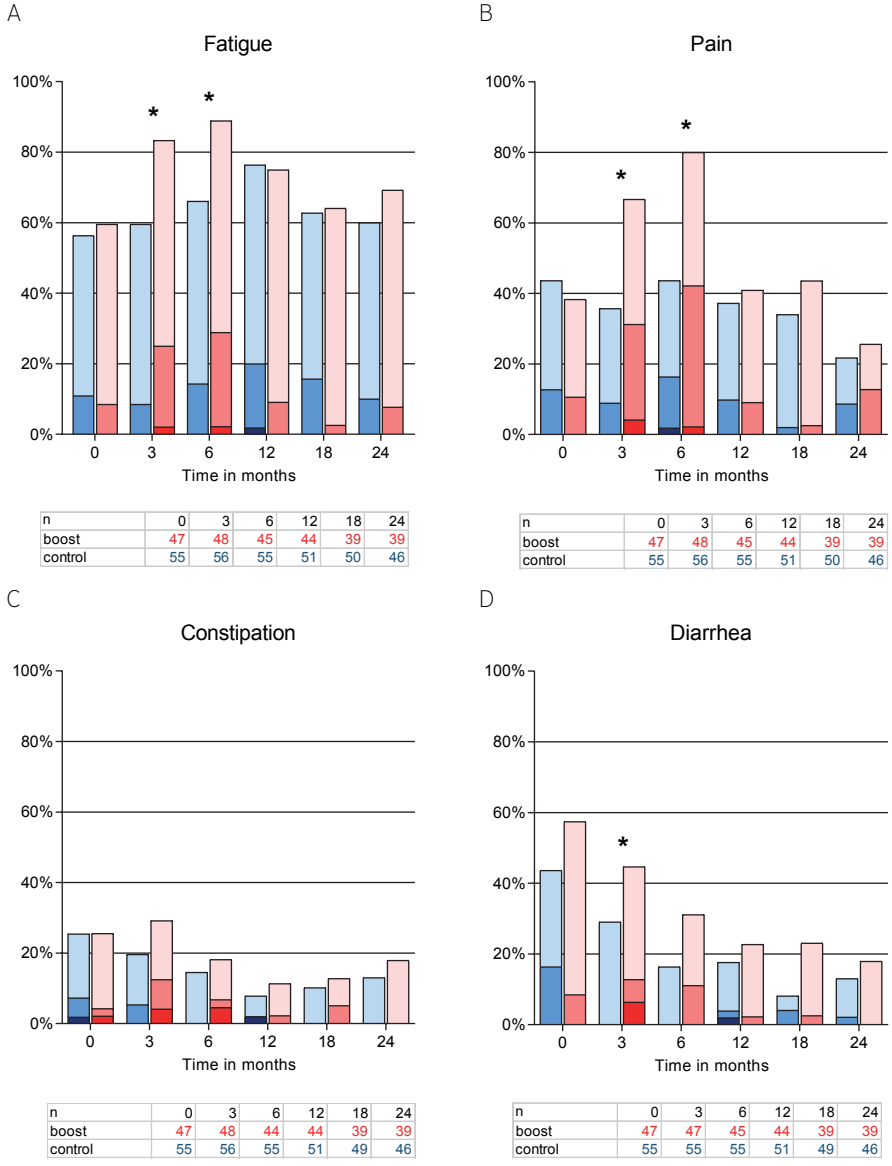
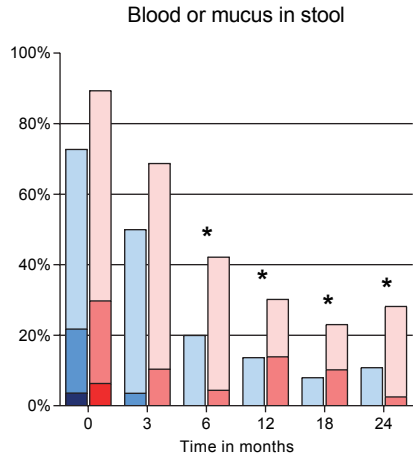


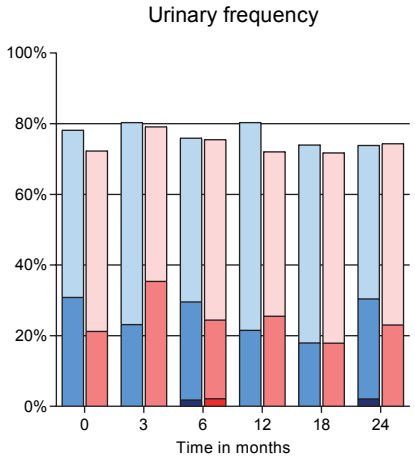
Figure 2A-G. Proportion of patients reporting symptoms after dose-escalated chemoradiation (boost group, red) and standard chemoradiation (control group, blue) in the per-protocol population, as was measured with the quality-of-life core and colorectal cancer-specific questionnaires (European Organisation for Research and Treatment of Cancer QLQ-C30 and -CR29) at baseline and at 3, 6, 12, 18, and 24 months after start of treatment. Symptom scores were categorized as no (0), mild (1 to 49), moderate (50 to 99), or severe (100) level of complaints. Significant between-group differences ($P < .05$), based on the Mann-Whitney U test, are marked with an asterisk (*).

E



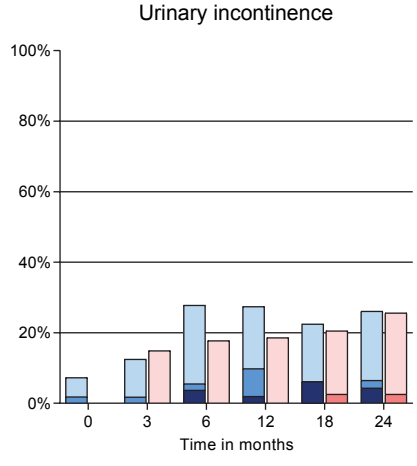
n	0	3	6	12	18	24
boost	47	48	45	43	39	39
control	55	56	55	51	50	46

F



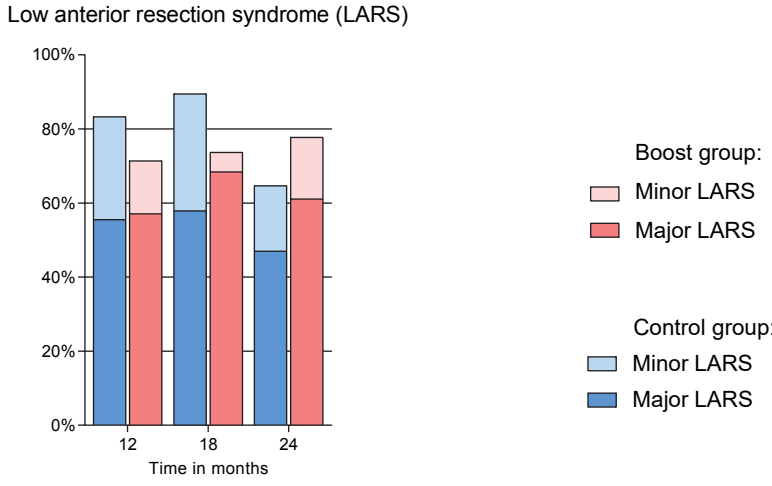
n	0	3	6	12	18	24
boost	47	48	45	43	39	39
control	55	56	54	51	50	46

G



n	0	3	6	12	18	24
boost	47	47	45	43	39	39
control	55	56	54	51	49	46

Figure 2A-G. Continued



n	12	18	24
boost	21	19	18
control	18	19	17

Figure 3. Proportion of patients reporting minor and major bowel dysfunction after dose-escalated chemoradiation (boost group, red) and standard chemoradiation (control group, blue) as was measured by the low anterior resection syndrome score at 12, 18, and 24 months in patients in the per-protocol population with bowel continuity at the moment of sending the questionnaire.

At 2 years after start of treatment, 5 of 64 patients in the boost group and 2 of 64 in the control group were deceased. Two-year overall survival was 92% (95% CI, 86 to 99) and 97% (95% CI, 93 to 100), respectively (P = .3, Supplementary Files 7,8). Information on disease recurrence was not available for 1 patient in the boost group and for 2 in the control group. The proportion of patients who experienced an event for DFS at 2 years was 16 of 63 in the boost group and 13 of 62 in the control group. Among them, 1 patient in the boost group and 2 patients in the control group experienced locoregional disease recurrence; 11 and 8 patients, respectively, experienced distant metastatic disease. Two-year DFS was 75% (95% CI, 65 to 86) in the boost group and 80% (95% CI, 70 to 90) in the control group (P = .9). These results were consistent in the per-protocol population (Supplementary File 9).

Discussion

Dose-escalated CRT resulted in a significantly stronger decline of small ES in global health at 3 and 6 months, a considerable decline in physical functioning at 6 months, a considerable and moderate decline in role functioning at 3 and 6 months, and a moderate decline in social functioning at 6 months compared with standard CRT. Furthermore, patients treated with dose-escalated CRT reported more pain at 3 and 6 months, more fatigue at 3 and 6 months, and more diarrhoea at 3 months. From 12 months onwards, patients treated with dose-escalated CRT reported similar QoL and symptoms as patients treated with standard CRT, apart from more complaints of blood and mucus in stool. Dose-escalated CRT did not influence DFS at 24 months.

Primary results of the RECTAL-BOOST trial showed comparable postoperative complications (26% vs 19%, P = .5) and comparable CTCAE Grade ≥ 3 toxicity during and 9 weeks after CRT (9% vs 8%, P = .75). Nonetheless, the current study with a focus on PROs found considerable effect of dose-escalated CRT on QoL and symptoms at 3 and 6 months after treatment. This effect remained consistent in sensitivity analysis, including only patients primarily treated with TME. Similar to our results, a previous observational study on QoL after rectal cancer treatment described deterioration in most QLQ-C30 functional domains within 6 months after start of neoadjuvant treatment, with worse deterioration after long-course CRT versus short-course radiation therapy [27]. Our findings underline the importance of collecting PROs in addition to physician reported outcomes such as postoperative complications and severe radiation toxicity, when evaluating a new intervention.

Dose-escalated CRT was administered in the RECTAL-BOOST trial with the aim to increase pCR, which has been suggested to be a surrogate marker for DFS [28]. Because pCR did not differ between groups, no difference in DFS was expected, which was confirmed in the current analysis. In line with our results, DFS was comparable following preoperative capecitabine-based chemoradiation intensified by a concomitant boost compared to the addition of oxaliplatin (75% vs 74%, P = .4) for distal cT2-3 rectal cancer in the INTERACT trial [29]. Experiencing disease recurrence can severely affect QoL [30]. However, we found no differences in DFS and, therefore, the differences in QoL and symptoms that we observed are not attributable to differences in disease recurrence.

Summarizing the previous and current RECTAL-BOOST results, a boost before CRT administered with conventional radiation therapy did not improve complete response rate nor 2-year DFS in LARC patients and resulted in a transient but considerable effect on QoL. This boost strategy is therefore not recommended. However, dose-escalated CRT initiated more tumour regression than standard CRT, suggesting that dose-escalation may have organ-preserving potential. In the RECTAL-BOOST trial, the minimum dose to the planned tumour volume was limited by nearby organs at risk and their surrounding margins [16]. Margins can be reduced by magnetic resonance-guided radiation therapy, a technique that offers high-precision radiation therapy through daily adaptation to the actual anatomy on magnetic resonance imaging [31,32]. Reduced margins offer better high-dose coverage of the tumour volume, which theoretically results in an increased chance on a complete response. Furthermore, radiation therapy with reduced treatment margins delivers a decreased dose to the surrounding healthy tissue, theoretically resulting in less radiation-induced toxicity. Clinical trials are needed to confirm whether magnetic resonance–guided dose-escalated chemoradiation therapy increases the probability of rectum-preserving treatment with acceptable effect on QoL and symptoms. Patients willing to participate in trials on dose-escalated chemoradiation therapy for rectal cancer should be counselled on the transient but considerable effect on QoL and symptoms.

Total neoadjuvant therapy, that is, addition of chemotherapy to standard fluoropyrimidine-based CRT, could be an alternative neoadjuvant strategy enabling rectum-sparing treatment. A recent meta-analysis showed that addition of chemotherapy before or after CRT led to similar pCR rates, but intensification of chemotherapy during CRT led to significantly higher pCR rates compared with standard CRT [33]. Intensification of CRT by addition of oxaliplatin in the German CAO/ARO/AIO-04 and ACCORD 12/0405-Prodige 2 trials had limited effect on QoL after treatment, but increased Grade ≥ 3 toxicity during treatment [34,35].

Blood and/or mucus in stool was the only symptom that remained more prevalent in the boost than in the control group from 6 months onwards. In a phase II trial on high-dose chemoradiotherapy and watchful waiting for T2-3 distal rectal cancer, predominantly mild bleeding from the rectal mucosa also was the most common physician-related toxicity, with a prevalence of 78% beyond 1 year of treatment (n=21 of 27) [36]. Rectal bleeding is the main sign of radiation proctitis, which

may occur in patients treated with LAR or in a WW strategy. Chronic radiation proctitis has consistently been associated with the volume of rectum receiving ≥ 60 Gy [37]. Bleeding occurs because of radiation-induced vessel damage, which causes ischemia and formation of new vessels that are prone to bleeding [38]. In most cases, the bleeding is mild and no treatment is required. For more severe cases, treatment that aims to protect the mucosa (e.g., sucralfate enemas and oral metronidazole) or reduce ischemia (e.g., hyperbaric oxygen) might mitigate the bleeding [38,39]. In our study population, one patient in the boost group received treatment with sucralfate enema for rectal bleeding.

When administering dose-escalated radiation therapy aiming for rectum-sparing treatment, it is important to protect bowel function [12,40]. A higher irradiation dose to the rectum and the anorectal complex has been associated with deteriorated anorectal function [10,41]. In our results, there was no indication for increased bowel dysfunction after dose-escalated CRT compared with standard CRT. Most patients with bowel continuity in both the boost and the control group reported major LARS at 12, 18, and 24 months after treatment, which is comparable to earlier studies that found approximately 65% major LARS among LARC patients treated with CRT and LAR [12,42]. Most cases of bowel dysfunction develop within the first 2 years after treatment [43]. However, our data do not exclude increased late-onset LARS after dose-escalated CRT. In line with our results, the HER-BERT study - a phase I dose-escalation study on a brachytherapy boost after external beam radiation therapy (EBRT) in rectal cancer patients unfit for surgery - found a significant increase in patient-reported bowel symptoms during EBRT and during brachytherapy until 2 weeks after end of treatment but similar patient-reported bowel symptoms to baseline at 2, 6, and 12 months after treatment [44]. Because bowel continuity was preserved in a low number of patients, our LARS data are based on small patient numbers and need to be interpreted with caution.

The RECTAL-BOOST was a pragmatic trial within PLCRC according to the TwiCs design, which has specific strengths and risks of bias. According to the TwiCs design, randomized trials are implemented within a cohort, which promotes efficiency and limits selective patient inclusion. A previous publication showed good comparability of the RECTAL-BOOST participants to LARC patients in the Dutch National Cancer Registry, supporting generalizability of our results [45].

In TwiCs, like in classic randomized controlled trials, the effect of the intervention may be diluted when many patients do not receive the assigned treatment. In TwiCs, patients are given the option to refuse the experimental intervention, which may lead to more dilution in the intervention arm than in the control arm (where patients are unaware of being part of a trial and all undergo the standard treatment). In the RECTAL-BOOST trial, the intervention acceptance rate was reasonably high (n=51 of 64, 80%). To prevent underestimation of the effect of dose-escalated CRT on QoL, per-protocol analysis was performed for PRO comparison.

The RECTAL-BOOST trial was not blinded. Owing to the inherent subjective nature of PROs, QoL of the boost group could have been affected by patient perception of the treatment (i.e., information bias) [46]. Control patients were not notified of being in the control group, so PROs of the control group could not have been affected by information/disappointment bias [47]. The boost group may have expected more toxicity, which could have led to overestimation of the effect of dose-escalated CRT on QoL.

Despite randomization, a bigger proportion of patients had LAR (41% vs 33%) or a WW strategy (22% vs 14%), and a smaller proportion of patients had abdominoperineal resection (33% vs 50%) in the boost compared with the control group. Because abdominoperineal resection has been associated with a bigger (negative) effect on QoL than LAR, this imbalance could have led to underestimation of the effect of dose-escalated CRT on QoL [48,49].

Lastly, the responses to the sexuality items of the EORTC CR-29 were too low to be presented. Those results would have been of interest because sexual dysfunction is a possible late toxicity of rectal cancer treatment [8]. Otherwise, our response rates were reasonably high. By applying a mixed model, only the few patients who replied to none of the questionnaires (n=4 of 115, or 3% of the per-protocol population) were excluded from PRO analysis, minimizing the risk of bias due to missing data [50].

Conclusion

Our results show that dose-escalated CRT has a considerable effect on QoL and symptoms at 3 and 6 months after treatment, that largely resolves thereafter. Dose-escalated CRT did not affect DFS at 2 years. Since the intervention did not improve pCR rate and does negatively impact QoL, the boost strategy as used in the RECTAL-BOOST trial is not recommended. Patients willing to participate in future trials on dose-escalated radiotherapy for rectal cancer should be counselled on the transient but considerable effect on QoL and symptoms.

References

1. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl_4):iv22-iv40.
2. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? Br J Surg 1982;69:613-616.
3. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev 2012;12 CD008368.
4. Guillem JG, Chessin DB, Cohen AM, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005;241:829-836 ; discussion 836-838.
5. Valentini V, Van Stiphout RGPM, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011;29:3163-3172.
6. Couwenberg AM, Burbach JPM, van Grevenstein WMU, et al. Effect of neoadjuvant therapy and rectal surgery on health-related quality of life in patients with rectal cancer during the first 2 years after diagnosis. Clin Colorectal Cancer 2018;17:e499-e512.
7. Juul T, Ahlberg M, Biondo S, et al. Low anterior resection syndrome and quality of life: An international multicenter study. Dis Colon Rectum 2014;57:585-591.
8. Marijnen CAM, van de Velde CJH, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial. J Clin Oncol 2005;23:1847-1858.
9. Pachler J, Wille-Jørgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2012;12 CD004323.
10. Pieniowski EHAA, Nordenvall C, Palmer G, et al. Prevalence of low anterior resection syndrome and impact on quality of life after rectal cancer surgery: Population-based study. BJS Open 2020;4:935-942.
11. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:501-513.
12. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of life in rectal cancer patients after chemoradiation. Dis Colon Rectum 2017;60:1032- 1040.
13. Haak HE, Maas M, Lambregts DMJ, et al. Is watch and wait a safe and effective way to treat rectal cancer in older patients? Eur J Surg Oncol 2020;46:358-362.
14. Dizdarevic E, Frøstrup Hansen T, Pløen J, et al. Long-term patient-reported outcomes after high-dose chemoradiation therapy for nonsurgical management of distal rectal cancer. Int J Radiat Oncol Biol Phys 2020;106:556-563.

