IMPROVING QUALITY OF LIFE IN RECTAL CANCER PATIENTS

DEVELOPMENT AND EVALUATION OF A MRI-GUIDED RADIATION BOOST STRATEGY

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Thesis with a summary in Dutch, Utrecht University
ISBN/EAN: 978-90-393-6700-1
NUR: 877

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Cover, graphic design and lay-out: Tessa-Norah Feenstra, Apeldoorn, The Netherlands,
www.tessanorah.com
Printing: Drukbedrijf.nl, Amsterdam, The Netherlands,
www.drukbedrijf.nl

The printing of this thesis was financially supported by:

Afdeling Radiotherapie Universitair Medisch Centrum Utrecht; ELEKTA B.V.; Koninklijke Philips Nederland B.V.; ChipSoft B.V.; Servier Nederland Farma B.V.;

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VERBETEREN VAN KWALITEIT VAN LEVEN IN PATIËNTEN MET RECTUMCARCINOOM –
ONTWIKKELING EN EVALUATIE VAN EEN MRI-GELEIDE BESTRALINGS-BOOST STRATEGIE

proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op maandag 19 december 2016 des middags te 2.30 uur

door

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geboren op 26 november 1985 te Utrecht

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PROLOGUE

This thesis presents three development-phases for a state-of-the-art radiation boost strategy aimed to improve response and long-term quality of life in rectal cancer patients. These phases consist of evidence-based rationalization, practical implementation and formal evaluation of this new strategy.

Boosting rectal tumors aims to increase response rates, which in turn will enable to select more patients to undergo minimally- / non-invasive treatments so that organ-preservation becomes an option. Organ-preservation specifically aims to spare rectal function and thereby could improve quality of life.

This thesis therefore presents how we can increase treatment responses by using higher radiation doses, how an MRI-based boost treatment can be practically implemented and evaluated in the clinic, and to which background results of this new treatment should be evaluated considering patient's quality of life.

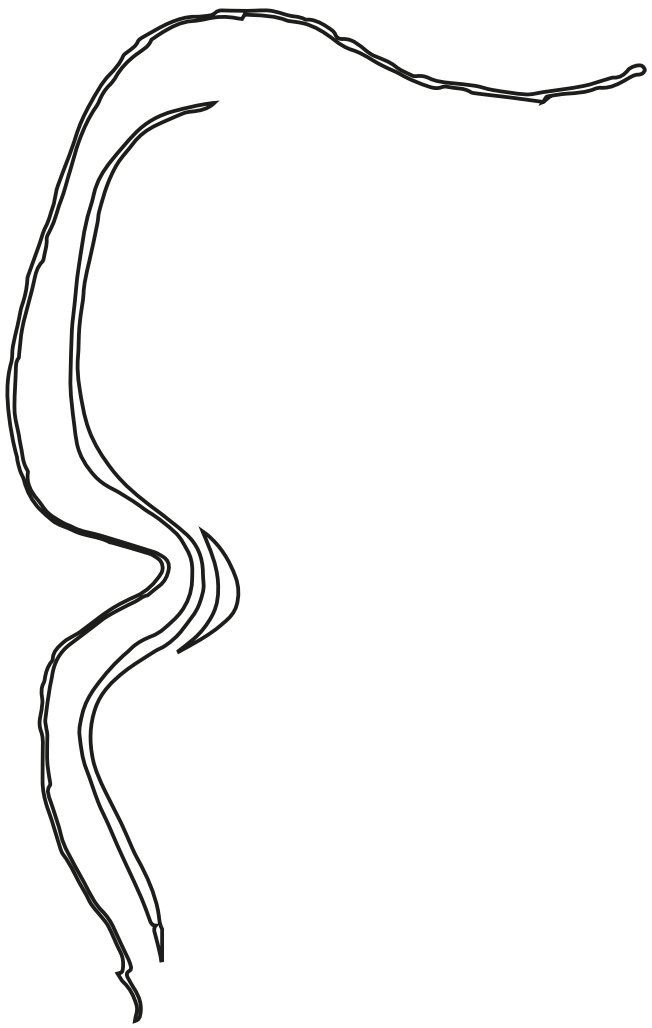
INTRODUCTION

PART 1

PART 2

PART 3

APPENDICES



CHAPTER 1

General introduction

CHAPTER 1
GENERAL INTRODUCTION

The incidence of rectal cancer has been increasing for years. Nowadays, some +4000 new cases are diagnosed yearly. Patients are classified into low-, mid- and high-risk sub-categories based on T(umor)N(ode)M(etastasis)-staging, which determines potential treatment options summarized in national guidelines (1). Locally advanced rectal cancer (threatened mesorectal fascia or N2) constitute approximately one third of new cases (2). Due to the introduction of multimodality treatment in the past decades (including surgery, radiotherapy and/or chemotherapy), the number of rectal cancer survivors has dramatically increased (3-9). Long-term outcomes have therefore become a progressively important outcome parameter in evaluation of newly introduced treatments. These outcomes include recurrence of disease and survival as well as outcomes indicating post-operative morbidity.

QUALITY OF LIFE

Post-treatment burden is often expressed and divided into functional impairment and quality of life effects. These subjective outcomes are most reliably obtained from patients directly and are therefore called patient-reported outcome measures (PROMs). To capture PROMs, a preferred method is to administer validated to patients at regular time-intervals. Multiple questionnaires should be used to capture both short- and long-term outcomes. In the past decade, interest for the use of PROMs in combination with oncological outcomes has increased to evaluate new treatments.

Regarding collection of patient-reported outcomes to compare treatments, electronic methods have shown to result in equivalent results as pen-and-paper questionnaires (10-14). Because of lower percentages of missing data and high response rates (15, 16), web-based methods may even be more feasible than paper versions. Especially nowadays since automatic reminders can easily be implemented (15-17) and patients are, overall, getting more web-avid (15, 18). The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry (19) is a Dutch initiative that provides a friendly environment to monitor, store and analyze (electronically) collected patient-reported outcomes. Furthermore it holds the unique opportunity to compare patient-reported data to population-based outcomes since a normalized dataset from healthy Dutch individuals is available within the same tool (20). This environment is therefore optimal to be used in cohort structures where large numbers of patients need to be assessed in order to evaluate treatment outcomes.

RECTAL CANCER TREATMENT

Rectal cancer treatment for mid- (T2-3N0-1) and high risk (T3N1, T4 or N2) tumors currently consists of radiotherapy (without or with chemotherapy respectively) followed by surgery (1). Surgery has been standardized since the late 90's by performing a total mesorectal excision which includes resection of the rectum and surrounding fatty enveloped (21). Radiation schedules on the other hand have been changing constantly over the past decades. With the introduction of pre-operative (neo-adjuvant) chemoradiation instead of post-operative (adjuvant) radiation the local recurrence rates have dropped and the rate of pathological complete responders (pCR) has increased (22). This has shown to benefit patients since it was shown that patients who reach a pCR after pre-operative therapy have better a prognosis expressed in improved disease-free and overall survival rates compared to non-complete

responding patients (23, 24). These favorable outcomes emphasize why new pre-operative treatments have the ambition to even further improve complete response rate in rectal cancer patients (25).

Despite advantages seen in patient survival, current treatments still come at the cost of considerable morbidity. This is observed in particular when surgery is preceded by radiation (22, 26-31). With the introduction of neo-adjuvant chemoradiation, however, a window has been created to assess tumor regression which could direct the choice for different surgical options. For patients with a clinical 'complete' or near-complete ('good') response, minimally-invasive or non-operative management could be considered in order to preserve optimal rectal functioning. Such less- or non-invasive (surgical) treatments are generally considered to benefit patients by aiming to improve remaining functional (bowel-related) outcomes and thereby maintaining optimal quality of life after treatment (29, 32). Initial results of such organ-preserving strategies look promising (33-42) but these trials (especially on non-operative management) are still little in number, sub-optimal in study-design, non-specific in patient-selection and still short in follow-up. These factors currently prevent reliable comparison against standard care, i.e. radical surgery. Nevertheless, these pioneering studies have provided a basis for many investigators to rethink the goals of 'neo-adjuvant' treatment. More and more groups are currently investigating whether or not neo-adjuvant treatments can be adapted into more 'definitive' treatments to let a larger proportion of patients benefit from the potential to omit surgery in the future (43).

To increase a patient's chances for organ-preserving strategies, the percentage of good responding patients should be maximized and the sensitivity and specificity of tests confirming this status should be optimized (43). Increasing response rates can most likely be obtained by increasing radiation doses (44) rather than adding extra or higher-dosed chemotherapy regimens since there is substantial recent evidence that the latter increases toxicity but not actual response rates (45-48).

In order to safely increase radiation dose delivery should be as focused as possible since healthy tissue irradiation may result in toxicity, which hampers quality of life outcomes. Toxicity after rectal cancer irradiation is most prominent when followed by surgery (26, 49, 50). Therefore, a combination of optimal dose delivery focused to the tumor together with non- or minimally-invasive surgical management would likely help patients to sustain their quality of life. This emphasizes the need for adequate imaging techniques for dose planning and delivery. Dose planning and delivery of radiation have traditionally been based on imaging to visualize tumors and or surrounding structures. Up to the late 90's, X-ray imaging was the standard technique used to identify bony target areas whereas tumors were not directly visualized. In the 2000's this technique was gradually replaced by CT imaging. CT had the advantage of being a 3 dimensional technique which improved visualization of the tumor and surrounding structures and thereby made dose planning and delivery more precise. Nevertheless, tumor definition on CT is still difficult resulting in the need to use large margins around target areas to ensure adequate dose delivery to the tumor (51, 52). To improve focused dose delivery to solely the tumor and sparing of healthy surrounding tissue, newer imaging techniques such as MR imaging can be used because of their superior soft-tissue contrast between tumors and soft surrounding tissue Also, MR imaging has the possibility to obtain functional images that can better discriminate tumors from their background and do not come with the burden of exposing patients to additional radiation. Therefore, MRI-guided radiotherapy (of escalated doses) seems to provide essential benefits over other imaging techniques since they allow more accurate dose delivery.

In summary, the rationale presented above presents two main paradigms:

01. 'more is more' when it comes to the relationship between high precision dose escalation and tumor response rates
02. 'less is more' when it comes to the relationship between surgical invasiveness and quality of life after treatment.

TREATMENT EVALUATION

This thesis mainly focuses on the first paradigm, improvement of response rates to chemoradiation, which aims to widen the application of less invasive (surgical) management to improved quality of life (the second paradigm). Newly developed treatments that fit these paradigms should, however, be formally evaluated before they can be introduced into patient care. Preferably, such evaluation is performed in settings where outcomes from routinely treated patients receiving standard care are used as the control group, and randomization is used to minimize the influence of confounding and effect-modifying factors. However, the classic randomized controlled trial has shown to possess multiple shortcomings that hamper their feasibility and the translation of results to daily clinic. These include slow recruitment (53-55), poor generalizability and high costs (56-59). This has been the basis for methodologists to develop alternative methods for efficient and robust comparison between new interventions and standard care. One such initiative was presented by Relton et al who proposed the 'cohort multiple Randomized Controlled Trial' (cmRCT) design (60). This design combines strengths of classic RCTs (i.e. randomization and strict follow-up) with advantages from prospective observational cohort studies including unselective recruitment from routinely treated populations, long-term follow up, and regular outcome measurements. CmRCT also provides the opportunity to evaluate multiple interventions at the same time against an equal background (standard care).

GOALS AND CHALLENGES

The goal is to improve quality of life in rectal cancer patients without compromising oncological outcome. This can potentially be accomplished by obtaining high complete response rates after neo-adjuvant therapy so that a large quantity of patients can proceed to organ-preserving treatments. Novel radiation treatments provide some of the most promising targets for increasing response rates as long as toxicity can be controlled. However, before such novel treatments can be implemented in routine practice, they have to demonstrate their superiority over standard care and their acceptance by patients. Evidence for both can potentially be obtained through the cmRCT design, which might enable to measure both simultaneously, efficiently and reliably.

This thesis describes the groundwork for development of a MRI-guided radiation boost strategy, and presents how clinical and patient-reported outcomes can be collected from routine care against which this intervention is evaluated. The thesis will conclude with an update on the currently ongoing randomized controlled trial that evaluates this novel treatments strategy (according to the cmRCT design) and will discuss new perspectives for potential future research.

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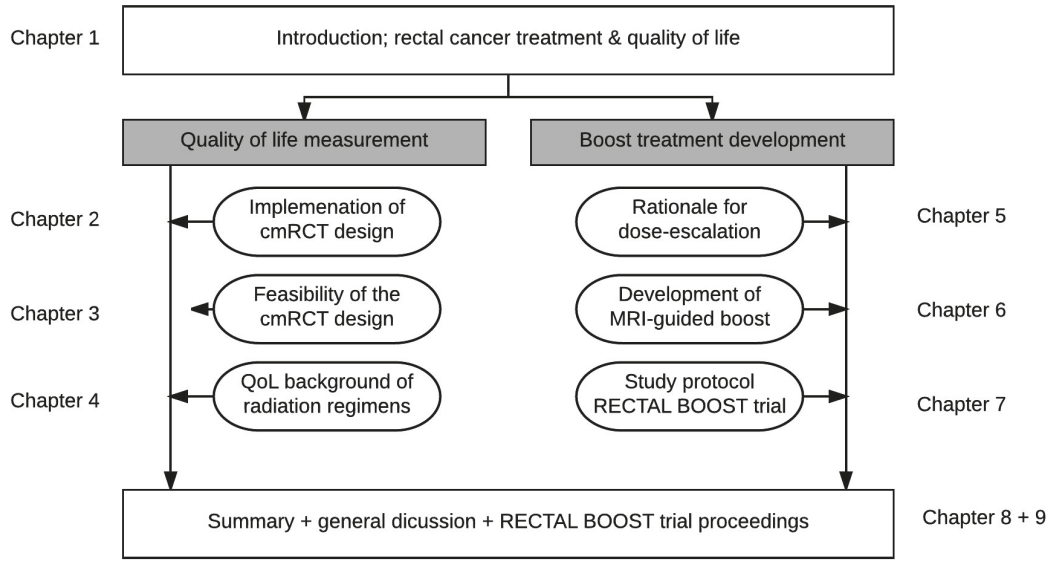


FIGURE 1 **Overview of the relationship between chapters of this thesis.**

THESIS OUTLINE

PART I: Patient-reported outcomes in rectal cancer patients. Implementation of a novel study design to measure and evaluate quality of life outcomes in rectal cancer patients in routine practice as well as in randomized controlled settings (see Figure 1).

Chapter 2 presents a comprehensive study designed according to the 'cohort multiple Randomized. Controlled Trial' (cmRCT) design, which illustrates how clinical and patient-reported outcomes can be measured and used to evaluate current and future/experimental rectal cancer treatments. More specifically, this chapter describes the development of the study protocol for the Prospective Dutch ColoRectal cancer Cohort (Dutch: 'Prospectief Landelijk ColoRectaal kanker Cohort' (PLCRC)).

Chapter 3 subsequently describes the clinical implementation of the novel cmRCT design into routine oncology practice.

Chapter 4 compares QoL between patients undergoing short-course radiotherapy versus chemoradiation before surgery.

PART II: Development and evaluation of a MRI-guided dose-escalation treatment in rectal cancer. It focuses on the development of an MRI-guided radiation dose-escalation treatment aimed to improve tumor response in patients with locally advanced rectal cancer (see Figure 1).

Chapter 5 describes the potential role for dose-escalation in response-improvement after neo-adjuvant radiation treatment of locally advanced rectal cancer by reviewing and meta-analyzing the literature that describes studies in which radiation doses of >60 Gy were used.
Chapter 6 illustrates the development and validation of a MRI-guided gross tumor volume (target) definition, which is used for dose-escalation planning in locally advanced rectal cancer.

Chapter 7 describes how the novel MRI-guided dose-escalation approach is evaluated according to the cohort multiple randomized controlled trial design.

PART III: Summary and general discussion

Chapter 8 presents a summary of results presented in this thesis.

Chapter 9 gives a Dutch summary ('Nederlandse samenvatting')

Chapter 10 presents a critical discussion on the presented evidence in this thesis against the background of recently published literature.

Appendices
Acknowledgements – Dankwoord
List of publications
CV

PART 1

PATIENT-REPORTED OUTCOMES

CHAPTER 2

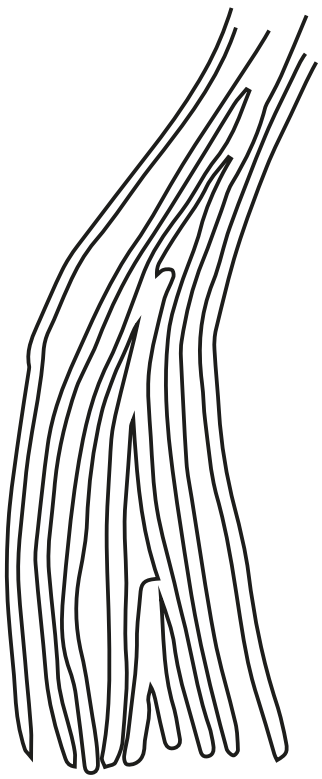
Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research

CHAPTER 3

Implementation of the 'cohort multiple randomized controlled trail' design for randomized evalutation of multiple interventions in routine clinical care

CHAPTER 4

Impact of short-course radiotherapy versus chemoradiation on quality of life in rectal cancer patients



CHAPTER 2

PROSPECTIVE DUTCH COLORECTAL CANCER COHORT: AN INFRASTRUCTURE FOR LONG-TERM OBSERVATIONAL, PROGNOSTIC, PREDICTIVE AND (RANDOMIZED) INTERVENTION RESEARCH

Published in: Acta Oncologica, 2016 Aug 25:1-8

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CHAPTER 2

ABSTRACT

BACKGROUND

Systematic evaluation and validation of new prognostic and predictive markers, technologies and interventions for colorectal cancer (CRC) is crucial for optimizing patients' outcomes. With only 5-15% of patients participating in clinical trials, generalizability of results is poor. Moreover, current trials often lack the capacity for post-hoc subgroup analyses. For this purpose, a large observational cohort study, serving as a multiple trial and biobanking facility, was set up by the Dutch Colorectal Cancer Group (DCCG).

METHODS / DESIGN

The Prospective Dutch ColoRectal Cancer cohort is a prospective multidisciplinary nation-wide observational cohort study in The Netherlands (yearly CRC incidence of 15,500). All CRC patients (stage I-IV) are eligible for inclusion, and longitudinal clinical data are registered. Patients give separate consent for the collection of blood and tumor tissue, filling out questionnaires, and broad randomization for studies according to the innovative cohort multiple randomized controlled trial design (cmRCT), serving as an alternative study design for the classic randomized controlled trial.

Objectives of the study include 1) systematically collected long-term clinical data, patient-reported outcomes and biomaterials from daily CRC practice and 2) to facilitate future basic, translational and clinical research including interventional and cost-effectiveness studies for both national and international research groups with short inclusion periods, even for studies with stringent inclusion criteria.

RESULTS

Seven months after initiation 650 patients have been enrolled, 8 centers participate, 15 centers await IRB approval and 9 embedded cohort- or cmRCT-designed studies are currently recruiting patients.

CONCLUSION

This cohort provides a unique multidisciplinary data, biobank, and patient reported outcomes collection initiative, serving as an infrastructure for various kinds of research aiming to improve treatment outcomes in CRC patients. This comprehensive design may serve as an example for other tumor types.

TRIAL REGISTRATION:

PLCRC is registered at Clinicaltrials.gov under NCT02070146.

INTRODUCTION

Worldwide, colorectal cancer (CRC) is the third most common malignancy in men and second in women [1]. With a continuously rising incidence, an estimated 1,35 million new cases are diagnosed yearly, associated with 694,000 annual deaths. In the past decades, substantial progress has been made in diagnosis and treatment of CRC, resulting in an increasing number of CRC survivors [2-8]. The implementation of national CRC screening programmes is expected to increase the incidence of CRC [9]. The increasing incidence of CRC, in combination with improved survival rates, has led to high numbers of people living with (the consequences of) CRC. In addition to treatment parameters and outcomes, also quality of life, workability, and daily functioning during and after CRC treatment are becoming increasingly important parameters in research.

There is no consensus on the use of prognostic parameters in CRC, and predictive factors for treatment are scarce. Also there is a growing availability of new molecular markers [10-13] and innovative treatment options. This puts increasing pressure on the current research system, since large numbers of patients are required to assess relevance or superiority before their implementation into clinical practice. This warranted large number greatly exceeds the amount of patients that currently participate in clinical trials (5%-15%) [14-16]. Low recruitment-rates may also imply selective inclusion of patients in trials rather than representative population samples [17], which may result in limited external validity of outcomes. The danger of the extrapolation of study results to the general population was recently shown. Survival outcomes of patients with metastatic CRC (mCRC) treated within the scope of a randomized study were significantly better than the survival outcomes in patients not fulfilling the study eligibility criteria and treated outside the trial with the same drugs during the same period [17, 18]. Moreover, study designs classically used for comparative research often lack the ability to provide sufficient data for subgroup treatment effects or post-hoc evaluation. For example, immunotherapy showed to be effective in mCRC patients with microsatellite instability (MSI). As MSI is only observed in 3-5% of the mCRC patients, the conduction of a large randomized phase 3 trial will be challenging [19]. It is therefore desirable to include all these patients in a large representative cohort of CRC patients who are prospectively followed for relevant outcomes that enables to study the value of novel prognostic and predictive biomarkers in large, but also small subgroups of patients. It would be ideal to use data from routine sources such as hospital systems or (cancer) registries, but these sources often lack the required detail about (changes in) treatments, doses, toxicity, and response, which is paramount for this purpose. As an alternative, a large observational cohort has the advantage that it can provide a standardized data-collection, dedicated data-monitoring and intensive follow-up, all of which are especially valuable for long term research in prognostic or predictive determinants.

Ideally, all new interventions should be evaluated in Randomized Controlled Trials (RCTs) since this is considered the gold standard to prove effectiveness. However, this design in itself is often not only complicated by slow recruitment rates and limited generalizability [15], it is also subject to a considerable delay between conceptualization and start, limited long-term follow-up, inadequate collection of patient-reported outcomes (PROMs), high non-completion rates and high costs [16]. An innovative alternative proposed for the classic RCT is the 'cohort multiple Randomized Controlled Trial' (cmRCT) [20]. This design was originally developed as an alternative for classic pragmatic RCTs, and combines useful features from both classic RCTs (randomization) and prospective observational cohort studies. The design is characterized by three features: 1) patient-centred informed-consent approach; 2) framework to systematically collect long-term clinical follow-up as well as PROMs; and

3) efficient recruitment for trials by asking patients to give 'broad consent for randomization' in future trials. Unique features of the cmRCT design are that it allows to conduct multiple randomized trials simultaneously and that patients can participate in multiple non-conflicting trials at the same time [20]. The design itself and its implementation in this study are explained in more detail in Box 2.

We believe that a prospective observational cohort study can provide a standardized and validated collection of long term clinical data, tissue and blood samples and PROMs to establish a continuous source for a variety of research purposes (Box 1). This research database can, among others, be used to investigate what (intrinsic and environmental) factors are associated with survival and PROMs, to find new predictive markers for treatment outcomes and side-effects, and to develop more accurate diagnostic tests and efficient follow-up surveillance strategies.

BOX 1: MAIN OBJECTIVES OF THE PROSPECTIVE DUTCH COLORECTAL CANCER COHORT (PLCRC):

- To execute a prospective observational cohort study aiming to include all Dutch CRC patients and follow them until death.
- To prospectively collect high quality data on medical history, comorbidities, clinical characteristics, imaging, pathology results, tumor characteristics, treatment, survival, recurrence, hospitalization, adverse events, toxicity and (long-term) outcomes of experimental interventions (Table 1).
- To collect, store and make available blood and tumor tissue samples.
- To systematically collect patient-reported outcomes on quality of life, workability and functional outcomes.
- To provide detailed data on daily clinical care in the Netherlands.
- To create an infrastructure to facilitate studies of different nature, including:
  A. Prognostic and predictive research
  B. Biological research and (epi-)genetic research
  C. Studies that compare novel therapies or interventions in a target population according to the innovative cohort multiple randomized controlled trial (cmRCT) design serving as a pragmatic alternative for classic RCTs.
  D. Cost-effectiveness studies

BOX 2: THE COHORT MULTIPLE RANDOMIZED CONTROLLED TRIAL DESIGN

The basis of the cohort multiple Randomized Controlled Trial (cmRCT) design is a prospective observational cohort of patients with a certain condition [20], in our case CRC, in which all patients in principle undergo standard care. Within this cohort, clinical characteristics and standardized outcome measures are collected at baseline and regularly during follow-up. Clinical and self-reported data are used to compare effectiveness and safety of trialled interventions.

Practically, when an RCT is conducted within the cmRCT cohort, the first step is to identify a subcohort of all patients eligible for the intervention. Some of these patients are randomly selected and offered the experimental intervention (intervention group). If patients accept the offer, they are sure to undergo the experimental intervention. If they refuse they will undergo standard care. Eligible patients in the subcohort not randomly selected (control group), undergo standard treatment and do not receive any information on the trial. Outcomes are compared between randomly selected and non-selected patients. This process can be repeated for multiple (experimental) interventions simultaneously, offering (more) reliable direct comparisons between interventions and standard care.

In the cmRCT design a patient-centered informed consent procedure is obtained [41] by asking all patients to give 'broad consent for randomization' after enrolment [41, 42] This allows researchers to randomly selected patients from the cohort, and offer them experimental interventions, while patients who are not randomly selected serve as controls and undergo standard care without further notification. When informing patients about broad consent for randomization, we explicitly state that not all patients that consent will be offered an experimental intervention since offers are based on random selection. When they got offered an experimental intervention they can either accept the intervention or they can refuse and undergo standard care. Also they are told that they may become (temporarily) ineligible for future trials if they already participate in a trial which measures interfering endpoints. We ensure that patients will never be withheld proven effective care.

With this consent procedure we aim to mimic clinical practice, where people are usually not told about treatments they will not / cannot receive. The patient centered informed consent is expected to prevent cross-over and disappointment bias, especially in situations where, regardless of clinical equipoise, a new intervention is highly preferred by doctors and patients. Asking broad consent for randomisation also deals with the controversial ethical aspect of pre-randomization (as introduced by Zelen [43]) by obtaining upfront consent from all patients for randomization and data use in future comparative research, thereby not randomizing patients without prior notification and their consent.

METHODS / DESIGN

CLINICAL

This is a project of the Dutch Colorectal Cancer Group (DCCG) and was launched as the prospective Dutch colorectal cancer cohort (Dutch: 'Prospectief Landelijk ColoRectaal kanker Cohort' (PLCRC)). The cohort is designed in accordance with the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement' guidelines [21]. The project aims to collect high quality clinical data, biomaterials and PROMs of a large cohort of CRC patients that are prospectively followed from primary diagnosis until death. All data are collected under a broad informed consent to facilitate future basic, translational and clinical research (Box 1). Furthermore, the cohort aims to serve as an infrastructure to conduct multiple simultaneous (randomized controlled) trials (according to the cmRCT design (Box 2)).

STUDY POPULATION

Patients with histologically proven CRC are eligible for participation if they are 18 years or older and have given written informed consent. Only mentally incompetent and non-Dutch speaking patients are withheld from participation. The aim of the PLCRC project is to include all eligible patients in The Netherlands, a country with a yearly incidence of 15,500.

INFORMED CONSENT

Study information is given by researchers, research assistants, nonphysician clinicians and/or physicians during routine hospital visits after initial diagnosis, preferably before start of treatment. 'General' informed consent is mandatory for participation in this study and allows the collection of long term clinical and survival data. Subsequently, patients are given the option to consent to 1) filling out questionnaires on health-related quality of life, functional outcomes and workability, 2) biobanking of tumor and normal tissue, 3) collection of blood samples, and 4) to be offered studies conducted within the infrastructure of the cohort, either in accordance with the cmRCT design or not. When participants are offered to participate in a trial or intervention, an additional informed consent needs to be signed before patients can be enrolled in that trial (Box 2). The PLCRC informed consent procedure is a dynamic process since patients can withdraw or alter their consent preferences at any time during the study.

After inclusion, participants are assigned a unique study identification(ID), which remains the only patient identifier throughout all further processes in the cohort's infrastructure. Cohort inclusion does not limit participation in other observational studies. However, patients may become temporarily ineligible to participate in clinical trials outside the cohort in case they already participate in a cohort-embedded trial that has interfering endpoints.

ETHICS

The study was originally initiated as a monocenter study for which it received approval of the medical ethical review committee of the University Medical Center Utrecht (The Netherlands) in June 2013 (METC 12-510). Subsequently, approval was extended by the same IRB for a multi-center set-up, which was implemented in September 2015. All new intervention studies trialled within the cohort require separate approval from a medical ethical review committee. Study protocols and final results of PLCRC trials are available on the website: www.plcrc.nl excluding study protocols of cmRCT trials, since this design does not allow patients enrolled in the control arm to be informed on these studies (box 2). PLCRC is registered at Clinicaltrials.gov under NCT02070146.

DATA COLLECTION AND ENDPOINTS

OBSERVATIONAL CLINICAL AND SURVIVAL DATA

Extensive observational clinical data (Table 1) are collected from medical charts by trained data-managers of the "Netherlands Comprehensive Cancer Organisation" (Dutch: Integraal Kankercentrum Nederland (IKNL) [22]) and does not require additional effort from participating hospitals or patients. The collected data is stored in the "Netherlands Cancer Registry" (Dutch: Nederlandse Kankerregistratie (NKR) [23]) Study specific data, not standardly collected in the NKR, is gathered separately by IKNL data managers, or by study-personal or researchers.

BIOBANKING OF BLOOD AND TUMOR TISSUE MATERIALS

Tumor tissues are collected after routine surgery and stored as five snap frozen tissue samples, two Formalin-Fixed Paraffin-Embedded (FFPE) tissue samples and two tissue sample cores for Tissue Micro Arrays. Blood samples (10ml serum and 10ml EDTA) are collected during routine blood withdrawal before treatment. Serum is divided over six 0.5ml samples and the EDTA sample is divided over six 0.5ml plasma samples and three 0.9ml pellet samples before being frozen and stored. Snap freezing of tumor tissue, FFPE processing and blood sample processing are performed locally in participating hospitals and transported to regional biobank facilities for long-term storage. To provide a sustainable infrastructure for biobanking, we established close collaborations with existing national organisations for use of their expertise, and to prevent duplicate data entry and unnecessary costs. These initiatives include the Dutch Biobanking and BioMolecular resources Research Infrastructure (BBMRI-NL; www.bbmri.nl) and the CTMM Translational Research IT (TraIT, www.ctmm-trait.nl).

LONGITUDINAL ASSESSMENT OF PROMS

Nationally and internationally accepted and validated questionnaires are used to measure PROMs, which include EORTC QLQ-C30 [24], -CR29 [25] and –CIPN20 [26], Euroqol- 5 dimensional (EQ-5D) [27], Work Ability Index (WAI) [28], Low Anterior Resection Syndrome (LARS) [29], Stoma quality of life scale (SQOLS) [30], Short Questionnaire to assess Health-enhancing physical activity (SQUASH) [31], Hospital Anxiety and Depression Score (HADS) [32], multidimensional fatigue score (MFI-20) [33] and the Self-administered Comorbidity Questionnaire (SCQ) [34]. Patients have the option to fill out paper questionnaires, or use the digital patient tracking system PROFILES (Patient Reported Outcomes Following Initial Long term treatment and Survivor Ship)[35]. Questionnaires are provided at enrolment (baseline) and 3, 6, 12, 18 and 24 months thereafter, followed by an annual questionnaire for the remainder of their participation or until death. The comprehensive selection of PROM questionnaires which are administered frequently at pre-defined time points enable the use of PROM outcomes as consistent endpoints in research. Within PROFILES, the option exists to compare PROMs of the PLCRC patient population to those of large population-based samples of cancer patients and a normative Dutch cohort.

DATA FOR FUTURE STUDIES

Data collected and stored in the NKR is at all times available to centres where the data were originally captured. Additional data required for future research, including study specific data not standardly collected in the NKR, PROMs and biomaterials, is available upon request.

SAFETY

The observational nature of this study eliminates the appearance of adverse events (AEs) and serious adverse events (SAEs) as a result of participation in this study. However, grade 3/4 incidents according to the Common Terminology Criteria for Adverse Events (CTCAE) are important outcome parameters in

research, and are therefore systematically collected. In cohort-embedded trials, reporting of SAE's occurs as specified in the separate trial protocols.

PROCEEDINGS

Recruitment of patients initially started in one center in February 2013. At this first site, a highly dedicated patient-routine was introduced in which almost all CRC patients visiting the radiotherapy department were approached for participation [36]. During the observed period, 90% of all approached patients consented to inclusion, of whom 90% additionally consented to receive questionnaires, 83% to the storage of biomaterials and 85% to 'broad consent for randomization' in future trials. From September 2015 onwards, recruitment has been extended to multiple centers throughout The Netherlands and more centers expect to start recruitment in the (near) future. Currently, 8 hospitals are open for inclusion, 15 hospitals are preparing or awaiting IRB approval and 650 patients have been enrolled of which 160 patients were included over the last three months. In addition 9 cohort studies that are currently recruiting patients have been embedded within the PLCRC infrastructure, including 2 RCTs that are designed according to the cmRCT design (Table 2). For both RCTs inclusion rates have looked promising so far, with numbers greatly exceeding those of other RCTs [16, 17,]. PLCRC patients may be eligible for both trials; therefore patients that participate in both trials are stratified according to their received neo-adjuvant treatment as a first step to investigate the feasibility of overlapping trials within the cmRCT infrastructure.

TABLE 1 **Clinical data collection within the Prospective Dutch Colorectal Cancer Cohort.**

PART A: Patient ID and data sources

Patient identification & demographics

- Patient- ID code
- Birth information (date and city)
- Gender

Data source

- Hospital
- Patient number within hospital

Data capture

- ID of person who captures data

Study participation within the cohort

- Number and name of studies/trails
- Date(s) of inclusion
- Date(s) of completed study/trail follow

PART B: Pre-treatment record

Medical history

Cancer specific

- Date, location, type, treatment, treatment outcome

Comorbidity

- Cardiac, pulmonal, vascular, gastrointestinal, neurological, gynelogical, urological, muscle/bones, endocrine

Intoxication

- Smoking at diagnosis
- Alcohol use diagnosis

Physical examination

- BMI (length & weight)
- WHO performance status

Diagnosis & tumor information

- Sequential tumor number
- Date of diagnosis
- Source/procedure of diagnosis

Laboratory investigations

- CEA

Diagnostic work-up

Endoscopy

- Date, hospital, procedure, procedure complete?

PART C: Treatment record

Radiotherapy*

- Setting (neo-adjuvant/adjuvant) Indication for radiotheraphy

Treatment

- Start date first fraction
- Standard: # fractions, fractions dose, total dose
- Boost: # fractions, fraction dose, total boost dose
- Total received dose fractions
- Stop/completion date
- Response (TRG, ycTNM)
- Adverse events (date, cause, management)

Medical oncology*

- Setting (neo-adjuvant/adjuvant) Indication for systemic theraphy

Treatment

- Start date first cycle
- Agent, dose, number of cycles
- Total received dose fractions
- Stop/completion date
- Response (TRG, ycTNM)
- Adverse events (date, cause, management)

Surgery*

- ASA classification

Procedure

- Date, hospital

PART D: Post-treatment / follow-up record

Oncological follow-up

Recurrence*

- Recurrence (date, number, location(s)
- Treatment of recurrence (new PART C entry)

Treatment

- Setting (curative / palliative)
- Metachronic metastates (date, number, location(s))
- Treatment of metastates (new PART C entry)
- Setting (curative / palliative)

Complications*

- Grade 3/4 adverse events or complications

Survival

- Date of last hospital visit
- Death (including date and cause)

TABLE 1 **Clinical data collection within the Prospective Dutch Colorectal Cancer Cohort.**

- Number of tumors/polyps, distance from anal verge
- Endoscopic treatment
- Type, differentiation, T-stage

Pathalogy

- Modalities, date(s), hospital
- cTNM, MRF involvement, distance from anal verge

Multidisciplinary Tumor Board

- Date & final staging

- Setting (elective/acute)
- Approach (open/laparoscopic/robot)
- Type((Sub)Total Colectomy, LAR, APR, Hartmann)
- Anastomosis (type, stapled/sewn)
- Date of discharge

Stoma

- Date, hospital
- Setting (elective/acute)
- Temporary/definitive
- Type (ilestoma, colostoma)
- Date of stoma reversal
- Peri-operative complications (anastomic leakage. abcess. ileus)
- Post operative complications (incl. wound complications)

Pathalogy*

- pTNM
- Tumor regression grade
- Radicality of resection
- Circumferential resection margin (CRM)
- # lymph nodes & # positive lynph nodes in specimen
- Angio - and lymphatic invasion
- Perforation of the bowel
- Molecular markers (BRAF, RAS, MSI status)

* Multiple entries are allowed within each tumor episode

TABLE 2 **Ongoing studies embedded in the PLCRC cohort currently recruiting patients.**

Name study	Design	Description of study
Rectal Boost	RCT*	Effect of a pre-operative dose-escalation BOOST versus standard chemoradiation on pathologic response rates in locally advanced rectal cancer [42]
Sponge	RCT*	Effect of a retractor SPONGE during laparoscopic rectal cancer surgery versus Trendelenburg positioning on perioperative complications and hospital stay [44]
PROTECT	Prospective cohort	PlcRc cOhorT: diEtary intake after diagnosis and ColorecTal cancer outcomes
CONNECTION	Validation study with different workpackages including a prospective cohort study	A nation-wide COloN CaNcer rEgistry and stratifiCaTION effort for the development and validation of genetic, proteomic and histopathological assays to stratify patients for adjuvant therapy
MEDOCC	Prospective cohort	Molecular Early Detection of Colorectal Cancer study to investigate the prognostic value of circulating tumor DNA [45]
SPECTRE	Pilot study	Ultra-high field 7.0 Tesla MR SPECTRoscopy to monitor capEcitabine metabolism in liver metastases
Recap	Case-control	Case match control study investigating the benefit of last line regorafenib treatment
Quality of life study 1	Prospective cohort	Impact of short-course radiation versus long-course chemoradiation for rectal cancer on quality of life
Quality of life study 2	Prospective cohort	Quality of life comparison between patients undergoing radiation followed by low anterior resection versus abdomino-perineal excision

Study population	Sample size (n)
T3 with threatened mesorectal fascia (<1 mm), T4 or N2M0 rectal cancer	60 versus 60
Stage I-IV CRC undergoing laparoscopic surgery	94 versus 94
Stage I-IV CRC	1000
Stage II - III colon cancer	NA
Stage II colon cancer	846
metastatic CRC	26
Metastatic colon cancer and metastatic RAS wildtype rectal cancer	125 versus 125
Stage II-IV rectal cancer	>60 versus >60
Stage II-IV rectal cancer	>100 versus >100

*Randomized controlled trial according to the cohort multiple randomized trial design (box 2)

DISCUSSION

This multidisciplinary prospective observational cohort study provides a validated and standardized collection of high quality clinical data, PROMs and biomaterials of a large cohort of CRC patients to facilitate future basic, translational and clinical research. By making this collection available to researchers upon request, the cohort foresees in the growing need for comprehensive data collection and sharing [36]. Through its broad eligibility the cohort is likely to reach high recruitment rates, thereby allowing to conduct highly powered analyses, improve recruitment rates to trials and reduce long inclusion periods for studies that use stringent inclusion criteria, i.e. aim to include specific subgroups of patients.

