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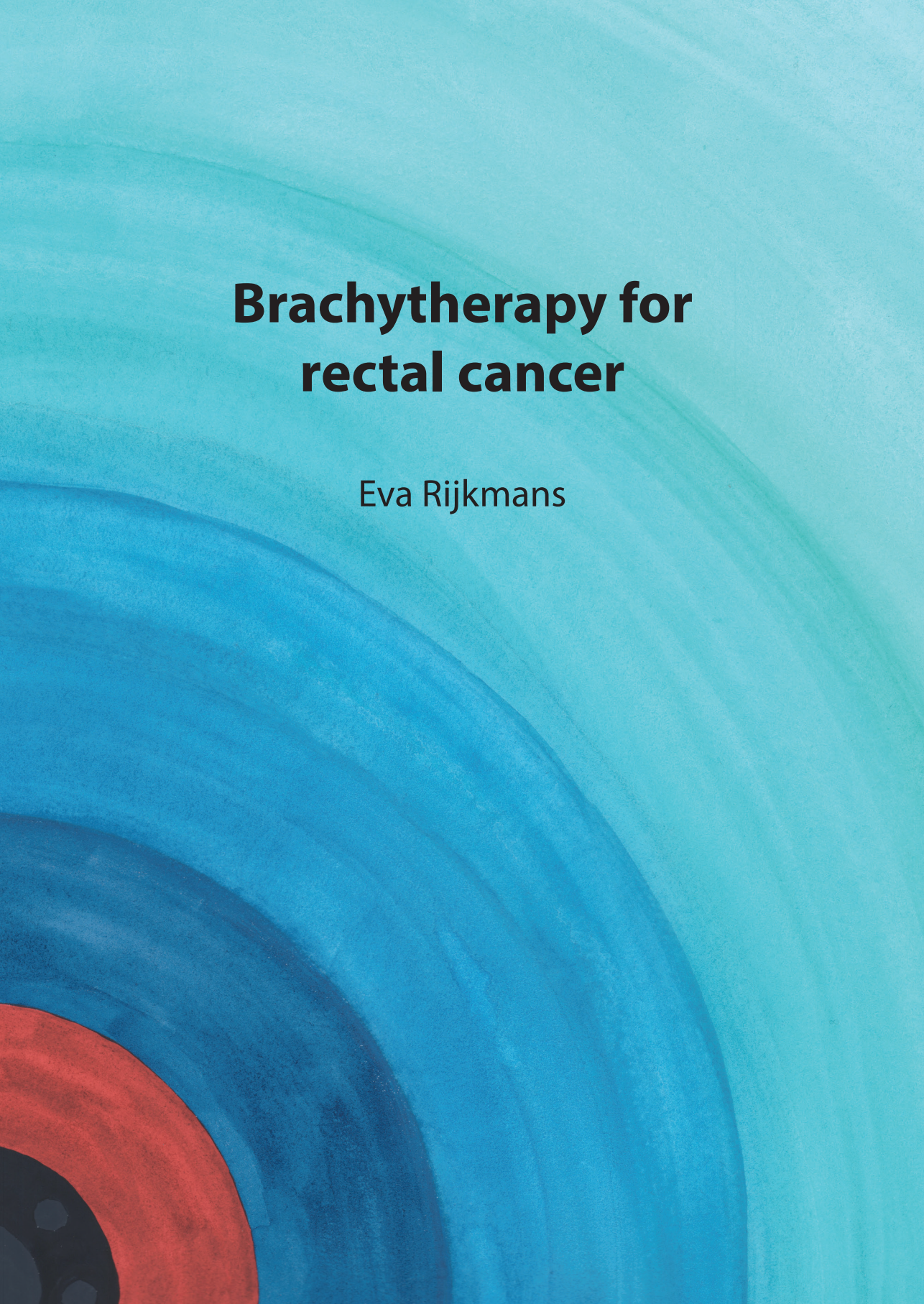