15. Burbach MPM, Verkooijen HM, Intven M, et al. RandomizEd controlled trial for pre-operAtive dose-escaLation BOOST in locally advanced rectal cancer (RECTAL BOOST study): Study protocol for a randomized controlled trial. Trials 2015;16(1):58. https://doi.org/ 10.1186/s13063-015-0586-4.
16. Couwenberg AM, Burbach JPM, Berbee M, et al. Efficacy of Dose-Escalated Chemoradiation on Complete Tumour Response in Patients with Locally Advanced Rectal Cancer (RECTAL-BOOST): A Phase 2 Randomized Controlled Trial. Int J Radiat Oncol Biol Phys June 2020 June 2020. https://doi.org/10.1016/j.ijrobp.2020.06.013.
17. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncol (Madr) 2016;55(11):1273-1280. https://doi.org/ 10.1080/0284186X.2016.1189094.
18. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: Introducing the "cohort multiple randomised controlled trial" design. BMJ 2010;340:963-967.
19. Van De Poll-Franse LV, Horevoorts N, EenbergenVan M, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: Scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer 2011;47(14):2188-2194. https://doi.org/10.1016/j.ejca.2011.04.034.
20. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.
21. Whistance RN, Conroy T, Chie W, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 2009;45:3017-3026.
22. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: Development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 2012;255:922-928.
23. Fokas E, Glynne-Jones R, Appelt A, et al. Outcome measures in multimodal rectal cancer trials. Lancet Oncol 2020;21:e252-e264.
24. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D BA, (on behalf of the EORTC Quality of Life Group). The EORTC QLQ-C30 Scoring Manual (3rd Ed). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
25. Bonnetain F, Fiteni F, Efficace F, Anota A. Statistical challenges in the analysis of health-related quality of life in cancer clinical trials. J Clin Oncol 2016;34:1953-1956.
26. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York: Academic Press; 1977 Revised ed.
27. Couwenberg AM, Burbach JPM, Intven MPW, et al. Health-related quality of life in rectal cancer patients undergoing neoadjuvant chemoradiation with delayed surgery versus short-course radiotherapy with immediate surgery: A propensity score-matched cohort study. Acta Oncol (Madr) 2019;58:407-416.

28. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. Lancet Oncol 2010;11:835-844.
29. Valentini V, Gambacorta MA, Cellini F, et al. The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer. Radiother Oncol 2019;134:110- 118.
30. Camilleri-Brennan J, Steele RJC. The impact of recurrent rectal cancer on quality of life. Eur J Surg Oncol 2001;27:349-353.
31. Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, et al. MRI/linac integration. Radiother Oncol 2008;86:25-29.
32. Intven MPW, de Mol van Otterloo SR, Mook S, et al. Online adaptive MR-guided radiotherapy for rectal cancer; feasibility of the workflow on a 1.5T MR-linac: Clinical implementation and initial experience. Radiother Oncol 2021;154:172-178.
33. Hoendervangers S, Burbach JPM, Lacle MM, et al. Pathological complete response following different neoadjuvant treatment strategies for locally advanced rectal cancer: A systematic review and meta-analysis. Ann Surg Oncol 2020;27:4319-4336.
34. Kosmala R, Fokas E, Flentje M, et al. Quality of life in rectal cancer patients with or without oxaliplatin in the randomised CAO/ARO/ AIO-04 phase 3 trial. Eur J Cancer 2021;144:281-290.
35. Azria D, Doyen J, Jarlier M, et al. Late toxicities and clinical outcome at 5 years of the ACCORD 12/0405-PRODIGE 02 trial comparing two neoadjuvant chemoradiotherapy regimens for intermediate risk rectal cancer. Ann Oncol 2017;28:2436-2442.
36. Appelt AL, Pløen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study. Lancet Oncol 2015;16:919-927.
37. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):123-129.
38. Leiper K, Morris AI. Treatment of radiation proctitis. Clin Oncol 2007;19:724-729.
39. Vanneste BGL, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: Tricks to prevent and treat. Int J Colorectal Dis 2015;30:1293-1303.
40. Quezada-Diaz FF, Smith JJ, Jimenez-Rodriguez RM, et al. Patient-reported bowel function in patients with rectal cancer managed by a watch-and-wait strategy after neoadjuvant therapy: A case-control study. Dis Colon Rectum 2020;63:897-902.
41. van der Sande, M. , Maas, M. , Melenhorst, J. , Breukink, S. , van Leerdam, M. & Beets, G. (9000). Predictive Value of Endoscopic Features for a Complete Response After Chemoradiotherapy for Rectal Cancer. Annals of Surgery, Publish Ahead of Print , doi: 10.1097/ SLA.0000000000003718.
42. Bregendahl S, Emmertsen KJ, Lous J, Laurberg S. Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: A population-based cross-sectional study. Color Dis 2013;15:1130-1139.

43. Kuku S, Fragkos C, Mccormack M, Forbes A. Radiation-induced bowel injury: The impact of radiotherapy on survivorship after treatment for gynaecological cancers. Br J Cancer 2013;109:1504-1512.
44. Rijkmans EC, van Triest B, Nout RA, et al. Evaluation of clinical and endoscopic toxicity after external beam radiotherapy and endorectal brachytherapy in elderly patients with rectal cancer treated in the HER-BERT study. Radiother Oncol 2018;126(3):417-423. https://doi.org/ 10.1016/j.radonc.2017.12.023.
45. Couwenberg AM, Burbach JPM, May AM, Berbee M, Intven MPW, Verkooijen HM. The trials within cohorts design facilitated efficient patient enrolment and generalizability in oncology setting. J Clin Epidemiol 2020;120:33-39. https://doi.org/10.1016/j.jclinepi.2019.12.015.
46. Roydhouse JK, Fiero MH, Kluetz PG. Investigating potential bias in patient-reported outcomes in open-label cancer trials. JAMA Oncol 2019;5:457-458.
47. Young-Afat DA, Verkooijen HAM, Van Gils CH, et al. Staged-informed consent in the cohort multiple randomized controlled trial design. Epidemiology 2016;27:389-392.
48. Guren MG, Eriksen MT, Wiig JN, et al. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. Eur J Surg Oncol 2005;31:735-742.
49. Konanz J, Herrle F, Weiss C, Post S, Kienle P. Quality of life of patients after low anterior, intersphincteric, and abdominoperineal resection for rectal cancer - A matched-pair analysis. Int J Colorectal Dis 2013;28:679-688.
50. Bell ML, Fairclough DL. Practical and statistical issues in missing data for longitudinal patient-reported outcomes. Stat Methods Med Res 2014;23:440-459.

Chapter 5

Most patients reported positively or neutrally of having served as controls in the trials within cohorts design

Maaike E. Verweij, Roxanne Gal, J. P. Maarten Burbach, Danny A. Young-Afat, Joanne M. van der Velden, Rieke van der Graaf, Anne M. May, Clare Relton, Martijn P.W. Intven and Helena M. Verkooijen

Journal of Clinical Epidemiology. 2022; 148: 39-47

Abstract

Aim

To evaluate patients' experience of having served as controls without a notification at the time of randomization in the context of the trial within cohorts (TwiCs) design.

Methods

Patients were asked for their opinion on having served as controls in TwiCs, before and after having been provided the trial results. Patients had provided broad consent to randomization at cohort entry and had served as controls in one of two TwiCs (an exercise program after breast cancer treatment or radiotherapy dose-escalation for rectal cancer).

Results

Two to 6 years after cohort entry, 15% (n=16) of all patients remembered having provided broad consent to randomization. Before disclosure of trial results, 47% (n=52) of patients thought positively, 45% (n=50) neutrally, and 2% (n=2) negatively of having served as controls in one of the two trials. Seventeen percent (n=18) of patients were positive, 65% (n=71) neutral, and 11% (n=12) negative about not having been notified when serving as controls. The survey results were comparable after disclosure of trial results.

Conclusion

These results support the use of the TwiCs design with the staged-informed consent procedure. Keeping patients engaged and aware of the consents provided might further improve patients' experience of serving as controls in TwiCs.

Introduction

Trials within cohorts (TwiCs) is a relatively new study design that offers an efficient alternative to classic randomized controlled trials (RCTs) for evaluating effectiveness of interventions [1]. The TwiCs design uses a prospective cohort study in which (multiple) pragmatic randomized trials may be embedded. For each trial, eligible patients are identified from the cohort and randomized into the intervention or the control group (Figure 1). Patients randomized to the intervention group are offered the experimental intervention, which they can accept or decline. Patients in the control group receive care as usual and are not explicitly informed about serving as controls in a trial. Their outcome measurements are routinely collected within the cohort and compared to outcomes of patients allocated to the intervention group.

While in TwiCs, the intervention is offered to patients after having been randomized to the intervention group, patients in classic RCTs provide consent to receiving the experimental intervention before randomization. Slow recruitment into classic RCTs is a common problem. Reasons why patients decline RCT participation include information overload and an aversion against their treatment being decided by chance [2,3]. Many patients who agree to participate in classic RCTs hope to be allocated to the experimental treatment arm. In these cases, allocation to the control arm may lead to disappointment bias, drop out after randomization, and crossover between study arms. TwiCs have been shown to be less susceptible to slow recruitment, crossover between treatment arms, and drop out after randomization to the control group than classic RCTs [4-8].

Several studies following the TwiCs design apply the staged-informed consent procedure (also known as two-stage consent) [9,10]. In the first stage, patients are asked for cohort participation, that is, consent to collection of medical data and study measurements such as patient-reported outcomes (PROs). In addition, patients are asked for broad consent to randomization (Figure 1). Here, patients consent to (a) randomization to future TwiCs, (b) being offered an intervention if selected for the intervention group, and (c) not being notified if selected for the control group. In a later stage, a trial-specific consent is sought from patients randomized to the intervention group of TwiCs.

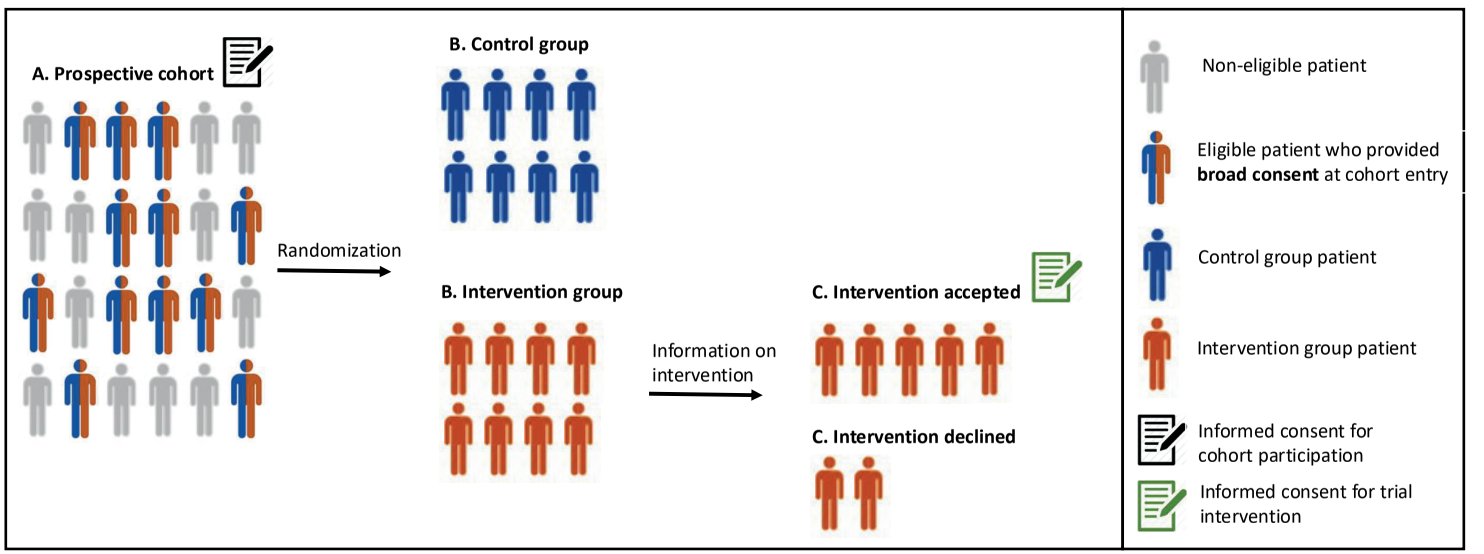


Figure 1. Trial within cohorts (TwiCs) design with the staged-informed consent procedure. Eligible patients who provided broad consent to randomization are selected from the cohort (A) and randomized into the control or the intervention group (B). Patients of the intervention group who accept the intervention are asked to sign a second trial-specific informed consent (C).

Introduction of the TwiCs design has led to discussions on the ethics of patients serving as controls without a notification at the time of randomization [10-12]. In a previous survey among cohort participants, we evaluated the acceptability of hypothetically serving as controls without an explicit notification [13]. Only 2% (n=2/62) of cohort participants stated they would experience negative emotions if their data would be used comparatively without their explicit knowledge. Currently, four TwiCs using the staged-informed consent procedure have been completed at the imaging and oncology division of the University Medical Centre Utrecht [14-17]. We performed a cross-sectional survey to evaluate how patients experienced effectively having served as controls without a notification at the time of randomization in two of these TwiCs.

Methods

Study population

This cross-sectional survey was conducted among patients with breast or rectal cancer who had served as controls in two TwiCs, that is, the UMBRELLA Fit and the RECTAL-BOOST trial [14,15,18,19]. The UMBRELLA Fit trial included 260 patients from the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaLuAtion (UMBRELLA) between October 2015 and February 2018 [20]. Patients treated for breast cancer who had a physically inactive lifestyle as assessed by cohort questionnaires at 12 to 18 months after treatment were randomized 1:1 to either standard follow-up or a 12-week exercise program. The primary end point of UMBRELLA Fit was quality of life (QoL) at 18 or 24 months after cohort enrolment.

The RECTAL-BOOST trial included 128 patients enrolled in the Dutch Prospective ColoRectal Cancer cohort (PLCRC) between September 2014 and July 2018 [21]. Patients with locally advanced rectal cancer were randomized 1:1 to standard neoadjuvant chemoradiation (CRT, 50 Gy in 25 fractions with concurrent fluorouracil-based chemotherapy) or dose-escalated CRT (standard CRT preceded by a radiotherapy boost of 15 Gy in five fractions). The primary end point was pathological complete response (pCR).

Vital status at the time of the survey was identified through the municipality registry. Patients who had withdrawn consent for cohort participation and/or broad consent to randomization and invitation to future studies were excluded.

The medical ethics committee of the University Medical Centre Utrecht approved study protocols for the UMBRELLA cohort, the UMBRELLA Fit trial, the PLCRC cohort, and the RECTAL-BOOST trial and waived the need for an ethical review of the present study.

Survey

A questionnaire was developed by a local team of epidemiologists, clinicians, and a medical ethicist. Some questions were adapted from a previous survey on understanding and acceptance of the TwiCs design, as designed by the same team [13]. Survey responses were not linked to clinical patient characteristics, allowing patients to freely express their honest opinions. The survey consisted of four questions on basic demographics and four questions about the experience of having served as controls in TwiCs without a notification at the time of randomization. The latter four questions were answered both before and after the trial results had been disclosed. Because the survey was conducted online, we ensured that patients were only able to read the trial results after having provided their opinion on having served as controls in TwiCs.

Control patients of the UMBRELLA Fit trial were informed that women in the intervention group were offered an exercise program, and that the intervention group reported comparable QoL, but less fatigue compared to women in the control arm. Control patients of the RECTAL-BOOST trial were informed that the boost intervention did not result in an improved pCR rate as compared to standard CRT and that patients treated with a radiation boost showed increased tumour regression and experienced more mild-moderate acute toxicity, such as transient diarrhoea.

A draft survey was first piloted among 10 UMBRELLA Fit and 10 RECTAL-BOOST patients. Pilot patients who provided their contact details were called to gauge their understanding of the survey. Based on the pilot study, a response option was added to the question whether and when patients would appreciate a reminder for the broad consent provided (i.e., one-time reminder 6 months after cohort entry). The definitive survey was then sent out to other eligible control patients. The survey was conducted between October 2020 and January 2021. Patients were first informed of the survey by a postal mail and invited to the online survey in Castor Electronic Data Capture system by an e-mail a week later. An automatic reminder was sent per e-mail if patients did not complete the survey within 1 week, followed by a one-time telephonic reminder within 2 weeks.

Statistical analysis

Responses to the pilot study were included in the main results. Incompletely filled out surveys were included in the results. Responses to the survey were presented using descriptive statistics. Free text comments provided with the online survey were categorized post hoc. SPSS, version 25 and R language, version 3.6.0 were used for a statistical analysis.

Results

Of the 130 breast cancer patients who had served as controls in the UMBRELLA Fit trial, 1.5% (n=2) were deceased and 25% (n=32) had withdrawn cohort consent. The remaining 96 patients were invited to participate in this survey, 76% (n=73) of whom responded and 73% (n=70) fully completed the questionnaire. Of the 64 rectal cancer patients who had served as controls in the RECTAL-BOOST trial, 14% (n=9) had deceased, 7.8% (n=5) had withdrawn cohort consent, and 1.6% (n=1) was lost to follow-up. The remaining 49 patients were invited to participate, 76% (n=37) of whom responded and completed the questionnaire.

All UMBRELLA Fit patients were female (Table 1). The median age was 62 years (interquartile rage [IQR] 56 to 67). Fifty five percent (n=40) received higher vocational education or went to university. In the RECTAL-BOOST group, 70% (n=26) were male and the median age was 68 years (IQR 61 to 75). Forty one percent (n=15) received higher vocational education or went to university.

Before the trial results were disclosed, 71% (n=52) of UMBRELLA Fit and 54% (n=20) of RECTAL-BOOST patients answered they did not remember that they had previously provided a broad consent to randomization (Table 2); 8.2% (n=6) respectively 30% (n=11) said they remembered a part of the broad consent and 16% (n=12) respectively 11% (n=4) fully remembered having provided a broad consent. Only 5.5% (n=6) of all patients indicated they sometimes had thought about the possibility of serving as controls without an explicit notification. Ten patients commented in the free text ''I never understood the possibility of serving as control without explicit notification'' and seven patients explained ''I forgot about the broad consent provided at cohort entry, because I was occupied with my rectal/breast cancer treatment at the moment consent was asked'' (Table 3).

Table 1. Self-reported baseline characteristics of breast and rectal cancer patients in the UMBRELLA Fit and RECTAL-BOOST trials within cohorts (TwiCs)

	UMBRELLA Fit (n=73)	**RECTAL-BOOST (n=37)**
Sex = male	0	26 (70.3)
Age (median, IQR)	62 (56 to 67)	68 (61 to 75)
Year of cohort inclusion		
2014	25 (34)	0
2015	16 (22)	7 (19)
2016	16 (22)	12 (32)
2017	4 (5.5)	9 (24)
2018	0	8 (22)
I do not remember	12 (16)	1 (2.7)
Highest completed education level		
Primary, secondary, or lower vocational education	33 (45)	22 (59)
Higher vocational education or university	40 (55)	15 (41)

Data are presented as frequencies (percentage) unless stated otherwise. Abbreviations: IQR, interquartile range.

Of all patients, 47% (n=52) reported positively, 45% (n=50) neutrally, and 1.8% (n=2) negatively of having served as controls in TwiCs (Table 2). Seventeen percent (n=18) were positive, 65% (n=71) were neutral, and 11% (n=12) were negative about not having received a notification at the time of randomization. Positive opinions were accompanied by free text comments such as "I appreciate that research on rectal/breast cancer treatment is performed" in 17 patients, "I'm happy to have contributed to the treatment of future rectal/breast cancer patients" in 13 patients, and "I trust that researchers have their reasons for not notifying me [at the time of randomization] when serving as control" in three patients (Table 3). Negative opinions were illustrated by comments such as "I'm disappointed/I dislike that I was not notified of serving as control [at the time of randomization]" in six patients.

After disclosure of the trial results, 53% (n=57) of all patients thought positively, 41% (n=44) neutrally, and 0.9% (n=1) negatively of having served as controls in the UMBRELLA Fit or RECTAL-BOOST trials (Table 2). Forty three percent (n=36) were positive, 50% (n=54) neutral, and 1.9% (n=2) negative about being selected for the control group by randomization. Twenty two percent (n=23) thought

positively, 62% (n=66) neutrally, and 6.5% (n=7) negatively about not having received a notification when serving as controls in these TwiCs. Positive opinions were supported by comments such as "I understand the scientific reasons for not notifying patients [at the time of randomization] of serving as control" in seven patients and "I think it's good that I was not notified of serving as control in a trial [at the time of randomization], because I was not selected for receiving the experimental treatment either way" in three patients. On the contrary, nine patients wrote "I would rather have been notified of serving as control [at the time of randomization]".

