Optimizing the treatment of locally advanced and recurrent rectal cancer

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DOI:
10.33612/diss.789782613

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Financial support for publication of this thesis by the following institutions and companies is gratefully acknowledged: Graduate School of Medical Sciences, Stichting Werkgroep Interne Oncologie and Rijksuniversiteit Groningen.

Printed by	Ipskamp Printing Enschede, the Netherlands
Design & layout	Bianca Pijl, www.pijlldesign.nl Groningen, the Netherlands

rijksuniversiteit
groningen

Optimizing the treatment of locally advanced and recurrent rectal cancer

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. ir. J.M.A. Scherpen
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 30 oktober 2023 om 14:30 uur

door

Esmée Anne Dijkstra

geboren op 7 juni 1994
te Meppel

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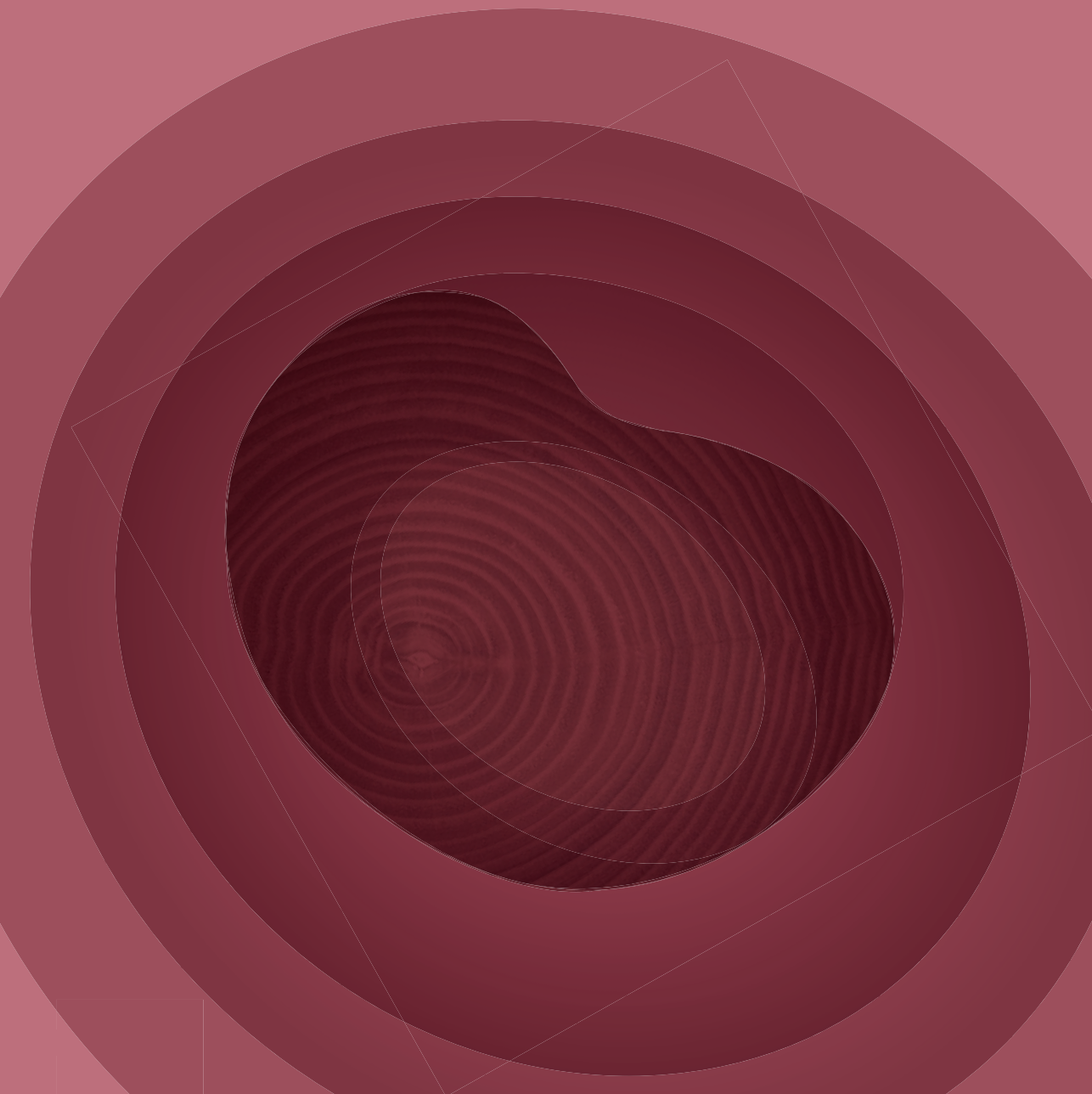

CHAPTER 1

General introduction

GENERAL INTRODUCTION

Rectal cancer epidemiology

In 2020 the incidence and mortality of rectal cancer was 732.210 and 339.022 worldwide, respectively[1]. The median age at rectal cancer diagnosis is 62 in male and 63 in female patients. The male:female ratio and the incidence:mortality ratio in rectal cancer in 2020 in western Europe was 2:1 and 3:1, respectively[1]. Since the introduction of the fecal occult blood test in 2014 in the Netherlands, the incidence of rectal cancer increased from 4082 in 2013 to 4936 in 2015[2]. In addition, tumors detected have more often a lower TNM stage. In the Netherlands, the incidence of rectal cancer was 3105 in 2020, where this was 3953 in 2019. This decline could be caused by the COVID-19 pandemic. In addition, during the COVID-19 pandemic, there were proportionately slightly more stage IV tumors. The figures for 2021 demonstrate an upward trend with an incidence of 3460. However, the preliminary results of 2022 demonstrate a small decrease again; the incidence in the Netherlands was 3181.
Rectal cancer may present in three ways: asymptomatic patients discovered by routine screening, suspicious symptoms and/or signs and emergency admission with intestinal obstruction. In 60-90% of patients, changes in bowel habits and in 80-90% blood in their stool is seen and 25-50% of patients experience abdominal pain[3].

Treatment of locally advanced rectal cancer

Locally advanced rectal cancer (LARC) is a term which is used worldwide. However, an international consensus on the definition of LARC is missing. According to the ESMO clinical guidelines, LARC is defined as patients with a cT3a/b tumor and extramural vascular invasion (EMVI)[4]. Treatment of LARC is a multidisciplinary task, entailing imaging, neoadjuvant treatment, surgery, postoperative treatment and follow-up. The strategies of diagnostics, neoadjuvant treatment and surgery, have improved over the past decades, leading to improved survival rates. Overall, the five-year local recurrence rate decreased to approximately 5-9% and the 3-year overall survival is 70-90%[5–7]. Although the local recurrence rate decreased with the improved treatment strategy, the distant metastasis did not decrease accordingly, with 5-year distant metastases rates above 25% in patients with resectable rectal cancer[8,9].

Improvement of diagnostic techniques

Improved diagnostics is one of the reasons for the improvement of rectal cancer treatment. Alongside physical examination and colonoscopy, the introduction of the fecal occult blood test has led to an increase in the incidence of rectal cancer as described before. With the fecal occult blood test, rectal cancer could be diagnosed in an earlier stage, leading to improved outcomes. In addition, advances in MRI and CT technology led to improvements in staging accuracy. Besides, MRI became part of the standard workup of patients with rectal cancer. Traditionally, MRI scans were used to plan the surgical approach, nowadays the MRI is also used for the clinical detection of clinical (near) complete responders aiming for organ preservation.

Improvement of surgical techniques

Due to a better understanding of the circumferential resection margin, the surgical strategy was changed and total mesorectal excision (TME) was introduced by Heald et al[10]. In a TME procedure, the entire mesorectal compartment is excised along anatomical planes. The specimen includes the rectum, surrounding mesorectum and perirectal lymph nodes, enclosed by the mesorectal fascia (MRF). The introduction of this standardized technique, together with improved detection of LARC patients, reduced the local recurrence rates from over 25% to approximately 10% at 5 years after surgery[11]. Robotic surgery is a relatively new approach in which better visualization and more accurate resection of the mesorectum might lead to even further improvement in oncological outcomes. However, this technique is still in its infancy. For long, surgery according to TME principles was the only curative treatment. Still, surgery is a very important factor in the treatment of rectal cancer.

Neoadjuvant treatment

Depending on the tumor stage of rectal cancer, in the Netherlands two treatment schedules are used as neoadjuvant treatment.

For intermediate-risk rectal cancer patients, i.e. very low cT3a/b, clear levators and, MRF- or cT3a/b in mid- or high rectum, cN1-2 and EMVI-, short-course radiotherapy (scRT; 5x5 Gy) is given[4]. Radiotherapy in these patients is followed by surgery according to TME principles within one week. In patients treated with preoperative radiotherapy and surgery, the overall survival rate at 5 years was 73%[9]. In addition, preoperative radiotherapy reduced the risk of local recurrence after surgery to 7%[9].

In case of high-risk rectal cancer, i.e. cT3 with MRF involved, cT4a/b or positive lateral lymph nodes, long-course chemoradiotherapy (CRT) is provided as 50.0-50.4 Gy in fractions of 1.8-2 Gy. The addition of neoadjuvant CRT before surgery according to TME principles, aims to downstage tumors, leading to improved locoregional control[4]. In addition, preoperative treatment is accompanied by less grade 3-4 toxicity compared to postoperative treatment[12,13]. However, the German CAO/ARO/AIO-94 study failed to demonstrate a benefit of preoperative versus postoperative long-course CRT regarding overall survival and distant metastases[12]. Currently, due to preoperative CRT, the local recurrence rates are approximately 5-9%[6]. Therefore, preoperative CRT became the new golden standard in patients with high-risk rectal cancer. Unfortunately, this new golden standard treatment did not decrease the distant metastasis rates. Therefore, the 5-year overall survival rate of high-risk rectal cancer patients is still below 75%.

Short-course radiotherapy

As an alternative to CRT, scRT with a delay prior to surgery has been used in unfit patients with high-risk rectal cancer, with positive results[4]. In the Stockholm III trial, randomized patients received scRT followed by immediate surgery, scRT followed by delayed surgery or CRT followed by delayed surgery. The analyses demonstrate that scRT followed by delayed surgery was accompanied by a higher downstaging rate and pathological complete response rate, compared to scRT followed by immediate surgery[9].

Total neoadjuvant treatment

Total neoadjuvant treatment consists of different treatment regimens. In literature it becomes not clear yet if total neoadjuvant treatment should consist of induction or consolidation chemotherapy combined with scRT, or induction or consolidation chemotherapy combined with CRT. In case of preoperative chemotherapy, it is thought that systemic chemotherapy could treat micrometastasis because of increased compliance compared to postoperative systemic chemotherapy due to being unfit after surgery[14]. In the RAPIDO trial, which is the basis of this thesis, patients receive six cycles of CAPOX or nine cycles of FOLFOX preoperatively based on the M1 schedule[14,15].

Postoperative treatment

In order to reduce systemic relapses, many centers administer postoperative chemotherapy. However, systematic reviews and meta-analyses were not able to demonstrated benefit of postoperative chemotherapy regarding overall survival, disease-free survival or distant recurrence[16,17]. Some guidelines recommend postoperative chemotherapy while others do not. Compliance with postoperative chemotherapy is suboptimal compared to preoperative treatment due to TME surgery (postoperative complications or unfitness of patients)[4].

Treatment-related toxicity, complications and health-related quality of life

It is well-known that the multimodality treatment (CRT and surgery) of LARC patients is accompanied by acute and late toxicity. The most frequently reported toxicity after the standard preoperative treatment is gastrointestinal symptoms, urinary dysfunction and sexual dysfunction[18]. Surgery also has its known specific complications e.g. anastomotic leakage and a low anterior resection syndrome are seen after a low anterior resection and perineal wound healing disorders after an abdominoperineal resection. Radiotherapy and the extension of the resection are important risk factors for developing these complications due to fibrosis and inflammatory reactions of the tissue[19]. When scRT and surgery are used in rectal cancer patients, comparable toxicity is demonstrated as compared to CRT[4]. However, when patients receive preoperative oxaliplatin-containing systemic chemotherapy, in the interval between radiotherapy and surgery, more patients experience neurotoxicity. In addition, it is known that multimodality treatment of LARC patients with CRT also has an effect on health-related quality of life. Fortunately, it may recover over time, however, it may take about 2-3 years to get health-related quality of life back to its 'old' level[20].

Recurrent rectal cancer

Neoadjuvant treatment of rectal cancer aims to downstage the tumor. Together with improved diagnostics and surgical techniques, the local recurrence rate has decreased over the past decades to approximately 5-9%[6].

Locally recurrent rectal cancer (RRC) has long been regarded as a rarely curable disease, because of limited preoperative therapy options and more difficult surgical procedures. These surgical procedures are more challenging because of the altered and varied anatomy of organs and critical structures of the pelvis as a result of the initial treatment. Other

complication factors are different tumor growth and post-treatment fibrosis. A previously performed study demonstrated 5-year overall survival rates of 28% in patients who were not treated with preoperative CRT for their primary tumor and 43% in patients who were treated with preoperative CRT for their primary tumor[21]. Fortunately, locally RRC patients are nowadays more often being treated in specialized centers for curative salvage surgery, often combined with (neo)adjuvant chemo and/or radiation treatment. Patients who did not receive neoadjuvant treatment for their primary tumor are able to receive CRT for their RRC. However, if patients already received CRT for their primary tumor, neoadjuvant treatment options are limited for RRC. Re-irradiation could be accompanied by toxicity and tissue damage. Re-irradiation with a lower radiotherapy dose could be an option. However, the question is how the oncological outcome is in RRC after re-irradiation compared to CRT.

OUTLINE OF THIS THESIS

As outlined previously, the current standard of care treatment of LARC is CRT followed by surgery according to TME principles. In some countries, postoperative chemotherapy is provided as well. It is known that by this multimodality treatment the local recurrence rate decreased and the overall survival improved. However, the high distant metastasis rate remains a problem. Therefore, this thesis aims to investigate options to further improve treatment strategies for patients with LARC or RRC in order to improve oncological outcomes, measure long-term toxicity, and health-related quality of life.

In the last years, trials are investigating total neoadjuvant treatment. In the international investigator-driven RAPIDO trial, patients were randomized between the standard of care or the experimental group. The standard of care treatment consisted of CRT followed by surgery, and optionally postoperative chemotherapy depending on the hospital policy. In the experimental treatment group, patients received scRT followed by systemic chemotherapy and thereafter surgery as a total neoadjuvant treatment regimen. The aim of the RAPIDO trial was to improve the distant metastases rate without increasing the locoregional failure rate. The majority of the information provided in this thesis is provided by the results of the RAPIDO trial. **Chapters 2a** and **2b** describe the primary outcome of the RAPIDO trial, which is disease-related treatment failure at three years.

It is well-known that the treatment of LARC patients is accompanied by an effect on health-related quality of life, bowel function and acute and late toxicity. However, trials comparing CRT with scRT followed by immediate surgery demonstrated no difference between the two treatment strategies in terms of late toxicity[22,23]. Besides, the Stockholm III trial demonstrated that a prolonged interval between scRT and surgery did not result in an increased rate of late toxicity[9]. Though, when oxaliplatin-containing systemic chemotherapy is prescribed in colon cancer, this is associated with a higher rate of toxicity[24]. Therefore in centers in which postoperative treatment with CAPOX is no policy in rectal cancer, the addition of 6 cycles of

preoperative CAPOX in the experimental group of the RAPIDO trial will result in additional toxicity. Health-related quality of life, bowel function and late toxicity in the RAPIDO trial, between the standard of care treatment and the experimental treatment, is studied in **Chapter 3**.

The pattern of locoregional recurrence after CRT is known. However, scRT followed by systemic chemotherapy in LARC patients is a relatively new treatment. **Chapter 4** describes patterns of locoregional failure (including early locoregional failure (no resection of the primary tumor and R2 resection) and locoregional recurrence after an R0/R1 resection) after the experimental treatment of the RAPIDO trial and compares this to the patterns of locoregional failure after the standard of care treatment at 5-year. Besides, risk factors for developing locoregional failure and locoregional recurrence and the location of locoregional recurrence are determined. In addition, we provide a 5-year update on Disease-related Treatment Failure, distant metastasis and overall survival.

Postoperative chemotherapy is prescribed in stage III colon cancer patients since it is associated with improved overall survival and a lower distant metastases rate. However, in rectal cancer patients the level of evidence for sufficient benefit is much lower as adjuvant studies in rectal were not optimal due to slow inclusion after TME, the introduction of the MRI scan and more optimal radiotherapy techniques. In **Chapters 5a** and **5b** the standard of care group of the RAPIDO trial is further examined. In this chapter, we compare patients from the standard of care group who did receive postoperative chemotherapy with patients from the standard of care group who did not receive postoperative chemotherapy. The potential benefit of oncological outcomes after postoperative chemotherapy is examined by using Propensity Score Stratification.

Little is known about the clinical and oncological outcomes after re-irradiation of patients with LARC. Neoadjuvant CRT also results in downsizing of the tumor in RRC patients. The main question is how the oncological outcome and safety are in RRC in case of re-irradiation with CRT with a lower radiotherapy dose compared to CRT with standard-dose radiotherapy (CRT). This question is answered in a retrospective study on LRR patients at the University Medical Center Groningen and the results are provided in **Chapter 6**.

A treatment strategy which is still under debate is intra-operative brachytherapy (IOBT). Besides the difference in literature regarding oncological outcomes, there are also differences in indications of IOBT. In some centers all patients with a chance of an R1 resection receive IOBT while in other centers prescribing IOBT was based on frozen sections. **Chapter 7** is a retrospective study which describes and analyzes the clinical selection strategy of IOBT in LARC or LRR patients at the University Medical Center Groningen.

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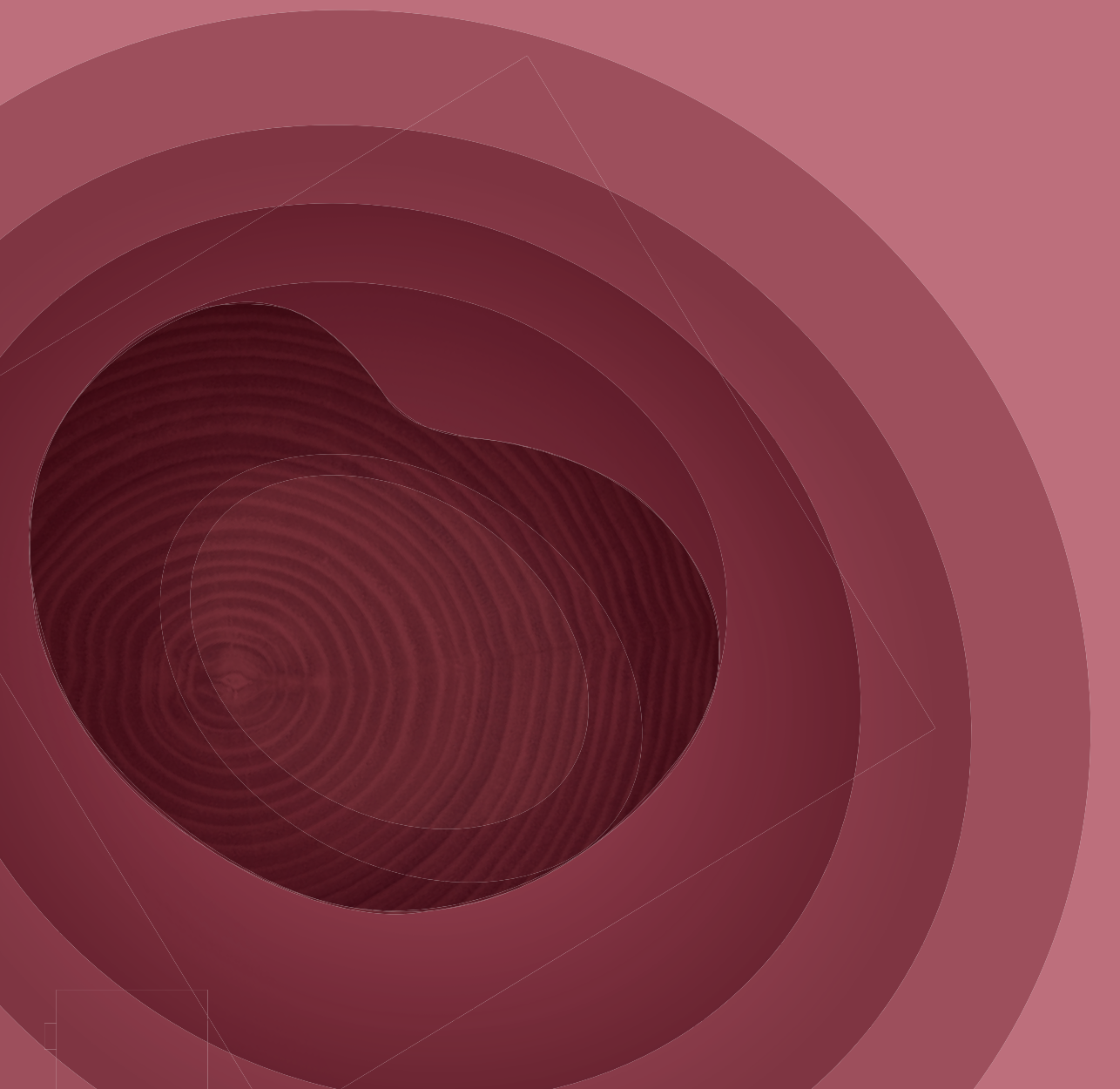

CHAPTER 2a

Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial

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Lancet Oncology. 2021: 22; 29-42

ABSTRACT

Background

Systemic relapses remain a major problem in locally advanced rectal cancer. Using short-course radiotherapy followed by chemotherapy and delayed surgery, the Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial aimed to reduce distant metastases without compromising locoregional control.

Methods

In this multicentre, open-label, randomised, controlled, phase 3 trial, participants were recruited from 54 centres in the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA. Patients were eligible if they were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, had a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma, which was classified as high risk on pelvic MRI (with at least one of the following criteria: clinical tumour (cT) stage cT4a or cT4b, extramural vascular invasion, clinical nodal (cN) stage cN2, involved mesorectal fascia, or enlarged lateral lymph nodes), were mentally and physically fit for chemotherapy, and could be assessed for staging within 5 weeks before randomisation. Eligible participants were randomly assigned (1:1), using a management system with a randomly varying block design (each block size randomly chosen to contain two to four allocations), stratified by centre, ECOG performance status, cT stage, and cN stage, to either the experimental or standard of care group. All investigators remained masked for the primary endpoint until a prespecified number of events was reached. Patients allocated to the experimental treatment group received short-course radiotherapy (5 × 5 Gy over a maximum of 8 days) followed by six cycles of CAPOX chemotherapy (capecitabine 1000 mg/m^2 orally twice daily on days 1–14, oxaliplatin 130 mg/m^2 intravenously on day 1, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m^2 intravenously on day 1, leucovorin (folinic acid) 200 mg/m^2 intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m^2 intravenously and fluorouracil 600 mg/m^2 intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14) followed by total mesorectal excision. Choice of CAPOX or FOLFOX4 was per physician discretion or hospital policy. Patients allocated to the standard of care group received 28 daily fractions of 1.8 Gy up to 50.4 Gy or 25 fractions of 2.0 Gy up to 50.0 Gy (per physician discretion or hospital policy), with concomitant twice-daily oral capecitabine 825 mg/m^2 followed by total mesorectal excision and, if stipulated by hospital policy, adjuvant chemotherapy with eight cycles of CAPOX or 12 cycles of FOLFOX4. The primary endpoint was 3-year disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, new primary colorectal tumour, or treatment-related death, assessed in the intention-to-treat population. Safety was assessed by intention to treat. This study is registered with the EudraCT, 2010-023957-12, and ClinicalTrials.gov, NCT01558921, and is now complete.

Findings

Between June 21, 2011, and June 2, 2016, 920 patients were enrolled and randomly assigned to a treatment, of whom 912 were eligible (462 in the experimental group; 450 in the standard of care group). Median follow-up was 4.6 years (IQR 3.5–5.5). At 3 years after randomisation, the cumulative probability of disease-related treatment failure was 23.7% (95% CI 19.8–27.6) in the experimental group versus 30.4% (26.1–34.6) in the standard of care group (hazard ratio 0.75, 95% CI 0.60–0.95; p=0.019). The most common grade 3 or higher adverse event during preoperative therapy in both groups was diarrhoea (81 (18%) of 460 patients in the experimental group and 41 (9%) of 441 in the standard of care group) and neurological toxicity during adjuvant chemotherapy in the standard of care group (16 (9%) of 187 patients). Serious adverse events occurred in 177 (38%) of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy. Treatment-related deaths occurred in four participants in the experimental group (one cardiac arrest, one pulmonary embolism, two infectious complications) and in four participants in the standard of care group (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression).

Interpretation

The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting. Therefore, the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.

INTRODUCTION

Standard of care for locally advanced rectal cancer consists of chemoradiotherapy followed by surgery according to total mesorectal excision principles after 6–8 weeks. In several countries, adjuvant chemotherapy is also part of the standard of care. Preoperative chemoradiotherapy aims to downstage tumours, leading to improved locoregional control with local recurrence rates of approximately 5–9%[1,2]. However, unfortunately the occurrence of distant metastases has not decreased accordingly.

Downstaging also occurs after short-course radiotherapy followed by delayed surgery, as found in the Stockholm III trial.[3] Although the evidence is not entirely conclusive, many centres administer adjuvant chemotherapy intended to reduce systemic relapses, but compliance is suboptimal[2,4,5]. Surgery can safely be delayed after short-course radiotherapy, creating a window of opportunity to deliver chemotherapy preoperatively instead of postoperatively—an approach that is expected to increase compliance[6,7]. We hypothesized that this approach might result in a decreased number of distant metastases without increasing the risk of locoregional failure, ultimately improving survival outcomes.

The Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation (RAPIDO) trial is based on the Dutch M1-trial[8] in which patients with metastatic primary rectal cancer received short-course radiotherapy, followed by six cycles of capecitabine, oxaliplatin, and bevacizumab, and surgery after 6–8 weeks. High chemotherapy compliance (42 (84%) of 50 patients received six cycles) and primary tumour downstaging in 20 (47%) of 43 patients were reported. Moreover, a pathological complete response of the primary tumour occurred in 11 (26%) of 43 patients[8]. Similarly, favourable experiences of combining short-course radiotherapy and subsequent chemotherapy have been reported in Sweden[6].

The main objective of the RAPIDO trial was to reduce disease-related treatment failure at 3 years with short-course radiotherapy followed by chemotherapy and total mesorectal excision compared with standard chemoradiotherapy, total mesorectal excision, and optional adjuvant chemotherapy (predefined by hospital policy). Data on compliance, toxicity, and postoperative complications in the RAPIDO trial have been published previously[9]. Here we present the primary endpoint after a median follow-up of 4.6 years.

METHODS

Study design and participants

The RAPIDO trial was an investigator-driven, open-label, randomised, controlled, phase 3 trial, done at in 54 hospitals and radiotherapy centres in seven countries (the Netherlands, Sweden, Spain, Slovenia, Denmark, Norway, and the USA). The study was coordinated by

the Clinical Research Center (Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands), including randomisation, trial and database management, quality assurance, and quality control (EM-KK and AGHR).

Patients were eligible for inclusion if they were aged 18 years or older, with a biopsy-proven, newly diagnosed, primary, locally advanced rectal adenocarcinoma with distal extension less than 16 cm from the anal verge. A pelvic MRI with at least one of the following high-risk criteria was required: clinical tumour (cT) stage cT4a or cT4b, extramural vascular invasion, clinical nodal (cN) stage cN2, involved mesorectal fascia (tumour or lymph node ≤1 mm from the mesorectal fascia), or enlarged lateral lymph nodes considered to be metastatic. For all staging, the TNM-5 classification was used[10]. Other inclusion criteria were that the patient must be mentally and physically fit for chemotherapy, have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–1, be assessed for staging within 5 weeks before randomisation, be available for follow-up, and provide written informed consent. Additionally the following laboratory results were required: a white blood cell count of 4.0×10^9 cells per L or higher, platelet count of 100×10^9 per L or higher, a clinically acceptable haemoglobin level, a creatinine level indicating renal clearance of 50 mL/min or higher, and bilirubin level below 35 µmol/L. Comorbidities were permitted. Exclusion criteria included extensive growth of the rectal tumour into the cranial part of the sacrum or the lumbosacral nerve roots indicating that surgery will never be possible even if substantial tumour downsizing is seen and presence of metastatic disease or recurrent rectal cancer.

The trial was carried out in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. Surgery was mandatory; therefore, a watch-and-wait strategy was considered a protocol violation. After central evaluation by the medical ethics committee of University Medical Center Groningen (Groningen, Netherlands (2011/098), the boards of directors or local ethics committees of all participating centres approved the protocol.

Randomisation and masking

Patients were recruited at the participating hospitals before commencement of any treatment and randomly assigned (1:1) by use of the ProMISe data management system (version 4.0) using a stratified and randomly varying block design (each block size was randomly chosen to contain two to four allocations), to either the experimental group or standard of care group. Stratification factors were institution, ECOG performance status (0 or 1), cT stage (cT2–cT3 or cT4), and cN stage (cN– or cN+). Randomisation was coordinated by the Clinical Research Center. All investigators remained masked to treatment assignment for the primary endpoint until the prespecified number of events was reached. Due to the nature of the intervention, patients and clinical staff were not masked to group assignment.

Procedures

A high-resolution, three-dimensional T2-weighted sequence MRI was mandatory before and after preoperative treatment. The protocol specified details on MRI reporting (appendix pp 24–137). MRI reports minimally included the following details: tumour height from the anorectal junction, morphology of the tumour, depth of extramural spread, presence or absence of extramural vascular invasion, mesorectal fascia involvement, breach of the peritoneal reflection by the tumour, presence or absence of mesorectal or extramesorectal lymph node metastases, and, at restaging, the response to preoperative treatment. Mesorectal lymph nodes with a short axis diameter of more than 10 mm and round shape, and those with a short axis of 5–9 mm and meeting at least two criteria of round shape, irregular border, or heterogeneous signal intensity on MRI were defined as metastatic[11]. Extra-mesorectal lymph nodes with an irregular border or heterogeneous signal intensity, or both, or round lymph nodes with a short axis diameter of more than 10 mm, or a combination of these factors, were considered to be metastatic.

An overview of both treatment regimens is provided in the appendix (figure S1). Patients in the experimental group were assigned to short-course radiotherapy (5 × 5 Gy), administered over a maximum of 8 days. Chemotherapy was preferably started within 11–18 days after the last radiotherapy fraction, but within at least 4 weeks. Chemotherapy consisted of six cycles of CAPOX (capecitabine 1000 mg/m^2 orally twice daily on days 1–14, oxaliplatin 130 mg/m^2 intravenously on day 1, and a chemotherapy-free interval between days 15–21) or nine cycles of FOLFOX4 (oxaliplatin 85 mg/m^2 intravenously on day 1, leucovorin (folinic acid] 200 mg/m^2 intravenously on days 1 and 2, followed by bolus fluorouracil 400 mg/m^2 intravenously and fluorouracil 600 mg/m^2 intravenously for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14). After completion of chemotherapy, surgery according to total mesorectal excision principles was planned after 2–4 weeks. The choice of CAPOX or FOLFOX4 was determined by the treating physician and according to hospital policy.
In the standard of care group, patients received radiotherapy in 28 daily fractions of 1.8 Gy up to 50.4 Gy or 25 fractions of 2.0 Gy up to 50.0 Gy, as per the decision of the treating physician and hospital policy, with concomitant twice-daily oral capecitabine 825 mg/m^2. Optional field reduction was recommended after 45 Gy (1.8 Gy schedule) or 46 Gy (2.0 Gy schedule), with the last fractions delivered to the tumour bed. Surgery according to total mesorectal excision principles was planned 6–10 weeks after the last radiotherapy fraction. If protocolised by the participating centre, adjuvant chemotherapy was administered within 6–8 weeks using eight cycles of CAPOX or 12 cycles of FOLFOX4.

In both groups, the clinical target volume for radiotherapy included the entire mesorectum with the primary tumour and relevant regional lymph nodes; an additional boost dose was optional. The clinical target volume of the boost was the assessable tumour with a 1 cm margin within the same anatomical compartment as where the tumour is located. In case of toxicity (according to Common Terminology Criteria for Adverse events (CTCAE) version 4) a dose

reduction of 25% or more (relative to the previous chemotherapy cycle) was protocolised (table S2a, b, c). Laboratory and adverse event monitoring during preoperative therapy was done before all cycles in the experimental group and weekly in the standard of care group. Adverse events related to preoperative and adjuvant therapy were assessed and graded by the local investigator using CTCAE version 4 and postoperative complications using the Clavien-Dindo classification[12]. Surgery was done according to total mesorectal excision principles; a partial mesorectal excision was accepted for proximal tumours. Open and laparoscopic approaches were allowed and at the surgeon's discretion. The completeness of resection was assessed using the residual tumour classification[13]. Pathological assessment of the resected sample was done according to national guidelines of each participating country and included standardised work up and reporting. The involvement of circumferential resection margins, quality of the sample, and complete tumour response (yes or no) were recorded. Quality of the resection was assessed at two different levels for abdominoperineal excision (mesorectum and anal canal) and at one level for anterior resection (mesorectum). A serious adverse event was defined as any untoward medical occurrence or effect that at any dose: results in death; is life threatening (at the time of the event); requires admission to hospital or extension of ongoing hospital stay; results in persistent or clinically significant disability or incapacity; is a congenital anomaly or birth defect; or is a new event of the trial likely to affect the safety of the participants, such as an unexpected outcome of an adverse reaction, lack of efficacy of a study drug used for the treatment of a life threatening disease, and major safety finding from a newly completed animal study.

A standardised, minimal follow-up schedule was defined, with clinical assessments at 6, 12, 24, 36, and 60 months after surgery, including carcinoembryonic antigen measurement. Total colonoscopy was obligatory within the first year unless done preoperatively. The study protocol mandated chest x-ray or CT of the thorax and liver ultrasound or CT of the abdomen at 12 and 36 months as a minimum. A colonoscopy was mandatory 60 months postoperatively. On indication, other diagnostics (eg, PET CT scan) were allowed, to confirm or detect recurrent disease. Functional outcome and health-related quality of life of patients who did not have a disease-related treatment failure event within 36 months after surgery were measured once, using three European Organisation for Research and treatment of Cancer (EORTC) questionnaires: the quality-of-life questionnaire for patients with cancer (QLQ-C30), the quality-of-life questionnaires for patients with colorectal cancer (QLQ-CR29; supplemented with questions related to sexual functioning from the prostate cancer (QLQ-PR25] and endometrial cancer (QLQ-EN24) modules and the quality-of-life questionnaire to assess chemotherapy-induced peripheral neuropathy (QLQ-CIPN20). The low anterior resection syndrome (LARS) scores, regarding bowel function, were also measured[14]. These questionnaires were available in the official languages of each country, except Slovenian. Hence patients from Slovenia were not assessable for the 3-year endpoint of quality of life.

Outcomes

The primary endpoint was disease-related treatment failure, defined as the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumour, or treatment-related death. Locoregional failure included locally progressive disease leading to an unresectable tumour, local R2 resection, or local recurrence after an R0–R1 resection. Locoregional regrowth after a clinical complete response and a watch-and-wait period was not considered a locoregional failure when followed by an R0–R1 resection. Disease-related treatment failure events were not centrally reviewed. Data collection continued after the first disease-related treatment failure event for separate analyses of locoregional failure and distant metastases. Although these were not protocolised secondary endpoints, the stated aim of RAPIDO to reduce systemic relapses without compromising local control justifies these analyses as separate outcomes. Other secondary endpoints were completion rate of neoadjuvant treatment, toxicity, R0 resection rate (resection margin of >1 mm), pathological complete response rate (no residual tumour at pathological assessment after surgery), surgical complications within 30 days, quality of life (in patients alive without disease-related treatment failure, 3 years after surgery), functional outcome, overall survival (time from randomisation to death from any cause), and local recurrence. Toxicity and surgical complications within 30 days have been reported elsewhere[9]. Quality-of-life outcomes will be reported in depth elsewhere.

Statistical analysis

After two protocol amendments, the primary endpoint was changed from disease-free survival to disease-related treatment failure. Around 1 year before the end of the inclusion period, it became apparent that disease-free survival, commonly used in adjuvant trials, was an inappropriate endpoint in a neoadjuvant trial, because patients are not disease free at randomisation and some will never become disease free. For this reason, the protocol was amended (version 3.1; Jan 8, 2016) and a new primary endpoint was formulated: time to disease related treatment failure. The change to this new endpoint was approved by the medical ethics committee and data safety monitoring board (DSMB), which did ongoing safety surveillance and evaluated interim analyses. The first planned and blinded efficacy interim analysis was done on Oct 17, 2017, after 226 disease related treatment failure events.

The second interim analysis was planned after 339 events. However, after a median follow-up exceeding 3 years, the total number of events (for which investigators were masked to treatment group assignment) was lower than anticipated and the required number of events (n=452) was expected to never be reached. Potential reasons for this situation are as follows: alteration of the endpoint (death due to other reasons and a new primary tumour, other than colorectal, are not events), a finite period of follow-up (statistical programs assume endless follow-up), and possibly better overall outcomes than projected. Therefore, the hypothesis changed from a decrease in events from 50% to 40%, to a decrease in the probability of

disease-related treatment failure events from 30% to 22.5% with the experimental treatment, approved by the medical ethics committee and DSMB (protocol version 3.2; June 13, 2019); appendix pp 24–137).

To detect a decrease in 3-year cumulative probability of disease-related treatment failure from 30% to 22.5%, corresponding to a hazard ratio (HR) of 0.715, a two sided log-rank test with 280 events would achieve 80% power at a two-sided α significance level of 0.05.

The primary analysis and the secondary endpoint analysis of overall survival were done in the intention-to-treat population (all patients randomly assigned to treatment, excluding those who withdrew informed consent or were ineligible), as were the analyses of locoregional failure and distant metastases. The secondary endpoints of R0 resection and pathological complete response were analysed in patients who had a resection; surgical complications were analysed in patients who had surgery with curative intent within 6 months; quality of life was assessed in patients who had resection, did not already develop a disease-related treated failure event, and responded in full to the questionnaires; and toxicity was analysed in all patients who started on their allocated treatment.

Using IBM SPSS Statistics (version 25.0), we compared proportions using the χ^2 test and continuous data, depending on the distribution, with Student's t test or the Mann-Whitney U test. All calculated median values are accompanied by an IQR and means with SDs. Using R (version 3.6.1), we did all survival analyses using the Kaplan-Meier method on an intention-to-treat basis. We calculated HRs and 95% CIs using Cox regression. Visual inspection of the cumulative hazards showed no evidence of violation of the proportional hazards assumption. For our separate analyses of locoregional failure, all patients, with and without distant metastases, were included, and for the separate analyses of distant metastases all patients, with and without locoregional failure, were included. Patients who were alive and disease free at last follow-up were censored. We used the reverse Kaplan-Meier method to calculate median follow-up. We calculated cumulative incidence of disease-related treatment failure accounting for non-treatment-related death as a competing risk. For distant metastases and locoregional failure, we calculated cumulative incidences accounting for all causes of death as a competing risk. For all competing risks analyses, we calculated and report cause-specific HRs. We calculated p values for all survival analyses on the basis of (cause specific) log-rank tests[15,16]. For pathological complete response, we calculated odds ratios (ORs) and 95% CIs.
To assess whether the main results were robust, we did sensitivity analyses to study the effect of timing of disease staging (ie, time-related bias), and to adjust for stratification factors. Additionally, in sensitivity analyses, we analysed the influence of hospital policy on adjuvant chemotherapy within the standard of care group on the endpoints of disease-related treatment failure, distant metastases, and locoregional failure using the Kaplan-Meier method. We did subgroup analyses on associations between the primary endpoint and baseline characteristics and present these analyses in a forest plot.

We did a post-hoc analysis of disease-free survival from surgery. Additionally, we calculated disease-free survival, as defined by Fokas and colleagues,17 which is similar to our definition of disease-related treatment failure but includes a second primary cancer, other than colorectal, and death from all causes as events. According to this definition, patients are not disease free at the start of the curves; rather they are event free.

The starting point for all analyses was date of randomisation. The significance threshold for all p values was 0.05. The RAPIDO trial is registered with EudraCT (2010-023957-12) and ClinicalTrials.gov (NCT01558921).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

RESULTS

Between June 21, 2011, and June 2, 2016, 920 patients were randomly assigned to the experimental group (468) or standard of care group (452), of whom 912 (99%) were eligible (462 in the experimental group and 450 in the standard of care group; figure 1). Baseline characteristics of eligible participants are shown in table 1.

Information on the proportion of participants in each group by year and country of inclusion is provided in the appendix (p 9). At the time of analyses (database lock was on June 19, 2020), median follow-up was 4.6 years (IQR 3.5–5.5). The median time between randomisation and surgery was 25.5 weeks (IQR 24.0–27.9) in the experimental group and 15.9 weeks (14.6–17.6) in the standard of care group.

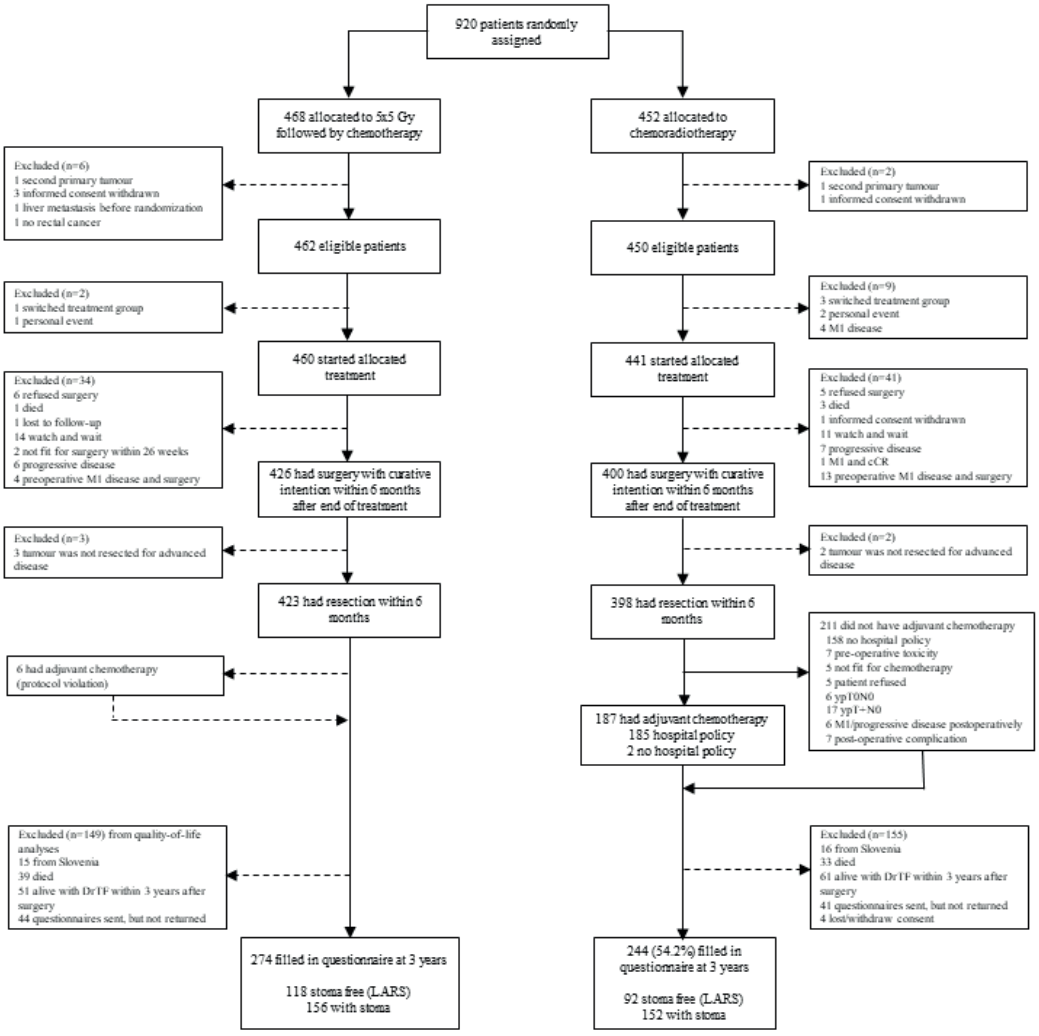


Figure 1 | Consort diagram

cCR clinical complete response; LARS low anterior resection syndrome; M1 metastatic disease.

Table 1 | Baseline characteristics of eligible patients

	Experimental group (*n*=462)		Standard of care croup (*n*=450)	
Sex				
Male	300	(65)	312	(69)
Female	162	(35)	138	(31)
Age at randomisation, years				
Median (IQR)	62	(55-68)	62	(55-68)
Range	31-83		23-84	
Age category				
< 65	280	(61)	270	(60)
≥ 65	182	(39)	180	(40)
Clinical T stage*†				
cT2	14	(3)	14	(3)
cT3	301	(65)	299	(66)
cT4	147	(32)	137	(30)
Clinical N stage*†				
cN0	42	(9)	35	(8)
cN1	118	(26)	120	(27)
cN2	302	(65)	195	(66)
Other high-risk criteria†				
Enlarged lateral nodes	66	(14)	69	(15)
Extramural vascular invasion positive	148	(32)	125	(28)
Mesorectal fascia positive	285	(62)	271	(60)
Number of high-risk per patient†				
1	158	(34)	168	(37)
2	160	(35)	146	(32)
3	98	(21)	96	(21)
4	39	(8)	29	(6)
5	7	(2)	11	(2)
ECOG performance status				
0	369	(80)	365	(81)
1	93	(20)	85	(19)
Distance from anal verge on endoscopy, cm				
< 5	103	(22)	115	(26)
5-10	181	(39)	153	(34)
≥ 10	146	(32)	151	(34)
Unknown	32	(7)	31	(7)
Treated in a hospital with policy for adjuvant chemotherapy				
Yes	273	(59)	265	(59)
No	189	(41)	185	(41)

Data are n (%), unless otherwise indicated. Percentages might not equal 100% due to rounding.

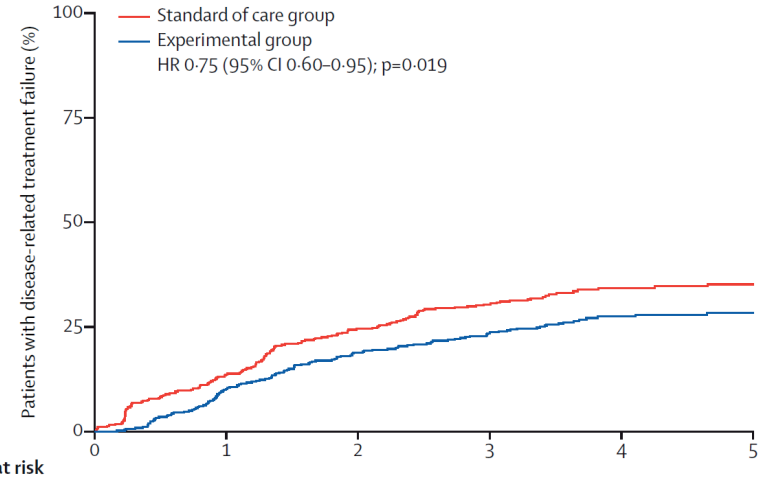
cN clinical nodal; cT clinical tumour; ECOG Eastern Cooperative Oncology Group; N stage nodal stage; T stage tumour stage.

*According TNM-5.

†MRI defined.

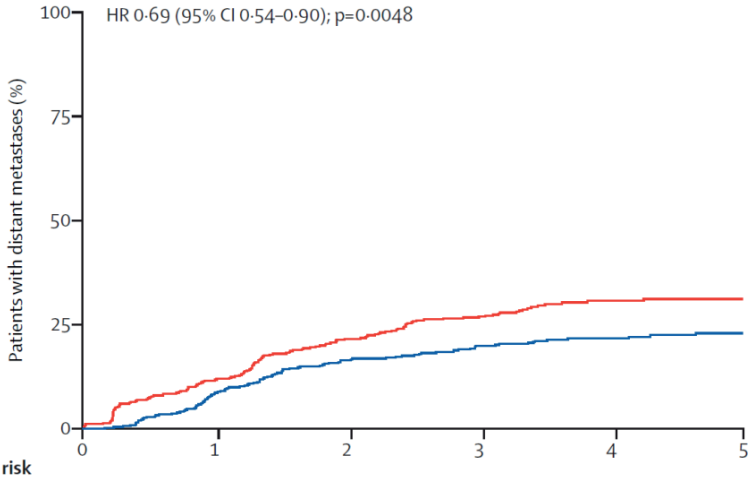
After reaching 128 disease-related treatment failure events in the experimental group and 152 events in the standard of care group, the difference between groups in disease-related treatment failure at 3 years was significant, with fewer disease-related treatment failure events in the experimental group than in the standard of care group (3-year cumulative probability of 23.7% (95% CI 19.8–27.6) vs 30.4% (26.1–34.6); HR 0.75 (95% CI 0.60–0.95); p=0.019; figure 2). Distant metastasis caused most disease-related treatment failures (table 2). At 3 years, the cumulative probability of distant metastases was 20.0% (95% CI 16.4–23.7) in the experimental group compared with 26.8% (22.7–30.9) in the standard of care group (HR 0.69 (95% CI 0.54–0.90); p=0.0048; figure 2). The cumulative probability of locoregional failure at 3 years was 8.3% (95% CI 5.8–10.8) in the experimental group compared with 6.0% (3.8–8.2) in the standard of care group (HR 1.42 (95% CI 0.91–2.21); p=0.12; figure 2).

A



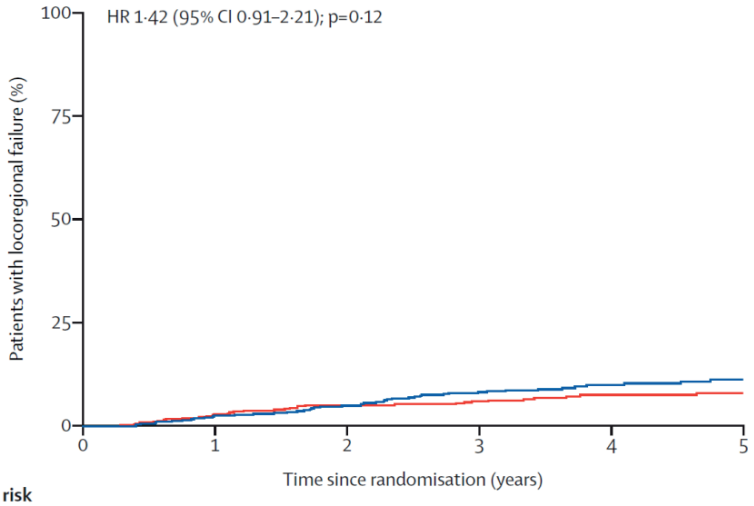
Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	385 (3)	334 (7)	300 (133)	159 (160)
Experimental group	462 (0)	462 (1)	411 (2)	367 (8)	339 (150)	179 (182)

B



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	390 (3)	343 (7)	311 (138)	164 (166)
Experimental group	462 (0)	462 (1)	414 (2)	372 (9)	349 (156)	189 (188)

C



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	428 (3)	405 (8)	379 (161)	209 (199)
Experimental group	462 (0)	462 (1)	436 (2)	411 (8)	384 (172)	204 (207)

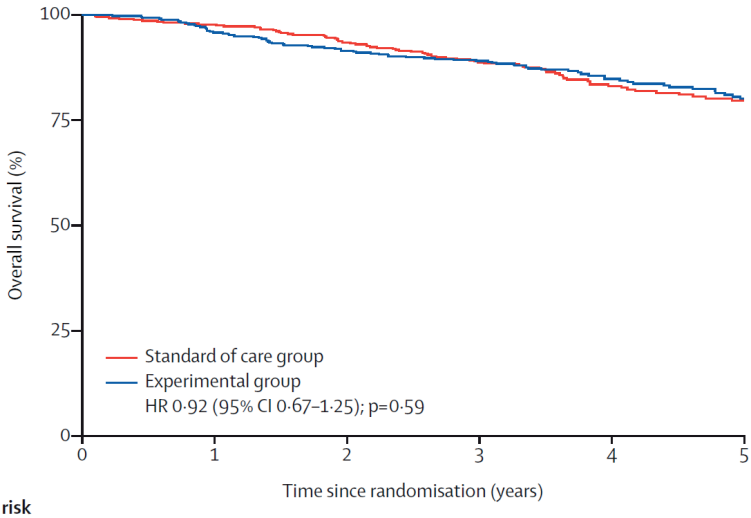
Figure 2 | Cumulative probability of disease-related treatment failure (A), distant metastases (B), and locoregional failure (C)

HR Hazard ratio.

The post-hoc subgroup analysis of disease-free survival from surgery, in patients with an R0 (>1 mm) resection within 6 months after the end of preoperative treatment is provided in the appendix (figure S2). Notably, randomisation in this subgroup comparison (743 of 902 eligible patients) is no longer guaranteed to be balanced with respect to important prognostic factors. Therefore, the comparison could be biased due to possible differences in type of resection and approach, resection rate, pathological response, and other factors, between the treatment groups. The adjusted disease-free survival according to a different definition by Fokas et al[17], which was similar to our definition of disease-related treatment failure but included a second primary cancer, other than colorectal, and death from all causes as events, had a hazard ratio of 0.75 (95% CI 0.60–0.93; p=0.010). However, according to this definition, patients are not disease free at the start of the curves, rather they are event free. Sensitivity analyses adjusting for possible time-related bias and separately for stratification factors showed similar results as the original analyses (figure s4, table S4). Local recurrence in each group is shown in table 2.

In the experimental group, median time between conclusion of radiotherapy and start of chemotherapy was 14 days (IQR 12–17) in patients who started allocated treatment. In the standard of care group, the optional field reduction after 45 or 46 Gy, as described in the protocol, was done for 102 (23%) of 441 patients who started treatment. Among patients who started allocated treatment, one (<1%) of 460 patients in the experimental group and ten (2%) of 441 in the standard of care group were given an external beam boost. Dose reduction of chemotherapy occurred in 201 (44%) of 460 patients in the experimental group, in 25 (6%) of 441 patients in the standard of care group during preoperative therapy, and in 64 (34%) of 187 patients during adjuvant chemotherapy in the standard of care group. Of the patients who started allocated treatment in the experimental group, 454 (99%) of 460 started with CAPOX. In the experimental group, 71 (15%) of 460 patients prematurely stopped preoperative chemotherapy. In the standard of care group, 40 (9%) of 441 patients prematurely stopped chemotherapy during preoperative (neoadjuvant) treatment and 69 (37%) of 187 who started adjuvant chemotherapy prematurely stopped chemotherapy during adjuvant treatment. Thus, in the experimental group, 389 (85%) patients completed preoperative chemotherapy compared with 401 (90%) patients in the standard of care group who completed chemotherapy. Reasons for stopping chemotherapy were toxicity (in 65 (14%) patients in the experimental group, 32 (7%) in the standard of care group during preoperative treatment, and 60 (32%) in the standard of care group during adjuvant therapy), disease progression (in one (<1%) in the experimental group, two (<1%) in the standard of care group during preoperative treatment, and one (1%) in the standard of care group during adjuvant therapy), and other (in one (<1%) in the experimental group, one (<1%) in the standard of care group during preoperative treatment, and three (2%) in the standard of care group during adjuvant therapy). Additional reasons in the experimental group were noncompliance (one (<1%), patient withdrew from study (two (<1%)), and unknown (one (<1%)). In the standard of care group, during preoperative treatment the reasons for prematurely stopping chemotherapy were unknown (five (1%)) and during adjuvant chemotherapy reasons were non-compliance (two (1%)), patient withdrew from study (two (1%)), and unknown reasons (one (1%)).