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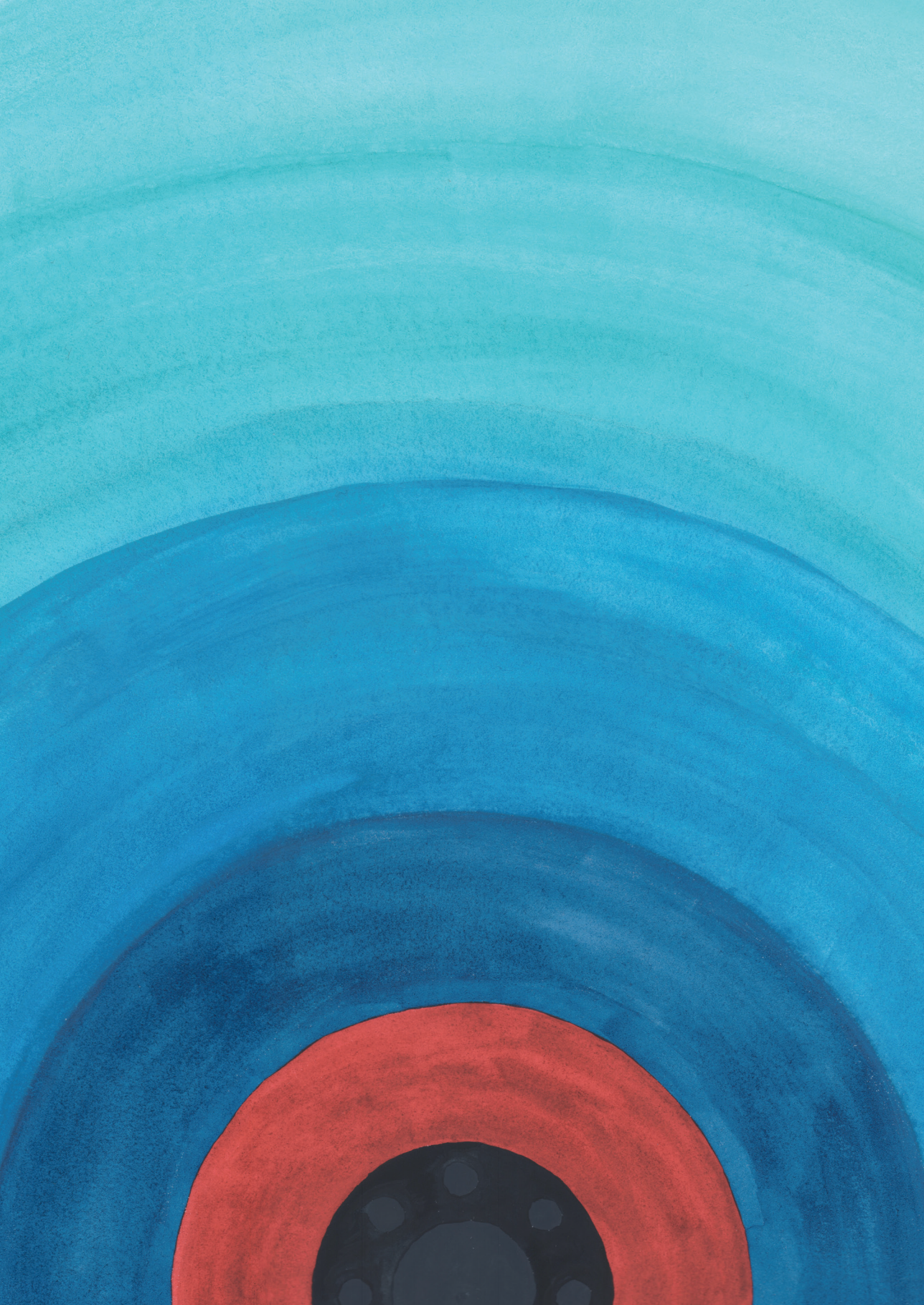

Chapter 1

Introduction and outline thesis

1. INTRODUCTION

1.1 Epidemiology

Colorectal cancer is the third most common cancer worldwide. One-third of all colorectal cancers are located in the rectum.[1,2] Rectal cancer is mainly observed in older patients with a median age of 70 years and approximately 30% being older than 75.[2,3] Figure 1 shows a clear increase in incidence in the past two decades, which is partly explained by aging of the population and partly by the introduction of a national screening program in 2014.[3,4] The proportion of patients that will be diagnosed in an early stage will likely rise due to nationwide screening.[5]

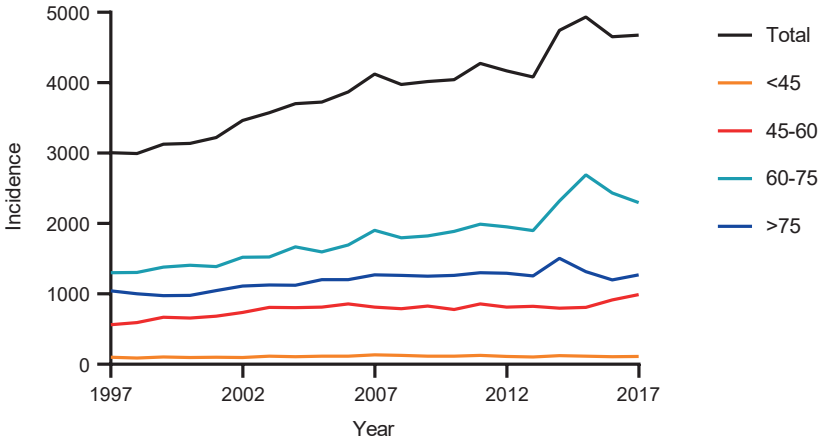

Figure 1. Netherlands Cancer Registry: incidence (total number of patients) and age distribution of rectal cancer in the Netherlands between 1997 and 2017.

1.2 Standard treatment

Standard treatment for non-metastasised rectal cancer is total mesorectal excision (TME). This resection technique was first described by Heald in 1982.[6,7] In the Netherlands, TME was implemented in the framework of the TME trial at the end of the 20th century. Nationwide, local recurrence rates improved from approximately 25% with blunt dissection to 11% with TME surgery.[8-11] Neoadjuvant radiotherapy further improves local control and two main schedules are accepted today as standard: Short course radiotherapy (SCRT) consisting of 5×5 Gy external beam radiotherapy and long course chemoradiotherapy (CRT) consisting of 25 fraction of 1.8-2.0 Gy with concurrent 5-fluorouracil or capecitabin.

Short course radiotherapy with immediate surgery was evaluated in three large randomised trials: the Swedish rectal cancer trial, the Dutch TME trial and the MRC CR07 trial. These trials showed that local recurrence is reduced by approximately 50%.[8,9,12] This resulted in a local

recurrence rate of 5% after 10 years in the TME trial. Although overall survival was not improved in the entire cohort, a subgroup analysis in patients with stage III rectal cancer with clear circumferential resection margins showed a significant increase in 10-year survival from 40% for patients undergoing TME surgery alone to 50% for patients treated with SCRT and TME surgery.[8] Neoadjuvant long course chemoradiotherapy (CRT) was investigated around the same time in several other trials with cT3-4/N+ tumours (EORTC 22921, FFCD 9203 and CAO/ARO/AIO-94). These showed superior local recurrance rates compared to neoadjuvant radiotherapy alone or postoperative chemoradiotherapy (6-8% vs. 13-16%).[13-17]

The results of aforementioned studies have led to differences in practice guidelines for neoadjuvant treatment around the world.[2,18,19] Current national guidelines in the Netherlands are displayed in Table 1.[19] Patients with early-stage rectal cancer have a low risk of local recurrence after TME surgery alone and currently no neoadjuvant radiotherapy is advised.[19] In patients with intermediate stage rectal cancer, SCRT is preferred over CRT because the former has a lower toxicity profile and comparable oncological outcomes.[20-22]