Fifty five percent (n=59) of patients indicated that a reminder for the broad consent provided at cohort entry would have been appreciated (Table 2). This reminder would preferably be received once at 6 months after cohort enrolment by 19% (n=20), each year by 30% (n=32), and every 6 months by 6.5% (n=7). Free text comments were "I would have liked to know about the possibility of serving as control without explicit notification" in five patients, "I would have liked to be reminded of the broad consent provided at cohort entry, because my opinion might have changed in the meantime" in three patients, and "If I had remembered providing broad consent to randomization at cohort entry, I would not have indicated a negative opinion [on serving as control without explicit notification]" in one patient.

Table 2. Survey responses of breast (n=73) and rectal cancer patients (n=37) on having served as controls in the UMBRELLA Fit respectively RECTAL-BOOST trials within cohorts (TwiCs), before (question 1-4) and after (question 5-8) having been provided the trial results

1. Do you remember that you provided broad consent for future randomization to clinical trials within PLCRC/UMBRELLA without a notification if selected for the control group?		
	UMBRELLA Fit (n=73)	**RECTAL-BOOST (n=37)**
No, I do not remember	52 (71)	20 (54)
I do not remember a consent for randomization, but I do remember that I would not be notified if selected for a control group	4 (5.5)	6 (16)
I do remember a consent for randomization, but I do not remember that I would not be notified if selected for a control group	2 (2.7)	5 (14)
Yes, I remember	12 (16)	4 (11)
Other, namely…	3 (4.1)	2 (5.4)
2. Was it on our mind that you might be selected for a control group of a clinical trial within PLCRC/UMBRELLA without an explicit notification?		
	UMBRELLA Fit (n=73)	**RECTAL-BOOST (n=37)**
No, because I did not remember providing a broad consent for future randomization	47 (64)	20 (54)
No, never thought about it however I did know that it might happen	20 (27)	14 (38)
Yes, sometimes (less than once a month)	4 (5.5)	2 (5.4)
Other, namely…	2 (2.7)	1 (2.7)
3. How do you think about having served as control in a clinical trial within PLCRC/UMBRELLA?		
	UMBRELLA Fit (n=73)	**RECTAL-BOOST (n=37)**
Negative	1 (1.4)	1 (2.7)
Neutral	34 (47)	16 (43)
Positive	33 (45)	19 (51)
Other, namely…	5 (6.8)	1 (2.7)

Table 2. Continued

4. How do you think about serving as control in a clinical trial within PLCRC/ UMBRELLA without being notified?		
	UMBRELLA Fit (n=72)	**RECTAL-BOOST (n=37)**
Negative	7 (9.7)	5 (14)
Neutral	48 (67)	23 (62)
Positive	10 (14)	8 (22)
Other, namely…	7 (9.7)	1 (2.7)
5. Now you know the trial results, how do you think about having served as control in the RECTAL-BOOST/UMBRELLA Fit trial?		
	UMBRELLA Fit (n=71)	**RECTAL-BOOST (n=37)**
Negative	1 (1.4)	0
Neutral	28 (39)	16 (43)
Positive	36 (51)	21 (57)
Other, namely…	6 (8.5)	0
6. Now you know the trial results, how do you think about being selected by randomization for the control group of the RECTAL-BOOST/UMBRELLA Fit trial?		
	UMBRELLA Fit (n=70)	**RECTAL-BOOST (n=37)**
Negative	1 (1.4)	1 (2.7)
Neutral	34 (49)	20 (54)
Positive	30 (43)	16 (43)
Other, namely…	5 (7.1)	0
7. Now you know the trial results, how do you think about serving as control in the RECTAL-BOOST/UMBRELLA Fit trial without being notified?		
	UMBRELLA Fit (n=70)	**RECTAL-BOOST (n=37)**
Negative	3 (4.3)	4 (11)
Neutral	42 (60)	24 (65)
Positive	17 (24)	7 (19)
Other, namely…	8 (11)	2 (5.4)

Table 2. Continued

8. Do you think we should remind PLCRC/UMBRELLA participants of the broad consent provided for future randomization to trials within the cohort?		
	UMBRELLA Fit (n=70)	**RECTAL-BOOST (n=37)**
No	29 (41)	11 (30)
Yes, one time reminder half a year after cohort enrolment	14 (20)	6 (16)
Yes, each year	17 (24)	15 (41)
Yes, each half year	4 (5.7)	3 (8.1)
Other, namely…	6 (8.6)	2 (5.4)

Free text comments that could be provided if patients ticked the option "other, namely…" or other answer options were categorized post hoc and are displayed in Table 3.

Table 3. Post hoc categorized free text comments by breast and rectal cancer patients on their experience of having served as controls in the trials within cohorts (TwiCs) design

N=17	"I appreciate that research on rectal/breast cancer treatment is performed"
N=13	"I'm happy to have contributed to the treatment of future rectal/breast cancer patients"
N=10	"I never understood the possibility of serving as control without explicit notification"
N=9	"I would rather have been notified of serving as control [at the time of randomization]"
N=7	"I forgot about the broad consent provided at cohort entry, because I was occupied with my rectal/breast cancer treatment at the moment consent was asked"
N=7	"I understand that randomization is necessary in clinical trials"
N=7	"I'm okay with not having been notified of serving as control [at the time of randomization]"
N=7	"I understand the scientific reasons for not notifying patients of serving as control [at the time of randomization]"
N=6	"I'm disappointed / I dislike that I was not notified of serving as control [at the time of randomization]"
N=5	"I would have liked to know about the possibility of serving as control without explicit notification"
N=4	"I cannot be bothered that I did not receive a notification when my data were used comparatively"
N=3	"I trust that researchers have their reasons for not notifying me when serving as control"
N=3	"I would have liked to be reminded of the broad consent provided at cohort entry, because my opinion might have changed in the meantime"
N=3	"I think it's good that I was not notified of serving as control in a trial [at the time of randomization], because I was not selected for receiving the experimental treatment either way"
N=1	"If I had remembered providing broad consent to randomization at cohort entry, I would not have indicated a negative opinion [on serving as control without explicit notification]"

Discussion

This cross-sectional survey demonstrated that a large majority of breast and rectal cancer patients reported positively or neutrally of having served as controls without an explicit notification in TwiCs. After being informed about the trial results, only 1% reported a negative attitude toward having served as controls and 7% towards not having received a notification when serving as controls. Responses did not vary by the type of intervention, by cancer site, or by knowledge about trial results. Recollection of having given broad consent to randomization was poor (15%). A small majority of patients (55%) noted that they would have appreciated being reminded of having provided broad consent to randomization, including a reminder of the possibility that they might act as controls without an explicit notification.

Our study gives the answer to an important question regarding the TwiCs design: how do patients experience serving as controls without an explicit notification [9-12]? Following the staged-informed consent procedure, patients provide consent for each research procedure they (may) experience, and control patients have provided consent for the use of their medical data comparatively without an explicit notification at cohort entry [10,11]. It has been argued that the broad consent provided at cohort entry may be considered ethically problematic because cohort participants do not know the aims of the TwiCs in which they may serve as controls [12]. Our results show that the great majority of patients thought positively or neutrally of having served as controls without an explicit notification in TwiCs. In the free text comments, control patients often indicated altruistic motivations, for instance that they were happy to have contributed to the future of other patients with breast/rectal cancer. Patients seem to value contributing to research on their condition more than providing explicit consent for each TwiCs in which their data are used comparatively.

In our survey, 1% reported negatively of having served as controls and 7% reported a negative attitude toward not having received a notification when serving as controls. This small group of patients expressed feelings of disappointment and the wish to have been notified of serving as controls. Some respondents suggested that a negative experience could have been prevented by (regular) reminders during cohort participation of having provided broad consent to randomization. Nonetheless, it remains inherent to the TwiCs design that patients are not informed on the experimental intervention when randomized to the control group.

Correct recollection of having given broad consent to randomization was reported by only 17% of breast cancer and 11% of rectal cancer patients at two to six years after cohort enrolment. In our previous survey among cohort participants, 76% remembered having provided broad consent to randomization at 2 weeks after cohort enrolment, which dropped to 42% at one to six months after cohort enrolment [13]. The recollection of the broad consent provided decreases over time. The ethical acceptability of randomizing patients to the control group without further notice seems questionable when broad consent is not recollected.

In the PLCRC and UMBRELLA cohorts, patients are provided both written and oral information on the TwiCs design upon cohort entry. In the UMBRELLA cohort, breast cancer patients are reminded of the TwiCs design by annual newsletters and annual research participant days. The recollection rates were slightly higher in the UMBRELLA cohort, but still insufficient. A solution for the poor recollection could be found in a dynamic informed consent model. Dynamic informed consent is a concept wherein patients are actively involved in research by regular (digital) updates on the studies which use their data, together with the option to continue to participate in the study, or to opt out of the consents provided [22]. Along these lines, three patients indicated that they would have liked to be reminded of having provided broad consent at cohort entry because their opinion could have changed in the meantime. Regarding the potential use of a dynamic informed consent model, patients in two previous focus group studies reacted mostly positive [23,24]. They thought that such a model could enhance autonomous choice of research participation, improve patient engagement, and trust in researchers. Dynamic informed consent could potentially further improve recollection of having provided broad consent to randomization and patients' experience of participating in studies following the TwiCs design.

Patients' experience of serving as controls without an explicit notification might be influenced by the stakes of a trial, that is, the potential benefit of the experimental intervention given the patients' current condition. Control patients might feel more strongly to have missed an opportunity when they are informed of having served as controls in a high stakes trial. A survey among 2,004 healthy individuals from the United States showed that slightly more participants would be fine with being randomized without further notice in a low stakes trial as compared to a high stakes trial [25].

As for the stakes of our TwiCs, the UMBRELLA Fit trial showed that an exercise program after breast cancer treatment did not improve QoL but did improve patient-reported fatigue. Since control patients, after being informed of these results, still have the possibility to follow an exercise program to improve fatigue, UMBRELLA Fit can be considered a low stakes trial with positive results. The RECTAL-BOOST trial demonstrated that dose-escalated CRT did not improve pCR, which is a surrogate marker for disease-free and overall survival in rectal cancer [26]. A complete response also indicates eligibility for nonoperative management [27]. The RECTAL-BOOST could therefore be considered a high stakes trial with negative results. Other than in the survey mentioned above, the differences in stakes did not lead to differences in the experience of control patients of the UMBRELLA Fit vs. the RECTAL-BOOST trial. Based on our current findings, we see no reason to stop conducting (high stakes) TwiCs. When a high stakes TwiCs with positive results has been finished, the experience of the control patients should be evaluated.

The response rate of this survey was reasonably high (76%). Patients who responded to the questionnaire were comparable to the original trial population in terms of age and gender [14,15]. However, women of the UMBRELLA Fit control group who had a higher level of education seemed more likely to respond to this questionnaire. It remains possible that the reason why some patients did not respond to the questionnaire is correlated to a specific opinion or understanding of the TwiCs design (non-response bias).

In this study, 25% of UMBRELLA patients had withdrawn consent for cohort participation at two to five years after inclusion. As a reason for cohort withdrawal, patients often indicate that they dislike to be regularly reminded of having had breast cancer. We do not think that withdrawal of consent for participation in UMBRELLA is related to patients' opinion on having served as controls in TwiCs.

Conclusion

Our results support use of the TwiCs design with a staged-informed consent procedure. Keeping patients engaged and aware of the consents provided could further improve patients' experience of serving as controls in TwiCs.

References

1. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: Introducing the "cohort multiple randomised controlled trial" design. BMJ 2010;340:963e7.
2. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999;52:1143e56.
3. Jenkins V, Fallowfield L. Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. Br J Cancer 2000;82:1783e8.
4. van der Velden JM, Verkooijen HM, Ayoung-Afat D, Burbach JP, van Vulpen M, Relton C, et al. The cohort multiple randomized controlled trial design: a valid and efficient alternative to pragmatic trials? Int J Epidemiol 2017;46:96e102.
5. Verkooijen HML, Roes K, van Gils CH. [Cohort multiple randomized controlled trial: a solution for the evaluation of multiple interventions]. Ned Tijdschr Geneeskd 2013;157:A5762.
6. Couwenberg AM, Burbach JPM, May AM, Berbee M, Intven MPW, Verkooijen HM. The trials within cohorts design facilitated efficient patient enrollment and generalizability in oncology setting. J Clin Epidemiol 2020;120:33e9.
7. Gal R, Monninkhof EM, van Gils CH, Groenwold RHH, van den Bongard DHJG, Peeters PHM, et al. The Trials within cohorts design faced methodological advantages and disadvantages in the exercise oncology setting. J Clin Epidemiol 2019;113:137e46.
8. Viksveen P, Relton C, Nicholl J. Benefits and challenges of using the cohort multiple randomised controlled trial design for testing an intervention for depression. Trial 2017;18:308.
9. Young-Afat DA, Verkooijen HAM, Van Gils CH, van der Velden JM, Burbach JP, Elias SG, et al. Staged-informed consent in the cohort multiple randomized controlled trial design. Epidemiology 2016;27: 389e92.
10. Vickers AJ, Young-Afat DA, Ehdaie B, Kim SY. Just-in-time consent: the ethical case for an alternative to traditional informed consent in randomized trials comparing an experimental intervention with usual care. Clin Trials 2018;15:3e8.
11. Kim SYYH, Flory J, Relton C. Ethics and practice of Trials within Cohorts: an emerging pragmatic trial design. Clin Trials 2018;15: 9e16.
12. Weijer C, Goldstein CE, Taljaard M. TwiC or treat? Are trials within cohorts ethically defensible? Clin Trials 2018;15:21e4.
13. Young-Afat DADA, Gal R, Gerlich AS, Burbach JPM, van der Velden JM, van den Bongard DHJG, et al. Oncology patients were found to understand and accept the trials within cohorts design. J Clin Epidemiol 2020;130:135e42.
14. Gal R, Monninkhof EM, van Gils CH, Groenwold RHH, Elias SG, van den Bongard DHJG, et al. Effects of exercise in breast cancer patients: implications of the trials within cohorts (TwiCs) design in the UMBRELLA Fit trial. Breast Cancer Res Treat 2021;190: 89e101.

15. Couwenberg AM, Burbach JPM, Berbee M, Lacle MM, Arensman R, Raicu MG, et al. Efficacy of dose-escalated chemoradiation on complete tumor response in patients with locally advanced rectal cancer (RECTAL-BOOST): a phase 2 randomized controlled trial. Int J Radiat Oncol Biol Phys 2020;108:1008e18.
16. Pielkenrood BJ, van der Velden JM, van der Linden YM, Bartels MMT, Kasperts N, Verhoeff JJC, et al. Pain response after Stereotactic body radiation therapy versus conventional radiation therapy in patients with bone metastases: a phase 2 randomized controlled trial within a prospective cohort. Int J Radiat Oncol Biol Phys 2021;110:358e67.
17. Couwenberg AM, Burbach MJP, Smits AB, Van Vulpen M, Van Grevenstein WM, Noordzij PG, et al. The impact of retractor SPONGE-assisted laparoscopic surgery on duration of hospital stay and postoperative complications in patients with colorectal cancer (SPONGE trial): study protocol for a randomized controlled trial. Trial 2016;17:132.
18. Gal R, Monninkhof EM, Groenwold RHH, van Gils CH, van den Bongard DHJG, Peeters PHM, Verkooijen HM, et al. The effects of exercise on the quality of life of patients with breast cancer (the UMBRELLA Fit study): study protocol for a randomized controlled trial. Trial 2017;18:1e10.
19. Burbach MPM, Verkooijen HM, Intven M, Kleijnen JP, Bosman ME, Raaymakers BW, et al. RandomizEd controlled trial for preoperAtive dose-escaLation BOOST in locally advanced rectal cancer (RECTAL BOOST study): study protocol for a randomized controlled trial. Trial 2015;16:58.
20. Young-Afat DA, van Gils CH, van den Bongard HJGD, Verkooijen HM. The Utrecht cohort for multiple BREast cancer intervention studies and long-term evaLuAtion (UMBRELLA): objectives, design, and baseline results. Breast Cancer Res Treat 2017; 164:445e50.
21. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, Dik VK, May AM, Meijer GA, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncol (Madr) 2016;55:1273e80.
22. Kaye, J., Whitley, E., Lund, D. et al. Dynamic consent: a patient interface for twenty-first century research networks. Eur J Hum Genet 23, 141-146 (2015). https://doi.org/10.1038/ejhg.2014.71
23. Spencer K, Sanders C, Whitley EA, Lund D, Kaye J, Dixon WG. Patient perspectives on sharing anonymized personal health data using a digital system for dynamic consent and research feedback: a qualitative study. J Med Internet Res 2016;18:e5011.
24. Wallace SE, Miola J. Adding dynamic consent to a longitudinal cohort study: a qualitative study of EXCEED participant perspectives. BMC Med Ethics 2021;22:1e10.
25. Miller DG, Kim SYH, Li X, Dickert NW, Flory J, Runge CP, et al. Ethical acceptability of post-randomization consent in pragmatic clinical trials. JAMA Netw Open 2018;1:e186149.
26. Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835e44.

27. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Riberio U, Silva e Sousa AH, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240(4):711e8.

Chapter 6

Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial

Maaike E. Verweij, Max D. Tanaka, Chavelli M. Kensen, Uulke A. van der Heide, Corrie A. M. Marijnen, Tomas Janssen, Tineke Vijlbrief, Wilhelmina M. U. van Grevenstein, Leon M. G. Moons, Miriam Koopman, Miangela M. Lacle, Manon N. G. J. A. Braat, Myriam Chalabi, Monique Maas, Inge L. Huibregtse, Petur Snaebjornsson, Brechtje A. Grotenhuis, Remond Fijneman, Esther C. J. Consten, Apollo Pronk, Anke B. Smits, Joost T. Heikens, Hidde Eijkelenkamp, Sjoerd G. Elias, Helena M. Verkooijen, Maartje M. C. Schoenmakers, Gert J. Meijer, Martijn P. W. Intven and Femke P. Peters

British Medical Journal Open. 2023; 13: e065010

Abstract

Aim

Organ preservation is associated with superior functional outcome and quality of life (QoL) compared with total mesorectal excision (TME) for rectal cancer. Only 10% of patients are eligible for organ preservation following short-course radiotherapy (SCRT, 25 Gy in five fractions) and a prolonged interval (4-8 weeks) to response evaluation. The organ preservation rate could potentially be increased by dose-escalated radiotherapy. Online adaptive magnetic resonance-guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable radiotherapy dose-escalation. This trial aims to establish the maximum tolerated dose (MTD) of dose-escalated SCRT using online adaptive MRgRT.

Methods

The preRADAR is a multicentre phase I trial with a 6+3 dose-escalation design. Patients with intermediate risk rectal cancer (cT3c-d(MRF-)N1M0 or cT1-3(MRF-)N1M0) interested in organ preservation are eligible. Patients are treated with a radiotherapy boost of 2×5 Gy (level 0), 3×5 Gy (level 1), 4×5 Gy (level 2) or 5×5 Gy (level 3) on the gross tumour volume in the week following standard SCRT using online adaptive MRgRT. The trial starts on dose level 1. The primary endpoint is the MTD based on the incidence of dose-limiting toxicity (DLT) per dose level. DLT is a composite of maximum one in nine severe radiation-induced toxicities and maximum one in three severe postoperative complications, in patients treated with TME or local excision within 26 weeks following start of treatment. Secondary endpoints include the organ preservation rate, non-dose-limiting acute radiation-induced toxicity and postoperative complications, oncological outcomes, patient-reported QoL and functional outcomes up to 2 years following start of treatment. Imaging and laboratory biomarkers are explored for early response prediction.

Ethics and dissemination

The trial protocol has been approved by the Medical Ethics Committee of the University Medical Centre Utrecht. The primary and secondary trial results will be published in international peer-reviewed journals.

Introduction

Introduction of the multimodal treatment consisting of neoadjuvant (chemo) radiotherapy and total mesorectal excision (TME) has improved oncological outcomes for patients with rectal cancer in the previous decades [1,2]. Multimodal treatment unfortunately is associated with long-term impaired quality of life (QoL) and bowel, urinary and sexual dysfunction [3,4]. In recent years, organ preservation has become possible for patients with rectal cancer who reach a (near) clinical complete response (cCR) after neoadjuvant (chemo)radiotherapy: patients with minimal or no residual tumour on physical examination, endoscopy and MRI after neoadjuvant treatment can be managed by local excision (LE) and/or active surveillance instead of TME [5]. When performed in appropriately selected patients, organ preservation has similar oncological outcomes as TME [6]. Since the morbidity of TME is averted, including the formation of an ostomy, organ preservation is associated with superior QoL and functional outcome [7,8].