Overall, 426 (92%) of 462 patients in the experimental group and 400 (89%) of 450 patients in the standard of care group (p=0.086) had surgery with curative intent within 6 months from the end of preoperative treatment. No differences were seen between the groups regarding type of approach (p=0.31) or type of resection (p=0.56; table S5a, b). The proportion of patients with R0 resection was high and similar in the two groups (table 2). Of the 826 patients who had surgery with curative intent, the tumour was unresectable in five (1%) patients (three in the experimental group and two in the standard of care group), leading to exclusion of these patients from pathological analyses. 120 (28%) of 423 patients in the experimental group had a pathological complete response compared with 57 (14%) of 398 in the standard of care group (OR 2.37 (95% CI 1.67–3.37); p<0.0001; table 2). 3-year overall survival was 89.1% (95% CI 86.3–92.0) in the experimental group and 88.8% (85.9–91.7) in the standard of care group (HR 0.92 (95% CI 0.67–1.25); p=0.59; figure 3).



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	438 (3)	418 (8)	392 (169)	214 (208)
Experimental group	462 (0)	462 (1)	442 (2)	421 (9)	403 (181)	216 (217)

Figure 3 | Overall survival

HR Hazard ratio.

Table 2 | Number of surgeries with curative intent, disease-related treatment failures, and pathological outcomes

	Experimental group	Standard of care group	*p*-value
All eligible patients			
Surgery with curative intent within 6 months after the end of preoperative treatment			0.086*
Yes	426/462 (92)	400/450 (89)	
No	36/462 (8)	50/450 (11)	
Disease-related treatment failure, first occurring	128 (23.7)†	152 (30.4)†	0.019†
Locoregional failure			
Local progression, unresectable tumour	1/128 (1)	1/152 (1)	
R2 resection	0	0	
Local recurrence	22/128 (17)	13/152 (10)	
Locoregional failure and distant metastasis‡			
Local progression, unresectable tumour	4/128 (3)	2/152 (1)	
R2 resection	1/128 (1)	0	
Local recurrence	7/128 (5)	4/152 (3)	
Distant metastasis	86/128 (67)	123/152 (81)	
New primary colorectal tumour	3/128 (2)	5/152 (3)	
Treatment-related death	4/128 (3)	4/152 (3)	
Patients with a resection within 6 months after the end of preoperative treatment			
Residual tumour classification			0.87*
R0 > 1 mm	382/423 (90)	360/398 (90)	
R1 ≤ 1 mm	38/423 (9)	37/398 (9)	
R2	3/423 (1)	1/398 (<1)	
Circumferential resection margin			0.92*
> 1 mm	385/423 (91)	363/398 (91)	
≤ 1 mm	38/423 (9)	35/398 (9)	
Differentiation grade during pathological assessment			0.09*§
Well differentiated	62/423 (15)	82/398 (21)	
Moderately differentiated	167/423 (39)	189/398 (47)	
Poorly differentiated	44/423 (10)	35/398 (9)	
No tumour	129/423 (30)	69/398 (17)	
Not assessed	21/423 (5)	23/398 (6)	
Pathological complete response			<0.0001*
Yes	120/423 (28)	57/398 (14)	
No	303/423 (72)	341/398 (86)	
Pathological T stage ¶			<0.0001*
ypT0	129/423 (30)	69/398 (17)	
ypTis	2/423 (<1)	1/398 (<1)	
ypT1	17/423 (4)	17/398 (4)	
ypT2	82/423 (19)	96/398 (24)	
ypT3	157/423 (37)	190/398 (48)	
ypT4	36/423 (9)	25/398 (6)	
Pathological N stage¶			0.017*
ypN0	317/423 (75)	273/398 (69)	
ypN1	75/423 (18)	78/398 (20)	
ypN2	31/423 (7)	47/398 (12)	
Postoperative M stage¶			0.70*
ypM0	420/423 (99)	369/398 (99)	
ypM1	3/423 (1)	2/398 (1)	

Data are n (%). Proportions might not equal 100% due to rounding.

M stage metastasis stage; N stage nodal stage; R0 clear resection margins; R1 resection margin of 0–1 mm; R2 macroscopic residual tumour; T stage tumour stage.

*p value calculated using χ^2 test.

†3-year cumulative probability; p value calculated using the log-rank test.

‡Locoregional failure and distant metastasis diagnosed simultaneously within 30 days of each other.

§p value calculated on the basis of well, moderately, and poorly differentiated.

¶According to TNM 5.

Table 3

Adverse events

	Experimental group								Standard of care group											
	During preoperative therapy (n=460)								During preoperative therapy (n=441)								During adjuvant therapy (n=187)			
	Grade 1-2		Grade 3		Grade 4		Grade 5		Grade 1-2		Grade 3		Grade 4		Grade 5		Grade 1-2		Grade 3		Grade 4	
General adverse events																						
Allergic reaction	19	(4)	5	(1)	1	(<1)	0		3	(1)	0		0		0		6	(3)	1	(1)	0	
Alopecia	9	(2)	0		0		0		6	(1)	0		0		0		3	(2)	0		0	
Cystitis	38	(8)	1	(<1)	0		0		97	(22)	0		0		0		9	(5)	0		0	
Fatigue or lethargy	297	(65)	14	(3)	0		0		255	(58)	6	(1)	0		0		118	(63)	10	(5)	0	
Febrile neutropenia	0		5	(1)	0		0		0		1	(<1)	0		1	(<1)	0		1	(1)	0	
Hand-foot syndrome	134	(29)	8	(2)	0		0		77	(17)	5	(1)	0		0		68	(36)	4	(2)	0	
Neurological toxicity	362	(79)	19	(4)	1	(<1)	0		30	(7)	1	(<1)	0		0		119	(64)	16	(9)	0	
Radiation dermatitis	24	(5)	2	(<1)	0		0		112	(25)	14	(3)	0		0		1	(1)	0		0	
Rash maculopapular	18	(4)	0		0		0		16	(4)	2	(<1)	0		0		5	(3)	0		0	
Weight loss	78	(17)	3	(1)	0		0		48	(11)	1	(<1)	0		0		22	(12)	0		0	
Other*	266	(58)	111	(24)	20	(4)	1	(<1)	235	(53)	46	(10)	8	(2)	2	(<1)	106	(57)	26	(14)	7	(4)
Gastrointestinal toxicity																						
Abdominal pain†	213	(46)	25	(5)	2	(<1)	0		161	(37)	6	(1)	2	(<1)	0		40	(21)	4	(2)	0	
Diarrhoea	225	(49)	75	(16)	6	(1)	0		220	(50)	40	(9)	1	(<1)	0		95	(51)	13	(7)	0	
Faecal incontinence	37	(8)	0		0		0		43	(10)	0		0		0		2	(1)	0		0	
Nausea	232	(50)	16	(3)	0		0		139	(32)	3	(1)	0		0		90	(48)	4	(2)	0	
Oral mucositis	49	(11)	3	(1)	0		0		23	(5)	0		0		0		21	(11)	0		0	
Proctitis	44	(10)	4	(1)	0		0		48	(11)	6	(1)	0		0		3	(2)	0		0	
Rectal bleeding	103	(22)	1	(<1)	0		0		93	(21)	3	(1)	0		0		2	(1)	1	(1)	0	
Rectal mucositis	43	(9)	3	(1)	0		0		53	(12)	3	(1)	0		0		5	(3)	0		0	
Rectal pain	106	(23)	4	(1)	0		0		135	(31)	5	(1)	0		0		22	(12)	0		0	
Vomiting	99	(22)	9	(2)	0		0		38	(9)	3	(1)	0		0		38	(20)	3	(2)	0	

Data is presented as n (%).

In the standard of care group, no grade 5 adverse events occurred during adjuvant chemotherapy. *According to Common Terminology Criteria for Adverse events version 4.0 (ear and labyrinth disorders, endocrine disorders, eye disorders, general disorders and administration site conditions, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, investigations, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms benign, malignant and unspecified [including cysts and polyps], nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders). †Due to constipation, obstruction, or other causes.

An overview of adverse events is provided in table 3. Grade 3 or higher adverse events during preoperative treatment occurred in 219 (48%) of 460 patients in the experimental group, compared with 109 (25%) of 441 patients in the standard of care group and during adjuvant chemotherapy in 63 (34%) of 187 patients in the standard of care group. The most common grade 3 or higher adverse event was diarrhoea in both treatment groups (table 3). Serious adverse events occurred in the experimental group in 177 (38%) of 460 patients and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy (table S6, table S7a, b, c). Diarrhoea was the most common serious adverse event in the experimental group during preoperative chemotherapy (41 (9%) of 460) and in the standard of care group during preoperative chemoradiotherapy (11 (3%) of 441). During adjuvant chemotherapy, the most common serious adverse event in the standard of care group was infectious complications (eight (4%) of 187). Postoperatively, the most common serious adverse events in both groups were wound-related events (appendix p 18).

At the time of database lock, 161 patients had died, including 80 (17%) of 462 patients in the experimental group (four (5%) deaths were treatment related (one cardiac arrest, one pulmonary embolism, two infectious complications); 63 (79%) were rectal cancer related; six (8%) were due to a second primary tumour; four (5%) were due to other causes; and three (4%) were due to unknown reasons) and 81 (18%) of 450 patients in the standard of care group (four (5%) were treatment related (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression); 66 (82%) were related to rectal cancer; seven (9%) were due to a second primary tumour; and four (5%) were due to other causes; table S7c).

Analyses of quality-of-life data are to presented in a subsequent publication; here, we present the number of respondents. 3 years after resection, 602 (73%) of 821 patients received quality-of-life questionnaires (318 in the experimental group and 284 in the standard of care group; figure 1). Responses were obtained from 517 (86%) of 602 patients (274 in the experimental group and 243 in the standard of care group), of whom four (1%) did not respond in full. Among 211 (26%) of 821 patients who did not have a disease-related treatment failure and who did not have a stoma, 207 (98%) responded to the LARS questionnaire on bowel function (116 in the experimental group and 91 in the standard of care group). In total, 402 (78%) of 517 patients completed the QLQ-CIPN20 questionnaire on neurotoxicity (217 in the experimental group, 109 in the standard of care group without adjuvant chemotherapy, and 76 in the standard of care group with adjuvant chemotherapy). The questionnaire responses are to be reported in a subsequent publication.

Subgroup analyses of disease-related treatment failure according to baseline characteristics were consistently in favour of the experimental group (figure S5). Of the 54 participating centres, 28 (52%) opted to administer adjuvant chemotherapy in the standard of care group. In sensitivity analyses, within the standard of care group, hospital policy on adjuvant chemotherapy did not affect the probability of disease-related treatment failure at 3 years (HR 1.18 (95% CI 0.85–1.64); p=0.32). Comparing hospitals with and without adjuvant chemotherapy policies in the standard of care group, similar probabilities of distant metastases (28.5% (95% CI 23.1–34.0) vs 24.4% (18.2–30.6); p=0.34) and locoregional failure (7.2% (4.1–10.4) vs 4.3% (1.7–7.3); p=0.20) were seen.

Among the 912 eligible patients, 25 (3%) were followed up according to the watch-and-wait strategy due to a clinical complete response (14 in the experimental group and 11 in the standard of care group). In the experimental group, two (14%) of 14 patients developed distant metastasis and one (7%) developed local regrowth; and in the standard of care group, one (9%) of 11 patients developed distant metastasis, one (9%) developed local regrowth, and one (9%) simultaneously developed distant metastasis and local regrowth (figure S6).

DISCUSSION

In this study, we found that patients treated with short-course radiotherapy followed by 18 weeks of systemic chemotherapy before surgery have a significantly lower probability of disease-related treatment failure at 3 years after randomisation than do patients undergoing standard of care chemoradiotherapy followed by optional adjuvant chemotherapy after surgery. Hospital policy regarding the use of adjuvant chemotherapy did not affect disease-related treatment failure in the standard of care group. Additionally, with the experimental treatment, the pathological complete response rate was double that in the standard of care group. Given the increased tendency to refrain from surgery in patients with a clinical complete response after preoperative treatment, the experimental treatment offers the potential opportunity for patients seeking organ preservation.

The lower probability of disease-related treatment failure in the experimental group than in the standard of care group can mainly be attributed to a decreased rate of distant metastases. A possible explanation for this reduction in distant metastases might be better compliance to preoperative chemotherapy in the experimental group than with adjuvant chemotherapy when offered in the standard of care group[9]; patients are generally in better condition before than after surgery. Fewer weeks of chemotherapy (18 weeks preoperatively vs 24 weeks postoperatively) could also have contributed to better compliance in the experimental group than in the standard of care group, and did not result in reduced efficacy. Justification for a reduced number of chemotherapy cycles has emerged in several adjuvant colon cancer trials, showing that 3 months of CAPOX is non-inferior to 6 months of CAPOX in terms of disease-free survival[18,19]. Predefined hospital policy regarding the use of adjuvant chemotherapy

did not affect disease-related treatment failure in the standard of care group, suggesting that the efficacy of postoperative chemotherapy might be low[20,21]. Systemic chemotherapy in the experimental group started approximately 18 weeks earlier than in the standard of care group, potentially leading to more effective eradication of possible micrometastases. Although some guidelines exclude proximal rectal cancers from preoperative radiotherapy or chemoradiotherapy, we believe exceptions exist (eg, in the presence of high-risk criteria).

The randomised Polish II study[22], which included 515 patients with locally advanced rectal cancer, also compared preoperative short-course radiotherapy followed by chemotherapy with chemoradiotherapy. No significant difference in the 3-year cumulative incidence of distant metastases between the experimental (30%) and standard groups (27%) was reported (relative risk 1.21 (95% CI 0.59–1.15) p=0.25)[22]. In the RAPIDO trial, the rate of distant metastases (20.0%) was lower in the experimental group than in the standard of care group (26.8%), which was similar to the standard group in the Polish II study. Although MRI was not mandatory in the Polish II study, this similarity in outcome indicates that the two trials enrolled similar patient populations. An explanation for the difference between the two experimental groups in these two studies might be the duration of preoperative chemotherapy: six cycles of CAPOX or nine cycles of FOLFOX4 in the RAPIDO trial versus three cycles of FOLFOX4 in the Polish II study. Further insight into how the number of chemotherapy cycles affects this outcome will come from the ongoing randomised STELLAR trial[23]. In the STELLAR trial, patients with MRI-staged non-metastatic locally advanced rectal cancer are given six cycles of CAPOX, divided into four preoperative cycles after short-course radiotherapy and two adjuvant chemotherapy cycles[23].

The overall probability of locoregional failure in the RAPIDO trial at 3 years is similar to previously published data[1,2,4,24]. A longer period between radiotherapy and surgery in the experimental group than in the standard of care group might have led to increased downstaging, and possibly a higher proportion of patients with a pathological complete response. However, for patients who had little or no response to therapy, the extended interval between randomisation and surgery in the experimental group compared with the standard of care group (median time 25.5 weeks (IQR 24.0–27.9) vs 15.9 weeks (14.6–17.6)) might be disadvantageous. The higher number of residual pathological T4 (ypT4) tumours in the experimental group than in the standard of care group (9% vs 6%) could indicate the presence of a small proportion of non-responding tumours that might actually progress during preoperative treatment. Hence, early response imaging could be advocated, enabling alterations in therapeutic approach.

In the Stockholm III trial,[25] with less advanced tumours than in our study population, pathological complete response was seen in 29 (10.4%) of 285 participants following short-course radiotherapy with delayed surgery compared with two (2.2%) of 94 participants after long-course radiotherapy[25]. In the experimental group of the RAPIDO trial, the pathological complete response rate was 28%. Apart from the longer interval between radiotherapy

and surgery in RAPIDO than in Stockholm III (>18 weeks vs 4–8 weeks), the addition of chemotherapy in RAPIDO is likely to have contributed to the higher rate of pathological complete response. In a study with four consecutive series of patients with intermediate-risk rectal cancer, pathological complete response rates increased from 18% (95% CI 10–30) after chemoradiotherapy alone to 38% (27–51) in patients receiving six cycles of modified FOLFOX6 in the interval between chemoradiotherapy and surgery[26]. Delivering additional cycles of chemotherapy and extending the interval between chemoradiotherapy and surgery seems to have added value in achieving pathological complete response, and is associated with a survival benefit[27]. A pooled analysis showed that patients with a pathological complete response after chemoradiotherapy have favourable outcomes regarding local control and overall survival[28]. Although no studies have yet shown that a pathological complete response achieved by the additional effect of chemotherapy is associated with improved prognosis, this outcome seems possible. Additionally, an adequately assessed clinical complete response followed by a watch-and-wait strategy is increasingly being used as an alternative to major surgery[29]. The experimental RAPIDO regimen resulted in a high rate of pathological complete response and could potentially be used to initiate a watch-and-wait strategy.

After a median follow-up of 4.6 years, no difference in overall survival was observed, but might be revealed with longer follow-up that will continue until 10 years after randomisation, according to the trial protocol.

The optimal timing of chemotherapy in a total neoadjuvant approach remains a matter of debate. The fear of local progression could justify a radiotherapy-first approach, whereas prioritising the early control of potential micrometastases would justify a chemotherapyfirst strategy. The chemotherapy-first strategy is under investigation in the PRODIGE 23 trial[30] (preoperative chemotherapy before chemoradiotherapy, followed by total mesorectal excision and adjuvant chemotherapy). The initial results showed significantly increased 3-year disease-free survival, metastasis-free survival, and pathological complete response rate compared with chemoradiotherapy followed by total mesorectal excision and adjuvant chemotherapy[30]. An obvious advantage of short-course radiotherapy as part of a total neoadjuvant approach is its short duration with minimal delay between the end of radiotherapy and start of systemic chemotherapy. To our knowledge, optimal timing for chemotherapy has been investigated in only one published randomised study so far[31]. In that study, patients having preoperative chemotherapy after chemoradiotherapy had fewer adverse events, better compliance to chemoradiotherapy, and higher pathological complete response rates than did patients who started with preoperative chemotherapy[31]. The long-term results on oncological outcomes are awaited[31]. Currently, chemoradiotherapy before preoperative chemotherapy appears to be the preferred option.

To exclude the potential bias of recurrent disease and treatment thereof, only patients without disease-related treatment failure at 3 years will be analysed in the RAPIDO trial with respect to quality of life, results of which will be published elsewhere.

In the experimental group of the RAPIDO trial, more serious adverse events of diarrhoea and neurological toxicity occurred than in the standard of care group, probably due to preoperative treatment with CAPOX. Another possible contributing factor to diarrhoea could be the longer period between diagnosis and removal of the tumour. Despite differences in toxicity between treatment groups during preoperative treatment, no effect on surgery was observed in our previous report of compliance, toxicity, and post-operative complications in the RAPIDO trial[9].

Concerns have been raised about short-course radiotherapy having lower efficacy than conventional chemoradiotherapy; however, to our knowledge, no randomised trials have compared the anti-tumour or downstaging effect of short-course radiotherapy and delayed surgery to chemoradiotherapy with a similar delay. Therefore, we cannot draw firm conclusions about relative efficacy between short-course radiotherapy and chemoradiotherapy. In the Stockholm III trial,[25] more downstaging and a higher pathological complete response rate were observed after short-course radiotherapy than after long-course radiotherapy, indicating that the tumour-cell kill effect is probably higher from five fractions of 5 Gy than from 25 fractions of 2 Gy, and not less, as the commonly used coefficients in the linear-quadratic formula indicate[32]. Additionally, the long-term consequences of short-course radiotherapy are under debate. Evidence indicates that short-course radiotherapy results in long-term morbidity[33]. However, the long-term morbidity caused by chemoradiotherapy is less studied than short-course radiotherapy, making a comparison difficult. Moreover, at least two randomised trials indicate no differences in late complications (i.e., at 3–5 years) between the two treatments[34,35]. Notably, most data on long-term consequences originate from trials using either two anterior-posterior portals or the conventional three dimensional-conformal radiotherapy technique instead of the currently used intensity-modulated radiation therapy or volumetric modulated arc therapy techniques. Furthermore, the target volumes have been reduced compared with the many studies on which our present knowledge of radiotherapy-induced late effects (i.e., at 4–10 years) after rectal cancer radiotherapy has been based[33]. With these newer techniques and the possibilities of daily adaptive therapy, doses to relevant organs at risk are substantially reduced. Therefore, the ultimate effects on long-term functional outcomes and morbidity require careful assessment in the coming years.

Our study has several limitations. Alteration of the primary endpoint during a trial is undesirable but was considered necessary because disease-free survival was inappropriate in a neoadjuvant trial on patients with high-risk locally advanced rectal cancer. Another potential limitation was the absence of a central review of baseline MRIs. Patients could have been under-staged or overstaged, although over-staging was most probably predominant[36]. However, bias towards one group is unlikely to have occurred because randomisation was stratified.

A prominent benefit of the experimental treatment reported here, especially in the context of the COVID-19 pandemic, is the decrease in the number of treatment days spent in health-care facilities, 12 days in the experimental group versus 25–28 days in the standard of care group for the preoperative period on the basis of typical treatment regimens. If adjuvant chemotherapy is given (8 treatment days in 24 weeks if CAPOX, 24 days if FOLFOX4), the reduction is even more pronounced. This reduction in time spent in hospital minimises the risk for these susceptible patients and improves hospitals' ability to implement physical distancing during the COVID-19 pandemic situation[37].

In summary, in patients with high-risk locally advanced rectal cancer, the RAPIDO trial shows that short-course radiotherapy followed by 18 weeks of chemotherapy before surgery decreases the probability of disease-related treatment failure compared with chemoradiotherapy with or without adjuvant chemotherapy, mainly by reducing the probability of distant metastases. Additionally, the high rate of pathological complete response in the experimental group can potentially contribute to organ preservation. Supported by previously reported high compliance and tolerability[9], this treatment could be considered as a new standard of care for patients with high-risk locally advanced rectal cancer. Future research could focus on assessing tumour response to preoperative treatment at an early stage and improving the efficacy of systemic therapy with the aim of decreasing distant metastases even further.

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SUPPLEMENTAL MATERIAL

Table S1 | Participating institutes and collaborative investigators

Number of patients recruited	Location (country)	Institute	Investigator (department)
106	Uppsala (Sweden*)	Akademiska Sjukhuset	C. Radu (clinical oncology) § L. Påhlman† (surgery)
71	Stockholm (Sweden*)	Karolinska Universitetssjukhuset, Solna	T. Fokstuen (clinical oncology) § T. Holm (surgery)
51	Breda (the Netherlands)	Amphia Ziekenhuis	A. J. Ten Tije (medical oncology) § R. M. P. H. Crolla (surgery)
		Dr. Bernard Verbeeten Instituut (Tilburg	T. Rozema (radiation oncology)
39	Barcelona (Spain*)	Vall d'Hebron Institut d'Oncologia	J. Capdevila (clinical oncology) § E. Espin (surgery)
36	Alkmaar (the Netherlands)	Noordwest Ziekenhuisgroep	M. P. Hendriks (medical oncology) W. H. Schreurs (surgery) § H. P. Kool (radiation oncology)
36	Ljubljana (Slovenia*)	Institute of Oncology Ljubliana	J. Benedik (medical oncology) I. Edhemovic (surgery) § V. Velenik (radiation oncology)
30	Linköping (Sweden*)	Linköpings Universitet	I. Verbiené (clinical oncology) § O. Hallböök (surgery)
28	Leeuwarden (the Netherlands)	Medisch Centrum Leeuwarden ‡	M. B. Polée (medical oncology) § C. Hoff (surgery)
		Radiotherapeutisch Instituut Friesland	A. Slot (radiation oncology)
25	Valencia (Spain*)	Hospital Clínico Universitario de Valencia	A. Cervantes (clinical oncology) § A. Espí Macías (surgery)
23	Groningen (the Netherlands)	Universitair Medisch Centrum Groningen	D.J.A. de Groot (medical oncology) § K. Havenga (surgery) J. C. Beukema (radiation oncology)

21	Sneek (the Netherlands)	St Antonius Ziekenhuis	G. J. Veldhuis (medical oncology) § D. Hess (surgery)
21	Zwolle (the Netherlands)	Isala Klinieken	M. Tascilar (medical oncology) § G.A. Patijn (surgery)
		Radiotherapeutisch Centrum Zwolle	J. Vos (radiation oncology)
20	Västerås (Sweden*)	Västmanlands Sjukhus	A. Piwowar (clinical oncology) § K. Smedh (surgery)
20	Saint Louis (United States*)	Washington University Medical School	P. Parinkh (clinical oncology) § H. Kim (clinical oncology) § M. L. Silviera (surgery)
20	Aalborg (Denmark*)	Aalborg Universitetshospital	L. Østergaard (clinical oncology) § F. Svendsen Jensen (surgery)
20	Barcelona (Spain*)	ICO Hospitalet. Hospital Duran I Reynals	R. Salazar (clinical oncology) § S. Biondo (surgery)
18	Den Haag (the Netherlands)	Haaglanden Medisch centrum	F.J.F. Jeurissen (medical oncology) A.W.K.S. Marinelli (surgery) H. M. Ceha (radiation oncology) § T.C. Stam (radiation oncology)
18	Lund/Malmö (Sweden*)	Universitetssjukhuset i Lund	A. Johnsson (clinical oncology) § M.L. Lydrup (surgery)
16	Den Haag (the Netherlands)	HagaZiekenhuis	P. Quarles an Ufford (medical oncology) § W.H. Steup (surgery)
15	Nijmegen (the Netherlands)	Radboud Universitair Medisch Centrum	S. A. Radema (medical oncology) § H. de Wilt (surgery) P. Braam (radiation oncology)
15	Kalmar (Sweden*)	Länssjukhuset i Kalmar	C. Bratthäll (clinical oncology) § J. Assarsson (surgery)
15	Valencia (Spain*)	Consorcio Hospital General Universitario Valencia	M. J. Safont (clinical oncology) § J.C. Bernal (surgery)

14	Kristiansand (Norway)	Sørlandet Sykehus Kristiansand	C. Kersten (clinical oncology) § O. Mjåland (surgery)
12	Utrecht (the Netherlands)	Diakonessenhuis	D. Ten Bokkel Huinink (medical oncology) § A. Pronk (surgery)
		Universitair Medisch Centrum Utrecht	O. Reerink (radiation oncology)
12	Groningen (the Netherlands)	Martini Ziekenhuis	J. M. van Rooijen (medical oncology) § A.F.T. Olieman (surgery) A.C.M. van den Bergh (radiation oncology)
12	Madrid (Spain*)	Hospital Ramón y Cajal	V. Pachón (clinical oncology) § J. die Trill (surgery)
11	Leiden (the Netherlands)	Leids Universitair Medisch Centrum	H. W. Kapiteijn (medical oncology) K.C.M.J. Peeters (surgery) § F.P. Peters (radiation oncology)
11	Hoofddorp (the Netherlands)	Spaarne Gasthuis	B. de Valk (medical oncology) § Q.A.J. Eijsbouts (surgery)
10	Amsterdam (the Netherlands)	Nederlands Kanker Instituut – Antoni van Leeuwenhoek	M. E. van Leerdam (medical oncology) § G.L. Beets (surgery) L.G.H. Dewit (radiation oncology)
10	Heerenveen (the Netherlands)	Tjongerschans Ziekenhuis	J. de Boer (medical oncology) § P.H.J.M. Veldman
10	Gouda (the Netherlands)	Groene Hart Ziekenhuis	W.M. van der Deure (medical oncology) § R.F. Schmitz (surgery)
10	Falun (Sweden*)	Falu Lasarett	A. Berglund (clinical oncology) § L. Österlund (surgery)
10	Umeå (Sweden*)	Norrlands Universitetssjukhus	B. Lindh (clinical oncology) § O. Lundberg (surgery)
10	Växjö (Sweden*)	Central Hospital Växjö	U. Palenius (clinical oncology) § S. Jangmalm (surgery)
9	Delft (the Netherlands)	Reinier de Graaf Gasthuis	A. C. M. van Luijtgaarden (medical oncology) § J.W.T. Dekker (surgery) J.M. Immink (radiation oncology)

9	Odense (Denmark*)	Odense Universitetshospital	P. Pfeiffer (clinical oncology) § K.E.J. Jensen (surgery)
9	Oslo (Norway)	Oslo Universitetssykehus HF Ulleval	M. Grønlie Guren (clinical oncology) § A.N. Nesbakken (surgery)
8	Assen (the Netherlands)	Wilhelmina Ziekenhuis	P. Nieboer (medical oncology) § W.A. Bleeker (surgery)
8	Hengelo (the Netherlands)	Ziekenhuisgroep Twente	E. J. M. Siemerink (medical oncology) § J.W.P. Vanstiphout (surgery)
8	Sundsvall (Sweden*)	Sundsvalls Sjukhus	P. Flygare (clinical oncology) § M. Walldén (surgery)
8	Valencia (Sweden*)	Hospital Universitari i Politècnic la Fe	J. Aparicio (clinical oncology) § E. Garcia Granero (surgery)
8	Borås (Sweden*)	Södra Älvsborgs Sjukhus	L. Malmberg (clinical oncology) § G. Svaninger (surgery)
7	Amsterdam (the Netherlands)	Onze Lieve Vrouwe Gasthuis Ziekenhuis	E. D. Kerver (medical oncology) § S. Festen (surgery)
7	Deventer (the Netherlands)	Deventer Ziekenhuis	A. L. T. Imholz (medical oncology) § R.J.I. Bosker (surgery)
		Radiotherapiegroep Deventer	J.H.M. Bekker (radiation oncology)
7	Göteborg (Sweden*)	Sahlgrenska Universitetssjukhuset	S. Ottosson (clinical oncology) § G. Carlsson (surgery)
6	Amsterdam (the Netherlands)	Amsterdam Universitair Medisch Centrum (loc. Academisch Medisch Centrum)	C.J.A. Punt (medical oncology) P. J. Tanis (surgery) § E.D. Geijsen (radiation oncology)
6	Karlstad (Sweden*)	Centralsjukhuset i Karlstad	B. L. Lödén (clinical oncology) § P. Hede (surgery)
6	Eskilstuna (Sweden*)	Mälarsjukhuset ‡	H. Hörberg (clinical oncology) § G. Dafnis (surgery)
5	Eindhoven (the Netherlands)	Catharina Ziekenhuis	G.J. Creemers (medical oncology) G.A.P. Nieuwenhuijzen (surgery) § H. van den Berg (radiation oncology)

3	Örebro (Sweden*)	Universitetssjukhuset	K. Villmann (clinical oncology) § P. Matthiessen (surgery)
2	Gävle (Sweden*)	Gävle Sjukhus	K. Kovacs (clinical oncology) § J. Hol (surgery)
2	Skövde (Sweden*)	Skaraborgs Sjukhus Skövde	J. H. Svensson † (clinical oncology) § J. Haux (clinical oncology) § S. Skullman (surgery)
1	Amsterdam (the Netherlands)	Amsterdam Universitair Medisch Centrum (loc. Vrije Universteit Medical Center)	J.J. van der Vliet (medical oncology) J.B. Tuynman (surgery) A. M. E. Bruynzeel (radiation oncology) §

* Hospital policy for adjuvant chemotherapy.

† Passed away.

§ Local PI.

‡ Changed hospital policy for adjuvant chemotherapy from yes to no during study.

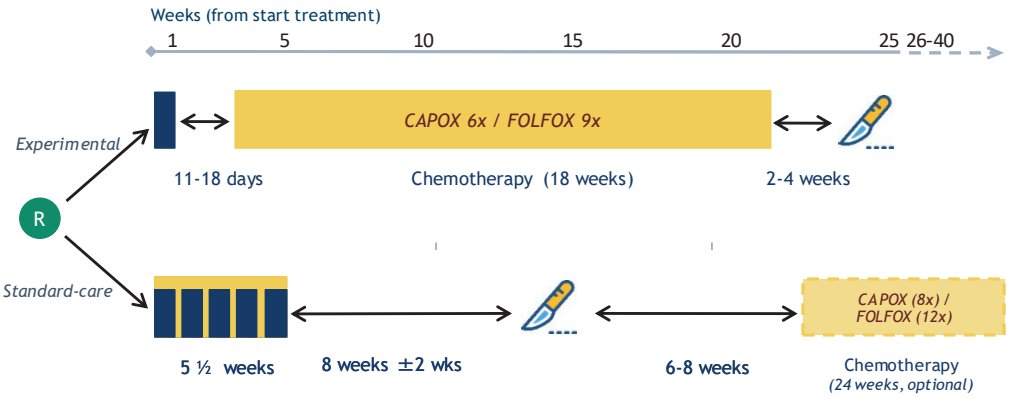


Figure S1 | Treatment regimen

Table S2a | Dose reductions capecitabine, 5-FU, leucovorin

	Grade 2	Grade 3	Grade 4
1ste occurrence	Interrupt treatment until recovery to grade 0-1 → continue with no dose reduction	Interrupt treatment until recovery to grade 0-1 → continue with 25% dose reduction	Interrupt treatment until recovery to grade 0-1 → continue with 50% dose reduction
2nd occurrence	Interrupt treatment until recovery to grade 0-1 → continue with 25% dose reduction	Interrupt treatment until recovery to grade 0-1 → continue with 50% dose reduction	Discontinue treatment
3rd occurrence	Interrupt treatment until recovery to grade 0-1 → continue with 50% dose reduction	Discontinue treatment	
4th occurrence	Discontinue treatment		

Table S2b | Dose reductions for oxaliplatin for sensory neuropathy

Sensory neuropathy	Oxaliplatin dose
Non-painful paresthesia ≥ 14 days or temporary (7-14 days) painful paresthesia/functional impairment	25% reduction
Persistent (pain≥ 14 days) painful paresthesia/functional impairment	Omit until recovery, then restart at 50%
Recurrent neurotoxicity after 50% dose reduction	Permanently discontinued

Table S2c | Dose reductions for specific toxicity

Toxicity during previous cycle	Grade	Next dose oxaliplatin	Next dose capecitabine, 5-FU, leucovorin
Diarrhoea	3/4	75%	75-50%
Mucositis	3/4	Full dose	75-50%
Skin	3/4	Full dose	75-50%
Hand-foot-syndrome	2/3	Full dose	According to table S2a
Neurotoxicity	According to table S2b	According to table S2b	Full dose
Other non haematologic toxicities	3/4	75%	75-50%

Table S3 | Addition table 1, inclusion characteristics of eligible patients

	Experimental (n = 462)	Standard-care (n = 450)
Year of randomization		
2011	7 (1.5)	10 (2.2)
2012	34 (7.4)	30 (6.7)
2013	96 (20.8)	107 (23.8)
2014	129 (27.9)	103 (22.9)
2015	148 (32.0)	142 (31.6)
2016	48 (10.4)	58 (12.9)
Country		
Denmark	16 (3.5)	12 (2.7)
The Netherlands	180 (39.0)	180 (40.0)
Norway	12 (2.6)	11 (2.4)
Slovenia	18 (3.9)	17 (3.8)
Spain	58 (12.5)	60 (13.3)
Sweden	168 (36.4)	160 (35.6)
United States	10 (2.2)	10 (2.2)

Data are n (%). Percentages may not equal 100 due to rounding.

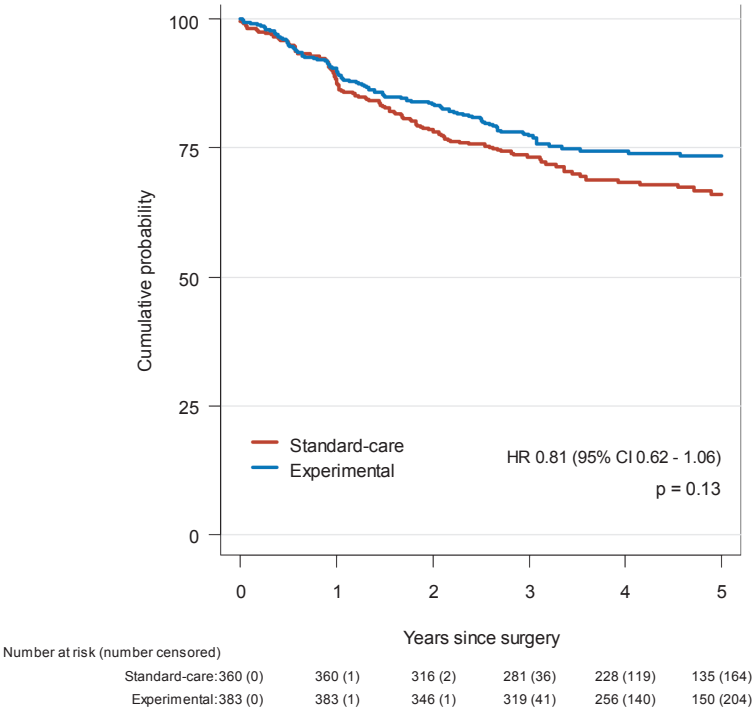
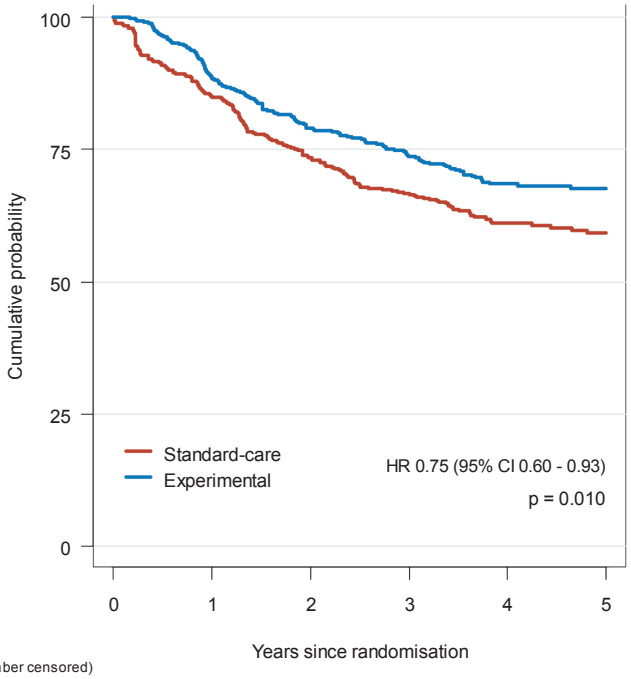


Figure S2 | Subgroup analysis of disease-free survival from surgery, in patients with an R0 (> 1 mm) resection within six months after end of preoperative treatment. Note that the randomisation in this subgroup comparison (743 out of 902 eligible patients) is no longer guaranteed to be balanced with respect to important prognostic factors. The comparison could therefore be biased due to possible differences in type of resection and approach, resection rate, pathological response, etc. between the treatment groups.



Number at risk (number censored)

Standard-care:	450 (0)	450 (2)	381 (3)	328 (7)	294 (130)	153 (154)
Experimental:	462 (0)	462 (1)	410 (2)	364 (8)	333 (149)	173 (180)

Figure S3 | Recently, Fokas et al.[1] brought forward an adjusted DFS, similar to our DrTF but including secondary primary cancer, other than colorectal, and death from all causes as events as well. Note that with this definition patients are not disease-free at the start of the curves, rather event-free.

1. Fokas E, Glynne-Jones R, Appelt A, et al. Outcome measures in multimodal rectal cancer trials. Lancet Oncol 2020; 21: e252–64.

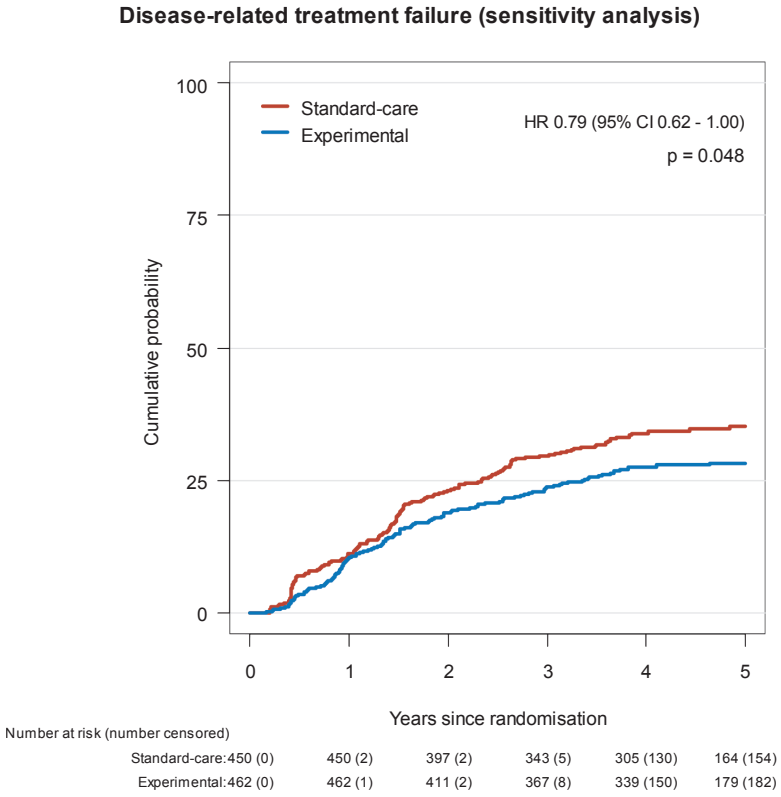


Figure S4 | Sensitivity analysis adjusting for possible time-related bias (DrTF)
Re-staging and surgery after preoperative treatment occurs approximately 10 weeks earlier (median time) in the standard-care group. To adjust for possible time-related bias, a sensitivity analysis was performed in which the timing of DrTF in the standard-care group was moved to 10 weeks later. Note that this sensitivity analysis overcorrects, since not all DrTF events are detected by imaging or during surgery (i.e. treatment-related death). The steep rise in the standard-care group still appears with the same rate of events, but at a later moment. The difference between the two groups remains statistically significant.

Table S4 | Sensitivity analyses adjusting for stratification factors

	Hazard Ratio	95% confidence interval	p-value
Adjusted disease-related treatment failure	0.76	0.60-0.96	0.024
Adjusted overall survival	0.94	0.74-1.19	0.68
Adjusted distant metastases	0.70	0.55-0.89	0.0063
Adjusted locoregional failure	1.45	1.15-1.84	0.099

As sensitivity analyses a Cox (cause-specific) proportional hazards frailty model was fitted with treatment, using ECOG, T- and N-stage as adjusting covariates, and with institution as a random (frailty) effect. The reason for adding institution as random effects rather than covariates is the large number of (often small) institutions.

Table S5a | Surgical details

Patients with surgery with curative intent within six months after the end of preoperative treatment	Experimental (n = 426)	Standard-care (n = 400)	p-value
Time to surgery since randomisation (weeks)			<0.0001 *
(median, [IQR])	25.5 [24.0 – 27.9]	15.9 [14.6 – 17.6]	
Type of approach			0.31 †
Laparoscopic	178 (41.8)	182 (45.5)	
Laparoscopic converted to open	42 (9.9)	29 (7.2)	
Open	206 (48.4)	189 (47.3)	
Type of resection			0.56 †
No resection	3 (0.7)	2 (0.5)	
Anterior resection, PME	41 (9.6)	33 (8.3)	
Low anterior resection, TME	207 (48.6)	190 (47.5)	
Abdominoperineal excision	149 (35.0)	160 (40.0)	
Hartmann's procedure	20 (4.7)	12 (3.0)	
Posterior pelvic exenteration	1 (0.2)	1 (0.3)	
Total pelvic exenteration	2 (0.5)	2 (0.5)	
Intersphincteric resection	3 (0.7)	-	

Data are n (%). Percentages may not equal 100 due to rounding. * P-value calculated with the Mann-Whitney U test. † P-values are calculated with chi-square. IQR = interquartile range. PME = partial mesorectal excision. TME = total mesorectal excision.

Table S5b | Additional surgical resections, as reported in the CRFs

	Experimental (n = 426)	Standard-care (n = 400)
Number of additional organs/structures resected		
None	393 (92.3)	364 (91.0)
1 organ/structure	16 (3.8)	24 (6.0)
2 organs/structure	15 (3.5)	7 (1.8)
3 organs/structure	2 (0.5)	3 (0.8)
4 organs/structure	- -	1 (0.3)
5 organs/structure	- -	1 (0.3)
Resected organ/structure (or part of)	**(n=52)**	**(n=56)**
Ovarium/uterus	20 (38.5)	16 (28.6)
Vagina	4 (7.7)	3 (5.4)
Vesiculae seminales/prostate/funiculus spermaticus	11 (21.2)	20 (35.7)
Urether/bladder	5 (9.6)	7 (12.5)
Colon/appendix	2 (3.8)	3 (5.4)
Short bowel	2 (3.8)	2 (3.6)
Spleen	1 (1.9)	- -
Liver	2 (3.8)	- -
Lateral lymph nodes	2 (3.8)	3 (5.4)
Sacrum/coccyx	1 (1.9)	- -
Levator/endopelvic fascia	1 (1.9)	2 (3.6)
Vertebral wall	1 (1.9)	- -

Data are n (%). Percentages may not equal 100 due to rounding.

Table S6 | Adverse events: highest grade reported per patient

	Experimental	Standard-care	
	During preoperative therapy	*During preoperative therapy*	*During postoperative therapy*
Highest grade adverse event reported by patient	(n = 460)	(n = 441)	(n = 187)
None	- (51.7)	7 (1.6)	3 (1.6)
Grade 1-2	238 (41.5)	323 (73.2)	119 (63.6)
Grade 3	191 (6.5)	98 (22.2)	58 (31.5)
Grade 4	30 (0.2)	10 (2.3)	7 (3.8)
Grade 5	1	3 (0.7)	-

Toxicity was graded according to the Common Terminology Criteria for adverse events (CTCAE) version4.0. Data are n (%). Percentages may not equal 100 due to rounding.

Table S7a | Number of serious adverse events per patient

	Experimental	Standard-care	
	(n = 460)	No adjuvant chemotherapy (n = 253)	Adjuvant chemotherapy started (n = 187)
None	283 (61.5)	166 (65.6)	124 (66.3)
1	125 (27.2)	70 (27.7)	51 (27.3)
2	35 (7.6)	12 (4.7)	7 (3.7)
3	15 (3.3)	5 (2.0)	3 (1.6)
4	1 (0.2)	-	3 (1.6)
5	1 (0.2)	-	-

Table S7b | Number of serious adverse events per treatment period

	Experimental	Standard-care
Before start of treatment	(n = 460)	(n = 441)
	3 (0.7)	2 (0.5)
During short-course radiotherapy	(n = 460)	-
	17 (3.7)	
During preoperative chemo(radio)therapy	(n = 460)	(n=441)
	155 (33.7)	73 (16.6)
Postoperatively	(n = 426)	(n = 400)
	73 (17.1)	80 (20.0)
During adjuvant chemotherapy	(n = 6)	(n = 187)
	1*	40 (21.4)

* Preoperative chemotherapy had to be stopped early (after four cycles of CAPOX) due to serious adverse events. After surgery, chemotherapy was continued.

Table S7c | Specification of serious adverse events

	Experimental	Standard-care
Before start of treatment	(n = 460)	(n = 441)
Fever	1 (0.2)	1 (0.2)
Ileus	-	1 (0.2)
Obstipation	1 (0.2)	-
Rectal hemorrhage	1 (0.2)	-

During preoperative treatment

	Experimental		Standard-care
	Short-course radiotherapy (n = 460)	Chemotherapy (n = 460)	Chemoradiotherapy (n = 441)
Abdominal pain/ obstipation /obstruction	5 (1.1)	22 (4.8)	10 (2.3)
Blood loss (oral, rectal, urine)	2 (0.4)	4 (0.9)	2 (0.5)
Cardiovascular disease	-	8 (1.7)	10 (2.3)
Dehydration/laboratory deviations	-	3 (0.7)	5 (1.1)
Diarrhoea	4 (0.9)	41 (8.9)	11 (2.5)
General weakness/fatigue	-	1 (0.2)	3 (0.7)
Infectious, abdominal	-	11 (2.4)	6 (1.4)
Infectious, other	4 (0.9)	14 (3.0)	8 (1.8)
Nausea/vomiting/anorexia	-	8 (1.7)	1 (0.2)
Psychological	-	1 (0.2)	2 (0.5)
Pulmonary	-	6 (1.3)	2 (0.5)
Thromboembolic	1 (0.2)	12 (2.6)	6 (1.4)
Other, abdominal	1 (0.2)	15 (3.3)	4 (0.9)
Other	-	9 (2.0)	3 (0.7)

	Experimental	Standard-care
Postoperatively	(n = 426)	(n = 400)
Anastomotic leak	5 (1.2)	6 (1.5)
Cardiovascular disease	1 (0.2)	1 (0.3)
Dehydration/high output stoma/diarrhoea	7 (1.6)	5 (1.3)
Ileus	8 (1.9)	10 (2.5)
Pain	4 (0.9)	1 (0.3)
Stoma-related	1 (0.2)	2 (0.5)
Thromboembolic	2 (0.5)	2 (0.5)
Urinary	3 (0.7)	3 (0.8)

Vomiting/anorexia/general weakness	3	(0.7)	3	(0.8)
Wound related	28	(6.6)	41	(10.3)
Other	11	(2.6)	6	(1.5)

	Experimental		Standard-care	
During adjuvant chemotherapy	(n = 6)		(n = 187)	
Abdominal pain/ obstipation /obstruction	-		3	(1.6)
Blood loss (oral, rectal, urine)	-		1	(0.5)
Cardiovascular disease	-		1	(0.5)
Dehydration/laboratory deviations	-		4	(2.1)
Diarrhoea	-		5	(2.7)
General weakness/fatigue	-		2	(1.1)
Infectious, abdominal	-		-	
Infectious, other	1		8	(4.3)
Nausea/vomiting/anorexia	-		2	(1.1)
Psychological	-		-	
Pulmonary	-		2	(1.1)
Thromboembolic	-		2	(1.1)
Other, abdominal	-		6	(3.2)
Other	-		4	(2.1)

Table S8 | Causes of death

	Experimental (n = 80)	Standard-care (n = 81)
Treatment-related death		
Preoperative		
Cardiac arrest *	1 (1.3)	-
Neutropenic sepsis	-	1 (1.2)
Aspiration after a fall	-	1 (1.2)
Suicide †	-	1 (1.2)
Postoperative		
Pulmonary embolism	1 (1.3)	1 (1.2)
Infectious complications	2 (2.5)	
Rectal cancer	63 (78.8)	66 (81.5)
Secondary primary tumour	6 (7.5)	7 (8.6)
Other	4 (5.0)	4 (4.9)
Unknown	3 (3.8)	-

* In the presence of electrolyte disturbances due to diarrhoea.

† Due to a severe depression after rectal cancer diagnosis.

		Experimental		Standard-care		Experimental versus standard-care	
		Event/ patients	DrTF probability at 3 year [95% CI]	Event/ patients	DrTF probability at 3 year [95% CI]	HR [95% CI]	$P_{interaction}$
Gender	Male	61/300	26% [21-31]	57/312	32% [26-37]	0.78 [0.59-1.03]	0.75
	Female	19/162	20% [14-26]	24/138	28% [20-35]	0.73 [0.47-1.12]	
Age	< 65	47/280	25% [20-30]	54/270	31% [26-37]	0.75 [0.56-1.02]	0.99
	≥ 65	33/182	22% [16-28]	27/180	29% [22-36]	0.75 [0.51-1.10]	
Clinical T-stage	cT2-T3	47/315	22% [17-27]	55/313	29% [24-35]	0.77 [0.57-1.03]	0.63
	cT4	33/147	27% [20-34]	26/137	32% [25-40]	0.74 [0.50-1.09]	
Clinical N-stage	cN0	6/42	14% [4-25]	7/35	23% [9-38]	0.93 [0.34-2.52]	0.78
	cN+	74/420	25% [21-29]	74/415	31% [27-35]	0.75 [0.59-0.95]	
Lateral nodes	-	63/395	22% [18-26]	71/380	32% [27-36]	0.70 [0.54-0.91]	0.14
	+	17/66	33% [22-45]	10/69	25% [15-35]	1.13 [0.64-2.01]	
EMVI	-	50/313	22% [17-26]	54/323	27% [23-32]	0.73 [0.55-0.99]	1.00
	+	30/148	29% [21-36]	27/125	38% [29-46]	0.75 [0.50-1.12]	
MRF	-	27/176	21% [15-27]	28/178	29% [22-36]	0.72 [0.49-1.07]	0.77
	+	53/285	26% [21-31]	53/271	32% [26-37]	0.77 [0.58-1.04]	
ECOG	0	60/369	23% [19-27]	66/365	30% [26-35]	0.74 [0.57-0.96]	0.78
	1	20/93	27% [18-36]	15/85	31% [21-41]	0.82 [0.48-1.39]	
Distance from anal verge	< 5 cm	16/103	25% [16-33]	19/115	30% [21-38]	0.77 [0.48-1.25]	0.93
	5-10 cm	34/181	21% [15-27]	27/153	28% [20-35]	0.77 [0.52-1.15]	
	≥ 10 cm	24/146	27% [20-35]	28/151	35% [27-43]	0.72 [0.48-1.08]	
Standard-care group	No	30/189	24% [18-31]	33/185	28% [22-35]	0.85 [0.59-1.24]	0.38
adjuvant hospital policy	Yes	50/273	23% [18-28]	48/265	32% [26-38]	0.70 [0.51-0.94]	0.75
Overall estimate		128/462	24% [20-28]	125/450	30% [26-35]	0.75 [0.60-0.95]	0.99

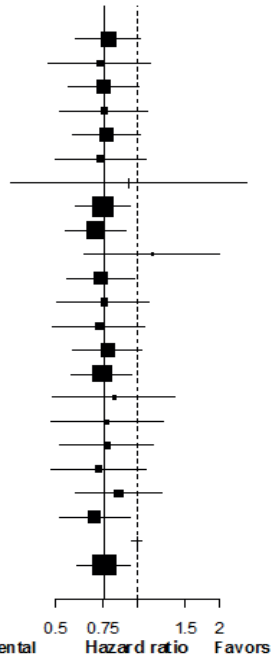


Figure S5 | Forest plot of the effect of treatment on DrTF according to randomisation characteristics and predefined hospital policy in the standard-care group on adjuvant chemotherapy

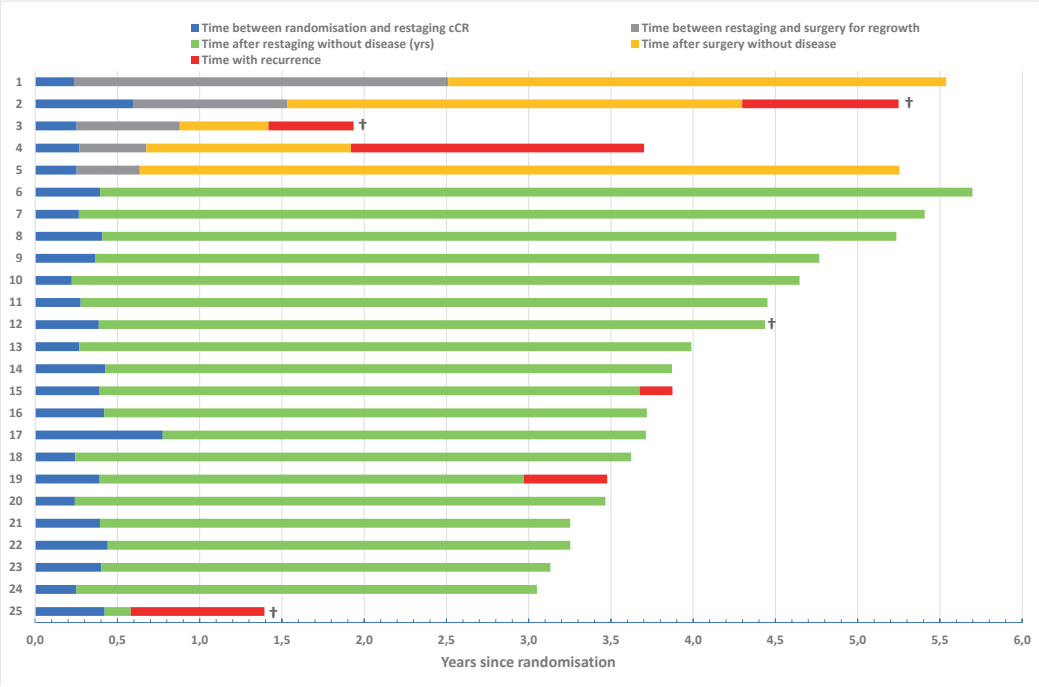
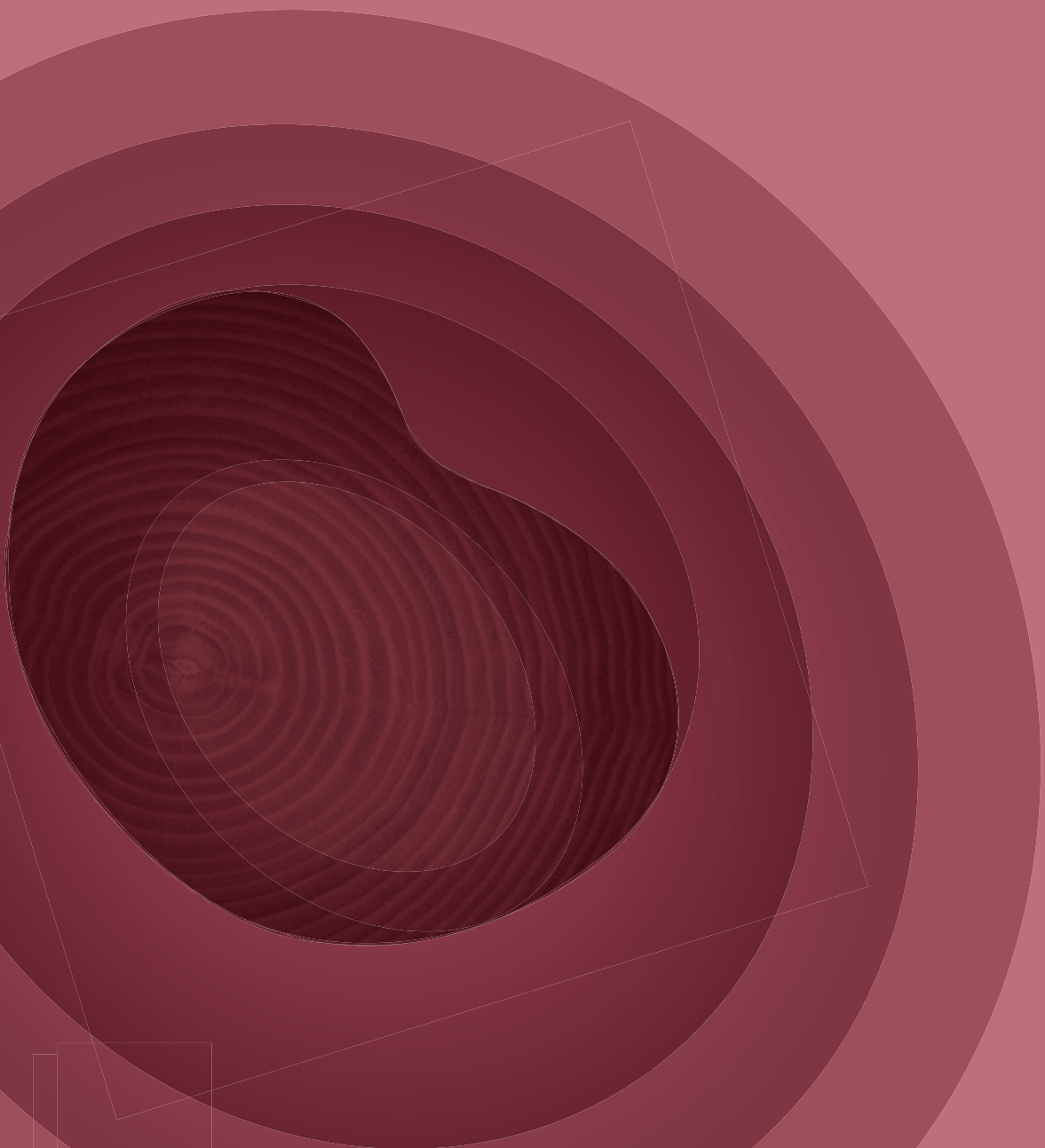


Figure S6 | Follow-up of patients with a W&W strategy



CHAPTER 2b

Interpreting the RAPIDO trial: Factors to consider – Authors' reply

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Lancet Oncology. 2021; 22: e90-e91

AUTHORS' REPLY

We thank Rob Glynne-Jones, Naveena Kumar, Jonathan Yuval and colleagues, and Alessandro Pastorino and colleagues for their interest in the RAPIDO trial[1]. We agree that statistical amendments in an ongoing trial are not preferred. However, we do not agree with the confronting statement of Yuval and colleagues that "without thorough reasoning for the change in the study hypothesis, the reader is left with the impression that the changes were made to fit the already known trial results". In the statistical analysis section, we clarify the reason for changing the endpoint[1]. Obviously, no information on treatment assignment was available during this process. Furthermore, all changes were approved by the independent data safety monitoring board and medical ethics committees. For completeness, disease-free survival results were included in the appendix, showing similar results to those for disease-related treatment failure.