Recently, based on the results of the Stockholm III trial, SCRT with delayed surgery was introduced as an alternative to SCRT with immediate surgery. Delayed surgery is associated with increased downsizing and a reduced risk of postoperative complications compared to immediate surgery.[23] The increased burden of acute toxicity is the main disadvantage and both options can be discussed with patients with intermediate-risk rectal cancer.[24] In patients with risk factors for local recurrence (cT4, N2 or threatened mesorectal fascia), SCRT with immediate surgery is associated with a high rate of local recurrence (17%) and CRT with delayed surgery to allow for downstaging is preferred.[14,25] The effect of SCRT with delayed surgery in these high-risk patients has not been investigated but is considered as an alternative to CRT if patients are not fit enough for concurrent chemotherapy.

Table 1. Dutch guidelines for local treatment in rectal cancer

Risk group	TNM stage	Standard treatment
Very early	cT1 sm1 N0	Local excision
Early (good)	cT1-3bN0, MRF-	TME surgery
Intermediate (bad)	cT3c-dN0 / cT1-3N1, MRF-	SCRT+TME surgery
Advanced (ugly)	cT(x)MRF+/cT4/cN2	CRT + TME surgery

Abbreviations: MRF: distance to mesorectal fascia: MRF- > 1 mm, MRF+ < 1 mm; TME: total mesorectal excision; SCRT: short course radiotherapy (5×5 Gy); CRT: chemoradiotherapy (45-50 Gy, 1.8-2 Gy/fraction + oral capecitabine 825 to 1,000 mg/m2 bidaily)

The developments in the treatment of localised rectal cancer since the 1990s have improved the 5-year overall survival from 51% to 65%. While prognosis for stage I is very good with 94% 5-year overall survival, the survival of patients with stage II (cT3/4) and stage III (cN+) is still compromised by the increased risk of distant metastases with a 5-year overall survival of 77% in stage II and 65% in stage III.[26] In many countries, adjuvant chemotherapy is advised in

patients with high risk factors based on the beneficial effects of chemotherapy on recurrence and survival in colon cancer.[27,28] In rectal cancer, however, several trials have reported negative or inconclusive results and in the Netherlands, postoperative chemotherapy is therefore currently not advised.[29] Possible explanations for the absence of a survival benefit of chemotherapy are the poor compliance of postoperative chemotherapy and the interval between diagnosis and start of chemotherapy.

A potential solution to both problems is the administration of chemotherapy prior to surgery. This was the rationale for the international multicentre phase III Rapido study. Neoadjuvant SCRT followed by 6 or 9 courses of chemotherapy before TME was compared with standard neoadjuvant CRT and TME followed by postoperative chemotherapy according to local guidelines.[30] The primary endpoint was defined as Disease-related Treatment Failure (DrTF), including locoregional/distant failure, new colon carcinoma and treatment-related death. A recent presentation at the annual meeting of the American Society of Clinical Oncology demonstrated that DrTF was significantly improved in the experimental arm, with 23.7% at three years compared to 30.4% after standard CRT. Although acute toxicity was increased in the experimental arm (48% vs. 25%), the postoperative toxicity of adjuvant chemotherapy (37%) is avoided. Detailed analyses demonstrated no difference in long-term toxicity, overall health-related quality of life or low anterior resection syndrome score. It is likely that this new approach will be introduced in guidelines around the world for locally advanced rectal cancer.[30,31]

Morbidity of standard treatment

While oncological outcomes with these standardised treatments are excellent, they are associated with severe morbidity. TME surgery is associated with postoperative complications in approximately 40% of patients and sexual, urinary and bowel function is often compromised.[24,32-35] Symptoms of faecal incontinence, soiling, urgency, increased stool frequency, painful stools, emptying difficulties, altered consistency and unpredictable variation in bowel motions are often reported and are summarised as low anterior resection syndrome (LARS).[36,37] Neoadjuvant (chemo)radiotherapy further increases this risk of postoperative morbidity.[33,37,38]

1.3 Considerations for treatment adaptation in elderly patients

TME surgery

Risks of morbidity and postoperative mortality are substantially increased in frail elderly patients. Analyses from the Dutch TME trial and Comprehensive Cancer Centre registry up to 2002 showed high postoperative complication rates of 50% in patients over 75 years of age and increased 6-month mortality of 13.4% in patients aged 75 to 85, increasing to almost 30% in patients aged 85 to 95 years.[39] Especially elderly patients with comorbidities and a high American Society of Anaesthesiology (ASA) classification were at increased risk of postoperative mortality. Figure 2 shows the one-month postoperative mortality by age and ASA classification

from these analyses.[39] Since the TME trial, improvements in surgical and anaesthetic techniques, as well as the introduction of geriatric assessments, have contributed to a reduction of these risks in elderly patients.[40-43] A recent analysis of a prospective cohort showed that the rate of postoperative complications (38%) is no longer increased in patients older than 70 years.[44] The impact of postoperative complications on quality of life is, however, more pronounced in elderly patients compared to their younger counterparts. Equally important, postoperative mortality is still increased by 5.5% after 1 month and 14.8% at 1 year in patients over 75.[44-46]