Over the past decades several other cancer registries and prospective observational cohort studies have been initiated in The Netherlands [37-40]. These initiatives serve different purposes, such as providing insight in incidence and prevalence, in the effects of nutrition, lifestyle or treatments in current daily practice, or to serve as a platform for monitoring quality of care. Often these databases or registries are used for various types of research, even though they were originally not intended for this (specific type of research) purpose. In addition, most of these existing cohorts are closed cohorts, or maintain restricted inclusion criteria that limit the inclusion to patients with certain cancer subtypes or to patients that received certain treatment(s). The PLCRC initiative differs in respect to these limitations by its dynamic design, its unlimited accrual potential, and by allowing the inclusion of CRC patients of all stages, independent of their received treatments. Furthermore, some of the registries contain data that are provided by healthcare professionals themselves. Therefore, these registries may lack adequate validation and monitoring of the included data, which likely increases the risk of misclassification and/or underreporting of (adverse) outcomes. By harboring independent data managers and monitors for the PLCRC cohort, we attempt to limit incorrect data registration, which should improve the robustness of outcomes and trial results from our cohort. Finally, the PLCRC cohort is unique in the sense that it provides a comprehensive dataset, which includes aggregated high quality multidisciplinary clinical information, biomaterials and PROMs, and with the possibility of performing studies according to the cmRCT design.

We acknowledge potential challenges and limitations arise from our cohort's infrastructure. First, by asking informed consent we introduce the risk of selection at a patient level (if specific subgroups do not provide consent as much as other subgroups), or, in case hospitals decide not to participate, at a hospital level. However, since we parallel our data to data from The Netherlands cancer registry (recording baseline and clinical data from all histologically confirmed CRC patients in The Netherlands), we are able to obtain insight in the selection that exists in our cohort both within and between participating and non-participating centers. Secondly, the cmRCT infrastructure is not appropriate for all types of research. Since experimental interventions are compared against standard care, the design does not allow placebo-controlled settings or the use of non-standardly measured outcomes. Nevertheless, such trials can still be embedded in the cohort as classic RCTs for which the cohort can be used as a recruitment pool. The high participation rates, high levels of consent to the additional consent options and the willingness of hospitals to participate in PLCRC indicate that this innovative design is feasible in the oncology practice, accepTable for patients and healthcare professionals, facilitate research projects and is likely to provide generalizable results. Future results are needed to confirm whether the cmRCT design indeed provides an accepTable alternative for classic pragmatic RCTs.

In summary, this cohort provides a unique high-quality multidisciplinary data collection initiative, including biobanking and PROMs, which serves as an infrastructure to perform various kinds of research in the field of CRC. The set-up allows evaluation of long-term clinical and PROMs of patients treated in current routine care, and that of patients treated by experimental interventions in a randomized controlled setting. This comprehensive design may serve as an example for research in other tumor types.

Competing interests

N. Hoogerbrugge is a consultant for AstraZeneca since June 2014

No competing interests exist for the other authors.

This project is funded by Dutch Cancer Society; Stand Up 2 Cancer; Bayer (unrestricted grant), Lilly (unrestricted grant), Merck (unrestricted grant), Roche (unrestricted grant).

Authors' contributions

JB, SK, VD, JM, HK, JI, CJ, GV, CP, AM, PS, MO, HV, MK contributed to the design of the study. All authors participated in writing and reviewing of the manuscript. Final approval was obtained from all authors.

Acknowledgements

Research supported by an SU2C-DCS International Translational Cancer Research Dream Team Grant (SU2C-AACR-DT1415). Stand Up To Cancer is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research."

We thank all participants and participating hospitals without whom this project is not possible.

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CHAPTER 3

IMPLEMENTATION OF THE 'COHORT MULTIPLE RANDOMIZED CONTROLLED TRIAL' DESIGN FOR RANDOMIZED EVALUATION OF MULTIPLE INTERVENTIONS IN ROUTINE CLINICAL CARE

Submitted to Journal of Clinical Epidemiology

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CHAPTER 3

ABSTRACT

INTRODUCTION

The classic randomized controlled trial (RCT) is the gold standard for evaluation of effectiveness of new innovations, but often associated with slow recruitment, poor generalizability and limited inter-trial comparability. The 'cohort multiple Randomized Controlled Trial' (cmRCT) design provides an infrastructure for multiple RCTs. The basis of cmRCT is prospective cohort from which patients can be randomly selected and offered experimental interventions.

METHODS

We implemented the cmRCT design in routine oncology practice for patients with colorectal-, breast cancer and bone metastases. We evaluated cohort participation rates, consent rates for randomization, trial inclusion rates and questionnaire response rates.

RESULTS

he far majority (64-88%) of patients agreed to cohort participation and 84-88% of these patients gave consent to future randomization. Most patients (81-100%) agreed to filling out questionnaires, and response-rates varied between 78-90% at baseline and 62-88% during follow-up. Demographic and clinical characteristics of rectal cancer patients with and without consent for randomization and/or consent for questionnaires were similar. Of all patients that visited our center and who were eligible for an RCT running within the rectal cancer cohort (BOOST trial), 67% (45/67) were actually randomized into the trial.

DISCUSSION

Implementation of the cmRCT design in clinical oncology practice is feasible, and shows potential for efficient recruitment and high generalizability.

INTRODUCTION

In oncology a many new treatments and (supportive) interventions are being developed. In order to confirm whether theoretical advantages of these innovations translate into actual benefits for patients, the effectiveness of all new interventions needs to be evaluated against standard care. The classic randomized controlled trial (RCT) is the gold standard for evaluation of new interventions. RCTs are, however, associated with recruitment difficulties [1-3] and poor generalizability of results due to strict in- and exclusion criteria [4-6]. A specific problem arises when multiple new interventions for the same cancer are in need of formal evaluation. By running separate trials for each new intervention, comparison of their effectiveness is complicated due to differences in eligibility criteria, endpoint definition and follow-up protocols.

To address issues of slow recruitment, poor generalizability and difficulties in outcome comparison, the 'cohort multiple Randomized Controlled Trial' (cmRCT) design [7] was proposed. The basis of cmRCT is a prospective cohort of patients with a certain condition, in which outcomes are measured at regular intervals. The cohort serves as an infrastructure for multiple RCTs to be conducted simultaneously. As described in Box 1 and the methods section, patients eligible for an experimental intervention are identified, some of whom are randomly selected and offered the intervention. CmRCT was first introduced in obesity research in a population-based setting [8]. We introduced the design, for the first time, into an oncology setting, with the aim for efficient evaluation multiple experimental interventions.

The aim of this paper is to evaluate feasibility and acceptability of cmRCT in terms of recruitment, generalizability and patients', researchers' and physicians' opinion.

METHODS

IMPLEMENTATION OF CMRCT

In September 2013, we implemented the cmRCT design at the radiation oncology department of the University Medical Center (UMC) Utrecht, the Netherlands. We set-up three cohorts of patients with (colo)rectal cancer [9], breast cancer [10], and bone metastases [11]. In August 2014, we integrated patient recruitment into routine clinical care: all eligible patients were systematically invited to meet a researcher before their first visit with the radiation oncologist. During this visit, patients were informed about the study and asked for signed informed consent. These appointments at the research desk, which is operated by researchers and research-assistants, are integrated in our department's electronic planning system.

We applied a 'staged-informed consent' procedure[12]. In the first stage, consent is sought for cohort participation, which includes collection of clinical and survival data, and patient-reported outcome measures (e.g. quality of life, workability, anxiety and depression, pain and fatigue [13-17]). At the same time, patients can additionally give 'broad consent for randomization'. Here, they give the investigators permission to randomize them in the near and far future, and to only be informed about - and invited to undergo - experimental interventions if they are allocated to the intervention arm (Box 1). Broad consent for randomization explicitly states that patients allow comparative use of their data, whether they are offered an intervention or not. At the second stage, when an intervention is trialed within the cohort, researchers offer randomly selected patients the intervention – which they may accept or refuse. Patients who accept the offered intervention sign additional informed consent, and patients who refuse, undergo standard care without signing additional consent. Patients who would be eligible for the new intervention, but who are not randomly selected, receive standard care and are not notified about the trial. Finally, in the third stage - when a trial is completed - aggregated disclosure of trial results is provided to all patients in the cohort (except those who have opted out).

EVALUATION OF IMPLEMENTATION

We evaluated the implementation of the cmRCT design on multiple levels: First, we describe the process of ethical approval. Second, we assessed generalizability, cohort participation rates, consent to receive patient-reported outcome measures (PROMs), i.e. questionnaires, and trial participation rates (broad consent for randomization). Demographic and clinical characteristics were compared in the rectal cancer cohort between patients who accepted and refused cohort participation, between patients with and without consent for filling out PROM questionnaires and between patients with and without broad consent for randomization. Cohort participation rates were expressed as the proportion of patients enrolled in the cohorts divided by the total population eligible for cohort-inclusion that visited our department since start of our cohorts. Patients who preferred not to meet a researcher were considered non-consenters and analyzed accordingly. Third, response rates to PROMs were calculated and demographic and clinical characteristics were compared within the rectal cancer cohort between participants who responded at least twice and those who never responded. Fourth, inclusion rates of eligible patients into trials and acceptance of the offered intervention was calculated for an RCT that is currently ongoing in the colorectal cancer cohort (RECTAL BOOST trial [18]). Patients visiting our department were systematically screened upfront for their eligibility to participate in this trial. All screened patients were logged, regardless of their eligibility or consent for the cohort. Fifth, patients' opinion and acceptance of the new design were assessed by means of a questionnaire provided to all patients approached for cohort participation. The questionnaire assessed adequacy of study-information, logistics and general level of satisfaction with the process ranging from 0 (i.e. extremely

dissatisfied) to 10 (i.e. extremely satisfied) (appendix). Five radiation oncologists (2 rectal cancer, 2 breast cancer and 2 palliative care specialists) with experience of patient recruitment into cohorts and RCTs were interviewed using a semi-structured guide. Pre-defined topics were identified through concerns raised by the ethical board and medical staff and were aimed to identify physician's how implementation of the design had influenced their work with emphasis on the ethical and logistical aspects. Interviews took place at least 2 months after the start of two trials within two cohorts.

APPENDIX - A

Standardized questionnaire and interview topics to evaluate experience of patients and physicians with logistical implementation of the cmRCT design into routine practice.

	Patients satisfaction satisfaction satisfaction	Answer
1	Did you receive information about the appointment with the researcher?	Yes / No
2	Did you read the study information folder prior to your visit?	Yes / No
3	Was the goal of the research appointment clear to you?	Yes / No
4	How did you feel about the order of the appointments: First with a researcher and then with your physician?	Fine / prefer other way around
5	Was there enough time to ask questions about the research you were invited to?	Yes / No
6	Can you rate your experience taking into account your research appointment and the order of today's appointments (between 0 and 10).	0 - 10

	Physician interview topics
	Ethics
1	Order of appointments (research-desk before clinic appointment)
2	Pre-randomization (physicians hear from the researcher to tell which patients, what)
3	Immediate randomization after patients visited the research-desk
4	Not telling patients in the control arm about the ongoing trial
	Time-management
5	Not being involved in processes of identification, eligibility check and randomization of patients
6	Only providing trial information to intervention arm patients (i.e. not having to inform control arm patients)
	Personal
7	Comfort to participate in clinical studies (when identification, consent and randomization are coordinated completely by researchers)
8	Autonomy of physicians
	Problems
9	Other problems that were encountered

RESULTS

The ethics board approved the colorectal cancer cohort in February 2013. Approval of the bone-metastases and breast-cancer cohorts was obtained in May and July 2013, respectively. Before obtaining ethical approval, the ethical board insisted that patients need to be informed about, and should give explicit informed consent for, the possibility of being offered experimental interventions in the future and to use their data comparatively when investigating treatment effects of experimental interventions against standard care.

Until June 2016, 2178 patients have been recruited into the cohorts (427 patients with rectal-, 1103 patients with breast cancer, and 648 patients with bone-metastases) (Table 1), representing 64-88% of all eligible patients visiting our clinic. After enrolment, 84-88% of cohort-participants gave additional 'broad consent for randomization' and 81-100% gave consent to fill out PROM questionnaires.

Questionnaire response rates varied between 78-90% at baseline and between 64-88% during follow-up (Table 1). Characteristics of patients within the cohort were comparable to the rectal cancer population refusing /not invited for cohort participation. Also, characteristics of patients within the cohort who did or did not consent to PROMs and broad consent for randomization were comparable, with the exception of a higher proportion of women not consenting to filling out PROM questionnaires and future randomization (Table 2).

Four trials have been embedded within the three cohorts (Table 3). In this paper we will focus on the the RECTAL BOOST trial (NCT01951521) [19] (Figure 1). In this trial, the effect of an irradiation boost in addition to neo-adjuvant chemoradiation on complete pathological response rate is investigated in patients with locally advanced rectal cancer. Since the start, 67 of all 108 screened patients visiting our department met inclusion criteria [19] (Figure 1). Of these, 15 patients (22%) did not participate in the cohort. Of the remaining 52 patients who consented, 49 gave broad consent for randomization, 45 of whom were actually randomized (67% of the total eligible patients). Twenty-three patients were allocated to the intervention arm and 22 to the control arm. Twenty patients in the intervention arm accepted the boost intervention (87%). Three patients refused because of personal reasons, fear of MRI and one patient was not prepared to have additional hospital visits. In the control arm, all patients underwent standard treatment without being informed of being on the trial.

Ninety-one routine care patients filled out the questionnaire on patient experience with the design. The majority of patients was aware that, during their first visit, they would see a researcher before meeting their radiation oncologist (n= 75, 83%). Seventy (77%) had read (some of) the study-information, 90 (98%) felt there was enough time for additional questions, and 82 (90%) approved of the fact that they were be asked informed-consent before seeing their physician. Patients rated the entire logistical process with 7.9 out of 10 (range 5-10).

Physicians were generally positive about the cmRCT design. They appreciated not having to bother with the processes of identification, providing information to, and randomization of, (potentially) eligible patients. Four of five physicians also liked that they only had to inform patients on treatments that they can actually receive. Only providing information about the experimental intervention to those actually being offered (instead of informing all patients) reduced their workload. Two physicians additionally mentioned they were more comforTable in inviting patients to trials in the cmRCT design, than in classic RCTs. Also, not having to cope with disappointed control arm patients was expressed as

an advantage by two physicians. Two physicians remained reluctant about the ethical validity of not informing control patients about being in a trial.

TABLE 1 **Participation-rates and questionnaire response-rates for three cmRCT-based cohorts.**

	Rectal cancer	Breast cancer	Bone-metastases	Total
Total patients visiting clinic (n)	487	1394	1009	2890
Cohort participation (n, %)	427 (88)	1103 (79)	648 (64)	2178 (75)
- Consent to receive PROMs (n, %)	383 (90)	1103 (100)*	523 (81)	2009 (92)
- Broad consent for randomization (n, %)	364 (85)	973 (88)	547 (84)	1863 (85)
PROMs return rates				
After diagnosis: **Baseline** (n, %)	344 / 383 (90)	839 / 1079** (78)	391 / 498** (79)	N/A
1st follow-up: **3m** (n, %)	269 / 305 (88)	734 / 963 (76)	**2wk** 264 / 429 (62)	N/A
2nd follow-up: **6m** (n, %)	226 / 265 (85)	609 / 830 (73)	**4wk** 257 / 382 (67)	N/A
3rd follow-up: **12m** (n, %)	156 / 199 (78)	388 / 533 (73)	**6wk** 235 / 367 (64)	N/A
4th follow-up: **18m** (n, %)	101 / 134 (75)	169 / 238 (71)	**8wk** 251 / 395 (64)	N/A
5th follow-up: **24m** (n, %)	35 / 49 (71)	52 / 79 (65)	**3m** 241 / 282 (76)	N/A
6th follow-up: (n, %)	-	-	**6m** 152 / 203 (75)	N/A
7th follow-up: (n, %)	-	-	**12m** 71 / 101 (70)	N/A

* consent for PROMs was mandatory in the breast cancer cohort.

**not all patients who consented to receive PROMs were sent questionnaires due to logistical problems.

NA = not available due to insufficient reporting in hospital system, n=number of patients, Xwk=X weeks, Xm=X months.

TABLE 2 **Demographic and clinical characteristics of the target population and consenting patients in the rectal cancer cohort.**

	All rectal cancer patients approached	With consent for cohort participation	With / without* broad consent for randomization		With / without * consent for PROMs		Patients with ≥6 months follow-up giving ≥2 / <2 * responses to questionnaires	
Number of patients	487	427	364	63	383	44	162	103
Age (mean, sd)	66.9 (11.4)	65.2 (11.0)	64.4 (10.7)	70.0 (11.3)	64.7 (10.9)	69.8 (11.3)	65.0 (12.1)	64.6 (10.1)
Sex (% male)	64.5	67.7	70.6	54.0	69.2	59.1	69.6	73.3
T-stage (%)								
1	-	0.8	0.6	0.0	0.6	0.0	0.9	0.8
2	-	9.2	9.9	5.3	9.8	4.8	8.8	9.8
3	-	66.0	65.8	70.2	66.5	66.7	55.8	74.4
4	-	17.3	18.0	14.0	17.2	19.0	23.9	9.8
unknown	-	6.8	5.6	10.5	6.0	9.5	10.6	5.3
N-stage (%)								
0	-	17.5	18.6	12.3	17.8	16.7	20.4	20.3
1	-	35.1	35.4	35.1	35.6	33.3	31.0	36.8
2	-	39.5	39.4	40.4	39.8	38.1	37.2	39.1
Unknown	-	7.9	6.6	12.2	6.8	11.9	11.5	3.9
M-stage (%)								
0	-	80.6	82.6	71.9	82.2	71.4	75.2	90.2
1	-	12.3	12.4	12.3	12.5	11.9	13.3	7.5
unknown	-	7.1	5.0	15.8	5.4	16.7	11.5	2.3

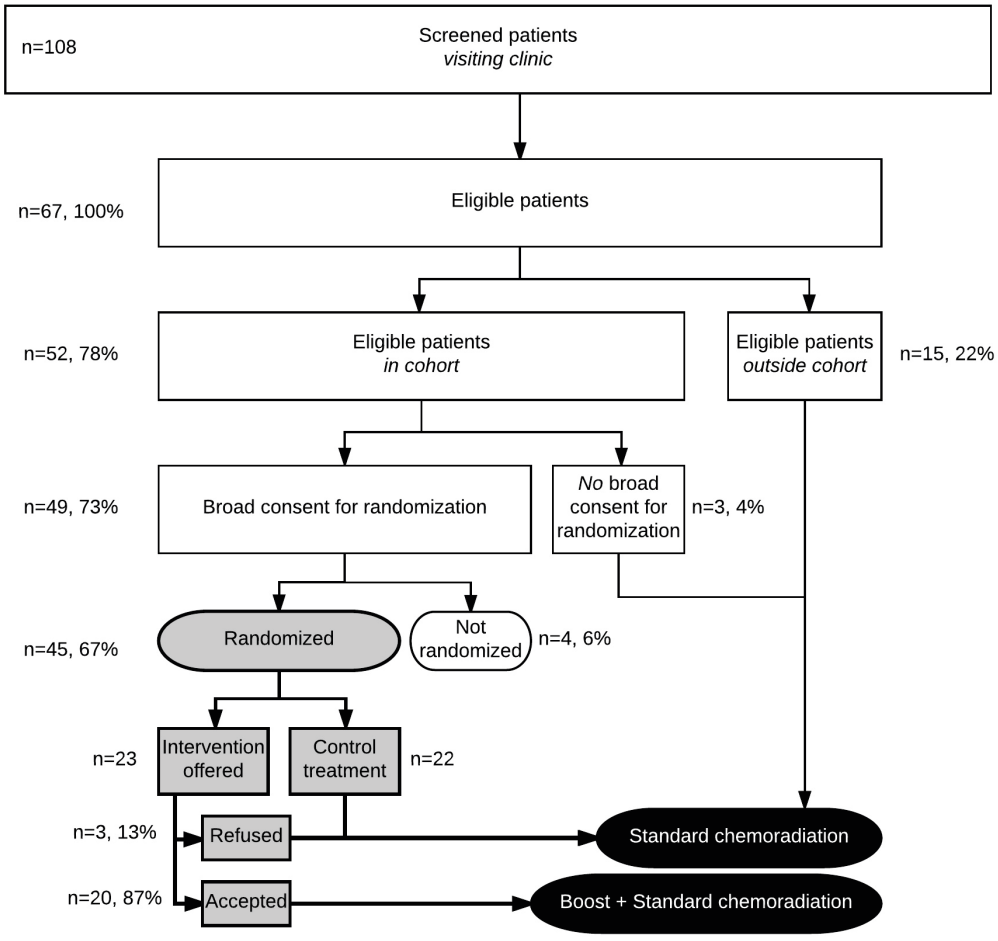

FIGURE 1 **Flowchart of approached patients that were potentially eligible for the RECTAL BOOST trial.**

Trial	Cohort	Population	Offered intervention	Control treatment *	Primary outcome	Secondary outcomes
RECTAL BOOST	Rectal cancer	Locally advanced rectal cancer patients	Boost (5 x5 3 Gy) in addition to chemoradiation	Chemoradiation alone	Pathological complete response rate	(Disease-free) survival, morbidity, QoL
SPONGE	Rectal cancer	Patients undergoing elective laparoscopic surgery	Rectractor sponge-assisted laparoscopic surgery	Standard laparoscopic surgery in Trendelenburg position	Length of hospital stay	Cardiac and pulmonary morbidity, QoL, survival
VERTICAL	Bone metastases	Patients with bone metastases	Stereotactic radiotherapy	Conventional radiotherapy	Pain response after 3 months	Vertebral compression, myelopathy, tumor control, QoL
FIT	Breast cancer	Inactive breast cancer survivors 12-18 months post diagnosis	Exercise program	None	PROMs: QoL, fatigue, physical activity level	Methodological: Participation rate, compliance, generalizability, satisfaction with the cmRCT design

DISCUSSION

This study describes the implementation of the cmRCT in a clinical oncology setting where multiple oncologic interventions are being developed. By introducing the cmRCT design, we aimed to improve recruitment and provide a facility for (multiple) randomized trials with high generalizability [7]. Our experience over the past two years show high cohort participation rates and high PROMs response rates, suggesting that patients find participation in a cmRCT-designed cohort accepTable. Also, the large majority of patients agree to future randomization for (experimental) interventions, which reduced the risk of selection bias in the trials embedded in the cohorts. Preliminary results of our first trial showed that 67% of all eligible patients who visit our department were actually randomized. Inclusion of such a high proportion of all eligible patients is rarely seen in classic (oncology) RCTs, in which usually between 5-20% of all eligible patients is randomized [20, 21] and trials often do not meet their predicted recruitment window [6, 22, 23].

Initial evaluation of the cmRCT design suggests that patients accept the design, recruitment is efficient and results can obtained fast and with high external validity. However, it is still unclear to what extent patients really understand the design and its implications. For physicians and researchers, advantages of the cmRCT were mainly practical. Enrolling patients into clinical research poses an (administrative) burden on physicians. In the cmRCT design, this burden is reduced substantially, as physicians only inform patients about treatments that they can actually undergo (i.e. only patients allocated to the intervention arm are informed about the experimental intervention and standard treatment, while control arm patients are only informed about standard treatment). Also, most physicians appreciated not having to cope with disappointed patients (those randomized to usual care i.e. the control arm) although clinical equipoise still existed. This approach harbours some ethical advantages, as research (recruitment to cohort and trials) is separated from clinical care [24]. In particular, our infrastructure aims to minimize selection of patient who end up in our cohort and trials by identifying and systematically approaching all patients to join our cohorts. This increases the generalizability of our cohorts as well as of the embedded trials.

We acknowledge that implementation of the cmRCT design has limitations. Firstly, setting up a cmRCT infrastructure in routine care is logistically challenging, time- and manpower consuming (thus expensive), and demands a dedicated and coordinated approach from all professionals involved. When a second cmRCT trial, with overlapping inclusion criteria, is embedded in the cohort, the randomization process has to be adapted, often requiring stratified randomization. Cohort patients who have participated in a previous trial may become (temporary) ineligible for participation in a second trial until reaching the endpoint or end of follow up of the first trial. This not only poses a logistical concern, but it also poses methodological and ethical concerns, including selection bias, and fair subject selection.

Selective refusal may occur when patients with certain characteristics (for instance male gender, older age, higher tumor stage or lower baseline quality of life status) refuse an offered intervention, whereas others without these characteristics accept the treatment. In classic RCTs, (selective) refusal rates lead to low recruitment because patients do not participate in the trial. In cmRCT, however, they characteristics of patients refusing can be monitored and refusals (selective or not) will provide a diluted estimate of the true intervention effect if analysed by intention-to-treat analysis. Solutions for analysis are available, in form of instrumental variable analysis, of which we have previously shown that they can provide equally valid effect estimates as classic RCTs [25]. Monitoring of refusal rates can

be of great value to physicians since it informs them in an early stage on whether or not patients are willing to undergo this particular experimental intervention.

We recognize that high participation rates, high PROM return rates, and the high proportion of eligible patients ending up in a trial are also result of a dedicated long-term effort of the researchers to run these logistical processes. Only by routinely embedding identification and a systematic approach of all patients for cohort participation, high cohort participation-, trial participation- and randomization rates are achievable. By implementing the cmRCT design, we have shown that embedding research into routine practice is feasible and well accepted by the large majority of oncologic patients. Because, in future, the number of innovations in need of (formal) evaluation is likely to increase, more efficient trial designs are needed which aim at high recruitment rates and efficient use of 'control' patients (i.e. patients undergoing standard treatment who explicitly consented to serve as comparison for patients undergoing experimental interventions). Our cmRCT approach may be a first step to an organization in which all patients are routinely entered into a cohort (according to an opt-out rather than an opt-in scenario), to have their data captured automatically and systematically, and to make them eligible for random allocation to experimental interventions.

In summary, this paper shows that setting up a cmRCT based infrastructure can be set-up in routine clinical oncology. The design was accepTable to patients, physicians and researchers. In oncology, the cmRCT design provides a promising instrument to perform randomized evaluation of (experimental) interventions, indicated by high recruitment- and high response rates with good g eneralizability.

Statements:

Conflicts of interest: none

Funding: none

The first author has the right to grant on behalf of all authors.

JB, DYA, JV, DB, OR, CG, MV and HV designed and analyzed the study. JB, DYA, JV, HV wrote a first draft of the manuscript which was revised and approved by all other authors.

Acknowledgements

The authors like to thank M.J.H. van Deursen, C.A.W. Muilenburg, M.A. Oudhof-Osnabrugge and C. Haaring for their dedication to realize this project.

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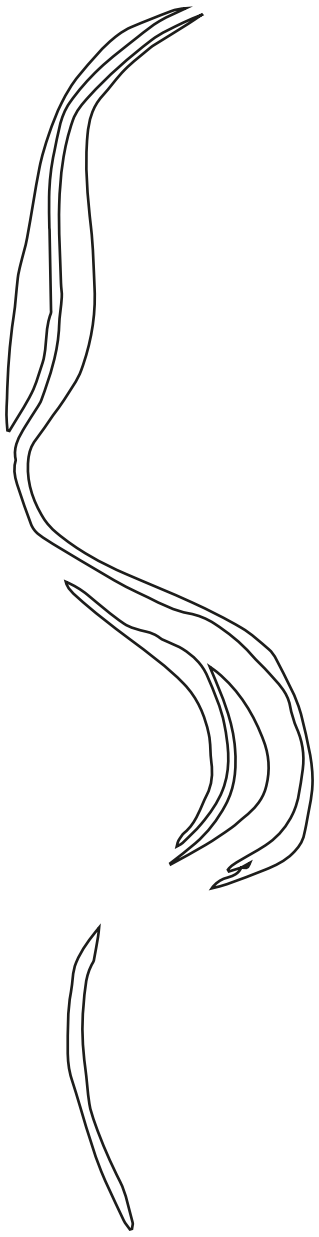

CHAPTER 4

IMPACT OF SHORT-COURSE RADIOTHERAPY VERSUS CHEMORADIATION ON QUALITY OF LIFE IN RECTAL CANCER PATIENTS

Submitted to British Journal of Surgery, September 2016

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CHAPTER 4

ABSTRACT

BACKGROUND

Patients with early-stage rectal cancer undergo direct surgery or short-course radiotherapy (scRT) followed by immediate surgery. Patients with advanced disease receive chemoradiation (CRT) with delayed surgery. In some cases, CRT induces complete clinical response, after which organ-preservation can be considered. Replacement of scRT by CRT in early tumors might allow organ-preservation in patients with early stage rectal cancer. It could, however, impair quality of life (QoL). This study compares QoL between scRT and CRT before, during and after treatment.

METHODS

In a multi-center prospective cohort, patients undergoing CRT or scRT with immediate surgery between February 2013 and December 2015 were identified (n=273). QoL was assessed by EORTC-C30 and -CR29 questionnaires at baseline 3, 6 and 12 months. To obtain comparable groups, propensity-scores for receiving CRT were calculated and used for restriction and adjustment. Longitudinal QoL-changes were analyzed by mixed models and compared between groups.

RESULTS

After restriction, 179 patients were included; 106 treated with CRT and 73 with scRT. CRT patients were younger, and had more advanced tumors. At baseline, QoL in scRT patients was comparable to CRT patients, except for significantly worse emotional scores. At 3 and 6 months, groups showed similar significant decreases in global health, physical, and social function, which returned to baseline levels at 12 months. Emotional scores significantly improved at 6 and 12 months in scRT patients. Only role and social function remained impaired in both groups. Sexual problems mainly existed at baseline, especially in CRT-group. There were no significant differences between the groups at any time point, except for worse emotional function in scRT patients at baseline and better function at 6 and 12 months.

CONCLUSION

During rectal cancer treatment, similar QoL changes are observed in patients undergoing scRT or CRT. For both groups, most QoL domains return to baseline-levels after 12 months, but role and social functioning remain impaired.

INTRODUCTION

Surgery is the cornerstone of rectal cancer treatment but is also associated with a 20-30% risk of postoperative morbidity, permanent stoma, anorectal dysfunction and impaired quality of life (QoL) [1, 2]. Preoperative treatment with radiotherapy (with chemotherapy) improves oncologic outcomes [3-5], but also further impairs QoL [6]. Rectum-preserving strategies, including local excision or 'watch and wait' strategies (ref) are increasingly offered to patients who have shown a complete clinical response following neo-adjuvant treatment [7-9].

The type of neo-adjuvant treatment depends on tumor size and resectability [10]. Preoperative short-course radiotherapy (scRT, 5x5Gy) is offered to patients with T3N0 tumors with threatened mesorectal-fascia or N1 to improve local control and survival [11, 12], while chemoradiation (CRT, 25x2Gy with concomitant capecitabine) with delayed surgery is offered to patients with locally advanced disease (N2 or threatened/involved mesorectal-fascia) in whom downsizing of the tumor is warranted[13-15]. Oncologic outcomes and toxicity proved to be similar between these regimens in a recent randomized trial [16]. In 15% of patients treated with CRT and delayed surgery, complete pathological response is observed [17, 18].

Immediate surgery following scRT patients, provides no time for tumor response to occur, and as such denies patients the option of rectum preserving treatment. Two recent trials demonstrate the that patients with early tumors can benefit from chemoradiation. A recent Danish trial showed that 78% (40/51) of patients with T2-3N0-1 reached a clinical complete response after CRT plus 15 Gy boost[7], and a multicenter study in very early (cT2) node negative patients showed that 94% (72 of 77) became eligible for organ-preservation after CRT [19]. Replacement of scRT with CRT may increase the proportion of patients eligible for rectum sparing interventions, but, due to its longer duration, inclusion of chemotherapy and long waiting time to surgery, may impair patients' QoL.
Thus far, only a few studies have compared QoL between the two regimens. The results of these studies have limited generalisabilty, since only T3-4 patients [20] or patients unfit for CRT [21] were included. The aim of this study was to compare QoL and symptoms following scRT and CRT in routinely treated, unselected, rectal cancer patients in the first year after diagnosis.

METHODS

In the Dutch prospective colorectal cancer cohort [22] we identified rectal cancer patients referred for radiation therapy at the University Medical Center Utrecht(UMCU) between February 2013 and December 2015. Patients with an indication for CRT who were deemed unfit by their physician were excluded from our analysis since these patients underwent scRT followed by delayed surgery instead of immediate surgery and do not fit the clinical question whether or not scRT can be replaced with CRT. All patients were routinely treated according to Dutch guidelines [10] and underwent IMRT-based neo-adjuvant (chemo-)radiation. Surgery took place in six referring centers and the UMCU . CRT was administered to patients with primarily unresecTable tumors (T3Nx with threatened mesorectal fascia, T4Nx or TxN2) and consisted of 25x2Gy with concomitant capecitabine, followed by surgery after 8-12 weeks. ScRT was administered to patients with primary resecTable tumors (cT1-3N1 or cT3N0 >5 mm extramural invasion; unthreatened mesorectal-fascia) and consisted of 5x5Gy followed by surgery within 1 week. For both schemes, surgery consisted of low anterior resection (LAR) with or without temporary deviating ileostomy (±3 months) or abdominoperineal resection (APR) with permanent colostomy. All participating centers performed open or laparoscopic surgery and two centers performed robotic surgery.

Demographic and patient characteristics, as well as clinical data including medical history, imaging, radiotherapy and surgery, were prospectively collected from patient files in the context of the cohort study. QoL and symptoms were assessed by means of paper and online questionnaires, before start of neo-adjuvant treatment (baseline) and at 3, 6 and 12 months. Questionnaires included the cancer-specific EORTC QLQ-C30 [23] and colorectal-specific QLQ-CR29 [24]. The QLQ-C30 is composed of 30 questions covering global health, five functional domains (physical, role, emotional, cognitive and social functioning), and symptoms (fatigue, pain, nausea and vomiting, diarrhea, constipation, insomnia, dyspnea, appetite loss and financial impact). The QLQ-CR29 consists of 29 questions on body image, stool, urinary and sexual function, abdominal and anal pain, and gastro-intestinal symptoms (stoma and non-stoma related). Quality of life outcomes were compared to a a normative age-matched Dutch cohort (n=1608) [25].

STATISTICAL ANALYSIS

Patients were categorized into scRT or CRT. Individual probability (propensity) to receive CRT was calculated by logistic regression analysis, with CRT (versus scRT) as dependent variable and age (continuous), comorbidity (yes/no), previous abdominal surgery (yes/no), T- (1-4), N- (0-2), M (0-1) stage, mesorectal-fascia involvement, surgical approach (open/laparoscopic/(other or not yet operated)) and surgical procedure (LAR/APR/(other or not yet operated)) as independent variables. Individual probabilities (propensity scores, PS) were used to restrict our study cohort to only include scRT and CRT patients with overlapping propensity scores so that, in theory, treatments were interchangeable. Baseline characteristics were compared between scRT and CRT patients (before and after restriction) using X2-test for proportions or T-test for continuous variables with normal distribution or Mann-Whitney U test otherwise.

QoL data were linearly transformed into scores between 0 - 100 for functional items according to the EORTC manual [26]. Scores of functional scales were visually checked for normality and presented as means when normally distributed and as medians otherwise. Symptom scales were presented as proportions of patients with no, mild, moderate or severe complaints on these four-scale questions.