A planned interim analysis indicated that the required number of events would not be reached, because disease-related treatment failure events would reach a plateau. By contrast, with disease-free survival and infinite follow-up, all patients would eventually experience an event. We therefore lowered the anticipated difference in events from 10% to 7.5% but maintained the same hazard ratio, with a lower power (80%).

We acknowledge that disease-related treatment failure is a new, not yet validated surrogate endpoint for overall survival. However, almost no rectal cancer trials have reported improved overall survival, with the exception of the Swedish Rectal Cancer Trial, in which a gain of 10% in 5-year overall survival was accomplished with short-course radiotherapy after an absolute difference in local recurrence rates of 16%[2]. An absolute difference of 7% in distant metastases, as seen in RAPIDO, would require a much larger sample size and longer follow-up to detect a difference in overall survival. However, we consider this reduction in metastases to be an important step towards reducing mortality in rectal cancer.

Despite the suggestion of Yuval and colleagues to evaluate adverse events on an intention-to-treat basis, we believe that the more commonly used as-treated basis provides more information.

Glynne-Jones and Pastorino and colleagues express concern about the increased locoregional failure rate in the experimental group of the trial. However, drawing conclusions from non-significant findings should be done with extreme care. The Polish II trial (including fixed cT3 and cT4 tumours and comparing standard chemoradiotherapy with short-course radiotherapy followed by three cycles of FOLFOX4) did not find a difference in the cumulative incidence of local failures at 10 years[3]. The statement that short-course radiotherapy is a suboptimal radiotherapy regime is not justified. Also, the concern of Kumar regarding cT4 tumours is not supported by the Polish II trial results.

A prolonged interval between conclusion of radiotherapy and surgery is beneficial for patients with tumours responding to neoadjuvant therapy, because it provides the opportunity for tumour downsizing or downstaging, or even a complete response. However, a subset of patients are poor responders, or even non-responders, at risk of disease progression during treatment. Irrespective of the type of preoperative treatment, patients progressing during neoadjuvant treatment are more likely to have ypT4 tumours and are at risk of non-radical resections. A high pathological complete response rate could therefore not be directly associated with the R0 rate, as suggested by Kumar. Only a very small proportion of patients showed tumour progression before surgery in either treatment group. MRI after three cycles of CAPOX, as was done at some centres, might identify poor responders and prevent disease progression if surgery is brought forward.

We understand the need for further information on histological tumour regression, but this was not a secondary endpoint (section 6.5.2 of the protocol merely describes regression grading) and analyses are planned after central review of the pathology.

Lastly, Pastorino and colleagues question whether the standard of care group reflects clinical practice because adjuvant chemotherapy was optional. The efficacy of adjuvant chemotherapy in this setting is debatable and not recommended in the national guidelines of the Netherlands, Norway, or Sweden (although all the Swedish centres except one opted for adjuvant chemotherapy in the trial). The lack of difference in disease-related treatment failure in the standard of care group, with or without a hospital policy for adjuvant chemotherapy, underlines our hypothesis that postoperative chemotherapy, in this context, is of low value.

In conclusion, despite these critical comments, we maintain that short-course radiotherapy and neoadjuvant chemotherapy is a valuable approach in the management of locally advanced rectal cancer.

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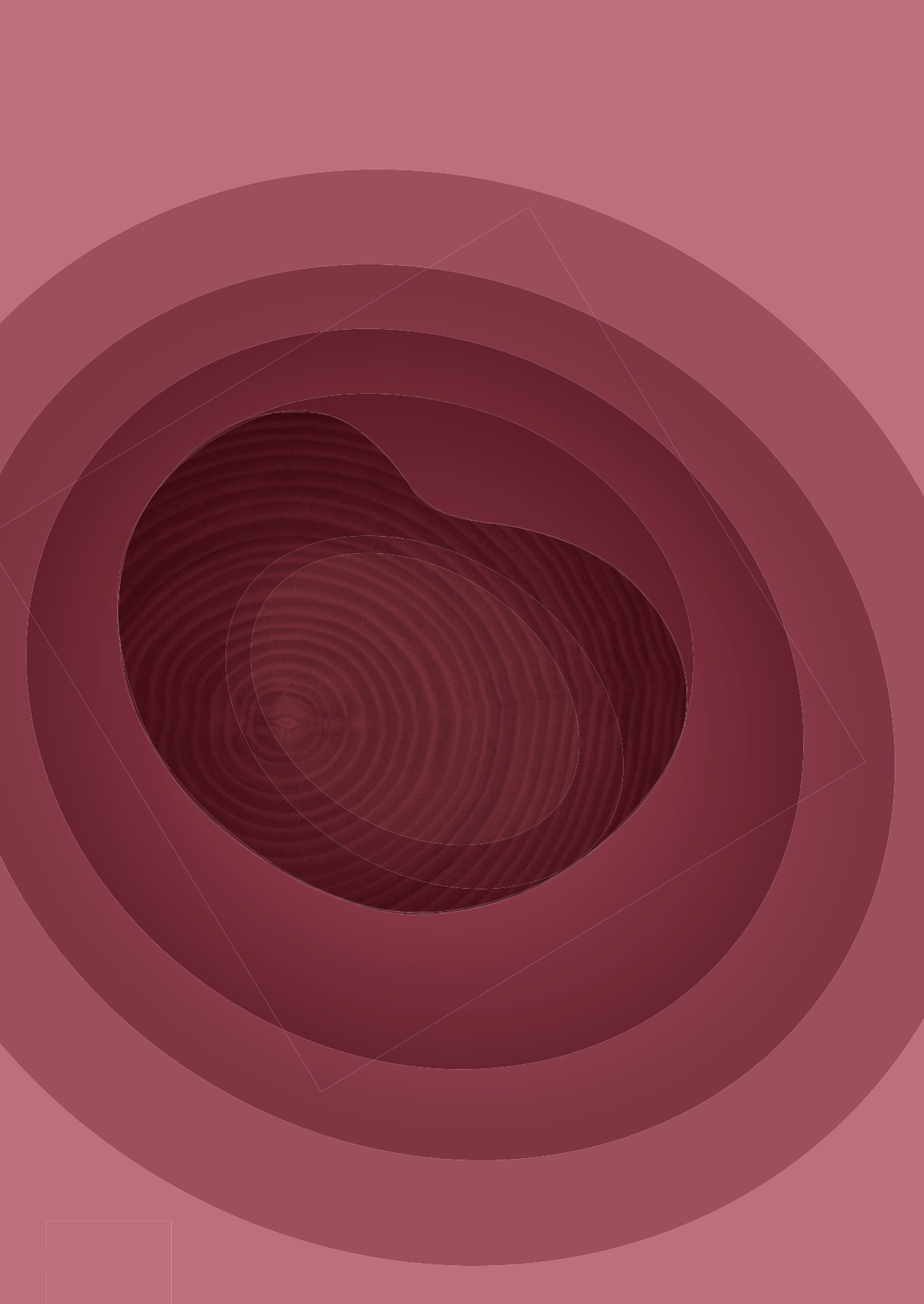

CHAPTER 3

Quality of life and late toxicity after short-course radiotherapy followed by chemotherapy or chemoradiotherapy for locally advanced rectal cancer – The RAPIDO trial

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Radiotherapy & Oncology. 2022; 171: 69-79

ABSTRACT

Background and purpose

The RAPIDO trial demonstrated a decrease in disease-related treatment failure (DrTF) and an increase in pathological complete responses (pCR) in locally advanced rectal cancer (LARC) patients receiving total neoadjuvant treatment (TNT) compared to conventional chemoradiotherapy. This study examines health-related quality of life (HRQL), bowel function, and late toxicity in patients in the trial.

Patients were randomized between short-course radiotherapy followed by pre-operative chemotherapy (EXP), or chemoradiotherapy and optional post-operative chemotherapy (STD). The STD group was divided into patients who did (STD+) and did not (STD-) receive post-operative chemotherapy. Three years after surgery patients received HRQL (EORTC QLQ-C30, QLQ-CR29 and QLQ-CIPN20) and LARS questionnaires. Patients who experienced a DrTF event before the toxicity assessments (6, 12, 24, or 36 months) were excluded from analyses.

Results

Of 574 eligible patients, 495 questionnaires were returned (86%) and 453 analyzed (79% completed within time limits). No significant differences were observed between the groups regarding QLQ-C30, QLQ-CR29 or LARS scores. Sensory-related symptoms occurred significantly more often in the EXP group compared to all STD patients, but not compared to STD+ patients. Any toxicity of any grade and grade ≥ 3 toxicity was comparable between the EXP and STD groups at all time-points. Neurotoxicity grade 1–2 occurred significantly more often in the EXP and STD+ group at all time-points compared to the STD- group.

Conclusion

The results demonstrate that TNT for LARC, yielding improved DrTF and pCRs, does not compromise HRQL, bowel functional or results in more grade ≥ 3 toxicity compared to standard chemoradiotherapy at three years after surgery in DrTF-free patients.

Keywords

Locally advanced rectal cancer; Quality of life; Total neoadjuvant treatment.

INTRODUCTION

Several studies demonstrated substantial late toxicity, compromised health-related quality of life (HRQL), and low anterior resection syndrome (LARS) after rectal cancer treatment[1,2]. Impairment is more often reported in patients who underwent pre-operative treatment and surgery compared to surgery alone[3-6]. Pre-operative short-course radiotherapy (scRT) with immediate surgery and chemoradiotherapy (CRT) (with delayed surgery) are associated with comparable late toxicity[7]. Postoperative chemotherapy, having the aim to decrease systemic recurrences, further adds morbidity[8].

Total neoadjuvant treatment (TNT) has gained increased interest under the assumption of improved systemic control by preoperative chemotherapy compared to post-operative chemotherapy[9-11].

The RAPIDO trial aimed to decrease disease-related treatment failure (DrTF) after scRT followed by systemic chemotherapy compared to CRT and optional post-operative systemic chemotherapy. The primary endpoint demonstrated a significant difference in DrTF events in favor of the experimental group compared to the standard-care group, 23.7% vs. 30.4%; $p = 0.019$, respectively[12]. Furthermore, the pathological complete response (pCR) rate was doubled in the experimental group (28% vs. 14%; $p < 0.0001$)12. The similarly designed STELLAR trial failed to demonstrate this advantage of TNT (pCR rate 17% after scRT with CAPOX pre- and postoperatively compared to 12% after CRT and postoperative CAPOX, $p = 0.134$)[13]. The current study aims to assess HRQL, bowel function, and late toxicity following TNT with scRT compared to standard CRT with or without postoperative chemotherapy in patients participating in the RAPIDO trial.

MATERIALS AND METHODS

Patient selection

The RAPIDO trial was an investigator-initiated, international, multicenter, phase III, randomized trial. It was centrally evaluated by the medical ethics committee of University Medical Center Groningen, the Netherlands (2011/098) and locally approved by all participating centers. Inclusion and exclusion criteria have been described[9,12,14]. In short, patients of 18 years or older were randomized (1:1) in case they had biopsy-proven, newly diagnosed rectal cancer less than 16 cm from the anal verge at endoscopy and at least one high-risk feature on MRI (cT4a/b, cN2, extramural vascular invasion, involved mesorectal fascia or enlarged lateral lymph nodes considered to be pathological). All RAPIDO trial patients who underwent a resection and were free from a DrTF event (defined as distant metastasis, locoregional failure, second primary (colorectal) tumor or treatment-related death) at three years after surgery were invited to participate in the HRQL analysis. The LARS questionnaire was completed by DrTF-free patients who underwent an anterior resection and did not have a remaining

diverting stoma three years after surgery. Due to the unavailability of questionnaires in the Slovenian language, patients from Slovenia were excluded. During follow-up, toxicity assessments according to the CTCAE version 4 were performed by the treating physician at 6, 12, 24, and 36 months. Toxicity was recorded for all resected patients without a DrTF at each time point. Patients in whom a DrTF event was detected within three months after toxicity assessment or questionnaire completion were excluded from further analyses.

Treatments

Patients were randomized to receive the experimental (EXP) or the standard-care (STD) treatment. The EXP treatment consisted of 5x5 Gy radiotherapy followed by six cycles of CAPOX or nine cycles of FOLFOX4 and surgery according to total mesorectal excision (TME) principles 2–4 weeks after the last chemotherapy. The STD treatment entailed long-course radiotherapy (28–25 x 1.8–2.0 Gy) and concurrent capecitabine followed by surgery after eight ± two weeks. Details of the treatments have been published[9,12,14]. According to hospital policy, patients in the STD group should or should not receive eight cycles of CAPOX or twelve cycles of FOLFOX4 post-operatively. To determine the effect of postoperative chemotherapy on HRQL, LARS, and late toxicity, the STD group was split into two subgroups: a group without (STD-) and a group with post-operative chemotherapy (STD+). All patients who started post-operative chemotherapy were assigned to the STD+ group, irrespective of the number of cycles they received.

The following questionnaires, developed by the European Organization for Research and Treatment of Cancer (EORTC), were used: QLQ-C3015, QLQ-CR2916 and QLQ-CIPN2017. To improve the evaluation of the sexual function in male patients, the QLQ-CR29 questionnaire was supplemented by questions 51, 52, 54, and 55 of the QLQ-PR2518. For female patients, question 59 was replaced by question 53, and questions 50–52 and 54 of the QLQ-EN2419 were added. In addition, bowel function was scored by the LARS questionnaire[20-21]. Information on the EORTC and LARS questionnaires is provided in the appendix. The distribution of patient-specific questionnaires was centrally managed by the Clinical Research Center of the LUMC, Leiden, the Netherlands. All participating centers received the questionnaires approximately 2 months in advance for further distribution to study participants. In case of a non-responding participating center, one reminder by e-mail was sent from the Clinical Research Center approximately one month after the anticipated response time. All completed questionnaires were returned to the Clinical Research Center for further central analysis. All questionnaires filled in 2.75–3.25 years after surgery by eligible patients were included in the analyses.

Toxicity according to the treating physician

Only the highest score of any toxicity at each measurement was included in the analyses. Toxicities were pooled in the following groups: blood and lymphatic, gastrointestinal, fatigue, allergic reaction, weight loss, nervous system, respiratory, renal and urinary, skin, sexual, or other toxicities. For each time-point of toxicity assessment, a window of +/- 3 months was accepted.

Statistical analysis

The HRQL scores and missing data of the QLQ-C30, QLQ-CR29 and QLQ-CIPN20 questionnaires were analyzed and interpreted according to EORTC guidelines[22]. The questionnaires consisted of single items, of which some were aggregated into multi-item scales. When responses were available for at least half of the items on a scale, all completed items were used for calculation. When more than 50% of responses on an item were lacking, the scale score was set to missing. Scoring ranges from 0 to 100 where a higher score represents a better function in functional scales and a lower score represents fewer symptoms in a symptom scale or item. Differences of 5–10 points on an EORTC HRQL function scale/item/symptom were considered a small clinically meaningful difference (hereafter small), 10–20 points a moderate clinically meaningful difference (hereafter moderate), and >20 points a large clinically meaningful difference (hereafter large)[23]. All items or symptoms with both clinical meaningfulness and statistically significant differences are reported here. All other items or symptoms with clinical meaningfulness which are not statistically significant are highlighted in grey in the supplementary appendix. Descriptive statistics were used to calculate means, frequencies, and percentages. Differences in means between the two (EXP and STD) and three groups (EXP, STD- and STD+) were tested by the independent t-test and ANOVA test, respectively. The Chi-square test was Health-related quality of life and late toxicity; RAPIDO-trial used to compare proportions. When significant differences between the three groups were revealed, post-hoc Bonferroni analyses were performed for pairwise comparisons between the group means. Multiple testing was corrected by considering a two-sided p-value of ≤0.01 to be statistically significant. SPSS for Windows (version 23.0, SPSS, Chicago, IL) was used for the statistical analyses.

RESULTS

In total, 920 patients were randomized in the RAPIDO trial. Of the 468 patients in the EXP group, 420 patients underwent surgery with curative intent. In the STD group, 396 out of 452 patients underwent surgery with curative intent. Reasons for exclusion of patients is provided in figure 1. Of the patients who underwent curative surgery, 15 patients were from Slovenia in the EXP group and 16 patients in the STD group. After exclusion of patients from Slovenian institutions and patients who had a treatment failure, questionnaires were sent to 574 patients alive, three years after surgery. Of those, 453 (78.9%) completed and returned the questionnaires within the set time limits. Of the 300 patients who were free of a stoma at three years and therefore eligible to receive the LARS questionnaire, 175 patients (58.3%) returned the questionnaire. Reasons for ineligibility and exclusions are provided in figure 1. For the toxicity analyses Slovenian patients were included, resulting in 706, 655, 590, and 560 evaluable patients (alive without a DrTF event) at 6, 12, 24, and 36 months after surgery, respectively (figure 1).

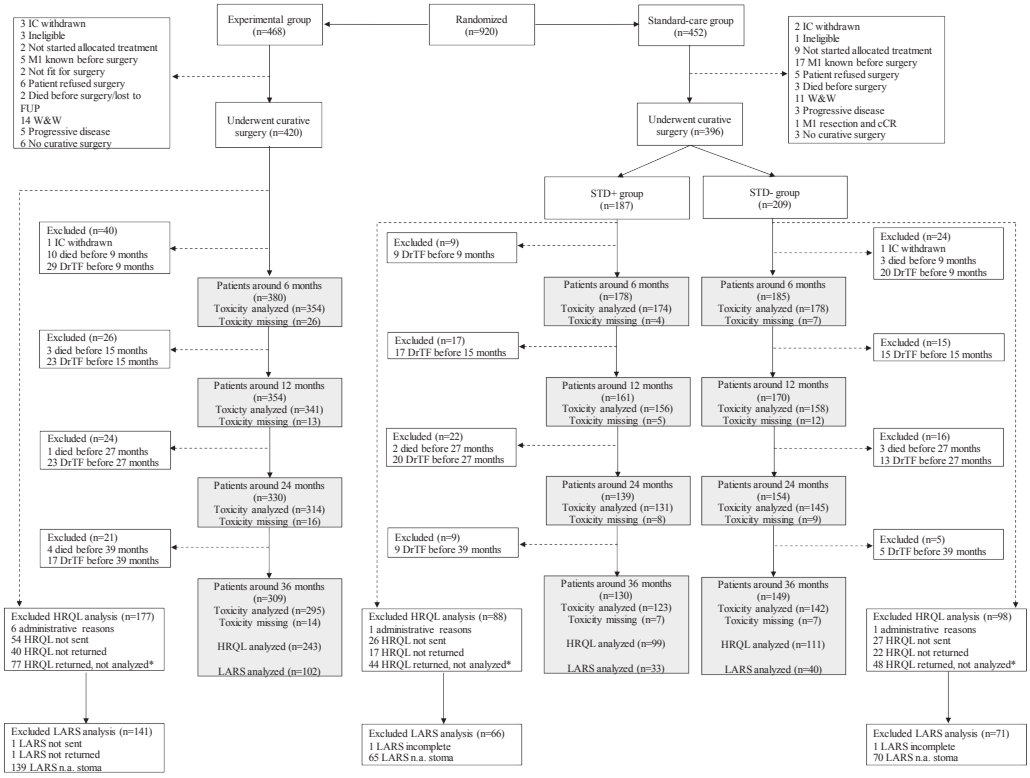

Figure 1 | Consort diagram

STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy; IC informed consent; DrTF Disease-related Treatment Failure; LARS low anterior resection syndrome.

EXP: 77 HRQL returned, not analyzed included 56 DrTF before 3 years, 17 Filled in, out of window and 4 DrTF within 3-3.25 years patients.

STD+: 44 HRQL returned, not analyzed included 36 DrTF before 3 years, 6 Filled in, out of window, 2 DrTF within 3-3.25 years patients.

STD-: 48 HRQL returned, not analyzed included 35 DrTF before 3 years, 12 Filled in, out of window, 1 DrTF within 3-3.25 years patients.

Of the 453 responders, 243 patients received the EXP and 210 the STD treatment, of whom 99/210 patients (47.1%) started post-operative chemotherapy. One patient in the EXP group received post-operative chemotherapy but was not excluded for further analyses. Non-responders to the questionnaire were significantly younger compared to analyzed patients. Other baseline and treatment characteristics were equally balanced between analyzed patients and non-responders (table S1). Table 1 provides the clinicopathological characteristics of the 453 evaluable patients who returned the HRQL questionnaires. Compliance to radiotherapy and chemotherapy is reported in table S2.

Table 1 | Clinicopathological characteristics of analyzed patients

	EXP (n=243)		STD (n=210)		*p*-value		STD+ (n=99)		STD- (n=111)		*p*-value§
Gender					0.08						0.22
Male	144	(59.3)	141	(67.1)			66	(66.7)	75	(67.6)	
Female	99	(40.7)	69	(32.9)			33	(33.3)	36	(32.4)	
Age at randomization (years)					0.75						0.07
(median, IQR)	63	(55-68)	62	(54-69)			60	(52-67)	65	(57-69)	
Distance from anal verge (endoscopy,cm)					0.62†						0.65†
<5 cm	46	(18.9)	50	(23.8)			19	(19.2)	31	(27.9)	
5-10 cm	102	(42.0)	73	(34.8)			36	(36.4)	37	(33.3)	
≥10 cm	79	(32.5)	71	(33.8)			41	(41.4)	30	(27.0)	
Unknown	16	(6.6)	16	(7.6)			3	(3.0)	13	(11.7)	
Type of approach					0.19						<0.0001
Laparoscopic	100	(41.2)	98	(46.7)			32	(32.3)	66	(59.5)	
Open	119	(49.0)	100	(47.6)			63	(63.6)	37	(33.3)	
Laparoscopic converted to open	24	(9.9)	12	(5.7)			4	(4.0)	8	(7.2)	
Type of surgery					0.44						0.16
(Low) Anterior resection	148	(60.9)	121	(57.6)			64	(64.6)	57	(51.4)	
Abdominoperineal resection	86	(35.4)	84	(40.0)			35	(35.4)	49	(44.1)	
Hartmann's procedure	7	(2.9)	5	(2.4)			-		5	(4.5)	
Other	2	(0.8)	-				-		-		
Pathological T-stage *					<0.0001						<0.0001
ypT0	96	(39.5)	42	(20.0)			17	(17.2)	25	(22.5)	
ypTis	2	(0.8)	1	(0.5)			-		1	(0.9)	
ypT1	13	(5.3)	10	(4.8)			7	(7.1)	3	(2.7)	
ypT2	45	(18.5)	59	(28.1)			24	(24.2)	35	(31.5)	
ypT3	72	(29.6)	91	(43.3)			47	(47.5)	44	(39.6)	
ypT4	15	(6.2)	7	(3.3)			4	(4.0)	3	(2.7)	
Pathological N-stage *					0.03						0.002
ypN0	203	(83.5)	165	(78.6)			73	(73.7)	92	(82.9)	
ypN1	35	(14.4)	28	(13.3)			13	(13.1)	15	(13.5)	
ypN2	5	(2.1)	17	(8.1)			13	(13.1)	4	(3.6)	
Stoma 3 years after surgery					0.11						0.25
No stoma	104	(42.8)	75	(35.7)			34	(34.3)	41	(36.9)	
Stoma	139	(57.2)	135	(64.3)			65	(65.7)	70	(63.1)	

Data are presented as n (%). Percentages may not equal 100% due to rounding.

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy; SD standard deviation.

§ p-value represents the difference in mean scores between the EXP, STD- and STD+ groups.

† p-value calculated in patients in which the distance to the anal verge was known.

* According TNM 5

No statistically significant and clinically meaningful differences regarding the EORTC QLQ-C30 and EORTC QLQ-CR29 scores were observed between the two (EXP vs. STD) (tables S3 and S4) or three (EXP vs. STD+ vs. STD-) groups (figures 2 and 3, detailed information in tables S3 and S4).

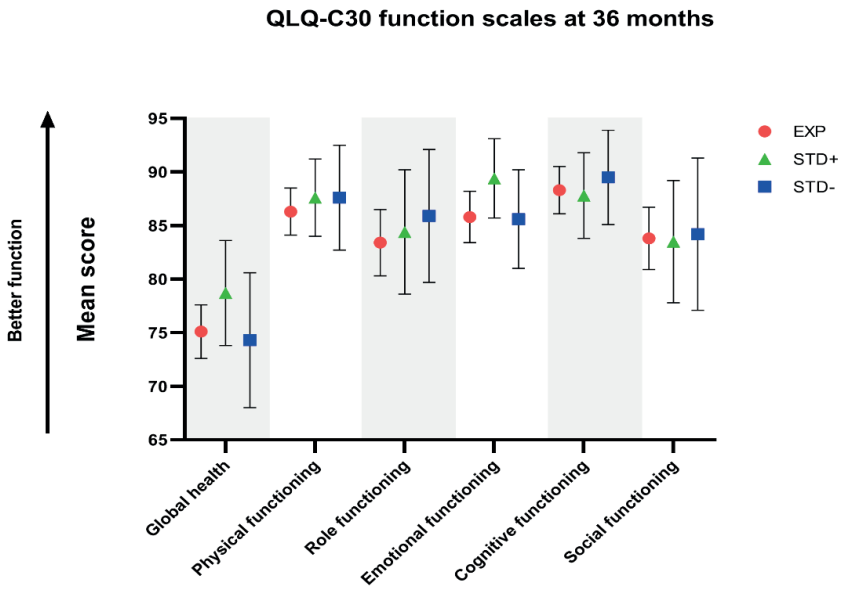

Figure 2 | EORTC QLQ-C30 function scales, provided as mean and 99% confidence interval. A higher score represents a better function

EXP experimental; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

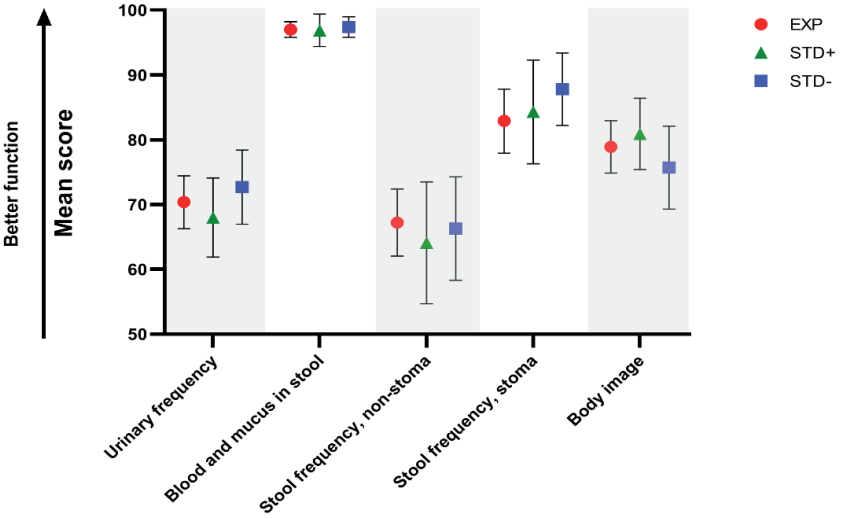

Figure 3 | EORTC QLQ-CR29 function scales, provided as mean and 99% confidence interval. A higher score represents a better function

EXP experimental; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

The EORTC QLQ-CIPN20 questionnaire revealed statistically significant and clinically meaningful differences with worse scores for the EXP group compared to the whole STD group for the sensory scale (EXP 20.1 vs. STD 11.0; $p < 0.0001$), but not for the motor (EXP 11.7 vs. STD 8.5; $p = 0.11$) or the autonomic scales (EXP 7.9 vs. 7.2; $p = 0.61$) (details in table S5). Clinically and statistically significant differences between the EXP and STD groups, in favor of the STD group were seen in tingling fingers or hands (small), tingling toes or feet (large), numbness toes or feet (moderate), pain in toes or feet (moderate) and trouble standing or walking (moderate). Comparison of the three groups for the items in the sensory score is displayed in figure 4, demonstrating that the EXP group experienced significantly more often pain in toes or feet ($p = 0.004$, moderate) than the STD+ group. For most items, the STD- group experienced fewer symptoms than either the EXP or the STD+ group (figure 4). Other than the items of the sensory score, clinically (all small) and statistically differences between the EXP and STD- in favor of the STD- group were seen in trouble handling small objects, overall QLQ-CIPN20 score and, the motor scale. Besides, a small clinically and statistically difference between the STD+ and STD- in favor of the STD- group was seen in the overall QLQ-CIPN20 score.

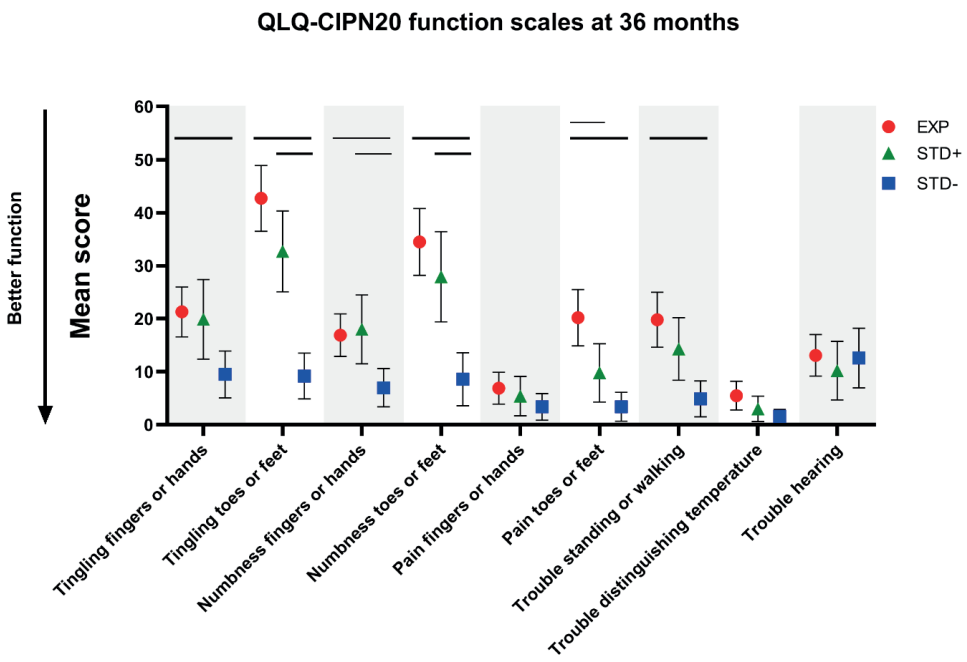

Figure 4 | EORTC QLQ-CIPN20 sensory scale, provided as mean and 99% confidence interval. A lower score represents a better function

The horizontal lines represent statistically significant differences between the groups; non-bold line $p<0.004$ and bold line $p<0.0001$.

EXP experimental; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

Major LARS occurred more frequently in the STD than in the EXP group (76.4% vs. 58.8%), but this difference was not statistically different (p = 0.02) (table S6). Major LARS in the STD+ and STD- was similar (73% vs. 78%, table S6).

Late toxicity over time regarding the EXP and STD group is summarized in table S7 and figure S4. Significant differences in all combined toxicity between the two groups were not found at any time point. At 6 months approximately 56% of patients in both groups experienced any toxicity and this declined over time to 28% and 29% for EXP and STD groups, respectively, at 36 months (table S7). Neurotoxicity was the most frequently reported toxicity. Grade 1–2 neurotoxicity was reported significantly more often in the EXP group at all time-points but toxicity grade 3 or higher did not differ significantly between the groups at any time-point (table S7 and figure S1). Concerning other grade 1–2 toxicities, some statistically significant differences were observed at 6 months: fatigue (9% vs. 17%) and skin toxicity (3% vs. 9%) for EXP vs. STD, respectively, but none of these differences remained statistically significant at 12, 24 or 36 months (table S7).

Late toxicity over time regarding the EXP, STD+ and STD- groups are summarized in figure 5a, 5b, and table S8. The total toxicity rate at 6 months was 55%, 67%, and 45% for the EXP, STD+ and STD- group, respectively. At 12 months after surgery, the corresponding figures were 51%, 46%, and 35%, respectively. At 36 months, inter-group differences have disappeared with 28%, 28%, and 30% of patients experiencing any toxicity, respectively. Neurotoxicity was reported most in the EXP and STD+ group and mainly concerned grade 1–2 toxicity. At 6 months after surgery, 34%, 43%, and 2% of patients experienced any grade of neurotoxicity for EXP, STD+ and STD-, respectively. Only 5 patients (1%) in the EXP group experienced grade 3 toxicity at this time-point (table S8). At 12 and 36 months, the frequency of neurotoxicity for EXP vs. STD+ was 29% vs. 27% and 14% vs. 11%, respectively. Grade ≥ 3 toxicity did not significantly differ between the three groups and was 9%, 9%, and 11% for EXP, STD+ and STD-, respectively at 6 months (table S8). However, some differences were observed for grade 1–2 toxicity. In table S8, grade 1–2 toxicities at 6 months in the three groups are presented.

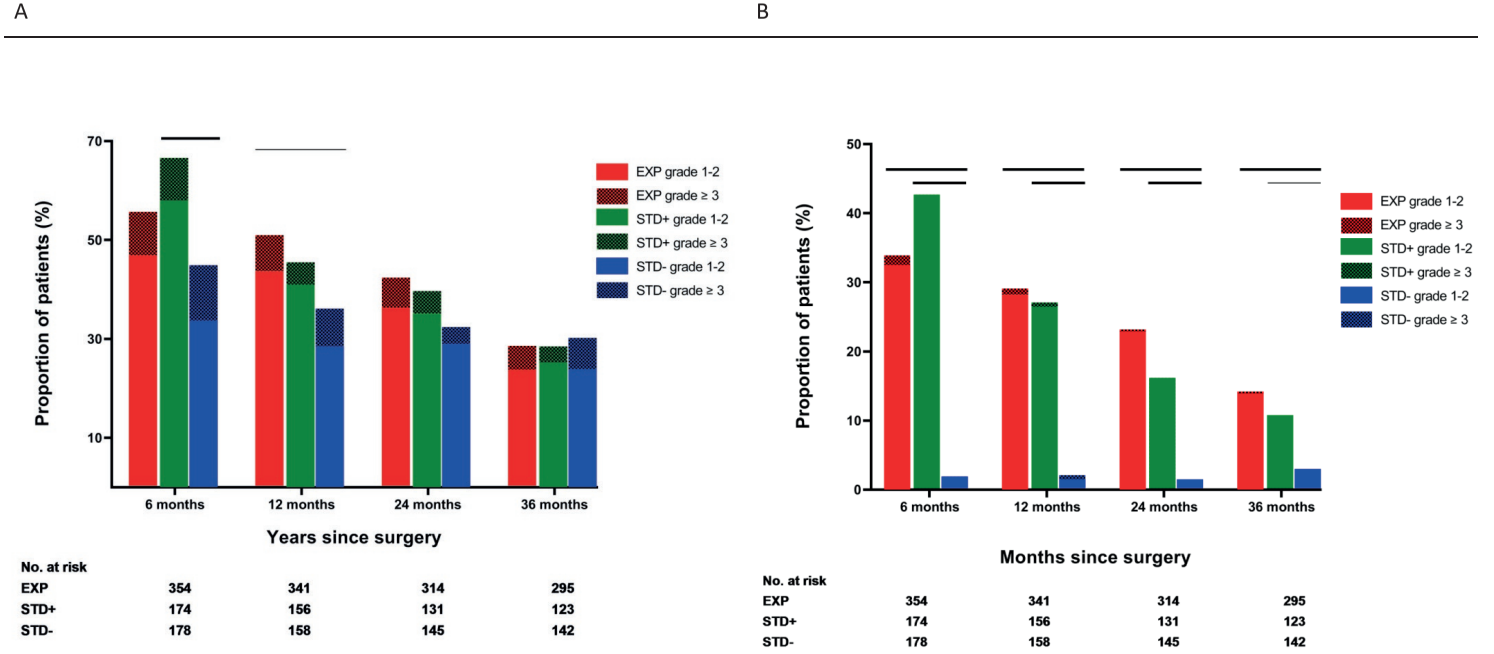

Figure 5 | A) Toxicity and B) neurotoxicity per follow-up moment regarding three subgroups n represents the number of evaluable patients (excluding missing)

Toxicity was scored with a range of 3 months at 6, 12, 24, and 36 months.

The horizontal lines represent statistically significant differences in any toxicity grade between the groups; non-bold line p=0.002 (in A) and p=0.010 (in B) and bold line p<0.0001.

DISCUSSION

The HRQL and long-term toxicity analyses of the RAPIDO trial reported here demonstrate that no significant differences are reported for either HRQL, bowel function, or late toxicity between the patients receiving TNT or standard CRT. In subgroup analyses, neurological toxicity and patient-reported neurological complaints were more often observed in patients receiving oxaliplatin, either in the pre- or post-operative settings.

The RAPIDO trial demonstrated that scRT followed by preoperative chemotherapy results in improved oncological outcomes, including increased pCR rates, compared to standard CRT12. This report on HRQL, toxicity, and functional outcome, demonstrates that scRT and pre-operative chemotherapy can also be delivered without increasing adverse long-term effects for patients.

Three years after surgery, most patients experienced major LARS in both groups, with 59% in the EXP and 75% in the STD group. These figures underline the need for other strategies, such as non-operative management for complete responders. However, one must be cautious to extrapolate functional outcome after surgery towards the outcome in a non-operative setting, given that the current figures are influenced by both the (neo)adjuvant treatment and by surgery. Given the relatively high pCR rate of 28% after scRT followed by chemotherapy[12] this treatment is a better alternative than CRT, when the aim is to avoid surgery. Despite that the LARS is not a validated questionnaire for bowel function after organ preservation, non-randomized studies demonstrate that organ preservation is associated with better bowel function compared to pre-operative CRT and surgery[24,25]. Surgery and radiotherapy are both contributing to the development of major LARS[26,27]. The use of oxaliplatin did most probably not have an effect on LARS since patients in the experimental group, all receiving oxaliplatin, experienced less often major LARS. The experimental approach results in at least similar, and possibly even better bowel function than standard CRT at three years after surgery. Deterioration of bowel function beyond 3–4 years after surgery is caused by aging of the patients[28].

In general, pre-operative RT followed by surgery is accompanied by increased late toxicity compared to surgery alone[29]. The comparison of scRT with immediate surgery and CRT, as has been done in the Polish and TROG trials, demonstrated no difference in late toxicity between the two groups[30,31]. Prolonging the interval between scRT and surgery did not change the risk of late toxicity, being about 40% in the Stockholm III trial (median follow-up 5.2 years)[32]. Despite the introduction of systemic chemotherapy after scRT, we noted less late toxicity three years after surgery (28%), which can possibly be explained by the introduction of more advanced radiation and surgical techniques compared to the Stockholm III trial[32]. An important note is that the late toxicity numbers in the Stockholm III trial represent any reported late toxicity at any time post-operatively, making a direct comparison between the

two trials difficult. Late toxicity results presented here are in line with the findings in the Polish II trial, with a similar design as the RAPIDO trial[33]. From this, we can again conclude that scRT combined with pre-operative chemotherapy can be considered as a safe treatment strategy.

As expected, the neurological toxicity was predominantly observed in patients receiving oxaliplatin-containing chemotherapy (either pre- or post-operatively). Recently published adjuvant trials in colon cancer[34] have demonstrated that reducing the number of CAPOX cycles from eight to four (or from twelve to six using FOLFOX), resulted in less toxicity without compromising oncological outcomes, at least for most subgroups. Extrapolating data from the colon cancer trials could lead to the assumption that the number of courses of CAPOX could be reduced from the six cycles used in the RAPIDO trial leading to reduced toxicity without compromising oncological outcomes. However, this assumption must be tested in trials.

The implementation of pre-operative chemotherapy inevitably leads to overtreatment for those who do not benefit from systemic chemotherapy. Further refinement of patient selection is therefore warranted. A more personalized approach based on imaging characteristics or biomarkers is not yet available. A careful weighing of expected benefits and harms should therefore be discussed with the patient in a shared decision-making process. The increasing interest in organ preservation makes this trade-off even more complicated; even though most patients will not develop distant metastases, they may benefit from an increased response with a subsequent greater chance for organ preservation.

It could be argued that a possible limitation of our study is that it is based on a subset of patients who were disease-free at time of analysis and underwent a curative resection. Since recurrence-related symptoms may blur HRQL and toxicity analyses, we feel this subset is justified. Besides, the RAPIDO trial cannot confirm nor refute this thought as patients with a recurrence did not receive HRQL questionnaires. The design of the trial included an optional post-operative chemotherapy policy in the CRT group. The decision to administer post-operative chemotherapy was indicated by center before the start of the trial, enabling us to compare the results of the group of patients who received post-operative chemotherapy and those who did not. However, some confounding may still be present, especially since patients who were unable to start with chemotherapy were included in the STD- group. A more favorable pathological stage may result in the omission of postoperative chemotherapy even if the policy for post-operative chemotherapy was present. However, additional intention-to-treat analyses did not demonstrate an influence of hospital policy on HRQL, bowel function, and late toxicity (data not shown). Another possible confounder is that compliance to the questionnaire was 79%, with non-responders being younger. Still, given that non-responders were equally divided over the two treatment groups, we feel this will not influence the results. In conclusion, the RAPIDO trial is the largest randomized study comparing TNT with conventional CRT with or without postoperative chemotherapy in patients with locally

advanced rectal cancer and high-risk features for recurrence. Despite the lack of overall survival benefit yet, we believe that the reduced DrTF and increased pCR rates, combined with similar HRQL, bowel function and (late) toxicity profiles up until three years after surgery, support the preference for TNT.

Funding
Funding for this study was acquired from the Dutch Cancer Foundation (CKS-2011-4997); the Swedish Cancer Society; the Swedish Research Council (project number K2014-99X-22481-01-3); the Spanish Ministry of Economy and Competitiveness through the Carlos III Health Institute EC11-423, and by the Spanish Clinical Research Network (SCReN-PT13/0002/0031; PT17/0017/0003; co-financed by European Regional Development Fund "A way to make Europe").

Declaration of interests
The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GAPH reports consulting fees from Roche, MSD, Amgen, and Novartis; consulting fees and research support to their institution from Bristol Myers Squibb; and research support to their institution from Seerave Foundation. AGHR and CJHvdV were partially funded by the EU's Horizon 2020 research and innovation programme under a Marie Skłodowska Curie grant award (H2020MSCAITN2019, grant agreement number 857894; project acronym: CAST). MPH reports consulting fees from MSD. JC reports consulting fees, travel expenses, and research support to their institution from Pfizer, Ipsen, and Eisai; consulting fees and research support to their institution from Bayer, Novartis, and Advanced Accelerator Applications; consulting fees from Sanofi, Exelixis, and Merck Serono; and research support to their institution from AstraZeneca. PJN reports honoraria from Ethicon and Johnson & Johnson. BG reports research support from the Swedish Cancer Society. All other authors declare no competing interests.

Acknowledgement
We thank all patients, treating physicians, and research support staff at all participating centers.

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SUPPLEMENTAL MATERIAL

Table S1 | Clinicopathological characteristics analyzed versus non-responders

	Analyzed (n=453)		Non-responders (n=79)		*p*-value
Treatment group					0.62
Experimental	243	(53.6)	40	(50.6)	
Standard-care	210	(46.4)	39	(49.4)	
Gender					0.03
Male	285	(62.9)	60	(75.9)	
Female	168	(37.1)	19	(24.1)	
Age at randomization (years)					0.005
(median, IQR)	63	(55-68)	59	(52-67)	
Distance from anal verge (cm)					0.25†
<5 cm	96	(21.2)	23	(29.1)	
5-10 cm	175	(38.6)	22	(27.8)	
≥10 cm	150	(33.1)	24	(30.4)	
Unknown	32	(7.1)	10	(12.7)	
Type of approach					0.02
Laparoscopic	198	(43.7)	46	(58.2)	
Open	219	(48.3)	25	(31.6)	
Laparoscopic converted to open	36	(7.9)	8	(10.1)	
Type of surgery					0.26
(Low) Anterior resection	269	(59.4)	43	(54.4)	
Abdominoperineal resection	170	(37.5)	35	(44.3)	
Hartmann's procedure	12	(2.6)	-		
Other	2	(0.4)	1	(1.3)	
Pathological T-stage *					0.64
ypT0	138	(30.5)	19	(24.1)	
ypTis	3	(0.7)	-		
ypT1	23	(5.1)	6	(7.6)	
ypT2	104	(23.0)	23	(29.1)	
ypT3	163	(36.0)	27	(34.2)	
ypT4	22	(4.9)	4	(5.1)	
Pathological N-stage *					0.47
ypN0	368	(81.2)	63	(79.7)	
ypN1	63	(13.9)	14	(17.7)	
ypN2	22	(4.9)	2	(2.5)	

Data are presented as n (%). Percentages may not equal 100% due to rounding.

Analyzed represents the number of patients who filled in the questionnaire on time.

† p-value calculated in patients in which the distance to the anal verge was known.

* According TNM5

Table S2 | Compliance to pre-operative and post-operative treatment

Experimental	(n=243)
All RT fractions	243 (100)
At least 75% of pre-operative chemotherapy	205 (84.4)
Standard-care without post-operative chemotherapy	(n=111)
At least 45 Gy radiotherapy	108 (97.3)
At least 5 weeks of pre-operative chemotherapy	103 (92.9)
Standard-care with post-operative chemotherapy	(n=99)
At least 45 Gy radiotherapy	99 (100)
At least 5 weeks of pre-operative chemotherapy	93 (93.9)
At least 1 cycle of post-operative chemotherapy	99 (100)
At least 75% of post-operative chemotherapy	58 (58.6)

Data are presented as n (%). Only patients who received at least one cycle of post-operative chemotherapy were included in the standard-care group with post-operative chemotherapy group.

Table S3 | Quality of life scores on the EORTC QLQ-C30 questionnaire

	EXP (n=243)			STD (n=210)			T-test	STD+ (n=99)			STD- (n=111)			ANOVA§
	n*	mean	SD	n*	mean	SD	*p*-value	n*	mean	SD	n*	mean	SD	*p*-value
Function scales														
Global health	242	75.1	(19.6)	208	76.6	(20.5)	0.43	99	74.3	(21.5)	109	78.7	(19.4)	0.22
Physical function	243	86.3	(17.9)	210	87.6	(16.4)	0.44	99	87.6	(18.4)	111	87.6	(14.5)	0.74
Role function	243	83.4	(24.6)	210	85.1	(23.0)	0.46	99	85.9	(22.9)	111	84.4	(23.3)	0.69
Emotional function	243	85.8	(19.1)	208	87.6	(15.5)	0.28	99	85.6	(16.3)	109	89.4	(14.6)	0.17
Cognitive function	243	88.3	(17.4)	207	88.6	(15.9)	0.85	98	89.5	(15.2)	109	87.8	(16.6)	0.76
Social function	243	83.8	(22.9)	207	83.8	(22.4)	1.00	98	84.2	(23.6)	109	83.5	(21.3)	0.98
Symptom scales														
Fatigue	243	20.4	(21.0)	210	19.8	(22.6)	0.79	99	20.9	(23.3)	111	18.9	(22.0)	0.76
Nausea/vomiting	243	2.7	(10.5)	210	2.4	(8.6)	0.69	99	3.0	(9.3)	111	1.8	(7.9)	0.61
Pain	243	15.6	(24.0)	210	12.2	(20.7)	0.12	99	13.0	(21.1)	111	11.6	(20.4)	0.26
Dyspnea	243	12.5	(21.1)	210	11.0	(19.3)	0.42	99	12.1	(18.1)	111	9.9	(20.4)	0.53
Insomnia	242	19.7	(26.5)	209	15.2	(24.0)	0.06	98	16.0	(25.0)	111	14.4	(23.2)	0.15
Appetite loss	243	4.5	(14.3)	210	6.5	(18.3)	0.20	99	8.1	(20.8)	111	5.1	(15.7)	0.18
Constipation	243	10.2	(20.7)	209	9.1	(18.7)	0.57	99	10.8	(20.7)	110	7.6	(16.7)	0.44
Diarrhea	243	11.9	(21.0)	207	15.5	(24.1)	0.10	98	18.0	(26.3)	109	13.1	(21.8)	0.08
Financial difficulties	243	9.1	(21.9)	206	9.1	(22.2)	1.00	98	9.5	(24.9)	108	8.6	(19.5)	0.96
Overall QLQ-C30 score$^{\beta}$		40.6	(4.6)		40.6	(4.5)	0.93		41.2	(4.8)		40.1	(4.1)	0.23

Percentages may not equal 100% due to rounding.

A higher score on the functional scales represents better functioning and a higher score on the single items represents worse symptoms.

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

* Number of patients who filled in the concerning question(s). β Sum score on all variables. § p-value represents the difference in mean scores between the EXP, STD+ and STD- groups.
Grey blocks represents small clinical differences (but not statistically significant) in insomnia (in favor of STD-) and diarrhea (in favor of EXP).