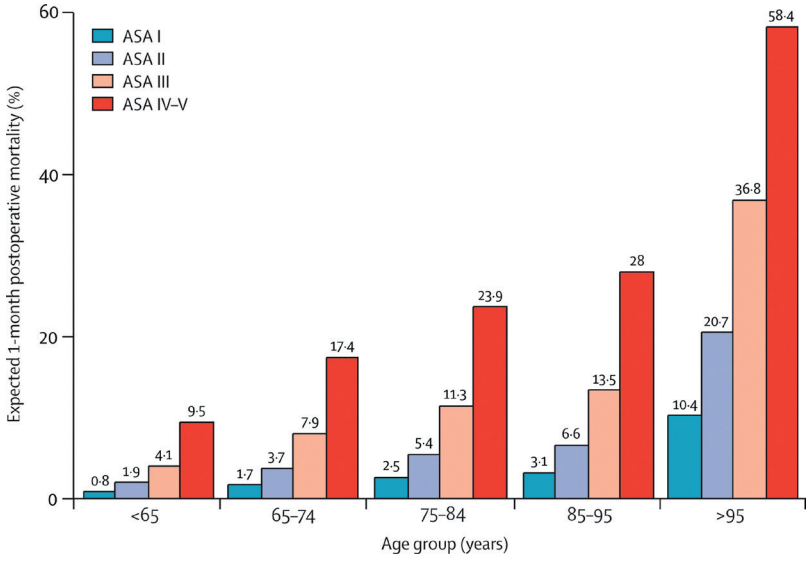

Figure 2. Expected 1-month postoperative mortality for a group of patients with stage 2 and stage 3 rectal cancer according to the Association of Coloproctology of Great Britain and Ireland score.*

Neoadjuvant (chemo)radiotherapy

Neoadjuvant (chemo)radiotherapy reduces the risk of local recurrence by approximately 50% (see Section 1.2 standard treatment). This improvement however comes at a cost of increased risk of complications and treatment morbidity. A subanalysis of the phase III ACCOR12/PRODIGE 2 study, which compared two chemoradiotherapy schedules (capecitabin/45Gy and capecitabin oxaliplatin/50Gy), further shows that elderly patients are at increased risk of severe acute toxicity compared to younger patients following the same regimen.[47] Also, the increase in postoperative complications (41% to 48%) and impact of bowel dysfunction

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on daily activities (22% to 34%), as observed in the TME trial, might be more relevant in frail patients than in fit patients.[32,44,48] Use of concurrent chemotherapy in long course radiotherapy is associated with a 4-fold increase in severe acute toxicity.[49]
In two randomised studies comparing CRT and SCRT, no difference in oncological outcome was observed. However, a favourable toxicity profile of SCRT was seen.[20,21,50] These observations demonstrate that, especially for frail patients, SCRT might be a good alternative to CRT. Alternatively, complete omission of the neoadjuvant treatment can be considered.[46,51] Data from a prospective colorectal cancer cohort between 2013 and 2016 indeed shows that elderly patients over 70 more often received SCRT with delayed surgery compared to younger patients (19% vs. 6%). Chemoradiotherapy was prescribed to 39% compared to 63% in younger patients and they were more likely to receive a permanent stoma (13% vs. 3%).[44]

Shared decision making based on geriatric assessment

Elderly rectal cancer patients represent a very heterogeneous group and a comprehensive geriatric assessment can be useful in guiding both physicians and patients in developing an integrated plan for care, treatment and follow-up. Comprehensive geriatric assessment is defined as a multidimensional, interdisciplinary diagnostic process focussing on an older cancer patient's medical, psychosocial and functional capacities. Patient's age is often less important than for example performance status and presence of comorbidities or geriatric syndromes.[42,43]
Two review articles provide an overview of considerations and treatment options in elderly patients with rectal cancer.[46,51] Wang et al. have composed a shared decision-making strategy which uses an algorithm for the management of the older cancer patient based on a comprehensive geriatric assessment by Balducci and Extermann:[51,52]

1) Fit patients: Patients who are functionally independent and have no serious comorbidity who may receive the full treatment.
2) Intermediate group: Patients in between the fit and frail groups, who may benefit from modified treatment with a lower toxicity profile.
3) Frail patients: Patients who are frail (dependence in one or more activities of daily living, three or more comorbid conditions, one or more geriatric syndromes), who are only candidates for palliative treatment.

Bujko et al. have developed a similar risk classification with four categories: (1) fit patients; (2) medium-fit patients, at surgical risk; (3) frail patients in whom radical surgery is contraindicated and (4) very frail patients. They provide several suggestions for radiotherapy adaptation for rectal cancer in each group. In the first two groups, adaptation of treatment volume and radiotherapy schedule is suggested, followed by surgical resection (either TME or local excision). For the third

group of frail patients, with a contraindication for surgery, a radical radiotherapy schedule is suggested as an alternative. And patients in the fourth group will likely be candidates for palliative radiotherapy alone.[46]

1.4 Radical radiotherapy

(Chemo)radiotherapy alone

As rectal cancer is a relatively radioresistant tumour, high doses are needed to achieve local control with radiotherapy alone.[53] To assess the chance of cure with radiotherapy alone (radical radiotherapy), the most reliable data can be extracted from surgical studies reporting the likelihood of a pathologic complete response (pCR) after neoadjuvant (chemo)radiotherapy. With standard dose fractionated external beam chemoradiotherapy (EBRT, 45-50 Gy in 1.8 Gy-2.0 Gy per fraction) a pCR is observed in approximately 16% of locally advanced tumours.[54,55] With dose escalation to 65 Gy or longer time until surgery, this number can be improved to 20-38%.[56-58] Furthermore, in early stages (cT1-3N0), the pCR rate is higher and the chance of cure with chemoradiotherapy alone is likely between 27-64%.[59-63]

In patients unfit for chemoradiotherapy, alternative schedules such as 5×5 Gy (SCRT), 13×3 Gy or 40-60 Gy in 2-4 Gy per fraction can be considered, but chances of a pathologic complete response are expected to be lower than with chemoradiotherapy.[64-66] Short course radiotherapy has resulted in a pCR rate of 10.4% in resectable tumours included in the Stockholm III trial.[23] Data from the Netherlands Cancer Registry show similar pCR rates of 9.3%.[67] Clinical T-stage was identified in this cohort as a significant predictor for tumour response and pCR rates decreased from 36.4% in cT1 tumours to 6.6% in cT4 tumours. In early stages a pCR with SCRT can be accomplished in around 32.2-35.9% based on two phase 2 studies in early rectal cancer using SCRT with local excision.[62,68]