For functional domains (global health, physical, emotional, role, cognitive and social function) higher scores indicate better functioning. For symptom scales higher scores indicate more complaints. Baseline scores were compared using T-tests. Mixed linear regression model was used to compare QoL changes within scRT and CRT patients over time (within-group differences) and to compare groups at different time-points (between-group). All models included a random intercept per patient. Fixed factors were treatment group, time (factor) and the interaction between treatment and time. Within- and between-group differences were both adjusted for PS, whereas between-group was also adjusted for patients' baseline scores. The within-group analysis included patients with at least one measurement. The between-group analysis included only patients with baseline plus at least one follow-up score. R was used with 'MatchIt' and 'opmatch' packages for propensity score calculation and restriction. SPSS (v21) was used for all other analyses.

RESULTS

Two-hundred seventy-three rectal cancer patients consented to cohort participation and filling out questionnaires. Seventy-three underwent scRT with immediate surgery and 159 CRT with surgery after 8-12 weeks. Forty-one patients received SCRT with delayed surgery and were excluded. After PS-based restriction, fifty-three patients with too high probabilities of receiving CRT were excluded (propensity scores (probabilities of receiving CRT) did not overlap with the scores of the sCRT group). A total of 179 patients were eligible for final analysis: 106 underwent CRT and 73 SCRT. CRT patients were younger (62 vs 68 years), had higher T- and N-stages (T4: 20% vs 0%, N2: 46% vs. 1%) and comparable M-stage (93% M0 in both groups) (Table 1). Surgical procedures and presence of permanent stoma (33% vs 39%) were also similar between groups. Questionnaire return rates were 139/179 at baseline (80% vs. 76% for SCRT- and CRT patients respectively), 126/167 at 3 months (72% vs. 78%), 112/149 at 6 months (74% vs. 76%), and 85/109 at 12 months (72% vs. 84%).

At baseline, global health, physical, role and social function scores were similar for scRT and CRT patients (Table 2). Only emotional function was significantly worse in scRT patients (72 vs. 82, p=0.05). All functional scores were comparable to those of the Dutch reference, except emotional function, which was lower in both groups.

Global health decreased significantly in scRT patients between baseline and 3 months (-10 points), but gradually returned to baseline-levels at 6 and 12 months (Figure 1, Table 2). CRT patients showed no significant changes over time and scores deviated with maximally 5 points from baseline-levels (Figure 1, Table 2). No significant differences were observed between groups at any time-point (Table 2). Physical function decreased significantly between baseline and 3 months in both groups (Figure 1, Table 2). At 6 months, scores remained significantly lower than baseline-levels. At 12 months, in the scRT group, physical functioning was still significantly lower than at baseline. No significant differences existed between groups at any time-point (Table 2).

ScRT patients showed a significant emotional improvement at 3, 6 and 12 months compared to baseline (Figure 1, Table 2). CRT patients remained more or less sTable over the whole period. Significant differences between groups favoring scRT were observed at 6 and 12 months when correcting for baseline – scores. Absolute emotional scores were comparable at 12 months.

Role function also decreased significantly –for both groups. For scRT patients the strongest drop in role function was seen at three months, while for CRT patients, role function was lowest at 6 months (Figure 1, Table 2). At 12 months, both groups had recovered in terms of role function, but scores remained lower than those observed at baseline (with a significant lower score for scRT patients Table 2). No significant differences existed between groups at any time-point (Table 2).

Social function showed a similar pattern over time as role function; a significant decrease in scores between baseline and 3 months and baseline and 6 months in both groups (Table 2). At 12 months, role function remained significantly impaired in scRT patients only (score at baseline was 85.0 compared to 69.1 at 12 months). No significant differences existed between groups at any time-point (Table 2). Cognitive function decreased significantly at 3 and 6 months compared to baseline level but improved at 12 months in CRT patients. In SCRT, no changes in cognitive function over time were observed (Figure 1, Table 2). No significant differences existed between groups at any time-point (Table 2). At 12 months, global health, physical-, (cognitive-) and role function scores had returned (within 10

points) to Dutch reference-levels (Figure 1), while role and social function remained considerably impaired.

Subgroup analysis of patients with a stoma (~80% of both groups) showed non-significant differences in functional outcomes between patients with a temporary ileo- or permanent colostomy within each group. Most remarkable was a 10-point lower role function score in colostomy versus ileostomy patients in both groups, followed only by a 20-point increase only for scRT colostomy patients at 6 months. This was not observed for CRT patients or ileostomy patients although some of the latter were reversed within this interval.

Regarding symptoms, CRT patients reported more moderate/severe diarrhea and anal pain than scRT patients at baseline (Figure 2). At 3 months, when scRT patients had already had surgery, while CRT patients had not, scRT patients reported more moderate/severe anal pain than CRT patients (35% vs. 25%), but less moderate/severe diarrhea. At 6 and 12 months, post-surgery for all patients, moderate/severe diarrhea and anal pain were similar. Moderate/severe anal pain persisted in ~20% of patients after 12 months. Sexual function response was low; for scRT patients, with 29% missings for scRT patients and 26% for CRT patients at baseline, and up to 32% and 29 % during follow-up respectively (Figure 4). Erectile dysfunction increased during follow-up in both groups, but was more pronounced after scRT. Sexual activity was particularly impaired in male CRT patients at baseline, but less during follow-up. No significant differences existed between groups during follow-up. In females, sexual reporting was low with little problems reported. Other symptoms (fatigue, pain, nausea, vomiting, constipation) showed no differences between groups.

TABLE 1 **Baseline characteristics of scRT and CRT patients before and after propensity score restriction**

	All patients		Patients after propensity score-based restriction	
	scRT	**CRT**	**scRT**	**CRT**
Patients (n)	73	159	73	106
Age (SD)	68.3 (40-85)	61.8 (26-82)	68.3 (40-85)	64.1 (46-82)
Gender (% Male)	57 (78.1)	115 (72.3)	57 (78.1)	80 (75.5)
Previous abdominal surgery (%)	19 (26.0)	58 (36.5)	19 (26.0)	32 (30.2)
T stage				
T1-2 (%)	20 (27.4)	6 (3.7)	20 (27.4)	6 (5.6)
T3 (%)	53 (72.6)	114 (71.7)	53 (72.6)	79 (74.5)
T4 (%)	0 (0)	35 (22.0)	0 (0)	21 (19.8)
Unknown	0 (0)		0 (0)	0 (0)
MRF involvement (%)	8 (11.0)	11 (70.4)	11 (15.1)	61 (57.5)
N stage				
N0 (%)	30 (41.1)	16 (10.1)	30 (41.1)	17 (16.0)
N1 (%)	35 (47.9)	41 (25.8)	35 (47.9)	40 (37.7)
N2 (%)	1 (1.4)	96 (60.4)	1 (1.4)	49 (46.2)
Unknown	6 (8.2)	6 (3.8)	6 (8.2)	0 (0)
M0 (%)	68 (93.2)	140 (88.1)	68 (93.2)	98 (92.5)
Surgical approach				
Open	10 (13.7)	25 (15.7)	10 (13.7)	10 (9.4)
Laparoscopic	51 (69.9)	103 (64.8)	51 (69.9)	74 (69.8)
Other/unknown/not yet operated	12 (16.4)	31 (19.5)	12 (16.4)	22 (20.7)
(Planned) Surgical procedure (%)				
LAR	40 (54.8)	70 (44.0)	40 (54.8)	44 (41.5)
APR	33 (45.2)	73 (45.9)	33 (45.2)	52 (49.1)
TEM/unknown	0.0	16 (10.1)	0.0	10 (9.4)
Postoperative stoma (%)				
No stoma	11 (15.1)	15 (9.4)	4 (5.5)	11 (10.4)
Ileostomy	36 (49.3)	60 (37.7)	36 (49.3)	43 (40.5)
Colostomy	24 (32.9)	58 (36.5)	24 (32.9)	41 (38.7)
Unknown/not yet operated	2 (2.7)	26 (16.4)	9 (12.3)	11 (10.4)
Response rates (%)				
Baseline	-	-	58 / 73 (79.5)	80 / 106 (85.5)
3 months	-	-	51 / 71 (71.8)	75 / 96 (78.1)
6 months	-	-	49 / 66 (74.2)	63 / 83 (75.9)
12 months	-	-	39 / 54 (72.2)	46 / 55 (83.7)

TABLE 2 **Within- and between-group differences estimates from mixed models analysis for regular scRT and CRT patients.**

Outcome	Group	Baseline		3 months						6 months		
		Within group baseline		N	Within group differences±			Between group differences±±		N	Within group differences±	
		N	Score		Score	95% CI	N	MD	95% CI		Score	95% CI
Global Health	scRT	58	73.6	51	63.3*	57.2 - 69.5	46	Ref		49	71.2	65.0 - 77.5
	CRT	80	75.1	75	72.2	67.2 - 77.2	62	6.0	--1.0 - 13.0	63	70.6	65.4 - 75.9
	P value		*0.71*					*0.09*				
Physical function	scRT	58	89.3	52	74.4*	68.5 - 80.3	47	Ref		49	81.2*	75.2 - 87.2
	CRT	81	87.0	75	77.6*	72.9 - 82.4	62	4.2	-2.8 - 11.1	63	77.5*	72.5 - 82.5
	P value		*0.26*					*.24*				
Emotional function	scRT	58	72.3	51	77.6	71.5 - 83.7	46	Ref		49	84.3*	78.1 - 90.5
	CRT	80	81.6	75	79.6	74.7 - 84.6	62	-5.7	-12.5 - 1.0	63	81.2	76.0 - 86.4
	P value		*0.05*					*.10*				
Role function	scRT	58	85.0	52	59.5*	50.8 - 68.3	47	Ref		49	70.4*	61.4 - 79.5
	CRT	81	81.5	75	66.5*	59.3 - 73.7	63	4.8	-6.3 - 16.0	63	60.6*	52.9 - 68.2
	P value		*0.10*					*.40*				
Social function	scRT	58	84.8	51	66.4*	59.5 - 73.3		Ref		49	77.5	70.5 - 84.6
	CRT	80	89.8	75	79.8*	74.2 - 85.4		8.9	-0.4 - 18.2	63	79.9*	73.9 - 85.9
	P value		*0.36*					*.06*				
Cognitive function	scRT	58	83.7	51	80.3	74.6 - 86.1		Ref		49	83.9	78.1 - 89.7
	CRT	80	91.7	75	86.3*	81.7 - 91.0		-1.4	-8.1 - 5.1	63	83.4*	78.5 - 88.3
	P value		*0.48*					*.66*				

				12 months				
	Between groups differences±±		N	Within group differences±			Between groups differences±±	
N	MD	95% CI		Score	95% CI	N	MD	95% CI
46	Ref		39	71.7	65.0 - 78.4	36	Ref	
53	-3.4	-10.5 - 3.8	46	74.3	68.5 - 80.2	41	2.5	-5.4 - 10.3
	0.36						*0.54*	
46	Ref		39	82.9*	76.6 - 89.3	36	Ref	
53	-3.5	-10.7 - 3.6	46	82.4	76.8 - 87.9	41	1.3	-6.4 - 9.1
	.33						*.73*	
46	Ref		39	85.7*	79.2 - 92.3	36	Ref	
53	-9.0	-15.9 - -2.1	46	82.8	77.2 - 88.5	41	-9.4	-16.8 - -1.9
	.01						*0.01*	
46	Ref		39	69.1*	59.4 - 78.9	36	Ref	
54	-11.4	-22.2 - 0.10	46	74.5	65.8 - 83.2	41	5.6	-7.0 - 18.1
	.052						*.38*	
46	Ref		39	74.2	66.5 - 81.8		Ref	
54	-3.9	-13.4 - 5.7	46	83.8	77.0 - 90.6		5.9	-4.5 - 16.3
	.08						*.26*	
46	Ref		39	88.4	78.3 - 90.5		Ref	
54	-5.8	-12.6 - 1.0	46	84.4	83.0 - 93.8		-2.0	-9.3 - 5.3
	.09						*.60*	

± Within group differences were corrected for the propensity score which is a composite adjustment including age, comorbidity, previous abdominal surgery, T-, N- and M-stage, mesorectal fascia involvement, surgical approach and surgical procedure.
±± Between group differences are corrected for the baseline score and propensity score (including age, comorbidity, previous abdominal surgery, T-, N- and M-stage, mesorectal fascia involvement, surgical approach and surgical procedure).
* significant within-group difference (p≤0.05) compared to score at baseline of this group
^ significant difference (p≤0.05) between scRT and CRT groups at baseline
scRT = scRT group, CRT = CRT group, P = p-value of between-group comparison, QoL = quality of life score , N = number of measurements, Score = adjusted score per group obtained from the within-group analysis, Ref = reference category, MD = mean difference in scores compared to the reference category adjusted for the propensity score (including age, comorbidity, previous abdominal surgery, T-, N- and M-stage, mesorectal fascia involvement, surgical approach and surgical procedure) and the baseline score.

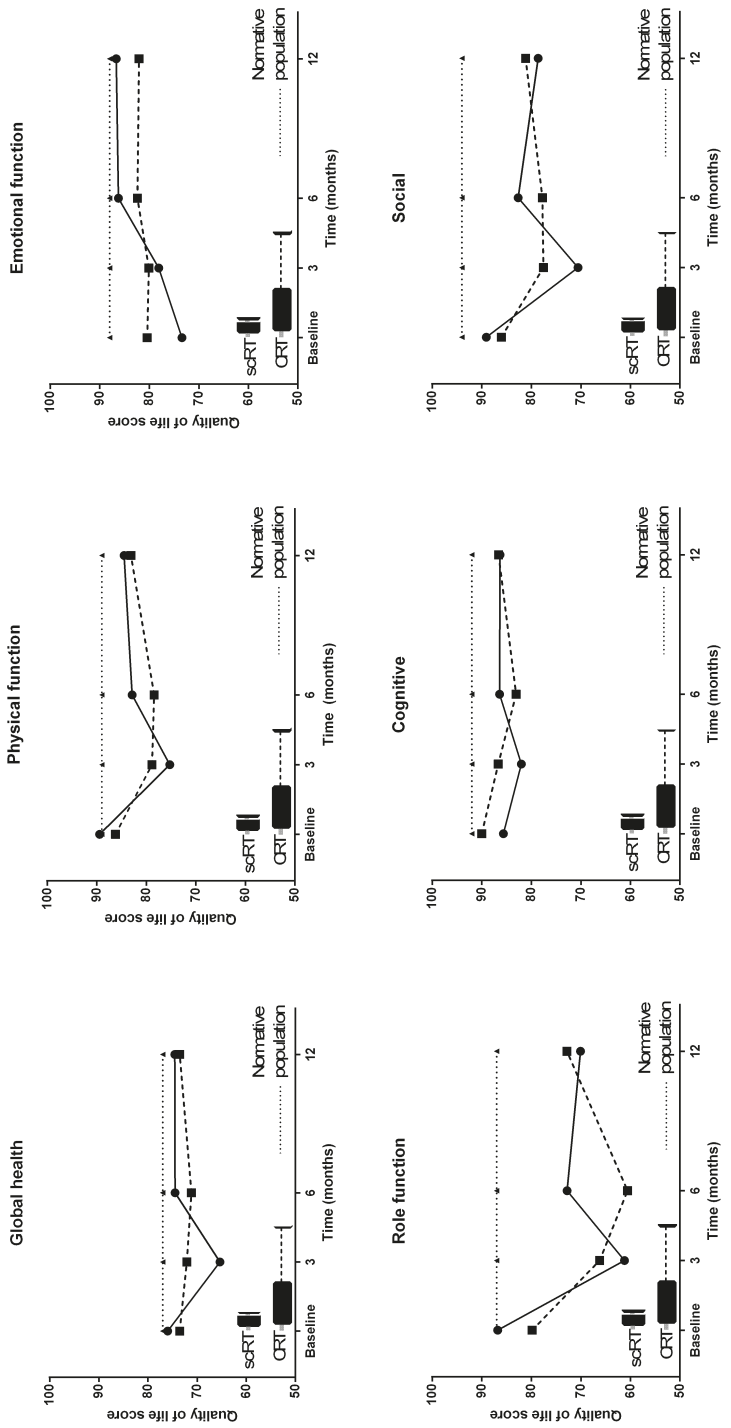

FIGURE 1 **Mean quality of life scores at baseline and follow-up for scRT and CRT-patients and the Dutch reference population.**

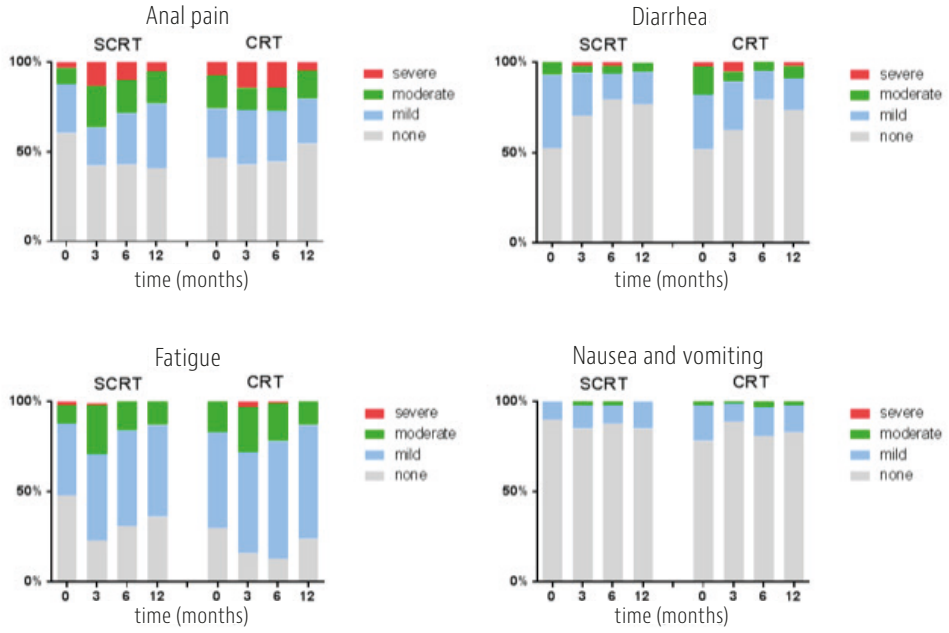

FIGURE 2 **Symptom reported at baseline and follow-up in scRT and CRT patients.**

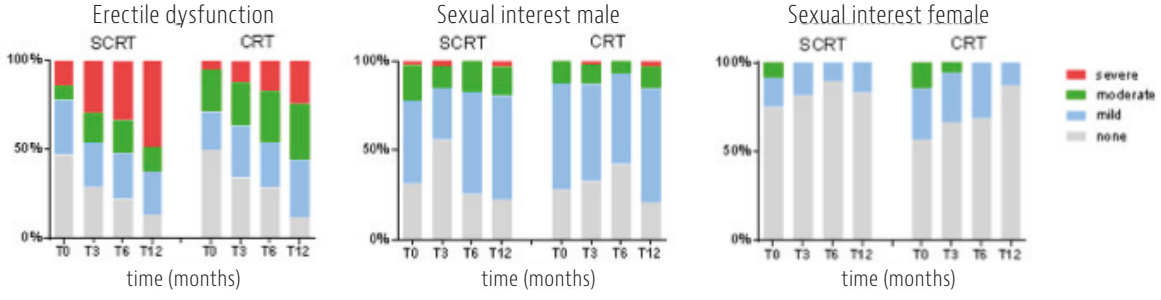

FIGURE 3 **Sexual function reported at baseline and follow-up in scRT and CRT patients.**

DISCUSSION

This study shows that the impact of neo-adjuvant treatment on QoL and symptoms is similar for patients treated with scRT and those treated with CRT. In terms of physical function, role function and social function, scRT patients generally showed the strongest reduction in scores at three months, while in CRT patients, these domains were mostly affected at 6 months. At 12 months, patients had more or less recovered to baseline levels in most functional domains, except for role and social function. For both groups, emotional function was lowest at baseline, and improved over follow-up, in particular for scRT patients. Having stomas was equally distributed and showed only minor influence on role function at 3 and 6 months.

Symptoms of anal pain, and fatigue were common, and persisted over time. Decreased functional scores suggested to be consequent with higher reporting of (bowel) symptom severity at the same time-point (especially anal pain). Diarrhea, most prominent in CRT patients at baseline and 3 months, diminished during follow-up. Sexual function was poorly reported, in particular in CRT patients, which increases the risk of selective reporting and making results difficult to interpret. However, an increase in erectile dysfunction seems to exist in both groups.

Our findings indicate that the impact of replacing scRT with CRT on QoL outcomes may be minimal. This is in line with previous studies which have also reported similar patterns of QoL following scRT and CRT [16, 20, 21]. In contrast to the present study, earlier studies were not always performed in routine settings but included trial patients that are often younger or with less comorbidity [27, 28]. Also, in one study scRT was followed by six additional chemotherapy cycles, which prolongs surgical interval, increases risk of adverse events/complications and therefore makes results hard to compare [16]. The Polish trial, with a comparable median follow-up of 12 months, was restricted to T3-4 patients with low/mid non-fixed rectal tumors [20]. The third study with a cross-sectional design [21] compared fit CRT patients with low tumors, with unfit scRT patients with predominantly mid/high tumors after a long follow-up > 4 years, but found comparable results of the present study after 12 months. Because of these differences in patient selection, treatments and follow-up periods, but also the use of less localized radiation techniques in previous studies - potentially increasing risk on toxicity [20, 21] - complicate direct comparison to our results.

There were no differences in surgical approach and procedures between groups. Nevertheless, lower tumors are more frequently treated with CRT and APR because of their proximity to the mesorectal fascia. However, from our data we are unable to tell whether there is an interaction between radiotherapy regimen and tumor height. Such an interaction may, however, become one of the key features in the future when selecting patients for local excision or non-operative management, since these patients with low tumors might benefit the most.

We used the Dutch reference scores to put patient scores into perspective. At 12 months, we found that following both CRT and scRT, patients scored lower than the reference population in practically all domains, in particular in the domains of role and social functioning. Some other studies, have also shown that patients report similar or better outcomes than the general population. German [21, 29, 30] and Norwegian [30, 31] cohorts unexpectedly showed better role function and bowel function for patients compared to normative cohorts [29, 31]. This could be explained by differences between study populations [20, 21, 25, 29-31] or differences in reference values between countries (based on national health status and cultural differences) [32]. In addition, it may be explained by the phenomenon of

'response-shift' that (cancer) patients may experience. Response shift, defined as a recalibration in internal standards and reconceptualization of what good quality of life entails, has previously been shown for patients with colorectal cancer who reported more positive on having a stoma with longer exposure to it [33] and by a study showing unaffected QoL scores despite a decline in objective physical condition [34]. It has been suggested not to correct patient-reported outcomes for such calibration-shifts, since they are inherent to the 'disease process' (diagnosis, treatment and follow-up) [35]. To clinicians this phenomenon is important, when when discussing treatments with their patients, [36].

Strengths of our study include the prospective and systematic measurement of QoL in a routine rectal cancer population and reasonably high response rates (comparable to other colorectal studies [20, 30, 37-42]). In total, ±90% of patients agreed to participate in the cohort and ±85% of them agreed to fill out questionnaires. Therefore, generalizability of our results is high. Third, we selected only patients for whom substitution of scRT with CRT is a realistic option based on overlapping propensity scores. Furthermore, exclusion of patients too fragile for CRT makes that our results are applicable to routine patients for whom organ-preservation can be considered as a treatment option.
We acknowledge this study has limitations. Our sample size is relatively small, and may therefore be underpowered to detect some – clinically relevant – differences. Also, we only followed patients until 12 months post diagnosis, while longer follow-up data may be relevant to inform patients. Another limitation includes the fact that we measured bowel symptoms by means of the QLQ-C30 and CR29. These questions may have been shown to have limited sensitivity for picking up changes over time [41]. Our data might suggest that severity of bowel symptoms could be associated with functional domain scores - as demonstrated in the present and a previous study [29] - adequate measuring of bowel function is essential. To optimally discriminate between symptom severity, two recently validated alternatives may therefore be considered in future studies - the LARS [43, 44] and MSKCC BFI [42] - which potentially have superior discriminative ability on bowel function effects induced by treatment compared to the EORTC questionnaires [41].

In summary, this study demonstrates that changes in QoL within the first 12 months after diagnosis are comparable between routinely treated rectal cancer patients receiving short-course radiotherapy or chemoradiation. This suggests that, in terms of QoL, CRT may be an accepTable alternative to SCRT for patients who seek organ-preservation. Future studies with longer QoL follow-up time and studies including organ-preservation strategies are required to establish the full potential of replacing scRT with CRT.

Acknowledgements

The authors would like to thank Marijke van Deursen and Cees Haaring for data collection and data management solutions.

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PART 2

DEVELOPMENT AND EVALUATION OF A MRI-GUIDED DOSE-ESCALATION TREATMENT

CHAPTER 5

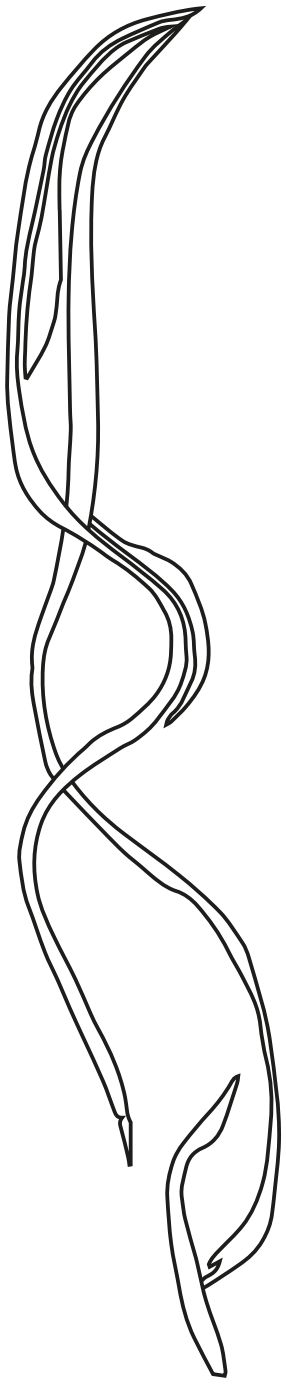
Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis

CHAPTER 6

Inter-observer agreement of mri-based tumor delineation for preoperative radiotherapy boost in locally advanced rectal cancer

CHAPTER 7

Randomized controlled trail for pre-operative dose-escalation boostin locally advanced rectal cancer – rectal boost study: study protocol for a randomized controlled trail



CHAPTER 5

IMPACT OF RADIOTHERAPY BOOST ON PATHOLOGICAL COMPLETE RESPONSE IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Published in: Radiotherapy and Oncology, October 2014, 113(1):1-9

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CHAPTER 5

ABSTRACT

PURPOSE

We conducted a systematic review and meta-analysis to quantify the pathological complete response (pCR) rate after preoperative (chemo)radiation with doses of ≥60 Gy in patients with locally advanced rectal cancer. Complete response is relevant since this could select a proportion of patients for which organ-preserving strategies might be possible. Furthermore, we investigated correlations between EQD2 dose and pCR-rate, toxicity or resectability, and additionally between pCR-rate and chemotherapy, boost-approach or surgical-interval.

METHODS AND MATERIALS

PubMed, EMBASE and Cochrane libraries were searched with the terms 'radiotherapy', 'boost' and 'rectal cancer' and synonym terms. Studies delivering a preoperative dose of ≥60 Gy were eligible for inclusion. Original English full texts that allowed intention-to-treat pCR-rate calculation were included. Study variables, including pCR, acute grade ≥3 toxicity and resectability-rate, were extracted by two authors independently. Eligibility for meta-analysis was assessed by critical appraisal. Heterogeneity and pooled estimates were calculated for all three outcomes. Pearson correlation coefficients were calculated between the variables mentioned earlier.

RESULTS

The search identified 3377 original articles, of which 18 met our inclusion criteria (1106 patients). Fourteen studies were included for meta-analysis (487 patients treated with ≥60 Gy). PCR-rate ranged between 0.0 – 44.4%. Toxicity ranged between 1.3 – 43.8% and resectability-rate between 34.0-100%. Pooled pCR-rate was 20.4% (95% CI 16.8 – 24.5%), with low heterogeneity (I2 0.0%, 95% CI 0.00 – 84.0%). Pooled acute grade ≥3 toxicity was 10.3% (95% CI 5.4 – 18.6%) and pooled resectability-rate was 89.5% (95% CI 78.2 – 95.3%).

CONCLUSION

Dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR-rates and accepTable early toxicity. This observation needs to be further investigated within larger randomized controlled phase 3 trials in the future.

INTRODUCTION

Colorectal cancer is the third most common cancer and often diagnosed in an advanced stage. Treatment of locally advanced rectal cancers (LARC) then consists of neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision (TME). The clinical outcome after CRT is largely dependent on tumor response to CRT [1, 2]. Overall, ~15% of patients experience a pathological complete response (pCR) at the standard radiation dose (45-50.4 Gy) [1, 3]. Complete response is relevant since this could select a proportion of patients for which organ-preserving strategies might be possible, either by local excision ([4, 5], ISRCTN14422743) or a "wait-and-scan" strategy [6-8].

Since response to radiotherapy is dose dependent in rectal cancer, dose escalation may lead to higher complete response rates [9-11]. A recent mathematical prediction model on pCR-rate indicated that 50% of patients could reach pCR after 92 Gy and that response exponentially increased after 60 Gy [12]. This was in line with a prediction-curve based ona large systematic review on dose response in patients with LARC [3, 12]. Nevertheless, dose-escalation trials using ≥60 Gy have not been systematically reviewed yet. Therefore, we conducted a systematic review and meta-analysis to quantify the pCR-rate after preoperative (chemo)radiation with doses of ≥60 Gy in patients with LARC. Furthermore, correlations between pCR-rate, acute grade ≥3 toxicity, chemotherapy, boost technique and surgical interval were studied.

METHODS

SEARCH STRATEGY

The PRISMA guidelines for systematic review and meta-analysis were used to conduct this review [13]. We searched the electronic PubMed, EMBASE and Cochrane databases with the last search performed on April 10th 2014. Synonym terms for 'radiotherapy', 'boost' and 'rectal cancer' were used (see supplement). The search was limited to articles published after 1988, because adjuvant treatment became progressively replaced by neo-adjuvant (chemo)radiation since. Duplicates were removed and additional papers were retrieved through cross referencing.

STUDY SELECTION

All studies in primary LARC patients (T3-4NxM0/fixed tumors) receiving a preoperative physical radiation dose of ≥60 Gy (with at least 45 Gy external beam radiation therapy (EBRT) to the whole tumor were eligible for inclusion. Original research, in English, with available full texts were included. Studies without our primary endpoint, palliative intent, or with previously irradiated patients were excluded, as well as studies using contact radiotherapy and/or X-ray treatment (CXR).

DATA EXTRACTION AND QUALITY ASSESSMENT

The primary outcome was the proportion of patients scheduled for preoperative ≥60 Gy radiation that reached pCR. PCR was defined as absence of residual cancer cells in the resected specimen. This was calculated by intention-to-treat i.e. the number of patients with pCR divided by all patients scheduled for preoperative ≥60 Gy radiation. If not so provided by the authors, pCR-rate was calculated from the data. Corresponding authors were contacted in case of insufficient information.

Secondary outcomes were acute grade ≥3 toxicity, and resectability rate. All toxicity scores were redefined to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.0) [14], and presented as the percentages of patients experiencing acute grade ≥3 toxicity. Resectability rate was defined as the percentage of patients with resecTable tumors after (chemo-) radiation divided by all patients scheduled for preoperative ≥60 Gy radiation. Furthermore, we extracted study-design, -size, demographics, the radiation protocol (total dose (EQD2-dose with alfa/beta=10 [12]), boost dose, radiation approach, margins, chemotherapy regimen (agent(s), administration protocol and doses), and time-to-surgery. Extraction was performed by two authors independently (JPMB and AMdH). In case of discrepancy consensus was reached between authors.

CRITICAL APPRAISAL

Study quality was assessed by pre-defined criteria (Table 2) based on items listed in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15]. Also study design, data presentation, and clinical characteristics that may have influenced the primary outcome were used. Quality assessment was also performed independently by two authors (JPMB and AMdH). Studies were eligible for meta-analysis if at least a valid pCR-rate could be calculated.

STATISTICAL METHODS

The R statistical environment (version 3.0.2, R Development Core Team, 2011) with 'metafor' package (version 1.9-1) was used for statistical analysis [16]. Potential publication bias was checked by funnel plots and rank correlation tests (Kendall's tau). PCR-rate, grade ≥3 toxicity and resectability rate were logit transformed, pooled, re-transformed and presented as proportions with 95% confidence interval (CI). Heterogeneity was assessed by the I2 statistic (i.e. estimated proportion of unexplained

inter-study variance) prior to pooling. Random effects models, using a restricted maximum likelihood estimator, were used in case of large inter-study variance (I2≥65%) to calculate a pooled estimate. Otherwise mixed- (25<I2<65%) or (≤25%) fixed effects models were used. Robustness of the pooled estimate was addressed by two sensitivity analyses (SA). The first SA excluded studies with pCR-rates lower than the 15% which we took as a reference standard based on large meta-analyses [1, 3], i.e. negative outliers. The second SA only included studies with an EQD2-dose of ≥60 Gy. Correlations between EQD2-dose and pCR-rate, toxicity and resectability, as wells as between pCR-rate and chemotherapy, boost-approach and surgical-interval were visualized in scatter plots and formally tested by Pearson's correlation test. P-values were considered significant if the p-value was below 0.05.

RESULTS

In total 3377 articles were identified (Figure 1). After removing duplicates, 2765 articles were screened on title and abstract. Seventy-one remaining articles were screened on full text, of which 54 were excluded for the following reasons: no full text available (n=20), studies not involving patients (n=4), not including patients with LARC (n=10), no curative setting (n=3), only included previously irradiated patients (n=1), preoperative dose of <60 Gy (n=5), already included (non-unique) patient-population (n=3), non English articles (n=2) and studies without our primary endpoint pCR (n=6). One additional article was identified by cross-referencing. Finally, 18 studies (1106 patients) were included for systematic review, consisting of 7 prospective single/multiple arm, 3 RCTs, 2 NRCTs and 6 phase I/II trials (see Table 1 and Figure 1) [17-34]. Five-hundred-thirty-nine patients (48.7% of identified patients) were scheduled for ≥60 Gy radiation with median of 21 patients per study (range 1-109). Median age ranged between 42-68 years. T-stage was reported in 9 studies for 342 of 539 patients (63.5%), with range 9.0-100%. Nodal status was reported in 6 studies for 321 patients (59.6%), with a range of 30.0-89.0%.

Treatment characteristics are summarized in Table 1. Total radiation dose varied between 60-75 Gy (EQD2 58.4 – 66.3 Gy), as an accumulation of standard EBRT (45-54 Gy) and boost dose (6-30 Gy). Twelve studies used EBRT only, 6 studies used brachytherapy only and two combined EBRT and brachytherapy. A simultaneous integrated boost (SIB) approach was used in two studies whereas four studies used a combination of SIB and sequential approaches. Target margins were mentioned in all but one study [21]. Most studies used 3-5 field box techniques with almost similar elective fields, predominantly defined by 1-1.5 cm anterior to the sacral wall, 1-2 cm outside the bony pelvis, the L5-S1 border and 3-5 cm caudal of the tumor. No studies used Intensity Modulated Radiotherapy (IMRT).

All but two studies administered 5-Fluorouracil (5-FU) based chemotherapy [21, 26], namely 5-FU, Uracil-Tegafur (UFT) or Capecitabine, at varying doses (see Table 1). Leucovorin was added in six studies and Oxaliplatin in two.

One study did not report toxicity at all [30]. In the other studies toxicity was mostly scored according to NCI (10 studies), Radiation Therapy Oncology Group (RTOG, 2 studies), or Response Evaluation Criteria in Solid Tumors list (RECIST, one study) criteria. Four studies did not report specifically which toxicity criteria were used, but did report if toxicity demanded treatment. Transformation to NCI criteria was chosen since it was predominant.

Interval to surgery varied between 2-10 weeks (median 7) after chemoradiation. Resectability ranged between 34.0-100%. Five studies reached 100% resectability [18, 21, 25, 30, 31]. Others ranged between 75.0-96.0% and one was limited to 34.0% [34]. Three studies did not report resectability rate. Most common reasons to omit surgery were disease progression, distant metastasis or patient refusal. Surgical complication data was scarce for the ≥60 Gy sub(group) specifically. Six studies reported wound infection, dehiscence or delayed healing problems in 0.0-16.0% [21, 23, 25, 29, 31, 32], one patient required small bowel resection [18], and two studies reported surgical complications in all patients [18, 34]. Eight studies used some form of standardized pathologic response assessment, of which four explicitly used the Mandard tumor regression grade (TRG) [35].

After critical appraisal 14 studies remained eligible for meta-analysis, representing 90.4% (487 of 539) of patients (Table 2). Unexplained inter-study variance (I2) was low for pCR pooling (0.0%, 95% CI 0.0

– 84.0%) and intermediate for grade ≥3 toxicity and resectability pooling (66.2%, 95% CI 25.5 – 89.6%, and 80.3%, 95% CI 56.1 - 92.9%, respectively). Consequently, a fixed effects model was used to calculate the pCR-rate estimate, and a random effects model for the grade ≥3 toxicity and resectability estimates. PCR-rate varied considerably between studies, from 0.0 to 44.4%. The pooled pCR-rate estimate was 20.4% (95% CI 16.8 – 24.5%) (see Figure 2). The funnel plot did not show asymmetry (Kendall's tau = -0.07, p=0.74) [36] (see supplement). Additionally, the first sensitivity analysis, excluding negative outlier pCR-rates below 15%, estimated the pCR-rate at 22.9% (95% CI 18.7 – 27.6%) and the second sensitivity analysis, using only studies with EQD2 doses of ≥60 Gy, estimated pCR-rate at 18.1% (95% CI 13.9 – 23.2%) (see Figure 2).