Table S4 | Quality of life scores on the EORTC QLQ-CR29 questionnaire

	EXP (n=243)			STD (n=210)			T-test	STD+ (n=99)			STD- (n=111)			ANOVA§
	n*	mean	SD	n*	mean	SD	*p*-value	n*	mean	SD	n*	mean	SD	*p*-value
Function scales														
Urinary frequency	238	70.4	(24.9)	206	70.5	(24.0)	0.97	98	68.0	(23.2)	108	72.7	(24.7)	0.40
Blood and mucus in stool	243	97.0	(7.4)	209	97.2	(7.6)	0.75	98	96.9	(8.7)	111	97.4	(6.4)	0.84
Stool frequency, non-stoma	118	67.2	(21.9)	91	65.2	(21.8)	0.51	45	64.1	(23.6)	46	66.3	(20.0)	0.71
Stool frequency, stoma	122	82.9	(21.5)	118	86.3	(18.6)	0.20	51	84.3	(20.1)	67	87.8	(17.3)	0.28
Body image	243	78.9	(24.9)	210	78.1	(24.1)	0.73	99	80.9	(21.6)	111	75.7	(26.0)	0.29
Sexual items														
Sexual activity (male)	138	71.0	(24.4)	144	67.8	(24.9)	0.25	68	68.1	(24.4)	76	67.5	(25.5)	0.51
Sexual functioning (male)[a]	76	59.4	(20.8)	83	52.4	(21.2)	0.04	39	55.6	(20.6)	44	49.6	(21.1)	0.05
Sexual activity (female)	92	85.7	(17.4)	65	82.1	(20.5)	0.23	30	77.8	(19.2)	35	85.7	(21.6)	0.12
Sexual functioning (female)[a]	34	58.5	(27.1)	22	58.7	(27.9)	0.98	13	48.1	(29.5)	9	74.1	(16.9)	0.09
Single items														
Urinary incontinence	240	12.9	(19.6)	205	13.7	(21.6)	0.71	97	12.0	(18.7)	108	15.1	(23.8)	0.52
Dysuria	239	3.9	(12.0)	206	3.2	(12.3)	0.56	98	2.7	(10.3)	108	3.7	(13.9)	0.72
Abdominal pain	243	10.3	(21.0)	210	12.5	(20.8)	0.25	98	11.1	(19.6)	111	13.8	(21.8)	0.34
Buttock pain	242	10.6	(20.2)	208	12.5	(22.3)	0.35	99	12.9	(23.8)	110	12.1	(21.0)	0.62
Bloating abdomen	243	13.4	(21.9)	209	15.5	(21.7)	0.33	98	16.8	(23.0)	110	14.2	(20.4)	0.43
Dry mouth	242	16.5	(24.5)	210	15.2	(23.3)	0.57	99	14.1	(21.9)	111	16.2	(24.6)	0.70
Hair loss	243	4.3	(13.7)	209	3.2	(12.7)	0.40	99	1.7	(8.8)	111	4.5	(15.2)	0.22
Taste loss	243	7.7	(18.8)	210	4.9	(13.9)	0.08	98	4.4	(14.0)	111	5.5	(13.9)	0.20
Anxiety	243	28.7	(27.4)	208	27.1	(24.0)	0.52	98	29.6	(23.9)	110	24.8	(24.1)	0.34
Weight	243	14.1	(24.7)	210	16.0	(21.4)	0.39	99	15.8	(20.9)	111	16.2	(22.0)	0.68
Single items, non-stoma														
Flatulence	118	41.8	(28.0)	90	43.3	(31.0)	0.71	43	37.2	(31.9)	47	48.9	(29.4)	0.15
Fecal incontinence	118	19.2	(24.4)	90	21.1	(25.2)	0.58	44	19.7	(26.2)	46	22.5	(24.4)	0.75
Sore skin	117	14.8	(23.8)	91	16.1	(24.0)	0.70	44	13.6	(25.2)	47	18.4	(22.9)	0.59
Embarrassment	118	27.9	(31.8)	92	28.6	(28.6)	0.83	45	23.0	(27.4)	47	34.0	(29.1)	0.21
Single items, stoma														
Stoma care problems	117	4.0	(15.3)	114	2.9	(10.5)	0.54	47	2.1	(8.2)	67	3.5	(11.8)	0.72
Flatulence	124	30.1	(26.0)	120	30.6	(26.8)	0.90	50	33.3	(26.9)	70	28.6	(26.8)	0.62
Fecal incontinence	123	18.4	(23.1)	117	16.0	(20.3)	0.38	51	14.4	(18.0)	66	17.2	(22.1)	0.54
Sore skin	123	16.5	(24.3)	117	15.7	(21.7)	0.66	50	16.7	(22.6)	67	14.9	(21.1)	0.88
Embarrassment	123	29.0	(31.4)	118	22.3	(25.8)	0.07	51	25.5	(24.6)	67	19.9	(26.6)	0.12

Percentages may not equal 100% due to rounding.
A higher score on the functional scales represents better functioning and a higher score on the single items represents worse symptoms.

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

[a] Sexual functioning items only apply to sexually active patients.

[*] Number of patients who filled in the concerning question(s).

[§] p-value represents the difference in mean scores between the EXP, STD+ and STD- groups.

Grey blocks represent clinical differences (which are not statistically significant).

- Differences between EXP and STD in favor of STD: embarrassment stoma (small)
- Differences between EXP and STD- in favor of STD-: female sexual functioning (moderate), embarrassment stoma (small)
- Differences between EXP and STD+ in favor of EXP: female sexual functioning (moderate)
- Differences between STD+ and STD- in favor of STD+: flatulence non-stoma (moderate), embarrassment non-stoma (small)
- Differences between STD+ and STD- in favor of STD-: female sexual activity (small), female sexual functioning (large), embarrassment stoma (small)

Table S5 | Quality of life scores on the EORTC QLQ-CIPN20 questionnaire

	EXP (n=243)			STD (n=210)			T-test	STD+ (n=99)			STD- (n=111)			ANOVA §
	n*	mean	SD	n*	mean	SD	*p*-value	n*	mean	SD	n*	mean	SD	*p*-value
Sensory scale		20.1	(18.9)		11.0	(13.7)	**<0.0001**		15.8	(15.9)		6.6	(9.4)	**<0.0001**
Tingling fingers or hands	238	21.3	(28.0)	208	14.4	(23.7)	**0.005**	99	19.9	(27.3)	109	9.5	(18.8)	**<0.0001**
Tingling toes or feet	238	42.7	(37.3)	207	20.3	(28.8)	**<0.0001**	98	32.7	(32.5)	109	9.2	(19.2)	**<0.0001**
Numbness fingers or hands	238	16.9	(25.4)	207	12.2	(22.0)	0.04	98	18.0	(26.3)	109	7.0	(15.8)	**<0.0001**
Numbness toes or feet	238	34.5	(37.4)	208	17.8	(27.8)	**<0.0001**	99	27.9	(31.8)	109	8.6	(19.5)	**<0.0001**
Pain fingers or hands	238	6.9	(19.0)	207	4.3	(15.0)	0.12	99	5.4	(17.0)	108	3.4	(12.8)	0.22
Pain toes or feet	236	20.2	(33.4)	208	6.4	(18.0)	**<0.0001**	99	9.8	(22.5)	109	3.4	(12.0)	**<0.0001**
Trouble standing or walking	236	19.8	(30.7)	207	9.3	(21.5)	**<0.0001**	98	14.3	(25.8)	109	4.9	(16.0)	**<0.0001**
Trouble distinguishing temperature	238	5.5	(17.1)	206	2.3	(11.7)	0.02	99	3.0	(12.7)	107	1.6	(10.6)	0.06
Trouble hearing	237	13.1	(24.2)	204	11.4	(21.2)	0.47	98	10.2	(18.8)	106	12.6	(23.2)	0.57
Motor scale		11.7	(13.6)		8.5	(12.2)	0.11		10.8	(14.1)		6.3	(9.8)	**0.002**
Cramps fingers or hands	238	9.7	(20.4)	208	7.5	(19.2)	0.26	99	9.4	(22.4)	109	5.8	(15.6)	0.22
Cramps toes or feet	238	19.3	(28.9)	206	15.9	(25.0)	0.18	99	18.5	(26.6)	107	13.4	(23.3)	0.16
Trouble holding a pen	238	4.5	(14.6)	207	3.4	(12.0)	0.39	99	4.7	(14.3)	108	2.2	(9.4)	0.28
Trouble handling small objects	238	15.3	(25.2)	208	10.7	(19.3)	0.03	99	14.5	(20.8)	109	7.3	(17.2)	**0.008**
Weakness in hands	238	11.9	(21.9)	208	10.6	(20.9)	0.51	99	12.5	(20.5)	109	8.9	(21.1)	0.39
Feet dropped downwards	238	6.3	(19.2)	208	3.0	(14.1)	0.04	99	3.0	(15.1)	109	3.1	(13.3)	0.13
Weakness in legs	238	14.8	(26.1)	205	11.4	(20.9)	0.05	98	12.6	(22.7)	107	8.4	(18.9)	0.07
Trouble using the pedals	198	6.6	(18.0)	167	3.2	(14.7)	0.05	77	4.8	(17.7)	90	1.9	(11.6)	0.08
Autonomic scale		7.9	(13.9)		7.2	(14.6)	0.61		8.8	(16.4)		5.7	(12.6)	0.25
Dizziness	238	9.1	(19.0)	204	8.8	(18.4)	0.88	98	11.2	(20.8)	106	6.6	(15.5)	0.21
Blurred vision	237	6.6	(15.0)	205	5.5	(15.5)	0.46	98	6.5	(16.3)	107	4.7	(14.8)	0.53
Erection disorders	198	6.6	(18.0)	167	3.2	(14.7)	0.05	77	4.8	(17.7)	90	1.9	(11.6)	0.08
Overall QLQ-CIPN20 score[β]		15.3	(14.2)		9.5	(11.5)	**<0.0001**		13.2	(13.4)		6.0	(8.0)	**<0.0001**

Percentages may not equal 100% due to rounding.

A lower score represents better functioning.

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

* Number of patients who filled in the concerning question(s)

β Sum score on all variables except trouble using the pedals and erection disorders.

§ p-value represents the difference in mean scores between the EXP, STD+ and STD- groups.

Grey blocks represent clinical differences (which are not statistically significant).

- Differences between EXP and STD- in favor of STD-: cramps toes or feet (small), weakness in legs (small)
- Differences between EXP and STD+ in favor of STD+: tingling toes or feet (moderate), numbness in toes or feet (small), trouble standing or walking (small)
- Differences between STD+ and STD- in favor of STD-: tingling fingers or hands (moderate), pain in toes or feet (small), trouble standing or walking (small), cramps toes or feet (small), trouble handling small objects (small)

Table S6 | LARS scores in patients without a stoma three years after curative surgery

	EXP (n=102)		STD (n=73)		T-test *p*-value		STD+ (n=33)		STD- (n=40)		X^{2}† *p*-value
LARS score					0.02§						0.04
No LARS	22	(21.6)	8	(11.0)			3	(9.1)	5	(12.5)	
Minor LARS	20	(19.6)	10	(13.7)			6	(18.2)	4	(10.0)	
Major LARS	60	(58.8)	55	(75.3)			24	(72.7)	31	(77.5)	

Data is presented as n (%).

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy; SD standard deviation; LARS low anterior resection syndrome.

§ Non-parametric test.

† p-value represents the difference between the EXP, STD+ and STD- groups.

Table S7 | Toxicity per follow-up moment regarding two subgroups

	At 6 months									
	Grade 1-2					Grade ≥3				
	EXP (n=354)		STD (n=352)			EXP (n=354)		STD (n=352)		
	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value
Any	165	(47)	161	(46)	0.82	31	(9)	35	(10)	0.59
Blood and lymphatic	6	(2)	7	(2)	0.77	0	(0)	1	(<1)	0.32
Gastrointestinal, any	61	(17)	71	(20)	0.32	8	(2)	12	(3)	0.36
Fatigue	30	(9)	59	(17)	**0.001**	1	(<1)	1	(<1)	1.00
Allergic reaction	0	(0)	1	(<1)	0.32	0	(0)	0	(0)	1.00
Weight loss	11	(3)	5	(1)	0.13	0	(0)	0	(0)	1.00
Nervous system, any	118	(33)	77	(22)	**0.001**	5	(1)	0	(0)	0.03
Respiratory	3	(1)	9	(3)	0.08	0	(0)	0	(0)	1.00
Renal and urinary	24	(7)	19	(5)	0.44	4	(1)	3	(1)	0.71
Skin, any	11	(3)	30	(9)	**0.002**	0	(0)	2	(1)	0.16
Sexual	27	(8)	25	(7)	0.79	0	(0)	1	(<1)	0.32
Other	54	(15)	69	(20)	0.13	17	(5)	22	(6)	0.40

EXP experimental; STD standard-care.

Table S7 | Toxicity per follow-up moment regarding two subgroups (continued)

	At 12 months									
	Grade 1-2					Grade ≥3				
	EXP (n=341)		STD (n=314)			EXP (n=341)		STD (n=314)		
	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value
Any	148	(43)	108	(34)	0.02	25	(7)	19	(6)	0.51
Blood and lymphatic	3	(1)	3	(1)	0.92	0	(0)	0	(0)	1.00
Gastrointestinal, any	58	(17)	52	(17)	0.88	6	(2)	6	(2)	0.89
Fatigue	14	(4)	21	(7)	0.14	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Weight loss	3	(1)	2	(1)	0.72	0	(0)	0	(0)	1.00
Nervous system, any	96	(28)	43	(14)	**<0.0001**	3	(1)	2	(1)	0.72
Respiratory	1	(<1)	0	(0)	0.34	1	(<1)	0	(0)	0.34
Renal and urinary	13	(4)	16	(5)	0.43	4	(1)	4	(1)	0.91
Skin, any	5	(2)	3	(1)	0.55	0	(0)	1	(<1)	0.30
Sexual	27	(8)	27	(9)	0.75	1	(<1)	1	(<1)	0.95
Other	36	(11)	31	(10)	0.77	14	(4)	6	(2)	0.10

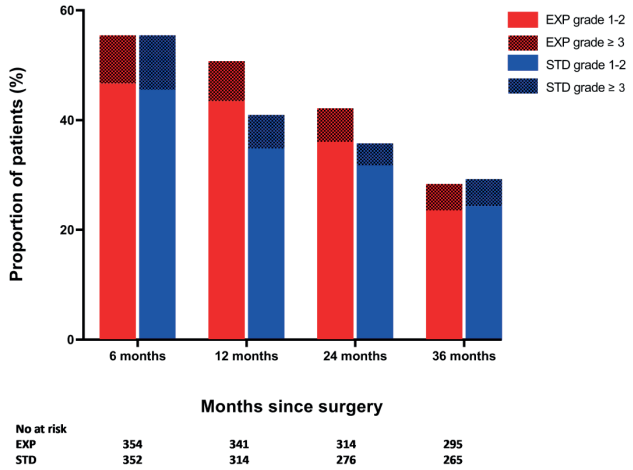
	At 24 months									
	Grade 1-2					Grade ≥3				
	EXP (n=314)		STD (n=276)			EXP (n=314)		STD (n=276)		
	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value
Any	113	(36)	88	(32)	0.29	19	(6)	11	(4)	0.26
Blood and lymphatic	0	(0)	1	(<1)	0.29	0	(0)	0	(0)	1.00
Gastrointestinal, any	52	(17)	48	(17)	0.79	6	(2)	4	(1)	0.67
Fatigue	11	(4)	12	(4)	0.60	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Weight loss	3	(1)	4	(1)	0.58	0	(0)	0	(0)	1.00
Nervous system, any	72	(23)	23	(8)	**<0.0001**	1	(<1)	0	(0)	0.35
Respiratory	0	(0)	1	(<1)	0.29	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	9	(3)	0.96	4	(1)	2	(1)	0.51
Skin, any	5	(2)	1	(<1)	0.14	0	(0)	0	(0)	1.00
Sexual	21	(7)	27	(10)	0.17	0	(0)	0	(0)	1.00
Other	25	(8)	33	(12)	0.10	14	(5)	6	(2)	0.13

Table S7 | Toxicity per follow-up moment regarding two subgroups (continued)

	At 36 months									
	Grade 1-2					Grade ≥3				
	EXP (n=295)		STD (n=265)			EXP (n=295)		STD (n=265)		
	n	(%)	n	(%)	p-value	n	(%)	n	(%)	p-value
Any	69	(23)	65	(25)	0.75	14	(5)	13	(5)	0.93
Blood and lymphatic	1	(<1)	3	(1)	0.27	0	(0)	0	(0)	1.00
Gastrointestinal, any	35	(12)	39	(15)	0.32	3	(1)	5	(2)	0.39
Fatigue	8	(3)	10	(4)	0.48	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Weight loss	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Nervous system, any	41	(14)	17	(6)	**0.004**	1	(<1)	0	(0)	0.34
Respiratory	0	(0)	0	(0)	1.00	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	10	(4)	0.81	3	(1)	2	(1)	0.74
Skin, any	1	(<1)	2	(1)	0.50	0	(0)	0	(0)	1.00
Sexual	14	(5)	24	(9)	0.043	1	(<1)	0	(0)	0.34
Other	20	(7)	16	(6)	0.72	10	(3)	6	(2)	0.43

EXP experimental; STD standard-care.v

A



B

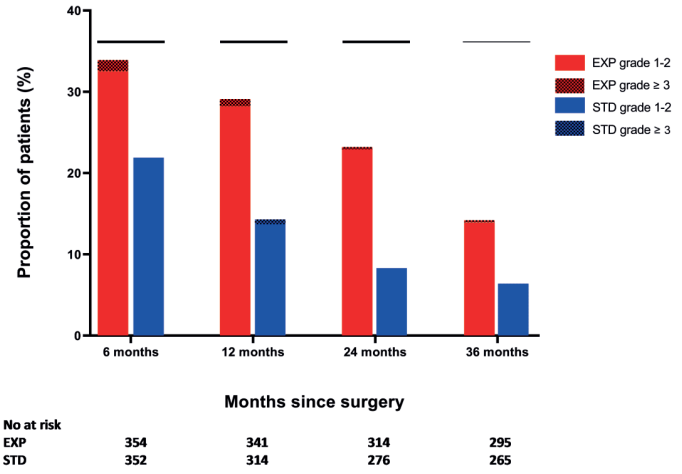


Figure S1 | (A) Toxicity per follow-up moment regarding two subgroups, (B) Neurotoxicity per follow-up moment regarding two subgroups

n represents the number of evaluable patients (excluding missing).

Toxicity was scored with a range of 3 months at 6, 12, 24, and 36 months.

The horizontal lines represent statistically significant differences in any toxicity grade between the groups; non-bold line p=0.002 and bold line p<0.0001.

EXP experimental; STD standard-care.

Table S8 | Late toxicity regarding three subgroups

	At 6 months													
	Grade 1-2							Grade ≥ 3						
	EXP (n=354)		STD+ (n=174)		STD- (n=178)			EXP (n=354)		STD+ (n=174)		STD- (n=178)		
	n	(%)	n	(%)	n	(%)	p-value	n	(%)	n	(%)	n	(%)	p-value
Any	165	(47)	101	(58)	60	(34)	**<0.0001**	31	(9)	15	(9)	20	(11)	0.61
Blood and lymphatic	0	(0)	1	(1)	0	(0)	0.22	0	(0)	1	(1)	0	(0)	0.22
Gastrointestinal, any	61	(17)	37	(21)	34	(19)	0.53	8	(2)	4	(2)	8	(5)	0.30
Fatigue	30	(9)	44	(25)	15	(8)	**<0.0001**	1	(<1)	1	(1)	0	(0)	0.60
Allergic reaction	0	(0)	1	(1)	0	(0)	0.22	0	(0)	0	(0)	0	(0)	1.00
Weight loss	11	(3)	1	(1)	4	(2)	0.19	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	118	(33)	74	(43)	3	(2)	**<0.0001**	5	(1)	0	(0)	0	(0)	0.08
Respiratory	3	(1)	8	(5)	1	(5)	**0.003**	0	(0)	0	(0)	0	(0)	1.00
Renal and urinary	24	(7)	3	(2)	16	(9)	0.01	4	(1)	0	(0)	3	(2)	0.26
Skin, any	11	(3)	26	(15)	4	(2)	**<0.0001**	0	(0)	2	(1)	0	(0)	0.05
Sexual	27	(8)	8	(5)	17	(10)	0.20	0	(0)	1	(1)	0	(0)	0.22
Other	54	(15)	39	(22)	30	(17)	0.12	17	(5)	9	(6)	13	(7)	0.48

	At 12 months													
	Grade 1-2							Grade ≥ 3						
	EXP (n=341)		STD+ (n=156)		STD- (n=158)			EXP (n=341)		STD+ (n=156)		STD- (n=158)		
	n	(%)	n	(%)	n	(%)	p-value	n	(%)	n	(%)	n	(%)	p-value
Any	148	(43)	64	(41)	44	(28)	**0.004**	25	(7)	7	(5)	12	(8)	0.44
Blood and lymphatic	0	(0)	0	(0)	1	(1)	0.21	0	(0)	0	(0)	0	(0)	1.00
Gastrointestinal, any	58	(17)	26	(17)	26	(17)	0.99	6	(2)	1	(1)	5	(3)	0.25
Fatigue	14	(4)	14	(9)	7	(4)	0.07	0	(0)	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Weight loss	3	(1)	2	(1)	0	(0)	0.40	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	96	(28)	41	(26)	2	(1)	**<0.0001**	3	(1)	1	(1)	1	(1)	0.94
Respiratory	1	(<1)	0	(0)	0	(0)	0.63	1	(<1)	0	(0)	0	(0)	0.63
Renal and urinary	13	(4)	7	(5)	9	(6)	0.64	4	(1)	1	(1)	3	(2)	0.59
Skin, any	5	(2)	2	(1)	1	(1)	0.73	0	(0)	1	(1)	0	(0)	0.20
Sexual	27	(8)	13	(8)	14	(9)	0.94	1	(<1)	1	(1)	0	(0)	0.59
Other	36	(11)	12	(8)	19	(12)	0.43	14	(4)	2	(1)	4	(3)	0.22

	At 24 months													
	Grade 1-2							Grade ≥ 3						
	EXP (n=314)		STD+ (n=131)		STD- (n=145)			EXP (n=314)		STD+ (n=131)		STD- (n=145)		
	n	(%)	n	(%)	n	(%)	p-value	n	(%)	n	(%)	n	(%)	p-value
Any	113	(36)	46	(35)	42	(29)	0.32	19	(6)	6	(5)	5	(3)	0.48
Blood and lymphatic	0	(0)	0	(0)	1	(1)	0.22	0	(0)	0	(0)	0	(0)	1.00
Gastrointestinal, any	52	(17)	27	(21)	21	(15)	0.39	6	(2)	2	(2)	2	(1)	0.91
Fatigue	11	(4)	5	(4)	7	(5)	0.79	0	(0)	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Weight loss	3	(1)	2	(2)	2	(1)	0.85	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	72	(23)	21	(16)	2	(1)	**<0.0001**	1	(<1)	0	(0)	0	(0)	0.64
Respiratory	0	(0)	1	(1)	0	(0)	0.17	0	(0)	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	4	(3)	5	(3)	0.98	4	(1)	1	(1)	1	(1)	0.80
Skin, any	5	(2)	0	(0)	1	(1)	0.28	0	(0)	0	(0)	0	(0)	1.00
Sexual	21	(7)	13	(10)	14	(10)	0.39	0	(0)	0	(1)	0	(0)	1.00
Other	25	(8)	15	(12)	18	(12)	0.26	14	(5)	2	(2)	4	(3)	0.26

Table S8 | Late toxicity regarding three subgroups (continued)

	At 36 months													
	Grade 1-2							Grade ≥ 3						
	EXP (n=295)		STD+ (n=123)		STD- (n=142)			EXP (n=295)		STD+ (n=123)		STD- (n=142)		
	n	(%)	n	(%)	n	(%)	p-value	n	(%)	n	(%)	n	(%)	p-value
Any	69	(23)	31	(25)	34	(24)	0.93	14	(5)	4	(3)	9	(6)	0.50
Blood and lymphatic	1	(<1)	1	(1)	2	(1)	0.46	0	(0)	0	(0)	0	(0)	1.00
Gastrointestinal, any	35	(12)	20	(16)	19	(13)	0.48	3	(1)	1	(1)	4	(3)	0.27
Fatigue	8	(3)	5	(4)	5	(4)	0.76	0	(0)	0	(0)	0	(0)	1.00
Allergic reaction	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Weight loss	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Nervous system, any	41	(14)	13	(11)	4	(3)	**0.002**	1	(<1)	0	(0)	0	(0)	0.64
Respiratory	0	(0)	0	(0)	0	(0)	1.00	0	(0)	0	(0)	0	(0)	1.00
Renal and urinary	10	(3)	3	(2)	7	(5)	0.54	3	(1)	1	(1)	1	(1)	0.94
Skin, any	1	(<1)	0	(0)	2	(1)	0.23	0	(0)	0	(0)	0	(0)	1.00
Sexual	14	(5)	14	(11)	10	(7)	0.05	1	(<1)	0	(0)	0	(0)	0.64
Other	20	(7)	7	(6)	9	(6)	0.92	10	(3)	0	(0)	6	(4)	0.09

EXP experimental; STD standard-care; STD+ standard-care with post-operative chemotherapy; STD- standard-care without post-operative chemotherapy.

Information on the EORTC QLQ-C30 questionnaire

The EORTC QLQ-C30[1] is a validated questionnaire to measure health-related QoL in cancer patients. The questionnaire consists of five different functional scales (global health, physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting) and six single items (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea and financial impact).

REFERENCE

1 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, 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(5):365–76.

Information on the EORTC QLQ-CR29 questionnaire

The EORTC QLQ-CR29[2], is divided into four function scales (urine frequency, blood and mucus in stool, stool frequency and body image) and 19 single items (urine incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, anxiety, weight, flatulence, fecal incontinence, sore skin, embarrassment, stoma care problems, sexual interest (men), sexual interest (women), impotence and dyspareunia). In addition, a higher score on the sexual items corresponds to a higher degree of health-related quality of life.

REFERENCE

2 van der Hout A, Neijenhuijs KI, Jansen F, van Uden-Kraan CF, Aaronson NK, Groenvold M, et al. Measuring health-related quality of life in colorectal cancer patients: systematic review of measurement properties of the EORTC QLQ-CR29. Support Care Cancer. 2019;27(7):2395–412.

Information on the EORTC QLQ-CIPN20 questionnaire

The EORTC QLQ-CIPN20[3] assesses symptoms and function limitations related to chemotherapy-induced peripheral neuropathy during the past week. This questionnaire is divided into three scales: sensory scale (tingling, numbness, pain, instability when walking or standing, distinguishing temperature, and hearing), motor scale (cramps, writing, manipulation small objects and, weakness) and autonomic scale (vision, dizziness after changing position and, erection disorder).

REFERENCE

3 Postma TJ, Aaronson NK, Heimans JJ, Muller MJ, Hildebrand JG, Delattre JY, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: The QLQ-CIPN20. Eur J Cancer. 2005.

Information on the LARS score

Bowel dysfunction was scored among patients without a stoma by the validated LARS score consisting of five questions about incontinence for flatus and liquid stool, frequency, clustering, and urgency and results were scored in 0-42 points[4,5]. A score of 0-20 points represents no LARS, 21-29 points minor LARS, and 30-42 points major LARS. Patients with missing items in the LARS score were excluded.

REFERENCE

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CHAPTER 4

Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared to long-course chemoradiotherapy and surgery – A five-year follow-up of the RAPIDO trial

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Annals of Surgery. 2023; DOI: 10.1097/SLA.0000000000005799

ABSTRACT

Objective
To analyse risk and patterns of locoregional failure (LRF) in patients of the RAPIDO trial at five years.

Summary Background Data
Multimodality treatment improves local control in rectal cancer. Total neoadjuvant treatment (TNT) aims to improve systemic control while local control is maintained. At three years, LRF rate was comparable between TNT and chemoradiotherapy in the RAPIDO trial.

Methods
920 patients were randomized between an experimental (EXP, short-course radiotherapy, chemotherapy, and surgery) and a standard-care group (STD, chemoradiotherapy, surgery, and optional post-operative chemotherapy). LRF, including early LRF (eLRF) (no resection except for organ preservation/R2 resection) and locoregional recurrence (LRR) after an R0/R1 resection, were analyzed.

Results
Totally, 460 EXP and 446 STD patients were eligible. At 5.6 years (median follow-up), LRF was detected in 54/460 (12%) and 36/446 (8%) patients in the EXP and STD groups, respectively (p=0.07), in which EXP patients were more often treated with 3D-CRT (p=0.029). In the EXP group, LRR was detected more often (44/431 (10%) vs. 26/428 (6%); p=0.027), with more often a breached mesorectum (9/44 (21%) vs. 1/26 (4); p=0.048). The EXP treatment, enlarged lateral lymph nodes, positive circumferential resection margin, tumor deposits, and node positivity at pathology were significant predictors for developing LRR. Location of the LRRs was similar between groups. Overall survival after LRF was comparable (HR 0.76 (95%CI 0.46-1.26); p=0.29).

Conclusion
The EXP treatment was associated with an increased risk of LRR whereas the reduction in disease-related treatment failure and distant metastases remained after 5 years. Further refinement of the TNT in rectal cancer is mandated.

Keywords
Locally advanced rectal cancer, total neoadjuvant treatment, locoregional failure, locoregional recurrence.

INTRODUCTION

Over the past decades, improved imaging, preoperative radiotherapy (RT) or chemoradiotherapy (CRT), and total mesorectal excision (TME) surgery have resulted in improved local control rates in patients with rectal cancer[1-3]. Despite these improvements, the systemic relapse rate has remained largely unaltered. The concept of total neoadjuvant treatment (TNT) was introduced to address the distant metastasis (DM) rate. Recently, the results of the RAPIDO trial demonstrated that preoperative short-course radiotherapy (scRT) followed by systemic chemotherapy (i.e., TNT) resulted in a decreased disease-related treatment failure (DrTF) rate (mainly by a decrease in DM, compared to standard CRT at three years of follow-up in high-risk locally advanced rectal cancer (LARC))[4]. However, less is known about locoregional failure (LRF) rates after TNT.

LRF can occur at different time points during rectal cancer management using TNT. In poor or non-responders to the neoadjuvant treatment, the tumor may be irresectable or lead to an R2 resection causing an early LRF (eLRF). In patients who undergo an R0 or R1 resection, an LRF may occur during follow-up as an LRR.

The aim was to investigate the rate and describe patterns of LRFs, including LRRs, in the experimental (EXP) and the standard-care (STD) treatment groups in the RAPIDO trial. Moreover, survival after an LRF was analyzed.

MATERIALS AND METHODS

Patient selection

The RAPIDO trial is an international, multicenter, phase III, randomized trial. It was approved by the institutional review boards of participating institutions (2010-023957-12). Details of the trial have been reported[5]. In short, patients with rectal adenocarcinoma, less than 16 cm from the anal verge at endoscopy and with high-risk features on MRI (cT4a/b, cN2, enlarged lateral lymph nodes (ELLN) considered to be metastatic, extramural vascular invasion (EMVI+) or involved mesorectal fascia (MRF+)) were randomized (1:1) to EXP or STD treatment. Patients were included between 2011 and 2016. The data lock for this report was March 11th, 2022.

Treatments

The EXP treatment consisted of 5x5 Gy radiotherapy, followed by six cycles of CAPOX or nine cycles of FOLFOX4. Within two to four weeks after this treatment, TME surgery was performed. The STD treatment consisted of long-course radiotherapy (28-25x1.8-2.0 Gy) and concurrent capecitabine, followed by surgery after eight ± two weeks. According to hospital policy, patients in the STD group could receive post-operative eight cycles of CAPOX or twelve cycles of FOLFOX4. Radiotherapy target volumes did not differ between the EXP and STD groups. The results from the primary and some secondary endpoints of the RAPIDO trial

have been reported[4,6].

Restaging was performed in the EXP group 1-2 weeks after the last chemotherapy cycle and 2-3 weeks before planned surgery in the STD group. Restaging was performed by CT of the thorax, abdomen, and pelvis and MRI of the pelvis. In the EXP group, an additional MRI of the pelvis was recommended in the middle of the neoadjuvant chemotherapy (week 12-14) to disclose any signs of progression. Treatment response was assessed after neoadjuvant treatment (based on baseline and restaging MRI reports) and after surgery (based on pathology reports). For this report, all patients with a decrease in T- and/or N-stage compared to baseline MRI stage were defined as good responders (i.e., downstaging was accomplished).

Follow-up

Follow-up was according to a standardized protocol. Outpatient visits were scheduled at 6, 12, 24, 36, and 60 months after surgery. The study protocol mandated a CT scan of the thorax and abdomen (or chest x-ray and liver ultrasound) at 12 and 36 months after surgery as a minimum. On indication, other diagnostics were performed, to confirm or detect recurrent disease.

Outcomes

A secondary endpoint in the RAPIDO trial and the primary endpoint in this study was LRF, including eLRF and LRR. eLRF was defined as patients having no surgery/non-resectional surgery unless this was in an organ preservation setting or R2 resection. Patients who were lost to follow-up, withdrew informed consent, or died before surgery were excluded from the analyses.

An LRR was defined as a locoregionally recurrent disease after a previous R0 or R1 resection. When watch-and-wait (W&W) patients with tumor regrowth underwent a curative resection, this was not scored as LRR. However, when any subsequent local recurrence after a radical resection in W&W patients, was considered as a LRR. Patients refusing surgery were grouped with those entering the W&W strategy since the predominant reason for refusal was no residual tumor. The two patients who were not operated up-front and much later had locally progressive disease were scored as LRR (figure 1 and table S1). Histopathological confirmation of an LRR was not mandatory when indicated by CT-, MRI-, and/or PET scans. Secondary outcomes included the location of the LRRs, and treatment of LRF. For this report, updated results for the RAPIDO endpoints DrTF, DM, and overall survival (OS) at 5 years were analyzed.

Location of LRR

The location of recurrent disease was recorded in the CRFs and centrally reviewed by imaging reports (MRI, CT, PET) and/or histology reports. Locations were classified according to Kusters et al.[7]: (supplementary appendix) In patients with large or multifocal LRRs, all involved subsites were recorded.

Statistics

The RAPIDO trial was powered for the primary endpoint (DrTF) but not for any secondary endpoints, including LRF reported here. LRF analyses were performed on an intention-to-treat basis on all eligible patients. LRR analyses were performed in all eligible patients who underwent an R0 or R1 resection (and in two non-operated patients who later developed progressive disease). Proportions were compared with chi-square tests and continuous parameters, depending on the distribution of the data, with the T-test or Mann-Whitney U-test. When a patient developed DM within 3 months (before or after) of an LRF, the DM was defined as synchronous. Univariate and multivariate Cox regression analyses were used to calculate the influence of baseline characteristics on the occurrence of LRF and LRR, and to calculate the influence of surgical and histopathological characteristics on LRR. The median follow-up was calculated by the reversed Kaplan-Meier method. The median survival time after diagnosis of LRF was calculated by the Kaplan-Meier method. Differences were assessed using the log-rank test. Cumulative incidence of DrTF, DM, and OS were calculated accounting for all causes of death as a competing risk. For all competing risk analyses, hazard ratios (HR) and 95% confidence intervals (CI) were calculated by Cox regression. In univariate analyses, a p-value of $p \leq 0.10$, and in all other statistical analyses $p \leq 0.05$ was considered statistically significant. SPSS for Windows (version 28, SPSS, Chicago, IL) and R-studio were used for the statistical analyses.

RESULTS

Study population

Nine hundred and twenty patients were randomized in the RAPIDO trial, of whom 906 (460 in the EXP and 446 patients in the STD group) were eligible for the LRF analyses (figure 1). Patients who underwent an R0/R1 resection, 857/906, were included in the LRR analysis (431 in the EXP and 426 in the STD group). The median follow-up was 5.6 years (IQR 5.4-7.5).

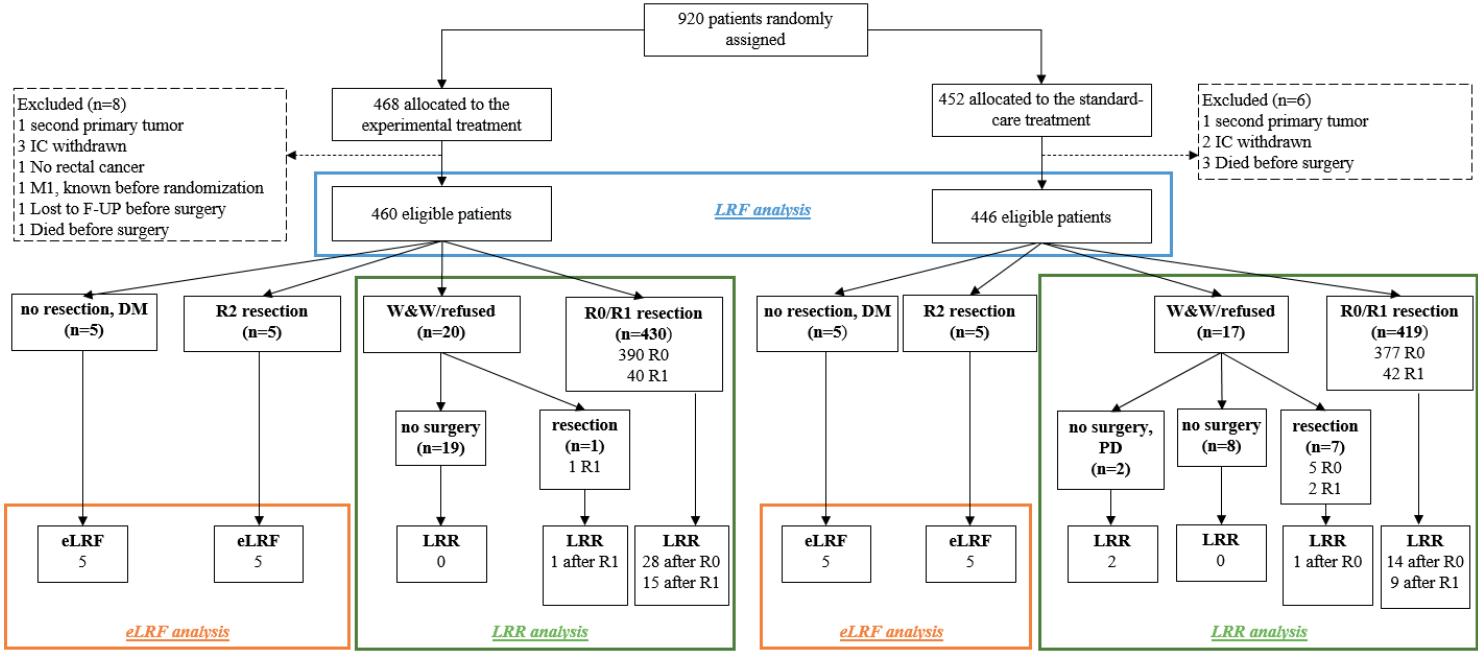

Figure 1 | Consort diagram

IC informed consent; F-UP follow-up; W&W strategy watch and wait strategy; DM distant metastasis; PD progressive disease.

Patients entering a W&W program or who 'refused surgery' according to the case record forms were grouped together since the predominant reason for the refusers was no remaining tumor/no need for surgery. These patients were included in the LRR analysis. The two patients who initially entered a W&W strategy/refused surgery but later developed regrowth without having surgery were scored as LRR. When W&W patients with tumor regrowth underwent a

Overall LRF

An LRF was detected in 54/460 (11.7%) and 36/446 (8.1%) patients in the EXP and STD groups, respectively (p=0.07). Baseline characteristics of patients included in the LRF analyses and in whom an LRF was detected are provided in table S1. No significant differences in baseline high-risk criteria between the two groups were found. Patients in the EXP group with an LRF received more often 3D-conformed radiotherapy (3D-CRT) compared to those in the STD group (p=0.029). The different types of LRFs, in relation to time after randomization, are demonstrated in figure 2.

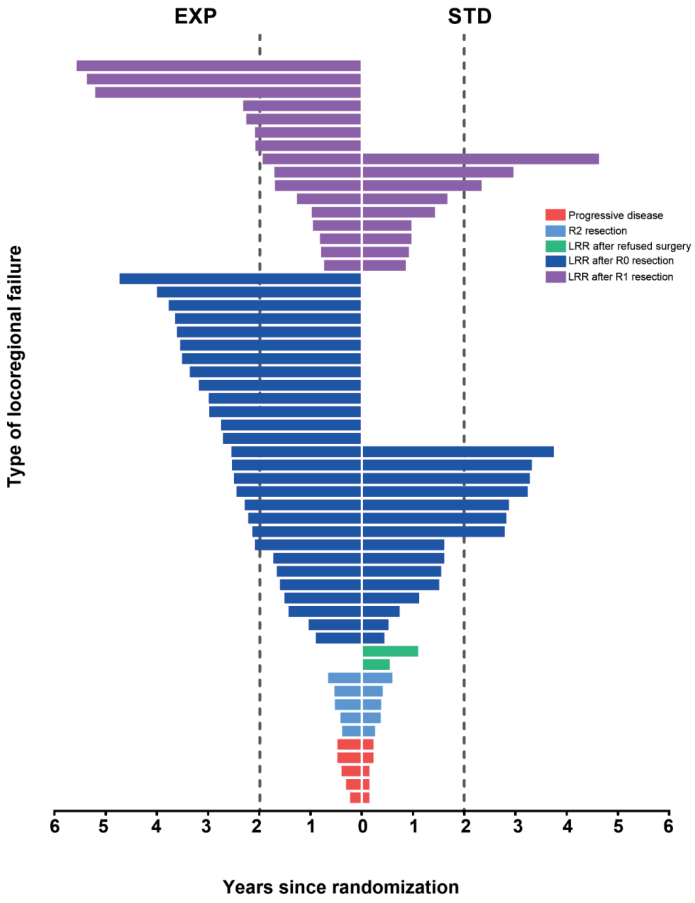

Figure 2 | Plot development of locoregional failure against time in years after randomization

Red: No resection surgery for other reasons than entering a W&W strategy (5 vs. 5). Light blue: R2 (residual tumor locally (all these patients also had distant metastases) (5 vs. 5). Green: locoregionally progressive disease after having refused surgery (0 vs. 2, referred to the LRR group) Dark blue: LRR after an R0 resection (28 vs. 15). Pink: LRR after an R1 resection (16 vs. 9).

eLRF

An eLRF occurred in 20 patients (10/460 in the EXP and 10/446 in the STD group, table S2). Eight and ten of these patients also developed DM in the EXP and STD groups, respectively. All of them developed DM before or synchronously with the eLRF. In univariate analyses, distance from the anal verge (p=0.049), presence of ELLN (p=0.002), and EMVI+ (p=0.014) were associated with an eLRF, but no statistically significant associations were found in the multivariate analysis (table S3).

LRR after an R0 or R1 resection

Totally, 886/912 (97%) patients were included in the LRR analyses (figure 1). Of them, 857 (97%) underwent an R0 or R1 resection. There were no statistically significant differences in R0 or R1 resection rates between the EXP and STD groups. A higher rate of LRR was detected in the EXP group compared to the STD group; 44/431 (10.2%) and 26/428 (6.1%), p=0.027. Following an R0 resection, LRR was more often detected in the EXP group (7.2% vs. 3.9%; p=0.049), and a similar numerical difference, but not statistically significant, was observed for R1 resected patients (39.0% vs. 20.5%; p=0.06).

Except for the mesorectum being more often breached in the EXP group, table S4, demonstrates no statistically significant differences in high-risk criteria and histopathological characteristics between LRR patients of the EXP and STD groups. In a multivariate Cox regression analysis (table 1), the EXP treatment (p=0.014) and ELLN (p=0.042) were associated with LRR.

Table 1 | Univariate and multivariate Cox regression analyses for locoregional recurrence regarding allocation group, distance from the anal verge and high-risk factors at baseline in patients who underwent an R0 or an R1 resection

Variable	Category	Univariate analyses			Multivariate analyses		
		n	HR (95% CI)	*P*-value	n	HR (95% CI)	*P*-value
Treatment	**Standard-care**	**426**	**1**		**426**	**1**	
	Experimental	**431**	**1.84 (1.12-3.02)**	**0.017**	**431**	**1.87 (1.14-3.07)**	**0.014**
Distance from anal verge (endoscopy) †	< 5 cm	196	1	0.829			
	5-10 cm	318	1.19 (0.63-2.27)				
	≥ 10 cm	282	1.094 (0.53-2.04)				
Clinical T4	No	582	1				
	Yes	275	0.99 (0.59-1.65)	0.959			
Clinical N2	No	267	1				
	Yes	590	1.38 (0.80-2.39)	0.252			
Clinical ELLN	No	**723**	**1**		**723**	**1**	
	Yes	**134**	**1.74 (0.99-3.04)**	**0.053**	**134**	**1.79 (1.02-3.13)**	**0.042**
Clinical EMVI+	No	557	1				
	Yes	300	1.13 (0.69-1.85)	0.621			
Clinical MRF+	No	271	1				
	Yes	586	1.25 (0.74-2.12)	0.412			

† In 61 patients the distance from the anal verge was unknown.
ELLN enlarged lateral lymph nodes considered metastatic; EMVI extramural vascular invasion; MRF mesorectal fascia
Test for interaction is p=0.89

The time from surgery to detection of an LRR was 1.8 years (IQR 1.2-2.6) in the EXP and 1.2 years (0.6-2.7) in the STD group (p=0.31), respectively. When an LRR was detected, 36/70 (52%) had prior or synchronous DM, being similar in both groups (EXP 22/44 (50%) vs. STD 14/26 (54%) (p=0.84).
Regarding radiation technique, patients from the EXP group developed more often an LRR after 3D-CRT compared to the STD group (11.6% (37/320) vs. 6.0% (18/298); p=0.016). The LRR rate was comparable after intensity-modulated radiation therapy (IMRT)/volumetric-modulated arc therapy (VMAT) (6.3% (7/111) vs. 6.2% (8/130) in the EXP and STD groups, respectively; p=0.96). Overall, a comparable number of patients developed an LRR after a (low) anterior resection or an abdominoperineal resection (8% vs. 7%). Following Hartmann´s procedure (n=37), an LRR was detected in 11 (30%) patients. Regarding TME quality, an intraoperative breach of the mesorectum occurred more often in the EXP group compared to the STD group (11% (42/378) vs. 6% (25/389); p=0.022). In patients with a breached mesorectum, LRR was more often detected in the EXP group (21% (9/42) vs 4% (1/25); p=0.053). In the Cox regression analyses on histopathological factors, the EXP treatment (p=0.004), positive circumferential resection margin (p<0.0001), tumor deposits (p=0.004) and ypN-stage (p=0.014) were associated with an LRR (table 2).

Post-treatment restaging MRI data was available for 841/859 (97.9%) patients. In total, 632/841 (75.1%) patients were assessed as good responders (80.1% vs. 70.1% (p<0.0001) in the EXP and STD groups, respectively. Overall, recurrent disease was less often detected in MRI-based good responders (6.8% vs. 12.0%; p=0.020). Based on histopathology reports, 773/857 (90.2%) were assessed as good responders (93.0% vs. 87.3% (p=0.008) in the EXP and STD groups, respectively). As with the MRI-based response evaluation, an LRR was significantly less often detected in good responders (6.9% vs. 16.9%; p<0.0001).

Table S5, provides the location(s) of the 44 and 26 LRRs of the EXP and STD groups, respectively. No statistically significant differences between the EXP and STD groups concerning location and number of involved locations were observed. However, presacral (19 vs. 9 patients) and anastomotic (14 vs. 3 patients) LRRs occurred numerically more often in the EXP compared to the STD group.

Table 2 | Univariate and multivariate Cox regression analyses of locoregional recurrence regarding allocation group and pathological factors after surgery in patients who underwent an R0/R1 resection

Variable	Category	Univariate analyses			Multivariate analyses		
		n	HR (95% CI)	*P*-value		HR (95% CI)	*P*-value
Treatment	**Standard-care**	**426**	**1**		**287**	**1**	**0.004**
	Experimental	**431**	**1.87 (1.14-3.07)**	**0.014**	**234**	**2.38 (1.33-4.27)**	
CRM	**CRM-**	**777**	**1**		**455**	**1**	**<0.0001**
	CRM+	**80**	**7.18 (4.36-11.82)**	**<0.0001**	**66**	**4.13 (2.25-7.59)**	
Differentiation grade at pathology*	**Well**	**151**	**1**	**0.016**	138	1	0.631
	Moderate	**377**	**0.74 (0.40-1.35)**		314	0.85 (0.44-1.65)	
	Poor	**82**	**1.87 (0.91-3.83)**		69	1.21 (0.54-2.73)	
Mesorectum assessment *	**Intact**	**700**	**1**		471	1	0.800
	Breached	**67**	**2.37 (1.21-4.68)**	**0.012**	50	1.11 (0.50-2.48)	
EMVI at pathology*	**EMVI-**	**744**	**1**		443	1	0.896
	EMVI+	**105**	**4.22 (2.53-7.01)**	**<0.0001**	78	1.05 (0.54-2.02)	
Tumor deposits*	**No**	**749**	**1**		**445**	**1**	**0.004**
	Yes	**95**	**3.96 (2.34-6.70)**	**<0.0001**	**76**	**2.43 (1.32-4.48)**	
ypN-stage*	**ypN0**	**604**	**1**	**<0.0001**	**336**	**1**	**0.014**
	ypN1	**166**	**3.03 (1.72-5.33)**		**115**	**2.19 (1.09-4.41)**	
	ypN2	**79**	**5.82 (3.18-10.64)**		**70**	**2.97 (1.38-6.38)**	
Tumor size at pathology*	**<40mm**	**703**	**1**	**0.001**	410	1	0.075
	≥40mm	**137**	**2.41 (1.43-4.06)**		111	1.76 (0.94-3.29)	

Two patients did not undergo curative surgery, therefore the initial number of patients included is 857 instead of 859.

§ Cox regression analysis performed in patients in which the differentiation grade was known

CRM circumferential resection margin.

* In case the variable was unknown for a patient, the patient was set to missing. Therefore, the number of patients included in the multivariate analysis is considerably lower.

Treatment of LRF

The treatment intention (curative/palliative) for patients with an LRF did not differ between the two groups (p=0.48). All 20 patients with an eLRF were treated with palliative intent. In case of an LRR, re-irradiation was delivered to 11/44 (25%) and 1/26 (4%) of the patients of the EXP and STD groups, respectively. Among these re-irradiated patients, 7 in the EXP group and one in the STD group underwent surgery. Two patients in the EXP and 4 patients in the STD group received only best supportive care for their LRR. Overall, surgical resection of the LRR was performed in 22/44 (50%) patients in the EXP group and 11/26 (42%) patients in the STD group. In both groups, when surgery was performed, it was mostly with curative intent (82%). The median survival of patients with an LRF was 1.6 years (0.6-3.2) in the EXP group and 1.2 years (0.4-2.4) in the STD group (p=0.29) (figure S1).

5-year update of oncological outcomes of the RAPIDO trial

At 5-years, the cumulative probability of DrTF was 27.8% (95% CI 23.7–31.8) in the EXP group and 34.0% (95% CI 29.6–38.4) in the STD group (HR 0.79 (95% CI 0.63–1.00); p=0.048. The cumulative probability of DM at 5 years in the EXP group was 23.0% (95% CI 19.2–26.8) and 30.4% (95%CI 26.1–34.7) in the STD group (HR 0.73 (95%CI 0.57–0.93); p=0.011. At 5 years the cumulative probability of OS was 81.7% (95%CI 78.2–85.22) in the EXP group compared with 80.2% (95% CI 76.5–83.9) in the STD group (HR 0.91 (95%CI 0.70–1.19); p=0.50).

DISCUSSION

Results from the RAPIDO trial demonstrated that the EXP treatment is associated with a decreased incidence of DM and an increased rate of pCR, and comparable LRF rates to the STD treatment at three years of follow-up[4]. With a longer follow-up (median 5.6 years), the rates of both LRF and LRR are higher in the EXP group compared to the STD group (12 vs 8%, p=0.07 and 10 vs 6%, p=0.03). Thus, although the RAPIDO trial demonstrated favorable outcomes concerning systemic control with a TNT approach, this report indicates a risk of compromising local control with the EXP treatment, despite a doubled chance to obtain pCR. With the prolonged follow-up, OS remains similar between the EXP and STD groups.

Early locoregional failures (eLRF) are rarely seen but occur at similar rates in the EXP and the STD groups of the RAPIDO trial. Most patients with eLRF, both among EXP and STD, also developed DM before or in conjunction with the eLRF. Patients with eLRF appear to represent a subset of patients who have an extremely poor prognosis irrespective of the treatment approach. We demonstrated that the vast majority of eLRF patients had cN2 and MRF involvement. Hopefully, future research may result in the identification of these patients pre-therapeutically (e.g., via bio-markers) and offer more personalized approaches. The rareness of eLRF constitutes an obstacle to meaningful statistical analyses of risk factors.

Of the patients in the RAPIDO trial, the overall LRR rate is 7.8% which is comparable to literature considering the locally advanced stages included[2,3,8,9]. However, the statistically significantly increased LRR rate in the EXP group compared to STD raises several questions. Analyses of patient and tumor characteristics reveal no imbalances between the two groups. However, a breach of the mesorectum is associated with an LRR[10]. A mesorectal breach occurred more often in the EXP group, and the increased risk of LRR in the EXP group was most pronounced in the breached group. scRT per se (compared to primary surgery) did not affect the plane of surgery in the MRC-CR07 trial11 but it may be speculated that the prolonged preoperative chemotherapy in the EXP group could yield a more fragile or fibrotic mesorectum and poorer specimen quality. This may, thus, provide one possible explanation for the increased rate of LRR in the EXP group.

The radiation technique was the only statistically significant different baseline/initial treatment characteristic when comparing the two groups of LRF patients. Patients from the EXP group received more often 3D-CRT while the STD group received IMRT/VMAT to a higher degree. During the time of RAPIDO inclusion (2011-2016), IMRT/VMAT, a relatively new radiation technique at the time, had become standard-of-care more commonly in patients treated with long-course CRT compared to scRT, although this difference did not reach statistical significance. There is no obvious explanation why patients treated with 3D-CRT more often had an LRR in the EXP group (12%) than in the STD group (6%) whereas no such difference was seen in patients treated with IMRT/VMAT (6% vs. 5%, respectively). Irradiated volumes concerning tumor coverage should not differ between the techniques and are therefore unlikely to be associated with an LRR. In addition, the excess risk of LRR in the EXP group was predominantly seen in the anastomotic region usually located centrally in the target volume. Whereas IMRT/VMAT always requires individual target volume delineation, this may not always be performed for 3D-CRT. Therefore, geographical misses may have occurred more often in the EXP than in the STD group, but more in-depth analyses are required to confirm this. Toxicity, on the other hand, may differ between the two radiotherapy techniques but this was not examined in this report.

An important difference between the EXP and STD groups concerns overall treatment time (OTT) before surgery, which is approximately 40 weeks in the EXP group vs. approximately 25 weeks in the STD group. Judging from MRI, a larger proportion of good responders were observed in the EXP group at restaging (80.1% vs. 70.1% ($p>0.0001$), and at histopathology (93.0% vs. 87.3% ($p=0.008$) compared to the STD group. In addition, at histopathology, a significantly higher proportion of patients had a tumor <40 mm in the EXP group ($p=0.003$), despite no difference in tumor size at baseline MRI ($p=0.38$). Although this indicates a higher response rate in the EXP group, it is conceivable that the prolonged OTT may be deleterious concerning local control for the small subset of patients who are poor responders. Therefore, when a TNT regimen is used, a response evaluation should be performed during the neoadjuvant therapy and not only after the completed schedule. Although objective responses to oxaliplatin-based chemotherapy in metastatic disease are frequently seen, the chemotherapy is the weakest component of the TNT concerning cell kill capability. Additionally, the observation that down-sizing occurred more often among EXP patients who still had a higher rate of LRR underlines that there may be a difference between down-sizing and down-staging. More low anterior resections and fewer abdominoperineal resections in the EXP group were performed despite no difference in tumor characteristics at baseline. It is conceivable that down-sizing may persuade surgeons to perform less extensive surgery including more sphincter preserving procedures although microscopic tumor deposits may remain. The observation that, numerically, anastomotic recurrences occurred more often in the EXP group could support such a notion. We believe the surgical plan should be based on the baseline MRI. Moreover, we demonstrated that tumor deposits predict LRR.

ELLN, a known predictive factor for locally recurrent disease[7,12,13], was significantly associated with an increased risk of LRR irrespective of treatment arm. During the time of RAPIDO inclusion, the awareness of the potential importance of ELLN and surgical proficiency for lateral lymph node dissection was less widespread than today. A lower 5-year lateral LRR rate was reported after CRT and TME with lateral lymph node dissection after the RAPIDO trial was already closed[13]. If current guidelines[13] regarding ELLN dissection had been applied, the LRR rate could potentially have been lower.

We classified the localization of LRR according to Kusters et al.[7]. In literature, several classification systems have been presented but most of these have not been validated against oncological outcomes[14]. The classification by Kusters et al. provides information regarding the location of the tumor[7] but it does not distinguish whether the LRR is above and below the peritoneal reflection which may be associated with oncological outcome[15]. Presacral and anastomotic LRRs, axial recurrences according to the MSKCC classification system, were more often observed in the EXP group and are more often amenable to surgical treatment[16]. This is reflected in a slightly higher rate of curatively intended surgery for the LRRs in the EXP group.