Prior to the era of chemoradiotherapy, a schedule of 13×3 Gy external beam radiotherapy was used in two clinical trials in France. The Lyon 90-01 and 96-02 trials, performed in cT2-3 tumours, show a pCR rate of 7-15% after 13×3 Gy.[69,70] Wang et al. described the effect of long course radical radiotherapy in a retrospective cohort including all patients who received 40-60 Gy in 2-4 Gy per fraction. A clinical complete response was observed in 30%, but 78% developed a regrowth during follow-up resulting in a local control of only 6.6%.[64]

Dose escalation

In order to increase the chance of a complete response using radical radiotherapy, dose escalation is needed. Dose-response analyses indicate that doses as high as 92 Gy (equivalent dose in 2 Gy per fraction [EQD2]) are needed to achieve a complete pathologic response in 50% of patients (see Figure 3).[53] However, external beam doses higher than 50-65 Gy can result in

excessive toxicity and dose escalation to radiation doses > 80 Gy is currently only possible with an intraluminal radiotherapy boost. Two options are currently available: contact X-ray (CXB) and HDR endorectal brachytherapy (HDREBT).

There are only two randomised studies using these techniques: The first was the Lyon 96-02 study which aimed for increased sphincter preserving surgery after a CXB boost. Patients with a cT2-3Nx tumour received 13×3 Gy EBRT with 85 Gy CXB in three fractions. Surgery was performed 5 weeks after EBRT and a pCR rate of 35% and near pCR rate of 57% was observed.[70] The second study by Jakobsen et al. was designed to increase the chance of a pathologic complete response in cT3-4 tumours. Patients received 50.4 Gy chemoradiotherapy and were randomised to an HDR brachytherapy boost of 2×5 Gy or no boost. The major pathologic response rate was increased from 29% to 44%, but pCR was the same in both groups with 18%. This is probably the result of the large tumours included in this study and limited effect of the HDREBT boost on pathologic lymph nodes.[71] Several cohort studies have however shown more promising results for use of an intraluminal radiotherapy boost for organ preservation with complete responses up to 94%.[72-78]

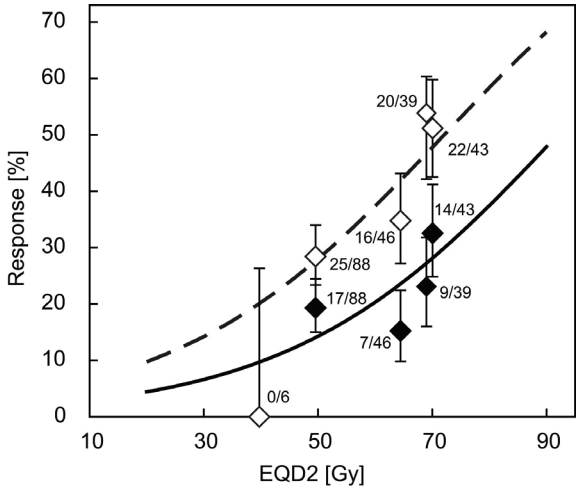

Figure 3. Dose-response relationships for complete and major response after preoperative chemoradiation therapy (CRT) for rectal cancer. Solid line, filled squares = pCR; dashed line, open squares = and major response (TRG1+2); Error bars indicate 68% confidence intervals. EQD2 = equivalent average dose to the tumour in 2-Gy fractions.*

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1.5 Intraluminal radiotherapy boost techniques

Contact X-ray (CXB)

Contact X-ray brachytherapy was developed in the 1930s in Germany as an alternative to radium brachytherapy in treatment of patients with cervical cancer and was further developed for rectal cancer in the 1950s by Professor Papillon in Lyon. Contact X-ray for rectal cancer (also referred to as the Papillon technique) delivers a very high dose to the rectal mucosa by using an X-ray tube with 50kV which is guided through a rigid rectoscope (see Figure 4.). The region irradiated is limited by the diameter of the rectoscope (max 3 cm) and the inverse square law. A surface dose of 100% will reduce to 50% at 6 mm and approximately one-third at 10 mm.[79,80] Dose is prescribed at the surface of the rectal tumour and is usually administered in 3-4 fractions of 20-30 Gy with a 2-week interval to allow for downsizing in between.[74]