The majority of patients with rectal cancer would rather opt for organ preservation than TME [9,10]. The chance of reaching a cCR and therewith eligibility for organ preservation depends on the neoadjuvant treatment schedule and the timing of response evaluation, among other clinical factors [11-13]. The standard neoadjuvant treatment for intermediate risk rectal cancer according to the Dutch guideline (cT3c-d[MRF-]N0M0 and cT1-3[MRF-]N1M0) is short-course radiotherapy (SCRT, 25 Gy in five fractions) [14]. After SCRT and an interval of 4-8 weeks, the complete response rate is approximately 10% [15]. This rate is low compared with complete response rates of approximately 16% following chemoradiation (CRT, 50 Gy in 25 fractions with a radiosensitiser) for locally advanced rectal cancer (LARC), 28% following SCRT and neoadjuvant systemic therapy for LARC in the RAPIDO trial, 28% following CRT and neoadjuvant systemic therapy in the PRODIGE23 trial, and even 60% of organ preservation at 3 years following CRT and neoadjuvant systemic consolidation therapy in the OPRA trial [16-19].

Table 1. Overview of previous studies on dose-escalated short course radiotherapy (SCRT) for rectal cancer

Study	Design	Patients	Treatment
Guckenberger, Radonc 2009 [22]	One-arm phase II, 2000-2007	cT2-4N0-2M0-1 (n=118)	SCRT of total 29 Gy in twice daily fractions of 2.9 Gy followed by immediate TME and adjuvant chemotherapy if pathology UICC stage ≥II
Bujko, Radonc 2013 [23]	Semi-randomized two-arm phase II, 2003-2010	cT1-3N0M0 and maximum tumour diameter ≤ 4 cm (n=89)	SCRT plus 4 Gy boost (n=64) vs. CRT of 50 Gy in 31 fractions plus 5 Gy boost with 5-FU and leucovorin (n=25) followed by LE. ypT2 or higher proceeded to TME.
Faria, Col Dis 2014 [24]	One-arm phase II, 2008-2011	cT3-4N0-2 or cT2N0-2 (n=52)	SCRT with integrated boost up to a total of 30 Gy and TME at 8 weeks [a]
Chakrabarti, AoO 2020 [25]	One-arm phase II, 2018-2018.	UICC stage II-II (n=43)	SCRT of 30 Gy in 6 fractions and two cycles of CapOx followed by TME at 6-8 weeks [a]

Significant differences (P < .05) are marked with an asterisk. A: after completion of SCRT. Abbreviations: cTNM, clinical tumour, nodal metastasis stage; SCRT, short course radiotherapy; TME, total mesorectal excision; UICC, Union for International Cancer Control;

Besides addition of neoadjuvant systemic therapy, escalation of the irradiation dose could well be another viable strategy to render more patients eligible for organ preservation after SCRT. The positive relationship between the irradiation dose and the tumour response is well recognised [20]. Meta-analysis demonstrated that dose-escalated CRT (with a total dose of ≥54 Gy) is associated with a relatively high pooled pathological complete response rate of 24% in LARC [21]. Dose-escalated SCRT has been investigated by only four trials (Table 1) [22-25].

	Acute radiation-induced toxicity	Postoperative complications	Tumour response	Comments
	Maximum Grade 1	Any complication: 27/118 (23%) Reoperation: n=18/118 (15%) Postoperative mortality: n=4/118 (3%)	ypT1 n=8/118 (7%) ypN0 n=53/118 (45%)	
	Grade 3: n=1/64 (2%) vs. n=2/25 (8%)	Any complication following LE: n=12/64 (19%) vs. n=8/25 (32%)	pCR: n=23/64 (36%) vs. n=16/25 (64%) * ypT0-1: n=43/64 (67%) vs. n=20/25 (80%)	Study was terminated early due to poor accrual. Patients with poor performance status were only eligible for SCRT arm. 17 patients (27%) did not receive the boost in the SCRT arm.
	Grade 3: n=4/52 (8%)	Reoperation: 1/52 (2%) Postoperative mortality: 1/52 (2%)	pCR: 5/52 (10%)	
	Grade 3-4: n=5/43 (12%)		pCR n=8/43 (18%)	

ypTNM, pathological tumour, nodal metastasis stage after neoadjuvant treatment and surgery; CRT, chemoradiation; 5-FU, 5-fluoro-uracil based chemotherapy; LE, local excision; pCR , pathological complete response; CapOx, capecitabine and oxaliplatin.

An important limiting factor for dose-escalating SCRT is the risk of radiation-induced toxicity. Recently, online adaptive resonance-guided radiotherapy (MRgRT) on a magnetic resonance linear accelerator (MR-Linac) has been implemented in clinical care [26,27]. In contrast to conventional radiotherapy, MRgRT allows for online visualisation of the tumour and surrounding organs at risk (OARs) on MRI during treatment and adaptation of the treatment plan to the current anatomy at each treatment fraction. This technique has unprecedented

accuracy and lowers the dose to the healthy tissues [28-30]. As a consequence, online adaptive MRgRT is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.

Adequate patient selection for dose-escalation is important, as some patients will experience radiation-induced toxicity and delay of surgery without the benefit of achieving a cCR. No biomarkers are currently clinically available for prediction of the response to radiotherapy. However, predictive value for the response to radiotherapy has been demonstrated for several biomarkers in blood, tissue, faeces and on MRI [31-33]. These biomarkers could potentially aid in response-based adaptation of the treatment plan. The current trial includes exploratory analyses of blood, faecal and tissue samples and (quantitative) MRI, in order to prepare for a response-adaptive dose-escalation strategy.

In conclusion, the rationale for the current trial is to offer patients with intermediate risk rectal cancer a higher chance of organ preservation using dose-escalated, online adaptive MRgRT on an MR-Linac. We designed a phase I trial to determine the maximum tolerated dose (MTD) of dose-escalated SCRT. The MTD is based on the incidence of dose-limiting toxicity (DLT), that is, acute radiation-induced toxicity and postoperative complications. The MTD will be the recommended dose for a subsequent phase II trial that will evaluate the efficacy of dose-escalated SCRT on the organ preservation rate. Meanwhile, imaging and laboratory biomarkers are explored for early prediction of the response to radiotherapy. This trial is the first step towards Response ADAptive Radiotherapy for organ preservation for rectal cancer: the preRADAR trial.

Methods

Study design

The preRADAR trial is a phase I multicentre trial that follows the 6+3 dose-escalation design. The trial is conducted at the University Medical Centre (UMC) Utrecht and the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, both in the Netherlands. A minimum of 6 and a maximum of 45 patients will be recruited. Participant enrolment has started in November 2021 and is expected to finish by February 2024. Follow-up for the primary endpoint is expected to finish by August 2024.

Objectives

The primary objective is to establish the MTD of dose-escalated SCRT in patients with intermediate risk rectal cancer. Secondary objectives are to determine non-dose-limiting acute radiation-induced toxicity, the 30-day and 90-day postoperative complication rate, the organ preservation rate at 6, 12 and 24 months, oncological outcomes at 24 months, patient-reported QoL and functional outcomes at 3, 6, 12, 18 and 24 months. The exploratory objective is to seek imaging and laboratory biomarkers that are predictive for the response to radiotherapy at an early stage of treatment.

Study population

Adult patients (≥18 years old) presenting to the participating centres with (1) biopsy-proven rectal adenocarcinoma, (2) classified as intermediate risk according to the Dutch guideline (cT3c-d[MRF-]N0M0 or cT1-3[MRF-]N1M0 based on the American Joint Committee on Cancer eighth edition) [14], (3) referred for neoadjuvant SCRT, (4) distal or midrectal tumour location (the upper border of the rectal tumour below the sigmoid take-off and the lower border below the peritoneal fold) [34], (5) judged fit for multimodal treatment by multidisciplinary tumour board meeting, and (6) interest in organ preservation, are eligible.

Exclusion criteria are mucinous carcinoma or neuroendocrine neoplasms, indication for additional SCRT and TME following LE, recurrent tumour or regrowth after previous treatment, extramesorectal pathological lymph nodes, extramural venous invasion, planned systemic therapy, history of inflammatory bowel disease, prior pelvic radiotherapy, concurrent pregnancy, orthopaedic hip implants or absolute contraindication for MRI.

Patient inclusion

Eligible patients are identified during multidisciplinary tumour board meetings. Patients are informed about the preRADAR trial by their treating radiation-oncologist, in both an oral and a written manner. Patients are free to accept or decline the intervention and have at least three days to consider their decision and sign the informed consent form. Trial participation includes consent to undergo the intervention and to participate in acute toxicity monitoring. Consent to collect blood, faeces, tumour tissue, additional MRI sequences, MRI sequences with intravenous contrast (i.e., dynamic contrast-enhanced [DCE]-MRI) and filling out

QoL questionnaires are optional. Additionally, patients are asked to share their medical data within the Prospective Dutch ColoRectal Cancer cohort (PLCRC) and the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac (MOMENTUM) Study [35,36].

Treatment

The study treatment consists of a radiotherapy boost of 2×5 Gy (dose level 0), 3×5 Gy (dose level 1), 4×5 Gy (dose level 2) or 5×5 Gy (dose level 3) on the gross tumour volume (GTV) in the week following standard SCRT (Table 2). SCRT is administered on the conventional elective volumes, consisting of the mesorectum, the presacral lymph nodes and the internal iliac lymph nodes [37]. Uniform planning target volume (PTV) margins of 4 mm are applied during SCRT, except for 6 mm in the ventral direction. The boost is delivered on the GTV consisting of the tumour and suspicious lymph nodes, if present. Lymph nodes are classified as suspicious if they are (1) ≥9 mm, (2) 5-9 mm and have two out of three malignant characteristics (irregular border, heterogeneous texture or round shape), (3) <5 mm and have all three malignant characteristics (measurements are of the short axis diameter) [14]. During the boost fractions, a uniform PTV margin of 5 mm is applied. The bowel cavity, bowel loops, bladder, left and right femoral head, the vagina and lumbosacral plexus are considered OARs (Supplementary File 1). Delineation of the target volumes and OARs of both SCRT and the boost is performed on a three-dimensional T2-weighted MRI and administered with online adaptive MRgRT on a 1.5 Tesla MR-Linac.

The trial starts at dose level 1 (5×5 Gy + 3×5 Gy boost). When, after the treatment of six patients, no radiation-induced DLT and less than one in three postoperative DLTs have occurred, the study progresses to the next dose level (see the Primary endpoint section and Figure 1). When one in six radiation-induced DLTs and/or one in three postoperative DLTs has occurred, three additional patients are added to the current dose level and adverse events are reassessed accordingly. Whenever more than one in six radiation-induced DLT or more than one in three postoperative DLTs occurs, the trial is stopped and the previous dose level is considered the MTD. While awaiting the occurrence of DLT in six (or nine) patients of the current dose level, newly presenting eligible patients are included to the previous dose level. Dose level 0 has been added to the preRADAR trial so that patient inclusion can continue while awaiting whether dose level 1 is safe. Since dose level 0 (5×5 Gy +

2×5 Gy boost) has the same biological effective dose as CRT, we consider it safe without testing. If less than one in six patients had radiation-induced DLT and less than three patients have been treated with TME, additional patients are added to the current dose level until at least three patients have been treated with TME.

Table 2. Dose scheme and biological equivalent doses compared for the current standard of short-course radiotherapy and the dose levels of the preRADAR trial

	Dose scheme	Physical dose (Gy)	Tumour dose (EQD2 α/β=10, Gy)	Normal tissue dose (EQD2 α/β=3, Gy)
Current standard	5×5 Gy	25.00	31.25	40.00
Dose level 0	5×5 Gy+2×5 Gy boost	35.00	43.75	56.00
Dose level 1	5×5 Gy+3×5 Gy boost	40.00	50.00	64.00
Dose level 2	5×5 Gy+4×5 Gy boost	45.00	56.25	72.00
Dose level 3	5×5 Gy+5×5 Gy boost	50.00	62.50	80.00

Patients will not proceed to the boost if treatment-related Grade ≥3 radiation-induced toxicity or signs of sacral plexopathy are present at the end of SCRT, nor when ≥80% GTV coverage for the boost is not achievable due to nearby OARs. When a patient does not proceed to the boost, an additional patient is included to the current dose level.

Acute toxicity monitoring

Patients are consulted before the start of treatment (baseline), at the end of SCRT (week 1), after the administration of the boost (week 2), at week 3, week 4, week 5 and every other week thereafter up to surgery or week 20 (Figure 2). Toxicity is registered at each consultation for proctitis, rectal pain, rectal haemorrhage, non-infective cystitis, urinary obstruction, fatigue, radiation dermatitis and other non-prespecified toxicities according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0 [38]. Simultaneously, patients are asked to fill out a low anterior resection syndrome (LARS) score questionnaire online or in a paper diary to monitor bowel function [39].

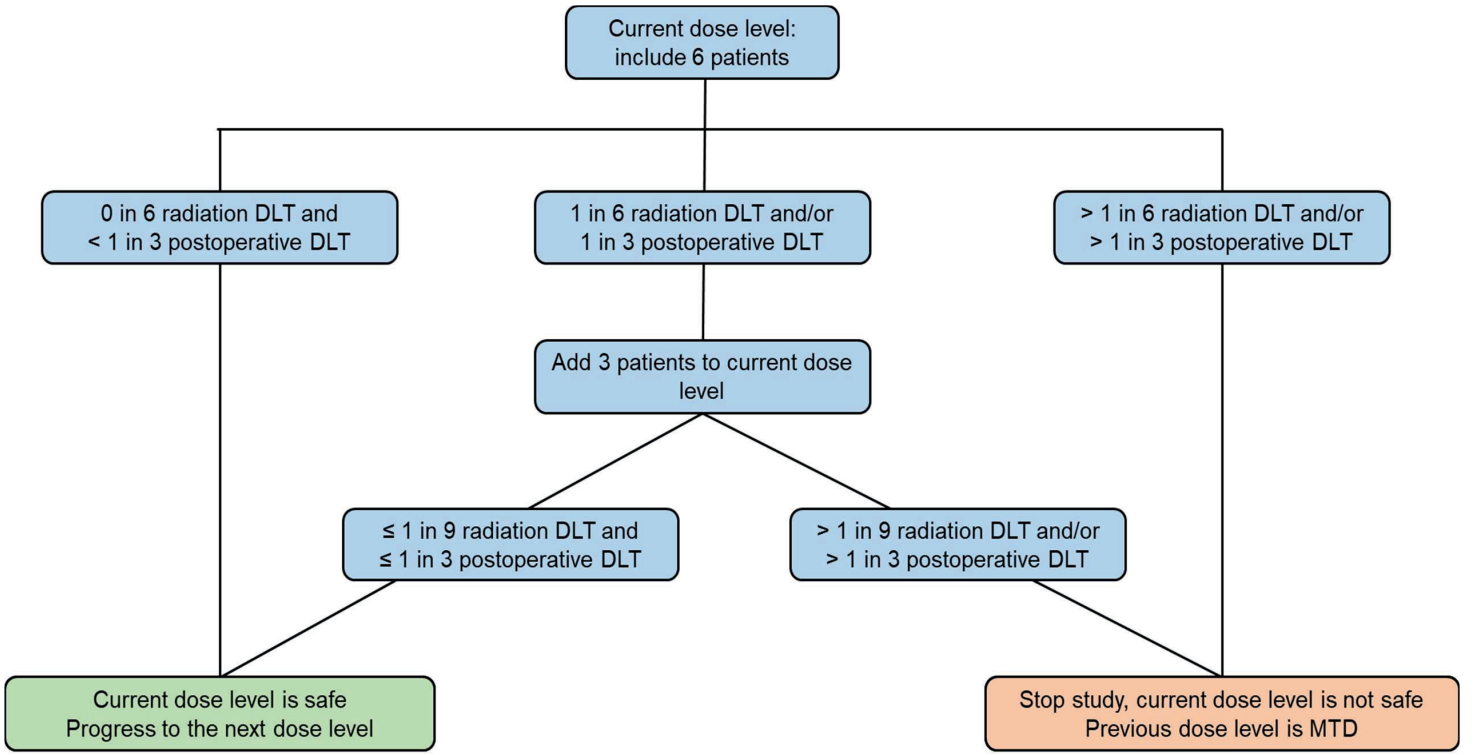


Figure 1. Study flow per dose level in the 6+3 design according to dose-limiting toxicity (DLT). Abbreviations: MTD, maximum tolerated dose.

Response evaluation

The first response evaluation is performed at 11 to 13 weeks following the start of treatment, using T2-weighted MRI, diffusion-weighted imaging (DWI) and endoscopy. A poor response at the first response evaluation is defined as downsizing of less than 50% of the maximum diameter of the primary tumour, residual tumour of more than 2 cm and/or persistent suspicious lymph nodes. Poor responders at the first response evaluation are planned for TME. All other patients proceed to the second response evaluation at 16 to 20 weeks, using T2-weighted MRI, DWI and/or endoscopy. When patients show a poor response on MRI, they may not proceed to endoscopy to avert this more invasive examination. A near-complete response is defined as minimal residual tumour without any signs of residual pathological lymph nodes, amenable for LE (ycT1N0). Near-complete responders are offered LE followed by active surveillance, or TME in case of irradical resection or >ypT1. A complete response is defined as no signs of residual tumour. Complete responders enter active surveillance. All other patients (i.e., patients with disease progression or a residual tumour not amenable for LE) are planned for TME. All patients treated with active surveillance are asked to participate in the Dutch Watch & Wait registry.

Follow-up

Patients are followed up according to local practice. In the Netherlands, follow-up after TME commonly consists of clinical consultation and carcinoembryonic antigen (CEA) measurement every three to six months during the first two years after start of treatment and every six to twelve months for the three years thereafter. Thoracoabdominal CT is performed at one year after start of treatment and on indication thereafter. For patients treated with active surveillance, the follow-up scheme consists of endoscopy and MRI every three months during the first year, every six months during the second year and every six to twelve months during year three to five after start of treatment.

Primary endpoint

The primary endpoint is the MTD based on the incidence of DLT per dose level. A maximum of either one in nine severe acute radiation-induced toxicities or one in three severe postoperative complications per dose level is considered safe.