Although based on a large, randomized trial, this report has several limitations. First, the RAPIDO trial was not powered for the secondary endpoint reported here. Second, a central review of MRIs, radiotherapy target volumes, dose volume histograms, delivered radiotherapy and histopathology specimens have not yet been performed, and information was mostly retrieved by CRFs. However, MRIs and histopathological specimens are currently being revised. Third, restaging MRI was performed in most patients, but not in all. Additionally, there may be unrecorded tumor characteristics, and peri- or intraoperative variables not accounted for.

The outcomes previously reported from the RAPIDO trial showed important gains from a TNT approach including a significant decrease in DrTF at 3 years and a doubled rate of pCR[4]. These gains were achieved with comparable health-related quality of life, bowel function, and late toxicity at three years[17]. However, the results after an R0/R1 surgery reported herein, showing statistically significantly decreased locoregional control rates in the EXP group prompt further refinements of the TNT approach. Early response assessment with interruption of the weakest part of the treatment, i.e., the chemotherapy, in case no response or even progression is seen, adequate coverage of the tumor-cell containing tissue volumes, dose-escalation, increased rate of lateral lymph node dissection on indication and a surgical plan based on initial pre-treatment MRI may all be important.

Acknowledgment
We thank all patients, treating physicians, and research support staff at all participating Centers.

Funding
Funding for this study was acquired from the Dutch Cancer Foundation (CKS-2011-4997); the Swedish Cancer Society; the Swedish Research Council (project number K2014-99X-22481-01-3); the Spanish Ministry of Economy and Competitiveness through the Carlos III Health Institute EC11-423, and by the Spanish Clinical Research Network (SCReN-PT13/0002/0031; PT17/0017/0003; co-financed by European Regional Development Fund "A way to make Europe").

Declaration of interest
PJN reports honoraria from Ethicon, Johnson & Johnson, and Amgen. GAPH reports consulting fees from Roche, MSD, Amgen, and Novartis; consulting fees and research support to their institution from Bristol Myers Squibb; and research support to their institution from Seerave Foundation. AGHR and CJHvdV were partially funded by the EU's Horizon 2020 research and innovation program under a Marie SkłodowskaCurie grant award (H2020MSCAITN2019, grant agreement number 857894; project acronym: CAST). MPH reports consulting fees from MSD. JC reports consulting fees, travel expenses, and research support to their institution from Pfizer, Ipsen, and Eisai; consulting fees and research support to their institution from Bayer, Novartis, and Advanced Accelerator Applications; consulting fees from Sanofi, Exelixis, and Merck Serono; and research support to their institution from AstraZeneca. BG reports research support from the Swedish Cancer Society. All other authors
declare no competing interests

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SUPPLEMENTAL MATERIAL

Table S1 | Baseline characteristics and radiation techniques of all eligible patients and of patients who developed a locoregional failure according to randomization

	included in the **locoregional failure** analyses.					in whom a **locoregional failure** was detected				
	Experimental (n=460)		Standard-care (n=446)		*P*-value	Experimental (n=54)		Standard-care (n=36)		*P*-value
Gender					0.17					0.63
Male	299	(65.0)	309	(69.3)		38	(70)	27	(75)	
Female	161	(35.0)	137	(30.7)		16	(30)	9	(25)	
Age (years)					0.72					0.83
Median (IQR)	62	(55-68)	62	(55-68)		61	(55-67)	61	(54-65)	
ECOG					0.60					0.46
0	368	(80.0)	363	(81.4)		45	(83)	32	(89)	
1	92	(20.0)	83	(18.6)		9	(17)	4	(11)	
High-risk criteria†										
cT4	149	(32.4)	138	(30.9)	0.64	17	(32)	13	(36)	0.65
cN2	317	(68.9)	310	(69.5)	0.85	41	(76)	29	(81)	0.61
Enlarged lateral nodes	70	(15.2)	73	(16.4)	0.64	13	(24)	10	(28)	0.69
EMVI +	165	(35.9)	150	(33.6)	0.48	19	(35)	19	(53)	0.10
MRF +	309	(67.2)	311	(69.7)	0.41	39	(72)	30	(83)	0.22
Distance from anal verge (endoscopy)					0.24§					0.85§
< 5 cm	101	(22.0)	113	(25.3)		9	(17)	8	(22)	
5 – 10 cm	181	(39.3)	153	(34.3)		20	(37)	14	(39)	
≥ 10 cm	146	(31.7)	149	(33.4)		19	(35)	12	(33)	
Unknown	32	(7.0)	31	(7.0)		6	(11)	2	(6)	
Radiation technique					0.11§					**0.029**
3D-CRT	339	(73.7)	306	(68.6)		45	(83)	22	(63)	
IMRT/VMAT	121	(26.3)	139	(31.2)		9	(17)	13	(37)	
Unknown	-		1	(0.2)						
Type of locoregional failure										0.28
Early locoregional failure*						10	(19)	10	(28)	
LRR after no surgery**						-		2	(6)	
LRR after R0 resection						28	(52)	15	(42)	
LRR after R1 resection						16	(30)	9	(25)	
Distant metastases										0.45
Yes, before/simultaneously with LRF						30	(56)	24	(67)	
Yes, after LRF						9	(17)	6	(17)	
No						15	(28)	6	(17)	

Data is presented as n (%). Percentages may not equal to 100 due to rounding.

EMVI extramural vascular invasion; MRF mesorectal fascia; 3D-CRT three-dimensional conformal radiation therapy; IMRT intensity-modulated radiation therapy; VMAT volumetric-modulated arc therapy; LRR locoregional recurrence.

† MRI defined.

§ p-value calculated in patients in which the result was known.

* Early locoregional failure was defined as no resection surgery for other reasons than entering a W&W strategy or an R2 resection.

**Patients who were categorized as having 'refused surgery' were grouped together with those entering [a] W&W strategy since it turned out that they did not have any remaining tumor. A W&W strategy was not according to the protocol; several physicians then rather wrote that the patient 'refused surgery' than that they entered that strategy.

Table S2 | Characteristics of patients with early locoregional failure

	Experimental (n=10)	Standard-care (n=10)
Gender		
Male	7	8
Female	3	2
Age (years)		
Median (range)	60 (56-66)	58 (51-63)
High-risk criteria †		
cT4	3	6
cN2	8	9
Enlarged lateral nodes	4	3
EMVI +	5	6
MRF +	9	9
Distance from anal verge on endoscopy		
< 5 cm	1	2
5 – 10 cm	4	2
≥ 10 cm	3	6
Unknown	2	-
Compliance to neoadjuvant treatment		
All RT fractions	10	-
≥75% of prescribed preoperative chemotherapy	8	-
At least 45 Gy	-	8
Distant metastases		
Yes; before/synchronously with LRF	8	10
Yes; after LRF	-	-
No	2	-

Data is presented as n.

EMVI extramural vascular invasion; MRF mesorectal fascia; RT radiotherapy; LRF locoregional failure.

† MRI defined

Table S3 | Univariate and multivariate Cox regression analyses of clinical characteristics regarding patients who did not undergo a curative resection*

Variable	Category	Univariate analyses			Multivariate analyses		
		n	HR (95% CI)	*P*-value	n	HR (95% CI)	*P*-value
Treatment	Standard-care	20	1				
	Experimental	29	0.61 (0.22-1.75)	0.361			
Distance from anal verge (endoscopy) †	< 5 cm	**18**	**1**	**0.049**	18	1	0.120
	5-10 cm	**16**	**6.01 (0.70-51.51)**		16	5.43 (0.63-46.90)	
	≥ 10 cm	**13**	**12.95 (1.55-108.30)**		13	9.88 (1.11-88.11)	
Clinical T4	No	37	1				
	Yes	12	1.34 (0.42-4.27)	0.586			
Clinical N2	No	12	1				
	Yes	37	2.22 (0.50-9.96)	0.296			
Enlarged lateral lymph nodes	No	**40**	**1**		40	1	
	Yes	**9**	**5.44 (1.87-15.87)**	**0.002**	7	3.20 (0.85-12.00)	0.084
EMVI+	No	**34**	**1**		33	1	
	Yes	**15**	**3.82 (1.32-11.05)**	**0.014**	14	2.00 (0.52-7.66)	0.312
MRF+	No	15	1				
	Yes	34	3.07 (0.69-13.74)	0.142			

* No curative resection entails no resection for any reason or an R2 resection

† In 2 patients (who developed failure up until curative surgery), the distance from the anal verge was unknown, these patients were set to missing. Therefore, the number of patients included in the multivariate analyses is lower.

EMVI extramural vascular invasion; MRF mesorectal fascia

Table S4 | High-risk criteria, radiation, surgical and pathological characteristics of patients who developed a locoregional recurrence

	Experimental (n=44)		Standard-care (n=26)		*P*-value
High-risk criteria at baseline†					
cT4	14	(32)	7	(27)	0.66
cN2	33	(75)	20	(77)	0.86
Enlarged lateral nodes	9	(21)	7	(27)	0.53
EMVI +	14	(32)	13	(50)	0.13
MRF +	30	(68)	21	(81)	0.25
Radiation technique					0.14
3D-CRT	37	(84)	18	(69)	
IMRT/VMAT	7	(16)	8	(31)	
Type of resection					0.18
Anterior resection, PME	-		-		
Low anterior resection, TME	23	(52)	9	(35)	
Abdominoperineal resection	12	(27)	11	(42)	
Hartmann's procedure	8	(18)	3	(12)	
Other	1	(2)	1	(4)	
Refused surgery	-		2	(8)	
Resection status (distance to distal margin, according to Wittekind)					0.93§
R0 > 1 mm	28	(64)	15	(58)	
R1 ≤ 1 mm	16	(36)	9	(35)	
Refused surgery			2	(8)	
Pathological complete response					0.19§
No	40	(91)	23	(88)	
Yes	3	(7)	-		
Unknown	1	(2)	3	(12)	
Mesorectum					
Intact	29	(66)	22	(85)	**0.048§**
Breached	9	(21)	1	(4)	
Missing	6	(14)	3	(12)	
Differentiation grade					0.92§
Well	9	(21)	7	(27)	
Moderate	22	(50)	9	(35)	
Poor	8	(18)	6	(23)	
Not assessed/unknown	5	(11)	2	(8)	
Pathological T-stage					0.38§
ypT0	3	(7)	-		
ypTis	-		-		
ypT1	-		-		
ypT2	5	(11)	4	(15)	
ypT3	30	(68)	16	(62)	
ypT4	6	(14)	4	(15)	
Unknown/refused surgery	-		2	(8)	
Pathological N-stage					0.26§
ypN0	21	(48)	9	(35)	
ypN1	14	(32)	7	(27)	
ypN2	9	(21)	8	(31)	
Unknown/refused surgery	-		2	(8)	

Table S4 | High-risk criteria, radiation, surgical and pathological characteristics of patients who developed a locoregional recurrence (continued)

Distance to circumferential resection margin of the tumor					0.67§
CRM- (>1 mm)	28	(64)	14	(54)	
CRM+ (≤1 mm)	16	(36)	10	(39)	
Unknown/refused surgery			2	(8)	
Tumor size at baseline MRI					0.44§
<40mm	4	(9)	4	(15)	
≥40mm	38	(86)	20	(78)	
Unknown	2	(5)	1	(4)	
Tumor size at histopathology					0.12§
<40mm	33	(75)	14	(54)	
≥40mm	10	(23)	10	(38)	
Unknown/refused surgery	1	(2)	2	(8)	

Data is presented as locoregional recurrence/population in numbers and percentages. Percentages may not equal 100% due to rounding

LRR Locoregional recurrence; EMVI extramural vascular invasion; MRF mesorectal fascia; IMRT intensity-modulated radiation therapy; VMAT volumetric-modulated arc therapy; CRM circumferential resection margin.

† MRI defined

§ p-value calculated in patients in which the value was known.

* Distance was missing in 4 patients of the experimental group and in 1 patient of the standard-care group.

Table S5 | Location of the locoregional recurrences (LRR)

	Experimental (n=450)	Standard-care (n=436)
No LRR†	406	410
All locations of LRR	N=44	N=26
Lateral	8	7
Presacral	19	9
Anterior	11	9
Anastomosis	14	3
Perineal	5	3
Other location	-	3
Single location of LRR	N=32	N=18
Lateral	4	3
Presacral	12	3
Anterior	7	5
Anastomosis	7	2
Perineal	2	2
Other location	-	3
Multifocal locations LRR	N=12	N=8
Lateral & anterior	1	2
Lateral & presacral	2	1
Lateral & perineal	1	-
Presacral & anterior	1	2
Presacral & anastomosis	3	1
Presacral & perineal	-	1
Anastomosis & perineal	2	-
Anastomosis & anterior	1	-
Lateral, presacral & anterior	-	1
Presacral, anterior & anastomosis	1	-

Data is presented as n.
LRR Locoregional recurrence
† Consists of no LRF or early failure

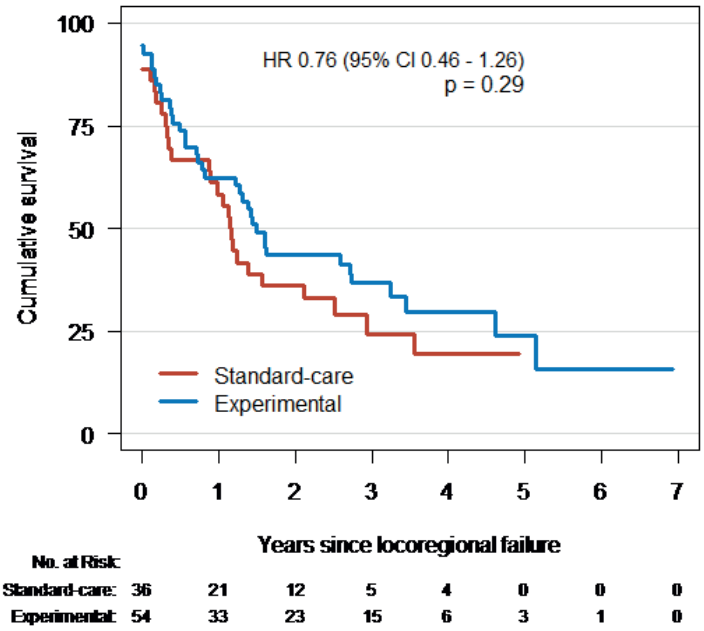

Figure S1 | Overall survival after diagnosis of a locoregional failure
The numbers are actual numbers

Definition of the location of LRR

The location of recurrent disease was recorded in the CRFs and centrally reviewed by imaging reports (MRI, CT, PET) and/or histology reports. Locations were classified according to Kusters et al.[1]:

- Lateral: pelvic side wall, immediately behind posterior ischiac spine, in the obturator compartment, or along iliac vessels;
- Presacral: predominantly midline, in contact with sacral bone;
- Anterior: predominantly midline, involving bladder, uterus, vagina, seminal vesicles, or prostate;
- Anastomosis: after low anterior resection or low Hartmann, at the staple line;
- Perineal: perineum, anal sphincter complex with surrounding perianal and ischiorectal space;
- Other.

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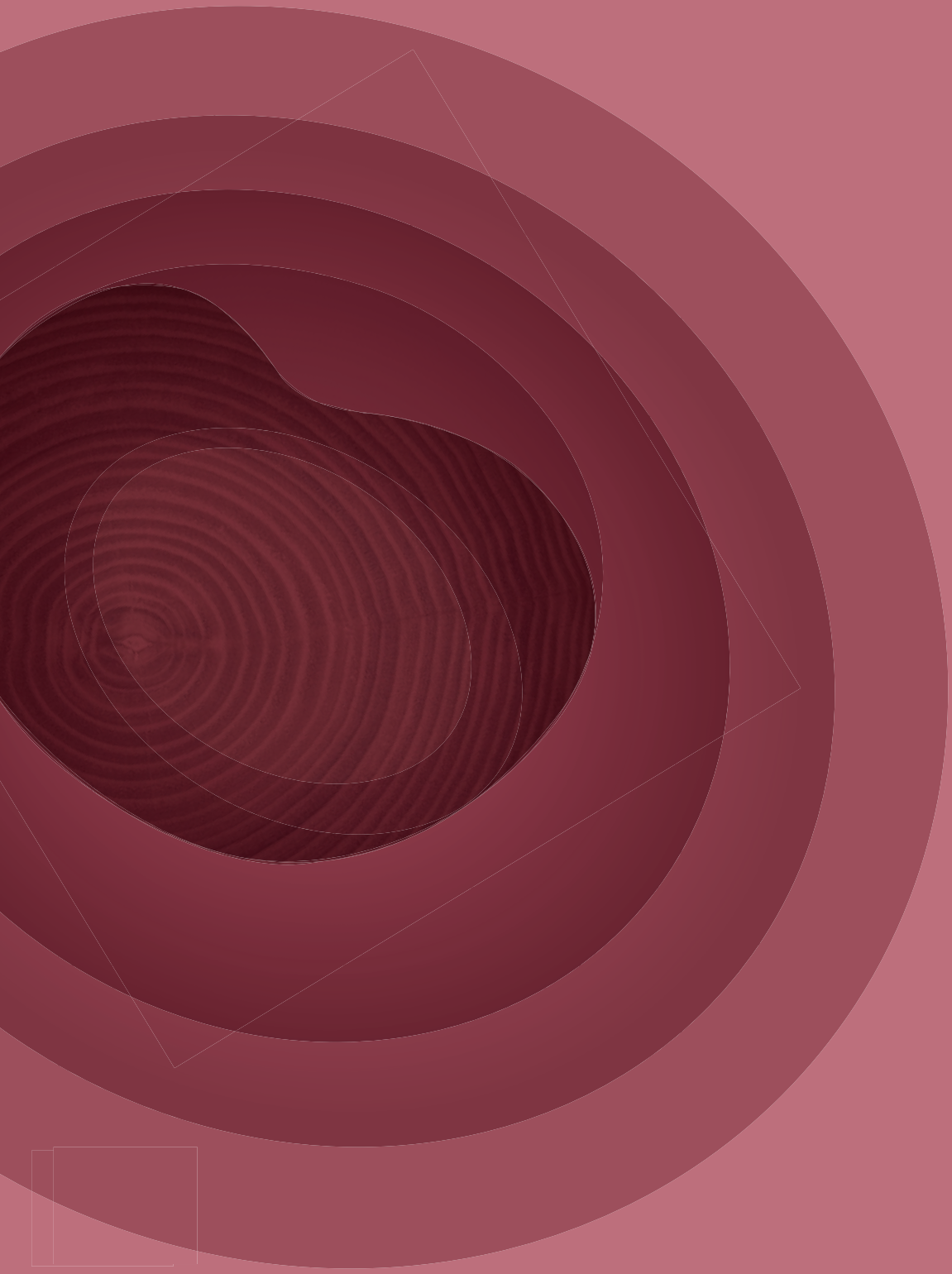

CHAPTER 5a

The value of post-operative chemotherapy after chemoradiotherapy in patients with high-risk locally advanced rectal cancer – Results from the RAPIDO trial

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ESMO open. 2023; 8. DOI: 2023.101158

ABSTRACT

Background
Preoperative chemoradiotherapy (CRT) rather than radiotherapy (RT) has resulted in fewer locoregional recurrences, but no decrease in distant metastasis rate for patients with locally advanced rectal cancer (LARC). In many countries, patients receive postoperative chemotherapy (pCT) to improve oncological outcomes. We investigated the value of pCT after preoperative CRT in the RAPIDO trial.

Patients and methods
Patients were randomised between experimental (short-course radiotherapy, chemotherapy, and surgery) and standard-of-care treatment (CRT, surgery and pCT depending on hospital policy). In this substudy, we compared curatively resected patients from the standard-of-care group who received pCT (pCT+ group) with those who did not (pCT- group). Subsequently, patients from the pCT+ group who received at least 75% of the prescribed chemotherapy cycles (pCT≥75% group) were compared with patients who did not receive pCT (pCT-/- group). By propensity score stratification (PSS), we adjusted for the following unbalanced confounders: age, clinical extramural vascular invasion, distance to the anal verge, ypT-stage, ypN-stage, residual tumour, serious adverse event (SAE) and/or readmission within 6 weeks after surgery and SAE related to preoperative CRT. Cumulative probability of disease-free survival (DFS), distant metastasis (DM), locoregional recurrence (LRR), and overall survival (OS) were analysed by Cox regression.

Results
In total, 396/452 patients had a curative resection. The number of patients in the pCT+, pCT>75%, pCT- and pCT-/- groups were 184, 112, 154 and 149, respectively. The PSS-adjusted analyses for all endpoints demonstrated hazard ratios between approximately 0.7-0.8 (pCT+ vs. pCT-), and 0.5-0.8 (pCT≥75% vs. pCT-/-). However, all 95% confidence intervals included 1.

Conclusion
These data suggest a benefit of pCT after preoperative CRT for patients with high-risk LARC, with approximately 20-25% improvement in DFS and OS and 20-25% risk reductions in DM and LRR. Compliance with pCT additionally reduces or improves all endpoints by 10-20%. However, differences are not statistically significant.

Keywords
Locally advanced rectal cancer, postoperative chemotherapy, oncological outcomes, propensity score stratification, adjuvant chemotherapy.

Highlights
- There might be a benefit of pCT after chemoradiotherapy for patients with LARC
- pCT both improves DFS & OS and reduces DM & LRR by 20-25%
- Compliance with pCT results in an additional 10-20% gain

INTRODUCTION

The introduction of preoperative (chemo)radiotherapy and total mesorectal excision (TME) have contributed to improved local control in patients with rectal cancer in the curative setting. However, this treatment has not led to a decrease in distant metastasis (DM). For this, postoperative chemotherapy (pCT) has been tested in several randomised trials, but the trials have not unequivocally proven that pCT decreases the risk of recurrence, nor improves survival[1,2]. Despite the lack of strong evidence, pCT is frequently administered according to several guidelines[3,4].

The administration of pCT aims to eradicate micrometastases to reduce the risk of recurrent disease and thereby improve survival[5]. Clinical trials have demonstrated improved overall survival (OS) in stage III colon cancer after pCT, which probably also applies to high-risk stage II colon cancer[6]. The lack of firm evidence in rectal cancer has generated much debate and, as a result, different treatment algorithms have been developed[7,8].

Compared to colon cancer, a disadvantage for rectal cancer patients is the prolonged interval between diagnosis and the start of pCT. This interval is generally about two months in colon cancer and at least four months in rectal cancer, depending on the preoperative treatment strategy[1,8]. In addition, postoperative complications, being more frequent following rectal cancer surgery, may result in further delay or even omission of pCT[9,10].

Therefore, total neoadjuvant treatment (TNT), with preoperative chemotherapy in addition to preoperative (chemo)radiotherapy, has been introduced in rectal cancer as an alternative strategy. The RAPIDO trial randomised patients with LARC at high-risk of recurrence between standard-of-care treatment (chemoradiotherapy (CRT) followed by TME and pCT depending on hospital policy) and an experimental treatment (short-course radiotherapy followed by preoperative chemotherapy, i.e., TNT, and TME). Significantly decreased disease-related treatment failure (DrTF) and DM rates in favour of TNT have been reported[11]. The decision to administrate pCT was optional in the standard-of-care group, following local guidelines, but was decided at each hospital prior to trial initiation. To advance knowledge about the value of pCT following CRT and radical surgery in high-risk LARC, patients in the standard-of-care treatment group of the RAPIDO trial were analysed.

MATERIALS AND METHODS

Patient selection and randomisation

The RAPIDO trial is a multicentre, phase III trial at 57 community and academic centres in 7 countries. It was approved by the institutional review boards of participating institutions (2010-023957-12). Inclusion and exclusion criteria have been described[11,12]. Briefly, patients aged 18 years or older were randomised (1:1) in case of biopsy-proven, newly diagnosed rectal cancer, less than 16 cm from the anal verge at endoscopy and at least one high-risk criterium

on MRI: cT4a/b, cN2, extramural vascular invasion (EMVI+), involved mesorectal fascia or enlarged lateral lymph nodes considered to be pathological. Patients were randomised to receive the experimental or the standard-of-care treatment. In this substudy, only patients from the standard-of-care group were included. The standard-of-care treatment entailed long-course radiotherapy (28-25 x 1.8-2.0 Gy) with concurrent capecitabine (825 mg/m2 twice daily on day 1 to 33–38, depending on the number of fractions) followed by surgery after eight ± two weeks. Before participation in the RAPIDO trial, all hospitals had to specify whether they would administer pCT. According to prespecified hospital policy, patients in the standard-of-care group should or should not receive eight cycles of CAPOX or twelve cycles of FOLFOX4 post-operatively.

Analyses

Patients included in the three analyses performed for this report are presented in figure 1. Analysis 1 was an intention-to-treat analysis including all patients who underwent a curative resection (R0 or R1) within six months after the end of CRT and compared all patients treated in a hospital with a policy to provide pCT (HP+ group) with those treated in a hospital with a policy not to provide pCT (HP- group).

Analysis 2 was a per-protocol analysis and aimed to determine the value of pCT in patients who actually received the intended treatment, so patients who did not receive pCT in the HP- group (pCT-) were compared with the patients who actually started pCT in the HP+ group (pCT+). To include only patients who were fit to undergo pCT, we excluded patients not compliant with preoperative CRT (compliance being defined as having received at least 45 Gy with concurrent capecitabine for at least 25 days), patients with a recurrence or who died before the start of pCT (start of pCT being defined as the medium time from surgery to start of pCT (6.7 weeks) to enable similar exclusion in the HP- group) and patients with a postoperative hospital stay exceeding 6 weeks.

Analysis 3 aimed to determine the benefit of compliance to pCT when a dose close to the scheduled could be given and compared patients who received at least 75% of the prescribed cycles pCT (pCT≥75% group) with those in the HP- group who did not receive any pCT (pCT-/- group). Compliance (pCT≥75%) was defined as at least 5 courses of CAPOX, 7 courses of FOLFOX4, or at least 4 courses of CAPOX and ≥1 course of capecitabine, or at least 7 courses of chemotherapy in total in case of a switch from CAPOX to FOLFOX4. In case of toxicity, dose reductions were allowed as described in the protocol, without violating the definition of compliance. Prior to the third analysis, patients were excluded in case recurrence or death within the median time needed to deliver 75% of pCT (approximately 19 weeks) occurred.

Statistics

Categorical variables were compared using chi-square tests and continuous variables, depending on the distribution of the data, by a T-test or a Mann-Whitney U test. All calculated means were accompanied by a standard deviation (SD) and median values by an interquartile

range (IQR). All tests were two-tailed, and p-values ≤0.050 were considered statistically significant. The median follow-up was calculated by using the reverse Kaplan-Meier method.

In this report disease-free survival (DFS), DrTF, DM, locoregional recurrence (LRR) and OS were calculated between the groups provided in figure 1. The primary endpoint of the RAPIDO trial was amended from DFS to DrTF when it became apparent that some patients never became disease-free during treatment. However, as this substudy only analysed patients who had a curative resection, it was considered more appropriate to use DFS instead of DrTF and define all endpoints since surgery instead of since randomisation. DFS was defined as the time from surgery till the first occurrence of DM, LRR, a new primary tumour, or death by any cause. DrTF was defined as the time from surgery till the first occurrence of DM, LRR, a new primary colorectal tumour or treatment-related death. DM was defined as a recurrence outside the pelvic region and LRR as any pelvic recurrence. Since DrTF was the primary endpoint of the trial and was reported before, and because of the great similarity with DFS, DrTF is provided in the online supplement.

Propensity score stratification (PSS) was used to adjust for an anticipated imbalance of confounders between the groups in analysis 2 (pCT+ vs. pCT-) and 3 (pCT≥75% vs. pCT-/- groups). Propensity scores were generated for each patient using a binary logistic regression in which pCT (yes or no) was the dependent variable and the following were covariates: age, EMVI, tumour distance to the anal verge at baseline, ypT-stage, ypN-stage, residual tumour classification (resection margin >1 mm [R0] or ≤1 mm[R1]), any serious adverse event listed in the study protocol (SAE) related to preoperative chemoradiotherapy and any SAE listed in the study protocol and/or readmission within 6 weeks after surgery. These confounders were selected through discussions between principal investigators of the RAPIDO trial. The methods of identifying and selecting confounders and their definitions are explained in detail in the supplementary appendix.

In the next step, 10 strata were created using visual binning and the range of each stratum was determined based on equal percentages of propensity scores. After stratification, each stratum contained patients of the pCT+ and the pCT- group (or pCT≥75% and pCT-/- groups in analysis 3) in which the confounders should be equally distributed. This equal distribution of confounders was checked and expressed by calculating a standardized difference (StD), with a StD between -10 and 10% suggesting a good balance between the groups in analysis 2 or 3[13].

Using the PSS-adjusted data, the cumulative probabilities of DFS, DrTF, DM, LRR, and OS were calculated by stratified Cox regression expressed as hazard ratio (HR) with 95% confidence intervals (CI). SPSS for Windows (version 28.0, SPSS, Chicago, IL) and R-studio (version 4.1.2) were used for the statistical analyses.

RESULTS

Study population and compliance

Of the 452 patients randomised to the standard-of-care treatment, 396 (87.6%) underwent a curative resection within six months of randomisation (figure 1). The ITT analysis included 160 patients in the HP- and 236 in the HP+ group (analysis 1). After the exclusion of patients who were not fit for pCT, who started pCT despite HP- or did not start pCT despite HP+, 338 out of 396 (85.4%) patients were included in analysis 2 (n=154 pCT- vs. n=184 pCT+). For analysis 3, 112/184 (61%) patients received a sufficient dose of pCT (i.e., pCT≥75%) and were compared with 149 patients in the pCT-/- group. At the time of the data lock (March 11, 2022), the median follow-up was 5.6 years (IQR 5.4-7.5).

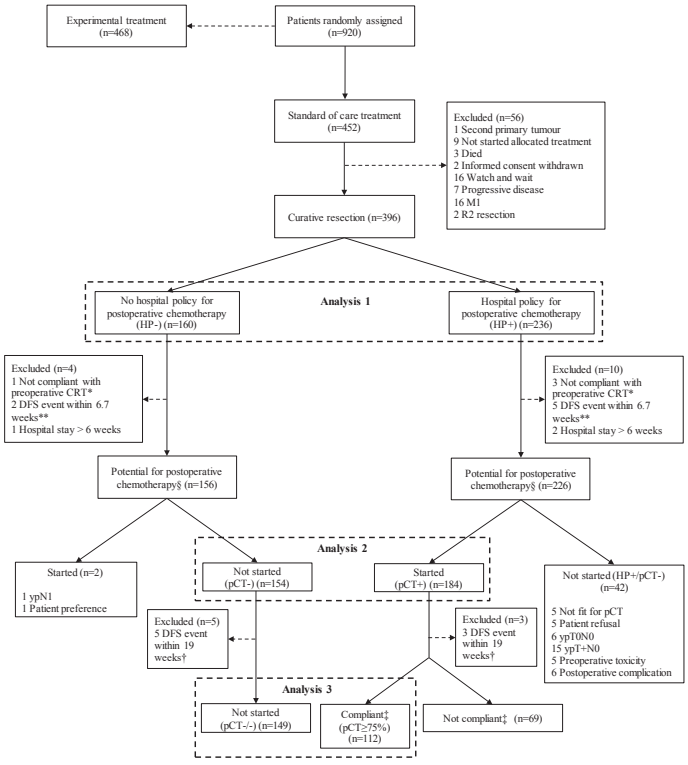

Figure 1 | M1 distant metastasis. R2 resection macroscopic residual tumour. HP hospital policy. DFS disease-free survival. pCT postoperative chemotherapy

* Compliance was defined as receiving at least 45 Gy of the prescribed preoperative radiotherapy with concurrent capecitabine for at least 25 days.

** Defined as a DFS event during the median time from surgery to the start of pCT.

§ Defined as being able to start treatment with curative intention within 12 weeks after surgery.

† Defined as a DFS event during the median time from surgery to receiving at least 75% of the prescribed number of cycles of pCT.

‡ Compliance was defined as receiving at least 75% of the prescribed number of cycles of pCT.

Intention-to-treat analysis (analysis 1)

Baseline characteristics of patients in the HP+ and HP- groups are presented in table S1 in the online supplementary. Table S2 shows an overview of which centres followed HP+ or HP-, how many patients per centre were treated in the HP+ and HP- groups, how many patients violated the protocol and reasons for protocol violations. The ITT analysis demonstrated no statistically significant differences between HP+ and HP- patients concerning DFS (HR 1.08 [95%CI 0.78-1.50]; p=0.65), DM (HR 1.17 [95%CI 0.79-1.74]; p=0.43), LRR (HR 1.37 [95%CI 0.51-3.64]; p=0.53) and OS (HR 1.03 [95%CI 0.67-1.61]; p=0.88) (table 1) .

Table 1 | Overview of the HRs with 95% CIs of the three analyses

Oncological outcome	HR	95% CI	*p-value*
Analysis 1: HP+ (*n*=236) *vs.* HP- (*n*=160)			
DFS	1.08	[0.78-1.50]	0.65
DM	1.17	[0.79-1.74]	0.43
LRR	1.37	[0.51-3.64]	0.53
OS	1.03	[0.67-1.61]	0.88
Analysis 2: pCT+ (*n*=184) *vs.* pCT- (*n*=154)			
DFS	0.78	[0.53-1.14]	0.20
DM	0.80	[0.51-1.26]	0.33
LRR	0.74	[0.26-2.15]	0.58
OS	0.82	[0.49-1.37]	0.44
Analysis 3: pCT≥75% (*n*=112) *vs.* pCT-/- (*n*=149)			
DFS	0.63	[0.38-1.03]	0.07
DM	0.61	[0.34-1.08]	0.09
LRR	0.49	[0.10-2.38]	0.38
OS	0.74	[0.38-1.44]	0.38

HR Hazard ratio, CI confidence interval, DFS disease-free survival, DM distant metastasis, LRR locoregional recurrence, OS overall survival

The value of pCT on oncological outcomes (analysis 2)

Baseline characteristics of patients in the pCT+ and pCT- groups are presented in table 2. It shows that 48/154 (31%) patients in the pCT- group and 66/184 (36%) in the pCT+ group had ypN+. Moreover, it shows significant differences in several characteristics, for which PSS-adjustment was performed. In table S3 the distribution of the selected confounders and the accompanying StD values before and after PSS are presented. figure S1 graphically illustrates that all confounders have an StD between -10 and 10% after PSS, representing an equal distribution of confounders between the pCT+ and pCT- groups, whereby potential bias is strongly diminished.

The Cox regression of analysis 2 demonstrated no statistically significant differences between the pCT+ and pCT- groups in the cumulative probability of any endpoint: DFS (HR 0.78 [95%CI 0.53-1.14); p=0.20, DM (HR 0.80 [95%CI 0.51-1.26]; p=0.33), LRR (HR 0.74 [95%CI 0.26-2.15]; p=0.58) and OS (HR 0.82 [95%CI 0.49-1.37]; p=0.44) (table 1).

Table 2 | Baseline, surgical and pathological characteristics of eligible patients

	pCT- (*n*=154)		pCT+ (*n*=184)		*p-value* pCT+ vs. pCT-
Gender					*0.68*
Male	107	(70)	124	(67)	
Female	47	(31)	60	(33)	
Age (years)					*0.66§*
Mean (SD)	60	(10)	61	(10)	
ECOG at baseline					*0.30*
0	126	(82)	142	(77)	
1	28	(18)	42	(23)	
High-risk criteria †					
cT4	34	(22)	65	(35)	***0.008***
cN2	103	(67)	131	(71)	*0.39*
Enlarged lateral nodes	20	(13)	30	(16)	*0.39*
EMVI +	34	(22)	80	(44)	***<0.0001***
MRF +	98	(64)	134	(73)	*0.07*
Number of high-risk criteria					***<0.0001***
1	67	(44)	39	(21)	
2	54	(35)	63	(34)	
3	21	(14)	58	(32)	
4	9	(6)	19	(10)	
5	3	(2)	5	(3)	
Distance from anal verge					*0.15ϐ*
< 5 cm	52	(34)	46	(25)	
5 – 10 cm	50	(33)	69	(38)	
≥ 10 cm	52	(34)	69	(38)	
Type of approach					***<0.0001***
Laparoscopic	97	(63)	59	(32)	
Open	44	(29)	114	(62)	
Laparoscopic → open	13	(8)	11	(6)	

Table 2 | Baseline, surgical and pathological characteristics of eligible patients (continued)

Type of resection					***0.050***
Anterior resection, PME	6	(4)	23	(13)	
LAR, TME	83	(54)	90	(49)	
APR, TME	58	(38)	65	(35)	
Hartmann's procedure	5	(3)	5	(3)	
Other	2	(1)	1	(1)	
Radicality of resection					***0.001***
R0 > 1 mm	148	(96)	157	(85)	
R1 ≤ 1 mm	6	(4)	27	(15)	
pCR					*0.51*
No	130	(84)	160	(87)	
Yes	24	(16)	24	(13)	
Differentiation grade					***0.0316***
Well + Moderate	104	(68)	132	(72)	
Poor	11	(8)	15	(8)	
No tumour	32	(21)	26	(14)	
Unknown	7	(5)	11	(6)	
Pathological T-stage					***0.018***
ypT0	32	(21)	26	(14)	
ypTis	1	(1)	-		
ypT1	7	(5)	9	(5)	
ypT2	43	(28)	36	(20)	
ypT3	62	(40)	99	(54)	
ypT4	9	(6)	14	(8)	
Pathological N-stage					*0.31*
ypN0	106	(69)	118	(64)	
ypN1	32	(21)	41	(22)	
ypN2	16	(10)	25	(14)	

Data is presented as n (%). Percentages may not equal 100 due to rounding.

pCT+ hospital policy for postoperative chemotherapy (pCT) and received pCT; pCT- no hospital policy for pCT and did not receive pCT; SD Standard deviation; EMVI extramural vascular invasion; MRF mesorectal fascia.

[§] Calculated with independent sample t-test.

[†] MRI defined.

[B] p-value calculated over the known values.

The value of a sufficient dose of pCT on oncological outcomes (analysis 3)

The distribution of confounders in the pCT≥75% and pCT-/- groups are presented in table S4. After PSS all confounders had a StD between -10 and 10% (table S4 and figure S2).

The Cox regression of analysis 3 demonstrated no statistically significant differences in the cumulative probability of any of the endpoints: DFS (HR 0.63 [95%CI 0.38-1.03]; p=0.07), DM (HR 0.61 [95% CI 0.34-1.08]; p=0.09), LRR (HR 0.49 [95% CI 0.10-2.38]; p=0.38) and OS (HR 0.74 [95%CI 0.38-1.44]; p=0.38) (table 1).

An overview of all HRs, 95% CIs and p-values of analyses 1, 2 and 3 are provided in table 1 and in table S5 of the online supplement including DrTF.

DISCUSSION

In this substudy, we explored the value of pCT after preoperative CRT for patients with high-risk LARC in the RAPIDO trial. The PSS-adjusted analyses suggest a potentially beneficial effect of pCT regarding all endpoints. The risk of a DFS-event, DM, LRR and death appears to be reduced by approximately 20-25% by pCT during a median follow-up of 5 years. Compliance with pCT may reduce the risk by another 10-20%. However, results must be interpreted with caution since they were not based on a randomised comparison and the differences observed were not statistically significant.

The rationale to administer fluoropyrimidine (FU) and oxaliplatin (Ox) as pCT in rectal cancer is mainly based on evidence from trials in colon cancer[14,15]. FU-based pCT improved DFS in stage II/III colon cancer[14,15]. FU/Ox- vs. FU-based pCT additionally improved DFS, with a HR of 0.80 (95%CI 0.69-0.93)[16] and similar HRs were observed in two other landmark studies[17,18]. The risk reduction regarding DFS-events in our analysis (HR 0.78 [95%CI 0.53-1.14]) is somewhat smaller, but similar to those in stage II/III colon cancer trials, which suggests that the addition of pCT after preoperative CRT in stage II and III rectal cancer might reduce recurrence risks and, thus, be of value.

Trials on pCT in rectal cancer can be characterised into two groups: (i) surgery followed by pCT or not and (ii) preoperative CRT (or RT alone) and surgery followed by pCT or not. In the first category, a Cochrane analysis demonstrated an added value of pCT[19]. However, its current relevance could be questioned because of heterogeneity between the studies, the chemotherapy mostly used is presently not considered adequate and TME was not standard-of-care in any study. In the second category, two systematic reviews from 2015, one from 2016 and one from 2022 compared different regimes of pCT which did not yield statistically significant differences in DFS and OS when FU or FU/Ox was compared to observation[1,2,20,21], except for Zhao et al. (HR of DFS 0.85 [95%CI 0.73-0.98]) when FU/Ox was compared to observation20. Despite the absence of firm evidence, several clinical guidelines make a (robust) proposal in favour of the adoption of pCT for rectal cancer patients after CRT and surgery[3,4] and remarkably, pCT is extensively used worldwide.

A disadvantage of administering chemotherapy postoperatively is that postoperative complications and decreased physical condition may delay or even lead to the omission of pCT. In our study, pCT was omitted in 34% of the patients who had a curative resection in the HP+ group. In randomised trials, pCT was omitted in approximately 25%[21-23]. Full compliance with pCT varies between 43-74%[1,22,24-27]. Although our study did not show statistically significantly improved oncological outcomes in compliant patients, the HRs for all endpoints were reduced/improved by 25-40% compared to 20-25% of the patients who received any chemotherapy cycle (analysis 3 vs. analysis 2). Thus, as compliance to chemotherapy appears to improve oncological outcome and the RAPIDO trial convincingly showed improved compliance with preoperative chemotherapy vs. pCT (84% vs. 61%), this may explain the superior results of the experimental treatment of the RAPIDO trial[11].

If pCT has favourable effects after CRT and surgery in rectal cancer, the option not to provide it to all patients in the standard-of-care group would have disfavoured the results of this group in the RAPIDO trial. Thus, the differences previously reported between the standard-of-care and experimental treatment in RAPIDO (in favour of the experimental treatment) could be interpreted as exaggerated. This hypothesis was demonstrated by a recent sensitivity analysis of Jimenez-Fonseca et al.28 and validated by a sensitivity analysis of the RAPIDO collaborative[29]. However, even if pCT had been mandatory in the standard-of-care treatment, less than two-thirds of the patients would have been treated (due to omission of 34% in our trial) with poor compliance, opposed to no omission and excellent compliance with preoperative chemotherapy in the RAPIDO trial. Therefore, it is our opinion that chemotherapy can be effective for some patients postoperatively but is more effective for more patients preoperatively. This is further substantiated by a sensitivity analysis that used the outcomes of this study to analyse the effect of the experimental compared to the standard-of-care treatment, had more patients been treated with pCT (i.e., more hospitals chosen to provide pCT) in the standard-of-care treatment[29].

The first article of the RAPIDO collaborative reported that hospital policy on pCT did not statistically significantly affect the primary and secondary outcomes, which may seem contradictory to the results of this study[11]. However, the previous results - a sensitivity analysis and a forest plot[11] - analysed the effect of HP, while analysis 2 and 3 of this article analysed the effect when pCT was initiated or provided to a compliant level (chosen as at least 75% of the number of cycles). The analysis in this article used 5-year follow-up data, with correction for confounders and exclusion of ineligible patients for pCT and those having a recurrence before/during pCT.

Our study is accompanied by some limitations. This report is based on a sub-group analysis of a non-randomised set of patients, which inevitably leads to cohorts with unequal characteristics. However, the analyses were adjusted for unbalanced confounders by using PSS. Moreover, the analyses were based on small cohorts resulting in a great degree of statistical uncertainty. However, the HRs are clearly below 1 and larger sample sizes may have obtained narrower CIs, potentially not including 1. If these risk reductions are true, they are also considered clinically relevant. Further, there might be a bias between countries, e.g., early in the trial there was a difference in attention to EMVI between nations and, as a result, EMVI was probably underreported in the Netherlands (which is the main country in which pCT was not given). If EMVI had been more consistently reported, the PSS groups might have been different. Besides, selecting confounders for the PSS analysis is an arbitrary process, often led by expert opinions. Other experts might select other confounders, possibly altering the outcomes. Nonetheless, the selected covariates are commonly considered important confounders in literature. Furthermore, PSS analyses cannot correct for unmeasured variables and, therefore, 'unmeasured bias' may remain. Lastly, the decision to administrate pCT was optional in the standard-of-care group, following national or regional guidelines, but made prior to trial initiation.

In conclusion, the PSS-adjusted data of the RAPIDO trial suggest a potential, although not statistically significant, benefit of pCT after preoperative CRT and TME for patients with high-risk LARC. This benefit seems to exist for the group of patients who could be treated within 6-12 weeks after curative surgery, which applies to approximately 80% of the patients. Our results add to the still limited evidence from randomised trials of a small gain in preventing recurrences, not sufficient to result in an OS gain as in colon cancer.

Acknowledgments
We thank all patients, treating physicians, and research support staff at all participating centres.
This work was supported by the Dutch Cancer Foundation (CKS-2011-4997); the Swedish Cancer Society; the Swedish Research Council (project number K2014-99X-22481-01-3); the Spanish Ministry of Economy and Competitiveness through the Carlos III Health Institute EC11-423, and by the Spanish Clinical Research Network (SCReN-PT13/0002/0031; PT17/0017/0003; co-financed by European Regional Development Fund "A way to make Europe").

Declaration of interest
PJN reports honoraria from Ethicon, Johnson & Johnson, and Amgen. GAPH reports consulting fees from Roche, MSD, Amgen, and Novartis; consulting fees and research support to their institution from Bristol Myers Squibb; and research support to their institution from Seerave Foundation. AGHR and CJHvdV were partially funded by the EU's Horizon 2020 research and innovation program under a Marie SkłodowskaCurie grant award (H2020MSCAITN2019, grant agreement number 857894; project acronym: CAST). MPH reports consulting fees from MSD. JC reports consulting fees, travel expenses, and research support to their institution from Pfizer, Ipsen, and Eisai; consulting fees and research support to their institution from Bayer, Novartis, and Advanced Accelerator Applications; consulting fees from Sanofi, Exelixis, and Merck Serono; and research support to their institution from AstraZeneca. BG reports research support from the Swedish Cancer Society. All remaining authors have declared no conflicts of interest.

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Methods of identifying and selecting confounders

In our study, we selected eight confounders via the following method. First, the first and second authors evaluated all variables available in the RAPIDO dataset and selected variables that could influence the exposure or the outcome in any possible way. Second, all potential confounders were discussed with the principal investigators of the RAPIDO trial, a statistician and the RAPIDO data managers to determine whether this variable was a true confounder. Out of 26 confounders, we excluded confounders with major similarity (for example excluding cTNM stage and including cT-stage) and selected the strongest confounders. Variables only related to the outcome were not selected, to prevent that an overwhelming number of variables in the PSS model could not reach a distributed balance given the number of included patients. The decision to in- or exclude the 26 possible confounders in the PSS analysis, is shown below.

Variable	Defined as	Reason to include or exclude in the PSS-analyses (analysis 2 & 3)
Age	<70 or ≥70 years	Include, since age of above 70 years in colon cancer often means that oxaliplatin is not used as postoperative treatment, only a fluoropyrimidine. Further, often used as a cut-off to perform a geriatric risk assessment regarding oncological treatment and although outcome and age are not directly associated, age can be related to increased complications/adverse events/toxicity.
Gender	Male of female	Exclude, gender is not directly associated with oncological outcome or whether or not to provide (p)CT.
Clinical T-stage at baseline	cT1, cT2, cT3 or cT4	Exclude, ypT-stage is considered a stronger confounder than clinical T-stage
Clinical N-stage at baseline	cN0, cN1 or cN2	Exclude, ypN-stage is considered a stronger confounder than clinical N-stage
EMVI at baseline	Yes or no	Include, EMVI is a known risk factor for distant metastasis, thereby it influences oncological outcomes and could be a reason to administer pCT.
MRF involvement at baseline	Yes or no	Exclude, since MRF is a risk factor for a non-radical resection (among others), but residual tumour is a stronger confounder.
Enlarged lateral lymph nodes at baseline	Yes or no	Exclude, in case of persisting enlarged lateral lymph nodes at the restaging MRI after neoadjuvant treatment (considered to be pathological), it is recommended to perform a lateral lymph node dissection instead of administering pCT.
ypT-stage	ypT0, ypT1+ypTis, ypT2, ypT3 or ypT4	Include, since ypT-stage is an important predictor of distant and local recurrence and guidelines (of colon and rectal cancer) often recommend patients with ypT3-4 (with high-risk criteria) to be treated with pCT.

ypN-stage	ypN0, ypN1 or ypN2	Include, since ypN-stage is an important predictor of distant and local recurrence and guidelines (of colon and rectal cancer) often recommend patients with ypN+ to be treated with pCT.
ypTNM-stage	Stage 0, I, II, III, IV	Exclude, since this is already represented in ypT- and ypN-stage
Residual tumour*	R0 or R1‡	Include, since this is an important predictor of local recurrence and guidelines (of colon and rectal cancer) state it can be considered (for example as a risk factor in stage II colon cancer) when discussing providing pCT
Distance from anal verge at endoscopy, at baseline	<5, 5-10 or ≥10 cm	Include, as tumours 10-15 cm from the anal verge can (partly) be considered to be colon cancer according to the sigmoid take-off definition (1) for which the added value of pCT is already evidence-based in stage III and stage II with high-risk criteria.
Clinical T4 at baseline	Yes or no	Exclude, since ypT-stage is a stronger confounder.
Clinical N2 at baseline	Yes or no	Exclude, since ypN-stage is a stronger confounder.
EMVI at pathological examination	Yes or no	Exclude, since EMVI was not routinely reported at pathological examination.
Pathological response	No regression, regression or complete response	Exclude, because this is already partly represented in ypT- and ypN-stage.
Type of resection	LAR (incl. PME), APR, Hartmann, other	Exclude, because the type of resection is not considered to influence whether or not pCT is provided and it is therefore not likely to be a confounder.
Histological differentiation grade in the surgical specimen	Well+moderate or poor	Exclude, although a poor differentiation is considered a bad prognostic factor. However, it cannot be reliably determined whether poor differentiation is due to changes from preoperative treatment or due to a true poor biological differentiation.
Extra nodal deposits	Yes or no	Exclude, is already represented in ypN-stage.
Number of fractions and days of preoperative CRT	<70%, 70-90% or >90%	Exclude. To fully rule out the effect of preoperative CRT, all patients who were not compliant to preoperative CRT were excluded from analysis ii and iii.
Postoperative complications	Clavien Dindo grade III+IV and/or readmission within 6 weeks: yes or no	Include, but as a new combination variable: serious adverse event and/or readmission within 6 weeks after surgery (yes or no), because a Clavien Dindo grade III or IV doesn't necessarily mean that pCT cannot be provided or will lead to decreased compliance.
Lymph node ratio	<10% or ≥10	Exclude, is already represented in ypN-stage.
Number of high-risk criteria	1, 2, 3, 4 or 5	Exclude, because cN2, cT4 and EMVI, MRF, ELLN are already included/represented.
Complications during/after preoperative CRT	Yes or no	Include, as serious adverse event during/after the preoperative CRT may influence choice of treatment and/or outcome after surgery.
Country	Denmark, Spain, The Netherlands, Norway, Sweden, Slovenia or USA	Exclude, since the variables that were different between countries were already included in the PSS analysis.
Plane of surgery	Mesorectal, intramesorectal or muscularis propria plane and in case of an APR also: outside levator, sphincteric or intramuscular/submucosal plane, which one was worst per patient.	Exclude, since residual tumour classification was considered as a similar but stronger confounder (2).

pCT postoperative chemotherapy; EMVI extramural vascular invasion; MRF mesorectal fascia; LAR low anterior resection; PME partial mesorectal excision; APR Abdominoperineal resection; CRT chemoradiotherapy; ELLN enlarged lateral lymph nodes; PSS propensity score stratification.

* Classification according to Wittekend et al; ‡ Patients with a R2 were excluded from the analyses since postoperative chemotherapy was with curative intention.

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2 Wang XT, Li DG, Li L, et al. Meta-analysis of oncological outcome after abdominoperineal resection or low anterior resection for lower rectal cancer. Pathol Oncol Res. 2015; 2: 19-27.

Table S1 | Baseline, surgical and pathological characteristics of patients in analyses 1 (HP+ vs. HP-) and HP+/pCT-

	HP+ (n=236)		HP- (n=160)		p-value HP+ *vs.* HP-	HP+/pCT- (n=42)	
Gender					0.77		
Male	162	(69)	112	(70)		33	(79)
Female	74	(31)	48	(30)		9	(21)
Age (years)					0.27§		
Mean (SD)	62	(10)	60	(10)		65	(11)
ECOG at baseline					0.48		
0	188	(80)	132	(83)		38	(91)
1	48	(20)	28	(18)		4	(10)
High-risk criteria †							
cT4	85	(36)	35	(22)	**0.003**	14	(33)
cN2	165	(70)	106	(66)	0.44	30	(71)
Enlarged lateral nodes	38	(16)	22	(14)	0.52	7	(17)
EMVI +	97	(41)	34	(21)	**<0.0001**	12	(29)
MRF +	171	(73)	101	(63)	**0.049**	31	(74)
Number of high-risk criteria					**<0.0001**		
1	54	(23)	70	(44)		13	(31)
2	82	(35)	57	(36)		14	(33)
3	69	(29)	21	(13)		9	(21)
4	24	(10)	9	(6)		4	(10)
5	7	(3)	3	(2)		2	(5)
Distance from anal verge					0.32		
< 5 cm	65	(28)	55	(34)		16	(38)
5 – 10 cm	88	(37)	51	(32)		15	(36)
≥ 10 cm	83	(35)	54	(34)		11	(26)
Type of approach					**<0.0001**		
Laparoscopic	80	(34)	102	(64)		17	(41)
Open	141	(60)	45	(28)		23	(55)
Laparoscopic → open	15	(6)	13	(8)		2	(5)
Type of resection					**0.038**		
Anterior resection, PME	27	(11)	6	(4)		3	(7)
LAR, TME	106	(45)	85	(53)		13	(31)
APR, TME	95	(40)	62	(39)		24	(57)
Hartmann's procedure	7	(3)	5	(3)		2	(5)
Other	1	(<1)	2	(1)		-	
Radicality of resection					**0.002**		
R0 > 1 mm	206	(87)	154	(96)		40	(95)
R1 ≤ 1 mm	30	(13)	6	(4)		2	(5)
pCR					0.57		
No	204	(86)	135	(84)		34	(81)
Yes	32	(14)	25	(16)		8	(19)
Differentiation grade					**0.018β**		
Well + Moderate	163	(69)	107	(67)		27	(64)
Poor	22	(9)	12	(8)		3	(7)
No tumour	35	(15)	34	(21)		8	(19)
Unknown	16	(7)	7	(4)		4	(10)
Pathological T-stage					**0.015**		
ypT0	35	(15)	34	(21)		8	(19)
ypTis	-		1	(1)		-	
ypT1	9	(4)	8	(5)		-	
ypT2	52	(22)	44	(28)		13	(31)
ypT3	124	(53)	64	(40)		20	(48)
ypT4	16	(7)	9	(6)		1	(2)
Pathological N-stage					0.69		
ypN0	162	(69)	110	(69)		39	(93)
ypN1	44	(19)	34	(21)		1	(2)
ypN2	30	(13)	16	(10)		2	(5)

Data is presented as n (%). Percentages may not equal 100 due to rounding.
HP+ hospital policy for postoperative chemotherapy; HP- no hospital policy for postoperative chemotherapy; HP+/pCT- policy for postoperative chemotherapy but did not receive postoperative chemotherapy; SD Standard deviation; EMVI extramural vascular invasion; MRF mesorectal fascia.
[§] Calculated with independent sample t-test.
[†] MRI defined.
[B] p-value calculated over the known values.