Acute grade ≥3 toxicity for boost patients was reliably reported in 11 of 18 studies. Data on late toxicity specifically for boost patients was scarce and therefore not further discussed in this paper. Acute toxicity consisted mostly of gastro-intestinal complaints, dermatitis, leukopenia/neutropenia and pain. Grade ≥3 toxicity was low (≤10%) in seven studies, higher in three (13.6, 33.0 and 42.6%) and a single-patient study had 100% (see Table 1) [18]. There was no asymmetry in the funnelplot (Kendall's tau = -0.1, p=0.76) (see supplement). The acute grade ≥3 toxicity estimate was 10.3% (95% CI 5.4 – 18.6%) (see Figure 3). The resectability estimate was 89.5% (95% CI 78.2 – 95.3%) (see Figure 3).

Total EQD2 dose did not correlate with acute grade ≥3 toxicity (Pearson -017, p>0.62) or resectability (Pearson -0.29, p<0.33). PCR-rate was not correlated with total EQD2 dose (Pearson 0.44, p>0.88), chemotherapy (5-FU only vs. 5-FU+Oxaliplatin) (Pearson 0.06, p>0.83), boost-approach type (EBRT, Brachy or EBRT/Brachy combination) (Pearson 0.06, p>0.85), nor with length of interval between radiotherapy and surgery (Pearson 0.10, p>0.74).

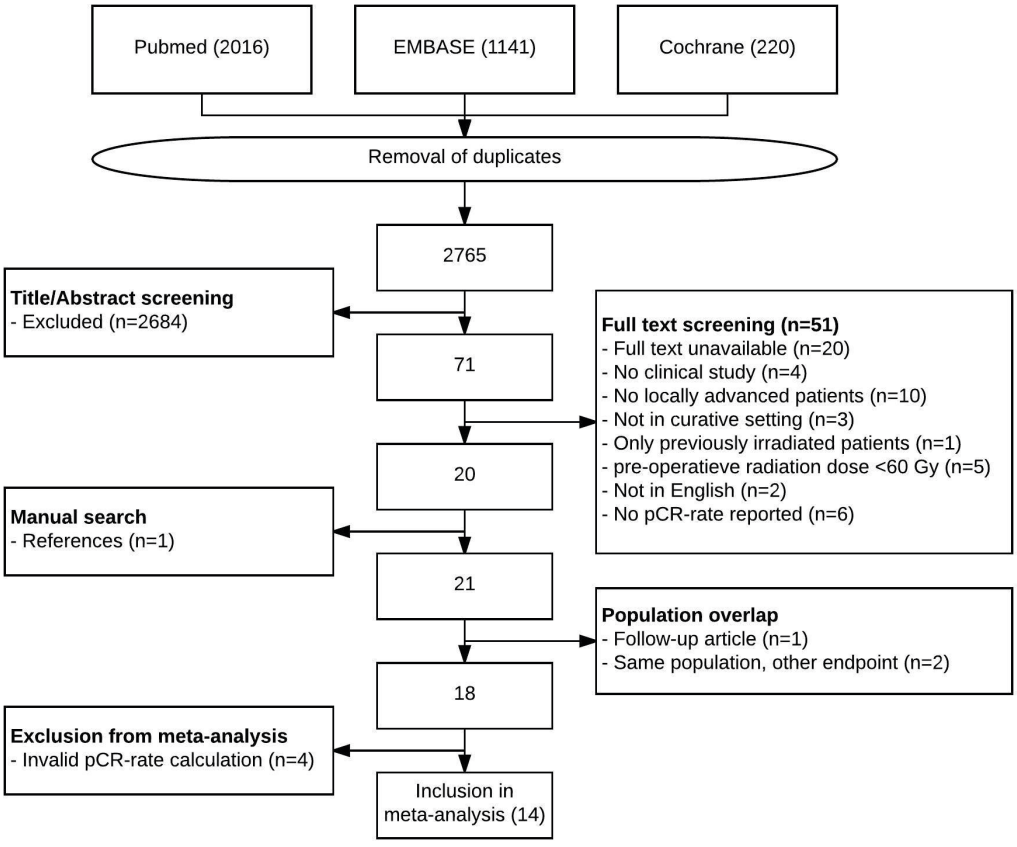


FIGURE 1 **Flow-chart of the study selection procedure.**

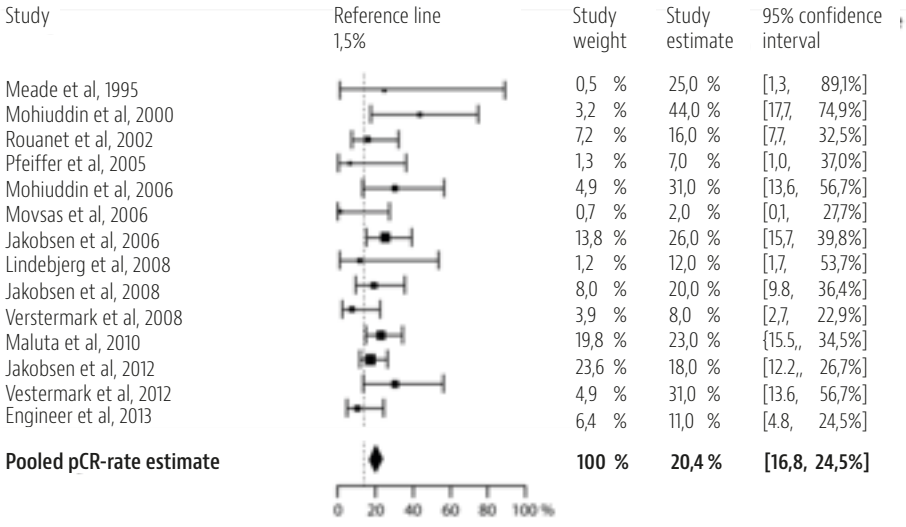
TABLE 1 **Characteristics of the included studies.**

Author, year	Study design	Total number of study patients (n)	Unique boost treated patients (n)	Median age (yr) of total study population	Fractions (standard)	Dose (standard) (Gy)	Fractions (boost)	Total dose (Gy)	EQD2 dose (total)	Boost approch
Marks et al., 1993	pSA	52	-	57	31x1,8/ 22x2,5	45,0	5x1	60	61-64	EBRT
Meade et al., 1995	nRCT	20	1	68	25x1,8	45,0	9x1,8	6	60	EBRT
Movsas et al., 1998	I/II	27	7	61	25x1,8	45,0	14x1,2 BID	62	60	EBRT
Mohiuddin et al., 2000*	nRCT	33	9	64	38x1,2 BID	50,0	12x1,2 BID	60	65	EBRT
Rouanet et al., 2002*	pSA	43	36	64	18x2,1	37,8	10,5x2,1	60	60	EBRT
Pfeiffer et al., 2005*	I/II	18	14	65	27x2	48,6	3x2	60	60	EBRT
Jakobsen et al., 2006*	pSA	50	50	61	27x2	54,0	3x2,5 Br HDR	65	66	Brachy
Mohiuddin et al., 2006*	RCT	106	16	57	38x1,2 BID	45,6	12x1,2 BID	60	56	EBRT
Movsas et al., 2006	II	22	21	64	25x1,8	45,0	14x1,2 BID	62	60	EBRT
Ho-Pun Cheung et al., 2007	pSA	70	29	64	25x1,8	45,0	9x1,8	6	60	EBRT
Sun Myint et al., 2007	pSA	16	16	-	25x1,8	45,0	1x10 Br HDR	75	61	Brachy
Jakobsen et al., 2008*	pSA	35	35	65	27x2	54,0	3x2,3 Br HDR	65	66	EBRT+ Brachy
Vestermark et al., 2008*	II	52	36	60	27x2	48,6	3x2	60	60	EBRT
Lindebjerg et al., 2009*	MA	135	8	65	27x2	60,0	3x2+5 Br HDR	60-65	66	EBRT+ Brachty
Maluta et al., 2010	II	76	76	60	25x2	50,0	5x2	60	60	EBRT
Jakobsen et al., 2012	RCT	243	109	63	28x1,8	50,4	2x5 Br HDR	60	62	Brachy
Vestermark et al., 2012*	I	16	16	62	27x2	48,6	3x2	06	60	Brachy
Engineer et al., 2013	RCT	90	44	42	25x1,8	45,0	11x1,8	65	64	EBRT

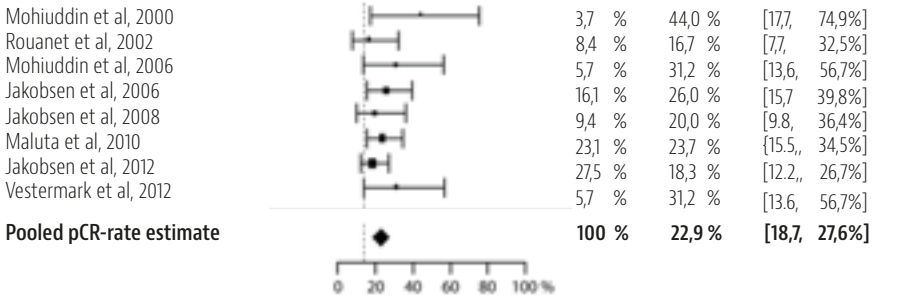
(pSA = prospective single arm study, I / II = phase I / II trial, (N)RCT = (non)randomized controlled trial, BID = bis in die (twice daily), Br HDR = brachytherapy high-dose rate, EQD2 = Equivalent 2Gy dose, 5-FU = Fluorouracil, UFT = Tegafur-uracil, Leu = Leucovorin, Oxi = Oxaliplatin, TEGAFOX = Uracil/ftorafur/leucovorin/Oxaliplatin, Cap = Capecitabine, n d.d. = in n daily doses, /d = per day, /wk = per week, SIB = simultaneous integrated boost, pCR = pathologic complete response. (* additional data obtained through the corresponding author)

Boost timing	Chemo-therapy in boost treated patients	Chemo-therapy dose	Maximal tumor distance from anal verge (cm)	T3 (%)	T4(%)	N+(%)	Interval to surgery (planned/median)	Resectability rate (%)	Percentage acute grade >3 toxicity for >60 Gy (sub)group (% grade 3 / grade 4)	Number of pCR events (boost patients only)	Percentage pCR (n)
SIB	-	-	0-3	-	-	-	4,8/-	100,0	-(-/-)	-	-
sequen-tial	5-FU (+Leu)	225mg/m2 d.d. (+30mg/m2 d.d.)	-	90,0	10,0	30,0	4,8/-	100,0	100 (-/100)	0	0,0
sequen-tial	5-FU	1000mg/m2/d for 4 days in week 1 & 4	12	78,0	32,0	-	4,6/-	-	85,7 (71,4/14,3)	-	-
sequen-tial	5-FU	225 mg/m2 d.d.	-	-	-	-	6-8/-	77,0	33 (33/0)	4	44,4
sequen-tial	-	-	6	84,0	16,0	30,0	2/-	100,0	-(-/-)	7	16,3
SIB+se-quential	UFT+Leu	150-300 mg/m2/d + 22,5 mg/d	-	-	-	-	6/5,7	78,0	5,6 (5,6/-)	1	7,1
sequen-tial	UFT+Leu	100mg/m2 3 d.d. 7,5 mg 3 d.d.	10	100,0	0,0	70,0	-/-	96,0	6,0 (6,0/-)	13	26,0
SIB	5-FU	225 mg/m2 d.d.	9	71,0	29,0	-	4-10/7	92,0	42,6 (-/-)	5	31,3
sequen-tial	5-FU	1000 mg/m2/d for 4 days in week 1 & 6	12	9,0	91,0	-	4-6/-	100,0	13,6 (-/-)	0	0,0
sequen-tial	-	-	-	-	-	-	10/-	-	-(-/-)	-	-
sequen-tial	5-FU/ Cap	750/1000 mg/m2 for 4 days in week 1&5 or 825 mg/m2/d	-	-	-	-	6-8/-	-	-(-/-)	7	43,8
sequen-tial	UFT+Leu	100 mg/m2 3 d.d. + 22,5 mg 3 d.d.	10	77,0	33,0	77,0	8/-	94,2	5,7 (5,7/0)	7	20,0
SIB+se-quential	UFT+Leu	100 mg/m2 3 d.d. + 22,5 mg 3 d.d	-	-	-	-	6/7,9	75,0	5,3 (3,5/0)	3	8,3
SIB+se-quential	5-FU +Leu	100 mg/m2 3 d.d. + 22,5 mg 3 d.d	10	-	-	-	8/-	100,0	-(-/-)	1	12,5
sequen-tial	5-FU +Oxi	200 m/m2/d +45 mg/m2/wk	12	89,0	11,0	54,0	4-6/-	100,0	1,3 (1,3/0)	18	23,7
sequen-tial	UFT+Leu or 5-FU	100 mg/m2 3 d.d. (Denmark) of 225/mg/m2/d (Canada)	10	84,0	16,0	89,0	8/-	92,6	10 (10/0)	20	18,3
SIB+se-quential	TEGA-FOX	pre-RT 100 mg/m2 3 d.d. + 7,5 mg 3 d.d. on day 1-14 + Oxi 130 mg/m2. Concurrent 100 mg/m2 3 d.d. + 22,5 mg 3 d.d. + 30-60 mg/ m2/wk ubcreasing with 10 mg/ m2/wk	-	-	-	-	>6/8,5	-	-(-/-)	5	31,3
sequen-tial	-	-	-	-	-	-	6-8/10	34,0	4,8 (4,8/0)	5	11,4

pCR-rate



Sensitivity analysis of studies with >15% pCR-rate



Sensitivity analysis of studies with >60 Gy EQD2

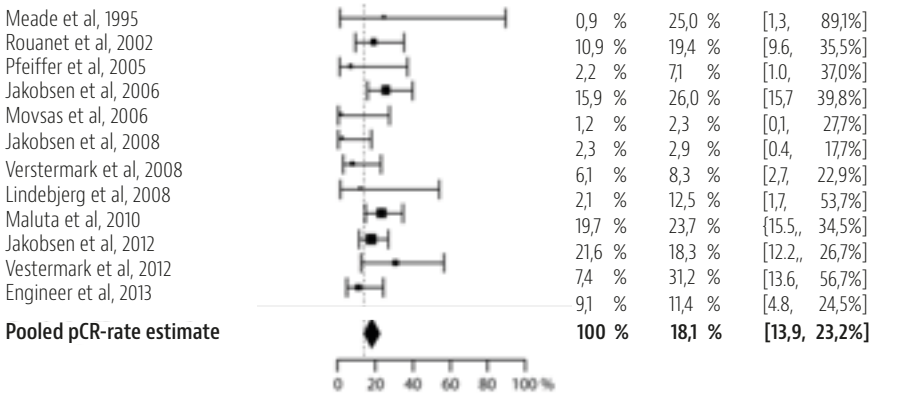


FIGURE 2

Meta-analysis forestplot of pCR-rates and pooled estimate in comparison to a reference line of control group (14.8%) (pCR = pathological complete response).

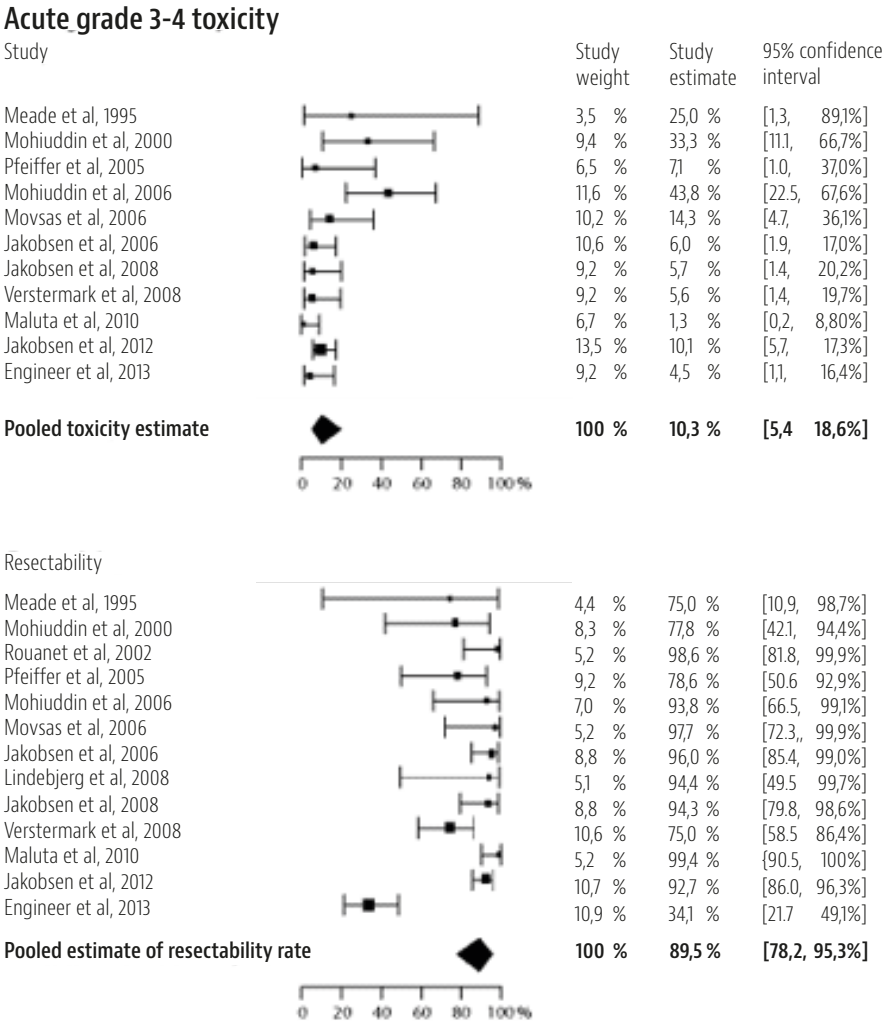


FIGURE 3 **Forest plot of available acute grade ≥3 toxicity and resectability with pooled estimate.**

TABLE 2 **Critical appraisal and eligibility assessment for meta-analysis.**

Author, year	Identification of LARC subgroup with > 60 Gy (y/n)	Standard chemotherapy protocol (y/n/na)	Surgical interval reported (y/n)	Standardized pathologic response assessment (y/n)
Marks et al., 1993	N	na	Y	N
Meade et al., 1995	Y	N	Y	Y
Movsas et al., 1998	Y	Y	Y	N
Mohiuddin et al., 2000*	N	N	Y	N
Rouanet et al., 2002*	N	na	Y	N
Pfeiffer et al., 2005*	Y	N	Y	N
Jakobsen et al., 2006*	Y	Y	N	Y
Mohiuddin et al., 2006*	Y	Y	Y	Y
Movsas et al., 2006	Y	Y	Y	Y
Ho-Pun-Cheung et al., 2007	N	na	Y	Y
Sun Myint et al., 2007*	N	N	Y	N
Jokobsen et al., 2008*	Y	Y	Y	Y
Vestermark et al., 2008*	Y	Y	Y	Y
Lindebjerg et al., 2009*	Y	Y	Y	Y
Maluta et al., 2010	Y	Y	Y	Y
Jakobsen et al., 2012*	Y	N	Y	Y
Vestermakr et al., 2012*	Y	N	Y	Y
Engineer et al., 2013	Y	na	N	N

	Reasons for drop-out and/or not undergoing surgery (y/n/na)	TNM-stage reported (y/n/na)	Acute grade >3 toxicity for boost patients only (y/n)	pCR recalculation possible (y/n)	Meta-analysis inclusion
	na	N	N	N	-
	Y	Y	Y	Y	yes
	Y	N	Y	N	-
	Y	N	Y	Y	yes
	na	Y	N	Y	yes
	Y	N	Y	Y	yes
	na	Y	Y	Y	yes
	Y	partly	Y	Y	yes
	Y	N	N	Y	yes
	na	N	N	N	-
	na	N	N	Y	-
	Y	partly	Y	Y	yes
	Y	N	Y	Y	yes
	na	partly	N	Y	yes
	na	Y	Y	Y	yes
	Y	partly	N	Y	yes
	Y	partly	Y	Y	yes
	Y	N	Y	Y	yes

y = yes, - = no, na = not applicable. (* additional data obtained through the corresponding author)

DISCUSSION

This meta-analysis shows a pCR-rate of 20.4% after preoperative ≥60 Gy radiation in patients with LARC, which was associated with low (10.3%) acute grade ≥3 toxicity and a high resectability rate (89.5%). Furthermore, no correlation between pCR-rate and toxicity, resectability, boost approach, chemotherapy or surgical interval was found.

The calculated pCR-rate estimate of this meta-analysis is in line with the prediction of the previously mentioned mathematical and clinical dose-response prediction models. These models further predict an exponential pCR-rate increase, i.e. degree of tumor cell destruction, which occurs after linear dose-escalation above 60 Gy. This is visualized by their S-shaped dose-response curve [3, 12]. We also showed that dose-escalation ≥60 Gy yielded comparable toxicity-rates as observed in direct and indirect control groups after standard dose [24, 32, 34, 37] or after SIB boost technique of 55.2 Gy [38]. Wiltshire et al. [11] also found a non-linear relation between dose-increase and toxicity, since their 40 Gy, 46 Gy, and 50 Gy dose levels were associated with 13%, 4%, and 14% acute grade ≥3 toxicity, respectively. Although we looked at a larger dose interval, toxicity remained comparable. None of the studies included in this meta-analysis used IMRT. However, modern radiation and/or planning techniques may further contribute to reduced toxicity dose reduction to healthy tissue (especially bowel-dose) [39]. Furthermore, we observed no confounding between type of concurrent chemotherapy (or radio-sentitizer) and pCR-rate. This was also previously illustrated in several studies that found comparable pCR-rates for different sources of 5-FU [40-44], or when Leucovorin was added as a synergistic agent [45]. Neither is there consistent evidence that combination chemotherapy of 5-FU with Oxaliplatin [46-50] or Irinotecan [51-53] significantly improved pCR-rates, since only the German CAO/ARO/AIO-04 trial found 17% vs. 13% pCR (odds ratio 1.40, 95% CI 1.02-1.92; p=0.038) with and without Oxaliplatin respectively [54]. Nevertheless, it is evident that these combined therapies increase acute grade ≥3 toxicity (mostly gastro-intestinal complaints, dermatitis and peripheral neuropathy). Therefore, we are confident that nor chemotherapy type nor its dose influenced the pooled pCR-rate estimate, which restrained us from calculating a biological effective dose for each chemotherapy type and its dose-level. We excluded studies using contact radiotherapy (CXR) since dose distribution is considerable different from other radiation methods. However, this technique could be used to deliver high doses to distal, small (less advanced), well-selected (remaining) lesions. Broad experience shows that CXR can however be safely combined with external-beam radiotherapy [55-59], and could improve 'good response' rates and sphincter preservation rates in those tumors [60].

The strength of this study is that it provides a reliable and robust pCR-rate estimate based on a systematic study selection and intention-to-treat analysis. Furthermore, the low heterogeneity between studies allowed to use a fixed-effects model to calculate a robust pCR-rate estimate, since this is a powerful tool to reveal a pattern of the true effects-size among more studies. Also, this could then be compared to a well-based estimate for a 'control' population [1, 3]. Nevertheless, inter-study pCR variability was present and most likely depends on case-mix. However, such noTable spread is not only present in our selected 'boost population' but is also present within the identified control populations presented by Maas et al. and Sanghera et al. [1, 3]. Furthermore, all doses from different radiation treatments (EBRT-SIB, -sequential or brachytherapy) were recalculated to EQD2 doses to provide an optimal comparison method and dose-response analysis over all approaches together.

The limitations of this study concern study selection, reporting, pathological assessment and timing of surgery. Firstly, our critical appraisal excluded four studies from the meta-analysis because pCR-rates

could not be recalculated from the provided data, leading to a smaller number of patients to pool. Nevertheless, we do not expect that those excluded studies would dramatically have influenced the pooled pCR-rate estimate since these studies represented only 9.6% (n=52) of the original identified sample of 539 patients. Nor did studies with <60 Gy EQD2-doses influence pCR-rate estimates. This robustness was indicated by the small positive 2.5% and negative 2.3% pCR-rate shift after sensitivity analyses that excluded 'negative outliers' or studies with EQD2 doses ≥60 Gy, respectively. However, small numbers are unfortunately inherent to feasibility, dose-finding and early phase (I-II) trials which leaves the opportunity to further strengthen the evidence by conducting larger randomized dose-escalation trials. Secondly, we were not able to study the association between T- or N-stage and pCR-rates since for most studies response rate according to T-/N-stage was not reported. Third, the pCR-rate estimate might still be underestimated since pathologic response could only be obtained from operated patients. Despite our intention-to-treat analysis, and although the resectability rate was high, more patients might have experienced a complete response. However, we conservatively assumed all non-surgical patients to have non-pCR which might be incorrect since in some patients surgery was omitted for other reasons such as a worsened condition, newly diagnosed metastasis or patient's refusal. Fourth, the pathologic assessment was different between studies, and therefore prone to bias. Ten of 14 included studies standardized assessment, of which 3 explicitly used Mandard's score [35]. Others only mentioned that one pathologist assessed if there was 'absence of viable tumor cells' in the specimen. Fifth, destruction of solitary tumour cells may continue long after termination of radiotherapy, indicating that timing of surgery impacts response assessment. Three studies have shown increased pCR-rates when surgery was postponed from 8 to 11 weeks post-radiation (from 11.5 to 14.0%) [61], and when shorter surgical intervals are compared to intervals of >6-8, or >7, weeks (from 13.7% to 19.5%, and 16% to 28.0% respectively) [62, 63]. A relative risk of 1.42 (1.19-1.68) for pCR was reported for intervals longer than 6-8 weeks as compared to intervals shorter then 6-8 weeks. Nevertheless, in our data we did not see an association between interval-length and pCR-rate, presumably because pCR-rate varied largely at each interval length with only a few studies available per interval-length point in the analysis. Such variation is common, and therefore often observed in systematic reviews on pCR-rates following CRT [1, 3, 64]. To further investigate the impact of prolonged intervals on pCR-rate and sphincter preservation, several randomized clinical trials are currently recruiting (GRECCAR6/NCT01648894 [65] and NCT01037049). Nonetheless, if such presumed time-effects allow extrapolation to when doses are escalated, pCR-rates and organ-preservation might even further benefit when longer intervals proof to be safe. Sixth, only a single study reported interval between radiotherapy and brachytherapy, which did not allow further meta-analysis. Finally, accelerated treatment (higher dose per fraction, i.e. simultaneous integrated boost) increases the biological effective dose which may benefit response [66, 67], especially when tumor-regrowth time is short [68, 69]. Nevertheless, some of these accelerated schedules remain challenging because of considerable toxicity [19, 24, 70-72] and peri/post-operative complications [72, 73]. It is likely that such toxicity originates from irradiation of surrounding tissues instead of the tumor, as a result of a previously acquired treatment plan not taking into account tumor-shrinkage during the course of radiation. The most optimal schedule for high doses thus remains to be investigated in the future.

In the future disease monitoring will become progressively important. To discover that some patients do not respond, and will thus not benefit from additional radiation, should not be kept until surgery, but should be monitored all along neo-adjuvant treatment to prevent over-treatment and create the opportunity to adjust treatment. This demands sensitive response-prediction tools employable concurrent to CRT. Such a non-invasive method capable of differentiating pathological good (TRG1-2) from bad/none responders (TRG3-5) early during CRT is diffusion-weighted MRI (DWI) [74, 75]. At the same time, this creates opportunity to identify those tumors likely to benefit from a sequential

radiation boost. Whereas the oncological outcome benefit for patients that reach pCR seems favorable, contradictory outcomes have been published after reaching a near pCR, ranging from good prognosis (comparable to pCR) [2, 76, 77] to poor prognosis (comparable to poor pathological response) [78-81]. For these patients, with a proven radiation-sensitivity but near complete response, early response-assessment could form a future tool to select them to undergo additional boost radiation in order further improve their response towards a cCR, which is in turn associated with better prognosis and anticipated improved quality-of-life if followed by an organ-preservation strategy.

Dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR-rates and accepTable early toxicity. This observation needs to be further investigated within larger randomized controlled phase 3 trials in the future.

Conflict of Interest Statement
There are no actual or potential conflicts of interest to declare.

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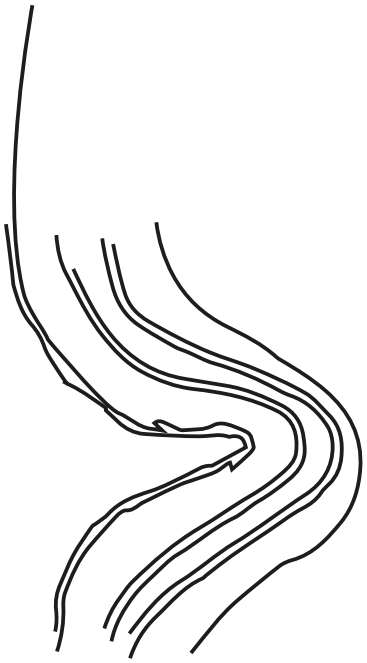

CHAPTER 6

INTER-OBSERVER AGREEMENT OF MRI-BASED TUMOR DELINEATION FOR PREOPERATIVE RADIOTHERAPY BOOST IN LOCALLY ADVANCED RECTAL CANCER

Published in: Radiotherapy and Oncology, 2016 Feb;118(2):399-407.

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CHAPTER 6

ABSTRACT

BACKGROUND

While surgery remains the cornerstone of rectal cancer treatment, organ-preservation is upcoming. Therefore, neo-adjuvant treatment should be optimized. By escalating doses, response can be increased. To limit toxicity of boost, accurate gross tumor volume (GTV) definition is required. MRI, especially undeformed fast spin echo diffusion-weighted MRI (DWI), looks promising for delineation. However, inconsistencies between observers should be quantified before clinical implementation. We aim to find which MRI sequence (T2w, DWI or combination) is optimal and clinically useful for GTV definition by evaluating inter-observer agreement.

METHODS

Locally advanced rectal cancer patients (tumors <10cm from anal verge) were scanned on 3T MRI transverse T2w and DWI (b=800 s/mm2). Three independent observers delineated T2w, DWI and combination (Combi) after training-set. Volumes, conformity index (CI), and maximum Hausdorff distance (HD) were calculated between any observer-pair per patient per modality.

RESULTS

Twenty-four consecutive patients were included. One patient had cT2 (4.2%), 19 cT3 (79.1%) and 4 cT4 (16.7%), with 2 clinical node negative (8.3%), 4 cN1 (16.7%), and 18 cN2 (75.0%) on MRI. From 24 patients, 70 sequences were available (24x T2, 23x DWI, and 23x Combi). Between observers, no significant volume differences was observed per modality. T2 showed significantly largest volumes compared to DWI (mean difference 19.85 ml, SD 17.42, $p<0.0001$) and Combi (mean difference 7.16 ml, SD 11.58, $p<0.0001$). Mean CI was 0.70, 0.71 and 0.69 for T2, DWI and Combi respectively ($p>0.61$). Average HD was largest on T2 (18.60mm, Max 31.40mm, Min 9.20mm).

DISCUSSION

Delineation on DWI resulted in delineation of the smallest volumes with similar consistency and mean distances, but with slightly lower Hausdorff distances compared to T2 and Combi. However, in lack of a gold standard it remains difficult to establish if delineations also represent true tumor. Study strengths were DWI adaptation to exclude geometrical distortions and training-set. DWI shows great potential for delineation purposes as long as sufficient experience exists and geometrical distortions are eliminated.

INTRODUCTION

While surgery remains to be the cornerstone of treatment in rectal cancer, a cautious shift towards organ-preserving (watchful waiting) strategies exists. When pursuing non-surgical treatment, optimization of neo-adjuvant strategies becomes more important. Since response to neo-adjuvant radiation is dose-dependent [1-4], dose-escalation may be used to increase clinical good-response rates to let more patients benefit from organ-preservation. The effect of dose-escalation was recently shown when ≥60 Gy treatment increased pathological complete response rate compared to normal dose (50 Gy), without worsening toxicity [1]. Nevertheless, different radiation protocols were used which showed considerable variation in toxicity- and response-rates. This indicates that dose-escalation is effective but that room exists for optimization of radiation techniques.

In order to develop an optimal boost strategy, i.e. to achieve high response rates with low toxicity, several factors are important besides dose-level itself. These include accurate gross tumor volume (GTV) definition, planned target volume (PTV)-margins accounting for tumor movement, dose-delivery techniques, and objective response and toxicity scoring. Most issues have been solved through intensity modulated radiotherapy (IMRT) limiting healthy-tissue irradiation, reduced PTV-margins after set-up verification improvements, and Mandard [5] and CTCAE [6] scoring systems. What remains to be investigated is which imaging modality should be used to accurately define target area for the boost. Imaging should be able to discriminate tumor tissue from its surroundings and should enable to deliver dose only to the tumor area - the GTV -, rather than to a larger area surrounding the tumor – the clinical target volume (CTV).

Magnetic resonance-imaging (MRI) is the image modality with the best soft-tissue contrast and highest level of detail able to discriminate tumors from their surrounding anatomy, better than CT or PET-CT. Also, MRI is non-invasive and has no radiation-exposure to patients. Especially diffusion-weighted MRI-imaging (DWI) looks promising since it is able to discriminate tumors from healthy tissue upon diffusion-restriction, i.e. cell density [7, 8]. Nevertheless, conventional DWI-sequences are prone to geometrical distortions, especially around air-tissue transitions [9]. To eliminate geometrical distortions, a Turbo Spin Echo (TSE) based DWI-sequence was developed: DWI-SPLICE [10]. Thus, in contrast to other DWI sequences, DWI-SPLICE allows direct registration of images to anatomical MR images. This makes this sequence feasible for delineation purposes. However, a problem with delineations always remains that, no matter how good image-quality is or how well anatomy is represented, they are prone to inconsistencies between observers. Moreover, a gold standard to validate delineations often lacks. Before introducing a new radiation protocol in the clinic, it is therefore mandatory to first assess delineation inconsistency between observers.

Although MRI has shown great delineation potential in rectal [11-13] and other cancers [14, 15], little experience exists with MRI-guided delineation for boost planning in rectal cancer [12, 16, 17]. This was only investigated once, and only for T2w and DWI alone [16]. Although hypothesized that DWI would improve consistency, it didn't. A combination of sequences was unfortunately not investigated. Therefore, in this study we aim to evaluate which MRI sequence (T2w, DWI) or their combination is optimal and clinically useful for GTV definition as used for boosting the tumor in addition to normal CRT [17]. We do so by evaluating inter-observer agreement and calculating distance parameters between delineated GTV contours by different observers. These measures should provide insight in the feasibility to use MRI-guidance for delivering a boost to the GTV.

METHODS

This study is designed and reported according to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) [18].

PATIENT SELECTION

Consecutive rectal cancer patients were screened for locally advanced disease (T3 with threatened mesorectal fascia, T4 or N2M0 [19]) to receive chemoradiation using MRI according to Dutch guidelines [20]. Tumors located ≤10cm from the anal-verge on MRI were eligible for inclusion in this prospective study. Inclusion criteria mimic RECTAL BOOST study-criteria [17]. Informed-consent was asked from all patients. A sample size of ≥20 patients was deemed appropriate to evaluate agreement between observers.

PATIENT POSITIONING AND IMAGE ACQUISITION

Patients were scanned one week prior to radiotherapy without bowel preparation in supine position on a flat Table-top without intravenous contrast. MRI scans were acquired on two 3T MRI units (Philips Ingenia Wide-Bore or Achieva 3TX). Images were obtained in transverse direction. Scan parameters of T2w and DWI-SPLICE Turbo-Spin-Echo (TSE) sequences are illustrated in Table 1. T2w images had a resolution of 0.9 x 0.9mm and slice thickness of 3 mm, while DWI-SPLICE had 2.02-2.5 x 2.02-2.5mm resolution with 4.0mm slice thickness. Two b-values (b=0 and 800 s/mm2) were obtained in the DWI-SPLICE with a free-breathing single-shot approach (Table 1). The differences between the MRI sequences result from adaptations of the sequences to the different hardware of the Ingenia and Achieva 3T scanners (Table 1), while maintaining the image quality. Since two MRI units were used, observers were asked after completion of the study to qualify if there had been potential differences in image quality between both units.

TARGET VOLUME DELINEATION

For each patient, available MRI images were transferred to in-house developed delineation software [21]. Three independent observers (radiation oncologist with 10 years experience in rectal cancer, radiation oncologist in-training with 5 years experience, and researcher with 2 years experience) were provided their own image sets: T2, DWI-SPLICE ('DWI') and combined sequences registered via identity transformation ('Combi'). First, a consensus meeting was organized to develop GTV-delineation instructions. Instructions were updated after a training-set (n=3). Observers were provided clinical information (endoscopy and digital examination). Cases from the training-set were excluded from analysis. First, all T2-images, and ≥1month thereafter DWI and Combi, were delineated. All images were delineated on transverse slices. In DWI (b=800 s/mm2) observers could adjust window- and level-settings to replicate clinical situations. All observers delineated blinded and independently from each other.