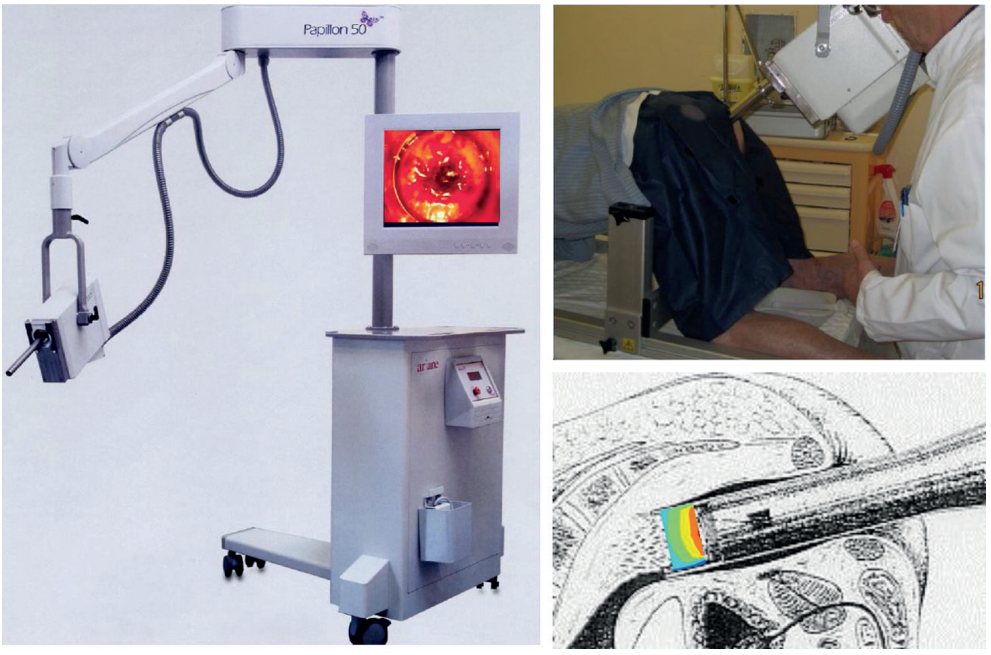

Figure 4. The Papillon 50 tm machine (Ariane Company UK, 2010). Irradiation of a rectal tumour with patient in knee-chest position. Dose display calculated with Monte Carlo showing the rapid fall off of the dose.*

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High dose rate endorectal brachytherapy (HDREBT)

The first reports on HDR brachytherapy for rectal cancer date back to 1988.[81,82] The development of high dose rate afterloading systems with relatively short treatment times made intraluminal brachytherapy for rectal cancers a realistic and practical option. Historically, there are two types of applicators developed for this purpose. The first is a rigid applicator with a central channel and optional shielding of 25-75% of the circumference. Positioning of this applicator is based on digital rectal examination or use of clips inserted during endoscopy and localisation of these clips with orthogonal X-rays. Dose is usually prescribed at 1 cm from the applicator surface and varies from 5-10 Gy per fraction.[76] This technique is mainly used in palliative care but has also been used as a boost to chemoradiotherapy in two dose-escalation trials initiated in Denmark.[71,75,76,83,84]

The second technique uses a flexible applicator with eight peripheral channels. It was developed by investigators of McGill University in Montreal for use in neoadjuvant radiotherapy. An inflatable semi-circular balloon is applied over the applicator, which is used to fixate the applicator within

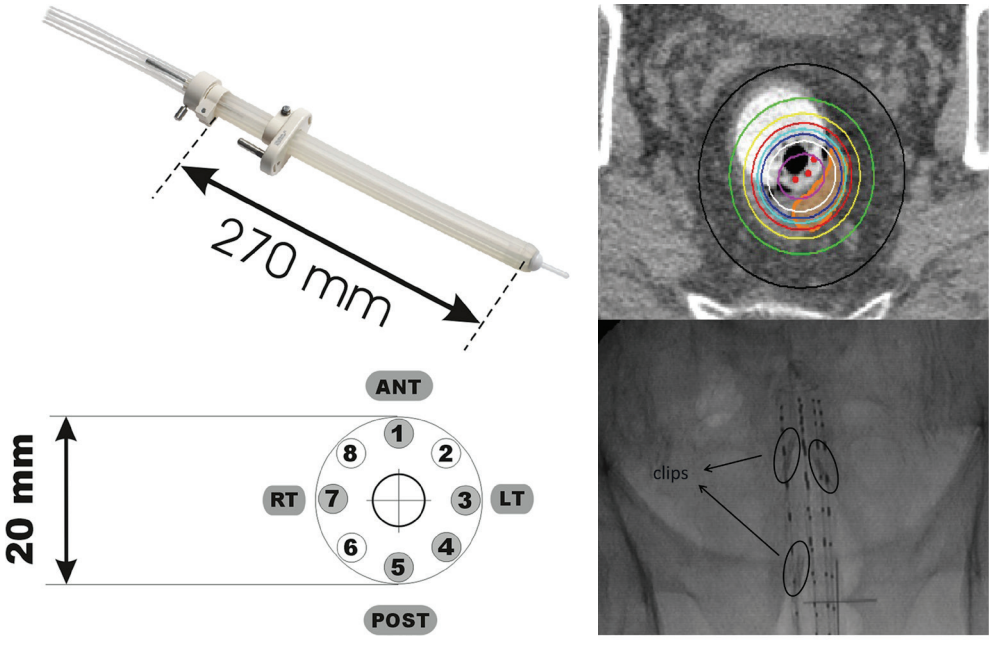

Figure 5. Left: Intracavitary mold applicator for HDR endoluminal brachytherapy (Elekta, Veenendaal); the bottom schematics represents the catheter positions. In catheter 1, 3, 4, 5 and 7, X-ray markers are placed.*
Right-top: axial slice of a planning CT and dose distribution. ● = active dwell position; isodose lines: Pink = 400%, Red 100%, Green 50% and Black 25% of prescribed dose.
Right-bottom: X-ray at time of treatment used for correction of rotation and depth of insertion.

* Left figure: Reprint with permission of Wiley from: Devic S, Vuong T, Moftah B, Evans M, Podgorsak EB, Poon E, et al. "Image-guided high dose rate endorectal brachytherapy." This article was published in Medical physics. 2007;34(11):4451-8. Copyright American Association of Physicists in Medicine (2007)

the rectal lumen and to divert the normal rectal mucosa on the contralateral wall. A CT scan is acquired with the applicator in situ and based on the diagnostic MRI and endoluminal clips placed during endoscopy, the tumour is delineated on the planning CT scan. Subsequently, a treatment plan with differential loading of the channels is constructed. The dose is prescribed at the radial margin of the tumour instead of a fixed distance from the applicator surface.[85,86] At time of treatment, adjustment of rotation and depth of insertion is accommodated by use of orthogonal X-rays with markers inserted in prespecified channels (see Figure 5). This image-guided technique allows for a more conformal dose distribution with increased sparing of normal tissue compared to a single channel catheter.[87]