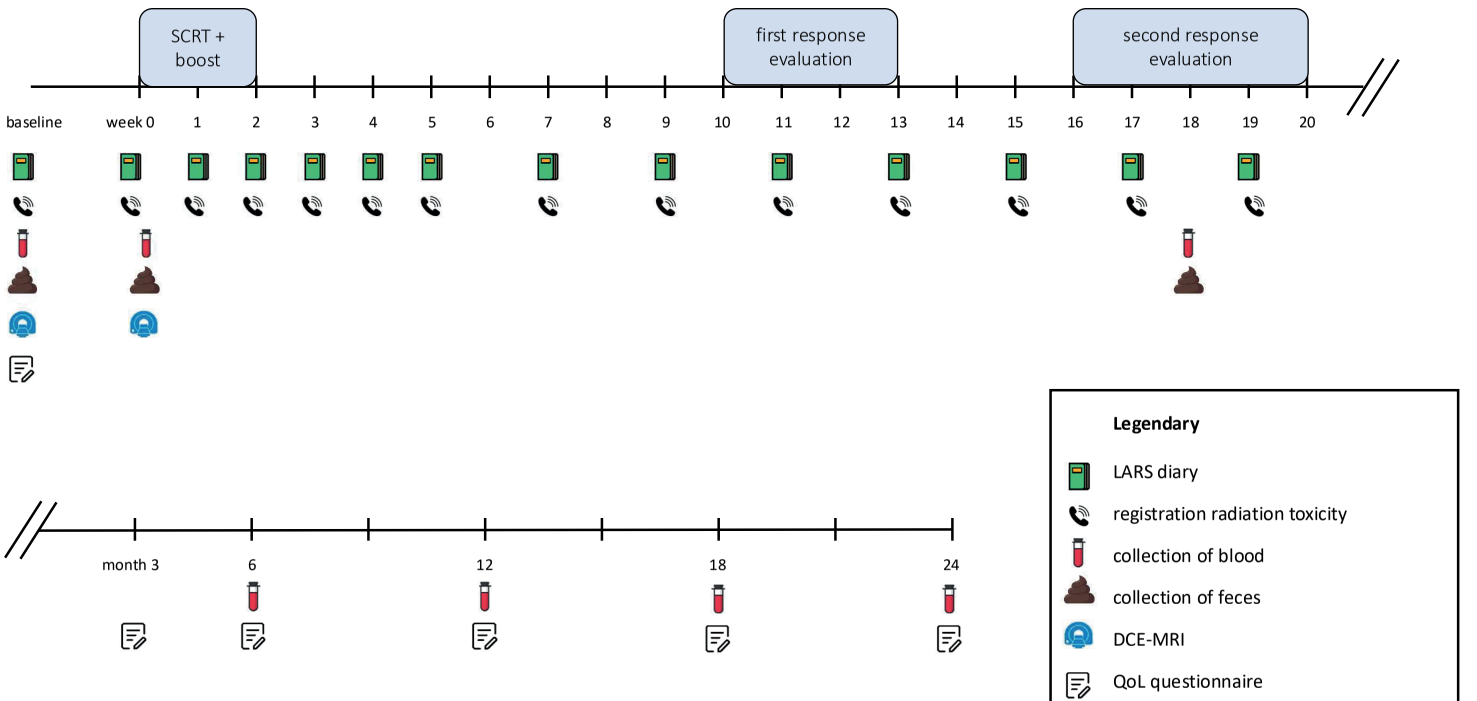


Figure 2. Patient timeline in the preRADAR trial. Abbreviations: SCRT, short-course radiotherapy, LARS, low anterior resection syndrome; DCE-MRI, dynamic contrast-enhanced MRI; QoL, quality of life.

Severe acute radiation-induced toxicity is defined as:

- Treatment-related (Supplementary File 2) Grade ≥4 radiation-induced toxicity according to the CTCAE version 5.0, occurring within 20 weeks after start of radiotherapy and before surgery [38];
- Treatment-related Grade 3 radiation-induced toxicity persisting beyond 12 weeks after start of radiotherapy;
- Postponing of surgery >20 weeks after start of radiotherapy due to any Grade of treatment-related toxicity, in patients with an insufficient response at the first and/or second response evaluation;
- In case of Grade 3-4 radiation-induced toxicity that was not prespecified, or Grade 3 radiation-induced toxicity newly occurring between 12 and 20 weeks after start of radiotherapy, the trial management team will judge if this classifies as a DLT on a case-to-case basis.

Severe postoperative complications are defined as Clavien-Dindo Grade 3b-4 complications occurring within 30 days postoperatively, in patients treated with TME or LE within 26 weeks following the start of treatment [40].

Secondary endpoints

The most important secondary endpoint is the organ preservation rate at 24 months, which is defined as an in-situ rectum, no ostomy and no residual or recurrent locoregional disease [41]. We chose this follow-up duration because 88% of local regrowths occur within the first 24 months of organ preservation [6]. Other secondary endpoints include:

- Feasibility of delivery of the boost based on GTV coverage;
- CCR and clinical near-complete response at the first and the second response evaluation;
- Non-dose-limiting acute radiation-induced toxicity as measured by the CTCAE assessments and LARS diaries up to 20 weeks following the start of treatment or, if planned earlier, up to TME [38,39];
- Non-dose-limiting 30-day and 90-day complications according to Clavien-Dindo, length of hospital stay and hospital readmittance in patients treated with TME or LE within 26 weeks following the start of treatment [40];
- Tumour regression grade on pathology according to Mandard and type and radicality of surgery in patients treated with TME and LE within 26 weeks following the start of treatment [42];

- Type and radicality of salvage surgery in patients with a local regrowth during Watch & Wait up to 24 months;
- Overall survival (OS) and disease-free survival (DFS) at 24 months [43];
- Late radiation-induced toxicity Grade ≥3 according to CTCAE version 5.0 presenting after 90 days up to 24 months;
- Patient-reported QoL and functional outcome as measured by the European Organisation of Research and Treatment of Cancer Quality of life Core and ColoRectal specific Questionnaire, LARS score, the International Index of Erectile Function, Urinary Distress Inventory, Incontinence Impact Questionnaire and McCoy Female Sexuality Questionnaire at baseline and at 3, 6, 12, 18 and 24 months following the start of treatment [39,44-48].

Translational research

Blood and faeces are collected at baseline, after the second radiotherapy fraction and at the second response evaluation. Blood is additionally collected at 6, 12, 18 and 24 months of follow-up. Blood is analysed for haematology, CEA, kidney function, albumin, C reactive protein, lactate dehydrogenase and circulating tumour DNA [31,32]. Faeces is analysed for the microbiome [33]. Tumour tissue is collected at diagnosis and at surgery. An MRI is routinely acquired pretreatment and additional sequences are acquired during the idle time of each radiotherapy fraction. In some centres, an extra MRI scan on an MR-Linac is performed pretreatment and a DCE-MRI is performed pretreatment and after the second radiotherapy fraction. The specific methodology for the translational part of the preRADAR trial is yet to be determined.

Data management and analysis

Clinical data are collected from the medical files and captured in an electronic case report form in Castor EDC. Data management details are reported in a separate data management plan. Technical treatment data are collected within the MOMENTUM cohort [36]. Patient-reported outcomes (PROs) are collected within PLCRC [35]. Human samples for translational research are stored at the Netherlands Cancer Institute.

The incidence of DLT will be calculated per dose level, excluding patients who did not proceed to the boost. Secondary toxicity outcomes are described in the same per-protocol population (i.e., non-dose-limiting radiation-induced toxicity

and postoperative complications, PROs and late radiation-induced toxicity). Secondary efficacy outcomes are described in the intention-to-treat population (i.e., organ preservation rate, feasibility of the boost, tumour regression grade, salvage surgery, OS, DFS). Outcomes will be analysed using descriptive statistics, a mixed-effects model (for PROs) or Kaplan-Meier method (for time-to-event data). Data of this phase I trial might be merged with data of the subsequent phase II trial.

Patient and public involvement

The Dutch patient federation for colorectal cancer (Stichting Darmkanker) was involved during the design phase of this trial. The definition of the primary outcome (DLT), the burden of the intervention and follow-up and the patient information leaflet were discussed with two patients. The patient federation officially declared their support for the current trial. They will remain involved during the evaluation of the results and designing the subsequent phase II trial. Patient information on the trial is displayed on the website (www.kanker.nl/trials).

Safety

A Trial Safety Committee has been appointed, consisting of an independent colorectal surgeon and a radiation-oncologist per centre. They have the right to temporarily stop the trial if any non-prespecified safety issues are of concern. If a patient dies within 20 weeks following the start of treatment or within 30 days postoperatively (in patients treated with TME or LE in 26 weeks following the start of treatment), the trial will be temporarily stopped to investigate if the event is related to the trial intervention. Serious adverse events (SAEs) that occur within 20 weeks following the start of treatment or within 30 days postoperatively, in patients treated with TME or LE within 26 weeks following the start of treatment, will be reported within 7 days of first knowledge through an online form to the Medical Ethics Committee of the UMC Utrecht. SAEs that occur after this period will be reported in the same manner if the local principal investigator considers the event to be related to the intervention.

Ethics and dissemination

This trial is designed in accordance with the 18th version of the World Medical Association Declaration of Helsinki, Good Clinical Practice and the Dutch Law. The trial protocol has been approved by the Medical Ethics Committee of the UMC

Utrecht in March 2021. The trial is registered at https://www.trialregister.nl/ (trial number NL8997). To ensure adequate data collection and confirmation to the trial protocol, an external monitor of the Netherlands Comprehensive Cancer Organisation will audit the trial two times per year. The primary and secondary trial results will be published in international peer-reviewed journals. After consent of both participating centres, sharing of pseudonymised data with other researchers within the scope of the current project is possible.

Discussion

The phase I preRADAR trial aims to establish the MTD of dose-escalated SCRT using online adaptive MRgRT in patients with intermediate risk rectal cancer, following a 6+3 dose-escalation design. Patients are treated with a boost of 2×5 Gy, 3×5 Gy, 4×5 Gy or 5×5 Gy in the week following standard SCRT on an MR-Linac. Maximum one in nine severe acute radiation-induced toxicities and one in three severe postoperative complications are accepted for a dose level to be considered safe. The MTD will be the recommended dose for the subsequent phase II RADAR trial that will evaluate the efficacy of dose-escalated SCRT using online adaptive MRgRT on the organ preservation rate.

Dose-escalated SCRT is administered as neoadjuvant monotherapy in the preRADAR trial. SCRT is the standard neoadjuvant treatment for intermediate risk rectal cancer in the Netherlands, since it is associated with similar survival and local recurrence rates as CRT, but significantly lower Grade 3-4 acute toxicity rates (risk ratio=0.13, 95% confidence interval [CI] 0.06 to 0.28, $P < .00001$) [49]. The favourable toxicity profile of SCRT is also illustrated by two recent trials on organ preservation for early rectal cancer: SCRT in the TREC trial was associated with 15% Grade ≥3 acute toxicity, while CRT in the CARTS trial came with 42% Grade ≥3 toxicity [50,51]. The two trials reported comparable organ preservation rates (64% vs 59%), although it should be acknowledged that the CARTS trial included slightly bigger tumours. The earlier GRECCAR2 and ACOSOG Z6041 trials reported acute radiation-induced toxicity Grade ≥3 rates of 20% and 39%, respectively, following CRT for organ preservation [52,53]. Based on these numbers, CRT might be considered overtreatment for inducing a cCR in intermediate risk rectal cancer.

Besides radiotherapy dose-escalation, the addition of neoadjuvant systemic therapy to (chemo)radiotherapy has been shown to achieve high complete response rates in the RAPIDO, PRODIGE23 and OPRA trials [17-19]. The study schedules came with 48%, 46% and 34% Grade ≥3 toxicity, respectively [54]. The RAPIDO and PRODIGE23 trials demonstrated improved DFS compared with CRT only as neoadjuvant strategy for LARC, but no OS benefit (yet). In the Netherlands, rectal cancer is not treated with adjuvant systemic therapy because an OS benefit never has been demonstrated following adequate TME [55]. Since patients with intermediate risk rectal cancer are at a substantially lower risk of distant metastases than LARC, the toxicity of neoadjuvant systemic therapy may not outweigh the benefits for this patient group [56]. Dose-escalated SCRT might become a more proportional strategy for improving organ-sparing probability in patients with intermediate risk rectal cancer.

The maximum incidence of DLT in the preRADAR trial was defined while thinking of the additional toxicity that patients would 'trade off' for averting TME. We believe that patients would accept mild-moderate complaints (Grade 1-2) and transient, severe complaints that limit self-care (Grade 3) in the weeks following radiotherapy as a 'trade-off' for a higher probability of organ preservation. However, long-lasting complaints that limit self-care (persisting Grade 3) as well as severe complaints that warrant hospital admission and an acute intervention (Grade 4) might outweigh the benefits of possibly omitting TME. We therefore defined DLT as acute radiation-induced toxicity Grade 4, long-lasting Grade 3 or the postponement of surgery >20 weeks due to any Grade of radiation-induced toxicity. Based on the low toxicity rate of dose-escalated SCRT in previous studies (Table 1), a 6+3 design was chosen over the classic 3+3 dose-escalation design, allowing a lower maximum incidence of radiation-induced DLT of one in nine patients instead of one in six. Furthermore, we deem it unacceptable if the intervention would significantly increase the probability of reoperation or intensive care unit admittance (Clavien-Dindo 3b-4) in patients who are treated with TME despite the study intervention. Based on an incidence of 10% to 15% complications requiring reoperation following TME, plus a sampling error (that may be bigger if fewer patients are operated upon), a dose level is considered safe when a maximum of one in three operated patients experiences postoperative complication Grade 3b-4 [57,58]. These subjective considerations for DLT were discussed with patients.

A possible limitation might be that late radiation-induced toxicity is not included as a DLT. Radiation-induced toxicity may newly occur for several years after treatment [59]. It is not feasible to include such long-term outcomes as DLT in a dose-finding trial. Studies in prostate and gynaecological cancer have shown acceptable levels of severe late radiation-induced toxicity with dosages of 80 Gy. The maximum biologically equivalent dose to late-responding healthy tissue (EQD2, α/β=3 Gy) in the preRADAR therefore does not exceed 80 Gy (Table 2) [60-62].

The number of patients in the current phase I trial will not be sufficient to answer the explorative questions. For these purposes, data will be merged with the subsequent phase II trial and possibly other rectal cancer trials of participating institutes.

Conclusion

In conclusion, the preRADAR trial will determine the MTD of dose-escalated SCRT using online adaptive MRgRT for intermediate risk rectal cancer, based on the incidence of acute radiation-induced toxicity and postoperative complications. Dose-escalated SCRT is administered as neoadjuvant monotherapy since it has a favourable toxicity profile compared to CRT and SCRT followed by systemic therapy. The maximum incidence of DLT has been defined as the additional toxicity that patients would 'trade off' for averting TME.

References

1. Heald RJ, Husband EM, Ryall RDH. The Mesorectum in Rectal cancer surgery—the clue to pelvic recurrence Br J Surg 1982;69:613-6.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total Mesorectal Excision for Resectable Rectal cancer. N Engl J Med 2001;345:638-46.
3. Marijnen CAM, van de Velde CJH, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. JCO 2005;23:1847-58.
4. Couwenberg AM, Burbach JPM, van Grevenstein WMU, et al. Effect of Neoadjuvant therapy and Rectal surgery on health-related quality of life in patients with Rectal cancer during the first 2 years after diagnosis. Clin Colorectal Cancer 2018;17:e499-512.
5. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus Nonoperative treatment for stage 0 distal Rectal cancer following Chemoradiation therapy. Ann Surg 2004;240:711-7.
6. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after Neoadjuvant treatment for Rectal cancer in the International watch & wait database (IWWD): an international Multicentre Registry study. Lancet 2018;391:2537-45.
7. Hupkens BJP, Martens MH, Stoot JH. Quality of life in Rectal cancer patients after Chemoradiation. Dis Colon Rectum 2017;60:1032-40.
8. Dizdarevic E, Frøstrup Hansen T, Pløen J, et al. Long-term patient-reported outcomes after high-dose Chemoradiation therapy for Nonsurgical management of distal Rectal cancer. Int J Radiat Oncol Biol Phys 2020;106:556-63.
9. Gani C, Gani N, Zschaeck S, et al. Organ Preservation in Rectal Cancer: The Patients' Perspective. Front Oncol 2019;9:318.
10. Couwenberg AM, Intven MPW, Burbach JPM, et al. Utility scores and preferences for surgical and organ-sparing approaches for treatment of intermediate and high-risk rectal cancer. Dis Colon Rectum 2018;61:911-9.
11. Bujko K, Partycki M, Pietrzak L. Neoadjuvant radiotherapy (5 × 5 GY): immediate versus delayed surgery. Recent Results Cancer Res 2014;203:171-87.
12. Petrelli F, Sgroi G, Sarti E, et al. Increasing the interval between Neoadjuvant Chemoradiotherapy and surgery in Rectal cancer: A meta-analysis of published studies. Ann Surg 2016;263:458-64.
13. Hoendervangers S, Couwenberg AM, Intven MPW, et al. Comparison of pathological complete response rates after Neoadjuvant short-course radiotherapy or Chemoradiation followed by delayed surgery in locally advanced Rectal cancer. Eur J Surg Oncol 2018;44:1013-7.
14. Primaire Behandeling Rectumcarcinoom - Richtlijn - Richtlijnendatabase, 2019. Available: https://richtlijnendatabase. nl/richtlijn/colorectaal_carcinoom_crc/primaire_ behandeling_ rectumcarcinoom_bij_crc.html

15. Erlandsson J, Lörinc E, Ahlberg M, et al. Tumour regression after radiotherapy for Rectal cancer - results from the randomised Stockholm III trial. Radiother Oncol 2019;135:178-86.
16. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835-44.
17. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29-42.
18. Conroy T, Bosset J-F, Etienne P-L, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:702-15.
19. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with Rectal adenocarcinoma treated with total Neoadjuvant therapy. J Clin Oncol 2022;40:2546-56.
20. Appelt AL, Pløen J, Vogelius IR, et al. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85:74-80.
21. Hearn N, Atwell D, Cahill K, et al. Neoadjuvant radiotherapy dose escalation in locally advanced Rectal cancer: a systematic review and meta-analysis of modern treatment approaches and outcomes. Clin Oncol (R Coll Radiol) 2021;33:e1-14.
22. Guckenberger M, Wulf J, Thalheimer A, et al. Prospective phase II study of preoperative short-course radiotherapy for Rectal cancer with twice daily fractions of 2.9 GY to a total dose of 29 GY--long- term results. Radiat Oncol 2009;4:67.
23. Bujko K, Richter P, Smith FM, et al. Preoperative radiotherapy and local Excision of Rectal cancer with immediate radical re-operation for poor responders: a prospective Multicentre study. Radiother Oncol 2013;106:198-205.
24. Faria S, Kopek N, Hijal T, et al. Phase II trial of short-course radiotherapy followed by delayed surgery for Locoregionally advanced Rectal cancer. Colorectal Dis 2014;16:66-70.
25. Chakrabarti D, Rajan S, Akhtar N, et al. P-14 dose escalated short-course radiotherapy in Rectal cancers: is this the way forward? Ann Oncol 2020;31:S93-4.
26. Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, et al. MRI/Linac integration. Radiother Oncol 2008;86:25-9.
27. Intven MPW, de Mol van Otterloo SR, Mook S, et al. Online adaptive MR-guided radiotherapy for Rectal cancer; feasibility of the Workflow on a 1.5t MR-Linac: clinical implementation and initial experience. Radiother Oncol 2021;154:172-8.
28. Boldrini L, Intven M, Bassetti M, et al. MR-guided radiotherapy for rectal cancer: current perspective on organ preservation. Front Oncol 2021;11:619852.

29. Eijkelenkamp H, Boekhoff MR, Verweij ME, et al. Planning target volume margin assessment for online adaptive MR-guided dose- escalation in rectal cancer on a 1.5 T MR-Linac. Radiother Oncol 2021;162:150-5.
30. Marchegiani F, Palatucci V, Capelli G, et al. Rectal sparing approach after neoadjuvant therapy in patients with rectal cancer: the preliminary results of the Resarch trial. Ann Surg Oncol 2022;29:1880-9.
31. Fischer J, Eglinton TW, Richards SJ, et al. Predicting pathological response to Chemoradiotherapy for Rectal cancer: a systematic review. Expert Rev Anticancer Ther 2021;21:489-500.
32. Morais M, Pinto DM, Machado JC, et al. ctDNA on liquid biopsy for predicting response and prognosis in locally advanced Rectal cancer: A systematic review. Eur J Surg Oncol 2022;48:218-27.
33. Yi Y, Shen L, Shi W, et al. Gut microbiome components predict response to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer: A prospective, longitudinal study. Clin Cancer Res 2021;27:1329-40.
34. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, et al. Definition of the Rectum: an international, expert-based Delphi consensus. Ann Surg 2019;270:955-9.
35. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. Acta Oncologica 2016;55:1273-80.
36. de Mol van Otterloo SR, Christodouleas JP, Blezer ELA, et al. The momentum study: an international Registry for the evidence-based introduction of MR-guided adaptive therapy. Front Oncol 2020;10:1328.
37. Valentini V, Gambacorta MA, Barbaro B, et al. International consensus guidelines on clinical target volume delineation in Rectal cancer. Radiother Oncol 2016;120:195-201.
38. USD of health and human services (institute). Common terminology criteria for adverse events (CTCAE) version 5.0. 2017.
39. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for Rectal cancer. Ann Surg 2012;255:922-8.
40. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
41. Rombouts AJM, Al-Najami I, Abbott NL, et al. Can we S ave the rectum by watchful waiting or T rans A nal microsurgery following (chemo) R adiotherapy versus T otal mesorectal excision for early RE ctal C ancer (STAR-TREC study)?: protocol for a multicentre, randomised feasibility study. BMJ Open 2017;7:19474.
42. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. clinicopathologic correlations. Cancer 1994;73:2680-6.
43. Fokas E, Glynne-Jones R, Appelt A, et al. Outcome measures in Multimodal Rectal cancer trials. Lancet Oncol 2020;21:e252-64.

44. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
45. Whistance RN, Conroy T, Chie W, et al. Clinical and Psychometric validation of the EORTC QLQ-Cr29 questionnaire Module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 2009;45:3017-26.
46. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822-30.
47. Uebersax JS, Wyman JF, Shumaker SA, et al. Short forms to assess life quality and symptom distress for urinary incontinence in women: The incontinence impact questionnaire and the urogenital distress inventory. Neurourol Urodyn 1995;14:131-9.
48. McCoy NL. The McCoy female sexuality questionaire. Qual Life Res 2000;9:739-45.
49. Zhou Z-R, Liu S-X, Zhang T-S, et al. Short-course preoperative radiotherapy with immediate surgery versus long-course chemoradiation with delayed surgery in the treatment of rectal cancer: a systematic review and meta-analysis. Surg Oncol 2014;23:211-21.
50. Verseveld M, de Graaf EJR, Verhoef C, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). Br J Surg 2015;102:853-60.
51. Bach SP, Gilbert A, Brock K, et al. Radical surgery versus organ preservation via short-course radiotherapy followed by Transanal endoscopic Microsurgery for early-stage Rectal cancer (TREC): a randomised, open-label feasibility study. Lancet Gastroenterol Hepatol 2021;6:92-105.
52. Rullier E, Rouanet P, Tuech J-J, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet 2017;390:469-79.
53. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol 2015;16:1537-46.
54. van der Valk MJM, Marijnen CAM, van Etten B, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol 2020;147:75-83.
55. Breugom AJ, Swets M, Bosset J-F, et al. Adjuvant chemotherapy after preoperative (Chemo)Radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:200-7.
56. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer. JCO 2004;22:1785-96.
57. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017;18:336-46.

58. Detering R, de Neree Tot Babberich MPM, Bos A, et al. Nationwide analysis of hospital variation in preoperative radiotherapy use for Rectal cancer following guideline revision. Eur J Surg Oncol 2020;46:486-94.
59. Joye I, Haustermans K. Early and late toxicity of radiotherapy for Rectal cancer. Recent Results Cancer Res 2014;203:189-201.
60. Pötter R, Dimopoulos J, Georg P, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in Brachytherapy of locally advanced Cervix cancer. Radiother Oncol 2007;83:148-55.
61. Mazeron R, Fokdal LU, Kirchheiner K, et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter embrace study. Radiother Oncol 2016;120:412-9.
62. Moulton CR, House MJ, Lye V, et al. Prostate external beam radiotherapy combined with high-dose-rate brachytherapy: dose-volume parameters from deformably-registered plans correlate with late gastrointestinal complications. Radiat Oncol 2016;11:1-13.

Chapter 7

General discussion

Treatment strategy

In the past, rectal cancer treatment strategy was decided based on the tumour, nodal, metastasis (TNM)-stage. Patients with a tumour of a higher oncological risk category underwent a more intensive treatment. Presently, watch-and-wait (WW) strategy in case of a clinical complete response (cCR) is a new possibility. Different neoadjuvant treatments are emerging. Patients are more often involved in choosing the rectal cancer treatment strategy.

Future: what treatment outcome matters most to the patient?

For the future, a further diversification of treatment strategies is foreseen. Patients will take the lead in rectal cancer treatment decision making. In order to guide patients through all the different treatment strategies, 'What treatment outcome matters most to you?' will become the main question during rectal cancer treatment consultation.

I want little toxicity during treatment

For patients to whom little toxicity during treatment matters most, a de-escalated treatment strategy is appropriate. The options of local excision instead of total mesorectal excision (TME) in early rectal cancer, leaving out short course radiotherapy (SCRT, 25 Gy in 5 fractions) in intermediate risk rectal cancer and swapping chemoradiation (CRT, 50 Gy in 25 fractions with a radiosensitiser) for SCRT in locally advanced rectal cancer were already discussed in the introduction (page 17-19). These strategies come with decreased acute toxicity and preserved functional outcome, but also increase the risk of disease recurrence.

However, treatment de-escalation is unlikely to result in an increased risk of disease recurrence in all patients. In the TNM staging system, no distinction is made between the lymph nodes in the mesorectal fat and the lateral lymph nodes (LLN, Figure 1) [1]. Only the lymph nodes in the mesorectal fat are excised during TME, while all locoregional lymph nodes are irradiated during (chemo)radiotherapy. The benefit in the local recurrence rate following addition of neoadjuvant (chemo) radiotherapy to TME in primary resectable node positive tumours, might have primarily been driven by irradiation of the LLN. Leaving out (chemo)radiotherapy in patients with suspected lymph nodes confined to the mesorectal fat might not compromise oncological outcome. A large Japanese cohort showed that patients

with T3-4(without involvement of the mesorectal fascia [MRF-])N0 and T1-4(MRF-) N1-2 without enlarged LLN treated with TME only had a 5-year risk of recurrence in the pelvic cavity of 2.2% and in the LLN of 1.9%, respectively [2]. Randomised trials are needed to shed light on the risks and benefits of leaving out neoadjuvant (chemo)radiotherapy in patients with primary resectable T1-4(MRF-)N1-2 without enlarged LLN.

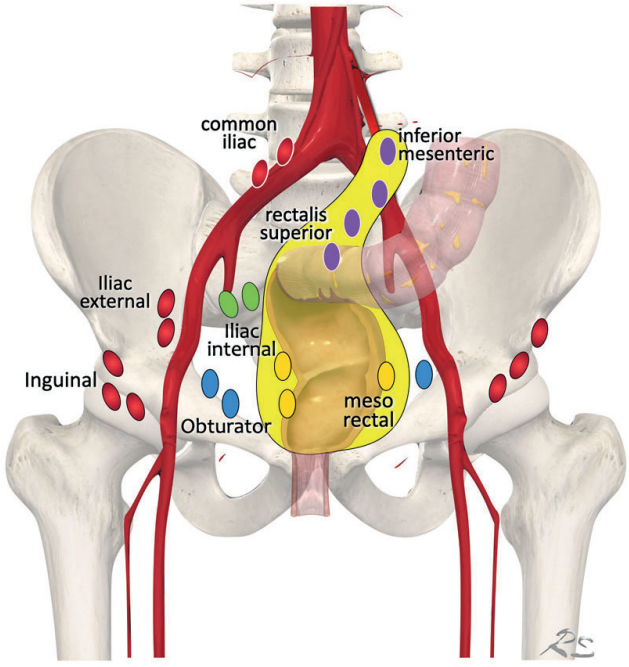


Figure 1. Suspected lymph nodes in the mesorectum and the mesocolon of the sigmoid (yellow area) as well as the lymph nodes in the obturator, internal iliac and presacral (not shown) region (lateral lymph nodes, LLN) are considered locoregional lymph nodes (N1-2). Suspected lymph nodes in the common iliac, external iliac and inguinal region (red) are considered distant metastases (M1). Only the lymph nodes in the mesorectum and the mesocolon of the sigmoid (yellow area) are excised during total mesorectal excision.

Radiation-induced proctitis is the main form of toxicity during treatment of rectal cancer **(chapter 2)**. The risk of radiation-induced proctitis is directly related to the irradiation dose on the rectum [3]. Following the line of thought that irradiation of LLN might be the primary driver of the effect of radiotherapy on

the locoregional recurrence rate, irradiating the LLN area's only and leaving out irradiation of the rectum could reduce toxicity during treatment while preserving oncological outcome in resectable T1-4a(MRF-)N1-2 with enlarged LLN.

Furthermore, healthy tissues in the rectum, mesorectum and the regional lymph node area's (clinical target volume, CTV) are currently irradiated with the same dose as the primary tumour and suspected lymph nodes (gross tumour volume, GTV) in order to treat possible micrometastases. However, a lower number of tumour cells require a lower irradiation dose to be treated effectively [4]. Clinically undetectable disease in the CTV would thus need a lower irradiation dose to be sterilised than clinical apparent disease (i.e. the GTV). Magnetic resonance guided radiotherapy (MRgRT) makes it technically feasible to irradiate the GTV with the standard dose, while reducing the dose to the CTV [5]. This concept is similar to the I-node study in head and neck cancer [6]. It would be interesting to investigate whether reduction of the radiotherapy dose to the CTV preserves oncological outcome and decreases toxicity compared to standard-dose radiotherapy.

Finally, organ preservation in case of a cCR after standard neoadjuvant treatment offers decreased toxicity during treatment, since it averts TME including possible postoperative complications. For patients to whom little toxicity during treatment matters most, the risk of acute toxicity during SCRT with a prolonged interval to response evaluation or CRT should be weighed against the 10% and 16% probability of organ preservation **(chapter 2, chapter 3)** [7].

I want to preserve long-term quality of life through organ preservation
There are many treatment options for patients to whom preserving long-term quality of life through organ preservation matters most. Which treatment strategy fits best, depends on what neoadjuvant treatment intensity patients are willing to accept for increasing the probability of organ preservation. In general, more intensive neoadjuvant treatments result in a higher probability of organ preservation. Unfortunately, no neoadjuvant strategy gives a 100% chance of organ preservation. This means that a proportion of patients will undergo intensified neoadjuvant treatment hoping to reach organ preservation, but will still need TME because of incomplete tumour response. In order to decrease the number of patients with double treatment burden (i.e. intensified neoadjuvant treatment and surgery), we need to improve our abilities to predict the tumour response to neoadjuvant treatment.

For patients with early rectal cancer, SCRT or CRT can enable organ preservation. SCRT and local excision for T1-2N0 rectal cancer resulted in 70% organ preservation in the randomised TREC trial [8]. Fifteen percent of patients experienced one or more Grade 3 toxicity following SCRT. During 3 years of follow up, patients reported higher quality of life and lower symptom scores on several domains compared to patients undergoing TME. CRT and local excision for T1-3N0 rectal cancer resulted in 64% organ preservation in the randomised CARTS trial [9]. Acute toxicity was not reported, but two patients (4%) died during CRT and two patients (4%) had to stop CRT because of a toxic reaction. In this trial, 50% of patients successfully treated with organ preservation reported major bowel dysfunction. A direct comparison between SCRT and CRT for organ preservation in cT1-3bN0 rectal cancer will be provided by the randomised STAR-TREC trial [10]. Outcomes of adjuvant CRT compared to completion TME in case of local excision of a high risk T1 or low risk T2 tumour will be provided by the TESAR trial [11]. Based on the currently available evidence, SCRT comes with similar probability of organ preservation but less toxicity than CRT for early rectal cancer. Quality of life and functioning following these regimens need further investigation.

Furthermore, a radiotherapy boost can be administered with the aim to achieve organ preservation, both as a primary treatment or as a secondary treatment in case of incomplete response following SCRT or CRT. Contact radiotherapy (Papillon) and high dose-rate endoluminal brachytherapy (HDREBT) can deliver high, local dosages while sparing the surrounding tissues. Papillon only suffices as monotherapy in small (< 3cm) and superficial (cT1-2) tumours [12–14]. Studies so far have small sample size and heterogeneous study populations, but show sustained organ preservation and good bowel function in the majority of patients [12–14]. HDREBT is more invasive than Papillon but suitable for T3-4 tumours. Three trials that combined external beam radiotherapy and HDREBT for organ preservation in intermediate risk and/or locally advanced rectal cancer showed high cCR rates of 61-86% [15–18]. In the HERBERT trial, late grade ≥ 3 proctitis occurred in 40% of patients, in contrary to the trial by Appelt et al., where perfect faecal continence was reported by 69% of patients at 2 years [16,18]. The randomised OPAXX trial will investigate the performance of HDREBT versus prolonged observation and local excision in case of a near complete response following SCRT for intermediate risk and CRT for locally advanced rectal cancer [19]. An external beam radiotherapy boost before CRT did not result in an improved pCR rate, but did result in improved tumour regression in locally advanced rectal cancer

in the randomised RECTAL-BOOST and the randomised INTERACT trial [20,21]. The external beam radiotherapy boost resulted in a significant but transient impact on quality of life in the RECTAL-BOOST trial **(chapter 4)**. Whether an external beam radiotherapy boost following SCRT using MRgRT will result in improved cCR rates while preserving quality of life in intermediate risk rectal cancer, will be evaluated by the preRADAR trial **(chapter 6)**. An external beam radiotherapy boost and contact radiotherapy were compared for T2-3bN0-1 rectal cancer in the randomised OPERA trial. Contact X-ray showed higher rates of 3-year organ preservation than an external beam boost (81% vs. 59%) and similar acute toxicity rates (grade ≥ 3 of 5% and 4%, respectively) [22]. Overall, administration of a radiotherapy boost seems a good option for patients who are motivated for organ preservation but who want to avoid the high toxicity rates seen during neoadjuvant systemic therapy. Contact radiotherapy and HDREBT are only feasible in small and non-circumferential tumours and seem preferable to an external beam radiotherapy boost when possible.

Addition of neoadjuvant systemic therapy (in the form of capecitabin and oxaliplatin [CAPOX], fluorouracil, folinic acid (leucovorin) and oxaliplatin [FOLFOX] or fluorouracil, folinic acid (leucovorin), irinotecan and oxaliplatin [FOLFIRINOX]) to SCRT or CRT for intermediate risk and locally advanced rectal cancer resulted in increased pCR or organ preservation rates (28-53%) in the randomised RAPIDO, UNICANCER-PRODIGE 23, OPRA and STELLAR trials [23–29]. TME was still considered the golden standard and WW a protocol violation in the RAPIDO and UNICANCER-PRODIGE 23 trials [23,27]. It is therefore unsure in what sustained organ preservation rates these treatment regimens would result. Systemic therapy (FOLFOX for 8 cycles of 2 weeks or CAPOX for 5 cycles of 3 weeks) before CRT (induction arm) versus systemic therapy after CRT (consolidation arm) resulted in very high 3-year sustained WW rates of 41% and 53%, respectively, in the OPRA trial [28]. In all four trials, the high complete response rates came at the expense of high acute grade ≥3 toxicity rates of 27-48%. Also, most trials only included fit patients (Eastern Cooperative Oncology Group [ECOG] performance status 0-1) and some trials had an age limit (age ≤ 75). No differences in long-term quality of life and bowel function were observed in the RAPIDO trial, except for increased sensory-related symptoms in patients receiving SCRT and systemic therapy (CAPOX in 6 cycles of 3 weeks or FOLFOX in 9 cycles of 2 weeks) compared to CRT [26]. Also, no differences in quality of life were observed at 12 and 24 months of follow up in the UNICANCER-PRODIGE 23 trial, except for more impotence in men in the CRT group compared to the neoadjuvant systemic

therapy (FOLFIRINOX for 6 cycles of 2 weeks) and CRT group [30]. In the NEO trial, neoadjuvant systemic therapy (FOLFOX for 6 cycles of 2 weeks or CAPOX for 4 cycles of 3 weeks) was administered to patients with early rectal cancer (T1-T3bN0) and followed by local excision. Here, 57% of patients had successful organ preservation. During systemic therapy, 21 grade 3 toxicity events and 8 grade 4 acute toxicity events were reported in a trial population of 58 patients [31]. The randomised PROSPECT trial aimed to improve functional outcome while preserving oncological outcome by administering neoadjuvant systemic therapy (FOLFOX in 6 cycles of 2 weeks) only followed by CRT in patients whose tumours decreased < 20% in size, in comparison to neoadjuvant CRT in T2N1 or T3(MRF-)N0-1 rectal cancer. Neoadjuvant systemic therapy showed non-inferiority with respect to disease-free and overall survival at 5 years [32]. pCR rates were 22% and 24%, respectively. During neoadjuvant treatment, patients reported substantially more complaints in the neoadjuvant systemic therapy group, but at 12 months following surgery, fatigue, neuropathy and sexual function was slightly better in the systemic therapy compared to the CRT group [33]. With similar rationale, the ongoing GRECCAR-16 trial is comparing neoadjuvant systemic therapy only (FOLFIRINOX for 6 cycles of 2 weeks) to neoadjuvant CRT for T1-3(MRF-) N1 or T3(MRF-)N0 rectal cancer [34]. In general, addition of neoadjuvant systemic therapy seems an option for young and fit patients who are willing to undergo an intensive treatment for a high probability of organ preservation.

It has not yet indisputably been established that WW strategy improves long-term quality of life and functioning compared to TME. Nevertheless, studies supporting this hypothesis are accumulating. A matched cohort study showed improved quality of life on the majority of functional domains and decreased bowel, sexual and urinary dysfunction following CRT and WW compared to CRT and TME at minimum 2 years after end of treatment [35]. Another matched cohort study showed improved social functioning, body image, bowel function and less impotence following CRT and local excision compared to CRT and TME at minimum 1 year after end of treatment [36]. So far, the only randomised data comes from the TREC trial, where patient-reported bowel function and quality of life were significantly higher following SCRT and local excision compared to direct TME up to 36 months after start of treatment [8]. In order to resolve any doubts, a randomised study should be conducted where local excision and/or WW is compared to TME in patients with a (near) cCR. Whether such a trial would get sufficient accrual is questionable, given that WW is already commonly used in clinical practice.

I want to live as long as possible

Few treatments have proven to result in a longer survival time than the traditional standard of TME, preceded by SCRT or CRT in case of a higher risk tumour. Organ preservation results in survival outcomes close to those following TME, but the risk of distant metastases is increased among patients with a local tumour regrowth [37]. For patients to whom survival matters most, the classical multimodal treatment generally seems the best option.

In selected cases of locally advanced rectal cancer, addition of neoadjuvant systemic therapy to CRT might improve survival. Systemic therapy is thought to be more effective in sterilising metastases when they are still small (i.e. occult metastases at start of treatment) than when they grow and become clinical apparent (i.e. metastases during follow up). Also, compliance to systemic therapy is better when administered before compared to after surgery [24,27,29]. In the RAPIDO trial, SCRT and neoadjuvant systemic therapy (CAPOX in 6 cycles of 3 weeks or FOLFOX in 9 cycles of 2 weeks) decreased the distant metastasis rate (23% vs. 30%, respectively) but increased the locoregional recurrence rate compared to neoadjuvant CRT at 5 years (12% vs. 8%, respectively) [38,39]. 5-year overall survival was similar [39]. Also, the OPRA trial showed similar 3-year DFS following neoadjuvant systemic therapy before CRT (induction arm, FOLFOX for 8 cycles of 2 weeks or CAPOX for 5 cycles of 3 weeks) or neoadjuvant systemic therapy after CRT (consolidation arm) compared to a historical cohort of CRT, TME and adjuvant systemic therapy [28]. However, the UNICANCER PRODIGE-23 trial showed improved 3-year DFS following neoadjuvant systemic therapy (FOLFIRINOX for 6 cycles of 2 weeks) and CRT compared to CRT only (76% vs. 69%) [27]. Systemic therapy is known to be less effective in patients who have been treated before with systemic therapy. Possibly, neoadjuvant systemic therapy delays the development of distant metastases but leaves less effective treatment options when metastases do develop. This theory is illustrated by a finding of the RAPIDO trial, wherein patients had shorter survival time after diagnosis of distant metastases in the SCRT and neoadjuvant systemic therapy group than the CRT group (2.6 vs. 3.2 years, respectively) [38]. Hence, it is yet to be confirmed whether the improved DFS of the UNICANCER PRODIGE-23 translates into improved OS. Lastly, the STELLAR trial showed similar DFS, distant metastasis and local recurrence rates, but improved OS at 3 years following SCRT and four cycles of CAPOX compared to CRT (87% vs. 75%) [29]. The survival results following neoadjuvant systemic therapy are thus conflicting. Possibly, neoadjuvant systemic therapy is only beneficial in a subgroup of patients

with the highest risk of distant metastases, such as patients with extramural venous invasion, circulating tumour DNA or high risk radiomic features on MRI [40–42]. Along these lines, the MEND-IT trial will be testing the UNICANCER-PRODIGE 23 regimen (FOLFIRINOX for 6 cycles of 2 weeks and CRT) in patients with locally advanced rectal cancer with imaging-based high risk futures [43].