Table S2 | Overview of centres and patients in the HP+ or HP- group, numbers on compliance with HP, protocol violations and reasons for protocol violations

Country	Centre, City	Numbers of patients per group						Reasons for protocol violation HP+/pCT-	Reasons protocol violation HP-/pCT+
		HP -	HP +	HP-/ pCT-	HP-/ pCT+	HP+/ pCT-	HP+/ pCT+		
NL	Catharina ziekenhuis, Eindhoven	2	0	2	0	0	0	NA	NA
NL	Leids Universitair Medisch Centrum, Leiden	5	0	4	1	0	0	NA	Patient's preference
NL	Haga ziekenhuis, Den Haag	5	0	5	0	0	0	NA	NA
NL	Alrijne ziekenhuis, Leiden	2	0	2	0	0	0	NA	NA
NL	Diakonessen ziekenhuis, Utrecht	5	0	5	0	0	0	NA	NA
NL	Amphia ziekenhuis, Breda	22	0	22	0	0	0	NA	NA
NL	Medisch Centrum Leeuwarden, Leeuwarden*	4	5	4	0	4	1	n=1 T0N0, n=2 T+N0, n=1 postoperative complication	NA
NL	Reinier de Graaf Gasthuis, Delft	3	0	3	0	0	0	NA	NA
NL	Noordwest Ziekenhuisgroep, Alkmaar	18	0	18	0	0	0	NA	NA
NL	Spaarne Gasthuis, Hoofddorp	5	0	5	0	0	0	NA	NA
NL	Amsterdam Medisch Centrum, Amsterdam	3	0	3	0	0	0	NA	NA
NL	St. Antonius ziekenhuis, Sneek	9	0	8	1	0	0	NA	ypN1
NL	Antoni van Leeuwenhoek ziekenhuis, Amsterdam	5	0	5	0	0	0	NA	NA
NL	Radboud Universitair Medisch Centrum, Nijmegen	6	0	6	0	0	0	NA	NA
NL	Tjongerschans ziekenhuis, Heerenveen	4	0	4	0	0	0	NA	NA
NL	Haaglanden Medisch Centrum Westeinde, Den Haag	8	0	8	0	0	0	NA	NA
NL	Onze Lieve Vrouwen Gasthuis, Amsterdam	3	0	3	0	0	0	NA	NA
NL	Wilhelmina ziekenhuis, Assen	4	0	4	0	0	0	NA	NA
NL	Deventer ziekenhuis, Deventer	3	0	3	0	0	0	NA	NA
NL	Universitair Medisch Centrum Groningen, Gronigen	10	0	10	0	0	0	NA	NA
NL	Ziekenhuisgroep Twente, Almelo	3	0	3	0	0	0	NA	NA
NL	Isala Klinieken, Zwolle	9	0	9	0	0	0	NA	NA
NL	Martini ziekenhuis, Groningen	6	0	6	0	0	0	NA	NA
NL	Groene hart ziekenhuis, Gouda	5	0	5	0	0	0	NA	NA
SE	Falu lasarett, Falun	0	3	0	0	0	3	NA	NA
SE	Centralsjukhuset, Karlstad	0	3	0	0	0	3	NA	NA
SE	Linköpings Universitet, Linköping	0	15	0	0	2	13	n=1 T0N0, n=1 postoperative complication	NA
SE	Norrlands Universitetssjukhus, Umeå	0	5	0	0	1	4	n=1 preoperative toxicity	NA
SE	Akademiska Sjukhuset, Uppsala	0	43	0	0	3	40	n=1 patient refusal, n=1 preoperative toxicity, n=1 postoperative complication	NA
SE	Västmanlands Sjukhus, Västerås	0	10	0	0	5	5	n=2 not fit for pCT, n=1 PD, n=2 preoperative toxicity	NA

Table S2 | Overview of centres and patients in the HP+ or HP- group, numbers on compliance with HP, protocol violations and reasons for protocol violations (continued)

SE	Mälarsjukhuset, Eskilstuna*	0	2	0	0	2	0	n=1 not fit for pCT, n=1 patient refusal	NA
SE	Sahlgrenska Universitetssjukhuset, Göteborg	0	2	0	0	0	2	NA	NA
SE	Universitetssjukhuset, Lund	0	9	0	0	5	4	n=2 T0N0, n=3 T+N0	NA
SE	Universitetssjukhuset, Örebro	0	1	0	0	0	1	NA	NA
SE	Karolinska Universitetssjukhuset, Stockholm	0	31	0	0	1	30	n=1 patient refusal	NA
SE	Sundsvalls Sjukhus, Sundsvall	0	2	0	0	0	2	NA	NA
SE	Central Hospital, Växjö	0	6	0	0	3	3	n=3 T+N0	NA
SE	Länssjukhuset, Kalmar	0	5	0	0	3	2	n=1 T0N0, n=2 T+N0	NA
SE	Södra Älvsborgs Sjukhus, Borås	0	4	0	0	2	2	n=1 not fit for pCT, n=1 postoperative complication	NA
ESP	Hospital Ramón y Cajal, Madrid	0	3	0	0	0	3	NA	NA
ESP	Consorcio Hospital General Universitario, Valencia	0	8	0	0	2	6	n=1 not fit for pCT, n=1 preoperative toxicity	NA
ESP	Hospital Universitari i Politècnic La Fe, Valencia	0	4	0	0	1	3	n=1 PD	NA
ESP	ICO Hospitalet Duran I Reynals, Barcelona	0	11	0	0	1	10	n=1 PD	NA
ESP	Vall d'Hebron Institut d'Oncologia, Barcelona	0	17	0	0	1	16	n=1 postoperative complication	NA
ESP	Hospital Clínico Universitario de Valencia, Valencia	0	12	0	0	2	10	n=2 postoperative complication	NA
NOR	Oslo Universitetssykehus, Oslo	4	0	4	0	0	0	NA	NA
NOR	Sørlandet Sykehus Kristiansand, Kristiansand	7	0	7	0	0	0	NA	NA
DEN	Odense Universitetshospital, Odense	0	1	0	0	1	0	n=1 T+N0	NA
DEN	Aalborg Universitetshospital, Aalborg	0	10	0	0	8	2	n=1 patient refusal, n=1 T0N0, n=6 T+N0	NA
USA	Washington University Medical School, Saint Louis	0	8	0	0	0	8	NA	NA
SLO	Onkološki inštitut Ljubljana, Ljubljana	0	16	0	0	4	12	n=1 patient refusal, n=1 PD, n=2 preoperative toxicity	NA

Data is presented as n.

Two hospitals (n=4 patients) were excluded from analysis 2 and 3 because of reasons outlined in the consort diagram.

HP- hospital policy without pCT; HP+ hospital policy with pCT; pCT postoperative chemotherapy; HP-/pCT-, hospital policy without pCT and did not provided pCT; HP-/pCT+ hospital policy without pCT and did provide pCT; HP+/pCT- hospital policy with pCT and did not provide pCT; HP+/pCT+ hospital policy with pCT and did provide pCT; NL Netherlands; SE Sweden; ESP Spain; NOR Norway; DEN Denmark; USA United States of America; SLO Slovenia; NA not applicable; PD progressive disease.

* Medisch Centrum Leeuwarden and Mälarsjukhuset originally chose for the HP+, but changed to HP- during the study. In Mälarsjukhuset, only 2 patients were randomised to HP+, thereafter the HP changed to HP- and no more patients were randomised to the standard-of-care treatment.

Table S3 | Distribution of confounders between the pCT+ and pCT- groups (analysis 2), before and after propensity score stratification adjustment

	pCT+ (n=184)		pCT- (n=154)		p-value	StD before PSS	StD after PSS
Age (years)					0.76	0.0321	0.0061
<70	158	(86)	134	(87)			
≥70	26	(14)	20	(13)			
EMVI at baseline					**<0.0001**	0.4681	0.0067
No	104	(57)	120	(78)			
Yes	80	(44)	34	(22)			
Distance from anal verge at baseline					0.15		
<5 cm	46	(25)	52	(34)		-0.1983	0.0061
5-10 cm	69	(38)	50	(33)		0.1046	-0.0050
≥10 cm	69	(38)	52	(34)		0.0834	-0.0007
ypT-stage					**0.019**		
ypT0	26	(14)	32	(21)		-0.1772	-0.0010
ypTis + ypT1	9	(5)	8	(5)		-0.0092	-0.0011
ypT2	36	(20)	43	(28)		-0.1960	0.0006
ypT3	99	(54)	62	(40)		0.2730	0.0004
ypT4	14	(8)	9	(6)		0.0720	-0.0005
ypN-stage					0.31		
ypN0	118	(64)	106	(69)		-0.0997	-0.0004
ypN1	41	(22)	32	(21)		0.0364	0.0079
ypN2	25	(14)	16	(10)		0.0986	-0.0095
Residual tumour stage					**0.001**	0.3785	0.0007
R0	157	(85)	148	(96)			
R1	27	(15)	6	(4)			
SAE and/or readmission within 6 weeks					0.48	-0.0762	0.0021
No	157	(85)	127	(83)			
Yes	27	(15)	27	(18)			
SAE related to preoperative CRT					**0.003**	-0.3186	-0.0001
No	174	(95)	131	(85)			
Yes	10	(5)	23	(15)			

Data is presented as n (%). Percentages may not equal 100 due to rounding.

The standardized difference (StD) represents the (im)balance of each confounder between the pCT+ and pCT- groups, before and after propensity score stratification (PSS) adjustment. Values outside the -0.1000% to 0.1000% range represent over-presence of a confounder in one of the groups, considered to represent substantial confounding. Values within the range represent a well-balanced distribution of a confounder between the groups.

pCT+ hospital policy for postoperative chemotherapy and received postoperative chemotherapy; pCT- no hospital policy for postoperative chemotherapy and did not receive postoperative chemotherapy; StD standardized difference; PSS propensity score stratification; EMVI extramural vascular invasion; SAE serious adverse event; CRT chemoradiotherapy.

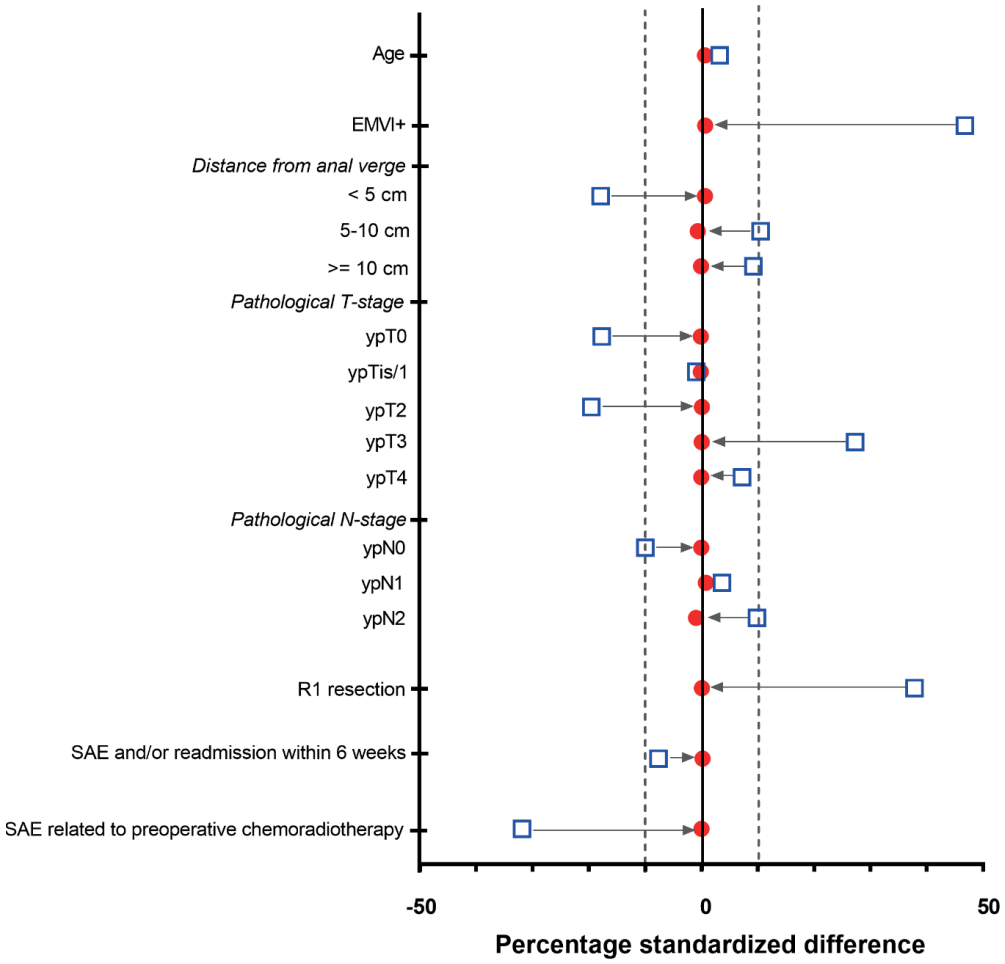


Figure S1 | Percentage standardized difference between the pCT+ and pCT- groups (analysis 2)
Percentage standardized difference before (blue square) and after (red dot) propensity score stratification (PSS), representing the (im)balance of each confounder between the pCT+ and pCT- groups. The dashed vertical lines indicate the (-)10% cut-off; values outside this range represent over presence of a confounder in one of the groups, considered to represent substantial confounding and values within this range after PSS represent a well-balanced distribution of confounders between the groups.
□ before PSS; ● after PSS.

Table S4 | Distribution of confounders between the pCT≥75% and pCT-/- (analysis 3), before and after propensity score stratification adjustment

	pCT≥75% (n=112)		pCT-/- (n=149)		p-value	StD before PSS	StD after PSS
Age (years)					0.46	-0.0949	0.0041
<70	101	(90)	130	(87)			
≥70	11	(10)	19	(13)			
EMVI at baseline					**<0.0001**	0.6073	-0.0063
No	56	(50)	116	(78)			
Yes	56	(50)	33	(22)			
Distance from anal verge at baseline					0.36		
<5 cm	32	(29)	52	(35)		-0.1289	-0.0038
5-10 cm	39	(35)	47	(32)		0.0636	0.0011
≥10 cm	41	(37)	50	(34)		0.0627	-0.0041
ypT-stage					**0.003**		
ypT0	12	(11)	32	(22)		-0.2971	0.0011
ypTis + ypT1	7	(6)	8	(5)		0.0384	0.0006
ypT2	18	(16)	42	(28)		-0.2945	-0.0009
ypT3	67	(60)	59	(40)		0.4125	-0.0033
ypT4	8	(7)	8	(5)		0.0703	-0.0067
ypN-stage					0.12		
ypN0	65	(58)	103	(69)		-0.2322	0.0015
ypN1	33	(30)	31	(21)		0.2015	-0.0032
ypN2	14	(13)	15	(10)		0.0759	-0.0082
Residual tumour stage					**0.001**	0.4149	-0.0004
R0	95	(85)	144	(97)			
R1	17	(15)	5	(3)			
SAE and/or readmission within 6 weeks					0.30	-0.1293	-0.0014
No	97	(87)	122	(82)			
Yes	15	(13)	27	(18)			
SAE related to preoperative chemoradiotherapy					**0.005**	-0.3703	-0.0007
No	107	(96)	126	(85)			
Yes	5	(5)	23	(15)			

Data is presented as n (%). Percentages may not equal 100 due to rounding.
The standardized difference (StD) represents the distribution of each confounder between the pCT+ and pCT- groups, before and after propensity score stratification (PSS) adjustment. Values outside the -0.1000% to 0.1000% range represent over-presence of a confounder in one of the groups, considered to represent substantial confounding. Values within the range represent a well-balanced distribution between the groups. pCT≥75% policy for postoperative chemotherapy and received 75% of the prescribed number of cycles of postoperative chemotherapy; pCT-/- no hospital policy for postoperative chemotherapy and did not receive postoperative chemotherapy; StD standardized difference; PSS propensity score stratification; EMVI extramural vascular invasion; SAE serious adverse event.

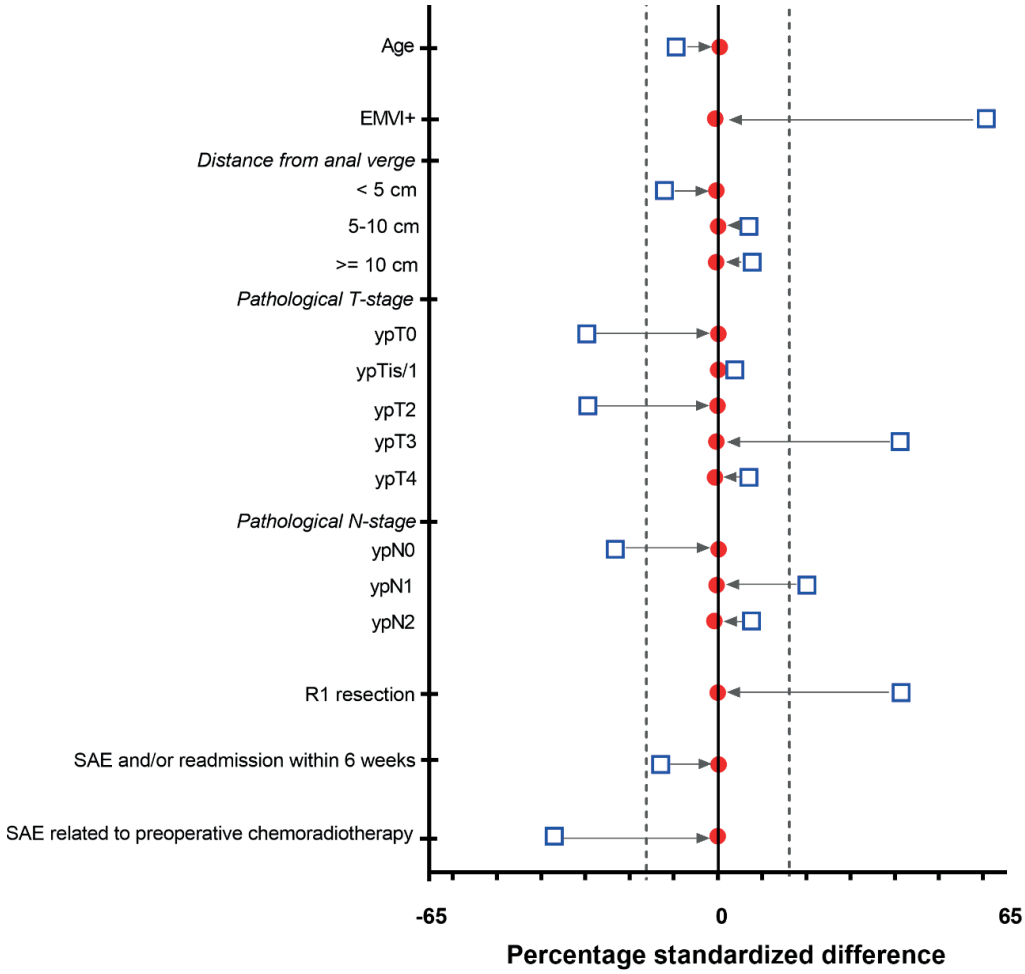


Figure S2 | Percentage standardized difference between the pCT≥75% and pCT-/- groups (analysis 3)

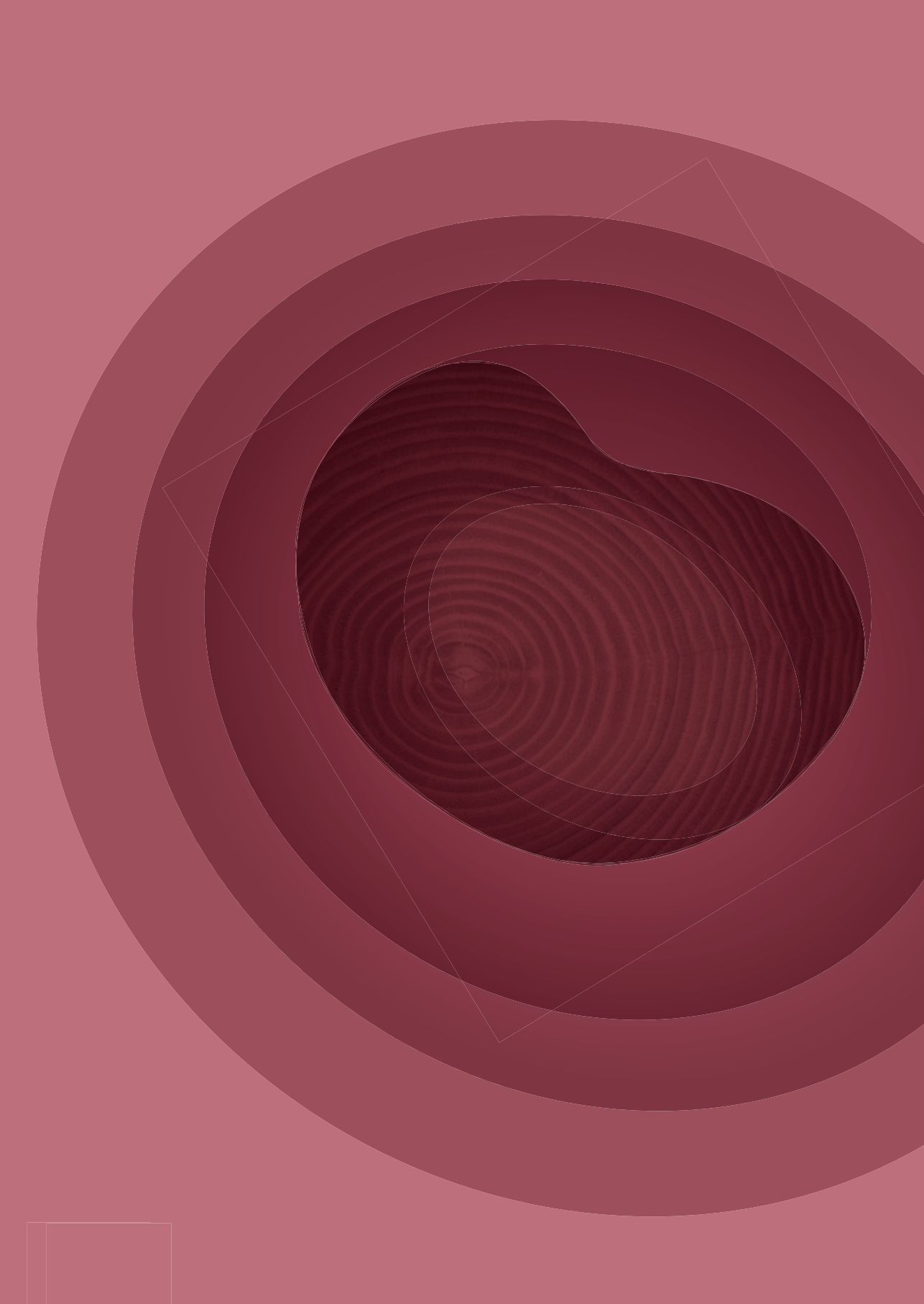
Percentage standardized difference before (blue square) and after (red dot) propensity score stratification (PSS), representing the (im)balance of each confounder between the pCT≥75% and pCT-/- groups. The dashed vertical lines indicate the (-)10% cut-off; values outside this range represent over presence of a confounder in one of the groups, considered to represent substantial confounding and values within this range after PSS represent a well-balanced distribution of confounders between the groups.

□ before PSS; ● after PSS

Table S5 | Overview of the HRs with 95% CIs of the three analyses (including DrTF)

Oncological outcome	HR	95% CI	p-value
Analysis 1: HP+ (n=236) *vs.* HP- (n=160)			
DrTF	**1.16**	**[0.79-1.68]**	**0.45**
DFS	1.08	[0.78-1.50]	0.65
DM	1.17	[0.79-1.74]	0.43
LRR	1.37	[0.51-3.64]	0.53
OS	1.03	[0.67-1.61]	0.88
Analysis 2: pCT+ (n=184) *vs.* pCT- (n=154)			
DrTF	**0.80**	**[0.52-1.25]**	**0.33**
DFS	0.78	[0.53-1.14]	0.20
DM	0.80	[0.51-1.26]	0.33
LRR	0.74	[0.26-2.15]	0.58
OS	0.82	[0.49-1.37]	0.44
Analysis 3: pCT≥75% (n=112) *vs.* pCT-/- (n=149)			
DrTF	**0.61**	**[0.35-1.05]**	**0.08**
DFS	0.63	[0.38-1.03]	0.07
DM	0.61	[0.34-1.08]	0.09
LRR	0.49	[0.10-2.38]	0.38
OS	0.74	[0.38-1.44]	0.38

HR Hazard ratio, CI confidence interval, DrTF disease-related treatment failure, DM distant metastasis, LRR locoregional recurrence, OS overall survival



CHAPTER 5b

Authors' reply – A sensitivity analysis of the RAPIDO clinical trial

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Annals of Oncology. 2023; 34: 446-447

AUTHORS' REPLY

We thank Jimenez-Fonseca and colleagues for their interest in the RAPIDO trial. The trial explored the value of pre-operative short-course radiotherapy followed by chemotherapy and surgery as total neoadjuvant therapy (TNT) against chemoradiotherapy, surgery and optional post-operative chemotherapy (pCT) as standard-of-care treatment in patients with high-risk locally advanced rectal cancer. They carried out a sensitivity analysis (SA) with aggregated 5-year follow-up data of the RAPIDO trial, simulating increasing proportions of patients who would be treated with pCT in the standard-of-care treatment and calculated hazard ratios (HRs) for disease-related treatment failure (DrTF)[1], demonstrating that HRs would remain <1 in most scenarios, favouring TNT. However, the statistically significant superiority of TNT disappears in some scenarios.

The HR regarding the value of pCT in the RAPIDO trial obtained by comparing patients in the standard-of-care treatment who did and did not receive pCT – using propensity score stratification to adjust for unbalanced confounders and possible bias introduced by the option to provide pCT – is 0.80 [95% confidence interval (CI) 0.52-1.25] for DrTF. Based on this HR, we carried out an SA including 10.000 simulated trials with the same number of patients randomized to TNT or standard-of-care treatment as the RAPIDO trial, in which different proportions of patients in the standard-of-care treatment were intended to be treated (ITT) with pCT of whom w70% subsequently actually received at least one cycle of pCT (based on RAPIDO data in hospitals with a policy to provide pCT). Afterwards, a proportional hazards model was fitted to the simulated trial data, yielding a simulated HR and 95% CI for TNT compared to standard-of-care treatment.

The results are demonstrated in figure 1, showing two important findings. Firstly, the HR is below 1.0 in all scenarios, indicating a lower chance of developing DrTF in favour of TNT. Secondly, when the ITT with pCT is approximately 60%, the 95% CI exceeds 1.0, indicating there is no longer a statistically significant difference in favour of TNT with regard to developing DrTF, which is in line with the SA of Jimenez-Fonseca et al[1].

However, it is questionable whether pCT is more effective than pre-operative chemotherapy. Firstly, pCT is frequently omitted because of post-operative complications or a decreased physical condition. This occurred in w30% of the patients in RAPIDO who started the standard-of-care treatment and were treated in hospitals with a policy to provide pCT. In randomized trials, pCT omission was ~25% after pre-operative chemoradiotherapy[2-4]. Secondly, full compliance with pCT after pre-operative chemoradiotherapy is poor, varying between approximately 40% and 70% in randomized trials[5]. In the RAPIDO trial, 64% of the patients were compliant with pCT (received ≥75% of the prescribed cycles). Both limitations play virtually no role in the TNT of the RAPIDO trial, since all patients who started TNT received pre-operative chemotherapy and compliance was 84%. Taken together, it is our opinion that systemic chemotherapy can be effective for some patients post-operatively, but is more effective for more patients pre-operatively, making TNT a superior treatment in high-risk locally advanced rectal cancer.

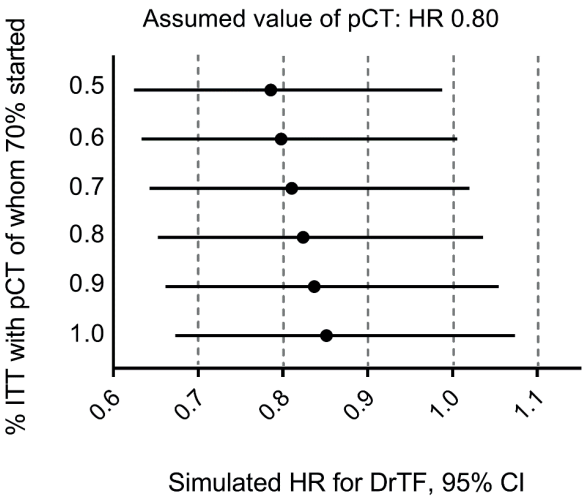

Figure 1 | Sensitivity analysis for disease-related treatment failure at 5-years follow-up in the RAPIDO trial.

The x-axis represents the simulated HR for DrTF with corresponding 95% CI between the total neoadjuvant treatment and the standard-of-care treatment with (on the y-axis) different proportions of patients from the standard-of-care treatment intended to be treated with pCT – of whom 70% actually received at least one cycle of pCT – assuming that pCT reduces the number of DrTF-events with a HR of 0.80.

HR hazard ratio, CI confidence interval, pCT postoperative chemotherapy, DrTF disease-related treatment failure, ITT intention to treat.

Funding

This work was supported by the Dutch Cancer Foundation [grant number CKS-2011-4997]; the Swedish Cancer Society; the Swedish Research Council (project number K2014- 99X-22481-01-3); the Spanish Ministry of Economy and Competitiveness through the Carlos III Health Institute [grant number EC11-423]; and by the Spanish Clinical Research Network [grant numbers SCReN-PT13/0002/0031, PT17/0017/0003] (co-financed by European Regional Development Fund 'A way to make Europe').

Disclosure

PJN reports honoraria from Ethicon, Johnson & Johnson and Amgen. GAPH reports consulting fees from Roche, MSD, Amgen and Novartis; consulting fees and research support to their institution from Bristol Myers Squibb; and research support to their institution from Seerave Foundation. CJHvdV was partially funded by the EU's Horizon 2020 research and innovation program under a Marie SkłodowskaCurie grant award (H2020MSCAITN2019, grant agreement number 857894; project acronym: CAST). BG reports research support from the Swedish Cancer Society. All other authors have declared no conflicts of interest.

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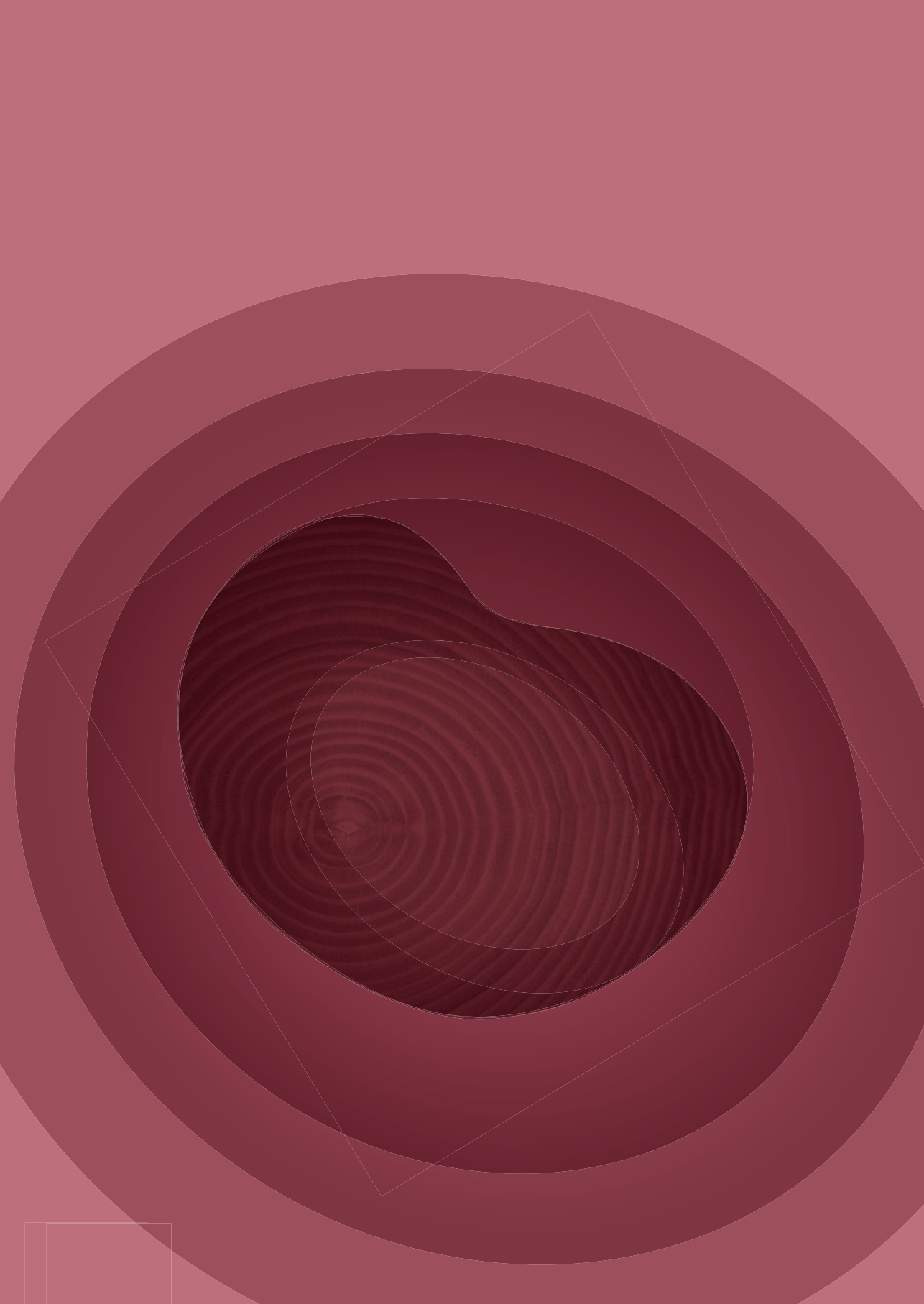

CHAPTER 6

Clinical selection strategy for and evaluation of intra-operative brachytherapy in patients with locally advanced and recurrent rectal cancer

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Radiotherapy & Oncology. 2021; 159: 91-97

ABSTRACT

Background and purpose

A radical resection of locally advanced rectal cancer (LARC) or recurrent rectal cancer (RRC) can be challenging. In case of increased risk of an R1 resection, intra-operative brachytherapy (IOBT) can be applied. We evaluated the clinical selection strategy for IOBT.

Materials and methods

Between February 2007 and May 2018, 132 LARC/RRC patients who were scheduled for surgery with IOBT standby, were evaluated. By intra-operative inspection of the resection margin and MR imaging, it was determined whether a resection was presumed to be radical. Frozen sections were taken on indication. In case of a suspected R1 resection, IOBT (1 x 10 Gy) was applied. Histopathologic evaluation, treatment and toxicity data were collected from medical records.

Results

Tumour was resected in 122 patients. IOBT was given in 42 patients of whom 54.8% (n=23) had a histopathologically proven R1 resection. Of the 76 IOBT-omitted R0 resected patients, 17.1% (n=13) had a histopathologically proven R1 resection. In 4 IOBT-omitted patients, a clinical R1/2 resection was seen. In total, correct clinical judgement occurred in 72.6% (n=88) of patients. In LARC, 58.3% (n=14) of patients were overtreated (R0, with IOBT) and 10.9% (n=5) were undertreated (R1, without IOBT). In RRC, 26.5% (n=9) of patients were undertreated.

Conclusion

In total, correct clinical judgement occurred in 72.6% (n=88). However, in 26.5% (n=9) RRC patients, IOBT was unjustifiedly omitted. IOBT is accompanied by comparable and acceptable toxicity. Therefore, we recommend IOBT to all RRC patients at risk of an R1 resection as their salvage treatment

INTRODUCTION

In the treatment of locally advanced rectal cancer (LARC) and recurrent rectal cancer (RRC), radiotherapy with concurrent chemotherapy followed by delayed surgery results in increased local control (LC)[1-4]. By this multimodality treatment downstaging occurs, which leads to a higher radical (R0) resection rate, resulting in a more favourable prognosis[5-11]. However, a radical resection may still be challenging[5,6,9,11-17].

Since local recurrence is associated with a poor quality of life and severe morbidity[18], it is important to maximise local control. Therefore, intra-operative brachytherapy (IOBT) can be used to give extra local therapy as resection margins may still be at risk of undetectable residual disease (R1)[19,20]. In literature however, there is yet no consensus if the addition of IOBT results in improved LC, overall survival (OS) and disease-free survival (DFS) in LARC and RRC patients[21,22]. A retrospective study demonstrated improved LC, OS and DFS after intraoperative radiotherapy (IORT) whereas two randomised trials failed to confirm these advantages of IORT[22-24].

During IOBT, dose-limiting organs such as the small bowel are kept out of the irradiation field, to decrease local toxicity[22,25]. In this way, the irradiation dose can be raised while optimising the balance between the local anti-tumour effects and toxicity. However, IOBT can be accompanied by severe side effects, such as bleeding and neuropathy[5,20,26]. Also, there is no consensus on the indication of IOBT/IORT. In some studies, all patients received IOBT/IORT, while in others the decision making was based on preoperative examinations, on microscopic or macroscopic remaining tumour (in which the definition of free resection margin differed) or on frozen sections[11,13,21].

The potential complication risks of additional IOBT should be weighed against the potential clinical benefits. Therefore, in our study IOBT was performed if an irradical (R1) resection was suspected based on the judgement of the surgeon and radiation oncologist. The primary aim of this study is to evaluate the accuracy of this clinical selection strategy for IOBT, and the secondary objective is to assess its toxicity.

MATERIALS AND METHODS

Between February 2007 and May 2018, 132 patients with adenocarcinoma of the rectum were evaluated and scheduled for resection with IOBT standby. Our institutional ethical review committee approved this analysis (METc number: 2019/069).

Staging was performed using endoscopy with biopsies, CT-scan of thorax/abdomen and (DW-) MRI-scan. Treatment policy was discussed in a multidisciplinary rectal cancer expert board. If patients were radiotherapy naïve, they received 50.0–50.4 Gy (2.0–1.8 Gy/ fraction daily) using a 3- or 4-field technique. Previously irradiated patients were re-irradiated with 30.0–30.6 Gy (2.0–1.8 Gy/fraction daily) using a 3- or 4-field technique[27]. Target volume for irradiation and re-irradiation was the tumour and suspected lymph nodes with margin, combined with the following lymph node regions: internal iliac regions, obturatorius regions, mesorectum and presacral area. Radiotherapy in LARC and RRC patients was usually combined with twice-daily capecitabine 825 mg/m^2. In case of distant metastasis, patients were treated according to the M1-regimen (5x5 Gy daily followed by six cycles of CAPOX-B)28. Patients were restaged approximately six weeks after neoadjuvant treatment and scheduled for surgery 8–12 weeks after completion of the neoadjuvant therapy. Low anterior resection (LAR), (extra levator) abdominoperineal resection (APR), anterior-, posterior- or total exenteration were performed. In some cases, the distal sacrum was resected.

IOBT was standby during the resection if inadequate resection margins were expected. During surgery, the surgeon, in collaboration with the radiation oncologist, determined the radicality of the resection by means of observation and palpation of the resection margin combined with information obtained from the preoperative MRI. In case of a clinically (expected) R1 resection, IOBT was performed. In case of an R0 or R2 resection, multiple irradical resection planes or a emodynamically unstable patient, IOBT was omitted. Frozen sections were not mandatory.

Our IOBT procedure largely corresponds to the procedure described by Deurloo et al.[29]. In preparation of the IOBT procedure, library plans were prepared, which are optimized at the reference depth of the complete target area except for the dwell positions at the angular points. During surgery, the size of the irradical resection was determined, into which the flexible intraoperative template (FIT) was placed. A FIT is a 5 mm thick flexible silicone template which contains parallel catheters spaced 1 cm apart. The FIT could be cut into the desired geometry. Because of the flexibility of the FIT, the FIT could be placed in the most optimal position in which the FIT is well aligned with the target volume. To define the target area, the FIT was placed at the tissue surface area, which was marked by clips. The treatment plans were selected from the library and a dose of 10 Gy was specified at the reference depth at 1 cm from the surface of the FIT. The total duration of the intraoperative irradiation was 10–

20 minutes. figure S1 demonstrated the adjustment and placement of the FIT. The specimen was fixed for 24 hours in formalin. The radicality of the resection was defined according to guidelines; R0: free surgical margins (>1mm), R1: microscopically involved margins (≤1mm) and R2: macroscopically involved margins[30].

Acute side-effects, within 30 days after surgery, and late side-effects, within 90 days after surgery, were retrospectively classified according to Clavien-Dindo[31] and the Common Terminology Criteria for Adverse Events version 532, based on the reports of the treated physician.

Statistics

Proportions were compared with chi-square tests and continuous parameters, depending on the distribution of the data, with T-test or Mann-Whitney U test. All tests were two-tailed, and p-values ≤ 0.05 were considered statistically significant. The positive predictive value (PPV) was calculated as the number of R1/2 resections at histopathological evaluation divided by the number of clinically suspected R1/2 resections during surgery. Sensitivity was calculated as the number of R1 frozen sections divided by the number of R1 resections at histopathological evaluation. Patients were followed-up until five years after surgery. Median follow-up was calculated from the date of surgery until censoring. The overall survival was calculated from the date of surgery until the last follow-up or death using the Kaplan-Meier method. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, New York, USA). The overall survival figure was conducted by R version 4.0.2.

RESULTS

In total, 132 patients were scheduled for surgery with IOBT standby. Patients' characteristics are shown in table 1. IOBT was performed in 42 patients. The IOBT-performed group (n=42) consisted of 24 LARC, and 18 RRC patients and the IOBT-omitted group (n=90) of 46 LARC and 44 RRC patients including ten patients by whom the tumour was not resected (figure S2). Of the patients with recurrent rectal cancer, 12 patients had actually recurrent sigmoid carcinoma located at the colorectal anastomosis in the pelvis.

Table 1 | Patient and preoperative treatment characteristics

	IOBT performed (n=42)				IOBT omitted (n=90)			
	LARC (n=24)		RRC (n=18)		LARC (n=46)		RRC (n=44)	
Gender								
Male	18	(75.0)	13	(72.2)	27	(58.7)	24	(54.5)
Female	6	(25.0)	5	(27.8)	19	(41.3)	20	(45.5)
Age in years								
(mean, range)	62	[33-79]	60	[41-72]	63	[35-83]	67	[36-80]
Histology tumour								
Adenocarcinoma	24	(100.0)	14	(77.8)	46	(100.0)	27	(61.4)
Neuroendocrine	0	(0.0)	1	(5.6)	0	(0.0)	1	(2.3)
Mucinous	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)
Unknown	0	(0.0)	3	(16.7)	0	(0.0)	15	(34.1)
cT- and N-stage								
cT3N0	2	(8.3)	10	(55.6)	1	(7.7)	17	(38.6)
cT3N+	6	(25.0)	1	(5.6)	18	(39.1)	8	(18.2)
cT4N0	4	(16.7)	5	(27.8)	5	(10.9)	12	(27.3)
cT4N+	12	(50.0)	2	(11.1)	22	(47.8)	7	(15.9)
cM-stage								
cM0	22	(91.7)	14	(77.8)	42	(91.3)	34	(77.3)
cM1	2	(8.3)	4	(22.2)	4	(8.7)	10	(22.7)
Location cM-stage								
Liver	1	(50.0)	0	(0.0)	4	(57.1)	6	(60.0)
Pulmonary	0	(0.0)	3	(75.0)	2	(28.6)	1	(10.0)
Lymphatic	1	(50.0)	0	(0.0)	1	(14.3)	2	(20.0)
Peritoneum	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)
Oligometastasis[a]	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)

Data is presented as n (%).

IOBT intra-operative brachytherapy; LARC locally advanced rectal cancer; RRC recurrent rectal cancer.

[a]symphysis pubis

Of the LARC patients (n=70), 84.3% received 50.0/50.4 Gy (n=59). In 96.6% of patients concomitant chemotherapy was given (n=57). Concomitant chemotherapy was omitted in two patients (3.4%) because of thrombopenia (n=1) and respiratory infection (n=1). In one patient (1.4%), chemoradiotherapy was prematurely stopped because of extreme anxiety regarding the treatment which did not resolve by medication. Nine patients (12.9%) received 5x5 Gy radiotherapy, of which six patients (66.7%) were treated according to the M1-regimen. One patient (1.4%) was treated with 30.6 Gy and concomitant capecitabine because of prior radiotherapy for a bladder tumour. Of the RRC patients (n=62), 58.1% (n=36) were re-irradiated with a total dose of 30.0/30.6 Gy and 97.2% (n=35) of them also received concomitant chemotherapy. In total, 24 radiotherapy naïve RRC patients (38.7%) received long-course radiotherapy, and 95.8% (n=23) received concomitant chemotherapy. Concomitant chemotherapy was omitted because of gastrointestinal toxicity during chemotherapy for the primary tumour (n=2). In total, two patients (3.2%) were treated with 5x5 Gy, of which one patient according to the M1 regimen.

The median interval between last neoadjuvant therapy and surgery for LARC was 13 weeks (interquartile range (IQR) 10–17 weeks) and for RRC 12 weeks (IQR 9–15 weeks). All LARC patients (n=70) and 90.3% of the RRC patients (n=56) underwent surgery (figure S2). Reasons to omit surgery were: tumour progression with no curative options (n=4) and patient refusal (n=2). During the resection, four RRC cases were irresectable and therefore not eligible for IOBT, leaving 122 patients in the analysis (figure S2). In 42 patients IOBT was given during the resection. The location of IOBT was lateral pelvic sidewall in 54.8% (n=23) and pre-sacral in 45.2% (n=19) of patients (table 2). An APR was significantly more often performed in IOBT-omitted patients.

Histopathological characteristics are listed in table 2, figures 1A and 1B. In total, 34.4% (n=42) patients received IOBT. Of these patients, IOBT was given in 41 (97,6%) because of clinical suspicion of an R1 resection, in the other patient who underwent IOBT the resection was clinically judged as R0; however, the frozen section showed an R1 resection. In the final histopathological evaluation 23 (54.8%) R1 and 19 (45.2%) R0 resections were found. In total, overtreatment with IOBT occurred in 19 patients; 14 out of 24 (58.3%) LARC and 5 out of 18 (27.8%) RRC patients. In the remaining 80 patients (65.6%), IOBT was omitted. In 76 patients (95.0%), an R0 resection was suspected during surgery. At histopathological evaluation, 63 resections (82.9%) were R0 and 13 resections (17.1%) were R1. Because of a negative frozen section, three times (3.8%) IOBT was omitted while an R1 resection was suspected. Once (1.3%), an R2 resection was accomplished. In conclusion, undertreatment occurred in 5 out of 46 (10.9%) LARC patients and 9 out of 34 (26.5%) RRC patients.

Table 2 | Surgical and pathology characteristics

	IOBT performed (n=42)				IOBT omitted (n=80)			
	LARC (n=24)		RRC (n=18)		LARC (n=46)		RRC (n=34)	
Type of resection								
LAR	6	(25.0)	2	(11.1)	16	(34.8)	4	(11.8)
APR	8	(33.3)	3	(16.7)	22	(47.8)	14	(41.2)
Anterior exenteration	1	(4.2)	3	(16.7)	2	(4.3)	0	(0.0)
Posterior exenteration	0	(0.0)	0	(0.0)	0	(0.0)	3	(8.8)
Total exenteration	9	(37.5)	5	(27.8)	6	(13.0)	7	(20.6)
Local excision	0	(0.0)	5	(27.8)	0	(0.0)	6	(17.6)
Location IOBT								
Sacral	13	(54.2)	6	(33.3)				
Pelvic bone	11	(45.8)	12	(66.7)				
IOBT planes								
1 plane	22	(91.7)	18	(100.0)				
2 planes	2	(8.3)	0	(0.0)				
Radicality of surgery (clinical judgement)								
R0 (>1mm)	0	(0.0)	1	(5.6)	43	(93.5)	33	(97.1)
R1 (≤1mm)	24	(100.0)	17	(94.4)	2	(4.3)	1	(2.9)
R2 (irradical)	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)
Radicality of frozen section								
R0 (>1mm)	4	(16.7)	1	(5.6)	9	(19.6)	15	(44.1)
R1 (≤1mm)	5	(20.8)	10	(55.6)	0	(0.0)	0	(0.0)
R2 (irradical)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
No frozen section taken	15	(62.5)	7	(38.9)	37	(80.4)	19	(55.9)
Radicality of pathology								
R0 (>1mm)	14	(58.3)	5	(27.8)	40	(87.0)	25	(73.5)
R1 (≤1mm)	10	(41.7)	13	(72.2)	5	(10.9)	*9	(26.5)
R2 (irradical)	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)
Overall judgement								
Correct judgement	10	(41.7)	13	(27.8)	40	(87.0)	25	(73.5)
Overtreatment[a]	14	(58.3)	5	(72.2)	-		-	
Underteatment[b]	-		-		5	(10.9)	9	(26.5)

Data is presented as n (%).

IOBT intra-operative brachytherapy; LARC locally advanced rectal cancer; RRC recurrent rectal cancer; R0 clear resection margins; R1 ≤ 1mm resection margin between 0 and 1 mm; R2 macroscopic residual tumour.

* One patient was haemodynamically unstable during surgery; therefore it was not possible to perform IOBT.

[a] IOBT performed and at histopathological evaluation R0

[b] IOBT omitted and at histopathological evaluation R1

In the total patient group (n=122), the PPV of the clinical evaluation was 53.3%. In case of LARC and RRC, the PPV was 44.4% and 66.7%, respectively. Frozen sections were taken in 44 patients (36.1%) and were accomplished with a low sensitivity of 61.1%. The sensitivity and specificity of frozen sections in LARC patients (n=18) was 40.0% and 76.9% and in RRC patients (n=26) 69.2% and 91.6%, respectively.

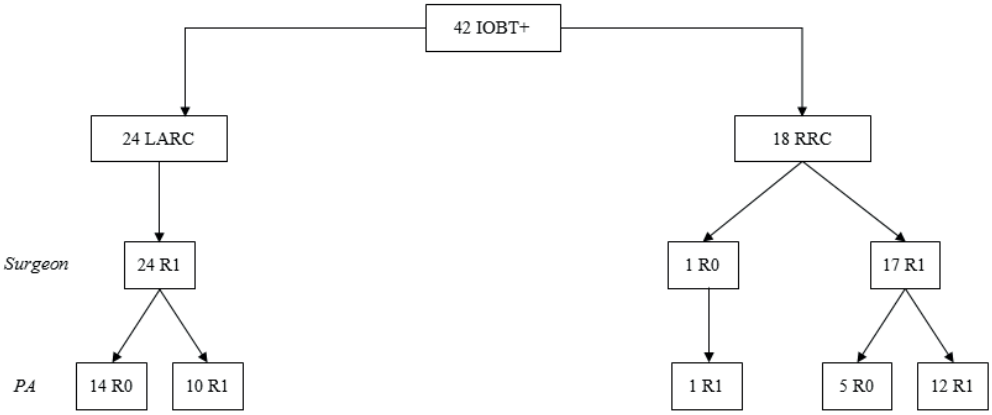

Figure 1A | Surgical and histopathological resection margin of IOBT performed patients

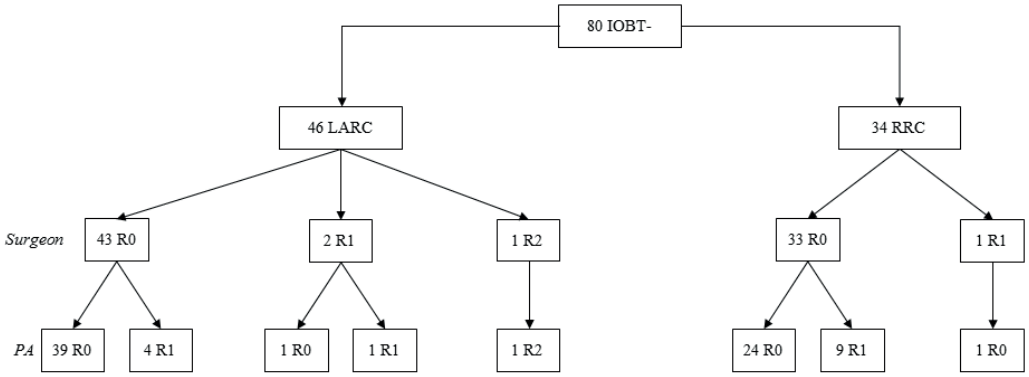

Figure 1B | Surgical and histopathological resection margin of IOBT omitted patients in patients with a resected tumour only

One patient (0.8%) died within 30 days. This patient died of acute pulmonary haemorrhage 15 days after surgery with unknown origin as cause of death. No grade IV toxicity occurred. Although not significant, acute pain grade I-II occurred numerically twice as often in patients who underwent IOBT (p=0.06). In total, 4.8% and 2.5% of the acute pain grade I-II were neuropathic in the IOBT-performed and IOBT-omitted group, respectively (p=0.51). Although also not significant, acute gastrointestinal toxicity grade III was more reported by patients in whom IOBT was omitted (p=0.029). In conclusion, there were no significant differences in acute and late toxicity between these groups (table 3).

Table 3 | Acute and late toxicity

	IOBT performed (*n*=42)		IOBT omitted (*n*=80)		*p*-value
Acute toxicity Grade 1-2[a]					
Gastrointestinal	4	(9.5)	14	(17.5)	0.24
Infections	10	(23.8)	13	(16.3)	0.31
Nervous system	3	(7.1)	8	(10.0)	0.60
Pain	13	(31.0)	13	(16.3)	0.06
Sexual	1	(2.4)	0	(0.0)	0.17
Urinary	12	(28.6)	25	(31.3)	0.76
Vascular	2	(4.8)	1	(1.3)	0.23
Wound dehiscence	9	(21.4)	11	(13.8)	0.28
Acute toxicity Grade 3-4[a, +]					
Gastrointestinal	1	(2.4)	9	(11.3)	0.09
Infections	3	(7.1)	3	(3.8)	0.41
Wound	3	(7.1)	2	(2.5)	0.22
Late toxicity Grade 1-2[b]					
Infections	0	(0.0)	1	(1.3)	0.47
Pain	2	(4.8)	2	(2.5)	0.97
Wound	1	(2.4)	2	(2.5)	0.97
Late toxicity Grade 3-4[b, +]					
Gastrointestinal	1	(2.4)	3	(3.8)	0.69
Infections	1	(2.4)	0	(0.0)	0.17
Vascular	1	(2.4)	0	(0.0)	0.17

IOBT intra-operative brachytherapy.

[a] according to Clavien Dindo,

[b] according to Common Terminology of Criteria for Adverse Events version 5

[+] no grade 4 toxicity occurred

The median follow-up was 35.3 months (interquartile range 19.6–51.8). Regardless of radicality, the overall survival three years after surgery was 80.2% in the IOBT-omitted LARC and RRC patients (n=80) and 68.6% in the IOBT-performed LARC and RRC patients (n=42) (p=0.007) (figure S3).

DISCUSSION

This is the first study which evaluates the clinical selection strategy for IOBT in LARC and RRC patients. This study demonstrates that in the vast majority (89.1%) of LARC patients, the judgement of the surgeon in collaboration with the radiation oncologist to omit IOBT was correct. However, in RRC, the clinical judgment on the radicality of the resection was correct in only 69.2% of patients. An R1 resection was diagnosed in 26.5% of IOBT-omitted patients. Overall, 17.5% of the total group of patients with IOBT standby were undertreated (IOBT-omitted in R1 resection).