Comparison of CXB and HDREBT

Both CXB and HDREBT have a steep dose gradient due to the inverse square law and are suitable for an endoluminal boost in radical radiotherapy. The techniques have never been formally compared, but CXB is preferred in small tumours because it results in a smaller irradiated volume due to complete shielding of tissue outside the circumference of the rigid proctoscope (see Figure 4 and 5). The clinical use of contact X-ray for rectal cancer is currently still limited because of the sparse availability of CXB machines, with only 11 machines in Europe (France, England, Switzerland, Sweden, Denmark, the Netherlands).[79] Important technical limitations are the restrictions in tumour size, accessibility of the tumour location with rigid endoscopy and the need for training of radiation oncologists in rigid rectoscopy. The volume that can be treated with HDREBT is much larger compared to CXB and is also not limited by the reach of rigid rectoscopy. Another advantage of the flexible applicator is that it is more comfortable for the patient than a rigid rectoscopy.

1.6 Rationale for the HERBERT study

The HERBERT study was initiated in 2007 by Professor Marijnen et al. to evaluate the feasibility of an HDR endorectal brachytherapy boost after external beam radiotherapy in elderly patients with rectal cancer who were unfit for chemotherapy or surgery. Because of the extensive experience in France with an internal CXB boost after 13×3 Gy, this schedule was selected for EBRT. The brachytherapy technique was adopted from the experience with neoadjuvant brachytherapy in Canada, as described above. In analogy with a brachytherapy boost in gynaecologic malignancies, a weekly brachytherapy schedule with three fractions was proposed. Because there were no data in the literature about the tolerability of a HDREBT boost, the study was designed as a brachytherapy boost dose escalation study which started with 3×5 Gy, six weeks after EBRT. Acute proctitis occurring within 6 weeks after brachytherapy was defined as dose-limiting toxicity and the primary endpoint was the maximum tolerated brachytherapy boost dose. Secondary aims were to evaluate the efficacy, toxicity and technique.

1.7 Aims and outlines of this thesis

In this thesis an alternative treatment option for frail or elderly patients with rectal cancer is evaluated. This treatment combines external beam radiotherapy with an endorectal brachytherapy boost and was evaluated in the HERBERT trial.

The basis of the treatment is external beam radiotherapy and the main limiting toxicity in external beam radiotherapy for rectal cancer is gastrointestinal toxicity. **Chapter 2** evaluates risk factors and dose-response relationships for gastrointestinal toxicity after chemoradiotherapy in patients with locally advanced rectal cancer. Three different methods for bowel contouring are compared and a review of the literature is performed to provide recommendations for dose constraints for small bowel loops and two commonly used alternative contours: bowelbag using EMBRACE guidelines and bowelbag using RTOG guidelines.

The primary outcome of the HERBERT trial is described in **Chapter 3**. Acute dose-limiting toxicity, clinical response to treatment, progression free- and overall survival and severe late toxicity are reported. **Chapter 4** provides a comprehensive overview of physician-reported, patient-reported and endoscopic toxicity. Further analyses on risk factors and dose-effect relationships for response and toxicity are provided in **Chapter 5.**

The technique used in the HERBERT study uses a single CT-based treatment plan for three brachytherapy fractions. A repeat CT side-study evaluates the added value of a CT-based adaptive approach in a subgroup of the HERBERT population. The results of this repeat CT study are described in **Chapter 6.** The next step in the optimisation of rectal brachytherapy will be MRI-guided brachytherapy. The REMARK study aims to select fiducial markers that are MRI compatible and can be used in MRI-guided radiotherapy for rectal cancer. **Chapter 7** describes the technical success rate and safety of implantation of four different gold fiducials in the rectal wall and the mesorectal fat in close proximity to the rectal tumour.

Chapter 8 provides a summary and **Chapter 9** a general discussion of the data presented in this thesis focussing on further development of endorectal brachytherapy and its use in treatment for rectal cancer.

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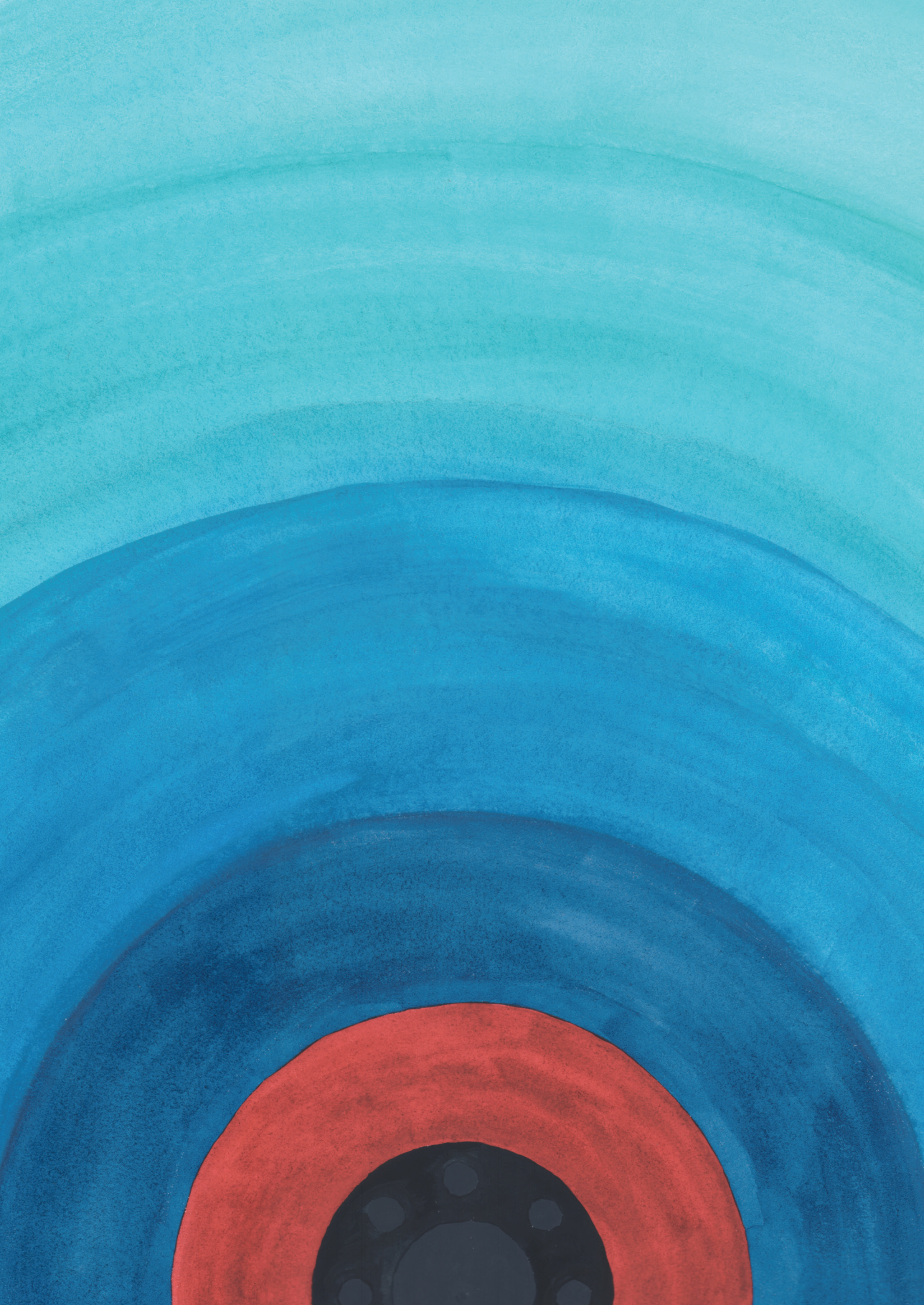