Survival following rectal cancer treatment could further be improved by recognizing and treating enlarged lateral lymph nodes (LLN). LLN are currently mentioned in only half of MRI reports for rectal cancer in the Netherlands [44]. However, patients with persistent enlarged LLN after neoadjuvant (chemo)radiotherapy have a significantly shorter DFS [45,46]. There is no consensus on how patients with enlarged LLN should be treated. A LLN dissection has been associated with an improved DFS in patients with persistent enlarged LLN [45,46]. Also, a radiotherapy boost on enlarged LLN has been associated with improved DFS [47,48]. Reporting on LLN before and after neoadjuvant treatment should become part of standard diagnostic procedures. The outcomes of up-front radiotherapy boost in all patients with enlarged LLN versus selective LLN dissection in patients with persistent enlarged LLN after neoadjuvant treatment should be investigated in a randomised trial.

Conclusion

The main question in rectal cancer treatment strategy has evolved from 'what type of tumour does the patient have?' to 'does the patient prefer treatment A or B for the type of tumour (response)?'. It will further evolve to 'what treatment outcome matters most to the patient?'. For patients to whom little toxicity during treatment matters most, leaving out radiotherapy or changing the radiotherapy strategy are good options. For patients to whom preserving long-term quality of life through organ preservation matters most, addition of radiotherapy in early rectal cancer, administration of a radiotherapy boost or addition of neoadjuvant systemic therapy are possibilities. For patients to whom survival matters most, the traditional multimodal treatment still seems most appropriate. Addition of neoadjuvant systemic therapy and treating enlarged LLN could further improve survival in selected cases.

References

1 Amin MB, Edge S, Greene F, *et al. AJCC Cancer Staging Manual (8th edition)*. Springer International Publishing 2017.

2 Yamamoto T, Kawada K, Matsusue R, *et al.* Identification of patient subgroups with low risk of postoperative local recurrence for whom total mesorectal excision surgery alone is sufficient: a multicenter retrospective analysis. *Int J Colorectal Dis*. Published Online First: 26 September 2022. doi: 10.1007/s00384-022-04255-y

3 Sanfratello A, Cusumano D, Piras A, *et al.* New dosimetric parameters to predict ano-rectal toxicity during radiotherapy treatment. *Physica Medica*. 2022;99:55–60.

4 Withers HR, Suwinski R. Radiation dose response for subclinical metastases. *Semin Radiat Oncol*. 1998;8:224–8.

5 Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, *et al.* MRI/linac integration. *Radiotherapy and Oncology*. 2008;86:25–9.

6 Reinders FCJ, de Ridder M, Doornaert PAH, *et al.* Individual elective lymph node irradiation for the reduction of complications in head and neck cancer patients (iNode): A phase-I feasibility trial protocol. *Clin Transl Radiat Oncol*. 2023;39:100574.

7 Ryan J, O'Sullivan DP, Kelly ME, *et al.* Meta-analysis of the effect of extending the interval after long-course chemoradiotherapy before surgery in locally advanced rectal cancer. British Journal of Surgery. 2019;106:1298–310. https://doi.org/10.1002/bjs.11220

8 Bach SP, Gilbert A, Brock K, *et al.* Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. *Lancet Gastroenterol Hepatol*. 2021;6:92–105.

9 Stijns RCH, De Graaf EJR, Punt CJA, *et al.* Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: The CARTS Study. *JAMA Surg*. 2019;154:47–54.

10 Rombouts AJM, Al-Najami I, Abbott NL, *et al.* Can we S ave the rectum by watchful waiting or T rans A nal microsurgery following (chemo) R adiotherapy versus T otal mesorectal excision for early RE ctal C ancer (STAR-TREC study)?: Protocol for a multicentre, randomised feasibility study. *BMJ Open*. 2017;7:19474.

11 Borstlap WAA, Coeymans TJ, Tanis PJ, *et al.* Systematic review Meta-analysis of oncological outcomes after local excision of pT1-2 rectal cancer requiring adjuvant (chemo)radiotherapy or completion surgery. Published Online First: 2016. doi: 10.1002/bjs.10163

12 Custers PA, Geubels BM, Huibregtse IL, *et al.* Contact x-ray brachytherapy for older or inoperable rectal cancer patients: Short-term oncological and functional follow-up. *Cancers (Basel)*. 2021;13:6333.

13 Sun Myint A, Smith FM, Gollins SW, *et al.* Dose escalation using contact X-ray brachytherapy (Papillon) for rectal cancer: does it improve the chance of organ preservation? *Br J Radiol*. 2017;90:20170175.

14 Dhadda AS, Martin A, Killeen S, *et al.* Organ Preservation Using Contact Radiotherapy for Early Rectal Cancer: Outcomes of Patients Treated at a Single Centre in the UK. *Clin Oncol*. 2017;29:198–204.
15 Rijkmans EC, Cats A, Nout RA, *et al.* Endorectal Brachytherapy Boost After External Beam Radiation Therapy in Elderly or Medically Inoperable Patients With Rectal Cancer: Primary Outcomes of the Phase 1 HERBERT Study. *Int J Radiat Oncol Biol Phys*. 2017;98:908–17.
16 Rijkmans EC, van Triest B, Nout RA, *et al.* Evaluation of clinical and endoscopic toxicity after external beam radiotherapy and endorectal brachytherapy in elderly patients with rectal cancer treated in the HERBERT study. *Radiotherapy and Oncology*. 2018;126:417–23.
17 Garant A, Magnan S, Devic S, *et al.* Image Guided Adaptive Endorectal Brachytherapy in the Nonoperative Management of Patients With Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2019;105:1005–11.
18 Appelt AL, Pløen J, Harling H, *et al.* High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: A prospective observational study. *Lancet Oncol*. 2015;16:919–27.
19 OPAXX - Home. https://www.opaxx.nl/Home/ (accessed 30 December 2023)
20 Couwenberg AM, Burbach JPM, Berbee M, *et al.* Efficacy of Dose-Escalated Chemoradiation on Complete Tumor Response in Patients with Locally Advanced Rectal Cancer (RECTAL-BOOST): A Phase 2 Randomized Controlled Trial. *Int J Radiat Oncol Biol Phys*. Published Online First: 19 June 2020. doi: 10.1016/j.ijrobp.2020.06.013
21 Valentini V, Gambacorta MA, Cellini F, *et al.* The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer. *Radiotherapy and Oncology*. 2019;134:110–8.
22 Gerard JP, Barbet N, Schiappa R, *et al.* Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2–cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2023;8:356–67.
23 Hospers G, Bahadoer RR, Dijkstra EA, *et al.* Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial. *Journal of Clinical Oncology*. 2020;38:4006–4006.
24 van der Valk MJM, Marijnen CAM, van Etten B, *et al.* Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer – Results of the international randomized RAPIDO-trial. *Radiotherapy and Oncology*. 2020;147:75–83.
25 Bahadoer R, Dijkstra E. Patterns of locoregional failure and distant metastases in patients treated for locally advanced rectal cancer in the RAPIDO trial. *European Journal of Surgical Oncology*. 2022;48:e34.

26 Dijkstra EA, Hospers GAP, Meershoek-Klein Kranenbarg E, *et al.* Quality of life and late toxicity after short-course radiotherapy followed by chemotherapy or chemoradiotherapy for locally advanced rectal cancer – the RAPIDO trial. *Radiotherapy and Oncology*. 2022;0. doi: 10.1016/j.radonc.2022.04.013

27 Conroy T, Bosset JF, Etienne PL, *et al.* Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:702–15.

28 Garcia-Aguilar J, Patil S, Gollub MJ, *et al.* Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. *Journal of Clinical Oncology*. 2022;JCO2200032.

29 Jin J, Tang Y, Hu C, *et al.* Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR). *Journal of Clinical Oncology*. 2022;40:1681–92.

30 Bascoul-Mollevi C, Gourgou S, Borg C, *et al.* Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER PRODIGE 23): Health-related quality of life longitudinal analysis. *Eur J Cancer*. 2023;186:151–65.

31 Kennecke HF, O'Callaghan CJ, Loree JM, *et al.* Neoadjuvant Chemotherapy, Excision, and Observation for Early Rectal Cancer: The Phase II NEO Trial (CCTG CO.28) Primary End Point Results. *Journal of Clinical Oncology*. 2023;41:233.

32 Schrag D, Shi Q, Weiser MR, *et al.* Preoperative Treatment of Locally Advanced Rectal Cancer. *New England Journal of Medicine*. 2023;389:322–34.

33 Basch E, Dueck AC, Mitchell SA, *et al.* Patient-Reported Outcomes during and after Treatment for Locally Advanced Rectal Cancer in the PROSPECT Trial (Alliance N1048). *Journal of Clinical Oncology*. 2023;41:3724–34.

34 Brouquet A, Bachet JB, Huguet F, *et al.* NORAD01-GRECCAR16 multicenter phase III non-inferiority randomized trial comparing preoperative modified FOLFIRINOX without irradiation to radiochemotherapy for resectable locally advanced rectal cancer (intergroup French-Greccar- Prodige trial). *BMC Cancer*. 2020;20:485.

35 Hupkens BJP, Martens MH, Stoot JH, *et al.* Quality of Life in Rectal Cancer Patients After Chemoradiation. *Dis Colon Rectum*. 2017;60:1032–40.

36 Pucciarelli S, Giandomenico F, De Paoli A, *et al.* Bowel function and quality of life after local excision or total mesorectal excision following chemoradiotherapy for rectal cancer. *British Journal of Surgery*. 2017;104:138–47.

37 van der Valk MJM, Hilling DE, Bastiaannet E, *et al.* Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *The Lancet*. 2018;391:2537–45.

38 Bahadoer RR, Hospers GAP, Marijnen CAM, *et al.* Risk and location of distant metastases in patients with locally advanced rectal cancer after total neoadjuvant treatment or chemoradiotherapy in the RAPIDO trial. *Eur J Cancer*. 2023;185:139–49.

39 Dijkstra EA, Nilsson PJ, Hospers GAP, *et al.* Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery: A 5-Year Follow-up of the RAPIDO Trial. *Ann Surg*. 2023;278:E766–72.
40 Siddiqui MRS, Simillis C, Hunter C, *et al.* A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *British Journal of Cancer 2017 116:12*. 2017;116:1513–9.
41 Wullaert L, van Rees JM, Martens JWM, *et al.* Circulating Tumour DNA as Biomarker for Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. *Cells*. 2023;12:2520.
42 Liu Z, Meng X, Zhang H, *et al.* Predicting distant metastasis and chemotherapy benefit in locally advanced rectal cancer. *Nature Communications 2020 11:1*. 2020;11:1–11.
43 van den Berg K, Schaap DP, Voogt ELK, *et al.* Neoadjuvant FOLFOXIRI prior to chemoradiotherapy for high-risk ("ugly") locally advanced rectal cancer: study protocol of a single-arm, multicentre, open-label, phase II trial (MEND-IT). *BMC Cancer*. 2022;22:957.
44 Sluckin TC, Hazen S-MJA, Horsthuis K, *et al.* Retrospective evaluation of n1 Sluckin TC, Hazen S-MJA, Horsthuis K, et al. Retrospective evaluation of national MRI reporting quality for lateral lymph nodes in rectal cancer patients and concordance with prospective re-evaluation following additional tr. *Insights Imaging*. 2022;13:171.
45 Schaap DP, Boogerd LSF, Konishi T, *et al.* Rectal cancer lateral lymph nodes: multicentre study of the impact of obturator and internal iliac nodes on oncological outcomes. *British Journal of Surgery*. 2021;108:205–13.
46 Ogura A, Konishi T, Beets GL, *et al.* Lateral Nodal Features on Restaging Magnetic Resonance Imaging Associated With Lateral Local Recurrence in Low Rectal Cancer After Neoadjuvant Chemoradiotherapy or Radiotherapy. *JAMA Surg*. 2019;154:e192172–e192172.
47 Meldolesi E, Chiloiro G, Giannini R, *et al.* The Role of Simultaneous Integrated Boost in Locally Advanced Rectal Cancer Patients with Positive Lateral Pelvic Lymph Nodes. *Cancers 2022, Vol 14, Page 1643*. 2022;14:1643.
48 Pang X, Huang L, Ma Y, *et al.* Management of Clinically Involved Lateral Lymph Node Metastasis in Locally Advanced Rectal Cancer: A Radiation Dose Escalation Study. *Front Oncol*. 2021;11:674253.

Appendices

Supplementary files
Nederlandse samenvatting
in niet-medisch taalgebruik
Ontwerp van de omslag
List of publications
Dankwoord
About the author

Supplementary files

Nederlandse samenvatting in niet-medisch taalgebruik

Inleiding

De endeldarm is het laatste deel van de dikke darm. De belangrijkste functie van de endeldarm is de opslag van ontlasting voor de toiletgang. De endeldarm bevindt zich tussen de interne geslachtsorganen en de blaas aan de voorzijde, en het heiligbeen aan de achterzijde. Elk jaar krijgen 3.200 mensen in Nederland de diagnose endeldarmkanker. Endeldarmkanker ontstaat in verreweg de meeste gevallen vanuit de slijmvliescellen die de binnenzijde van de darm bekleden. Kanker kan ontstaan wanneer opeenvolgende mutaties ervoor zorgen dat een cel ongeremd gaat delen en in andere weefsels in kan groeien. Risicofactoren voor endeldarmkanker zijn onder andere het mannelijk geslacht, een hogere leeftijd, alcoholgebruik, roken, overgewicht, inflammatoire darmziekten en familiaire aanleg voor darmkanker. Darmkanker kan een veranderd ontlastingspatroon, bloedverlies bij de ontlasting, buikpijn, gewichtsverlies en bloedarmoede veroorzaken. De diagnose wordt gesteld wanneer tijdens kijkonderzoek van de dikke darm (*coloscopie*) een darmtumor wordt gezien, en bij weefselonderzoek van deze tumor kankercellen worden gevonden. Na de diagnose darmkanker wordt de uitbreiding van de ziekte in kaart gebracht met een MRI-scan van het kleine bekken en een CT-scan van de buik en de borstkast. De ziekte-uitbreiding wordt beschreven aan de hand van de diepte van ingroei van de tumor in de darmwand (*Tumor*, T-stadium), aanwezigheid van uitzaaiingen in de nabije lymfeklieren (*Nodal*, N-stadium) en aanwezigheid van uitzaaiingen op afstand (*Metastasis*, M-stadium).

Behandeling

Verleden: wat voor soort tumor heeft de patiënt?

Vroeger was overleving doorslaggevend in de keuze van de behandeling van endeldarmkanker. Een belangrijke voorspeller voor overleving is het TNM-stadium. Patiënten met een hoger TNM-stadium kregen een intensievere behandeling aangeboden. Een operatie waarbij de gehele endeldarm wordt verwijderd en vaak een stoma wordt aangelegd, was de hoeksteen van de behandeling. Mensen met laag risico endeldarmkanker (T1-2N0M0) werden direct geopereerd. Bij

mensen met middelhoog risico endeldarmkanker (T3N0M0 of T1-3N1M0) werd de operatie voorafgegaan door een kort schema bestraling (vijf bestralingen van 5 Gy). Bij mensen met hoog risico endeldarmkanker (T4N0M0 of T1-4N2M0) werd de operatie voorafgegaan door een lang schema bestraling (25 bestralingen van 2 Gy) gecombineerd met een chemopil (*chemoradiatie*). In de periode dat deze combinatie van operatie, bestraling en chemotherapie standaardzorg werd, verbeterde de overleving van endeldarmkanker aanzienlijk.

Heden: wil de patiënt behandeloptie A of B voor zijn type tumor(respons)?
Parallel met de verbeterde overleving is er meer aandacht gekomen voor kwaliteit van leven na de behandeling. De behandeling van endeldarmkanker blijkt een sterke negatieve invloed te hebben op kwaliteit van leven. Na afronding van de behandeling blijven mensen last houden van incontinentie voor ontlasting, incontinentie voor urine en impotentie of pijn bij het vrijen. Het merendeel van deze klachten is te wijten aan de endeldarmoperatie.

Sinds kort weten we dat een niet-operatieve behandeling mogelijk is bij een klein deel van de patiënten. Na bestraling (en chemotherapie) is bij sommige mensen geen tumor meer voelbaar of zichtbaar bij rectaal toucher, bij kijkonderzoek van de endeldarm en op een MRI-scan van het kleine bekken (*een volledige tumorrespons*). In dat geval kan van de endeldarmoperatie worden afgezien. Bij deze orgaansparende behandeling komen patiënten elke drie maanden in de eerste twee jaar terug naar het ziekenhuis voor controle. Er is namelijk 25% risico op achtergebleven losse tumorcellen die niet zichtbaar waren op de scan, maar die wel opnieuw kunnen uitgroeien tot een tumor. Als de tumor terug groeit, moet alsnog een endeldarmoperatie worden gepland. De overleving van mensen die een orgaansparende behandeling zijn gestart na een volledige tumorrespons, komt dichtbij de overleving van mensen die wel geopereerd zijn en bij wie geen tumorcellen werden aangetroffen in de verwijderde endeldarm. Ook zijn er steeds meer aanwijzingen dat orgaansparende behandeling gepaard gaat met een betere kwaliteit van leven en minder problemen bij ontlasten, plassen en seks dan een endeldarmoperatie. Het merendeel van endeldarmkankerpatiënten zou een orgaansparende behandeling verkiezen boven een operatie. Echter, slechts weinig patiënten komen in aanmerking voor orgaansparende behandeling met de traditionele behandelstrategieën. Geen van de patiënten met laag of middelhoog risico endeldarmkanker maakt kans op orgaansparende behandeling wanneer de

endeldarmoperatie direct na de diagnose of direct na het korte schema bestraling wordt gepland. Na chemoradiatie voor hoog risico endeldarmkanker bereikt 16% van de patiënten een volledige tumorrespons. In de laatste jaren is er een aantal nieuwe behandelstrategieën bijgekomen, waarbij het bereiken van een volledige tumorrespons en het mogelijk maken van orgaansparende behandeling een belangrijke nieuwe uitkomst is. Tegelijkertijd heeft een deel van de patiënten nog steeds de voorkeur voor een directe endeldarmoperatie. Artsen bieden patiënten steeds vaker een keuze tussen verschillende behandelingen.

Dit proefschrift

Een van de momenten waarop patiënten een keuzemogelijkheid wordt geboden, is bij het plannen van het kort schema bestraling en operatie voor middelhoog risico endeldarmkanker. Een lotingsonderzoek heeft laten zien dat langer wachten tussen bestraling en operatie (4-8 weken) een hogere kans geeft op een volledige tumorrespons en een lager risico op complicaties na de operatie dan direct opereren na de bestraling (< 1 week). Tijdens de langere wachttijd was er echter een 7% risico op ziekenhuisopname door bijwerkingen van de bestraling. In **hoofdstuk 2** zijn de bijwerkingen tijdens de wachttijd na kort schema bestraling van 51 Nederlandse endeldarmkankerpatiënten in kaart gebracht. Een op de drie patiënten had in de weken na de bestraling zo veel darmklachten, dat ze tijdelijk aan huis gebonden waren. Eén patiënt werd eerder geopereerd vanwege aanhoudende darmklachten. Niemand werd in het ziekenhuis opgenomen vanwege bijwerkingen van de bestraling. In **hoofdstuk 3** vergeleken we de postoperatieve uitkomsten na kort schema bestraling met een directe operatie ten opzichte van een langere wachttijd tot operatie. Hiertoe maakten we gebruik van de gegevens van de nationale Nederlandse registratie voor darmchirurgie. We konden het voordeel in postoperatieve complicaties na een langere wachttijd niet bevestigen, maar wel de hogere kans op een volledige tumorrespons na de langere wachttijd wel (10% t.o.v. 0%). Op basis van **hoofdstuk 2 en 3** concluderen we dat een langere wachttijd tussen kort schema bestraling en operatie voor endeldarmkanker een veilig alternatief is voor direct opereren. Een langere wachttijd zou aangeboden moeten worden aan patiënten die geïnteresseerd zijn in orgaansparende behandeling. Maar wanneer patiënten niet geïnteresseerd zijn in orgaansparende behandeling, is direct opereren nog steeds een goede behandelstrategie.