STATISTICAL ANALYSIS

As further specified below, volumes, conformity index, mean distance (MD) and maximal Hausdorff distances (HD) were calculated per modality to evaluate agreement, contour shapes and locations. To investigate contour sizes, volumes were calculated per observer, per patient, and per modality. Volume sizes are visually presented and analyzed between observers per modality and between modalities. To investigate volume differences between DWI and T2 and their correlation with absolute DWI volume, Bland Altman plots indicate DWI volumes against T2 volumes within patients. Another Bland Altman plot shows absolute DWI volume against the factor by which DWI volumes are increased

on T2, to indicate if volume size differences depend on DWI volume size.

To investigate inter-observer variation, a generalized conformity index (CI) for overlap between ≥3 observers was calculated per patient per modality: with Ai, or Aj being the different delineations [22]. A Fleiss' kappa was also calculated as an additional measure of inter-observer consistency (between 0-1) [23] to allow comparison with other studies. Given the number Vi of voxels contoured by exactly i observers (i = 1, ..., n), the resulting overall kappa is represenTable as a ratio of weighted sums of the Vi [23]. CI or Fleiss' kappa = 1 indicates perfect agreement among observers, >0.8 very good, 0.7-0.8 good, 0.7-0.6 moderate, <0.6 low, and 0 indicates no agreement. CI and Fleiss' kappa's were calculated only for cases that had T2 and DWI available. We analyzed difference in CIs between modalities. Additionally, CIs were plotted against mean volumes per modality and checked for correlation. A simple linear regression was plotted in case significant correlation existed to indicate how volume influences CI.
To assess differences in contour shapes and locations within patients, a distance between center of mass (dCOM) of each observer-pair is calculated within patients. The dCOM is expressed as the length of the 3 dimensional vector and presented as mean (SD) with a range per modality.

To evaluate separation between contours-borders, two distance parameters were calculated per observer-pair per modality. Hausdorff distances (HD) were calculated, representing the maximum of the shortest distances from any delineated point to the other contour. The maximum of the shortest HDs was determined over all observer pairs per modality (HD). In a similar manner, a mean distance (MD) between contours was determined as the average distance between all observers over all points of contours within one patient on one modality. The HD en MD are graphically represented for each modality, and differences between modalities were analyzed. All analysis between modalities concern paired data, and were therefore analyzed by repeated measures ANOVA and paired T-tests to identify statistical significant differences ($p<0.05$).

TABLE 1 **MR Scan protocol parameters**

	Achieva 3TX		Ingenia Wide-Bore	
	T2	DWI-SPLICE	T2w TSE	DWI-SPLICE
EPI / Turbo Spin Echo (TSE)	TSE	TSE	TSE	TSE
Repetition time (ms)	9403	6129	5627	16081
Echo time (ms)	110	93	110	67
Echotrain length	20	single-shot	28	64
In plane resolution (mm × mm)	0.8 x 0.85	2.02 x 2.02	0.9 x 1.07	2.5 x 2.5
Refocusing control (angle)	120	50	110	50
Slice thickness (mm)	3.0	4.0	3.0	4.0
Slice gap (mm)	0	0	0	0
No. of slices	70	18	70	42
No. of Signal Averages (NSA)	2	2 (b=0 s/mm2) 8 (b=800 s/mm2)	2	2 (b=0 s/mm2) 6 (b=800 s/mm2)
Sensitivity encoding (SENSE) factor	3	2	2.8	2
Fat suppression	-	SPIR	-	SPIR
Halfscan (factor)	No	0.6	No	No
Matrix (pixels x pixels)	376 x 298	124 x 123	332 x 327	168 x 128
Water fat shift (pixels)	Max (2.182)	User defined (2.0)	Max (0.981)	Max (0.642)
Acquisition time (min)	6:35	2:39	4.:53	5:22

RESULTS

PATIENT CHARACTERISTICS

Twenty-four consecutive patients (20 males and 4 females, median age 66.0 years (26-80)) were included. All tumors were locally advanced and had indication for CRT [20]. Patient characteristics are shown in Table 2. One patient (4.2%) had clinical T2, 19 cT3 (79.1%) and 4 cT4 (16.7%). Clinical nodal stage was negative in 2 patients (8.3%), cN1 in 4 (16.7%), and cN2 in 18 (75.0%). One patient had metastasis (4.2%). Mean distance from the anal-verge was 4.2cm (0-10cm). From 24 patients, a total of 70 sequences were obtained (24x T2, 23x DWI, and 23x Combi). In one patient DWI was not available because there were technical problems during the scan. After completion of the study, the observers reviewed image quality of both MR units and concluded that there was no difference which could have precluded the ability to use images of both units for delineation.

VOLUME MEASUREMENTS

An example of delineated structures is provided in Figure 1 and the appendix provides two examples of images obtained at both MR units to indicate comparable image quality of both (Figure A). Volumes per observer and per modality are presented in Figure 2. Between observers no significant volume differences were observed within each modality. T2 showed significantly larger volumes than DWI (mean difference 19.85 ml (SD 17.42), $p<0.0001$) and Combi (mean difference 7.16 ml (SD 11.58), $p<0.0001$). Volumes on Combi were also significantly larger than on DWI (mean difference 12.69 (SD 10.96), $p<0.0001$). The volume increase ratio between DWI and T2 volumes varied between 1-3 times but was independent of DWI volume (Pearson -0.17, $p>0.16$) (Figure 3).

AGREEMENT AND DISTANCE MEASURES BETWEEN CONTOURS

The mean conformity index (CI) was 0.70, 0.71 and 0.69 for T2, DWI and Combi respectively. Fleiss' kappa was 0.82 on all modalities. CI and Fleiss' kappa's did not differ significantly between our three modalities ($p>0.61$ and $p>0.71$ respectively) (Figure 4), indicating delineation consistency is comparable between modalities.

CIs and mean volumes were correlated on T2 (Pearson 0.61, $p<0.002$) and Combi (Pearson 0.61, $p<0.002$), but not on DWI (Pearson 0.24, $p>0.27$) (Figure 5). On T2, per ml volume increase the CI increased by 0.001 (SE 0.000, R2 0.367, $p<0.002$) with intercept at 0.61. For Combi, per ml volume increase the CI increased by 0.002 (SE 0.000, R2 0.371, $p<0.002$) with intercept at 0.61.

Mean dCOMs per modality are presented in Figure 6. T2 showed to have the largest mean dCOM (3.30mm) and Combi the lowest (2.57mm), indicating T2 had most shape and location variability. Mean dCOMs were not significantly different between modalities ($p>0.70$). dCOM variance was 2 times larger on T2 than on DWI or Combi, although one outlier existed on DWI. In retrospect, observers agreed the least experienced observer had delineated an artifact which results in an unrealistically high dCOM value.

Contours were separated the widest on at least one point considering the largest mean HD on T2 (18.59mm, max 31.41mm, min 9.16mm) compared to DWI (mean HD 14.42mm, min 4.03mm, max 49.10mm) (Figure 6). DWI again showed the outlier case (49.10mm). On Combi, mean HD was between T2 and DWI values (Figure 6). Repeated measures ANOVA showed a significant difference in HD between modalities ($p<0.006$), with a significant mean HD difference of 4.80mm between T2 and DWI ($p<0.04$) but a non-significant difference between T2 and Combi ($p>0.06$) or DWI and Combi ($p>0.61$). Separation over the whole contour-border was also largest on T2 (MD=1.80mm) and smallest on DWI

(MD=1.49mm). Considering our voxel size of ≥2.0 x ≥2.0mm on DWI, an average MD smaller than one voxel exists between observers. Again, the outlier case showed an increased MD on DWI (9.05mm). There were no significant differences between modalities in MD (p>0.19).

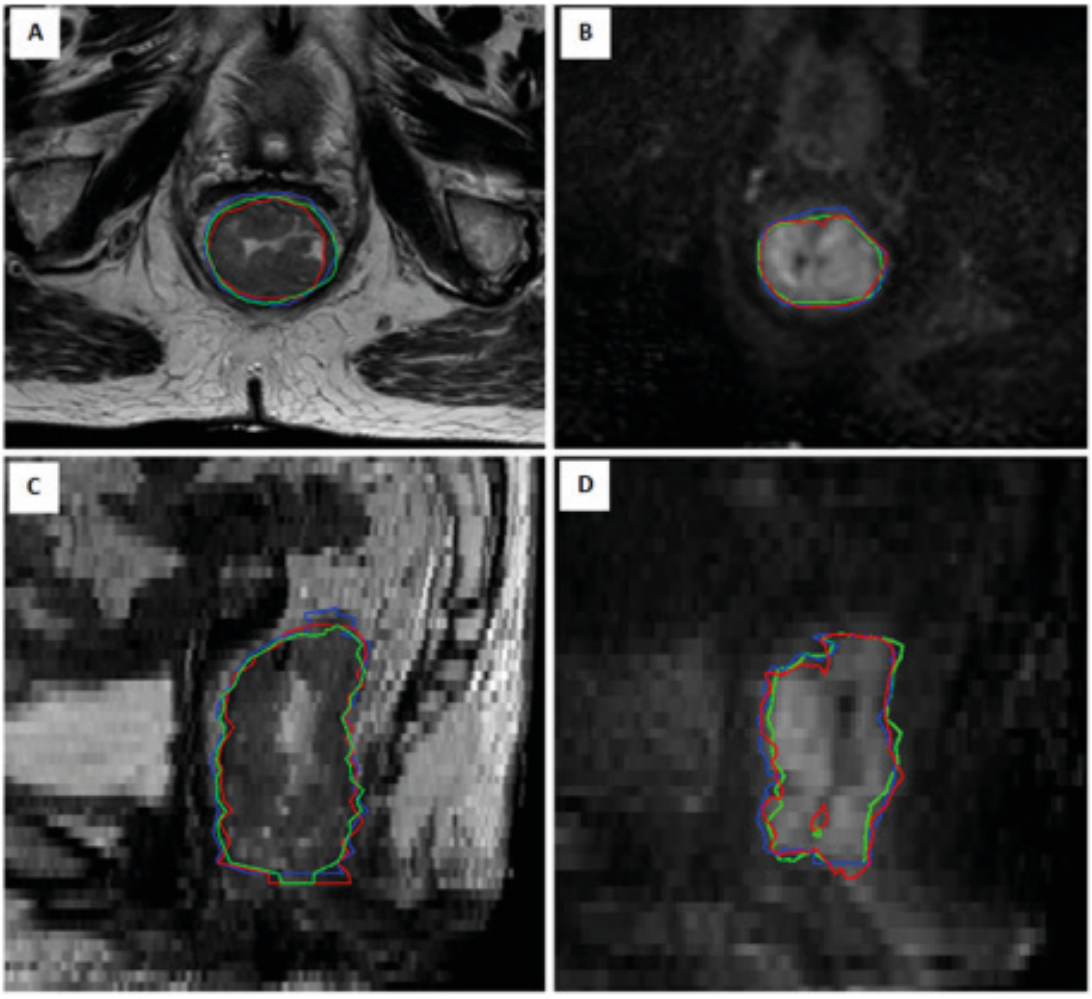
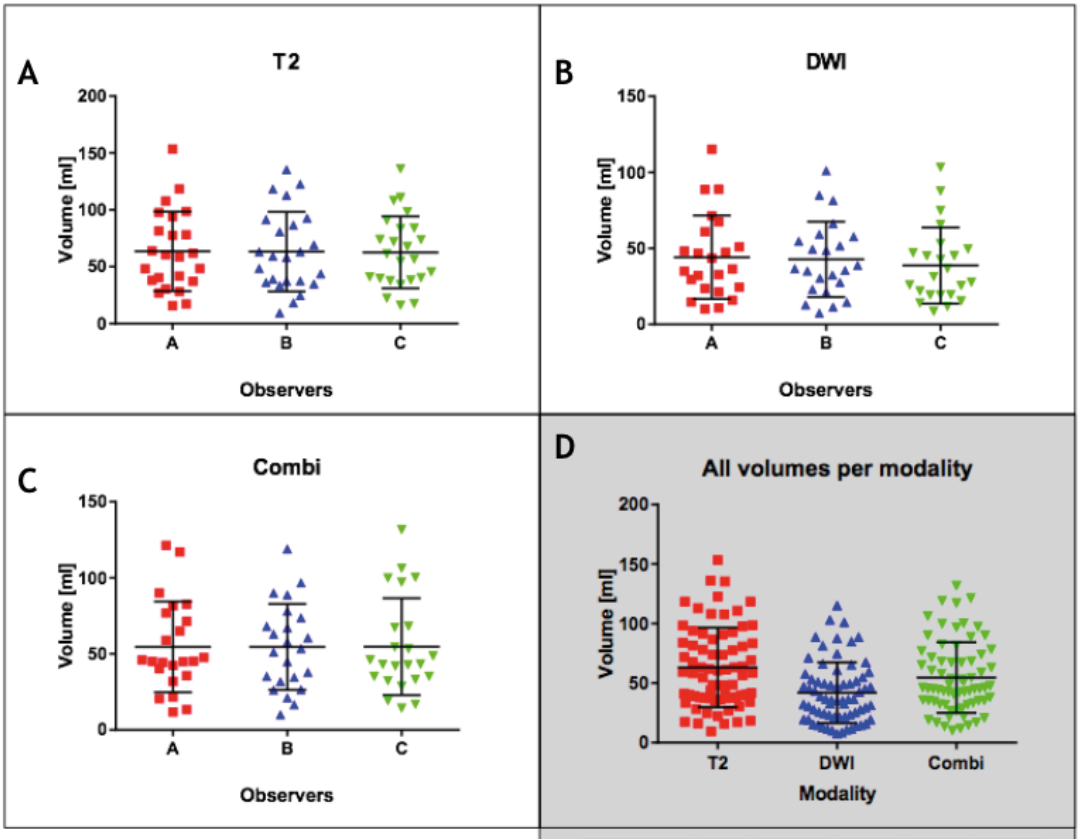


FIGURE 1

Representative example of delineations in one patient of three observers on T2w (A & C) and DWI (B & D) sequences in transverse (A & B) and sagittal (C & D) direction.

TABLE 2 **Baseline characteristics of patients**

Baseline characteristics	
Patients (n)	24
Age (mean, range)	66.0 (26-80)
Male (%)	20 (83.3)
T stage	
T2	1 (4.2)
T3	19 (79.1)
T4	4 (16.7)
N-stage	
N0	2 (8.3)
N1	4 (16.7)
N2	18 (75.0)
Metastases	1 (4.2)
Mean distance from anal verge (cm)	4.2 (0-10)
Available scans	
T2 (%)	24 (100)
DWI (%)	23 (95.8)
Combi (%)	23 (95.8)



	N	Mean	SD	Min	Max
T2	72	63.16	33.39	9.38	153.40
DWI	69	41.94	25.49	7.60	115.18
Combi	69	54.63	29.54	10.12	131.68

FIGURE2 Volumes per modality per observer (A, B & C), and for all observers combined per modality (mean, sd) (D).

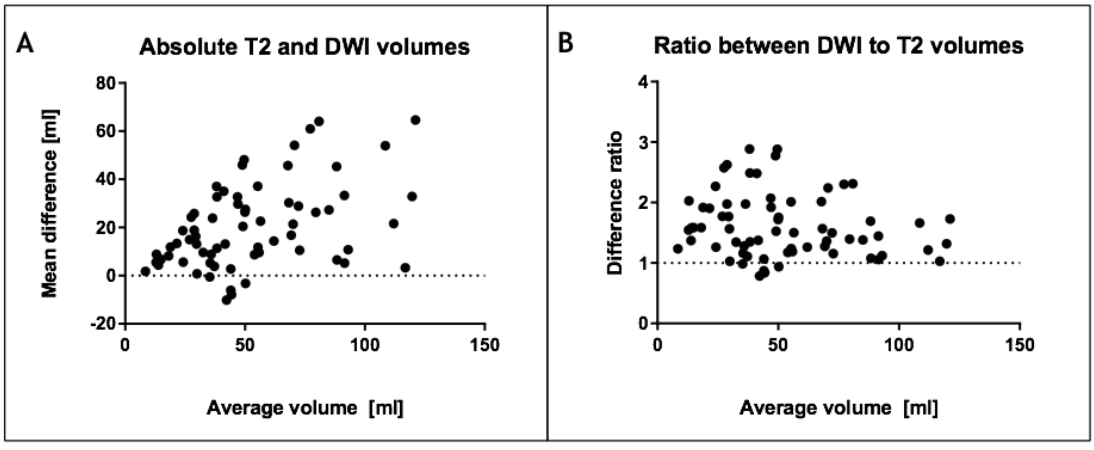
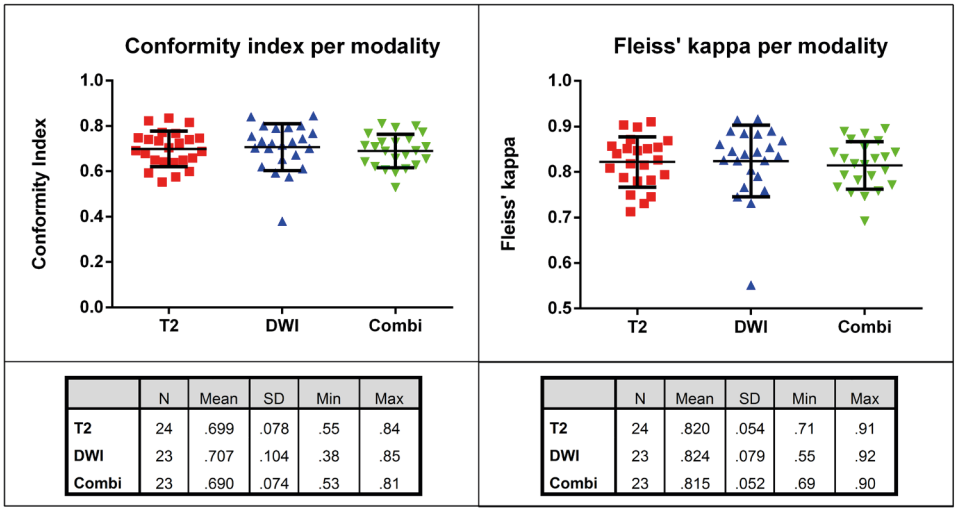


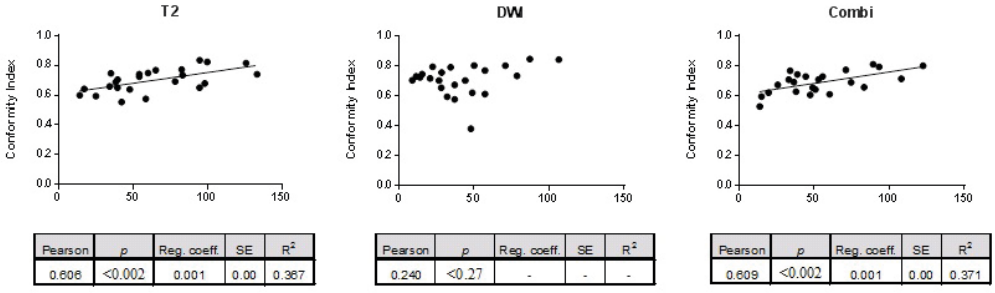
FIGURE 3 Bland Altman plots representing absolute (A) and relative volume differences (B) between contours delineated by three observers on T2 and DWI.



	N	Mean	SD	Min	Max
T2	24	.699	.078	.55	.84
DWI	23	.707	.104	.38	.85
Combi	23	.690	.074	.53	.81

	N	Mean	SD	Min	Max
T2	24	.820	.054	.71	.91
DWI	23	.824	.079	.55	.92
Combi	23	.815	.052	.69	.90

FIGURE 4 Conformity index (A) and Fleiss' kappa (B) values per modality for three observers.

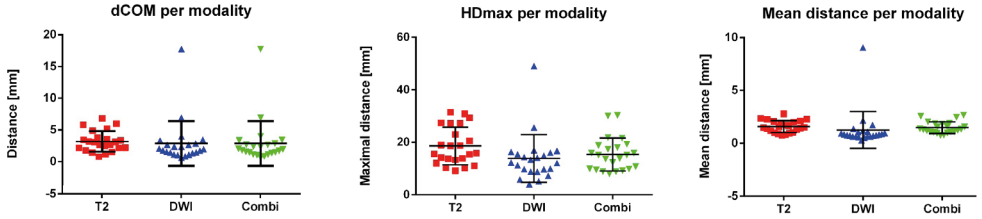


Pearson	p	Reg. coeff.	SE	R^2
0.606	<0.002	0.001	0.00	0.367

Pearson	p	Reg. coeff.	SE	R^2
0.240	<0.27	-	-	-

Pearson	p	Reg. coeff.	SE	R^2
0.609	<0.002	0.001	0.00	0.371

FIGURE 5 Correlation between volumes and conformity indexes (IC's) for T2 (A), DWI (B), and Combi (C) modalities.



dCOM	N	Mean	SD	Min	Max
T2	24	3.30	1.67	0.79	6.83
DWI	23	2.88	3.51	0.63	17.74
Combi	23	2.57	1.60	0.77	5.39

HDmax	N	Mean	SD	Min	Max
	24	18.62	7.01	9.16	31.41
	23	13.82	9.06	4.03	49.10
	23	15.38	6.26	8.01	30.27

MD	N	Mean	SD	Min	Max
	24	1.61	0.57	0.75	2.79
	23	1.26	1.75	0.29	9.05
	23	1.48	0.56	0.73	2.66

FIGURE 6 The distance between centers of mass (dCOM) (A), maximal Hausdorff distances (HDmax) (B), and mean distances (MD) (C) of contours within each observer-pair per modality.

DISCUSSION

In this study, two MRI sequences and their combination (T2 and DWI) were used for GTV-delineation in locally advanced rectal cancer by three observers with the purpose of identifying GTV-delineation consistency and separation between contours. This is the first study to actually calculate distance parameters, providing crucial information for development of MRI-guided GTV boost strategies complementary to standard chemoradiation which is directed to the entire CTV. Agreement between GTV delineations performed by the different observers was good and was comparable between different MRI sequences. Our results are in concordance with results of a previous rectal cancer delineation study [16]. Namely, the best consistency was reached on DWI images [16]. New findings of our study are inter-observer agreement improvement with larger volumes, and comparable agreement after combined T2-DWI sequences compared to both sequences alone. This last finding may be due to the fact that some observers tend to rely mostly on T2-images while others prefer to trust the DWI-images more. Combining both scans, however, can also introduce a new inconsistency-factor since images have to be co-registered and topography can be different between sequences. Therefore, this study used a DWI SPLICE [9] sequence which is specifically designed to acquire geometrically undistorted DWI images.

In contrast to the previous delineation study, we performed an analysis to calculate distances between contours since this is crucial before contours can be used in a clinical radiotherapy setting [16]. Also, we used the combination of sequences in our study, which was not done in the previous study potentially because co-registration of DWI to T2 was difficult because of geometrical distortions in their SE-EPI DWI [16]. When looking at volume sizes, we found that T2 volumes were significantly larger than DWI volumes (approximately 2-3 times), with larger T2 volumes showing higher inter-observer consistency. Larger volumes on T2 may results from the fact that distinguishing between oblique-sectioned rectal wall and tumor can be difficult. Consequently, this area can become delineated as tumor, thereby increasing volumes dramatically. Such difficulties mainly depend on image quality, resolution and angulation of images. Volume differences observed in this study might therefore have been larger than those found by Regini et al [16] or than those observed in prostate MRI delineation-studies [15, 24]. Analysis investigating the center of mass indicated that the delineated structures were often close to one-another and that most had comparable shapes. The shortest maximal distance between contours, an important measure for radiotherapy planning purposes, furthermore indicates the close localization of contours between observers. Nevertheless, some contour-regions remained widely separated. In our study this was more distinct on T2 than on DWI images, and regions with the largest separation were later reviewed to depend on delineated artifacts. As artifacts may always arise on MR images, it is difficult to reach perfect conformity. Nevertheless, we are positive that MRI provides a feasible and safe method for GTV delineation.

This study was initiated under the assumption that regions which are most likely to contain tumor are most important when considering a boost in order to reach a complete clinical response (cCR). In lack of a gold standard – i.e. pathologic validation - it remains impossible to know how well delineations actually represent true tumor. Unfortunately, pathologic validation of delineations remains difficult in the setting of neo-adjuvant treatment since pre-radiotherapy delineations are hard to compare with pathologic results retrospectively since tumors often shrink and deform as a result of chemoradiation. Therefore, we have to assume in this study that an area delineated by multiple observers is most likely to contain tumor. We must also emphasize that this study focuses solely on identifying delineation consistency between observers, and that it does not aim to identify which regions truly contain

tumor, i.e. does not focus on delineation accuracy. Furthermore, T2 and DWI sequences may both be prone to marginal missing of low density tumor spread, but this does not play a role when aiming to identify a GTV area and is inherent to resolution and quality of MR scans. Nevertheless, we feel that in this study image quality has been optimal and that this is certainly no less compared to standards used in current literature. By only boosting the region most likely to contain tumor , i.e. the GTV, surrounding healthy-tissue can potentially be spared whereas boosting an entire CTV would also irradiate healthy tissue. Boost only the GTV is of particular benefit in regard to functional outcomes a cCR is followed up by watchful waiting instead of radical surgery. When watchful waiting is applied, the same MR sequences may not only play a role in delineation of tumors, but may also be used to select patients with a cCR. For this purpose MR sequences are being optimized and new sequences are being developed, such as functional (DWI, MR spectorscopy) and very high-resolution 7Tesla. These modalities are currently also under investigation in our institution [17, 25] in order to provide a comprehensive (MR-based) watchful waiting strategy to patients in the future.

MRI-based delineation in rectal cancer is relatively new. Nowadays there is only one study available that investigated inter-observer agreement [16]. Unfortunately, this study did not calculate CIs or Fleiss' kappa's as measures of inter-observer agreement, but only compared volumes between observers (as discussed above). In comparison with prostate cancer studies on delineation agreement, we showed a considerably higher conformity on multiparametric (0.61) [14], T2w (0.61) and DWI (0.51) [15] imaging. This encourages to use MR for GTV delineation instead of CT, which is the current standard for CTV delineation. Delineation of GTV volumes on CT resulted in contradictory volumes when compared to MRI GTV volumes [11, 13], which is most likely depended on worse soft-tissue contrast on CT. Whereas CT is primarily used to define CTVs, CT-based CTV delineation showed comparable conformity indexes to what we obtained in this study for MR-based GTV delineation [26]. Although the CT-based study by Nijkamp et al was not aimed to identify delineation-uncertainties for boost purposes, their presented uncertainty-level indicates to what extent uncertainty is accepted in current routine clinical practice. Nevertheless, there are some studies that boost entire CTVs based on these uncertainties. They either use CT-based CTV or box techniques, thereby taking for granted comparable - or even larger - uncertainties [1]. Remarkably, toxicities observed in these studies are comparable between boost (≥60Gy) normal dose (50Gy) [1]. It seems thus safe to boost mesorectal regions, and it may be even better accepTable to boost a GTV based on MR imaging, than to boost a CTV based on CT imaging, because both uncertainties are comparable and dose delivered outside a CTV is potentially more damaging to healthy tissue than dose delivered outside a GTV which still stays within the CTV.

One of the strengths of our study is that we used an adapted our DWI-sequence, i.e. the SPLICE-DWI, to eliminate geometrical distortions in our DWI images. Because we obtained geometrically correct DWI-images we could co-register DWI images to T2 images with close-to-perfect anatomical overlap. This improved anatomical interpretation of the images and thereby benefitted our delineations. Because DWI-SPLICE acquisition is slower than other DWI sequences, only 2 b-values could be acquired per patient, reducing accuracy of ADC quantification. However, for delineation purposes it is more essential to obtain geometrically correct images than producing robust ADC-values. We choose to use b=800 images because of our previous experience with this b-value [27-30]. Nevertheless, acquiring multiple b-values images can be of added value when performing qualitative assessment or when artifacts are encountered. Another strength of this study is that a delineation guideline was developed upfront and that a training-set was provided to all observers. This is not standard in delineation studies, and not done in the previous rectal cancer MR delineation study [16], but may help to reduce delineation inconsistency [26]. This emphasizes the need for training, consensus and experience in delineation practice. In routine practice however, processes of peer-review and supervision are already

common. Therefore, when MR-guided delineation becomes integrated into practice, development of guidelines and building experience under supervision are paramount since they may reduce toxicity in patients.

We acknowledge our study has limitations. A first limitation is that artifacts were delineated as tumor. Although instructions included how artifacts needed to be identified (by checking ADC maps) and although clinical information was available, artifacts sometimes remained difficult to distinguish from tumor (as described above). Especially in the rectum where movement and air accumulation exist, motion and susceptibility artifacts can arise. While most images in our study lacked artifacts, one patient had an artifact that was unrecognized and delineated by our most inexperienced observer. This produced an unrealistically large dCOM and HD for this patient. This emphasizes the existence of a learning-curve in regard to recognition of artifacts, especially on DWI images. In experienced observers DWI-delineation by can consistent, which was previously indicated by comparing volumes after repeated delineation in one observer [29] and the finding of an excellent reproducibility of mean ADC-values performed by multiple observers [31]. To improve DWI-delineation consistency, image optimization through increased voxel sizes and/or reduction of the number of averages may improve signal-to-noise-ratio, thereby reducing artifact occurrence. Other measures to eliminate bowel movement are however not recommended [32]. Although artifacts occurred in our study, we feel that DWI possesses great potential to be used for delineation as long as sufficient experience exists and geometrical distortions are minimized.

In the near future, interest to use MRI for delineation of pelvic tumors will likely increase [33-36]. As experience will grow, MR sequences may even be used to deliver non-homogenous doses since functional sequences can be used to indicate where regions with the highest tumor cell-density are located. These areas may need a higher dose than other regions in order to obtain cCR. Our data imply that T2 images result in tumor sizes 3 times that on DWI, implying that boosting a T2-delineated GTV could lead to unnecessary healthy-tissue irradiation. Especially considering that in our study rectal wall was sometimes delineated as tumor. Or, the other way around, that DWI delineations underestimate tumor size and response-rates might not improve as was anticipated because not all of tumor cells are targeted. Another issue that should be taken into account when boosting a GTV is tumor movement during radiation. In a previous study of our group it was shown that 95% of the distance of tumor movement, i.e. intra-fraction motion, was limited to 2.3mm during 90% of the scan time (of one minute) [37]. This indicates that tumor motion during radiation is limited, and that margins needed to correct for tumor motion during radiation consist of less than twice the distance of margins needed to correct for inter-observer variability. Together, these distance parameters may results in small margins surrounding the tumor. The use of IGRT in this setting is paramount since this can provide real-time day-to-day information on tumor location and potentially on motion patterns. Besides that DWI sequences can be used for delineation-purposes, they may also be used for response-monitoring during treatment. Acquiring DWI-images during treatment may in the future give rise to novel adaptive strategies that generate new treatment plans according to the observed remaining cell-density at each day/week during treatment. To develop such individualized treatment plans, reliability of DWI-images and inter-observer consistency during treatment should be investigated first.

In conclusion, our study presents MRI-based GTV-delineation with good agreement between observers. Delineation on DWI resulted in the smallest volumes compared to T2 or a combination of these sequences. Conformity indexes were similar between sequences, even though delineated volumes were smaller on DWI. Also, the Hausdorff distance on DWI was smaller than on T2, which indicates that, in our dataset, delineation consistency on DWI was at least comparable to T2. However,

a golden standard lacks for validation of delineations and imaging artifacts remain an issue. Overall, our results indicate MRI-based GTV-delineation is feasible for boost purposes as long as DWI is optimized, experience is sufficient, and consensus is reached between multiple observers.

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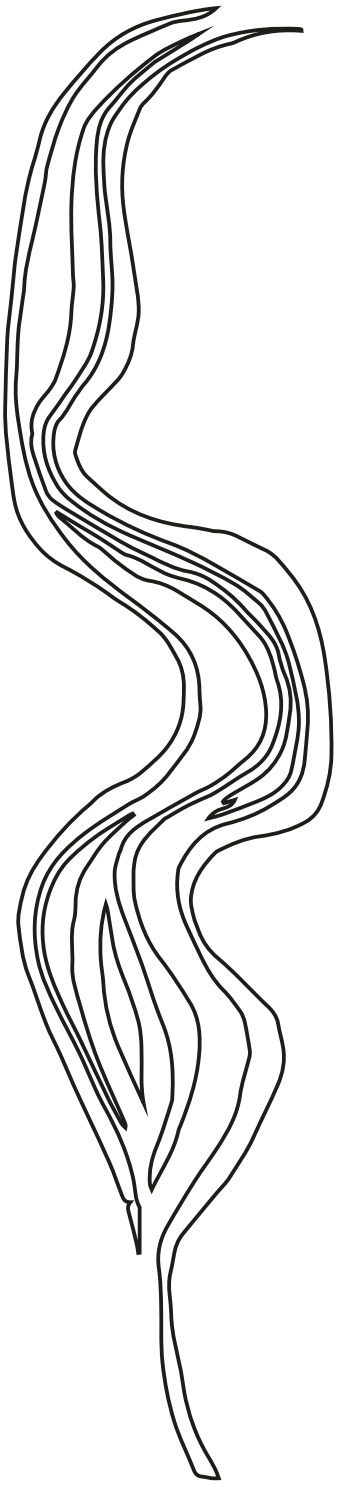

CHAPTER 7

RANDOMIZED CONTROLLED TRIAL FOR PRE-OPERATIVE DOSE-ESCALATION BOOST IN LOCALLY ADVANCED RECTAL CANCER – RECTAL BOOST STUDY: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

Published in: Trials, 2015 Feb 22;16:58.

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CHAPTER 7

ABSTRACT

BACKGROUND

Treatment for locally advanced rectal cancer (LARC) consists of chemoradiation (CRT) and surgery. Approximately 15% of patients show a pathological complete response (pCR) after CRT. Increased pCR rates can be achieved through dose-escalation, thereby increasing the number patients eligible for organ-preserving treatments to improve quality-of-life. A randomized comparison of chemoradiation response rates in patients with LARC treated with 65 vs. 50 Gy has not yet been performed. Objective: This trial investigates pathologic tumor response rate, clinical response, toxicity levels, quality of life (QoL) and (disease-free) survival in patients with LARC treated with 65 Gy chemoradiation compared to 50 Gy standard chemoradiation (sCRT).

METHODS

Informed consent is only obtained from patients that accept the boost, whereas all eligible patients have previously given informed consent to be offered experimental interventions according to the 'cohort multiple Randomized Controlled Trial' (cmRCT) design. SCRT consists of 50 Gy (25x2Gy) combined with capecitabine. The boost (without concomitant chemotherapy) is given prior to sCRT and consists of 15 Gy (5x3Gy) delivered to the gross tumor volume (GTV). The primary endpoint is pathologic complete tumor response, Mandard I. Secondary endpoints include acute grade 3-4 toxicity, good pathologic response, clinical response, surgical complications, QoL, and (disease free-) survival. Data will be analyzed by intention-to-treat.

This study follows the 'cohort multiple Randomized Controlled Trial' (cmRCT) design: rectal cancer patients are included in a prospective cohort in which clinical baseline, follow-up and survival data, together with standardized quality-of-life are registered. Eligible patients - histologically confirmed LARC (T3NxM0 <1mm from mesorectal fascia, T4NxM0 or TxN2M0) located ≤10 cm from the anal-rectal transition with consent to be offered experimental interventions - form a sub-cohort. From this subcohort (n=120), a random sample will be offered the boost in addition to sCRT (n=60). Patients in the subcohort who are not randomly selected will undergo sCRT alone (n=60). Data will be analyzed according to intention-to-treat.

DISCUSSION

We choose to deliver the boost prior to sCRT so that we do not have to adjust the GTV for tumor shrinkage that occurs during sCRT. By using small margins we try to limit unnecessary irradiation of healthy tissue. This trial will be performed within the cmRCT design that aims to overcome common shortcomings of classic randomized controlled trials, like slow recruitment, disappointment bias in control-arm patients, and poor generalizability.

TRAIL REGISTRATION

NL46051.041.13 (Dutch trial registry, 22-08-2013) and NCT01951521. Clinicaltrials.gov, 18-09-2013).

INTRODUCTION

Colorectal cancer is the second most common cancer in women and third in men worldwide [1]. Almost one third of Dutch colorectal cancers are located in the rectum [2]. Rectal cancers are treated by surgery, preceded by chemoradiation in case of locally advanced disease. Chemoradiation consists of a total dose of ~50 Gy combined with capecitabine. With this treatment regimen, approximately 15% of patients show a pathological complete tumor response (pCR) [3, 4], classified by Mandard as tumor regression grade 1 (TRG1) [5]. In a recent meta-analysis we showed that doses of ≥60 Gy were associated with increased pCR rate to 20.4%, without compromising toxicity [6].

Patients with good clinical response, either pCR (TRG 1) or near pCR (TRG 2), might be eligible for organ-preserving approaches. These strategies pursue to deliver an optimal quality of life without compromising the oncologic outcome. Recently, several protocols have been developed that either use local excision ([7-9]) or a "wait-and-scan" [10-12] policy in which patients are not operated primarily. In addition, patients who reach a pCR often show reduced local recurrence and improved (disease-free) survival probabilities compared to patients with a poor response (TRG3-5) [3, 13-15], possibly driven by a favorable tumor biology.

Thus, by escalating preoperative radiation dose the number of patients with a good clinical response or pCR eligible for organ preserving treatment can potentially be increased. However, response rates after high dose external radiation with 65 Gy have not yet been investigated in a randomized setting. Therefore we set-up an explorative trial, the RECTAL BOOST study (NCT01951521)), to compare tumor pCR rates (TRG1), pathologic good responses, toxicity levels, clinical response and quality-of-life between patients treated with 65 Gy chemoradiation (15 Gy boost plus 50 Gy chemoradiation) and those treated by standard 50 Gy chemoradiation (sCRT).