In our study, only patients with a clinically suspected R1 resection received IOBT. We demonstrated corresponding PPVs of 53.3%, 44.4% and 66.7% in the total patient group, LARC and RRC patients, respectively. A high PPV indicates that when a tumour was clinically predicted as R1/2, this was usually true. To the best of our knowledge, no other studies are determining PPV of the clinical selection strategy. Comparable to our research, there are two other studies in which not all patients received IOBT[11,13]. In these studies, R0 based on frozen section analysis was used for decision-making. However, frozen sections can provide false negative diagnosis and are time-consuming[33,34]. In the current study, we sampled for frozen sections in 36.1% of cases and reached a low sensitivity of 61.1%. In RRC patients frozen sections were taken more often (in 61.1% and 44.1% in the IOBT-performed and IOBT-omitted, respectively). This suggests that the resection in RRC patients is more difficult to judge for radicality, and then a frozen section could be useful. However, accurate clinical judgement of resection margin for frozen section analysis is usually hampered by fibrosis after previous resection or previous preoperative radiotherapy[35]. Because of this, the more aggressive biological behaviour of RRC and most importantly, the resection which is beyond normal anatomic surgical planes, could result in a higher risk of positive resection margins (R1)[36-38]. However, the specificity of a frozen section was only 50% in LARC patients in which an R0 resection was obtained and IOBT was performed (n=9), respectively (data not shown). Besides, the sensitivity and specificity of all LARC patients in which a frozen section was taken was 40.0% and 76.9%, whereas the sensitivity and specificity was 69.2% and 91.6% in RRC patients respectively. In addition, in only 47.7% of all LARC patients who received IOBT (n=24) because of an R1 resection, were also scored as an R1 resection at histopathological evaluation. Therefore, frozen sections should be omitted in LARC patients.

Although not significant, acute pain grade I-II was reported twice as often in patients who underwent IOBT reported (p=0.06). This may be explained by the fact that an extensive resection was performed in this patient group. Furthermore, acute nervous system toxicity grade I-II was comparable between the groups and occurred in 7.1% and 10.0% in the IOBT-performed and IOBT-omitted group, respectively. Neuropathy is a serious toxicity20. In our study, nervous system toxicity and neuropathic pain occurred only as grade 1–2 (in total: 11.9% (n=5) in IOBT-performed and 12.5% (n=10) in IOBT-omitted patients). Haddock et al. demonstrated comparable grade 1–2 neuropathy symptoms of 12.4% of patients[20]. However,

Haddock et al. used IORT instead of IOBT, which is known for its homogeneous target and greater depth dose[39]. It seems that most acute pain grade I-II was related to the extension of the resection and that this was comparable between the groups (23.8% vs. 13.8% in the IOBT-performed and IOBT-omitted group, respectively (p=0.16), data not shown). Since postoperative morbidity (grade ≥ 3) is most often related to the extent of the resection[40], it could be expected that IOBT dependent complications might occur more than 90 days after surgery.

Acute gastrointestinal toxicity grade III was numerically more reported by IOBT-omitted patients (p=0.09). All acute gastrointestinal toxicity, accept for anastomotic leakage, occurred in patients who underwent an APR. The extensiveness of an APR is probably associated with an increased risk of systemic inflammatory response which may result in hypotension and therefore more gastrointestinal toxicity. Possibly the small numbers contributes to the numerical difference in gastrointestinal toxicity. Without clear explanation, anastomotic leakage occurred in 14.7% of the patients who underwent a LAR or anterior exenteration (data not shown). The radiotherapy target volume in both groups was tumour with margin, the mesorectal area and presacral and internal iliac lymph node region. So target volume, and therefore organs at risk, does not explain the numerical difference in gastrointestinal toxicity.

We demonstrated a three-year overall survival of 68.6% and 80.2% in IOBT-performed and IOBT-omitted patients, respectively. Since IOBT-omitted patients lived significantly longer, this suggests that the clinical selection strategy went well. However, the patient groups in our study are small and heterogeneous. Besides, in 14 patients (17.5%) in who IOBT was omitted an R1 resection was found at histopathological evaluation. So conclusions must be drawn with caution. Besides, two randomised trials failed to demonstrate a survival benefit of IOBT-performed patients as well[22,23].

There are some limitations of the current study. IOBT is not often performed in the Netherlands, therefore the numbers are small. Besides, the patient population is heterogeneous. The CTCAE scoring system is used retrospectively, which could have resulted in underestimation of the toxicity. However, we believe that the number of retrospectively scored toxicity is accurate, since toxicity was asked at every follow-up moment. Though, toxicity results should be interpreted with cautions.

In our study patients received 1x10 Gy IOBT only in case an irradical resection was suspected. However, the accurate selection of an expected irradical resection margins was difficult, resulting in undertreatment (R1 resection and IOBT-omitted) in 17.5% (14/80) of the patients. In the current study, the use of frozen sections did not seem to improve the accuracy. Promising devices and methods to improve detection of R1 margins per-operatively could be the use of bevacizumab-800CW by back-table and intraoperative fluorescence-guided imaging, computer navigation-assisted surgery or diffuse reflectance spectroscopy[41,42].

Conclusions

We demonstrated that correct clinical judgement to perform IOBT occurred in 41.7% of LARC patients and 72.2% of RRC patients. In IOBT-omitted patients, a correct clinical judgement was accomplished in 87.0% of LARC and 73.5% of RRC patients. Since only 10.9% of the LARC patients were undertreated, we can conclude that the clinical selection strategy in LARC patients went well in the vast majority of patients. However, 26.5% of RRC patients were undertreated (IOBT-omitted and R1 resection at histopathology). Moreover, patients who received IOBT had acceptable toxicity and comparable toxicity to patients who did not receive IOBT. Based on the current results, we recommend performing IOBT in all RRC patients at risk of an R1 resection since in RRC it is often their salvage treatment, and IOBT is accompanied by acceptable toxicity. For RRC patients who are at risk of an R1 resection we advise to refer this patient to a hospital which is able to perform IOBT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to thank all referral hospitals (table S1) for their contribution to follow-up data.

Sources of support

None

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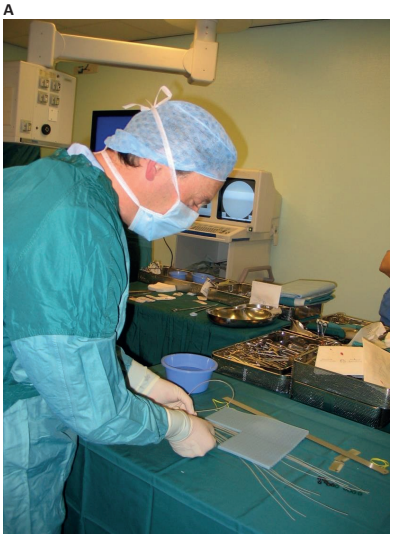
SUPPLEMENTAL MATERIAL

A



B

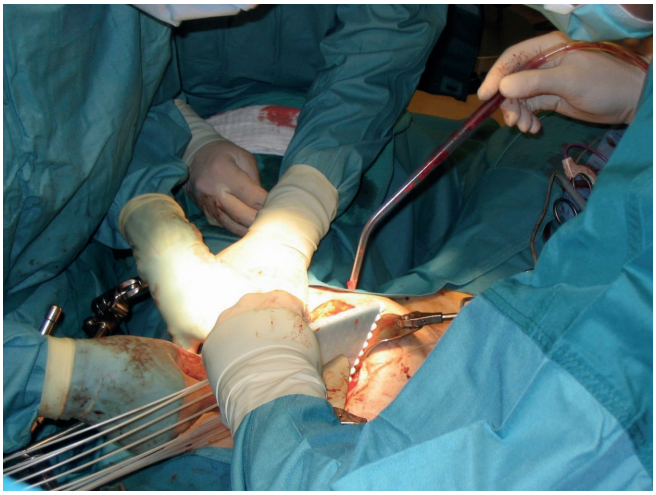


Figure S1 | A Intra-operative brachytherapy procedure; adjustment of the FIT. B Intra-operative brachytherapy procedure; placement of the FIT

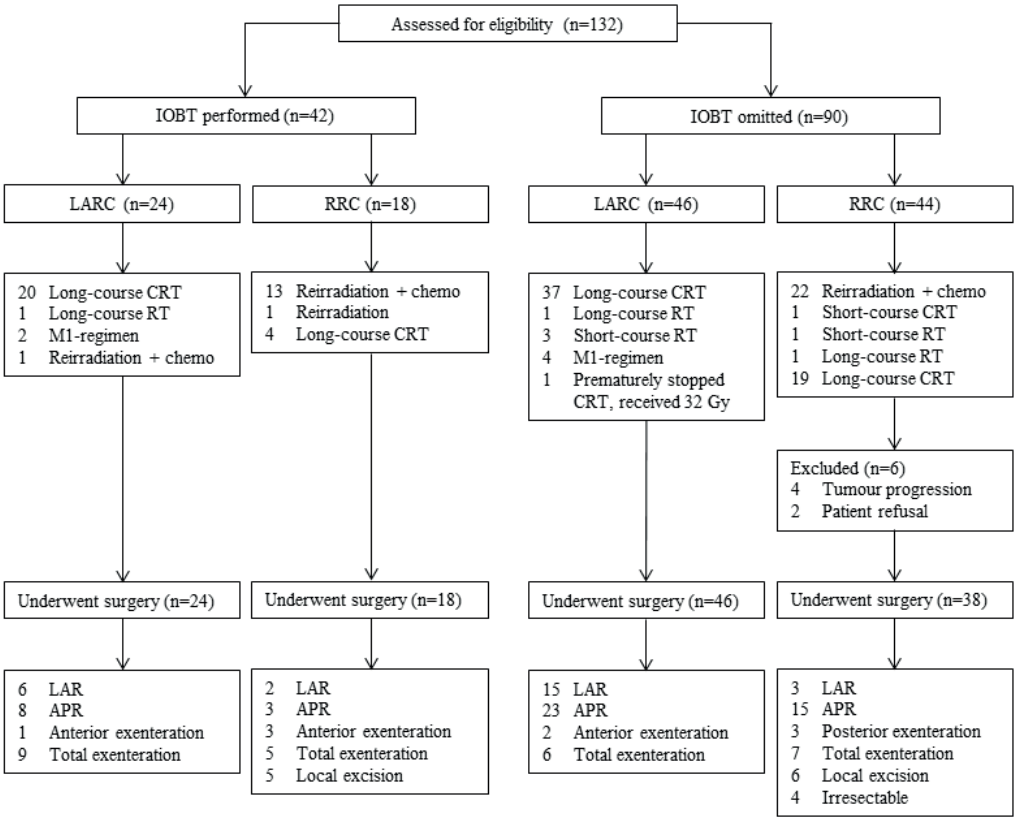


Figure S2 | Consort diagram

IOBT intra-operative brachytherapy; LARC locally advanced rectal cancer; RRC recurrent rectal cancer; CRT chemoradiotherapy; RT radiotherapy; M1-regimen 5x5 Gy radiotherapy followed by bevacizumab, capecitabine and oxaliplatin and surgery; LAR low anterior resection; APR abdominoperineal resection.

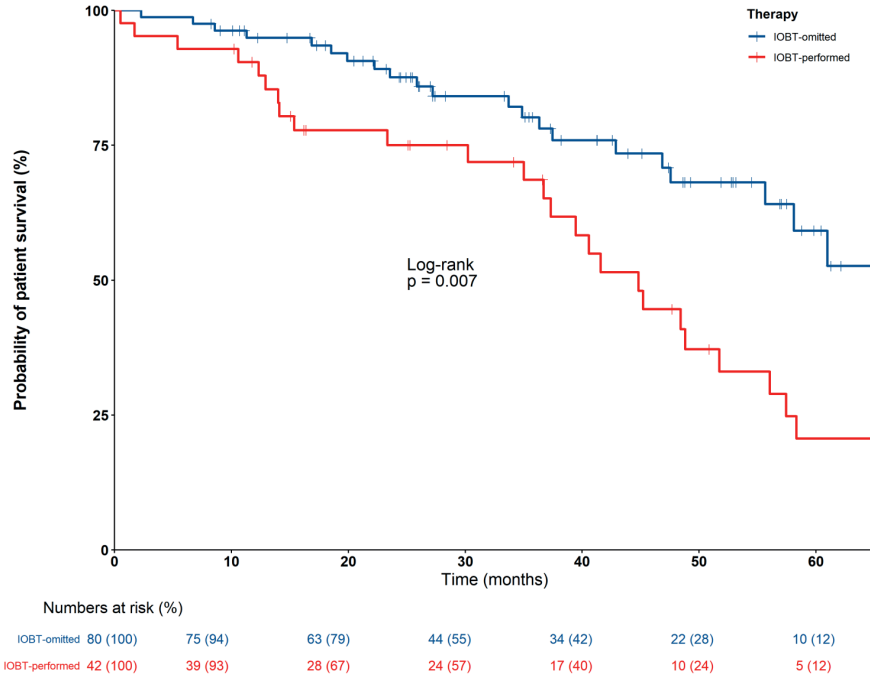
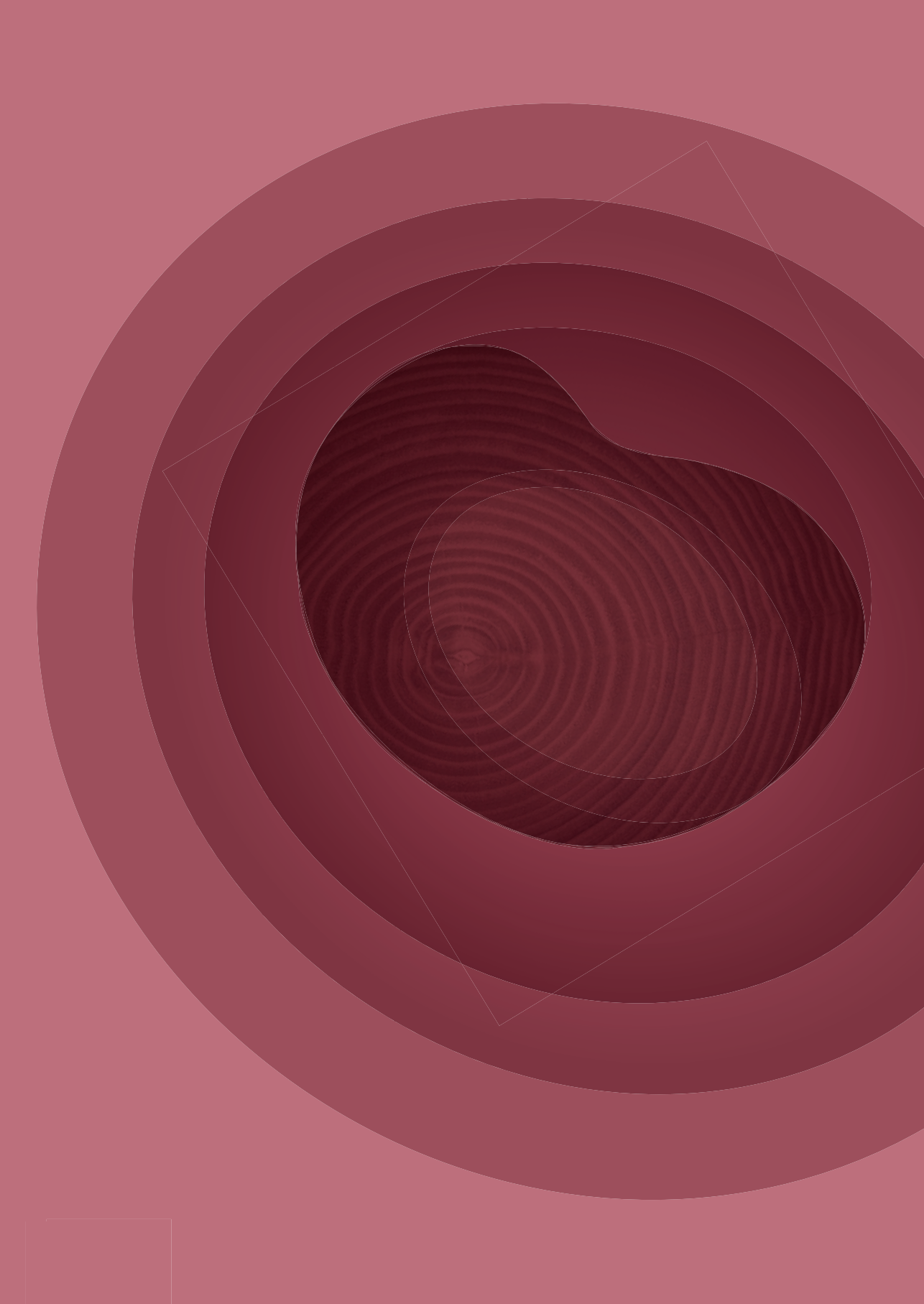


Figure S3 | Overall survival in IOBT-performed and IOBT-omitted patients

Table S1 | Participating institutes and collaborative investigators

Location	Institute	Department	Investigator
Almelo	Ziekenhuisgroep Twente	Department of surgery	I.F. Faneyte
Assen	Wilhelmina Hospital	Department of surgery	S.T. van Vugt
Deventer	Deventer Hospital	Department of surgery	R.J.I. Bosker
Drachten	Nij Smellinghe Hospital	Department of surgery	I.T.A. Pereboom
Enschede	Medisch Spectrum Twente	Department of surgery	P. Steenvoorde
Emmen	Scheper Hospital	Department of surgery	R.A. Schasfoort
Groningen	Martini Hospital	Department of surgery	P.C. Baas
Hardenberg	Röpcke-Zweers Hospital	Department of surgery	M.F. Lutke-Holzik
Heerenveen	Tjongerschans Hospital	Department of surgery	F. Wit
Hoogeveen	Bethesda Hospital	Department of surgery	F.W.H. Kloppenburg
Leeuwarden	Medical Center Leeuwarden	Department of surgery	M.A. Kaijser
Meppel	Diaconessenhuis Meppel	Department of surgery	F.N.L. Versluijs-Ossewaarde
Scheemda	Ommelander ziekenhuis Groningen	Department of surgery	D.P. de Vries
Sneek	Antonius Hospital	Department of surgery	D.A. Hess
Winterswijk	Streekziekenhuis Koningin Beatrix	Department of surgery	B. Inberg
Zwolle	Isala Klinieken	Department of surgery	A.D. van Dalsen



CHAPTER 7

Re-irradiation in patients with recurrent rectal cancer is safe and feasible

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Annals of Surgical Oncology. 2021; 28: 5194-5204

ABSTRACT

Background

There is no consensus yet for the best treatment regimen in patients with recurrent rectal cancer (RRC). This study aims to evaluate toxicity and oncological outcomes after re-irradiation in patients with RRC in our center. Clinical (cCR) and pathological complete response (pCR) rates and radicality were also studied.

Methods

Between January 2010 and December 2018, 61 locally advanced RRC patients were treated and analyzed retrospectively. Patients received radiotherapy at a dose of 30.0–30.6 Gy (reCRT) or 50.0–50.4 Gy chemoradiotherapy (CRT) in cases of no prior irradiation because of low-risk primary rectal cancer. In both groups, patients received capecitabine concomitantly.

Results

In total, 60 patients received the prescribed neoadjuvant (chemo)radiotherapy followed by surgery, 35 patients (58.3%) in the reRCT group and 25 patients (41.7%) in the long-course CRT group. There were no significant differences in overall survival (p=0.82), disease-free survival (p=0.63), and local recurrence-free survival (p=0.17) between the groups. Patients in the long-course CRT group reported more skin toxicity after radiotherapy (p=0.040). No differences were observed in late toxicity. In the long-course CRT group, a significantly higher cCR rate was observed (p=0.029); however, there was no difference in the pCR rate (p=0.66).

Conclusions

The treatment of RRC patients with re-irradiation is comparable to treatment with long-course CRT regarding toxicity and oncological outcomes. In the reCRT group, less cCR was observed, although there was no difference in pCR. The findings in this study suggest that it is safe and feasible to re-irradiate RRC patients.

INTRODUCTION

Despite the improved treatment of primary rectal cancer, recurrent rectal cancer (RRC) remains a problem. After long-course neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) for locally advanced rectal cancer (LARC), RRC is seen in 5–9% of patients[1-3]. Intermediate-risk primary tumors (cT1-3N1, cT3N0 with >5 mm extramural vascular invasion (EMVI) or distant to the mesorectal fascia (MRF) >1 mm) are treated with 595 Gy radiotherapy followed by TME. In intermediate rectal cancer patients, the risk of RRC is approximately 5%[4]. Even in low-risk rectal cancer patients (cT1-2N0 or cT3N0 with ≤5 mm EMVI, MRF >1 mm) in whom neoadjuvant radiotherapy is omitted, there is still a 4–6% chance of RRC[5,6].

In cases of intermediate primary rectal cancer or LARC, patients receive (chemo)radiotherapy. If RRC occurs in these prior irradiated patients, the neoadjuvant re-irradiation dose is limited[7] by the risk of potential normal tissue complications[8]. Nonetheless, is re-irradiation with a lower dose still effective? In the literature, there is no consensus for the best treatment regimen in patients with RRC[9-11].
Re-irradiation doses range from 15.0 to 49.2 Gy and 30.0 to 30.6 Gy, and median doses of 40.8 Gy[12-14]. A study has been conducted that determines the radiotherapy dose on the basis of retreatment interval[15], and the systematic review by Tanis et al. demonstrated that there are studies providing adjuvant radiotherapy in the case of RRC. Furthermore, chemotherapy was not always used as a radiosensitizer[10].

In RRC, just as in LARC, neoadjuvant CRT could be used to downstage and downsize the tumor, resulting in a better chance of an R0 resection. However, resection of RRC is more difficult because of the altered and varied anatomy of organs and critical structures in the pelvis as a result of the initial treatment. Furthermore, differences in tumor growth and the presence of post-treatment fibrosis make the resection more challenging. Therefore, the risk of an R1 resection is substantial[16-18], resulting in worse survival[11]. To obtain free resection margins (R0), an extensive (i.e. multivisceral) resection procedure must often be performed[19-22].

This study aimed to evaluate toxicity and the oncological outcome of low-dose re-irradiation and concurrent chemotherapy, compared with high-dose primary radiotherapy and concurrent chemotherapy, in RRC patients. Furthermore, radicality, clinical complete response (cCR) and pathological complete response (pCR) rates after neoadjuvant treatment were evaluated.

METHODS

Overall, 61 consecutive patients with clinically resectable locally advanced RRC without distant metastasis during staging and who received neoadjuvant (chemo)radiotherapy between January 2010 and December 2018 were retrospectively evaluated. This study was conducted in accordance with the Declaration of Helsinki. Our Institutional Review Committee approved this analysis and waived informed consent because of the retrospective study design.

Local recurrent disease was defined as clinically and/or histopathologically proven recurrent disease within the pelvis. Staging was performed using (diffusion-weighted imaging) magnetic resonance imaging (MRI), computed tomography (CT) scan, and colonoscopy with biopsies if possible. All patients were then discussed in a multidisciplinary rectal cancer board meeting to determine the best treatment strategy. According to Kusters et al., the tumor location was classified into the following subsites: lateral (pelvic sidewall, immediately behind the posterior ischiac spine, in the obturator lymph node compartment, or along the iliac vessels), presacral (predominantly midline, in contact with the sacral bone), anterior (predominantly midline, involving the bladder, uterus, vagina, seminal vesicles, or prostate), anastomosis (after low anterior or low Hartmann, at the staple line), and perineal (perineum, anal sphincter complex with surrounding perianal and ischiorectal space)[23].

Patients who previously received radiotherapy for their primary tumor were re-irradiated with 30.0–30.6 Gy (2.0–1.8 Gy/fraction daily) using a three- or four-field technique, and received concurrent capecitabine 825 mg/ m2 twice daily (on working days). The second group of radiotherapy-naïve patients were irradiated with 50.0–50.4 Gy (2.0–1.8 Gy/fraction daily) using a three- or four-field technique, and also received concurrent capecitabine 825 mg/ m2 twice daily (on working days). In both groups, the radiotherapy target volume was tumor with margin, the mesorectal area, and presacral and internal iliac lymph node regions[24]. Approximately 6 weeks after neoadjuvant treatment, patients were restaged and were then discussed in the multidisciplinary board to determine the clinical response and resection strategy.

Surgery was planned 8–12 weeks after the completion of CRT. The following resections were performed: low anterior resection, abdominoperineal resection, partial pelvic exenteration, total pelvic exenteration, abdominosacral resection, and other type of resection (not organically bound). In the case of a potential irradical resection (R1), intraoperative brachytherapy (IOBT) was scheduled. Frozen sections were not mandatory to determine if IOBT should be performed. A flexible intraoperative template (FIT) was used to cover the irradical area, while 1 9 10 Gy was applied at 1 cm of the FIT.

All specimens were fixed in formalin for at least 24 h. Resection margin status was classified as follows: R0 resection (free margins (>1 mm)), R1 resection (microscopically involved margins (≤ 1 mm)), and R2 resection (macroscopically involved margins)[25]. pCR defines the absence of residual tumor in the totally embedded resection specimen.

During and after neoadjuvant treatment, outpatient visits were scheduled to check the well-being of the patient. Any physical complaints during radiotherapy and chemotherapy were reported in the patients' file by the radiotherapist and medical oncologist, respectively. In retrospect, we graded these symptoms according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5[26]. Acute postoperative toxicity within 30 days after surgery and late postoperative toxicity within 90 days after surgery were reported in the medical file by the surgeon. We graded these symptoms in retrospect according to the Clavien–Dindo classification27 for acute toxicity, and CTCAE version 526 for late toxicity. Follow-up was routinely performed with yearly CT scanning of the thorax and abdomen, regular carcinoembryonic antigen (CEA) testing, and outpatient visits.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software version 23 for Windows (IBM Corporation, Armonk, NY, USA). Proportions were compared using Chi-square tests, and continuous parameters, depending on the distribution of the data, were compared using a t test or Mann–Whitney U test. A two-sided p value of < 0.05 was considered statistically significant. The sensitivity of MRI-based cCR was calculated as the percentage of the number of cCRs on MRI divided by the number of pCRs at histopathological evaluation, while the specificity of MRI-based cCR was calculated as the percentage of the number of non-cCRs on MRI divided by the number of non-pCRs at histopathological evaluation. Sensitivity of the radicality of the resection and frozen sections was calculated as the percentage of the number of R0 resections during surgery or on frozen sections divided by the number of histopathological R0 resections. The specificity was calculated as the percentage of the number of R1 resections during surgery or as a result of the frozen section, divided by the number of R1 resections at histopathological evaluation. Median follow-up was calculated using the reverse Kaplan–Meier method. Overall survival (OS) was calculated from the date of resection until the last follow-up or death by all causes; disease-free survival was calculated from the date of resection until the date of recurrence (local and/or distant), last follow-up, or death by all causes; and local recurrence-free survival (LRFS) was calculated from the date of resection until the date of local recurrence, last follow-up, or death by all causes. OS, DFS, and LRFS were calculated using the Kaplan–Meier method and were tested using the log-rank test.

RESULTS

Between January 2010 and December 2018, 61 patients were diagnosed with locally advanced RRC without distant metastasis at staging (35 reCRT and 26 radiotherapy-naïve patients). All primary tumor and patient characteristics are shown in table 1. Reasons why patients in the long-course CRT group did not receive neoadjuvant radiotherapy for the primary tumor are summarized in table 1. Other reasons for no neoadjuvant therapy in the long-course CRT group were double tumor in the colon and rectum (n=3), previous prostate carcinoma requiring radiotherapy (n=1), adenocarcinoma accidentally found (n=5), and unknown (n=1). In table 2, the RRC tumor and patient characteristics are shown. The median interval between primary tumor resection and diagnosis of RRC was 25 months [interquartile range (IQR) 19–48] in the reCRT group (n=35) and 20 months (IQR 13–41) in the long-course CRT group (n=26). In 85.2% of patients, the RRC was preoperatively histologically proven. Reasons why the RRC was not preoperatively histologically proven were: not able to perform a biopsy (n=2), negative biopsy result with a strong suspicion of recurrent disease (n=4), and not performed but strongly suspected recurrence (n=3).

Table 1 | Patient and treatment characteristics of the primary rectal tumour

	ReCRT (n=35)		Long-course CRT (n=26)		*p*-value
Gender					0.52
Male	20	(57.1)	17	(65.4)	
Female	15	(42.9)	9	(34.6)	
Age (in years)					0.030
Median [IQR]	62	[52-69]	68	[63-73]	
Tumour stage					0.027
cT1-2N0	7	(20.0)	10	(38.5)	
cT1-2N+	1	(2.9)	1	(3.8)	
cT3-4N0	10	(28.6)	6	(23.1)	
cT3-4N+	17	(48.6)	5	(19.2)	
Unknown	-		4	(15.4)	
Type of neoadjuvant treatment					
50.0/50.4 Gy with chemotherapy	19	(54.1)			
25 Gy	15	(42.9)			
Prematurely stopped*	1	(2.9)			
Reason no neoadjuvant treatment					
cT1-2N0 tumour			10	(38.5)	
Rectosigmoid carcinoma			4	(15.4)	
High proximal rectal tumour			2	(7.7)	
Other			10	(38.5)	
Type of resection					0.016
LAR	13	(37.1)	15	(57.7)	
APR	20	(57.1)	4	(15.4)	
TEM	1	(2.9)	4	(15.4)	
Hartmann	1	(2.9)	-		
Total exenteration	-		1	(3.8)	
Other	-		2	(7.7)	
Definite pathology resection					0.37
R0	26	(74.3)	20	(76.9)	
R1	8	(22.9)	3	(11.5)	
R2	-	-	1	(3.8)	
Unknown	1	(2.9)	2	(7.7)	
Histology tumour at histopathological evaluation					0.39
Adenocarcinoma	34	(97.1)	26	(100.0)	
Mucinous	1	(2.9)	-	-	

Data are n (%).

IQR interquartile range; CRT chemoradiotherapy; LAR low anterior resection; APR abdominoperineal resection; TEM transanal endoscopic microsurgery; R0 clear resection margins; R1 ≤ 1mm resection margin between 0 and 1 mm; R2 macroscopic residual tumour.

*Received 46.8 Gy due to radiation proctitis with severe pain.

Table 2 | Patient characteristics of the recurrent rectal tumour

	ReCRT (n=35)		Long-course CRT (n=26)		*p*-value
Gender					0.52
Male	20	(57.1)	17	(65.4)	
Female	15	(42.9)	9	(34.6)	
Age (year)					0.030
Median [IQR]	65	[53-72]	70	[64-75]	
Histology tumour (preoperative)					0.10
Adenocarcinoma	26	(74.3)	26	(100.0)	
Negative result biopsy	4	(11.4)	-		
No biopsy taken	5	(14.3)	-		
Location Marijnen					0.025
Lateral	12	(34.3)	4	(15.4)	
Presacral	4	(11.4)	3	(11.5)	
Anterior	10	(28.6)	2	(7.7)	
Anastomosis	6	(17.1)	13	(50.0)	
Perineum	3	(8.6)	4	(15.4)	
Tumour stage					0.027
cT1-2N+	1	(2.9)	1	(3.8)	
cT3-4N0	28	(80.0)	14	(53.8)	
cT3-4N+	6	(17.1)	10	(38.5)	
cTx*N0	-		1	(3.8)	

Data are n (%).

CRT chemoradiotherapy; IQR interquartile range.

* Tumour cannot be assessed.

The location of the locally advanced RRC was mostly lateral in the reCRT group (34.3%) and at the site of the anastomosis in the long-course CRT group (50.0%). Although not significant, lateral recurrence occurred about twice as often in the reCRT group (34.3% vs. 15.4%, p=0.10). Overall, there was a significant difference in tumor location (p=0.025).

In the reCRT group (n=35), all patients received radiotherapy as scheduled. Chemotherapy was omitted in one patient (2.9%) because of the severe prior adverse effects of capecitabine (severe nausea, vomiting, and diarrhea) and two patients (5.7%) prematurely stopped chemotherapy because of severe diarrhea (n=1) and coronary spasm (n=1).

In the long-course CRT group (n=26), one patient (3.8%) received 5 x 5 Gy radiotherapy only. In addition, chemotherapy was omitted in this patient because of age (80 years) and comorbidities. This patient had less extensive neoadjuvant treatment and was therefore excluded from further analysis, leaving 25 patients in the long-course CRT group, all of whom were treated with radiotherapy and received concurrent chemotherapy (table 3). One patient (4.0%) prematurely stopped chemotherapy because of thrombopenia.

A cCR was seen on MRI imaging in one (2.9%) and five patients (20.0%) in the reCRT and long-course CRT groups, respectively (p=0.029) (table 3). Sensitivity and specificity of MRI-based cCR were 33.3% and 100% in the reCRT group and 66.6% and 86.4% in the long-course CRT group, respectively.

Surgical characteristics are shown in table 3. Every patient underwent surgery (n=60) and the median time between the end of neoadjuvant treatment and surgery was 11 weeks (IQR 9–14) in the reCRT group and 13 weeks (IQR 10–15) in the long-course CRT group. The type of resection in the reCRT group was more than twice as often not organ-specific, but not significant (p=0.17). Frozen sections were taken in only 18 patients (16 in the reCRT group and 2 in the long-course CRT group). The sensitivity and specificity of frozen sections in the total patient group were 85.7% and 72.7%, respectively.

IOBT was performed significantly more often in the reCRT group (14 vs. 4, p=0.046). Overall, an R1 resection was suspected perioperatively in 18 patients. All but one patient received IOBT; in that patient, IOBT was omitted because of a negative frozen section (R0). Once IOBT was performed in a patient in whom it was judged that an R2 resection was accomplished, the frozen section however demonstrated an R1 resection. Overall, 4 of 18 patients (22.2%) were overtreated with IOBT (R0 resection and IOBT performed). In all patients in the long-course CRT group in whom the surgeon judged the resection was R1, IOBT was performed; at histopathological evaluation, 50% of these resections were R1. The accuracy of intra-operative judgment of radicality of resection is accompanied by a sensitivity and specificity of 80.0% (12 perioperative R0/15 pathological R0) and 64.7% (11 perioperative R1/17 pathological R1) in the reCRT group, and 88.9% (16 perioperative R0/18 pathological R0) and 33.3% (2 perioperative R1/6 pathological R1) in the long-course CRT group, respectively.

Histopathologically proven R0 resections were accomplished in 42.9% and 68.0% of patients in the reCRT group and long-course CRT group, respectively (p=0.05). R1 resections were seen in 51.4% of reCRT patients and 24.0% of long-course CRT patients (p=0.033). Overall, 5.7% of patients in the reCRT group were irresectable. In the long-course CRT group, 4% of patients were irresectable, and in 4% of patients an R2 resection was accomplished. There were no significant differences in pCR (8.6% and 12.0% in the reCRT and long-course CRT groups, respectively; p=0.66) (table 3).

Table 3 | Neoadjuvant treatment and surgical characteristics of the recurrent rectal tumour

	ReCRT (n=35)		Long-course CRT (n=25)		*p*-value
ReCRT-group					
30.0/30.6 Gy without chemotherapy	1	(2.9)			
30.0/30.6 Gy with chemotherapy	34	(97.1)			
Completed n(C)RT	32	(94.1)			
Long-course CRT-group					
50.0/50.4 Gy with chemotherapy			25	(100.0)	
Completed n(C)RT			24	(96.0)	
cCR					
Yes	1	(2.9)	5	(20.0)	0.029
Partial	20	(57.1)	13	(52.0)	0.69
No	12	(34.3)	7	(28.0)	0.61
Tumour growth	2	(5.7)	-		0.22
Type of resection					0.24
LAR	-		3	(12.0)	0.035
APR	11	(31.4)	12	(48.0)	0.19
Partial exenteration	3	(8.6)	-		0.13
Total exenteration	9	(25.7)	5	(20.0)	0.61
ASR	1	(2.9)	1	(4)	0.81
Other (not organically bound)	11	(31.4)	4	(12.0)	0.17
IOBT					0.046
No	21	(60.0)	21	(84.0)	
Yes	14	(40.0)	4	(16.0)	
Radicality of resection by PA					0.11
R0	15	(42.9)	17	(68.0)	0.054
R1	18	(51.4)	6	(24.0)	0.033
R2	-		1	(4.0)	0.23
Irresectable	2	(5.7)	1	(4.0)	0.76
pCR					0.44
Yes	3	(8.6)	3	(12.0)	0.66
Partial	-		1	(4.0)	0.23
No	32	(91.4)	21	(84.0)	0.38
Histology tumour at histopathological evaluation					0.45
Adenocarcinoma	30	(85.7)	22	(88.0)	0.80
Mucinous	2	(5.7)	-		0.22
No rest tumour (pCR)	3	(8.6)	3	(12.0)	0.66
Tumour differentiation grade					0.029
Well	8	(22.9)	9	(36.0)	0.27
Well-moderately	5	(14.3)	9	(36.0)	0.050
Moderately	15	(42.9)	1	(4.0)	0.001
Poorly	2	(5.7)	2	(8.0)	0.73
Irresectable	2	(5.7)	1	(4.0)	0.76
pCR	3	(8.6)	3	(12.0)	0.66

Data are n (%).

CRT chemoradiotherapy; n(C)RT neoadjuvant (chemo)radiotherapy; cCR clinical complete response; LAR low anterior resection; APR abdominoperineal reaction; ASR abdominosacral resection; IOBT intra-operative brachytherapy; PA pathology; R0 clear resection margins; R1 ≤ 1mm resection margin between 0 and 1 mm; R2 macroscopic residual tumour; pCR pathological complete response.

No differences were observed in the number of grade I– II (p=0.48) and grade III (p=0.76) tumors, and no grade IV or V toxicities were reported (table 4). Only two patients in the reCRT group experienced grade III toxicity after radiotherapy (n=1, obstruction) and chemotherapy (n=1, diarrhea). Patients who were treated with long-course CRT reported skin toxicities significantly more often (p=0.040); no differences were observed in chemotherapy-related toxicity. In regard to surgery, there were no significant differences in acute or late postoperative toxicity (table 4), and there was no difference between neoadjuvant-related toxicity and interval until tumor recurrence (<1 year or ≥ 1 year between surgery of the primary tumor and the start of neoadjuvant treatment of RRC; p=0.80).

Table 4 | Toxicity related to neoadjuvant chemoradiotherapy and surgery

	ReCRT (n=35)		Long-course CRT (n=25)		*p*-value
Patients who reported toxicity after nCRT (any grade)	17	(48.6)	14	(56.0)	0.57
Highest grade adverse event reported per patient (CTCAE)					
Grade I-II	15	(42.9)	13	(52.0)	0.48
Grade III	2	(5.7)	1	(4.0)	0.76
Toxicity related to radiotherapy (CTCAE)					
Gastrointestinal toxicity	8	(22.9)	7	(28.0)	0.65
Nervous system toxicity	2	(5.7)	1	(4.0)	0.76
Skin toxicity	2	(5.7)	6	(24.0)	0.040
Urinary toxicity	-		1	(4.0)	0.23
Toxicity related to chemotherapy (CTCAE)					
Blood toxicity	1	(2.9)	1	(4.0)	0.81
Cardiac toxicity	1	(2.9)	-		0.39
Gastrointestinal toxicity	4	(11.4)	2	(8.0)	0.66
Nervous system toxicity	-		1	(4.0)	0.23
Skin toxicity	3	(8.6)	-		0.13
Patients who reported toxicity after surgery (any grade)	29	(82.9)	19	(76.0)	0.57
Highest grade adverse event reported per patient (CD/CTCAE)					
Grade I-II	20	(57.1)	14	(56.0)	0.93
Grade III	9	(25.7)	5	(20.0)	0.61
Acute toxicity (CD)					
Gastrointestinal toxicity	7	(20.0)	6	(24.0)	0.71
Infection	8	(22.9)	6	(24.0)	0.92
Neurological toxicity	15	(42.9)	9	(36.0)	0.59
Sexual toxicity	1	(2.9)	-		0.39
Renal toxicity	9	(25.7)	8	(32.0)	0.59
Wound healing disorder	10	(28.6)	5	(20.0)	0.45
Late toxicity (CTCAE)					
Infection	2	(5.7)	-		0.22
Insufficient fracture	1	(2.9)	-		0.39
Neurological toxicity	6	(17.1)	5	(20.0)	0.78
Renal toxicity	1	(2.9)	-		0.39
Wound healing disorder	-		1	(4.0)	0.23

Data are n (%).

CRT chemoradiotherapy; nCRT neoadjuvant chemoradiotherapy; CTCAE Common Terminology Criteria of Adverse Events; CD Clavien-Dindo.

The median follow-up in the reCRT group was 53 months (IQR 25–53), and 38 months (IQR 17–65) in the long-course CRT group. The 3- and 5-year OS for the reCRT group was 64.9% and 21.3%, respectively, and in the long-course CRT group, 3- and 5-year OS was 40.1% and 32.1%, respectively (p=0.82) (figure 1). The median interval between RRC and re-recurrent disease was 13 months (IQR 5–20). Patients in the reCRT group had 3- and 5-year DFS rates of 19.0% and 19.0%, respectively, and in the long-course CRT group, 3- and 5-year DFS was 25.8% and 25.8%, respectively (p=0.63) (figure 2). In the reCRT group, LRFS was 50.7% and 50.7% 3 and 5 years after surgery, and 86.5% and 86.5% in the long-course CRT group, respectively (p=0.17) (figure 3). The use of IOBT does not influence the risk of developing local re-recurrent disease (p=0.44) (figure S1).

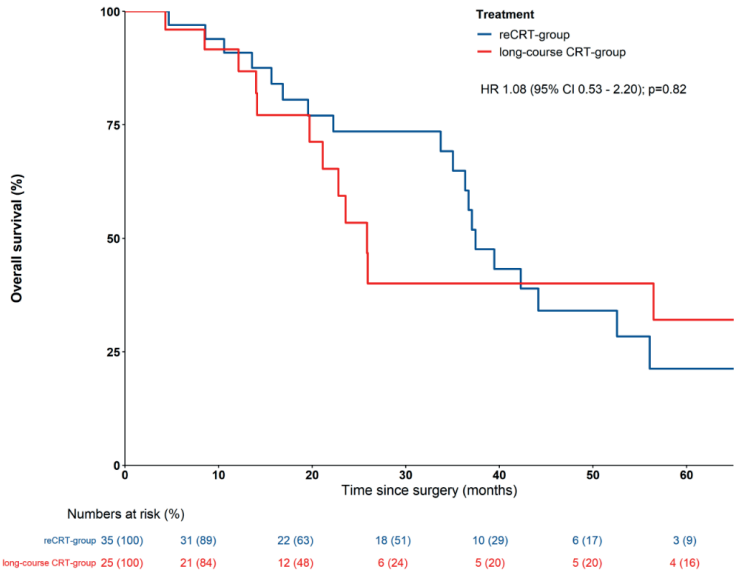

Figure 1 | Overall survival

CRT chemoradiotherapy, HR hazard ratio, CI confidence interval

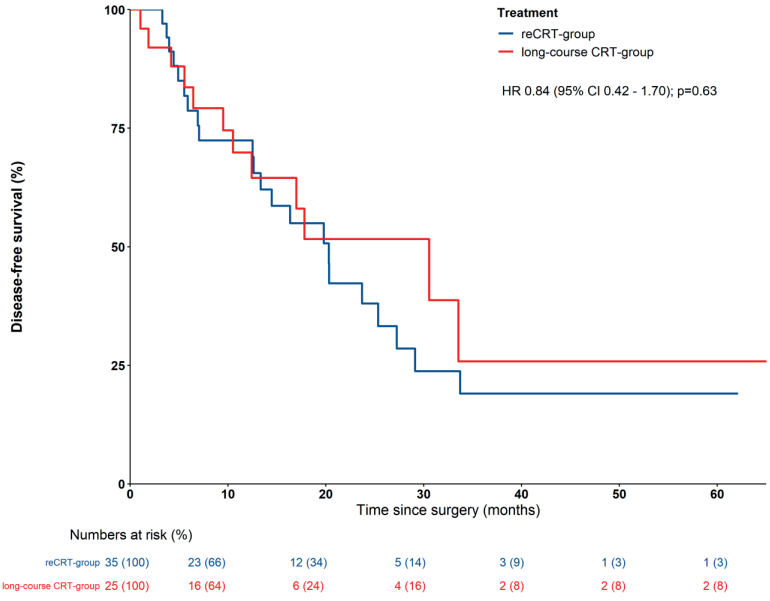

Figure 2 | Disease-free survival

CRT chemoradiotherapy, HR hazard ratio, CI confidence interval

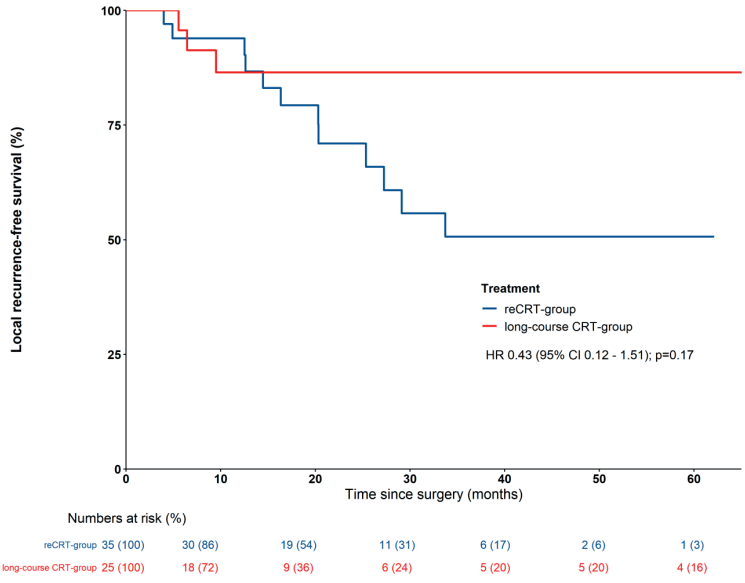

Figure 3 | Local recurrence-free survival

CRT chemoradiotherapy, HR hazard ratio, CI confidence interval

DISCUSSION

The primary purpose of this study was to evaluate toxicity and oncological outcomes in patients with RRC after reCRT compared with long-course CRT.

No acute grade IV or V toxicities were reported. Acute grade III toxicity occurred in two patients in the reCRT group (5.7%, diarrhea and obstruction). Studies with the same re-irradiation regimens (mostly combined with chemotherapy) showed a higher incidence of grade III–V acute toxicity of 6–9%[14,28]. In both these studies, toxicity was also scored retrospectively, which does not explain the difference in acute toxicity. Furthermore, after a higher median re-irradiation dose (34.5–50 Gy), mostly combined with chemotherapy, grade III–IV toxicities occurred in 4–9% of cases[12,15,29]. A recently published meta-analysis showed 11.7% acute grade III or higher toxicity after re-irradiation (2 prospective studies of 11 included studies)[9]. Patients in the long-course CRT group in our study reported significantly more skin toxicity (p=0.040). This could be explained by the fact that patients in the long-course CRT group received much more capecitabine, which is known for its skin toxicity[30].

We have shown 3-year OS rates in the reCRT group of 64.9%; however, in previously conducted studies, using the same regimen, the 3-year OS rates varied between 49% and 66%[14,15,18]. A meta-analysis, in which the radiotherapy doses ranged between 16 and 40.8 Gy, found a 3-year OS rate of 51.7%[9]. Regarding radicality, pCR, OS, DFS, and LRFS, we did not find any significant differences between the two groups, which suggests that re-irradiation is just as effective as irradiation. Furthermore, we demonstrated 3- and 5-year LRFS rates of 50.7% and 50.7% in the reCRT group, while an additional study with a higher median re-irradiation dose showed 3- and 5-year local control of 46.6% and 38.8%, respectively[12]. This suggests that a higher re-irradiation dose does not correlate with better local control. In addition, the study by Alberda et al., in which the same treatment strategy was used, demonstrated 3-year local control of 48.6%, which is comparable with our study[18]. In the case of re-irradiation, radiotherapy response did occur in this group; however, there was the possibility of selection of radiotherapy-resistant tumors that could relapse. In the long-course CRT group, patients had initially relatively low-risk primary tumors (not requiring radiotherapy) that relapsed unexpectedly, which is probably a negative risk factor. In contrast, the reCRT group included patients with intermediate- or high-risk tumors who required radiotherapy as part of their initial treatment, and in which a recurrence could be expected. Therefore, the selection of tumors with differences in biological behavior might have been different.

The location of the recurrence was most often lateral in the reCRT group (34.3%) and at the anastomosis in the long-course CRT group (50.0%). After all, patients in the reCRT group were previously irradiated because the primary tumor was a locally advanced tumor that often recurs at the borders of the radiotherapy field. This has also been confirmed by the Dutch TME trial demonstrating that lateral recurrences occurred in 25% of patients who received radiotherapy (5 x 5 Gy followed by immediate surgery). In addition, that study also showed

that lateral recurrences are associated with poor prognosis[23]. This is because it is more difficult to achieve an R0 resection at the lateral resection borders[1], which may explain the significant difference in the R1 resection rate between the two groups in our study. However, in the reCRT group, it was found there was no difference in survival between lateral recurrences and recurrences at other places (p=0.14, data not shown). Of those patients who did not receive radiotherapy in the TME trial, local recurrences at the site of the anastomosis occurred in 24.4%, which is much lower than the 50.0% found in our study. Furthermore, the TME study showed that preoperative radiotherapy reduced the anastomotic recurrence rate[23], which explains the lower number of anastomotic recurrences in the reCRT group in our study (17.1%).

Although the R1 resection rate was higher in the reCRT group (51.4% vs. 24.0%), this is possibly not explained by the lower radiation dose in the re-irradiation group. After all, patients in the reCRT group were previously irradiated because the primary tumor was a locally advanced tumor that often recurs at the borders of the radiotherapy field, which makes the resection more difficult[31]. Perhaps re-irradiation more often results in non-response. Therefore downsizing of the tumor will not occur, which in turn may hamper a radical resection. An R0 resection was seen in 42.9% of patients in the reCRT group. In studies using a comparable re-irradiation schedule, the R0 resection rate varied between 46% and 70%, while the R0 resection rate was 35.6% after a higher median re-irradiation dose of 40.8 Gy[12,14,18,28]. This demonstrated that there is no association between the median re-irradiation doses and the R0 resection rate. The R0 resection rate after long-course CRT in the study by Alberda et al. was 63%, which is comparable with the 68% found in our study[18].

IOBT was significantly more often used in the reCRT group (40% vs. 16%), which we believe is because it is the last resort in re-irradiated RRC patients, given the fact that patients in the long-course CRT group are still able to receive the re-irradiation schedule in case of re-recurrent disease. The higher number of R1 resections in the reCRT group could also be explained by the use of IOBT, since IOBT is only performed in cases an R1 resection is suspected. However, the use of IOBT does not influence the cumulative probability of developing local re-recurrent disease (p=0.44). The decision to perform IOBT was at the discretion of the surgeon, together with the radiation oncologist. The accuracy to correctly judge the radicality of resection was accompanied by a sensitivity of 80.0% in the reCRT group and 88.2% in the long-course CRT group. This difference could be explained by fibrosis, which could be more prominent in the reCRT group due to radiotherapy. Fibrosis makes a resection more difficult, which could also be the reason why frozen section pathology was more often performed in the reCRT group (45.7% vs. 8%).

In the study by Valentini et al., which had a higher re-irradiation dose (40.8 Gy), the pCR rate was approximately 8.5%[12]; however, in the study by Alberda et al., which used the same re-irradiation regimen as our study, the pCR rate was 4%[18], which is approximately twice as low as in our study (8.6%). The accumulated pCR rate in our study was 10%, which is lower than the 19% found in the study by Voogt et al.[32]. In this retrospective study, patients received induction

chemotherapy consisting of three cycles of CAPOX or four cycles of FOLFOX followed by the same long-course CRT or re-irradiation schedules as in our study[32]. This almost double pCR rate suggests that the use of oxaliplatin may result in more downstaging and down-sizing of the tumor, an hypothesis that is supported by the fact that the R0 resection rate in the total group was higher (63% vs. 53%) in the study by Voogt et al.[32].

Fibrosis often occurs after neoadjuvant treatment of RRC. At restaging with MRI, it is challenging to distinguish fibrosis from tumor tissue, and thus it is difficult to determine if a cCR occurred. This could be the reason for the significant difference in cCR on MRI between the two groups in favor of the long-course CRT group. As these radiotherapy-naïve patients received an overall lower radiotherapy dose to the pelvis compared with the reCRT group, likely results in less fibrosis. Therefore, it could be that patients in the reCRT group are more often under-staged at restaging, whereas patients in the long-course CRT group are over-staged. Another explanation is that recurrent disease could be accompanied by negative selection, with a lower chance of a complete response. It is therefore risky to use a wait-and-watch (W&W) strategy. The oncological outcomes after a W&W strategy are unknown in RRC. In our study, an MRI-based cCR was accomplished in 2.9% of reCRT patients, while the pCR rate in these patients was 8.6%. Therefore, the sensitivity and specificity of MRI-based cCR were 33.3% and 100% in the reCRT group, respectively. In addition, the degree of (pre-existing) fibrosis related to the previous radiotherapy and surgery possibly also led to the difference in non-organ bound resections (31.4% vs. 12.0% in the reCRT and long-course CRT groups, respectively).

Depending on the time interval, normal tissue possibly recovers after radiotherapy. In cases where the interval is ≥ 1 year, it is considered safe to re-irradiate patients with a dose of 30 Gy[13,15]. In the reCRT group, we showed a median interval between prior radiation and the onset of re-irradiation of 29 months. Based on the absence of high-grade toxicities in the current study and the limited toxicity reported in the studies by Valentini et al., Das et al., and Koom et al.[12,15,19], a higher re-irradiation dose (30–40 Gy) could be considered if the interval is ≥ 1 year.

The treatment of RCC has become more sufficient during the last decades. Earlier, we reported an historical cohort of patients from our center, revealing a 5-year OS rate of 19%33 to 32% in the current study. LRFS increased from 30% to 39% 5 years after surgery to 86.5% in patients who received long-course CRT[33,34]. Moreover, in the study by Reerink et al., the distant metastasis rate after the treatment of RRC decreased from 57.5% to 40% in the present study in the case of long-course CRT[33]. There are some possible explanations for the differences. First, there were differences in treatment characteristics; only 12.5% of patients in the study by Reerink et al. received concurrent chemotherapy and some patients received postoperative radiotherapy[33]. Second, MRIs were not performed in the previously conducted studies[33,34]. Third, there was often no standardized follow-up[33]. Finally, the quality of CT scans has increased over the last decades, possibly resulting in better selection.

In the literature, there is as yet no consensus on the best treatment for RRC patients who received (chemo)radiotherapy for their primary tumor; the radiotherapy doses for RRC ranged from 15.0 to 49.2 Gy. In addition, chemotherapy is not always prescribed[35]. This makes it harder to compare the results of our study with the currently available literature. In addition, as in our study, most literature contains heterogeneous data. Other limitations are the retrospective nature of the study, which may have resulted in an underestimation of the treatment-related toxicities and the occurrence of a small sample size, however recurrence of rectal cancer is relatively rare (recurrence rate of 5–9%). Therefore, we would recommend an (inter)national prospective cohort study to consider outcomes and toxicity.

Conclusion

Re-irradiation is well tolerated and is associated with low toxicity and comparable oncological outcomes. Although re-irradiation was associated with lower cCR, there was no difference in pCR. In the re-irradiation group, an irradical resection was more often achieved (not significant), which may be due to the more challenging locations of the recurrence compared with CRT-naïve patients. We conclude that it is safe and feasible to re-irradiate RRC patients.

Acknowledgement

The authors would like to thank all referral hospitals (table S1) for their contribution to the follow-up data.