Een andere strategie om de kans op een volledige tumorrespons te vergroten is bestralen met een hogere dosis op de tumor en verdachte lymfeklieren (een *bestralingsboost*). De RECTAL-BOOST trial was een lotingsonderzoek in het UMC Utrecht waarin patiënten met hoog risico endeldarmkanker behandeld werden met standaard chemoradiatie of chemoradiatie gevolgd door een bestralingsboost. Na beide behandelingen was er geen verschil in het aantal volledige tumorrespons. Wel zagen we vaker een goede, maar onvolledige tumorrespons bij patiënten die behandeld waren met de bestralingsboost. In **hoofdstuk 4** beschrijven we de kwaliteit van leven in de twee jaar na behandeling van deelnemers aan de RECTAL-BOOST trial. Patiënten die behandeld waren met de bestralingsboost, gaven een slechtere kwaliteit van leven en meer pijn, vermoeidheid en diarree aan op 3 en 6 maanden na de behandeling. Dit effect klaarde daarna grotendeels op. Voor toekomstige experimentele onderzoeken naar een bestralingsboost, moeten deelnemers worden voorgelicht over het tijdelijke effect op kwaliteit van leven. De RECTAL-BOOST trial maakte gebruik van een nieuwe onderzoeksopzet. De ervaring van de trial deelnemers met deze onderzoeksopzet is geëvalueerd in **hoofdstuk 5.** Op basis van de betere tumorrespons na de bestralingsboost in de RECTAL-BOOST trial, zijn we nog steeds hoopvol dat een bestralingsboost de kans op orgaansparende behandeling kan vergroten. **Hoofdstuk 6** beschrijft het protocol voor de preRADAR trial waarin we de nieuwe, preciezere MRI-gestuurde bestraler inzetten voor het geven van een bestralingsboost na kort schema radiotherapie voor middelhoog risico endeldarmkanker.

Discussie

Toekomst: welke behandeluitkomst is het meest belangrijk voor de patiënt?
Voor de toekomst voorzien we een verdere uitbreiding van de behandelmogelijkheden. Niet artsen, maar patiënten zullen de leiding nemen in de keuze van de behandeling. Om patiënten naar de best passende behandelstrategie toe te leiden, zal 'Welke behandeluitkomst is het belangrijkste voor u?' de voornaamste vraag worden in de spreekkamer. Voor patiënten die weinig bijwerkingen tijdens de behandeling het meest belangrijk vinden, zijn het uitsnijden van de tumor in plaats van het verwijderen van de gehele endeldarm (bij laag risico endeldarmkanker), het weglaten van bestraling of het veranderen van de bestralingsstrategie mogelijkheden. Voor patiënten die voornamelijk kwaliteit

van leven willen behouden door middel van orgaansparende behandeling, zijn het toevoegen van bestraling (bij laag risico endeldarmkanker), het bestralen met een bestralingsboost of het toevoegen van chemotherapie aan de voorbehandeling goede opties. Voor patiënten die het meeste waarde hechten aan zo lang mogelijk blijven leven, blijft de traditionele combinatie van endeldarmoperatie, voorafgegaan door bestraling bij een middelhoog of hoog risico tumor, het best passend. Het toevoegen van chemotherapie aan de voorbehandeling en het herkennen en behandelen van vergrote lymfeklieren buiten het endeldarmvet zou de overleving nog verder kunnen verbeteren.

Ontwerp van de omslag

Dit proefschrift gaat over de balans vinden tussen de uitkomsten van de behandeling van endeldarmkanker. Over hoe de behandeling van endeldarmkanker niet meer alleen wordt bepaald op basis van het type tumor van de patiënt, maar hoe de voorkeur van de patiënt ten aanzien van behandeluitkomsten steeds meer meeweegt. Zo past het voor sommige patiënten om te behandelen met bestraling, chemotherapie en operatie, omdat ze langdurige overleving de belangrijkste behandeluitkomst vinden. En voor andere patiënten past een voorbehandeling met extra chemotherapie of een hogere dosis bestraling, omdat ze het meeste belang hechten aan behoud van kwaliteit van leven door orgaansparende behandeling. Voor weer andere patiënten past het om terughoudend te zijn met behandelen, omdat ze bovenal weinig bijwerkingen tijdens de behandeling willen. Deze gedachte komt terug in het ontwerp van de omslag. Er is een balans tussen het vlak met de kleurrijke bloemen, dat staat voor 'alles uit de kast halen' aan behandeling, en het witte vlak, dat staat voor terughoudend zijn met behandeling. Deze twee vlakken vormen samen een yin-yang, het symbool van balans. De bloemen zijn door Maaike verzameld tijdens haar reis door Colombia en Peru. Het concept van balans tussen intensief behandelen en terughoudend zijn met behandeling is doorgevoerd in de hoofdstukpagina's, waar gekleurde bloemen in balans zijn met zwart/wit bloemen.

List of publications

Verweij, M. E., Hoendervangers, S., von Hebel, C. M., Pronk, A., Schiphorst, A. H. W., Consten, E. C. J., Smits, A. B., Heikens, J. T., Verdaasdonk, E. G. G., Rozema, T., Verkooijen, H. M., van Grevenstein, W. M. U., & Intven, M. P. W. **Patient- and physician-reported radiation-induced toxicity of short-course radiotherapy with a prolonged interval to surgery for rectal cancer.** Colorectal Disease. 2023; 25: 24-30. https://doi.org/10.1111/codi.16315

Verweij, M. E., Franzen, J., van Grevenstein, W. M. U., Verkooijen, H. M., & Intven, M. P. W. **Timing of rectal cancer surgery after short-course radiotherapy: national database study.** British Journal of Surgery. 2023; 110, 839-845. https://doi.org/10.1093/BJS/ZNAD113

Verweij, M. E.*, Hoendervangers, S.*, Couwenberg, A. M., Burbach, J. P. M., Berbee, M., Buijsen, J., Roodhart, J., Reerink, O., Pronk, A., Consten, E. C. J., Smits, A. B., Heikens, J. T., van Grevenstein, W. M. U., Intven, M. P. W. & Verkooijen, H. M. **Impact of dose-escalated chemoradiation on quality of life in patients with locally advanced rectal cancer: 2-year follow-up of the randomized RECTAL-BOOST trial.** International Journal of Radiation Oncology, Biology and Physics. 2022; 112, 694–703. https://doi.org/10.1016/j.ijrobp.2021.09.052

Verweij, M. E., Gal, R., Burbach, J. P. M., Young-Afat, D. A., van der Velden, J. M., van der Graaf, R., May, A. M., Relton, C., Intven, M. P. W. & Verkooijen, H. M. **Most patients reported positively or neutrally of having served as controls in the trials within cohorts design.** Journal of Clinical Epidemiology. 2022; 148: 39-47. https://doi.org/10.1016/j.jclinepi.2022.04.015

Verweij, M. E., Tanaka, M. D., Kensen, C. M., Heide, U. A. van der, Marijnen, C. A. M., Janssen, T., Vijlbrief, T., Grevenstein, W. M. U. van, Moons, L. M. G., Koopman, M., Lacle, M. M., Braat, M. N. G. J. A., Chalabi, M., Maas, M., Huibregtse, I. L., Snaebjornsson, P., Grotenhuis, B. A., Fijneman, R., Consten, E. C. J., Pronk, A., Smits, A. B., Heikens, J. T., Eijkelenkamp, H., Elias, S. G., Verkooijen, H. M., Schoenmakers, M. M. C., Meijer, G. J., Intven, M. P. W. & Peters, F. P. **Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial.** British Medical Journal Open. 2023; 13: e065010. https://doi.org/10.1136/BMJOPEN-2022-065010

Smits, F. J. *, **Verweij, M. E.***, Daamen, L. A., van Werkhoven, C. H., Goense, L., Besselink, M. G., Bonsing, B. A., Busch, O. R., van Dam, R. M., van Eijck, C. H. J., Festen, S., Groot Koerkamp, B., van der Harst, E., de Hingh, I. H., Kazemier, G., Klaase, J. M., van der Kolk, M., Liem, M., Luyer, M. D. P., Meerdink, M., Mieog, J. S. D., Nieuwenhuijs, V. B., Roos, D., Schreinemakers, J. M., Stommel, M. W., Wit, F., Zonderhuis, B. M., de Meijer, V. E., van Santvoort, H. C.+, Molenaar, I. Q.+ **Impact of complications after pancreatoduodenectomy on mortality, organ failure, hospital stay, and readmission - analysis of a nationwide audit.** Annals of Surgery. 2022; 275: 222-228. doi:10.1097/SLA.0000000000003835

Eijkelenkamp, H., Boekhoff, M. R., **Verweij, M. E.**, Peters, F. P., Meijer, G. J., Intven, M. P. W. **Planning target volume margin assessment for online adaptive MR-guided dose-escalation in rectal cancer on a 1.5 T MR-Linac.** Radiotherapy and Oncology. 2021; 162: 150-155. doi:10.1016/j.radonc.2021.07.011

Fahim, M., Couwenberg, A. M., **Verweij, M. E.**, Dijksman, L. M., Verkooijen, H. M.+, Smits, A. B.+ **SPONGE-assisted versus Trendelenburg position surgery in laparoscopic sigmoid and rectal cancer surgery (SPONGE trial): randomized clinical trial.** British Journal of Surgery. 2022; 109: 1081-1086. doi:10.1093/BJS/ZNAC249

Walma, M. S., Brada, L. J., Patuleia, S. I. S., Blomjous, J. G., Bollen, T. L., Bosscha, K., Bruijnen, R. C., Busch, O. R., Creemers, G. J., Daams, F., van Dam, R., Festen, S., de Groot, D. J., de Groot, J. W., Haj Mohammad, N., Hermans, J. J., de Hingh, I. H., Kerver, E. D., van Leeuwen, M. S., van der Leij, C., Liem M. S., van Lienden, K. P., Los, M., de Meijer, V. E., Meijerink, M. R., Mekenkamp, L. J., Nederend, J., Yung Nio, C., Patijn, G. A., Polée, M. B., Pruijt, J. F., Renken, N. S., Rombouts, S. J., Schouten, T. J., Stommel, M. W. J., **Verweij, M. E.**, de Vos-Geelen, J., de Vries, J. J. J., Vulink, A., Wessels, F. J., Wilmink J. W., van Santvoort, H. C., Besselink, M. G.+, Molenaar, I. Q.+ **Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort.** European Journal of Surgical Oncology. 2021; 47: 699-707. doi:10.1016/j.ejso.2020.11.137

Dankwoord

Onderzoek doen is teamwork en dat geldt ook voor dit proefschrift. Bedankt aan iedereen die aan dit werk heeft bijgedragen en die de onderzoekstijd leuker heeft gemaakt!

Beste patiënten, bedankt dat jullie tijd en energie vrijmaakten voor deelname aan wetenschappelijk onderzoek, in een periode dat tijd en energie soms spaarzaam waren. Dat deden jullie niet voor jezelf, maar in de hoop bij te dragen aan een betere behandeling voor de patiënten na jullie. Ik bewonder dat jullie zo open over persoonlijke dingen spraken en dat er – ondanks het serieuze onderwerp van het onderzoek – nog plaats was voor humor. Ik heb veel plezier beleefd aan gesprekken met jullie.

Beste promotor, beste Lenny, bedankt dat ik van jou mocht leren. Je kritische blik, toekomstvisie en vermogen om complexe zaken in heldere taal uit te leggen zijn ongekend. Jij ziet direct welke stappen nodig zijn om een onderzoeksvraag betrouwbaar te beantwoorden of een innovatie naar de kliniek te brengen. Ondanks dat je vele promovendi begeleidt, ben je persoonlijk en begaan. Zo stuurde je me een appje of mijn eerste 'master epi' tentamen goed was gegaan en kwam je op een minder moment – ondanks de covid restricties – naar me toe om me een hart onder de riem te steken. Na een gesprek met jou, was ik weer gemotiveerd om verder te gaan.

Beste tweede promotor, beste Martijn, bedankt dat ik altijd bij je binnen mocht lopen. Als ik even niet meer wist hoe ik iets aan moest pakken of op moest schrijven, bracht een sparsessie met jou me weer op de goede weg. Ik denk dat jouw onderzoekslijn naar MRI-gestuurde radiotherapie voor gastro-intestinale tumoren veel gaat bijdragen aan het vakgebied. Helaas was jouw passie voor de radiotherapie niet voor mij besmettelijk... Maar het lijkt me mooi om in de toekomst, voor mij vanuit een rol binnen de chirurgische oncologie, met jou samen te blijven werken.

Beste copromotor, beste Helma, bedankt dat je mij begeleidde, ook in tijden dat je wel iets anders aan je hoofd had. Ik vond het fijn om jou met je nuchtere, chirurgische blik en donkere humor in mijn promotieteam te hebben. Ik liep graag even bij je

langs om 'bij te kletsen'. Ook bedankt voor dat je met me mee wilde denken wat de goede vervolgstappen waren voor mijn ambities binnen de chirurgie.

Lieve Arthur en Floris, zonder jullie had ik de finishstreep niet gered. We hebben samen heel veel lol gehad en elkaar door moeilijke momenten heen gesleept. Alle rondjes UMC, DiOchKo's (DinsdagOchtendKoffie), running jokes... ik ga ze missen. Het is niet anders dan logisch om dit traject met jullie als mijn paranimfen samen af te sluiten.

Collega-onderzoekers, lieve Fia, Lando, Mike, Dieuwke, Charisma, Osman, Guus, Hidde, Jikke, Eline en anderen, promoveren is ontberen maar met steun van leuke collega's een stuk makkelijker. Bedankt voor het meedenken, samenwerken en samen ontspannen buiten het onderzoek doen om.

Beste medewerkers van het trialbureau, bedankt voor de ondersteuning bij het onderzoek. In het bijzonder Anette, ik werkte graag met jou samen. Met jouw doortastendheid en no-nonsense mentaliteit waren stomme klusjes zoals mappen vullen voor de METc zo gedaan. En Jacco, bedankt dat ik altijd bij je terecht kon wanneer ik tegen technische hindernissen aanliep.

Beste wetenschapsstudenten, Lotte en Jolien, bedankt voor jullie bijdrage aan twee mooie onderzoeksprojecten. Ik heb jullie met plezier begeleid en hoop dat jullie onderzoeksskills hebben opgedaan die van pas zullen komen in jullie verdere medische en wetenschappelijke ontwikkeling.

Beste Q, of het nou is als begeleider van de wetenschapsstage, supervisor in de kliniek, persoonlijk begeleider van de PhD of als lid van de examencommissie, het is altijd gezellig om jou weer tegen te komen. Bedankt voor je aanmoediging en hulp de juiste keuzes te maken.

Beste Maarten Burbach, bedankt voor jouw rol als bonus begeleider tijdens de PhD. Na een telefoongesprek met jou, zag ik weer de grote lijnen en de mogelijkheden.

Beste Femke Peters, bedankt voor jouw inzet voor de preRADAR trial. Ik vind het knap hoe nauwkeurig jij dingen uitzoekt; dat laat zien dat je alleen het beste voor de patiënten wilt. Ik hoop dat de RADAR onderzoekslijn, samen opgezet met Martijn

Intven, Max Tanaka en vele collega's van het UMCU en NKI-AvL, de behandeling van patiënten met rectumcarcinoom kan verbeteren.

Beste Djamila Boerma, dankzij jouw tip heb ik op deze positie binnen 'een leuk, multidisciplinair onderzoeksproject' gesolliciteerd. Bedankt voor je hulp en vertrouwen!

Lieve vrienden en familie, ik ben dankbaar voor hoe veel fijne mensen ik aan mijn zijde heb.

Lieve Else, Aniek, Jasper, Daniel en Yosha, Rosa, Leo en Merel, bedankt voor alle lol en gekkigheid op feestjes, en de vriendschap daarbuiten.

Lieve Oom Chiel en Heleen, wat fijn dat jullie 'om de hoek' in Utrecht wonen. Bedankt dat ik altijd even bij jullie langs kan waaien.

Lieve kitechicks; Liselot, Maxine, Philip, Afra, Kay en Laura, bedankt voor het geweldige jaar op Curaçao. Op nog vele uren samen op het water!

Lieve tante Ria, ik ben blij dat wij vriendinnen zijn. Bedankt voor al je leuke ideeën, goede gesprekken en betrokkenheid.

Lieve Wills, wij kunnen elkaar vinden in onze passie voor de chirurgie, sportiviteit en eigenwijsheid. Bedankt voor alle gezellige borrels, sportsessies en intellectuele discussies.

Lieve Nina, van 'giechel 1 zonder hoofdletter' en 'Giechel 2 met hoofdletter' op de basisschool tot nu nog steeds goede vriendinnen op ons 30e. Bedankt voor al die jaren vriendschap.

Lieve Nadia, bedankt voor je humor, relativering en originaliteit. Maatjes tot in het verzorgingstehuis!

Lieve pap en mam, bedankt dat jullie me altijd steunen en me de vrijheid geven mijn eigen weg te gaan.

Mi querido Abrahán, muchas gracias para venir a Holanda para mí. Espero que tú puedes encajar en la Sociedad Holandesa, que tú vas a recibir muchas oportunidades para desarrollarte y que tú vas a tener una vida feliz aquí. Tú eres la persona la más optimista, relajada y atenta que yo conozco y estoy muy orgullosa de tenerte al lado de mí.

About the author

Maaike Verweij was born on the 10th of April 1994 in Zaanstad, the Netherlands. She grew up in Haarlem with her brother and her parents. After graduating with distinction from the Sancta Maria Lyceum in Haarlem in 2012, she moved to Groningen to study Medicine at the Rijksuniversiteit Groningen. During the course of her studies, Maaike felt herself drawn to the surgical specialty. She did her final internship in the Dept. of Surgery of the Ziekenhuisgroep Twente and moved to Utrecht in 2018 for a research internship under the supervision of Quintus Molenaar at the Dept. of Surgery of the University Medical Centre of Utrecht. The internship resulted in her first scientific publication. After graduating medical school in 2018, Maaike worked as a resident not in training at the Dept. of Surgery of the St. Antonius Hospital in Nieuwegein. This job strengthened her dream of becoming a gastro-intestinal surgeon. In 2019, she started a PhD on the treatment of rectal cancer under the supervision of Helma van Grevenstein, Martijn Intven and Lenny Verkooijen at the Division of Imaging & Oncology of the University Medical Center of Utrecht. The PhD included initiating a phase I trial on dose-escalated radiotherapy for rectal cancer and coordinating several other projects on side effects during treatment and quality of life following treatment of rectal cancer. Although doing full-time research during the covid lockdowns wasn't easy, she completed the PhD and meanwhile graduated with distinction from a Master's in Epidemiology at the University of Utrecht. Following these three years of research, Maaike moved to Curacao to enjoy the perks of a tropical island whilst working hard as a resident not in training at the Dept. of Surgery of the Curacao Medical Center. Recently, she moved back to the Netherlands in the company of her boyfriend Abrahan and two dogs she found on the streets of Curacao. They live together in Utrecht. She is currently working in a general practice, but is looking for a new position at a Dept. of Surgery, where she is hoping to pursue her dream of becoming a gastrointestinal surgeon.

In her free time, Maaike likes to be active and practices pole dancing, kitesurfing and weightlifting. She is interested in the yet unknown and has visited many countries, including Australia, Thailand, a medical internship in Surinam, a research internship in Bordeaux and a voyage through Colombia and Peru following the working year at Curacao. Furthermore, she enjoys spending time with family and friends, playing with her dogs or going to harder styles parties.