METHODS

STUDY DESIGN

This study is conducted within the ProspectIve data CollectioN Initiative on Colorectal cancer (PICNIC) project [16]. The prospective observational PICNIC cohort includes colorectal cancer patients of all stages and collects baseline demographic and clinical data, as well as prospective clinical follow up and patient reported outcome measures (PROMs). The study follows the 'cohort multiple Randomized Controlled Trial' (cmRCT) design [17] and provides a pragmatic infrastructure for multiple randomized controlled trials.

PATIENT RECRUITMENT

At enrollment in the PICNIC cohort, patients are asked informed consent for prospective collection of clinical, survival and PROMs. In addition, according to the cmRCT design, we ask patients' consent to being randomly selected to receive offers on experimental interventions in the future, and to use their data comparatively.

From the PICNIC cohort, we will identify all patients eligible for the boost intervention based on the following inclusion criteria: 1) histologically confirmed locally advanced rectal cancer, defined as T3 with threatened mesorectal fascia (<1mm), T4 or N2M0 [18] (based on Dutch guidelines for chemoradiation in rectal cancer [19], in which N2 is defined as ≥4 positive nodes visible with diameter > 9 mm or 5-9 mm combined with 2 of three following characteristics: irregular border, heterogeneous, or round-shaped), 2) tumor should be located ≤10cm from the anal-rectal transition, and 3) previously obtained informed consent to be randomly offered experimental interventions. Patients are ineligible in case of inflammatory bowel disease, pregnancy, previous radiation to the pelvis, contra-indication for Capecitabine, and inadequate comprehension of the Dutch language in speech and/or writing. Female patients in whom the tumor is located on the anterior wall close to the vagina are also ineligible because the maximum tolerated dose to the vagina does not allow for dose-escalation when the tumor is in proximity.

RANDOM SELECTION

Patients within the PICNIC cohort that meet the above inclusion criteria form a sub-cohort of eligible patients (Figure 1). From this sub-cohort, a random sample is selected on a 1:1 basis with varying block sizes (n=6-8) using a centrally available computer program. Patients are stratified by type of anticipated surgery (low anterior resection, abominoperineal resection or other). Randomly selected patients are offered the experimental intervention (boost in addition to sCRT) by their treating physician. If they accept, they will sign additional informed consent to receive the boost. Patients who refuse the boost will receive care as usual, i.e. sCRT. Patients from the sub-cohort that will not be randomly selected will not be informed about the boost intervention.

STANDARD TREATMENT

Standard chemoradiation (sCRT) consists of 50 Gy (25 x 2 Gy on week days) combined with capecitabine. Radiation dose is delivered by intensity-modulated radiation therapy (IMRT), which is standard-care, to the planned target volume (PTV), which comprises the gross tumor volume (GTV) and clinical target volume (CTV). Target volumes are delineated on computed tomography (CT) combined with T2 and diffusion weighted (DWI) MRI images according to guidelines [20]. The CTV follows the mesorectal fascia up to the recto-sigmoid curvature and stretches maximally to 4 cm caudal of the tumor sparing the sphincter in case of a low anterior resection (LAR) or includes the

FIGURE 1 **Flowchart of patient inclusion**

sphincter-complex + 1cm margin in case of an abdominoperineal resection (APR). The lymp node regions (internal iliac and obturator) stretch from the caudal end of the v. iliaca communis downward to the crossing of the internal iliac vessels under the m. piriformis, laterally limited by the pelvic muscles. The obturator region stretches from the m. obturatorius to the m. levator, ventrally limited by the ureter or dorsal side of the neurovascular bundle without inclusion of the vesiculae, uterus and vagina. Lateral and dorsal border are marked by the pelvic muscles and ventral iliac region. In addition, the presacral region stretches from the upper level of the iliac vessels to mesorectum, ventrally limited 2cm from the sacrum including the a. rectalis superior and excluding the neuroforamina. The PTVCTV50 is a non-uniform margin around the CTV according to local protocol consisting of an expansion of 13mm ventrally, 9mm dorsally, 10mm laterally and 10mm cranio-caudally (Figure 2). The prescribed dose to the PTVCTV50 is that 95% of the prescribed dose should cover ≥ 99% of the PTV volume. Radiation is delivered with an external beam linear accelerator. For position verification the sCRT protocol consists of cone-beam CT before the first three fractions and weekly thereafter.

Capecitabine is administered twice a day orally on treatment days at a dose of 825 mg/m2, taken two hours before each radiation fraction and twelve hours later. Hematologic toxicity is tested every two weeks. Surgery is performed 10-12 weeks post-radiation according to the Dutch guidelines [21]. Total mesorectal excision (TME) surgery, either low anterior resection (LAR) or abdominoperineal resection (APR), is performed depending on location and extensiveness of the tumor [22].

Two routine MRI scans are acquired using an in-house developed magnetic resonance imaging (MRI) protocol, consisting of T2 and diffusion weighted (DWI) sequences [23]. The first scan (2 weeks prior to radiation) is used for radiation planning and the second (9 weeks post radiation) for preoperative response evaluation. Direct preoperative the surgeon will also perform DRE and rectoscopy for clinical response evaluation.

BOOST INTERVENTION

The experimental boost intervention consists of 15 Gy (5 x 3 Gy on week days) to the gross tumor volume (GTV) without concomitant chemotherapy. The boost is delivered in the week prior to the start of sCRT. A cumulative GTV dose of 65 Gy is delivered over the full treatment course of 30 fractions (6 weeks). This results in a equivalent dose in 2 Gy fractions (EQD2) of 66.3 Gy (α/β= 10 Gy [24]. GTV delineation is based on T2 and DWI images, no CTVGTV65 margin is applied and the PTVGTV65 is defined by a non-uniform margin of +11mm in the anterior-posterior, +7 mm in lateral and +13 mm in cranial-caudal directions around the GTV, which represent tumor movement that was observed on in-house daily MRI scans and set-up errors [25]. A Volumetric Modulated Arc Therapy (VMAT) stereotactic treatment plan is generated for boost patients, whereas IMRT is standard-care used in the control arm, that accumulates the boost and standard chemoradiation doses (Figure 2). The maximally allowed cumulative dose within the GTV is 80 Gy (123% of 65 Gy), and the volume receiving 95% of the prescribed dose should be larger than 99% of the PTVGTV65. Maximum dose around, and dose prescription to, the PTVCTV50 is similar to the elective sCRT field, i.e. 53.5 Gy. Daily online cone-beam CT's are used for positioning before each boost fraction and the sCRT position verification protocol follows thereafter.

Organs at risk (OARs) consist of the bowel bag (excluding sigmoid), bladder, vagina and anal sphincter. Dose constraints for the OARs remain unchanged for boost patients, namely the dose to 1cc of the OARs (D1cc) should be ≤ 53.5 Gy and the volume receiving 45 Gy is aimed to be less then 195cc for the bowel bag (excluding the sigmoid). OAR constraints are leading over PTVGTV65 coverage and may thus limit GTV dose if necessary. If dose prescriptions cannot be reached, a panel of radiation oncologists will discuss the feasibility and anticipated safety of the treatment plan and decide to continue or

Inclusion criteria	Exclusion criteria
Participant in the PICNIC project	Metastatic disease
Informed consent obtained for being offered experimental interventions within the PICNIC project	Inflammatory bowel disease
Informed consent obtained for questionnaires on patient reported outcomes within the PICNIC project	Prior radiation to the pelvis
Tumor distance of ≤10cm from ano-rectal transition	Inadequate understanding of the Dutch language in speech and/or writing
Indication for chemoradiation based on Dutch guidelines.	Recent pregnancy ≤1 year ago
No contra-indication for MRI	No indication for chemoradiation based Dutch guidelines.
World Health Organization performance status: 0-2	At least one contra-indication for capecitabine administration

adapt the plan towards accepTable OAR constraints, taking into account anatomical limitations and planned surgery. One additional MRI scan is obtained in patients that receive the boost for response prediction purposes at the end of the second week (after 10 fractions).

PRIMARY ENDPOINT

The primary endpoint of this study is pathologic complete tumor response (pCR) which is classified according to Mandard classification as Tumor Regression Grade 1 (TRG1) [5], i.e. a sterile tumor in the specimen with absence of residual cancer cells. Experienced gastrointestinal pathologists use a standardized protocol to evaluate the specimens [26], and central review of pathology is performed.

SECONDARY ENDPOINTS

Secondary endpoints include non-complete pathologic responses (TRG2-5), acute grade 3-4 toxicity, clinical response, surgical complications, quality of life (QoL), disease free- and overall survival. The non-complete pathologic responses are categorized as 'good' (TRG1-2) or not good (TRG3-5) by the pathologist. A radiation oncologist will assess toxicity at weekly visits during the radiation treatment, as well as four weeks and four months after completion of sCRT. Toxicity is recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [27]. Long-term toxicity, (serious) adverse events (SAEs), hospitalization and other health related problems are registered within the context of the PICNIC cohort during clinical follow-up and annual patient-administered questionnaires on health and oncological status. Clinical response evaluation is based on MRI imaging (9 weeks after completion of chemoradiation, i.e. the week before surgery), digital rectal examination (DRE) and rectoscopy which are both performed right before surgery under anesthesia. MRI and DRE are standardly performed in all patients, while rectoscopy is only performed in intervention-arm patients that showed a good response on MRI. For the MRI, a combination of T2 and DWI sequences is used to measure residual tumor tissue in the initially delineated tumor region and its surrounding elective radiation field. Surgical complications are registered up to 30 days after the primary surgery in all patients, and after closure of the diverting stoma in patients who previously underwent a LAR. For safety reasons, occurrence of anastomic leakage is monitored closely in the LAR-subgroup by daily review of post-operative patient charts for 30 days. Quality-of-life data are recorded by means of either electronical/internet-based (www.profilesregistry.nl) or pencil-and-paper questionnaires. For this purpose, Cancer-specific Quality of Life questionnaires from the European Organization for Research and Treatment of Cancer (EORTC) are used, including the core (QLQ-C30 [28]) and colorectal cancer-specific (QLQ-CR29 [29, 30]) questionnaires. The EORTC QLQ-C30 covers five functional scales, three symptoms scales, a global QoL scale and six single-items. The EORTC QLQ-CR29 assesses urinary, bowel and/or stoma, psychological and sexual related QoL issues, as well as side-effects from chemotherapy. These questionnaires are provided at diagnosis (baseline) and 3, 6, 12, 18 and 24 months thereafter. Survival and disease-free survival are monitored within the PICNIC project through clinical follow-up records and via a link with the Dutch Cancer Registry. Disease-free survival is defined as the time in absence of a rectal cancer local recurrence or metastasis.

SAFETY

According to the Dutch law, the investigator reports SAEs within 15 days following notification through a government-based internet portal (ToetsingOnline.nl) to the accredited IRB that approved the protocol. SAEs that result in death or are life threatening will be reported within 7 days.

Since this is an explorative dose-escalation study, an independent Data Safety Monitoring Board (DSMB) will recommend on continuation of the study based on safety results, focusing on toxicity and anastomotic leakage. The DSMB consists of an expert surgeon, radiation oncologist and statistician,

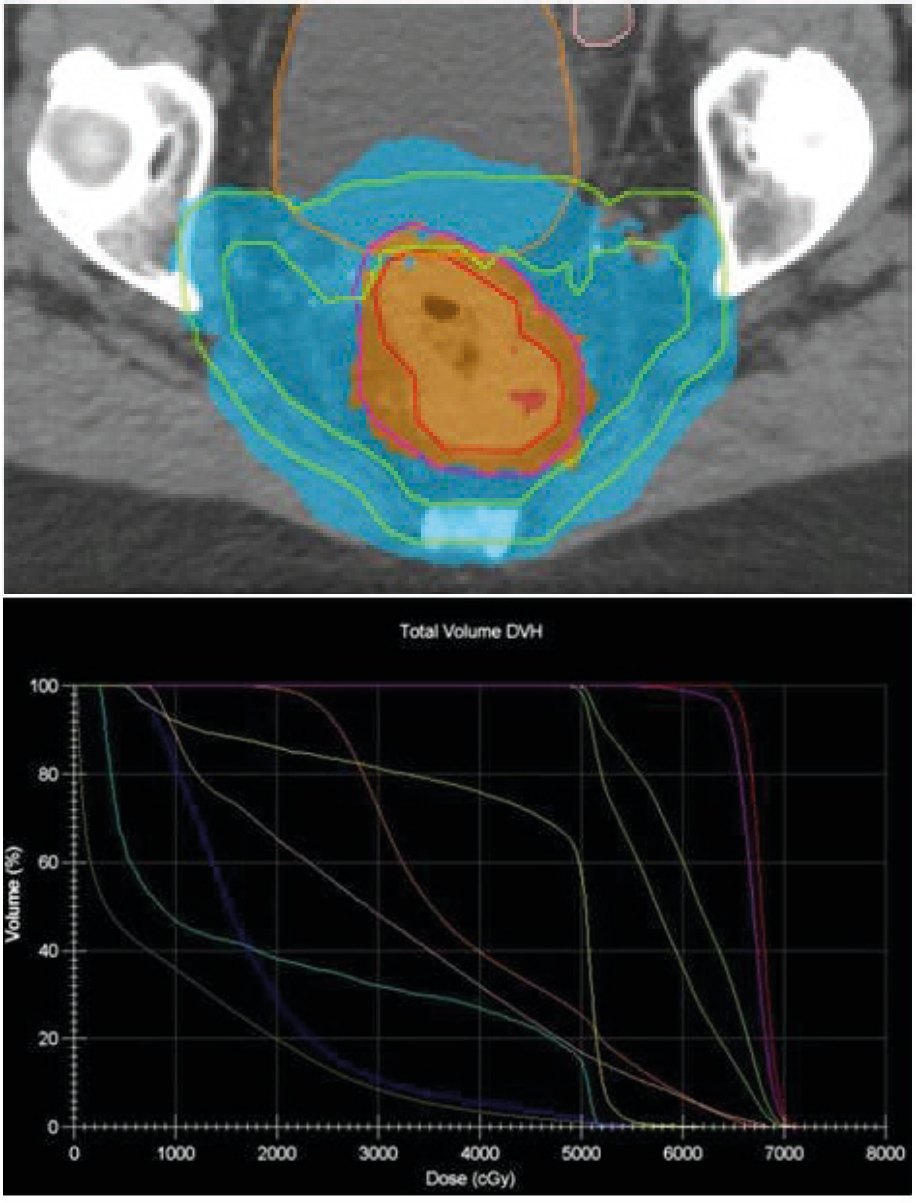

FIGURE 2 **Example of boost planning**

and is annually or after every SAE provided with the raw data on the primary and secondary outcomes (including toxicity, surgical complications and survival). After the first ten patients with LAR have undergone boost treatment, inclusion of patients scheduled for LAR will be stopped for eight months to let the DSMB compare anastomotic leakages between boost and control arms. The eight month period will consist of the time between sCRT to primary surgery (10-12 weeks) and primary surgery to bowel reconstruction including the postoperative monitor period (16-20 weeks). Only inclusion of patients undergoing LAR is halted during this stop since patients undergoing APR have no risk on anastomotic leakage because of their permanent stoma. The DSMB analyzes the data independently of the investigators and reports their advice on continuation of the study to the sponsor, who will decide on continuation / stop of the study.

SAMPLE SIZE CONSIDERATIONS

Based on our center's experience, we assume that 13% of patients will reach pCR if undergoing standard treatment (sCRT). Based on a prediction-model of Appelt et al [31] we expect the pCR rate to be 30% after 65 Gy. Since we consider this study preliminary work for subsequent studies aiming at even higher dose increases, we deem it important to find an effect if there really is one, but less important to unjustly find an effect. Therefore, we use a one-sided alfa of 15%, since it is unlikely that the pCR rate after boost treatment will be lower than after sCRT, in combination with a power of 80% since we do not want to increase uncertainty when a 'negative' result is achieved. We further expect that approximately 80% of the patients who receive a boost offer will accept. Patients who are offered the boost treatment but refuse to undergo the boost, will remain in the intervention arm and receive sCRT. We expect no cross-over from the control arm to the intervention arm, since only patients who are randomly selected to be offered the boost are informed and offered, while the other patients undergo standard treatment without being informed about the boost trial. Taking into account the estimated response rates together with a 20% refusal rate in the intervention arm, we require 60 patients per arm to demonstrate a statistically significant difference. We expect to complete recruitment within 3 years.

DATA-ANALYSIS

Data will be analyzed according to the intention-to-treat principle (ITT). Data of eligible patients, who were randomly offered the boost (intervention arm) will be compared to eligible patients that were not randomly selected (control arm). In case of drop out (i.e. no surgery following chemoradiation), a worst-case analysis will be performed, in which all non-resected BOOST patients are classified as non-complete responders, while all non-resected control patients are classified as complete responders. However, since omission of surgery is not common practice in our institution, we expect these numbers to be small. In case of substantial boost-treatment refusal in the intervention arm, complier average causal effect (CACE) analysis is performed to deal with differences in compliance of treatment in the different arms [32]. Outcomes include tumor pCR rate (TRG1), good pathological response (TRG1-2), clinical response, grade 3-4 toxicity, quality of life, recurrence rates, disease-free and overall survival. The primary outcome (proportion of patients with pCR) will be presented in proportions and compared by means of Chi-square test. Toxicity will be presented as the overall and/or time-point specific incidence of grade 3-4 toxicity and differences will be tested with the Chi square test. Quality-of-life will be compared at multiple points in time. A relevant change in the patient's perspective is indicated by a 10% difference or more than 0.5 of the standard deviation [33]. Quality-of-life data will be analyzed by mixed-effects models Differences in disease-free and overall survival rates will be analyzed by Kaplan-Meier analysis and Log rank test. Differences with a p-value <0.05 are considered statistically significant, except for the primary endpoint where $p<0.15$ has been pre-specified.

ETHICS

IRB approval was obtained separately for both the PICNIC project (including the cmRCT infrastructure) and the RECTAL BOOST from the ethical body of the UMC Utrecht (under reference numbers 12/510 and 13/522 respectively). The PICNIC project is published on clinicaltrials.gov under NCT02070146 [16] and the RECTAL BOOST study under NCT01951521 [34].

DISCUSSION

The RECTAL BOOST study aims to quantify the effect of an external beam radiation boost of 15 Gy prior to standard chemoradiation (50 Gy) on pathologic complete response rates in patients with locally advanced rectal cancer. Toxicity, clinical (complete) response, (surgical) complications, (disease-free) survival and feasibility of boost delivery are secondary endpoints. This study assesses in a randomized fashion whether a 65 Gy external beam radiation (EBR)-only regimen could safely increase the proportion of patients with tumor pCR (TRG1) to preoperative chemoradiation. Although contact X ray [35] and brachytherapy, EBR and EBR-brachy combined studies [6] showed response-, sphincter-saving- and organ-preservation benefits at doses up to 60 Gy, such benefits have not been shown at the 65 Gy dose level reached by an EBR-only approach.

High rates of good responders are important, as this will increase the number of patients eligible for organ-preserving treatment strategies. These strategies aim to improve the quality-of-life in good responding patients while maintaining good oncologic, and possible survival, benefits. Nevertheless, the value of tumor regression has not yet been confirmed as a surrogate endpoint for oncologic outcome in this setting. In the current study however, all patients, including those with a good clinical response to preoperative treatment, will undergo surgery since pathological response is the primary endpoint of this study. Also, resection remains the standard according to Dutch guidelines [19]. Therefore, future randomized studies in patients with good clinical responses after (boost) chemoradiation are needed to further assess the effect of radical surgery versus organ-preservation on quality-of-life, toxicity and (disease-free) survival. This study aims to quantify response by the current gold standard, i.e. pathology, which can be correlated to the clinical response data that are also obtained in this study. Thereby, this study provides important insight in the results of dose-escalation that would otherwise lack in a trial that combines dose-escalation and omission of surgery together.

In this study we choose to deliver the boost prior to chemoradiation to obtain maximal tumor visibility in order to avoid dose administration to healthy tissue. The rationale underlying this is that GTV deformation is likely to occur during sCRT due to tumor shrinkage, as well as and inflammatory reaction resulting in edema. This makes boost imaging and delineation of the tumor more difficult and less reliable, and may result in overestimation of the remaining GTV. When larger areas would then incorrectly be irradiated, surrounding healthy tissue might receive more dose than planned. From our own data on patients receiving 5x5 Gy radiation, we know that tumor shrinkage does not yet occur during the first week, which implies that GTV delineations made prior to irradiation remain adequate throughout the first week of (chemo)radiation. This allows single GTV delineation for boost dose planning prior to sCRT. Furthermore, IMRT is chosen since this is the standard of care in our hospital and this study is set-up as a single-facility trial. Direct applicability of these results should thus be considered when extrapolated to other centers in which different radiation techniques are used.

We have chosen to apply the cmRCT design which aims to overcome common shortcomings of classic randomized controlled trials (RCTs), like slow recruitment, disappointment bias in patients randomized to the control arm, and poor generalizability. Not uncommonly, oncological patients possess strong preferences towards experimental treatments that are (often) falsely regarded to be superior. This prevents such patients from taking part in randomized studies, thereby diminishing recruitment-rates for RCTs. Furthermore, patients that remain willing to participate in RCTs often represent a younger, healthier, higher-educated sub-group, and once participating, these patients are unfortunately often only allowed to participate in one trial at a time. All this makes recruitment for RCTs difficult and

prone to selection-bias. Because the cmRCT design uses a cohort as a recruitment pool, it represents the routine population more adequately since cohort-inclusion is generally less selective. Since this baseline may also evolve over time, the cmRCT furthermore provides the advantage that effectiveness of experimental interventions becomes compared to the most up-to-date available standard care that it should compete with, instead of outdated treatments, which is often the case whenever classic RCTs are published. A new aspect brought by the cmRCT design is that it provides the opportunity to evaluate acceptance-rates of offered treatments. This gains new insights into patient-preferences and reasons for refusal of experimental interventions that become increasingly important. It forces clinicians and researchers to rethink their treatment approach at an much earlier stage when, for instance, a large proportion of patients would decline an offered treatment. Overall, efficient less selective recruitment, collection of long-term outcomes and early preference-monitoring could reduce research-costs significantly when conducting RCTs within the cmRCT design.

In conclusion, the RECTAL BOOST study is a pragmatic randomized trial that aims to quantify the effect of dose-escalation to 65 Gy on pathological complete response rate in patients with locally advanced rectal cancer treated with preoperative chemoradiation. If the proportion of good responders can be increased by dose-escalation, this could provide an option to increase the number of patients that may benefit from organ-preserving strategies in the future.

TRIAL STATUS

Ethical approval for this trial was obtained in June 2014. Recruitment started in September 2014. Current proceedings are presented in the general discussion of this thesis (see page 248).

Competing Interest

The authors declare that they have no competing interests.

Authors' Contributions

JPMB, HMV, MI, OR designed and coordinate the study procedures. WMUVG, MK helped design the study. JJEK, ME, BWR, ES, BVA designed, performed and calculated treatment plan parameters. All authors read and approved the manuscript.

Acknowledgements

There are no acknowledgements for this article. There is no funding for this trial.

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PART 3

SUMMARY AND GENERAL DISCUSSION

CHAPTER 8

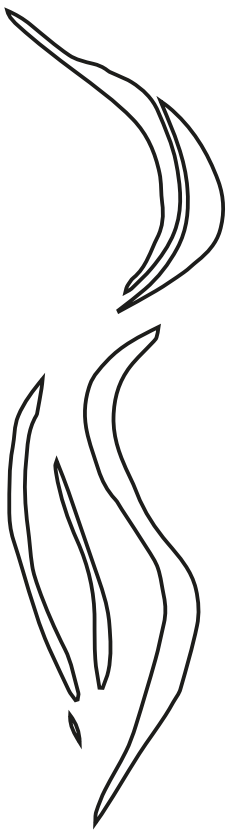
Summary

CHAPTER 9

Nederlandse samenvatting

CHAPTER 10

General discussion



CHAPTER 8

SUMMARY

CHAPTER 08

PART I: QUALITY OF LIFE IN RECTAL CANCER PATIENTS

Chapter 2 presents how we electronically embedded the capture process of patient-reported outcomes in routine care. Questionnaires are sent out at regular intervals (at diagnosis, 3, 6, 12, 18 and 24 month, and yearly thereafter) and results can be combined with patient characteristics. Furthermore, the design of this multidisciplinary prospective observational cohort study (the PLCRC* project) provides validated and standardized collection of clinical data as well as survival outcomes over a longer period of time. The selection of questionnaires is kept dynamic to keep up with changing relevance in outcomes, and currently includes several tools to measure different aspects of patient-wellbeing including quality of life, symptoms, workability and bowel function. Furthermore, this initiative has been designed to efficiently evaluate new treatments by facilitating the conduction of multiple (simultaneous) randomized controlled trials in the 'cohort multiple Randomized Controlled Trial (cmRCT) design.

In **Chapter 3** we show the cmRCT design obtained ethical approval and was implemented successfully in our clinic in February 2013. Since its start we demonstrated a promising inclusion-rates of 88% of rectal cancer patients into our cohort. Furthermore, 85% of patients gave consent to be randomized in future trial and 90% consented to receive PROMs. Return rates of questionnaires were 90% at baseline and varied between 71-88% during follow-up. Ethical approval for the first randomized controlled trial in the rectal cancer cohort was obtained in June 2014. Analysis of rectal cancer patient characteristics showed that cohort participants, participants who consented to receive questionnaires and participants who consent to be randomized for trials within the cohort had comparable characteristics as patients who did not give these consents. This indicates that results following from our data is representative to the entire rectal cancer population who visits our clinic and that results from trials carried out within the context of our cohort can be generalized to daily care.

In **Chapter 4** we have used our first data obtained in the cohort to evaluate quality of life in routinely treated patients after two radiotherapy regimens. This chapter indicates that the impact of short-course radiotherapy and chemoradiation on quality of life is similar within the first year following diagnosis. Both groups, consisting of 106 chemoradiation patients and 79 short-course radiotherapy patients, demonstrated comparable quality of life trajectories in terms of global health, physical-, role- and social-functioning. We observed that decreased functioning was almost always consistent with higher reporting of (bowel) symptoms. After 12 months, only physical functioning remained impaired in short-course radiotherapy but not in chemoradiation patients compared to their baseline. These results strengthen the idea that short-course radiotherapy could be replaced safely with chemoradiation in terms of quality of life for patients with medium-risk tumors who seek the opportunity to undergo organ-preservation when reaching a clinical 'good' or 'complete' response after neo-adjuvant treatment.

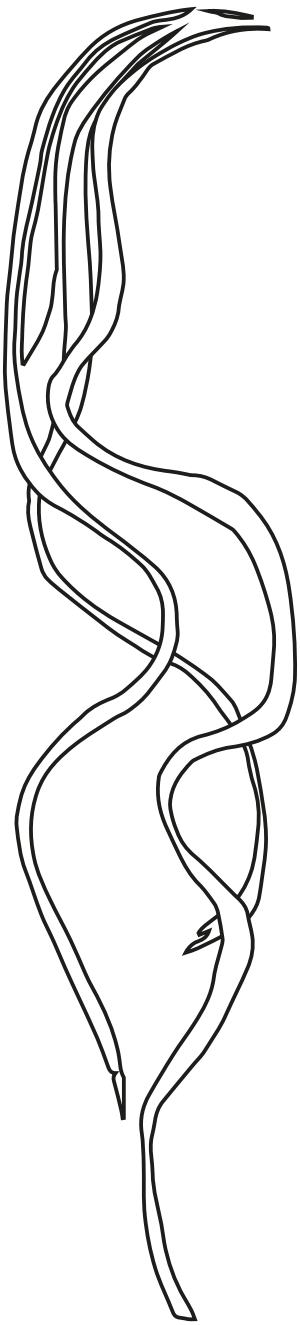
PART II: DEVELOPMENT OF AN INNOVATIVE RADIATION BOOST TREATMENT

Chapter 5 presents evidence for safe and effective dose-escalation during neo-adjuvant radiation treatment. We demonstrated that higher response-rates could be reached by elevating the radiation dose to ≥60 Gy compared to standard care (50 Gy), 20.4% vs. 15%. These findings were based on a systematic literature search that resulted in 14 studies with a total of 487 patients that could be pooled and analyzed. Pooled grade ≥3 toxicity rate was 10.3% and pooled resectability-rate was 89.5%, which are both comparable to rates presented in current literature. Data of this study was used to discover and validate the safety of a radiation dose above 60Gy to boost patients in a subsequently designed trial.

Chapter 6 proves that it is clinically feasible to use MRI for guidance of dose delivery in locally advanced rectal tumors. Furthermore it shows that variation between observers does not pose a potential throwback regarding the safety of dose delivery as long as observers are experienced in delineating rectal tumors. Several MR-sequences, both anatomic and functional, resulted in comparable agreement between observers. No significant volume differences were observed between observers in each modality. T2 anatomical images resulted in the largest volumes while DWI images gave the smallest volumes. Mean conformity index, a measure for overlap between delineated contours, was comparable between modalities around 0.70. Average maximal distance between two contours was largest on T2 (18.60mm, Max 31.40mm, Min 9.20mm). This study therefore indicates the safe accuracy of DWI, solely or in combination with T2, to use for radiation boost planning.

Chapter 7 describes the strategy used for evaluation of the MRI-guided radiation boost treatment in a pragmatic randomized controlled setting. The primary outcome, proportion of pathological complete response, is compared between a regimen containing boost plus standard chemoradiation (intervention) versus standard chemoradiation alone (control). This study follows the cmRCT design and is embedded into the cohort infrastructure presented in **Chapter 2.** Eligible patients - histologically confirmed LARC (T3NxM0 <1mm from the mesorectal fascia, T4NxM0 or TxN2M0) located ≤10 cm from the anal-rectal transition with consent to be offered experimental interventions – are selected from the larger cohort and form a sub-cohort. From this subcohort, a random sample is offered the boost in addition to chemoradiation (50 Gy in 25 fractions of 2Gy combined with capecitabine). Informed consent is obtained from all patients that accept the boost offer. The pre-chemoradiation boost consists of 15 Gy (5 daily fractions of 3Gy) to the tumor volume delineated on MRI. Patients in the subcohort who are not randomly selected function as the control group and undergo chemoradiation alone. Secondary endpoints include acute grade 3-4 toxicity, surgical complications, QoL, and disease free- and overall survival. Data is analyzed according to intention-to-treat.

The trial started in September 2014. The discussion chapter of this thesis includes the latest update on inclusion rates of the trial.



CHAPTER 9

NEDERLANDSE SAMENVATTING

CHAPTER 09

PART I: KWALITEIT VAN LEVEN IN PATIËNTEN MET RECTUMCARCINOOM

Hoofdstuk 2 laat zien hoe we het elektronisch registreren van patiënt-gerapporteerde uitkomsten hebben geïntegreerd in de logistiek van onze dagelijkse kliniek. Het design van de presenteerde multidisciplinaire prospectieve observationele cohort studie (het PLCRC project) is erop gericht om gevalideerde en gestandaardiseerde uitkomsten te verzamelen over een langere periode (van inclusie tot aan de dood). Binnen dit project worden klinische uitkomsten geïntegreerd met patiënt-gerapporteerde uitkomsten. Deze laatste worden verzameld door op vast tijdstippen vragenlijsten uit te zenden (ten tijde van diagnose, 3, 6, 12, 18 en 24 maanden na diagnose en jaarlijks daarna). De selectie van vragenlijsten is dynamisch waardoor er rekening gehouden wordt met welke uitkomsten relevant zijn voor klinische vraagstukken die uitgezocht (gaan) worden. De huidige set bestaat uit een selectie van vragenlijsten waarin verschillende aspecten van het welzijn van patiënten gemeten wordt, o.a. kwaliteit van leven, bijwerkingen, de mogelijkheid om te werken en darm-gerelateerde symptomen. Daarnaast is deze studie ontworpen om op efficiënte wijze meerdere nieuwe interventies te evalueren binnen meerdere (gelijktijdig lopende) gerandomiseerde studies volgens het principe van het 'cohort multiple Randomized Controlled Trial (cmRCT) design.

Hoofdstuk 3 beschrijft het verkrijgen van ethische toestemming en de daaropvolgende implementatie van het cmRCT design. Vanaf de start in februari 2013 behalen we veel belovende inclusie percentages: 88% van de patiënten met rectumcarcinoom die onze kliniek bezoek wordt geïncludeerd. Daarnaast geeft 85% van deze geïncludeerde patiënten additioneel toestemming om gerandomiseerd en uitgenodigd te worden om een experimentele interventie te ondergaan in de toekomst. Ook geeft 90% toestemming om vragenlijsten te ontvangen waarin patiënt-gerapporteerde uitkomsten gemeten worden. In juni 2014 is toestemming verkregen voor het uitvoeren van de eerste gerandomiseerde studie binnen dit cohort. Analyse van patiënt karakteristieken liet zien dat deelnemende patiënten, patiënten die additioneel toestemming gaven voor randomisatie in toekomstige studies en patiënten die vragenlijsten wilde ontvangen, gelijk waren aan de die van patiënten die deze toestemmingen niet gaven. Dit suggereert dat de verkregen uitkomsten uit deze data representatief zijn voor de gehele populatie rectumcarcinoom patiënten die onze kliniek bezoekt. Hierdoor zullen resultaten van uitgevoerde studies binnen ons cohort waarschijnlijk goed generaliseerbaar zijn naar de gehele populatie rectumcarcinoom patiënten.

Hoofdstuk 4 beschrijft de eerste studie waarin kwaliteit van leven data gebruikt wordt die uit het PLCRC cohort verkregen is. In dit hoofdstuk worden twee radiotherapie behandelingen met elkaar vergeleken op basis van hun effecten op de kwaliteit van leven van patiënten met rectumcarcinoom. Hieruit blijkt dat de impact van korte voorbestraling gelijk is aan die van chemoradiatie gedurende het eerste jaar na diagnose. Beide groepen, bestaande uit 79 kort voorbestraalde patiënten en 106 chemoradiatie patiënten, lieten een vergelijkbare trend in functionele kwaliteit van leven uitkomsten zien aangaande globale gezondheid, fysieke functie, rol functie en sociale functie. Het rapporteren van lagere functionele scores was consistent met het rapporteren van meer last van symptomen. Na 12 maanden was alleen fysieke functie beperkt in de kort voorbestraalde patiënten maar niet in de chemoradiatie patiënten vergeleken met hun uitgangspositie. Deze resultaten steunen de gedachte dat korte voorbestraling veilig vervangen zou kunnen worden door chemoradiatie in patiënten met een 'gemiddeld risico tumor' in termen van kwaliteit van leven, zodat deze patiënten een kans krijgen om een 'goede' of zelfs 'complete' respons te behalen na voorbehandeling waardoor ze in aanmerking zullen komen voor orgaan-sparende behandelingen.

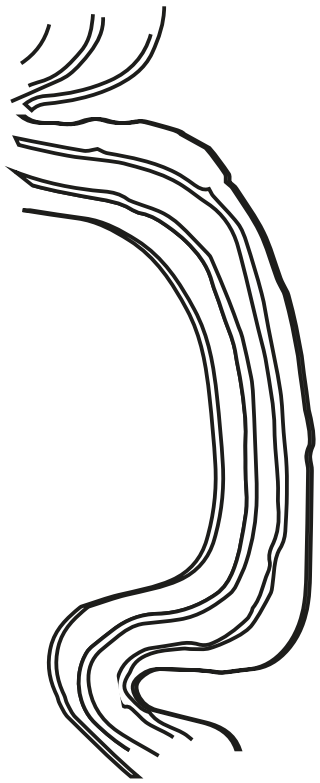
PART II: ONTWIKKELING VAN EEN INNOVATIEVE BESTRALINGS BOOST BEHANDELING

Hoofdstuk 5 presenteert bewijs dat het escaleren van de bestralingsdosis tijdens neo-adjuvante behandeling veilig en effectief is. In dit hoofdstuk laten we zien dat er hogere response percentages behaald worden wanneer de dosis verhoogd wordt tot ≥60 Gy in vergelijking met de standaard gegeven 50 Gy, 20.4% vs. 15%. Deze bevindingen zijn gebaseerd op eerder gepubliceerde studies. Door systematische de literatuur te doorzoeken werden er 14 studies geïdentificeerd. Hierin werden in totaal 487 patiënten geanalyseerd. Resultaten van deze studies werden gebundeld. Tevens lieten de gebundelde resultaten zien dat graad 3 toxiciteit 10.3% was en dat 89.5% van de patiënten operabel was na deze behandeling. Beiden percentages zijn vergelijkbaar met de huidige literatuur na standaard chemoradiatie. De resultaten van deze studie zijn gebruikt als rationale voor het ontwerp van een gerandomiseerde gecontroleerde studie naar de effectiviteit en veiligheid van een bestralings boost.

In **Hoofdstuk 6** laten we zien dat het klinisch haalbaar is om MRI beelden (magnetische resonantie beeldvorming) te gebruiken voor het plannen van bestralingsdosis in de lokaal gevorderde rectumcarcinomen. Dit hoofdstuk laat tevens zien dat de variatie waarin individuen tumoren intekenen geen potentiele bedreiging vormen voor de veiligheid waarmee deze tumoren bestraald kunnen worden zolang deze individuen getraind zijn. Verschillende MRI sequenties, anatomisch en functioneel, resulteerde in vergelijkbare overeenstemming tussen intekenaars. Er werden geen significante verschillen geobserveerd tussen de intekenaars binnen de verschillende sequenties, al resulteerde de anatomische T2 beelden in de grootste volumina en de functionele diffusie-gewogen beelden (DWI) in de kleinste volumina. De 'conformiteits-index', een maat voor overeenstemming en overlap tussen ingetekende contouren, was gelijk tussen deze modaliteiten en lag rond de 0.70. De gemiddelde maximale afstand tussen twee contouren was het grootst tussen op T2 beelden (18.60mm, Max 31.40mm, Min 9.20mm).Deze studie laat zien dat het veilig is om DWI, alleen of in combinatie met T2 beelden, te gebruiken voor het intekenen rectumcarcinomen ten behoeve van het geven van radiotherapie.