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SUPPLEMENTAL MATERIAL

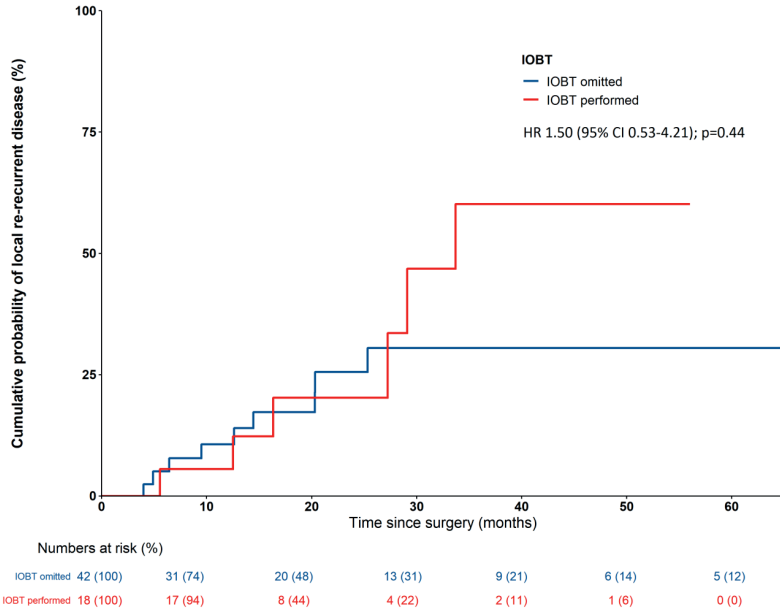
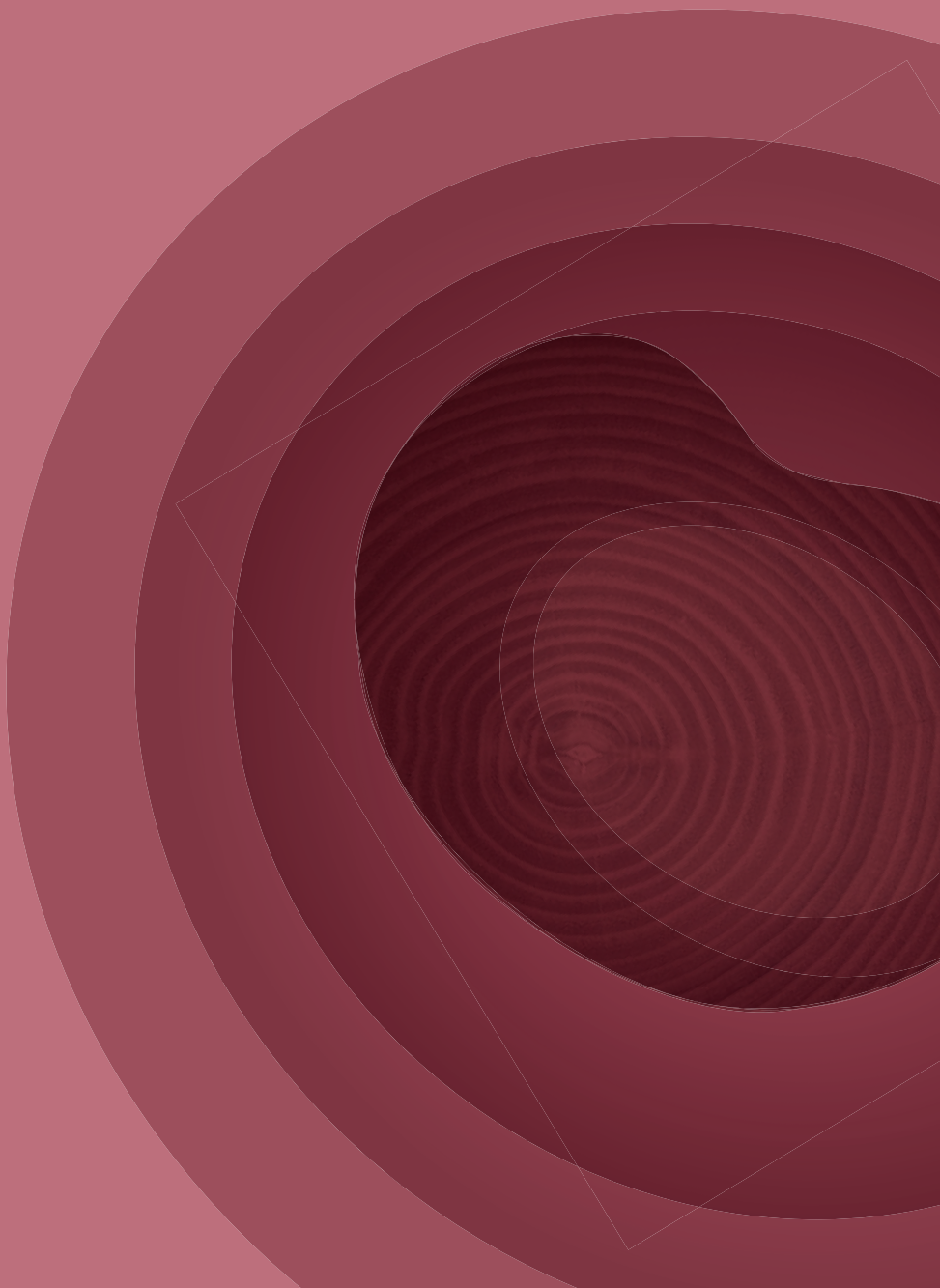


Figure S1 | Cumulative probability of developing local re-recurrent disease

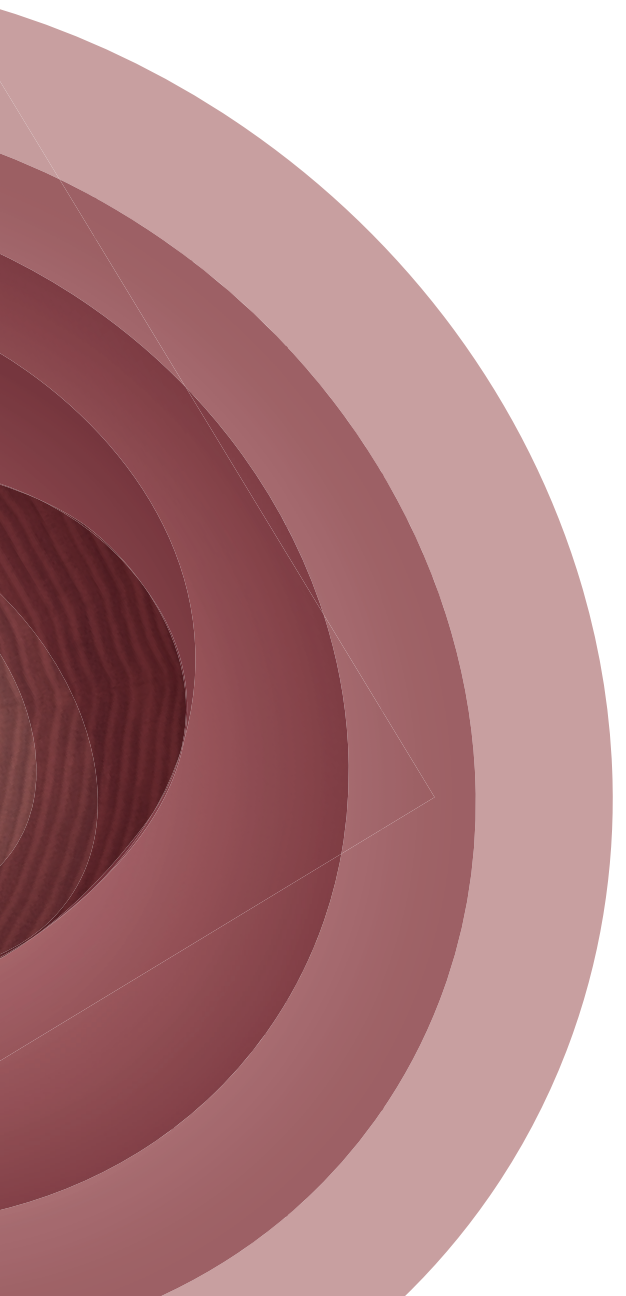
Table S1 | *Participating institutes and collaborative investigators*

Location	Institute	Department	Investigator
Almelo	Ziekenhuisgroep Twente	Department of surgery	I.F. Faneyte
Assen	Wilhelmina Hospital	Department of surgery	S.T. van Vugt
Deventer	Deventer Hospital	Department of surgery	R.J.I. Bosker
Drachten	Nij Smellinghe Hospital	Department of surgery	I.T.A. Pereboom
Enschede	Medisch Spectrum Twente	Department of surgery	P. Steenvoorde
Emmen	Scheper Hospital	Department of surgery	R.A. Schasfoort
Groningen	Martini Hospital	Department of surgery	P.C. Baas
Hardenberg	Röpcke-Zweers Hospital	Department of surgery	M.F. Lutke-Holzik
Heerenveen	Tjongerschans Hospital	Department of surgery	F. Wit
Hoogeveen	Bethesda Hospital	Department of surgery	F.W.H. Kloppenburg
Leeuwarden	Medical Center Leeuwarden	Department of surgery	M.A. Kaijser
Meppel	Diaconessenhuis Meppel	Department of surgery	F.N.L. Versluijs-Ossewaarde
Scheemda	Ommelander ziekenhuis Groningen	Department of surgery	D.P. de Vries
Sneek	Antonius Hospital	Department of surgery	D.A. Hess
Winterswijk	Streekziekenhuis Koningin Beatrix	Department of surgery	B. Inberg
Zwolle	Isala Klinieken	Department of surgery	A.D. van Dalsen



CHAPTER 8

General discussion and future perspectives



GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Background

Forty years ago, the overall survival after the diagnosis of stage I-III rectal cancer was approximately 30-69% and the pelvic recurrence rate was approximately 15-40%[1-6]. Improved imaging techniques, preoperative treatment and surgery according to total mesorectal excision principles, resulted in improved oncological outcomes; the 5-year pelvic recurrence rate was lowered to 4-15% and the 5-year overall survival improved to 69-87% in stage I-III rectal cancer[7-10]. Although the number of local recurrences decreased, the number of distance metastasis did not, with a 5-year distant metastasis rate above 25% in stage II-III rectal cancer[11,12]. Therefore, reducing the number of distant metastasis, and improving quality of life, are key points in the multimodality treatment of patients with locally advanced rectal cancer (LARC).

The rationale for total neoadjuvant treatment

Originally, just as in colon cancer, systemic chemotherapy is given postoperatively. However, its benefit is not clear, mainly due to changing imaging techniques combined with slow accrual of patients in studies after (chemo)radiotherapy ((C)RT) and TME. In addition, a difference in the effect of postoperative therapy between embryological, anatomical and physiological characteristics between the colon and the rectum cannot be ruled out. In case systemic chemotherapy is given preoperatively, it is associated with high compliance ranging from 84-95%[13-17]. Since total neoadjuvant treatment (TNT) is thought to be associated with a decrease in the distant metastases rate, multiple phase II and III trials have been performed in patients with locally advanced rectal cancer[16-19]. In the RAPIDO trial, we demonstrated that the use of TNT resulted in a significant decrease in the distant metastasis rate at 3-year (26.8% vs. 20.0%, p=0.0048) and at 5-year (30.4% vs. 23.0%, p=0.011) (chapter 2 and 4).

Overview total neoadjuvant treatment trials

In the RAPIDO trial, the TNT treatment existed of short-course radiotherapy (scRT) followed by 6 courses of CAPOX (or 9 courses of FOLFOX) followed by surgery (chapter 2). The STELLAR trial also used scRT in the experimental group. However, in their study in both treatment groups, the given systemic chemotherapy consisted of 6 courses of CAPOX (postoperatively in the standard group and 4 courses preoperatively and 2 courses postoperatively in the experimental group)[18]. In the CAO/ARO/AIO-23 trial patients received preoperative CRT and either 3 courses of FOLFOX6 as induction chemotherapy or as consolidation chemotherapy[14]. In the OPRA trial, preoperative induction vs. consolidation chemotherapy in combination with CRT was also investigated, but with 8 courses of FOLFOX16. In the PRODIGE 23 trial, patients received CRT, surgery and 6 courses of mFOLFOX6 postoperatively or 6 courses of FOLFIRINOX preoperatively followed by CRT, surgery and 6 courses of postoperative mFOLFOX6[17].

A doubled pathological complete response (pCR) rate, as a result of preoperative systemic chemotherapy, was seen in the RAPIDO trial (14% vs. 28%) (chapter 2), PRODIGE 23 trial (12% vs. 28%)[17] and in the STELLAR trial (12% vs. 22%)18. In addition, consolidation chemotherapy results in an improved pCR rate/organ preservation compared to induction chemotherapy[14,16]. In all of these randomized trials, no difference in locoregional failure was seen at three years[14,16-18] (chapter 2). However, in the studies with a substantially increased dose of systemic chemotherapy, compared to the standard treatment, a decrease in the distant metastasis rate and an increase in disease-free survival (DFS) (or disease-related treatment failure) was found17 (chapter 2). The STELLAR trial is the only recently published trial which demonstrates an increase in 3-year overall survival after TNT[18].

The effect of waiting time between neoadjuvant treatment and surgery on pathological complete response

The optimal timing between (chemo)radiotherapy and surgery is not clear from the recently published and above-mentioned randomized trials. Traditionally, the waiting time between CRT and surgery was around 6 weeks. Randomized studies have been performed investigating the optimal timing between CRT and surgery. However, conflicting results have been published[20-23]. The lowest pCR rates in these studies were found when surgery was performed within 8 weeks (10.0-15.0%)[20,21,23]. When surgery was performed beyond 8 weeks, the pCR rate varied between 17.4-18.6% in LARC patients[20,23]. The highest pCR rate was found in the study by Akgun et al; they found a pCR rate of 29% when surgery was performed between weeks 10 and 11 after CRT[20]. A meta-analysis demonstrated that an interval of 8 weeks or more is associated with greater odds of a pCR and tumor downstaging[24]. In addition, this higher pCR rate was translated into a reduced distant metastasis rate but not into a reduced locoregional recurrence rate or improved overall survival rate[24]. However, an even longer waiting time between CRT and surgery may increase pelvic fibrosis, as also demonstrated in the RAPIDO trial (chapter 4). Though, according to Garcia-Aguilar et al., more pelvic fibrosis, due to a longer waiting time, does not result in a more technically difficult resection[25]. In addition, a prolonged waiting time could be hazardous for patients with a poor response to preoperative treatment.

Future research on the timing of surgery

Because the optimal timing of surgery in relation to CRT is still controversial, several research is currently being done. For example the TiMiSNAR study (NCT03465982) and the ST812 study (NCT03607370). In these currently recruiting, randomized trials, stage II-III rectal cancer patients who underwent surgery 8 weeks after the end of CRT will be compared to patients who underwent surgery 12 weeks after the end of CRT. The primary outcome of these studies is pCR. Another retrospective cohort study in stage II-III rectal cancer patients is the CRONOS study (NCT04717947), wherein more than 900 patients are compared between a short interval (≤8 weeks), an intermediate interval (8-12 weeks) and a long interval group (>12 weeks). No data from this study are published up till now.

The effect of preoperative chemotherapy on pathological complete response

A non-randomized phase II study by Garcia-Aguilar et al. investigated the effect of the addition of preoperative chemotherapy between long-course CRT and surgery according to TME principles[25]. In the first group, no additional chemotherapy was given, in the second group patients received 2 cycles of mFOLFOX6, the third group received 4 cycles and the fourth group received 6 cycles of preoperative chemotherapy. They demonstrated that no additional chemotherapy was associated with a pCR rate of 18%, while the addition of chemotherapy, and as a result, the increased time interval between CRT and surgery (from 8.5 weeks in group 1 up to 19 weeks in group 4), was associated with pCR rates up to 38% in the group with the most cycles of chemotherapy[25]. As also the time to surgery increased, it is not possible to fully prove that only chemotherapy has an impact on improved pCR rates, however, an increased dose of chemotherapy, correlated with an increasing pCR rate is suggestive of an effect of systemic chemotherapy. In the PRODIGE 23 trial, the time between CRT and TME was the same in both groups, however, the addition of 6 courses of FOLFIRINOX induction chemotherapy also resulted in an increase in pCR rate from 12 to 28%, compared to the other treatment group of the PRODIGE 23 trial[17].

The number of courses of systemic chemotherapy in total neoadjuvant treatment

As part of TNT, the optimal number of courses of preoperative systemic chemotherapy, as induction or consolidation, on DFS is not clear yet.

In colon cancer, postoperative chemotherapy has increased the survival rate. Historically the gold standard to define the benefit of postoperative therapy has been improvement in OS. However, DFS at 3 years appears to be an acceptable surrogate for 5-year OS, especially for stage III disease. In stage III colon cancer, patients previously received 6 months of systemic chemotherapy. However, due to recently published research, the treatment time of systemic chemotherapy decreased to 3 months since it is non-inferior to 6 months (3-year DFS was 76.7% in the 3 months group compared to 77.1% in the 6 months group, p=0.012) and is associated with less toxicity and improved quality of life[26,27]. For example, in patients receiving 6 vs. 3 months of postoperative chemotherapy grade 2 or higher peripheral neuropathy decreased from 58% to 25%, respectively[26,27].

However, providing systemic chemotherapy after TME in rectal cancer is associated with lower compliance compared to postoperative chemotherapy in colon cancer. In the Polish II study, patients with cT3 or cT4 rectal cancer were randomized between an experimental (scRT and 3 cycles of FOLFOX4 preoperative) or standard of care treatment (long-course chemoradiotherapy)[28]. At 3 years, the overall survival rate was improved in the experimental group (73% vs. 65%. p=0.046), whereas there was no difference in DFS between the groups (53% in the experimental group and 52% in the standard of care group). At 8 years, however, there was no difference in overall survival anymore (49% in both groups)[29]. This data suggests that 6 weeks of preoperative chemotherapy is not sufficient. The experimental group of the RAPIDO trial (6 courses of preoperative systemic chemotherapy), was associated with an improved disease-related treatment failure rate compared to the standard of care treatment (20% vs. 27% at 3 years, chapter 2, and 28% vs. 34% at 5-years, chapter 4). The PRODIGE trial

demonstrated that if induction systemic chemotherapy (6 cycles of FOLFIRINOX) is given preoperatively as well, the distant metastases rate decreases and the DFS improves[17]. The non-randomized phase II study of Garcia-Aguilar et al. demonstrated that the 5-year DFS rate was 50% when no additional chemotherapy was prescribed, whereas the 5-year DFS was 76% when the patient received 6 cycles of preoperative chemotherapy and 86% when 4 cycles of preoperative systemic chemotherapy were given[25].

An ongoing trial is the LARCT-US trial from Sweden (NCT03729687). In this phase II study, patients with LARC receive scRT followed by 4 courses of CAPOX and surgery. The rationale for providing 4 courses of preoperative chemotherapy was derived from the previously mentioned colon trials[26,27]. The primary outcome of the LARCT-US trial is pCR and clinical complete response. In addition, DFS, the neoadjuvant rectal score and toxicity will be evaluated. The estimated completion date of the study is June 2024.

Toxicity in the treatment of rectal cancer

Since the introduction of surgery according to TME principles, the cumulative risk of local recurrence at 5 years decreased from 15-45% to 2.7%[10]. In addition, OS improved to 87.5% at 5 years[10]. By adding preoperative treatment, the local recurrence rate improved even further[30]. However, the multidisciplinary treatment of rectal cancer with preoperative (C)RT and surgery, is associated with acute and long-term toxicity and risk of postoperative complications[31-37].

After TME alone, patients experienced fecal incontinence during the day (38%) or at night (17%), anal mucus loss (15%) and anal blood loss (3%)37. The TME-trial also demonstrated that at 24 months, 24% of the male patients and 10% of the female patients were not sexually active anymore after surgery[38]. In addition, sexual functioning, erection disorders, ejaculation disorders, vaginal dryness and dyspareunia are more common after surgery. Urinary incontinence varies between 4-50%[39]. Approximately 35% of patients experience major low anterior resection syndrome[40,41]. In case of major low anterior resection syndrome, patients could experience variable unpredictable bowel function, altered or increased stool frequency, painful stools, emptying difficulties, urgency, incontinence and/or soiling.

Watch-and-wait

Due to the reported toxicity after surgery, organ preservation after neoadjuvant treatment has gained interest to prevent patients from unnecessary toxicity and improve their quality of life[42-46]. Habr-Gama and colleagues were the first who described a watch-and-wait strategy for rectal cancer patients with a clinical complete response[42]. In their study, the 5-year overall survival was 88% (resection group) vs. 100% (watch-and-wait group) and the 5-year DFS was 83% in the resection group vs. 92% in the watch-and-wait group[42]. Habr-Gama et al. also demonstrated that watch-and-wait patients had statistically significantly higher resting pressure (51 mmHg vs. 31 mmHg) and squeeze pressure (146 mmHg vs. 102 mmHg) of the anal sphincter and rectal capacity (145 ml vs. 103 ml) compared to patients who underwent local excision[46]. In a study by Hupkens et al., quality of life results improved after a watch-and-

wait strategy compared to patients who underwent TME[45]. Moreover, several studies suggest that the OS rate in patients in the watch-and-wait group is comparable to those patients who achieve a pCR after radical surgery[42,47-51].
Since randomized trials investigating TNT demonstrated improved pCR rates of up to 28%, a watch-and-wait strategy could be beneficial for patients seeking organ preservation[16-19] (chapter 2).

Several clinical trials are currently being conducted on the watch-and-wait strategies (e.g. NCT05000697 (CCHOWW-trial), NCT03840239 (TESS trial) NCT04095468 and NCT04009876). Most TNT strategies include oxaliplatin-containing systemic chemotherapy which is associated with increased (neuro)toxicity rates compared to neoadjuvant CRT (chapter 3). Approaches which could probably minimize the cumulative neurotoxicity are: interrupting and reintroducing oxaliplatin administration, lengthening the duration of infusion, various pharmacologic agents (i.e., calcium/magnesium, glutathione, etc.) and antioxidant[52].

Immunotherapy in the treatment of rectal cancer
In the last years, tumor microenvironment has emerged as an important source of potential therapeutic targets. One of these targets is PD-L1 and CTL4. Immunotherapy (for example pembrolizumab, which is an anti-PD-L1 antibody) can eliminate tumor cells and metastases by activating the immune system[53]. To date, promising results of immunotherapy have been published in colon cancer patients with metastatic disease and with microsatellite instability-high (MSI-H) in which high clinical and pathological complete response rates are seen[54-56]. For example, André et al. showed that pembrolizumab was associated with higher progression-free survival (17 months vs. 8 months), complete or partial response (44% vs. 33%), and fewer disease-related adverse events grade 3 or higher (22% vs. 66%) in colorectal cancer[54]. In the Netherlands, pembrolizumab is used as first-line treatment in the treatment of patients with metastasized MSI-H colorectal cancer. In addition, Chalabi et al. demonstrated that the combination of ipilimumab and nivolumab in colon cancer results in a 100% pathological response (of which 57% pathological complete response) in MSI-H patients[55]. A small phase 2 study by Cercek et al. found 100% cCR after using dostarlimab in LARC[56]. This suggests that in patients with rectal cancer with an MSI-H tumor more often organ preservation could be accomplished by using immunotherapy. However, the prevalence of MSI-H in colorectal cancer patients is approximately 5-20% (depending on tumor stage and ethnicity of the population)[57]. Currently, many trials are investigating different immunotherapy regimens in MSI-H and microsatellite-stable rectal cancer patients (e. g. NCT03854799, NCT04643041, NCT04357587). Results have to be awaited. Besides immunotherapy, other targets could be of added value in colorectal cancer, since the response to neoadjuvant treatment is heterogeneous in (colo)rectal cancer. Identification of other cancer pathways on genetic, proteomic and epigenetic level can contribute to a better understanding of colorectal cancer. For example, circulating tumor DNA is thought to be an effective indirect predictive biomarker in metastasized colorectal cancer patients and is currently investigated in trials (NCT05629442, NCT05081024).

Radiotherapy and immunotherapy in the treatment of rectal cancer

Radiotherapy is also responsible for increasing the expression of immune checkpoints, which results in changes in the tumor microenvironment[58]. Radiotherapy can induce the upregulation of PD-L1 expression in tumor tissue. The combination of radiotherapy and immunotherapy could therefore result in an even more pronounced tumor response. However, it is not clear whether immunotherapy should be provided as induction or as consolidation therapy. This is currently investigated in the multicenter, phase II, TORCH trial (NCT04518280). In this trial, MSI-H and microsatellite-stable patients are included. The combination of radiotherapy (with or without preoperative chemotherapy) and immunotherapy is currently also being investigated in other trials (e. g. NCT04663763, NCT05507112, NCT05215379, NCT04558684, NCT05215379).

Local recurrence

Although high-risk rectal cancer patients were included in the RAPIDO trial (approximately 30% cT4 tumors), a high response was seen on MRI after preoperative treatment. Based on the post-treatment MRI, downstaging was accomplished in 80.1% of the patients in the experimental group and in 70.1% in the standard of care group ($p<0.0001$). The decision of the surgeon to perform a TME in the experimental group in 92% compared to the standard of care group in 88%. Besides, based on the histopathology results, downstaging was accomplished in 93.0% of the experimental group and in 87.3% of the standard of care group ($p=0.008$). The pCR rate was significantly higher in the experimental group compared to the standard of care group (28% vs. 14%) (chapter 2). Despite more downstaging in the experimental group, the R0-resection rate was comparable between the groups (both 90%) (chapter 4). Chapter 4 demonstrated that at 5 years, locoregional recurrence occurred more often in the experimental group (10% vs. 6%), they were found more often at the anastomosis and presacral compared to the standard of care group. The 3-year locoregional recurrence rate in other TNT trials is comparable to the RAPIDO trial[16-19] (chapter 2).

A higher rate of local recurrences in the experimental group of the RAPIDO trial can be explained in several possible ways. At first, surgery in the TNT strategy of the RAPIDO trial is delayed; the overall treatment time in the experimental group is 40 weeks compared to 25 weeks in the standard of care group. This could be disadvantageous for non-responders or poor responders. In addition, prolonged preoperative systemic chemotherapy could yield a more fragile or fibrotic mesorectum and poorer specimen quality. This is supported by the fact that more breached mesorectal fascia planes were described in the EXP group. Next to this, a more fragmented way of tumor response can happen after intensive neoadjuvant chemotherapy and this way may result in a more difficult intra-operative but also pathological assessment to conclude a definite R0 resection. Finally, since TNT is associated with a high downstaging and downsizing rate, less extensive surgery might be performed leading to less wide resection margins. This is supported by the fact that less APRs have been performed in the experimental group versus the standard of care group in the RAPIDO trial (chapter 4). Further in depth analysis on this topic is currently performed, with extensive review of radiology, pathology, surgical planning and radiotherapy fields.

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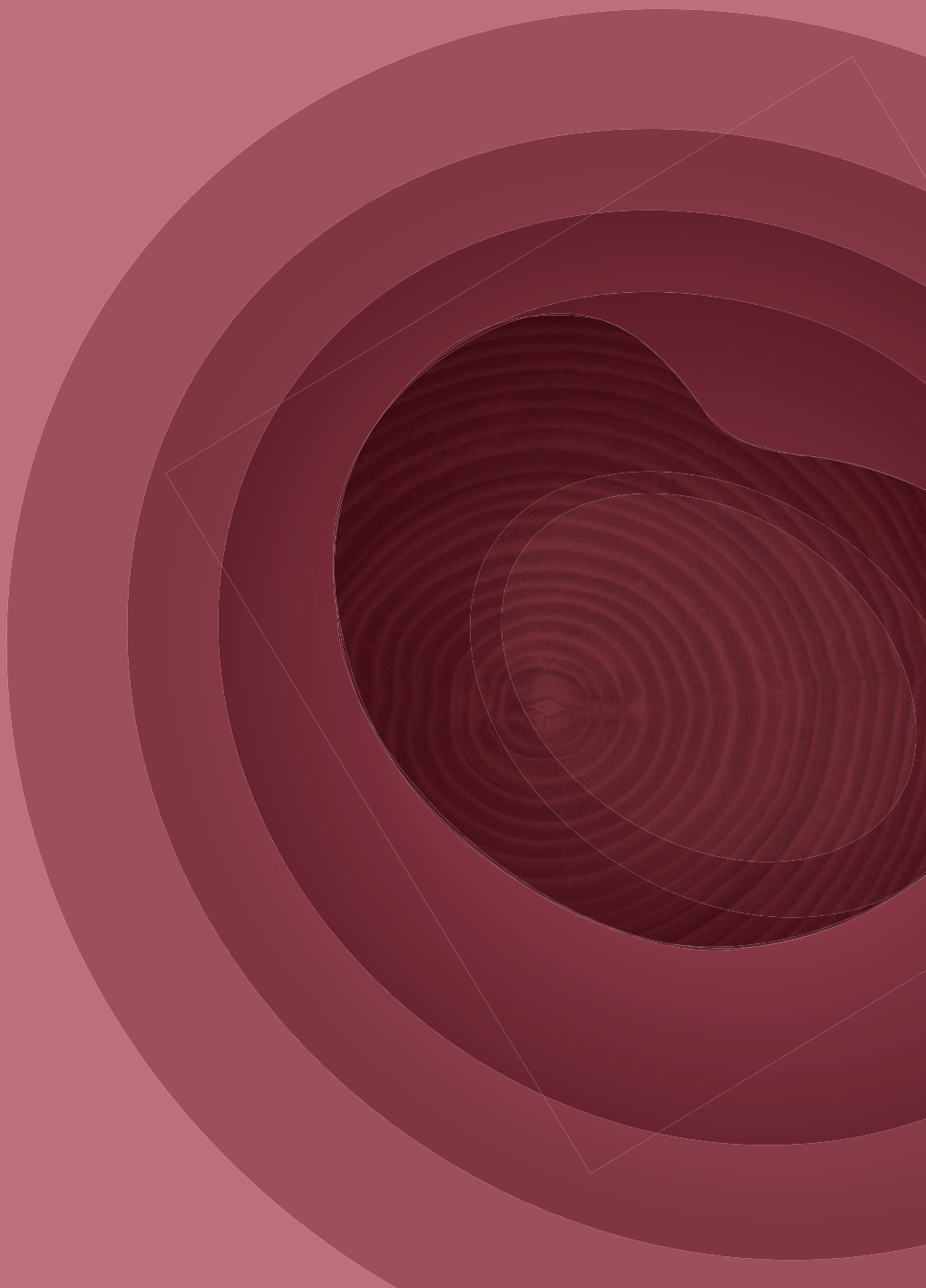

APPENDICES

NEDERLANDSE SAMENVATTING

Veertig jaar geleden was de totale overleving na de diagnose van stadium I-III rectumcarcinoom ongeveer 30-69% en het recidiefpercentage in het kleine bekken ongeveer 15-40%. Verbeterde beeldvormingstechnieken, preoperatieve behandeling en chirurgie volgens de principes van totale mesorectale excisie resulteerden in betere oncologische resultaten; het recidiefpercentage in het bekken na 5 jaar werd verlaagd tot 4-15% en de 5-jaars overleving verbeterde tot 69-87% bij stadium I-III rectumcarcinoom. Hoewel het aantal lokale recidieven afnam, nam het aantal afstandsmetastasen niet af. In stadium II-III rectumcarcinoom is het percentage afstandsmetastase na 5 jaar meer dan 25%. Derhalve zijn vermindering van het aantal afstandsmetastasen en verbetering van de levenskwaliteit belangrijke punten in de multimodale behandeling van patiënten met lokaal gevorderd rectumcarcinoom (LARC).

In **hoofdstuk 2** werd de experimentele (EXP) en de standaardbehandeling (STD) van de RAPIDO-studie vergeleken. Het primaire doel van deze studie was een afname van het aantal ziekte-gerelateerde falen van de behandeling na 3 jaar na de EXP-behandeling in vergelijking met de STD-behandeling. Ook werd de algemene overleving en de acute toxiciteit na beide behandelingen geëvalueerd. De RAPIDO-studie toonde een significante afname van de 3-jaars cumulatieve kans op ziekte-gerelateerd falen van de behandeling van 23,7% in de EXP- en 30,4% in de STD-groep (p=0,019). Dit statistisch significante verschil werd verklaard door de afname van de cumulatieve kans op afstandsmetastase op 3 jaar in de EXP-groep (20,0% vs. 26,8%; p=0,0048). Er werd geen verschil gevonden in de cumulatieve kans op locoregionaal falen na 3 jaar (8,3% in de EXP- vs. 6,0% in de STD-groep; p=0,12). De pathologische complete respons werd verdubbeld; 14% in de STD-groep en 28% in de EXP-groep. Daarnaast werd er geen verschil gevonden in de 3-jaars algehele overleving, deze was 89,1% in de EXP-groep en 88,8% in de STD-groep (p=0,59). De meest voorkomende graad 3 of hoger bijwerking tijdens de preoperatieve therapie in beide groepen was diarree (18% in de EXP-groep en 9% in de STD-groep) en tijdens postoperatieve chemotherapie was dit neurologische toxiciteit in de STD-groep (9%). Ernstige bijwerkingen traden op bij respectievelijk 38%, 34% en 34% van de patiënten in de EXP-groep, in de STD-groep zonder postoperatieve chemotherapie en in de STD-groep met postoperatieve chemotherapie. De verbeterde uitkomsten in de EXP-groep zouden kunnen wijzen op de grotere doeltreffendheid van preoperatieve systemische chemotherapie in vergelijking met postoperatieve chemotherapie. Daarom kan de EXP-behandeling worden beschouwd als een nieuwe behandelingsoptie bij patiënten met een vergevorderd rectumcarcinoom.

In **hoofdstuk 3** werd de kwaliteit van leven en darmfunctie na 3 jaar onderzocht. Tevens werd de late toxiciteit na 6, 12, 24 en 36 maanden in de EXP- en de STD-groep van de RAPIDO-studie geëvalueerd. Kwaliteit van leven en darmfunctie werd gescoord door patiënten die gevalideerde EORTC- vragenlijsten en LARS-vragenlijsten (specifieke klachten na rectum resectie) hadden ingevuld. De gebruikte EORTC-vragenlijsten waren de QLQ-C30 (algemene kwaliteit van leven), QLQ-CR29 (kwaliteit van leven bij colorectale kankerpatiënten specifiek)

en QLQ-CIPN20 (chemo-geïnduceerde perifere neurologische toxiciteit). Late toxiciteit werd gescoord door de behandelend arts tijdens de follow-up (poliklinische bezoeken). Voor een eerlijke vergelijking werden niet alleen de twee behandelingsgroepen vergeleken, maar werd de STD-groep verder onderverdeeld in patiënten die wel (STD+) en geen (STD-) postoperatieve chemotherapie kregen. Er werd geen statistisch significant verschil gevonden tussen de twee groepen wat betreft de EORTC QLQ-C30, QLQ-CR29 en LARS-vragenlijsten op 3 jaar. Sensorische symptomen (meestal in de voeten) traden echter significant vaker op in de EXP-groep in vergelijking met alle patiënten uit de STD-groep, maar niet in vergelijking met de STD+-patiënten. Elke toxiciteit van elke graad was vergelijkbaar tussen de EXP-groep en STD-groepen op alle tijdstippen, evenals graad ≥ 3 toxiciteit. Neurotoxiciteit graad 1-2 kwam echter significant vaker voor in de EXP-groep en STD+- groep op alle tijdstippen in vergelijking met de STD--groep. Neurotoxiciteit van graad ≥ 3 trad slechts op bij een zeer kleine minderheid (1%) van de EXP-patiënten. Concluderend is er 3 jaar na de operatie geen verschil in levenskwaliteit. Patiënten uit de EXP-groep ervoeren echter vaker graad 1-2 neurotoxiciteit.

Patronen van locoregionaal falen na de EXP-behandeling van de RAPIDO-studie werden vergeleken met de STD-behandeling in **hoofdstuk 4**. Locoregionaal falen werd gedefinieerd als vroeg locoregionaal falen (geen resectie (behalve orgaan sparend of R2-resectie) en locoregionaal recidief na een R0/R1-resectie. Bij de mediane follow-up van 5,6 jaar werd locoregionaal falen vaker vastgesteld in de EXP-groep (54/460 (12%) vs. 36/446 (8%); p=0,07). Patiënten in de EXP-groep werden significant vaker behandeld met 3-dimensionale conforme radiotherapie (3D-CRT) (p=0,029). Daarnaast werd een locoregionaal recidief na een R0/R1-resectie statistisch significant vaker vastgesteld in de EXP-groep (44/431 (10%) vs. 26/428 (6%); p=0,027). Bij de EXP-patiënten met een locoregionaal recidief werd vaker een doorbroken mesorectum gevonden (9/44 (21%) vs. 1/26 (4%); p=0,048). Via Cox-regressie werd gevonden dat de EXP-behandeling, vergrote laterale lymfeklieren, positieve circumferentiële resectiemarge, tumorafzettingen en positieve lymfeklieren bij pathologie onderzoek significante (onafhankelijke) voorspellers waren voor het ontwikkelen van een locoregionaal recidief. Mede vanwege het kleine absolute aantal locoregionale recidieven (44 vs. 26) werd er geen statistisch significant verschil gevonden in de locatie van het locoregionaal recidief. Wel werd een locoregionaal recidief numeriek vaker vastgesteld bij de anastomose en presacraal in de EXP-groep. De algehele overleving na locoregionaal falen was vergelijkbaar tussen beide groepen (HR 0,76 [95%CI 0,46-1,26]; p=0,29). In hoofdstuk 2 toonden wij de oncologische uitkomsten in de RAPIDO-studie na drie jaar. In hoofdstuk 4 hebben wij een update gegeven van de oncologische uitkomsten na vijf jaar follow-up. Na vijf jaar is er nog steeds een statistisch significant verschil in ziekte-gerelateerd falen van de behandeling in het voordeel van de EXP-groep (27,8% vs. 34,0%; p=0,048), wat wordt verklaard door een statistisch significant verschil in afstandsmetastasen (23,0% vs. 30,4%; p=0,011), allen in het voordeel van de EXP-groep. De algehele overleving was vergelijkbaar tussen de twee groepen (81,7% in de EXP-groep vs. 80,2% in de STD-groep; p=0,50). Concluderend, is de

EXP-behandeling geassocieerd met een verhoogd risico op een locoregionaal recidief, terwijl de EXP-behandeling wel nog steeds gepaard gaat met een significante afname van ziekte-gerelateerd falen van de behandeling met name door minder afstandsmetastasen na 5 jaar.

De waarde van postoperatieve chemotherapie in de STD-groep van de RAPIDO-studie is bestudeerd in **hoofdstuk 5**. In deze studie werden patiënten uit de STD-groep die een curatieve resectie ondergingen en postoperatieve chemotherapie kregen (pCT+ groep) vergeleken met patiënten uit de STD-groep die geen postoperatieve chemotherapie kregen (pCT- groep). Bovendien werden patiënten uit de pCT+-groep die ten minste 75% van de voorgeschreven chemotherapiecycli kregen (pCT≥75%-groep), vergeleken met patiënten die geen pCT kregen (pCT-/-groep). De cumulatieve kans van ziektevrije overleving, afstandsmetastasen, locoregionaal recidief en algehele overleving werd geanalyseerd met behulp van Cox-regressie. De analyses werden gecorrigeerd voor confounders door middel van propensity score stratificatie (PSS). De voor PSS gecorrigeerde analyses lieten de volgende hazard ratio's zien bij vergelijking van de pCT+ met de pCT- groep: ziektevrije overleving; HR 0,78 [95%CI 0,53-1,14]; p=0,20, afstandsmetastasen; HR 0,80 [95%CI 0,51-1,26]; p=0,33, locoregionaal recidief; HR 0,74 [95%CI 0,26-2,15]; p=0,58 en algehele overleving; HR 0,82 [95%CI 0,49-1,37]; p=0,44. De voor PSS gecorrigeerde analyses voor pCT≥75% versus pCT-/- op alle eindpunten lieten hazard ratio's zien tussen ongeveer 0,5-0,8. Alle 95%-betrouwbaarheidsintervallen omvatten echter de 1. Concluderend suggereren onze resultaten een voordeel van pCT voor patiënten met lokaal gevorderde rectumcarcinoom die worden behandeld met preoperatieve chemoradiotherapie van 20-25%. Compliant zijn aan de postoperatieve chemotherapie geeft een extra voordeel van 10-20%. De verschillen zijn echter niet statistisch significant.

In hoofdstuk 6 werd de klinische selectiestrategie voor intra-operatieve brachytherapie (IOBT) bij patiënten met lokaal gevorderde rectumcarcinoom en het recidief rectumcarcinoom onderzocht. Daarnaast werden de acute en late toxiciteit en de oncologische uitkomsten bestudeerd. Door intra-operatieve inspectie van de resectiemarge in relatie tot preoperatieve MRI-beelden werd bepaald of een resectie radicaal was. Op indicatie werden vriescoupes genomen. Bij een vermoedelijke R1-resectie werd IOBT toegepast. Van de 122 patiënten waarbij de tumor werd verwijderd, kregen 42 patiënten (34%) IOBT. Van de 42 patiënten die IOBT kregen, had 54,8% een histopathologisch bewezen R1-resectie. In 54,8% van de gevallen werd dus terecht IOBT gegeven. Van de 80 patiënten bij wie IOBT achterwege werd gelaten, hadden 65 patiënten een histopathologisch bewezen R0-resectie. IOBT werd dus terecht achterwegen gelaten in 81,3% van de gevallen. Bij de LARC-patiënten (n=70) werd 58,3% van de patiënten overbehandeld (R0, met IOBT) en 10,9% onderbehandeld (R1, zonder IOBT). In het geval van een recidief rectumcarcinoom (n=52) werd echter 26,5% van de patiënten onderbehandeld. Er werden geen significante verschillen gevonden in acute en late toxiciteit tussen de groepen met en zonder IOBT. Aangezien een relatief groot aantal patiënten met recidief rectumkanker onderbehandeld was (26,5%), en IOBT gepaard gaat met aanvaardbare toxiciteit, is IOBT voor alle patiënten met een recidief rectumcarcinoom die risico lopen op een R1-resectie te overwegen.

In **hoofdstuk 7** werd de toxiciteit en de oncologische resultaten na her-bestraling of primaire chemoradiatie bij patiënten met recidief rectumcarcinoom onderzocht, met aanvullend de klinische en pathologische complete respons en radicaliteit van de resectie. Patiënten met recidief rectumcarcinoom kregen radiotherapie in een dosis van 30,0-30,6 Gy (en gelijktijdig capecitabine) indien de patiënt ook al radiotherapie had gehad bij de primaire tumor (reCRT-groep). Indien de patiënt voor de primaire tumor nog geen radiotherapie had gehad, dan kreeg de patiënt chemoradiotherapie (50,0-50,4 Gy en gelijktijdige capecitabine, CRT-groep). In totaal kregen 60 patiënten de neoadjuvante (chemo)radiotherapie gevolgd door chirurgie, 35 patiënten (58,3%) in de reCRT-groep en 25 patiënten (41,7%) in de CRT-groep. Er waren geen significante verschillen in algehele overleving (p=0,82), ziektevrije overleving (p=0,63) en lokaal recidiefvrije overleving (p=0,17) tussen de groepen. Patiënten in de CRT-groep rapporteerden meer huidtoxiciteit (p=0,040). Er werden geen verschillen waargenomen in late toxiciteit. In de CRT-groep werd een significant hogere klinische complete respons waargenomen (p=0,029). Er was geen verschil in pathologische complete respons (p=0,66). De behandeling van patiënten met recidief rectumcarcinoom met her-bestraling is vergelijkbaar met chemoradiotherapie wat betreft toxiciteit en oncologische uitkomsten. De bevindingen van deze studie suggereren dat het veilig en haalbaar is om patiënten met een recidief rectumcarcinoom opnieuw te bestralen.

DANKWOORD

Het introductiegesprek van prof. Hospers over de start van de coschappen in het UMCG, en het gesprek over onderzoek wat daaruit volgde, bleek het begin te zijn van dit proefschrift. De afgelopen jaren heb ik met veel plezier en enthousiasme mogen werken aan mijn onderzoek. Echter was het niet zo'n mooie reis geweest zonder de hulp van een fantastisch team om mij heen.

Naast alle patiënten die hebben deelgenomen aan de studies, wil ik een aantal mensen in het bijzonder bedanken. Om te beginnen wil ik mijn (co)promotoren **prof. dr. G.A.P. (Geke) Hospers, dr. B. (Boudewijn) van Etten** en **prof. dr. C.J.H. van de Velde** bedanken.

Beste **Geke**, dank voor alle fijne gesprekken die we samen hebben gevoerd. Vaak als ik op je kamer langskwam, of later telefonisch toen ik in Deventer woonde, ging het over werk en konden we daarna heerlijk kletsen over van alles en nog wat. Voor mij ben en was je een veilige haven in de wereld van de wetenschap. Onze brainstorm sessies over onderzoek kon ik altijd erg waarderen. Tegen mijn familie heb ik wel eens gezegd dat jij mijn moeder in het onderzoek was.

Beste **Boudewijn**, waar Geke mijn moeder in het onderzoek was, was jij mijn vader. Ik zie mijzelf nog zo jouw kamer binnenlopen de eerste keer, super spannend was dat. Al snel gaf ook jij mij dat veilige gevoel. Naast mijn copromotor was je ook mijn begeleider van mijn semi-arts stage. Op zowel wetenschappelijk als medisch inhoudelijk vlak, heb ik veel van je geleerd, waarvoor dank.

Beste **prof. dr. C.J.H. van de Velde**, ook u wil ik hartelijk danken voor de fijne samenwerking. Uw enorme hoeveelheid kennis op het gebied van het locally advanced rectum carcinoom heeft mij zeker verder gebracht.

Tevens wil ik graag de leescommissie, bestaande uit **prof. dr. J.H.W. de Wilt, prof. dr. J.A. Langendijk** en **prof. dr. W.B. Nagengast**, bedanken voor het beoordelen van mijn proefschrift.

Daarnaast waren de andere leden van PI's (principal investigators) van de RAPIDO-studie ook zeer nauw betrokken bij een groot deel van de totstandkoming van mijn proefschrift. Ik wil dan ook **prof. dr. C.A.M. (Corrie) Marijnen, prof. dr. B. (Bengt) Glimelius** en **assoc. prof. dr. P.J. (Per) Nilsson** ontzettend bedanken voor hun tomeloze inzet.

Beste **Corrie**, ik zou iets kunnen zeggen over mijn waardering voor je kritische blik op de manuscripten die ik heb mogen schrijven. Echter weet ik dat je dit al vaak genoeg gelezen hebt. Ik wil je vooral bedanken voor de fijne en laagdrempelige samenwerking. Samen in Madrid nog even mijn presentatie voor de ESTRO oefenen, heb ik bijvoorbeeld als zeer prettig ervaren.

Dear **Bengt**, it was an honour and pleasure working with you. In my opinion you are our walking encyclopaedia. I always appreciated your fast responses to emails we sent you. Even when you are 'out of civilisation', you are a quick responder. It remains unfortunate that it was not possible to work in your lab in Uppsala because of the COVID-19 pandemic. But thank you for your hospitality when I came to your lab for one week.

Dear **Per**, I would like to thank you gratefully for your valuable feedback. You always come up with something new to investigate. Sharp as a knife I would say.

Daarnaast had ik mijn RAPIDO manuscripten ook zeker niet kunnen schrijven zonder de hulp van **prof. dr. H. (Hein) Putter, Renu Bahadoer, Wouter Zwart, Elma Meershoek-Klein Kranenbarg** en **Annet Roodvoets**.

Best **Hein**, jij bent de spil in het web wat statistiek betreft. Ik heb veel van je geleerd maar was ook heel blij dat ik op je terug kon vallen in momenten van statistische-paniek.

Renu, mijn RAPIDO-maatje, de aantal uren dat wij elkaar gesproken hebben, of het nou in het echt was, via skype, via teams of via de telefoon, zijn ontelbaar. Bloed, zweet en tranen hebben we met elkaar gedeeld. Maar kijk eens even wat we samen hebben neergezet. Ik ben trots op ons werk. Kill two birds with one stone.

Wouter, mijn Groningse opvolger op het prachtige RAPIDO-project. Een betere opvolger had ik mij niet kunnen wensen. Ik hoop van harte dat wij in de toekomst in de chirurgische wereld nog vaker mogen samen werken.

Beste **Elma** en **Annet**, hartelijk dank voor jullie tomeloze inzet voor de RAPIDO-studie. Met een grote studie als de RAPIDO-studie is en was het voor ons arts-onderzoekers fijn dat jullie er altijd waren en het overzicht hadden over de data.

Mijn collega's van de Y3 en later U4 wil ik bedanken voor de gezellige tijd. Helaas gooide COVID-19 veel roet in het eten waardoor we maar een jaar echt met elkaar op de kamer hebben gezeten. Ondanks dat, **Annemarie, Bart, Bertha, Daan, Ellen, Gabriela, Harm, Jahlisa, Jasper, Johannes, Jorianne, Laura, Pim, Roos, Sara** en **Wouter**, bedankt voor de leuke tijd en pauze momentjes die we met elkaar hebben gedeeld.

Ook de collega's van de afdeling chirurgie van het **Deventer ziekenhuis**, het **Martini Ziekenhuis** en het **UMCG** wil ik bedanken. In het Deventer Ziekenhuis heb ik mijn eerste stappen gezet als dokter. In het Martini Ziekenhuis mocht ik mij als ANIOS verder verfijnen waardoor ik kon en mocht solliciteren voor de opleiding tot chirurg. Sinds juli van dit jaar ben ik begonnen aan de opleiding tot chirurg in het UMCG.

Lieve **familie**, dank voor alle interesse tijdens mijn geneeskunde studie en het schrijven van mijn proefschrift.

Verder wil ik de mensen die mij het aller dierbaarst zijn extra bedanken.

Om te beginnen met jou lieve **May**. Je bent mijn allerbeste vriendin sinds we vanaf HAVO 2 bij elkaar in de klas zaten. Een onafscheidelijk duo zijn we samen; EsMay. Om jou te vragen als mijn paranimf was voor mij dan ook niet meer dan logisch. Ik ben heel blij dat jij met mij het pad bewandeld hebt van de HAVO tot aan nu. Dank dat je altijd een luisterend oor voor mij wilt zijn. Dank dat je mij soms naar de Plaza Sportiva sleept. Dank dat jij, jij bent. Ik ben super trots op je.

Lieve **Nadine**, dat klinkt raar. Dus noem ik je, zoals altijd, ook hier **Pien**. Lieve Pien, twee handen op een buik, dat zijn wij. Ook al ben je mijn 'kleine' zusje, en zeggen mensen dat wij qua uiterlijk niet veel op elkaar lijken, van binnen zijn we één. Twee zielen, één gedachte. Daar ben ik je ontzettend dankbaar voor. Gelijk vanaf de start van mijn PhD-traject, had ik al gevraagd of jij mijn paranimf wilde zijn. Dit speciale moment van promoveren, wil ik juist zo graag delen met jou en May aan mijn zijde. De stap die jij gaat zetten de aankomende tijd is echt heel erg groot, ik vind dat zo stoer van je. Leiding geven aan een grote organisatie is niet niets. Ondanks dat je inmiddels een prachtige volwassen vrouw bent, blijf je voor altijd mijn kleine zusje. Pien, ik hou van jou.

Lieve **Maarten**, inmiddels zijn wij 12 jaar samen en hebben wij in deze jaren heel veel met elkaar gedeeld. Veel gelachen maar ook gehuild. Jij bent mijn steun en toeverlaat, mijn rots in de branding. Je haalt het beste uit mij naar boven. Lieve Maarten, ik wil je bedanken voor wie je bent. Ik ben zo trots op jou hoe jij je de afgelopen jaren hebt ontwikkeld; van industrieel productontwerper naar arbeidsdeskundige. Samen hebben wij nog zo veel moois in het vooruitzicht. Het eerste wat op ons pad komt is ons prachtige huis in Hengelo waarvan we 1 november 2023 de sleutel krijgen. Samen met Kuna (onze lieve kater) zullen wij halverwege volgend jaar die kant op gaan. Maar eerst nog even samen klussen in ons nieuwe huis. Ook dat gaat zeker goed komen.

Lieve **pap** en **mam**, praktisch gezien wil ik jullie bedanken voor alles! Bedankt dat jullie mij op de wereld hebben gezet, haha. Bedankt voor de onvoorwaardelijke liefde en steun. Zonder jullie was ik nooit zover gekomen als ik nu ben. Bedankt **mam** voor de vele momenten waarop we urenlang non-stop kunnen kletsen, bedankt dat ik alles met je kan delen en bedankt voor alle stukken die jij voor mij taalkundig hebt nagekeken. Deze is uiteraard ook weer perfect geworden. Bedankt pap voor alle grappen en grollen, voor de heerlijke skivakanties en voor de oneindige inspiratie. Zonder jou was ik nooit EA Flex begonnen. Hard werken is ons zeker met de paplepel ingegoten.
De band die wij als gezin met elkaar hebben is iets waar veel mensen jaloers op zijn. Die band is zo omdat jullie voor ons zo'n goede stabiele en fijne basis hebben neergezet. Wij hebben met ons vieren al zoveel meegemaakt en mooie herinnering gemaakt. Het is heerlijk om af en toe in de weekenden thuis te komen. Een oase van rust en liefde. Ik kijk ontzettend uit naar onze toekomst als gezin. Ik gun jullie ook de rust en de ruimte van het prachtige huis aan het water welke vanaf 1 november 2023 van jullie is. Voor de oplettende lezer; ja het klopt! Mijn ouders en Maarten & ik krijgen op dezelfde dag de sleutels van onze nieuwe huizen! Bijzondere band, voor altijd. Als gezin hebben wij altijd één spreuk. Deze spreuk staat op elke verjaardagskaart of andere kaarten voor een speciale gelegenheid. Ik kan dan ook niet anders afsluiten dan met deze spreuk.

'Blijf zoals je bent, dan ben je goed.'

Esmée Dijkstra
Groningen, oktober 2023

CURRICULUM VITAE

Esmée Anne Dijkstra werd op 7 juni 1994 geboren te Meppel. Esmée groeide op met haar ouders en zusje in Steenwijk. In 2011 behaalde zij haar HAVO diploma aan de RSG Trompmeesters te Steenwijk. Hierna behaalde zij haar VWO diploma. In 2013 begon Esmée met de studie Geneeskunde aan de Rijksuniversiteit Groningen.

Gedurende de studie Geneeskunde heeft Esmée bij de huisartsenpost te Heerenveen, Almelo en Groningen gewerkt. Tijdens het eerste jaar van de Master Geneeskunde ontstond de interesse in onderzoek doen op het colorectale gebied. In datzelfde jaar is Esmée begonnen met onderzoek onder leiding van prof. G. A. P. Hospers en dr. B. van Etten. Ook gedurende de overige jaren van de Master Geneeskunde, bleef Esmée actief binnen het onderzoek. Esmée doorliep haar Master Geneeskunde in het UMCG te Groningen (4e jaar), het ZGT te Almelo (5e jaar) en het UMCG te Groningen (6e jaar).

Na het behalen van haar artsenbul in 2019, begon Esmée aansluitend met een PhD-traject onder leiding van prof. G. A. P. Hospers, prof. C. J. H. van de Velde en dr. B. van Etten. Gedurende twee jaar werkte zij fulltime aan haar onderzoek op het gebied van het locally advanced rectum carcinoom en het recidief rectum carcinoom. Hierbij was het grootste project de RAPIDO-studie. Voor haar onderzoek heeft Esmée de Schoemaker prijs van de Nederlandse Vereniging voor Heelkunde voor beste publicatie 2021 in ontvangst mogen nemen en is zij genomineerd voor de prijs Best Proffered Paper op het congres van de European Society of Surgical Oncology (ESSO) in 2021. Naast haar onderzoek werkte Esmée in de weekenden als arts-assistent op de afdelingen vaatchirurgie en HPB-chirurgie in het UMCG te Groningen.

In oktober 2021 hervatte Esmée haar klinische werkzaamheden en startte zij als ANIOS chirurgie in het Deventer Ziekenhuis. Van oktober 2022 tot en met juni 2023 heeft Esmée als ANIOS chirurgie in het Martini Ziekenhuis gewerkt, waarna zijn vanaf 1 juli 2023 begonnen is aan de opleiding tot chirurg. De eerste jaren van haar opleiding zij zal volbrengen in het UMCG te Groningen en het ZGT te Almelo.

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[*] *Contributed equally*