Hoofdstuk 7 beschrijft een strategie waarmee het effect van een MRI geleide bestralings boost geëvalueerd wordt in een pragmatisch gerandomiseerde gecontroleerde omgeving. De primaire uitkomstmaat, percentage patiënten met een pathologisch complete response, wordt vergeleken tussen een groep patiënten die de boost (5 x 3 Gy) plus chemoradiatie ontvangt (interventie arm) en een groep die alleen chemoradiatie ontvangt (controle arm). Deze studie volgt het principe van het cmRCT design en is ondergebracht in de infrastructuur gepresenteerd in Hoofdstuk 2. Patiënten die in aanmerking komen – patiënten met histologisch lokaal gevorderde tumoren (T3NxM0 met een afstand van <1mm vanaf de mesorectale fascie, T4NxM0 or TxN2M0) gelegen op ≤10 cm afstand van de anus met toestemming om gerandomiseerd te worden voor experimentele interventies – worden geselecteerd uit het cohort en vormen een sub-cohort. Uit dit sub-cohort wordt een willekeurige selectie van patiënten geselecteerd die de boost behandeling (15 Gy in 5 fracties van 3 Gy) aangeboden krijgen voorafgaand aan chemoradiatie (50 Gy in 25 fracties van 2Gy gecombineerd met capecitabine). Toestemming voor deze behandeling wordt enkel verkregen van patiënten die deze voorgestelde behandeling accepteren. Patiënten in het sub-cohort die niet geselecteerd werden functioneren als controle groep en ondergaan enkel chemoradiatie. Secundaire uitkomstmaten bestaan uit graad 3-4 toxiciteit, chirurgische complicaties, kwaliteit van leven en (ziektevrije) overleving. Data wordt geanalyseerd volgens het intentie-tot-behandeling principe.

Deze studie is gestart in september 2014. In de (Engelstalige) discussie worden de meest recente inclusie aantallen van de studie gepresenteerd.



CHAPTER 10

GENERAL DISCUSSION

CHAPTER 10

This thesis presents results of studies that have led to the development of a MRI-guided radiation boost treatment and implementation of the RECTAL BOOST trial.

In **PART I**, we described the process leading to implementation of the 'cohort multiple Randomized Controlled Trial' (cmRCT) infrastructure for collection of clinical data and patient-reported outcomes. We showed this infrastructure can be used to obtain outcomes from patients in routine care (**Chapter 4**) as well as that it has the potential to serve as a multi-trial facility, in which new interventions are compared against standard care (**Chapter 7**). However, with our first cmRCT ongoing, we have to await whether the theoretical advantages of the cmRCT design can be met.

WHY THE CMRCT DESIGN?

The cmRCT design was developed by Clare Relton and colleagues to overcome four major shortcomings of classic RCTs: 1) difficult patient recruitment, 2) concerns about patient information and consent, 3) limited capability of reliable treatment comparison and 4) problems related to patient preferences for new interventions ('new is better'). Additional benefits of the cmRCT include regular measurement of outcomes over longer periods of time, simultaneous randomized evaluation of multiple interventions and the ability to obtain relevant outcomes for routine care based on a pragmatic approach. Most of these concerns and advantages were implicitly addressed throughout this thesis but will be discussed below.

The information and randomization process of standard RCTs is rather confusing from a patient's perspective. Patients are being asked three questions simultaneously, namely 1) whether they want to participate in research, 2) whether they want to learn about experimental interventions being trialed, and 3) whether they want to be randomized. These concerns are tackled by cmRCT and further addressed by integrating a staged-informed consent procedure [1] into our cohort infrastructure (**Chapter 3 & 7**). After patients join the cohort they are asked for consent to be randomized and offered experimental interventions in the future ('broad consent for randomization'). This method is different than how it was initially proposed by Relton et al. In their paper they proposed that all patients could be offered interventions and that they would not be informed about this upfront. The choice to apply one or the other may depend on the setting from which patient are recruited. If the population is very large and has broad inclusion criteria (such as a population-based cohort at risk of obesity [2] or 'elderly at risk of falls' [3]) the probability of actually being offered an intervention is very small. In this case, to inform all patients on this possibility may potentially harm patients more than it would benefit them: it could lead to disappointment when they are not offered anything. On the other hand, when inclusion criteria are more narrow and participants have a higher probability to be offered an intervention (such as in our rectal cancer cohort), it seems more meaningful to inform patients upfront. Also, this provides patients with no interest in joining additional research to never be bothered by trial offers again. In our rectal cancer cohort we therefore chose to use the staged-informed consent approach, which showed that 85% of patient in the cohort agreed to be randomly selected and offered interventions in the future. Furthermore, **Chapter 3** showed that patients who did consent to broad randomization had similar characteristics as those who did not consent, which indicates that the risk of selection bias is limited.

Difficulty with recruitment is a common concern in RCTs and can lead to reduced power, low generalizability or early abortion of trials [4, 5]. The theory on which the cmRCT design stands proposes that recruitment into observational cohort studies is often easier and less selective, and that, by using

a cohort as a basis for trial recruitment, generalizability and recruitment can be improved. Within the context of the national colorectal cancer cohort (PLCRC, **Chapter 2**) we showed that 88% of the rectal cancer patients visiting our clinic were recruited into cohort and that the majority of eligible patients were randomized (67%) (**Chapter 3**). This is a lot higher than the proportion of eligible patients being randomized in other (oncological) RCTs [4, 5]. We believe that the staged informed consent procedure contributed to these high rates. By allowing patients to separately consent to whether they want to participate in research, whether they want to be randomized and to whether they are willing to undergo an experimental intervention, we may have included patients that would otherwise not have consented to an RCT in which these three items are asked within one question. Also, by systematically sending out study information before the first appointment with the radiation oncologist, and by and by systematically offering all patients to participate in the cohort before they meet with their radiation oncologist, only a small minority of patients was not informed about the cohort, and not considered for randomization. A recent Cochrane review identified three major improvements that can be made to promote recruitment [6], i.e. 1) have a dedicated person (or tool) check eligibility of patients (we systematically approached each patient with rectal cancer referred to our clinic), 2) involve medical personnel (we regularly informed our staff members about proceedings with the cohort) and have dedicated researchers performing recruitment (which we do at a dedicated 'research-desk' (**Chapter 3**).

A key feature of the cmRCT design is to deal with patient preferences by resembling a 'real world' situation in which patients may choose which treatments they will undergo rather than being told about two treatments and randomly allocated to one of them. In the RECTAL BOOST trial we see that the majority of patients who are randomized to the intervention arm (boost), accept the experimental treatment (**Chapter 3**). The acceptability (or preference) to undergo interventions is strongly dependent on the nature of the intervention and the potential risks it may bring. Also, due to the pragmatic nature of the cmRCT design it is possible for patients to undergo other consecutive treatments than originally prescribed in the protocol. This is observed in the RECTAL BOOST study where some patients have (already) chosen to undergo organ-sparing treatment whereas the trial protocol prescribed radical surgery. Intention to treat analysis deals with this by using a composite endpoint (discussed later).

Preferences of patients change over time and so do preferences of physicians. Standard care evolves (for example from standardly performing laparoscopic to robotically-assisted surgery in some centers). Since the cmRCT uses standard care as control treatment, patients will always have to make a 'real-world' choice between an up-to-date standard care and the offered intervention. This will provide the latest information on the acceptability of trial interventions and will give the more realistic expectation of the benefits that an experimental intervention can bring to routine care once it is. To further assess preferences of patients within our rectal cancer cohort, we are currently looking at how patient rate different treatment scenario's, which should indicate to physicians which treatments they prefer – and are potentially accepTable - and should therefore be considered to further be developed or trialed.

Theoretically, data can be used very efficiently in the cmRCT design when it comes to simultaneous evaluation of trialed interventions since patients can function as 'controls' in multiple trials. This topic was recently put into practice in our rectal cancer cohort by implementing a second RCT. This trial evaluates the use of retractor sponge-assisted laparoscopic surgery versus standard laparoscopic surgery in Trendelenburg positioning (SPONGE trial) [7]. The inclusion criteria for this trial partially overlap with the inclusion criteria of the RECTAL BOOST trial (**Chapter 7**), namely all rectal cancer

patients that are eligible for the RECTAL BOOST trial and can be operated in a elective setting with laparoscopy are also eligible for the SPONGE trial. Whereas in other settings these trials would compete in patient-recruitment, potentially leading lower rates for both, the cmRCT showed to be able to include a high percentage of eligible patients who could reliably be stratified according to their received or planned treatments.

When designing and incorporating a second trial into the cohort, one has to take into account potential overlapping of the impact of previous intervention(s) on the outcome (interaction). In the SPONGE trial, for example, hospital stay (the primary outcome in the SPONGE trial) may be influenced by a previous boost intervention, which might increase the risk of post-operative morbidity. The same applies to other endpoints such as quality of life. Also, a consequence of embedding multiple trials is that it will generate many subpopulations of patients who have undergone different combinations of treatments, which requires larger sample sizes to maintain adequate power in each analysis. Although the feature of a multiple trial facility is looks promising, implementation of consecutive trials should be performed with caution and with special attention to already running trials. Ongoing trials within cmRCT cohorts will provide more detailed insights in the ability of the cmRCT design to deal with the challenges mentioned above.

A last proposed key feature of the cmRCT infrastructure, namely longitudinal data collection (of patient-reported outcomes, also showed to be feasible in our clinic: 90% of the participating patients agreed to receive questionnaires and response-rates varied between 71-90%. We assume internal validity of obtained PROMs is high since we observed comparable characteristics in patients who consented to receive PROMs and responded to questionnaires as those who did not (**Chapter 3**). Furthermore, the cmRCT design is dynamic and allows adaptations in outcomes that are measured, especially when it comes to different sets of PROMs over time.

A cmRCT infrastructure may not always be the best trial design. Because interventions are compared to standard care, it is impossible to conduct placebo-controlled trials. Also, within very small communities it may be harder to keep control patients ignorant of trialed interventions, which is one of the key features of cmRCT. Trials requiring additional measurements outside routinely measured outcomes are also difficult to implement [8] since these violate control patients to only undergo standard care. Last, trials that investigate treatments that are not desired by patients will likely also pose problems because of high refusal rates leading to a major dilution in observed treatments effect [9]. It will, however, inform researchers in a very early stage about the intolerance of patients to undergo this treatment.

MEASUREMENT OF PATIENT REPORTED OUTCOMES

Methods to collect patient-reported outcomes within cohorts are manyfold. Within the prospective national colorectal cancer cohort (PLCRC [10]) we chose to provide patients the option to choose between pen-and-paper or electronic surveys to patients, both of which are integrated in an online data-collection platform PROFILES [11]. Paper and electronically collected outcomes are equivalent in data-capturing quality, comparable in psychometric properties and equal in (test-retest) reliability [12-19]. With both options available we anticipated to obtain the highest response rates and lowest chance of selection bias. In the rectal cancer population selection bias could be an issue since a considerable subpopulation (especially the elderly) may still have limited access to or is partially capable of using computers to fill out electronic surveys. We also observed that this could be an issue since our cohort has a mean age of 67 years (SD 11) (**Chapter 3**). However, acceptance of electronic capturing is growing [17, 20, 21].

Chapter 4 presents the first study based on patient-reported PLCRC quality of life data. This study compares quality of life outcomes between two radiation regimens in routinely radiated patients. As discussed above, internal validity is potentially high. However, from earlier colorectal cancer trials we know that results from trial patients can be considerably different than those observed in routine practice [22]. This may be due to the fact that studies often have difficulty recruiting [5] and often include a younger, healthier and more positive sub-population who are likely to experience a smaller impact of treatments (especially on soft outcomes such as quality of life). When comparing quality of life data from **Chapter 3** to other published data, we found that our rectal cancer patients reported similar outcomes following treatment as those observed in other European RCTs and cohort studies [23-26]. Still, surgeons in southern European countries are less likely to construct temporary and definitive stomas than surgeons in northern European countries, even in low-lying tumors. This may be due to cultural differences in interpretation of the impact of having a stoma on quality of life. Even when quality of life is weighed against oncological benefit of treatments, some patients and physicians may be willing to accept a higher chance on recurrence if this potentially provides just a slight benefit in quality of life. Thus, comparability in absolute terms (i.e. quality of life outcomes measured in questionnaires) does not necessarily mean that outcomes are also subjectively generalizable between populations.

When evaluating quality of life it must be kept in mind that perspectives of patients change over time. This is defined as a change in internal standards when patients report on their quality of life (22). This process is called 'recalibration' and 'reconceptualization' of what 'good' quality of life entails [27]. Effects of response shifts are more pronounced in general quality of life measures, such as global health, than in more specific aspects, such as symptoms. It is unclear what processes influence the occurrence of response shifts or how long it takes for them to occur, but it is likely that the more time passes the more internal standards become affected. In our own studies we also observed this effect since symptoms were more frequently reported during treatment but these had little or no effect on global QoL measures. Also, patient' scores in Chapter 4 showed to be almost comparable to the healthy Dutch population at 12 months whereas they experienced more symptoms. Hence, the conclusion that QoL is similar between two treatment groups showing comparable outcomes cannot be drawn that easily. For true comparison, quality of life data should rather be interpreted together with symptom data and should be viewed against a background of patients with an equal background, preferably through randomized comparison, for which the cmRCT provides an promising infrastructure.

THE RATIONALE FOR DOSE-ESCALATION

PART II describes why and how we developed a MRI-guided radiation boost treatment and how it is currently being evaluated against standard care in a randomized setting.

In **Chapter 7** we investigated whether or not increasing radiation dose improves pathological complete response rates in locally advanced rectal cancer patients [28]. In a meta-analysis, we estimated that 20.4% pathologic complete responses could be obtained after increasing the radiation dose to >60 Gy, which would mean an increase of 5% compared to 15% observed after standard 45-50 Gy [28, 29]. Acute grade >3 toxicity rates were expected to remain equal between >60 Gy and standard doses. Interestingly, all studies analyzed in our meta-analysis used older (nowadays outdated) radiation techniques compared to the techniques used today. Modern techniques include intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) which have the improved ability to target radiation dose and limit radiation of healthy tissue. Therefore, these techniques are thought

to contribute to a (further) reduction in toxicity [30]. Furthermore, our finding of the dose-response relationship between dose and oncologic outcome but not between dose and toxicity enables to increase radiation doses to even higher levels. Nevertheless, findings in our meta-analysis were limited by differences in assessment of the primary outcome, pathologic complete response (pCR), as described. Pathologic assessment was not always standardized and timing of assessment differed somewhat between studies. Both may have led to over- or underestimation of results based on the fact that 'the more you look, the more you will find' and that longer intervals lead to higher pCR-rates [31, 32]. Future studies should therefore apply strict standardization of pathological assessment or should use composite endpoints that consist of pathological assessment and disease-free survival, which is associated with pCR [28]. On the other hand, patient selection for novel organ-preserving treatments relies on clinical and not pathologic response assessment. Although many tools are being evaluated for their potential to predict pathologic response (including endoscopy (+ biopsy), MRI, diffusion-weighted MRI and PET [33-35]), response assessment is still not optimal and may benefit from a dynamic rather than a 'one-point-in-time' approach.

REPRODUCIBILITY OF THE BOOSTING TECHNIQUE

After our meta-analysis provided evidence that dose-escalation is safe and may have oncologic benefits, we developed of a boost strategy presented in **Chapter 5**. Here, MR-imaging is used to plan dose delivery instead of CT-imaging. By introducing MR imaging into the process of radiation planning, multiple processes were added to the treatment-planning chain which may all introduce additional uncertainty. As discussed, a new DWI-sequence had to be developed to match and merge with anatomical MR images, inter-observer agreement results led to formation of new treatment margins that are used in dose planning, and MR-images have to be projected on CT-images that are used on the machines in the clinic. All these processes may reflect on toxicity outcomes. Therefore, the implementation of MR-guided planning complicates the interpretation of toxicity results if compared to previous (boost) studies. Unfortunately, we are currently the only center applying an MRI guided radiation boost in rectal cancer and can thus not compare our findings to peer-reviewed literature. However, with increasing availability of MR scanners in (radiotherapy) clinics more MRI guided dose-escalation for rectal cancer will be implemented in near future.

Other methods besides external beam radiation are also available to deliver a radiation boost. These include endoluminal approaches such as brachytherapy or contact X-ray applicators which are introduced closely onto the surface of the tumor. These therapies are, however, only feasible when lesions are small (maximally 4 centimeter) and when reachable by the device (approximately below 10-12cm from the anal verge). One of the largest brachytherapy studies recently showed that a 60Gy external beam + 5 Gy brachytherapy dose in 51 patients with T2-3 tumors led to a complete response in 40 patients whose 1-year local recurrence rate was 15.5% [36]. The most recent data from contact X-ray therapy showed that is can safely be combined with external beam and in recent patients results in up to 95% complete response at 2 months [37]. Contact X-ray combined with 'watch and wait' results in 93% stoma-free of surviving patients (82%) at median 20 months follow-up [38]. Together, these trials provide preliminary evidence for the safety and usefulness of endoluminal dose delivery in combination with external beam radiation, but future trials are required to investigate the optimal combination between these two treatments and whether or not they truly complement each other.

UPDATE ON THE RECTAL BOOST TRIAL

The RECTAL BOOST trial started in September 2014. The latest update (September 2016) learns that a little over 50% of patients have been recruited (30/60 in the boost arm and 32/60 in the control arm). The trial is currently expanded to a multi-center setting, which includes the MAASTRO clinic in Maastricht, The Netherlands. We expect that the trial will be completed by August 2017 and that the first short-term results can be presented shortly thereafter. For now, it is too early to comment on the results of the trial since we still have insufficient power to draw definitive conclusions.

Important outcomes of the RECTAL BOOST trial include acceptability of the offered intervention (5 additional boost fractions of 3 Gy), toxicity rates, (post-operative) morbidity and oncologic outcomes. The latest update (September 2016) also shows that out of the first 30 patients who were randomized to be offered the boost intervention, 27 (90%) accepted to undergo the boost (compared to 23 patients randomized and 20 (87%) accepting the boost in **Chapter 3**). The current acceptance rate is more or less comparable to the 80% that was anticipated during the design of the trial (noting that we still have insufficient power to definitively evaluate the acceptance rate). However, since this is the first trial we have yet to discover whether or not the acceptability rates of offered interventions within cmRCT settings can be translated into routine practice. There is no evidence on this topic yet (from other international cmRCT trials).

The primary outcome, pathological complete response rate, has shown to be more difficult to establish than initially anticipated. Because the pragmatic design recruited patients have the opportunity to already undergo organ-preservation treatments instead of radical surgery in case of a complete clinical response. Some of the included patients have indeed done so. As a consequence, the number of patients from whom pathologic specimens are available is smaller than the initially planned number of cases in intention-to-treat analysis. We therefore have to use a composite endpoint, consisting of pathological complete response and 2-year recurrence rate. A period of 2 years for recurrence rate was chosen since previous data showed that 90% of recurrences occur within the first 2 years [36, 39, 40], thereby providing a good predictor of complete responses.

The RECTAL BOOST trial has been logistically implemented within our routine clinic setting. Implementation was approved and supported by the ethical board and most staff members, and recruitment is so far efficient (i.e. **Chapter 3** presents that 67% of eligible patients visiting our clinic were actually randomized). This demonstrates that a cmRCT design can indeed be used in a hospital setting as a facility for patient recruitment into trials and to store and use patient characteristics for randomization.

FUTURE PERSPECTIVES

This thesis has focused on implementation of an infrastructure to systematically capture clinical and patient-reported outcomes and to efficiently conduct randomized evaluation of (multiple) experimental interventions (simultaneously). In specific, the development, implementation and evaluation of a MRI-guided boost radiation strategy are described throughout this thesis against the background of recently obtained outcomes from routinely treated rectal cancer patients. The goal of this thesis is to present one way of optimizing response rates in future patients so that a larger proportion may proceed to organ-preservation and experience improved quality of life.

OPTIMIZING TREATMENT

Dose-escalation is just one way of improving oncologic outcomes and quality of life in rectal cancer patients. Many other ways can be imagined (Figure 1) between diagnosis and 'survivorship'. Possible interventions range from more accurate diagnostic tools, to interventions aimed at better response rates and quality of life (eg. intensified radio-or chemotherapy, minimally invasive surgery, supportive care during or after treatment). But, by all means, the potential targets (as presented in Figure 1) are non-exhaustive.

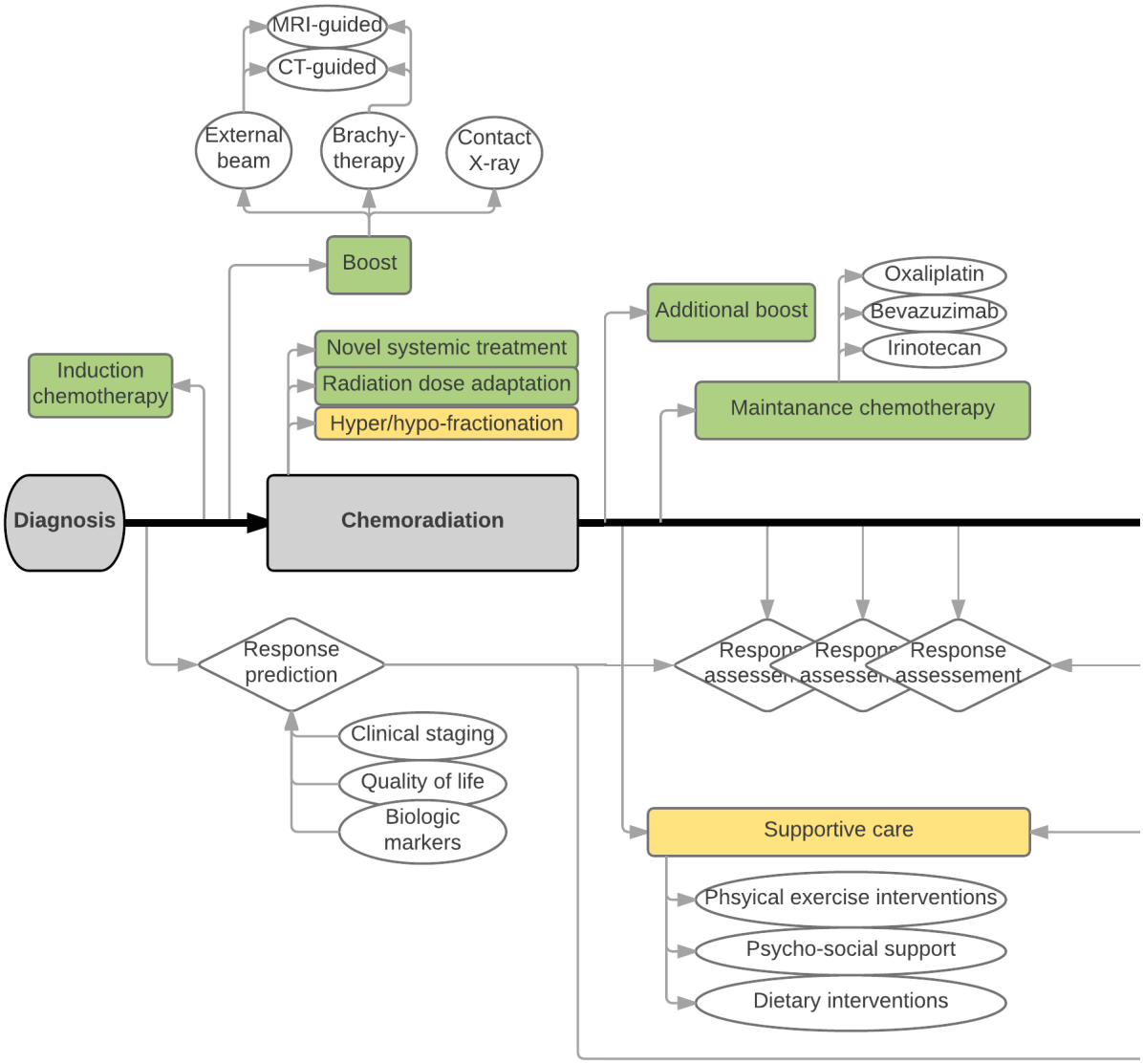
Currently, escalating radiation dose accounts as one of the most promising targets for response rate improvement. Two other major targets, chemotherapy and prolonged intervals between radiotherapy and surgery may also contribute although evidence is non-consistent and heterogeneous. Intensified chemotherapy with added agents such as oxaliplatin or irinotecan traditionally appeared to only increase toxicity and not response rates, but more recent studies also report advantages [41-43]. Extension of surgical interval after neo-adjuvant therapy demonstrated to benefit response rates since longer intervals led to higher chance of pathological complete response. Intervals exceeding 7 or 8 weeks had an odds ratio of 1.12 – 1.56 [31, 44] and >12 week intervals resulted in even higher percentages (OR 1.94) [31, 32]. This effect was, however, not uniform between studies [45, 46]. Because there is still clinical equipoise on the use of extra chemotherapy agents or extended intervals, future trials, in selected patients, should aim to integrate multiple interventions in a pragmatic sense. As discussed above, the cmRCT is in particular suiTable to investigate if certain combinations of treatment possess added potential to elevate response rates and select a higher number of patients for minimally invasive rectal cancer management. However, safety should be critically monitored among these studies since most modalities still have only weak evidence suggesting their benefits.

This thesis supports the idea that quality of life can be improved by optimizing neo-adjuvant treatment so that the necessity for invasive surgical interventions can be reduced. We currently find ourselves at a point in time where minimally-invasive or non-operative management have become a serious options for patients and physicians to consider, but at which there is still a lack of robust evidence on their feasibility and safety. More and more studies are being published and a wider variety of groups is currently working on non-operative management. Outcomes obtained in (often) highly selected patients have shown that non-operative management is feasible, safe in selected cases, and oncologically safe. The Brazilians [40, 47], New Yorkers [48-50] and Dutch [51, 52] have been forerunners in this field since its first appearance in the early 2000's. Nowadays also groups in the UK [53] and Denmark [36] provide evidence on the feasibility of non-operative management. Yet, evidence is still not robust and subject to (unintentional) selection. Therefore, an international database was recently launched to monitor outcomes after organ-preservation (www.iwwd.org) and a comprehensive trial was designed to evaluate non-operative management [49]. Such initiatives should provide more

definitive answers regarding the role of non-operative management in rectal cancer care, and should indicate which treatments lead to the highest percentage of complete responders and which tools are best to select patients for organ-preservation [54, 55]. Until better evidence is available, these strategies should not be used in routine care but only be applied in strictly monitored research settings where they can be evaluated formally.

CONCLUSION

This thesis presented the development of a MRI-guided radiation boost strategy prior to neo-adjuvant chemoradiation to improve response rates and increase the proportion of patients amenable to organ-preserving treatments. We implemented its evaluation into routine care by using the 'cohort multiple Randomized Controlled Trial' design, which pragmatically allows patients to proceed to radical surgery, local excision or non-operative management. This thesis also presented the quality of life background against which this new boost treatment will be evaluated within the RECTAL BOOST trial.


MRI-guided
CT-guided
External beam
Brachy-therapy
Contact X-ray
Boost
Induction chemotherapy
Novel systemic treatment
Radiation dose adaptation
Hyper/hypo-fractionation
Additional boost
Oxaliplatin
Bevazuzimab
Irinotecan
Maintanance chemotherapy
Diagnosis
Chemoradiation
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Psycho-social support
Dietary interventions

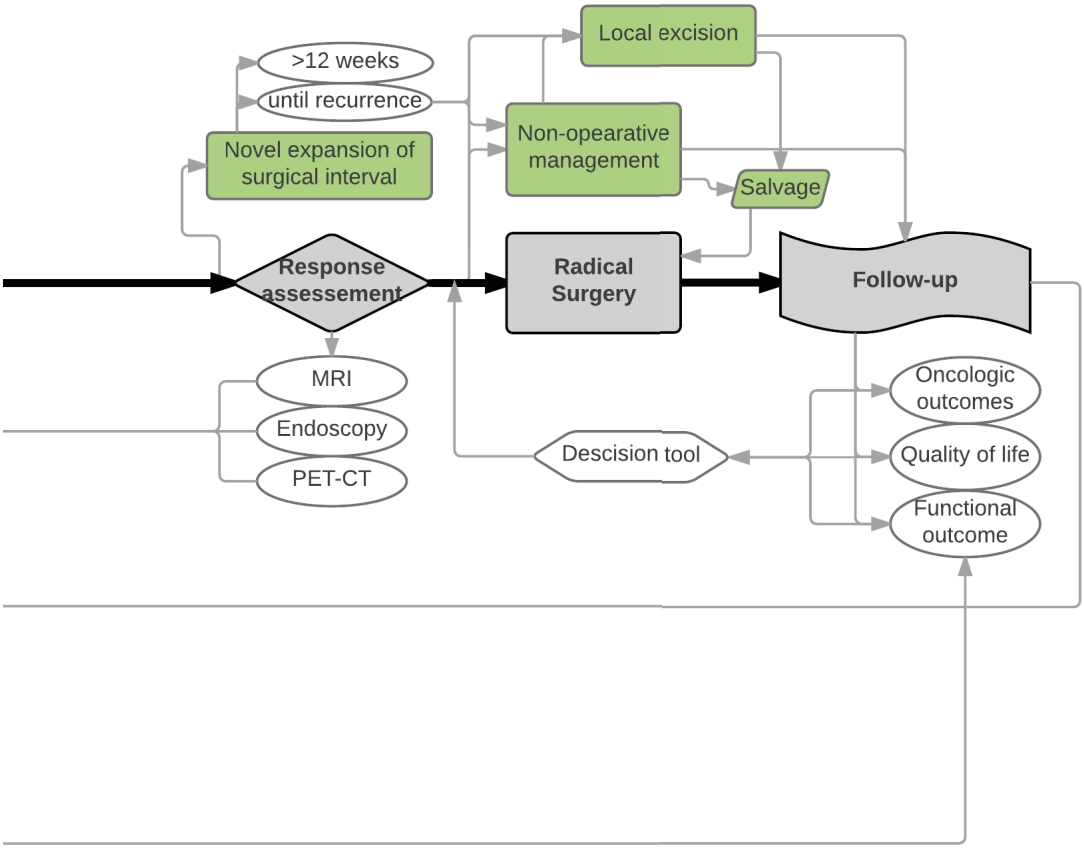

FIGURE 1

Potential decisions on offered interventions that future locally advanced rectal cancer patients who consent to 'broad consent for randomization' have to make according to the cmRCT design.
(Grey = standard treatment, Green = currently trialed interventions, Yellow = potential future trial interventions)

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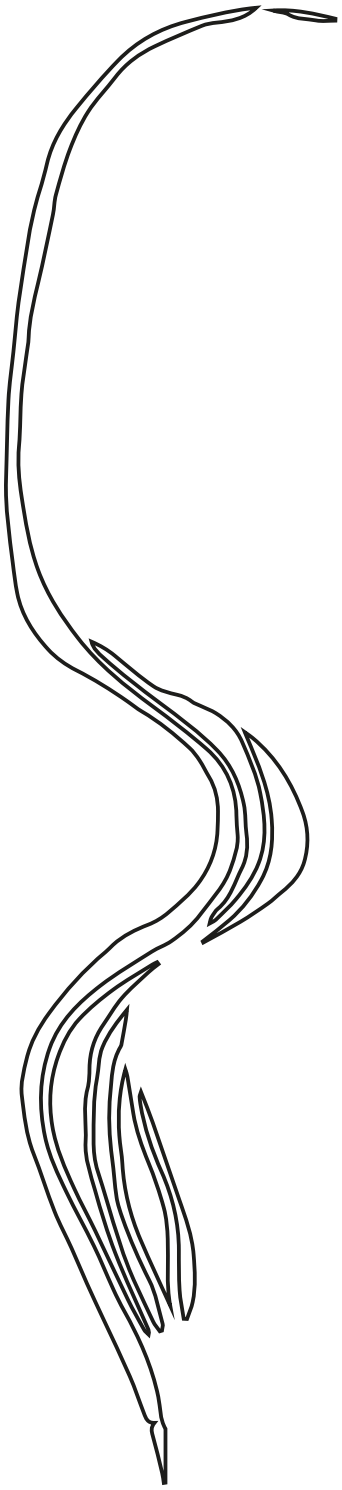
APPENDICES

APPENDICES

Acknowledgements - Dankwoord
List of Publications
Curriculum Vitae



ACKNOWLEDGEMENTS – DANKWOORD

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Zonder de inspanningen van een grote verscheidenheid aan mensen was dit proefschrift nooit tot stand gekomen. Dit dankwoord gaat daarom uit naar alle mensen die mij direct en indirect hebben geholpen, bekritiseerd en gestuurd gedurende de tijd dat ik aan dit proefschrift heb gewerkt. Toch beslaat het dankwoord slechts een korte beschrijving van mijn dank aan ieder van jullie. Het is daarom niet te interpreteren als volledig en zeker niet als exclusief.

PATIËNTEN

Beste patiënten gediagnosticeerd met een rectumcarcinoom, nabestaanden en uw familie, als eerst wil ik u bedanken - zonder uw bereidwilligheid was dit boek nooit tot stand gekomen!

Ik dank u voor uw overweging deel te nemen aan één van de in dit proefschrift beschreven onderzoeken (ongeacht of u besloot mee te doen of niet), voor uw openhartigheid, uw bereidwilligheid om belangeloos bij te dragen en voor de energie die u gestoken heeft om indirect bij te dragen aan het verbeteren van de kwaliteit van leven voor toekomstige rectumcarcinoom patiënten. Ik heb daar groot respect voor. Ik wens u, uw nabestaanden en uw familie een voorspoedige en kwalitatief bevredigende toekomst toe.

PROMOTIECOMMISSIE

Geachte promotor, geachte Prof. Dr. M. van Vulpen, beste Marco, vanaf mijn eerste kennismaking ben ik gegrepen door je overweldigende enthousiasme en grootsdenkendheid ('alles kan, ga het maar doen'). Jij bent de eerste die mij ooit vertelde dat chirurgie ooit overbodig zou worden (voor patiënten met rectumcarcinoom), maar ook diegene die volhield dat je mij nog wel zou overtuigen dat ik radiotherapeut zou willen worden. Dat eerste is ons gelukt, daar is dit boek het bewijs van. Het tweede – zoals ik je altijd heb volgehouden – gaat je nog steeds niet lukken... Desalniettemin ben ik je er ongelofelijk dankbaar voor dat dit nooit reden voor jou is geweest om mij niet alle mogelijkheden te bieden die je als jonge, ambitieuze promovendus kon verzinnen – het volste vertrouwen om een geheel nieuw project van scratch op te zetten, de (financiële) steun voor het volgen van de master epidemiologie, je deur die altijd open stond, het er steeds aan helpen herinneren aan 'waar gaan we naar toe?' en uiteindelijk je geweldige stimulans om mijn fantastische buitenlandstage in Memorial Sloan Kettering Cancer Center (New York) werkelijkheid te maken. Ik ben trots op wat ik in de afgelopen 4 jaar onder jou enthousiasme en supervisie neer heb mogen zetten en ben daarom ontzettend blij dat we deze dag samen mogen vieren.

Geachte promotor, geachte Prof. Dr. I.H.M. Borel Rinkes, beste Inne, je hoeft elkaar niet vaak te spreken om te weten dat je elkaars enthousiasme en vertrouwen deelt. Ook bij jou stond de deur altijd open en heb ik daar een paar keer heel dankbaar gebruik van gemaakt op momenten die voor mij heel leuk, belangrijk of moeilijk waren. Ik waardeer het enorm dat je me als onderzoeker - maar meer nog als mens - hebt geholpen bij de keuzes die ik (met name aan het eind van m'n promotietraject) heb moeten maken. Ik dank je ervoor dat ik me hierin altijd gesteund heb gevoeld. Andersom ben ik jaloers op jou drive, toegankelijkheid en enthousiasme, en kijk ik er daarom naar uit om ooit weer samen te mogen werken in welke vorm dan ook.

Geachte co-promotor, beste Dr. H.M. Verkooijen, lieve Lenny, ik vind dit het leukste en het moeilijkste stukje van m'n proefschrift om te schrijven :). Ik heb vanaf het allereerste begin zoveel steun van je gekregen, zoveel met je gelachen en zoveel zelfvertrouwen en vrijheid gekregen dat ik m'n werk nooit zo goed had kunnen doen als ik dit niet had gehad. Het eerste wat in me naar boven komt waar ik je voor wil bedanken heeft niets te maken met werk. Ik wil je bedanken voor hoe jij mij een paar keer hebt opgevangen en me er bovenop hebt gekregen toen ik even in een hele moeilijke tijd zat. Je eerlijke, directe en soms afgewogen advies en dat je me nooit veroordeelde als ik het op mijn eigen manier wilde doen hebben me enorm gesteund. Ik ben jaloers op je vastberadenheid, eerlijkheid, ambitie, toegankelijkheid, uitnodigendheid en hoe je met beiden-voeten-op-de-grond staat en helder kan blijven nadenken over alle kleine en grote beslissingen die je moet maken. De uitspraak van jou die me daarbij altijd bij zal blijven is "Spijt is sowieso een nutteloze emotie... reflectie niet" die ik heel dankbaar als stelling voor m'n promotie heb gebruikt. Jou onvoorwaardelijke steun die ik vanaf het allereerste moment gevoeld heb – uitend in dat je mij al na twee maanden alleen naar het AVL te stuurde om daar onze studie te presenteren - heeft ervoor gezorgd dat ik met heel veel zelfvertrouwen gewerkt heb en dat ik nog meer uit mezelf en uit ons project heb kunnen halen dan dat ik ooit had gedacht. Ik vind het bijzonder om te ervaren dat jij de mening van je promovendi (bijvoorbeeld over 'ons cmRCT') altijd net zo waardevol meeweegt als van ieder (internationale) hotshot. Ik heb dan ook enorm veel van je geleerd als onderzoeker, als supervisor, als vertrouwenspersoon en als vriendin. Ik hoop dat ik later ook net zo positief, open, vrolijk en evenwichtig in het leven sta als jij en dat ik net zo om zal gaan met mensen om me heen als jij. Daarnaast wil ik je bedanken voor alle duizende woordgrappen die we samen over 'rectum/recta/recti/rectums' hebben gemaakt, jou ideeën van 'moeten-we-niet-een-borrel-organiseren' (die vaak bij jou thuis begonnen met een fles Hugo), op het goeie moment mij Marc Broussard laten horen, je uitnodiging voor de croissant-lunch tijdens de Tour de France, alle volledig met rood gemarkeerde artikelen die ik van je terug kreeg waar ik zo lang op had zitten typen, alle tijd die we daarna dan samen achter jou computer gingen zitten om het samen weer te herschrijven, jou voorstellen van 'zullen-we-dan-in-de-stad-afspreken', je net-te-flapuit opmerkingen over iedereens kleren/haar/schoenen/opmerkingen/maniertjes/etc..., onze 'even-ventileren' momenten nadat we weer een hele frustrerende meeting hadden gehad en de niet-te-stoppen slappe lach die we op ons laatste congres in London hadden van de man die schreeuwend z'n presentatie gaf! Al deze momenten hebben mijn promotietijd onvergetelijk gemaakt. Dankjewel en ik hoop je nog heel lang te blijven spreken, zien of horen.

Geachte oud co-promotor, beste Dr. O. Reerink, beste Onne, het is zo ontzettend jammer dat we dit mooie boek nooit samen hebben kunnen afmaken. Jij bent degene die mij enthousiast heeft gemaakt, die me overtuigede van het idee om te gaan boosten en die me altijd gesteund heeft en die me alle ruimte gaf om het op te zetten. Ik weet niet of ik je, zeker de laatste tijd, meer als co-promotor of als vriend heb gezien. Ik heb me altijd zo vertrouwd bij je gevoeld en kon alles met je delen; werk en persoonlijk. Ik vind het dan ook heel waardevol en speciaal we deze band zelfs na je afscheid uit Utrecht nog steeds af en toe bezegelen met een kop thee en een goed gesprek. Jou opmerking in mijn eerste jaar: 'pas op dat je niet teveel ballen in de lucht probeert te houden, al weet ik dat je het kan', typeert me en is me altijd bijgebleven. Dit heeft er uiteindelijk voor gezorgd dat dit mooie boek heb af kunnen maken. Jou 'erfenis' bestaat niet alleen uit de rode draad die de basis vormt voor mijn proefschrift, maar hangt ook aan de muur van mijn oude kamer op Q2 – de Pulp Fiction poster die ik overnam toen je vertrok. Deze poster heeft me er altijd aan herinnerd hoe belangrijk jij het vond om jezelf te kunnen zijn op je werk, hoe relaxt jij omgaat met mensen (die dat ook doen) en hoe toegankelijk je bent. Ik hoop dat ik later net zoals jij met m'n werk en de keuzes in m'n leven om kan gaan als jij.

Geachte co-promotor, beste Dr. M. Intven, beste Martijn, ik heb heel veel respect voor hoe jij je in je nieuwe rol als mijn co-promotor hebt getransformeerd – als mede rectum-promovendus waardeerde ik altijd al je toegankelijkheid, je altijd tijd willen maken om te helpen, je vrolijkheid en je gedetailleerde input om 'onze' boost behandeling van de grond te krijgen (Onne, jij en ik), maar in je nieuwe rol waardeer ik nog meer hoe jij je als 'opvolgend'- co-promotor toch bescheiden wist op te stellen zonder dat dit ten koste ging van je positieve input, je enorme kennis over radiotherapie en response-assessment en je vooruit-denkendheid. Jou vertrouwen in mij en al je hulp bij álles wat ik ooit over radiotherapie heb geschreven ben ik je daarom enorm dankbaar voor. Ik hoop dat 'onze' boost een katalysator is voor de rest van je carrière en dat ik nog heel veel met je mag samenwerken in de toekomst.

BEOORDELINGSCOMMISSIE

Geachte leden van de beoordelingscommissie, Prof. Dr. G.J.A. Offerhaus (voorzitter - pathologie, UMC Utrecht), Prof. Dr. G. Beets (chirurgie, Antoni van Leeuwenhoek, Amsterdam), Prof. Dr. J.J.W. Lagendijk (radiotherapie, UMC Utrecht), Prof. Dr. P. Lambin (MAASTRO clinic, Maastricht), Prof. Dr. M.R. Vriens (chirurgie, UMC Utrecht), zeer veel dank voor al uw interesse, tijd en energie die u in mij, in mijn proefschrift en in de verdediging hiervan hebt willen steken.
Speciale dank wil ik uitspreken aan Prof. Dr. M.R. Vriens voor het mij op willen nemen in de chirurgie-onderzoekers groep waardoor ik aan alle leuke dingen (wetenschapsdag, (oud-)assistentendiner, skireizen, chirurgencup, etc.) heb kunnen deelnemen.
Daarnaast wil ik ook speciale dank uitspreken aan Prof. Dr. G. Beets voor het leggen van het eerste contact tussen mij en Dr. Temple omdat dit geresulteerd heeft in een fantastische klinische onderzoeksstage in Memorial Sloan Kettering onder haar supervisie.

PARANIMFEN

Beste paranimf, beste Joost Veenbrink, lieve Jopie, mijn oudste vriend - van samen knikkers verzamelen en elke dag naar school fietsen tot clubgenoten en als paranimf samen in het zweetkamertje zitten. Bijna alle stadia van ons hele leven hebben we samen beleefd. Ik kan altijd bij je terecht en je staat altijd voor me klaar als het tegen (of heel erg mee) zit, om me vervolgens weer even met beide benen op de grond te zetten. Ik waardeer je altijd aanwezige vrolijkheid, je positieve houding naar alles, dat je altijd iets weet te vinden om samen over te lachen, dat lekker makkelijk voor jou ook lekker gezellig betekent, dat je dingen nooit moeilijker maakt dan dat ze zijn, dat je je eigen enthousiasme altijd wil delen en dat je me accepteert zoals ik ben. Ik vind het geweldig om ook deze dag weer met je te delen en je bent een geweldige vriend voor me.

Beste paranimf, beste Danny Young-Afat, lieve Danny, kamergenoot, cmRCT-maatje, fellow-New-Yorker en soulmate, ik ga je spontane net-te-harde lach, je openheid, je geduldige luisteren, je lekker-samen-klagen, je altijd uitnodigen om mee te doen en je enthousiasme voor alles dat we in New York samen deden missen. Ik vind het fantastisch en ben heel blij dat ik deze dag zo intensief met je kan delen en hoop ontzettend dat we ooit weer samen zullen werken. Meer dan alles hoop ik dat we de band die we hebben opgebouwd voor altijd zullen vasthouden.

COLLEGA'S EN ONDERSTEUNERS

Beste 'cmRCT-drieling', lieve Joanne en Danny, ik vind het ongelofelijk bijzonder hoe wij als drie totaal verschillende mensen zo naar elkaar toe zijn gegroeid in de drie jaar die we gedeeld hebben en samen aan het cmRCT gewerkt hebben. Hoe wij een totaal nieuw studie-design praktisch haalbaar gemaakt hebben, hoe we hiervoor de volledige logistiek van een afdeling omgegooid hebben, hoe we er alles aan gedaan hebben om elkaar te ondersteunen in onze onderzoeken en hoe we het beste uit elkaar hebben weten te halen is voor mij nog steeds ongelofelijk – maar we hebben het gedaan! De één groen, een andere geel en de laatste rood, samen wisten we het perfecte team te vormen dat elkaar in toom kon houden maar ook elkaar op stoom kon krijgen. Tijdens ons laatste congres in London merkte ik hoe wij soms aan één blik voldoende hebben. We zijn ooit met de term de 'drieling op reis' begonnen als titel van onze Whatsapp groep toen we alle drie in het buitenland zaten, maar ik hoop dat we nog deze term nog vaak gaan gebruiken als we weer op (cmRCT) congres gaan, met elkaar eten of bijpraten over wat we tegenwoordig doen.
Joanne, ik heb enorm respect voor jou als mens - alles waar ik te weinig van heb, heb jij genoeg van (of dit andersom ook geldt mag je zelf zeggen). Je geduld, je oneindige interesse in mensen en je dat je altijd voor anderen klaar staat benijd ik enorm. Ik vind het geweldig om te ervaren hoe jij gegroeid bent sinds we elkaar kennen en hoe we hier alle drie van hebben mogen profiteren. Ik heb vaak onbewust veel kracht geput uit jou doorzettingsvermogen en de wil die jij hebt om dingen tot in de puntjes voor te bereiden en te doorgronden. Mede door jou kritische blik, je streven naar perfectie en je onuitputtelijke verantwoordelijkheidsgevoel hebben we alle drie een hele mooie promotie neer kunnen zetten en hebben we nu drie fantastisch draaiende lopende cohorten.

Beste opvolgster, beste Alice, ik kan me geen betere, enthousiastere, eerlijkere en ambitieuzere opvolgster voorstellen. Ik vind het fantastisch dat je je vanaf je onderzoeksstage al meteen volledig hebt ingezet en meteen met je eigen ideeën kwam, maar ook dat je je vanaf het begin al verantwoordelijk hebt gevoeld om al het lopende over te pakken (ook de vervelende taakjes) en dat je hier nooit over geklaagd hebt. Ik vind het geweldig om 'mijn' opgezette projecten aan jou door te kunnen geven omdat ik in jou mijn eigen enthousiasme en drive herken. Ik ben dan ook heel jaloers op de tijd die jij nog in Utrecht te gaan hebt totdat we straks op jou verdediging staan. Heel veel succes, de wereld ligt aan je voeten en geniet er vooral oneindig hard van!

Beste rectum onderzoeksgroep van de afdeling radiotherapie, Beste Onne, Martijn, Lenny, Jean Paul, Alice, Marielle, Enrica, Bram, Bas, Martijn, Guus en Mirjam, jullie hebben mij op de goeie momenten afgeremd en tot diepgang gepusht. Ik vind het bewonderingswaardig hoeveel diepte we wekelijks in inhoudelijke discussies hebben gehad en hoe goed we de boost behandeling hierdoor neer hebben kunnen zetten. Daarnaast wil ik jullie bedanken voor het geduld dat jullie hebben gehad voor de tijd die het gekost heeft om het cohort op te zetten, het conformeren aan de logistieke timing en de eisen die het cmRCT-design met zich meebracht wat betreft het uitvoeren van de behandeling. Zonder jullie was de boost bij een tekening op papier gebleven in plaats van een intekening op MRI-beelden die via een conebeam CT-scans overgezet wordt naar een actueel behandelplan waarmee de patiënt bestraald wordt.

Beste (oud-)kamergenoten, beste Tim, Juliette, Peter, Danny en Sofie, samen met jullie heb ik 4 jaar lang de beste versie van mezelf kunnen zijn. Door jullie gezelligheid ging ik altijd met heel veel plezier naar m'n werk. Ik blijf me altijd herinneren de vrijdagmiddag muziekuurtjes, het keihard-lachen-als-je-begint-te-schelden-tegen-de-telefoon-als-je-net-ophangt, het samen stoeien met epidemiologie vragen/toetsen/SPSS en R, de steun die we bij elkaar zochten als het thuis even minder ging, het

zoveel mogelijk van elkaar overschrijven uit studieprotocollen, het (laten) ophangen van de Pulp Fiction poster, het elkaar uit de brand helpen als er iets moest gebeuren maar vooral het eindeloos veel lachen om niks!

Beste overige arts-onderzoekers van de afdeling radiotherapie, beste Mariska, Hanne, Meta, Lisanne, Sofie, Lucas, Max, Juliette, Ramona, Sophie en Madelijn, zo divers als radiotherapeuten zijn zo divers zijn ook de onderzoekers op onze afdeling geweest. Ik vond het leuk en interessant om met jullie allemaal te werken. Jullie hebben me soms goed in toom weten te houden en hebben me ook veel nieuwe inzichten gegeven. Ik vond het bijzonder om met de meeste van jullie de 'Insights' cursus te doen en om te merken hoe vertrouwd en saamhorig wij als groep in die jaren onbewust zijn geworden (als je elkaar niet al goed had leren kennen dan was dit wel een heel heftige kennismaking (met jezelf)). Deze cursus stond voor mij symbool voor de groep die we waren; divers, ambitieus, geïnteresseerd en vergevingsgezind. Ik heb met heel veel plezier met jullie allemaal gewerkt, geluncht en gelachen. Het ga jullie allemaal goed en ik ben benieuwd waar we allemaal gaan belanden!

Beste PLCRC promovendi, beste Vincent, Alice, Sophie, en Kaitlyn, van niks tot 1000+ patiënten! We hebben het allemaal gedaan; van protocollen schrijven, amendementen indienen, SOPs opstellen en zakkaartjes drukken tot presenteren aan (koppige) specialisten, logistieke problemen oplossen, rennen met de cohort-telefoon op zak en (gelukkig) uiteindelijk includeren van patiënten. Ik wil jullie heel hard danken voor al jullie inzet, alle samen gevloekte woorden, alle samen-redden-we-de-deadline-wel momenten en alle gezellig borrels voor als er weer wat te vieren viel. Ik hoop alles wat we hebben gedaan er straks voor zorgt dat jullie boekjes mooier, voller en gedenkwaardiger zijn dan deze. Succes nog even!
Sophie, als er in één artikel veel bloed, zweet en tranen zitten dan is het ons Hoofdstuk 2 wel! Dank voor de eindeloze keren dat je zei "ik vind dit stukje toch nog niet goed genoeg hoor…". Door jou is het stuk geworden hoe het nu is, en dat is in mijn ogen een hele solide basis voor alles wat er ooit uit PLCRC voort komt. Ik vind het geweldig hoe jij je daarnaast volledig hebt ingezet om PLCRC een succes te maken en ben heel blij dat we samen zoveel hebben kunnen lachen en alle wekelijkse perikelen is even lekker konden bespreken ;).
Vincent, dank voor alles wat je gedaan hebt voor wat later het PLCRC zou gaan heten. Ik vind het bijzonder dat je je 3 jaar zo ingezet hebt voor iets waarvan je al snel wist hoe weinig dit voor jou eigen promotie zou opleveren. Zonder jou doorzettingsvermogen, energie en drive was PLCRC nu nog steeds een idee op papier. Ik heb heel veel plezier gehad om dit project samen met jou te gaan doen en later samen te werken in het Meander. Hopelijk doen we dit in de toekomst nog vaker!

Beste PLCRC-onderzoeksgroep, beste Lenny, Miriam, Helma, Martijn, Peter en Geraldine, dank voor een hele leerzame en interessante tijd met jullie. Van jullie onderlinge dynamiek en wetenschappelijke kennis heb ik heel veel geleerd. Door al onze wekelijkse meetings en discussies ben ik me steeds meer kunnen gaan realiseren hoe belangrijk het voor onderzoekers om open en eerlijk over persoonlijke-, afdelings-, beroepsgroep- en/of anderszins stakeholders belangen te spreken, omdat deze toch aardig van elkaar kunnen verschillen als je ogenschijnlijk hetzelfde onderzoeksdoel nastreeft. Ik ben heel blij dat ik dit als promovendus heb mogen meekrijgen, dat jullie mij hier volledig in hebben meegenomen, dat wij als promovendi wel altijd beschermd zijn en dat ik van jullie het vertrouwen en de ruimte heb gekregen om m'n eigen ambities en ideeën uit te kunnen werken. Ik hoop dat we met PLCRC iets neer hebben gezet waar we nu nog niet van kunnen overzien hoe het straks een vlucht zal nemen en dat we nog lang met elkaar mogen samenwerken binnen dit geweldige en diverse initiatief!

Beste 'trialbureau dames', beste Marijke, Tineke en Marianne, zonder jullie inzet, acceptatie voor

verandering en waren er nu pas een tiental patiënten geïncludeerd, hadden we pas van een handjevol vragenlijsten verzameld en was er pas van een enkeling data ingevoerd. Jullie nieuwe baan als 'cohort-dame' hebben jullie vanaf het begin uiterst serieus genomen en met evenveel verantwoordelijkheid uitgevoerd. Hierdoor zijn er inmiddels al meer dan 400 rectum patiënten in het UMCU zijn geïncludeerd, meer dan 60 patiënten gerandomiseerd in de BOOST studie en al minstens twee artikelen gepubliceerd over kwaliteit van leven in onze patiënten. Jullie hebben hier misschien niet altijd direct genoeg credits voor gekregen maar ik realiseer me heel goed dat jullie de olie in de motor zijn geweest gezien jullie voor ons alle lopende zaken draaiende hielden. Mijn dank hiervoor is heel groot omdat ik zonder jullie nog steeds achter m'n computer in het Q-gebouw had gezeten en dit boek er nog lang niet was geweest!

Beste andere trialbureau medewerkers, beste Saskia, Anneke, Shanta en Cees, dank voor alles waar jullie mee geholpen hebben; METC procedures, monitoring visites, databases bouwen, data invoeren en query's bouwen. Als ik dit allemaal zelf had moeten doen dan zat ik er nu nog. Jullie deur stond altijd open en we konden met alle vragen bij jullie terecht zonder dat jullie hier ooit iets voor terug vroegen. Heel veel dank want zonder jullie was dit proefschrift er niet geweest.

Beste staf-artsen en arts-assistenten van de afdeling radiotherapie, dank voor jullie steun en toewijding aan de logistiek rondom het cmRCT design, de 'cohort-poli' en de boost behandeling. Jullie medewerking is essentieel geweest in het slagen van mijn promotieonderzoek.

Beste secretaresses, beste Leonie en Judith, dank voor de op-een-na gezelligste kamer op de radiotherapie! Het was een verademing om na een dag computeren is even lekker over de gang te lopen en dan voor een multimap een uur-lange stop bij jullie te maken om over niks te praten en om gekke mensen op de gang te lachen ;). Leonie, ontzettend bedankt voor je tip om bij het koffers inpakken vacuümzakken voor je kleren te gebruiken – m'n kast ligt nu vol met kleren uit New York!

Beste niet eerder genoemde medewerkers van de afdeling radiotherapie, beste fysici, laboranten, afsprakenbureau medewerkers, baliemedewerkers en vrijwilligers, dank voor jullie toegankelijkheid en flexibiliteit voor alle geplande en ad-hoc dingen die ik van jullie gevraagd heb over de jaren. Ik realiseer me dat een pot snoep en een kerstkaart op de bali en/of de U9-14 nooit voldoende is geweest om jullie allemaal te bedanken.

Beste chirurgische begeleider, beste Helma, dankzij jou kwam ik echt in beeld bij de chirurgie. In het begin onder jou naam abstracts insturen naar de wetenschapsdag, en later meegaan met skiën, organiseren van skiën, hakken op de chirurgencup/dagen en vooral veel 'even bijpraten' bij jou op je kamer. Mede door jou ben ik nooit uit het oog verloren dat ik graag chirurg wil worden en ik hoop dan ook dat we ooit samen zullen opereren!

Beste perifere samenwerkende specialisten, beste Anke, Maartje, Esther, Paul, Apollo en Niels, zonder jullie was waar we nu staan nooit van de grond gekomen. Jullie enthousiasme, ambitie en steun om je aan onze studies te committeren is de katalysator geweest voor het bereiken waar we nu staan; het uitvoeren van een heel innovatieve en vooral goedlopende gerandomiseerde trial waar we elke geïncludeerde patiënt recht mee doen. Ik kijk ernaar uit om over een (half) jaar met jullie samen te komen en de eerste resultaten te bespreken!

Beste Nicole en Lonneke, dank voor jullie geweldige ambitie om zo'n breed platform op te zetten voor het verzamelen van patiënt-gerapporteerde uitkomsten. In het bijzonder wil ik Nicole bedanken

voor alle keren dat je onze vragen hebt moeten beantwoorden, aanpassingen op de site hebt moeten doorvoeren, de database moest bijwerken en de ritjes die je naar het UMC moest afleggen. Het was een verademing om te merken dat dit nooit teveel gevraagd was waardoor we nu zulke mooie projecten hebben lopen. Het is dan ook fantastisch om te realiseren dat dit proefschrift pas 'the tip of the iceberg' vormt voor alles wat jullie infrastructuur mogelijk maakt voor onderzoek naar kwaliteit van leven in de toekomst.

Beste niet eerder genoemde co-auteurs van artikelen in dit proefschrift, dank voor al jullie tijd, energie en geduld – we hebben een geweldige serie artikelen neergezet. Zonder de bijdrage van ieder van jullie had ik hier vandaag niet gestaan.

OVERSEAS COLLEAGUES

Dear Dr. C. Relton, dear Clare, thanks for sharing your opiphany on research purpose and methodology in the BMJ. Your aim to make research efficient, valuable and patient-centered again has been – and will be - a tremendous help to future evaluation of innovative healthcare treatments. Due to collaboration we have not only gotten to know you as the 'godmother' of the 'cohort multiple Randomized Controlled Trial' design, but also as a mother of a kidnapped - and later famous - DJ, a chocolate sharing investigator, an enthusiastic, super-approachable, inviting, down-to-earth, ambitious, hard-working, funny, attentive and interested colleague. Your initiative to co-organize two international symposia, your visit to Utrecht and our countless Skype conversations have always been reminders for me to keep in mind the purpose of our research – to help and not to harm patients while doing it. I sincerely hope to stay in touch as much as we have been in the past years and hope that we will together experience how the cmRCT design (a.k.a. Trials within Cohorts (TwiCs)) will evolve globally the coming years. It's a great honor to see you across the table today as one of my opponents.

Dear Prof. Dr. J. Garcia-Aguilar, dear Julio, thank you for the great opportunity you have given me to work at the Colorectal Service of Memorial Sloan Kettering Cancer Center, New York City, USA. It has been a great pleasure and a privilege to be part of such an ambitious, visionary and super-friendly environment where I immediately felt at home. I admire your work-ethic as much as your personal interest in everyone you work with. I greatly appreciated the way in which you have supported me during my research as well as in how you are happy to help me achieve my goals in my professional life by writing an amazing recommendation letter. Both will serve as a thorough basis for all that I can accomplish in my (professional) future, and I too, hope for us to work together again in the future.

Dear Dr. L.K. Temple, dear Larissa, you have been an amazingly ambitious, skillful and visionary force for me in Memorial Sloan Kettering. I was stunned by your enthusiasm, inexhaustible energy and skillful critical judgment which you are using to rethink, remodel and improve patient-reported outcomes so that they are easy to use for improvement of rectal cancer care and outcomes of patients. Your immediate warm-welcome, dedication and interest in me personally have been the basis of an unforgettable time for me in New York. I hope we will find the opportunity to meet again soon and to catch up and continue to work on all that we've started. Even more than that, I wish you all the best as the new chief of the Colorectal Surgery department at Rochester University, NY.

VRIENDEN EN DIERBAREN

Beste Tessa-Norah, hoe bizar is het dat één treinritje met een vouw- en een racefiets kan leiden tot dit fantastisch vormgegeven boek. Ik wil je heel erg bedanken voor al je energie, ideeën, tijd en de vriendschap die je hierin hebt gestoken. Je hebt er een persoonlijke missie van gemaakt om alles perfect te maken. Ik was heel erg geraakt toen je me de eerste versie liet zien in een cafeetje en je hebt tot op het laatste om weten te gaan met mijn eindeloze "ik vind dit nog niet goed-" opmerkingen en dat waardeer ik enorm. Wat mij betreft mogen we allebei ontzettend trots zijn op het eindresultaat (jij op de vormgeving en ik op de inhoud) en zou het niet misstaan in de collectie van 'The Whitney'. Hopelijk kunnen we het daar ooit samen gaan neerzetten.

Beste huisgenoot, beste Thomas, helaas hebben we elkaar nog maar het meest meegemaakt op mijn slechtste momenten: avonden achter m'n laptop om promotie af te maken, gesloopt van werk als beginnende ANIOS en onzekerheid rondom het solliciteren. Laten we dit gaan inhalen als alles achter de rug is en we straks beiden klaar zijn met onze promoties!

Beste jaarclub Badjas, beste Oli, Diemel, Jopie, Friem, Kareltje, Knuuf, Stok, Sloot, Papi, Bies, Lampie, Sjon, Alf, Real, Kers, Slobbe, Bas, Diek en Julio, wat mooi om eindelijk weer (met z'n allen) terug te zijn in Utrecht waar we elkaar hebben leren kennen 12 jaar geleden. Dank voor al jullie vriendschappen waardoor ik een fantastische tijd in Utrecht heb gehad, ik goed door een moeilijke tijd in Maastricht ben gekomen en daarna weer met heel veel zin naar Amsterdam kon terugkeren. Als groep maken we veel met elkaar mee, veel van hetzelfde maar ook steeds nieuwe dingen die ons nog meer met elkaar verbinden en waardoor ik me nog meer realiseer hoe speciaal een jaarclubband is. Ik vind het daarom mooi om te zien hoe wij als 30+-jarige mannen nog steeds met elkaar kunnen lachen, zuipen, sporten, party'en, steunen en naar elkaar toe kunnen blijven groeien! "Strak strak in je badi...." enz.

Beste jongens van 't Begijnehof 1bis te Utrecht, beste (oud-)huischgenoten, vandaag is een thuiswedstrijd. Dank voor alle steun die ik van jullie heb gevoeld toen ik moest knallen met m'n bachelor om dit nog (een beetje goed) af te ronden, toen ik besloot naar Maastricht te vertrekken en toen ik ongeveer elke vrijdagsavond meteen m'n tas kon dumpen en in de stad kon aansluiten met zuipen, het logeren in één van jullie bedden, de het-blijft-altijd-hetzelfde-ondanks-dat-je-weg-bent-gevoel, de eerlijkheid om elkaar af en toe even goed de waarheid te zeggen, alle emotionele momenten op 't Hof en daarna en alle flauwe grappen die jullie de afgelopen 4 jaar gemaakt hebben over mij en mijn onderzoek – de endeldarm blijft een fascinerend orgaan ;). "1bis, 1bis, het is zo lekker vies... Ja-la-la-la-laaa Ja-la-la-la-laaa"

Beste El-Tento's, beste Joost, Thijs, Luke, Wouter, Chris en Peute, wat is het super mooi om deze dag met jullie te delen! We zien elkaar misschien niet regelmatig genoeg maar met jullie geldt dat je elkaar niet vaak hoeft te zien om te weten dat je vrienden bent - dat is een gevoel wat veel dieper gaat. Dank dat ik bij jullie mezelf kan zijn en voor jullie vriendschap. Aan het lijstje van alle mooie momenten die we samen al beleefd hebben (Mo Texel, Kampong A&B feesten, Dorpstraat, logeren bij Iwan de Verschrikkelijke, met Chrisje van O. in Kroatisch colloseum disco, curlen met Gus, pinda's gooien in de Bierfabriek, fietsen in de Ardennen, Wouter's promotie en meest recent nog zeilen in Friesland) kunnen we na vandaag dan ook de senaatszaal van de Universiteit Utrecht toevoegen! Laten we nog lang zulke dingen blijven doen en natuurlijk vraagt elk (om in de termen van de Bacardi Thizer te blijven) 'evenementje' traditiegetrouw weer om een lijstje. Dus hier alvast een aftrapje waar jullie mee aan de

slag kunnen:

- Zweetkamertje
- Afgehaakt na twee zinnen
- Jopie ook sterk gespeeld
- ...

Lieve Anique, van iedereen ben ik jou het meest dankbaar omdat jij mij het meest intensief meegemaakt en gesteund hebt. Het is bijna niet mogelijk om het gevoel dat jij me hebt gegeven op te schrijven en je hiervoor te bedanken. De steun die je me onbewust gaf door er gewoon te zijn is voor mij heel belangrijk geweest. Je wist me altijd te raken met je eerlijkheid en kwetsbaarheid, je wilde me altijd helpen, je zorgde altijd dat ik mezelf kon zijn, je wilde me altijd – en soms te vaak en ongevraagd - bekritiseren (als dat nodig was), je vergaf me altijd als ik thuis weer eens chagrijnig was, je kon altijd voor mij relativeren als ik zelf in cirkeltjes aan het denken was, je kon heel hard om (en iets daarna ook met) mij lachen, je gaf me altijd het gevoel belangrijk voor iemand te zijn door zelf ook steun bij mij te zoeken en je hebt me ontelbare keren gevraagd "Maart, wat wil je zelf?" als ik weer eens vastzat in m'n eigen gedachten. Ik ben heel blij dat ik alle enthousiaste, mooie en grappige momenten in m'n promotietijd net zo goed met jou heb mogen delen als de frustrerende, lastige en moeilijke momenten; en dat we dat nu nog steeds doen. Jij hebt me meer zelfvertrouwen en zelfbewustzijn gegeven dan wie dan ook. Dit zal ik m'n hele leven bij me dragen en op terug kunnen vallen en daar ben ik je heel dankbaar voor. Ik hoop dat we de diepe band die we hebben blijven voelen en dat we elkaar zullen blijven steunen zoals dat we dat de afgelopen 4 jaar hebben gedaan.

Lieve Anita en Niek, dank voor jullie liefde en het vormen van een veilige plek waar ik me altijd thuis voel en de deur altijd open staat.

Lieve Mam, Peet en Ruub, dank voor jullie onvoorwaardelijke liefde, steun en dat jullie er altijd - op jullie eigen manier - voor me zijn en mij liefhebben. Ik kan mijn dank hiervoor niet in woorden opschrijven maar weet dat jullie het van binnen hetzelfde voelen als ik.

LIST OF PUBLICATIONS

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'Health-related Quality of Life during rectal cancer treatment: comparison between patients undergoing low anterior versus abdominoperineal resection.'
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PRESENTATIONS

* invited speaker

* 'Early outcomes of TAVI in MUMC'
Clinical Investigator Science Symposium, Maastricht, 2008

'Opereren zonder Snijden', Academische Jaarprijs, NWQ publieksprijs
Academie van Wetenschappen, Halve finale, 2013

* 'The cmRCT design and evaluation of interventions for rectal cancer '
UMC Utrecht, Utrecht, 2013

* 'Radiotherapy boost in locally advanced rectal cancer'
UMC Utrecht, Utrecht, 2013

* 'PICNIC Project and the cohort multiple Randomized Controlled Trial'
International cmRCT symposium Collaboration Sheffield University - UMC Utrecht, 2013

'cmRCT voor pre-operatieve radiotherapie boost in lokaal gevorderd rectumcarcinoom'
Heelkunde wetenschapsdag, Karel V, Utrecht, 2013

'Impact of radiation boost on pathological complete response-rate in locally advanced rectal cancer: a systematic review and meta-analysis'
IMAGO wetenschapsdag, Universiteit Utrecht, 2013

'Impact of radiation boost on pathological complete response-rate in locally advanced rectal cancer: a systematic review and meta-analysis'
33rd European Society of Radiation Oncology congress, Vienna, Austria, 2014

'RECTAL BOOST trial'
World Rectal Conference, Leiden, 2014

'Impact of radiation boost on pathological complete response-rate in locally advanced rectal cancer: a systematic review and meta-analysis'
Chirurgendagen, Veldhoven, 2014

'SPONGE trial: Gebruik van spons in rectum chirurgie'
Heelkunde wetenschapsdag, Domplein, Utrecht, 2014

* 'Logistical challenges of the cmRCT in a hospital setting'
International cmRCT symposium, London, UK, 2014

* 'Logistical challenges of the cmRCT in the clinic – the UMC Utrecht'
GE Research meeting, UMC Utrecht, 2014

* 'Radiotherapie dosis escalatie bij preoperatieve CRTx bij rectumcarcinoom'
Regionale Tumor Werkgroep Gastro-Enterologie (TWGE), IKNL, 2014

'SPONGE trial – randomized comparison of retractor sponge-assisted vs conventional laparoscopic rectal cancer resection'
Wetenschapsdag Heelkundige kliniek, Utrecht, 2015

'Quality of life in patients undergoing radiotherapy and sphincter sparing surgery or rectal amputation'
3rd European Society of Radiation Oncology Forum, Barcelona, Spain, 2015

'Feasibility of using the 'cohort multiple Randomized Controlled Trial' design to conduct the RECTAL BOOST study'
European Congress of Epidemiology, Maastricht, 2015

'Quality of life in patients undergoing Low Anterior resection versus AbodminoPerineal resection'
NVGE najaarsvergadering, Veldhoven, 2015

* 'The role of Boost Radiation in Rectal Cancer'
8th Annual Eur. Multidis. Colorectal Cancer Congress, Amsterdam RAI, 2016

Posters 'The PICNIC project (ProspectIve data CollectioN Initiative on Colorectal cancer)'
33rd European Society of Radiation Oncology congress, Vienna, Austria, 2014

'Feasibility of using the 'cohort multiple Randomized Controlled Trial' design to conduct the RECTAL BOOST study'
3rd European Society of Radiation Oncology Forum, Barcelona, Spain, 2015

CURRICULUM VITAE

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Johannes Peter Maarten Burbach was born on November 26th 1985 in Utrecht, The Netherlands. He spent his younger years in Bunnik and graduated from the Herman Jordan Montessori Lyceum in Zeist in 2004. That year Maarten started at the University of Utrecht in Biomedical Sciences. He achieved his Bachelor degree in 2008 and went on to Medical School at the University of Maastricht. Here, Maarten was part of a selected cohort of students following a dedicated 'Medical Doctor – Clinical Researcher' program. On his own initiative, Maarten spend two months as a clinical fellow in Shirati KMT Hospital, Tanzania, where he assisted on wards and in operations. Furthermore, Maarten took part in multiple studies within the department of Cardiothoracic Surgery in Maastricht under supervision of Dr. L. van Garsse, cardiothoracic surgeon. Maarten defended his thesis titled 'Early outcomes of Trans-Apical Aortic Valve Implantation' successfully and obtained his Master of Science degree together with his Medical Doctor degree in the summer of 2012. Subsequently, Maarten decided to leave Maastricht and return to the University Medical Center in Utrecht where he was invited by Prof. Dr. M. van Vulpen to the Department of Radiotherapy to start on a Doctor of Philosophy (PhD) program in rectal cancer under tutelage of Dr. H.M. Verkooijen and Dr. O. Reerink (later replaced by Dr. M. Intven). Prof. Dr. I.H.M. Borel Rinkes was later involved to provide further guidance from the Department of Surgery. His PhD project aimed to evaluate novel radiation treatments in rectal cancer. Maarten dedicated himself to the initiation and launch of (parts of the) Prospective Dutch ColoRectalcancer Cohort (PLCRC), which form the basis of Chapter 2, 3, 4 and 7 of this thesis. In the context of this multidisciplinary project he worked closely with, among others, Dr. M. Koopman (Medical Oncologist), Prof. Dr. P.D. Siersema (gastro-enterologist), and Dr. W.M.U. van Grevenstein (colorectal surgeon), Within the PLCRC infrastructure Maarten implemented a randomized controlled trial to evaluate a newly developed MRI-guided radiation boost treatment (Chapter 5, 6 and 7). In 2014, Maarten was asked by Dr. C. Relton to be part of the organizing committee of the '1st International Trials within Cohorts symposium' held in London, United Kingdom. In 2016, he was approached again to take seat in this committee. Maarten's scientific work in Utrecht was predominantly performed between September 2012 and August 2015. Simultaneously to his PhD, Maarten achieved a second Master of Science / Post-graduate program in the field of Clinical Epidemiology. He was registered as a clinical epidemiologist in the summer of 2015. At the end of his PhD, Maarten was invited as a research fellow to visit the Colorectal Surgery Service of Memorial Sloan Kettering Cancer Center, New York City, United States of America by Prof. Dr. J. Garcia-Aguilar (colorectal surgeon and chief of the surgical colorectal service). For a period of 6 months, he worked under direct supervision of Dr. L.K. Temple (colorectal surgeon) and participated in multiple projects on quality of life and worked on validation of different tools to measure bowel function. After his return, Maarten started as a surgical resident (Arts Niet In Opleiding tot Specialist; ANIOS) in the Meander Medical Center in Amersfoort, The Netherlands, where he was supervised by Dr. E.C.J. Consten and Dr. P.M. Verheijen (colorectal surgeons). Currently, Maarten is working in Amersfoort as a surgical resident and has a declaration of hospitality for the Department of Radiotherapy in the University Medical Center Utrecht in order to continue his work on rectal cancer and quality of life.

In his spare time, Maarten is a fanatic sportsman (field hockey and cycling) and has participated in several ambitious sports events (national champion (field hockey), Ringvaart Regatta (100km rowing) and Tour for Life (cycling)). Maarten enjoys to travel far outside of Europe (USA, China, Tanzania, India, Sri Lanka, Ecuador and Colombia) but, evenly so, appreciates spending time with his close friends in and around Amsterdam where he is currently living.