Chapter 2

Gastrointestinal toxicity in chemoradiotherapy for rectal cancer: comparison of three bowel contouring methods and evaluation of dose-response and risk-factors

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Submitted

ABSTRACT

Purpose

Gastrointestinal (GI) toxicity is one of the main dose-limiting toxicities in radiotherapy and practical dose-constraints are needed. This study compares three widely used guidelines for bowel contouring. In addition, we provide a review of the literature for dose-response relationship for GI toxicity.

Material and methods

A historical cohort of patients with locally advanced rectal cancer treated with neoadjuvant (chemo)radiotherapy was used. V5Gy-V50Gy dose volumes for small bowel loops (SBL), bowelbag following EMBRACE guidelines (EMBRACE-BB) and bowelbag following RTOG guidelines (RTOG-BB) were compared and correlated to physician reported acute and patient reported late toxicity. A review of the literature was performed assessing dose constraints for SBL, EMBRACE-BB and RTOG-BB.

Results

157 patients were evaluable for acute and 73 for late toxicity. The main risk factor for acute toxicity was prior abdominal surgery and for late toxicity concurrent chemotherapy. No significant dose-response relation was observed for acute or late toxicity. DVH parameters of EMBRACE-BB and RTOG-BB were significantly correlated to SBL. The strongest correlation was observed for EMBRACE-BB (ρ=0.9). The results of the literature review support a constraint of 165 cc for SBL V15Gy for grade 2-3 acute GI toxicity. Using the correlation observed in our cohort a constraint of 356 cc for the EMBRACE-BB V15Gy was calculated.

Conclusions

Prior abdominal surgery and chemotherapy should be included in NTCP modelling for GI toxicity. The bowelbag as defined by EMBRACE guidelines is highly suitable as a fast and practical bowel contouring alternative to small bowel loops and should be further evaluated in rectal cancer studies.

INTRODUCTION

Worldwide, neoadjuvant chemoradiotherapy followed by total mesorectal excision is the standard of care in patients with locally advanced rectal cancer.[1-3] Radiotherapy to the pelvic area can cause damage to healthy tissues resulting in acute and late side effects, reducing quality of life.[4-6] The bowels are considered to be the main dose-limiting organs for pelvic irradiation. Radiotherapy planning techniques such as intensity modulated or volumetric arc therapy, which are now standard practice in most institutions, allow increased sparing of organs at risk.[4,6,7]
To develop reliable constraints for the irradiated bowel, a consistent definition of this organ at risk is essential. Contouring of individual small bowel loops is often regarded as the gold standard and has proven to be of value for constraints with regard to acute grade ≥ 3 diarrhea.[8,9] However, contouring of separate loops is time consuming and disregards the day-to-day variation of various loops.[10,11] In theory, alternatives such as contouring of the bowel cavity, whole abdomen or bowelbag may overcome this problem, but lack a consistent definition.[12-14] In addition, the clinical significance of these alternative contours remains undetermined.[14] Also, with improved radiation techniques the occurrence of acute grade ≥ 3 gastrointestinal (GI) toxicity is decreased. In order to further optimise the treatment, constraints for acute grade ≥ 2 and late GI toxicity are needed.
In the current study we compared three bowel contouring definitions and evaluated both clinical and dosimetric risk factors for acute and late gastrointestinal toxicity in treatment of locally advanced rectal cancers.

MATERIALS & METHODS

A historical cohort of patients with locally advanced rectal cancer (LARC) treated with neoadjuvant chemoradiotherapy at the Leiden University Medical Center (LUMC) and Haaglanden Medical Center (HMC) between 2003-2010 was used. Details of this cohort were described previously.[15,16] Patients of whom DVH parameters could not be reconstructed and patients with prior malignancies, prior pelvic radiotherapy, local recurrences or metastatic disease at presentation were excluded from the current analyses. The local ethics committee approved this study, and informed consent was obtained from patients completing the questionnaires.

Treatment

Patients were treated with 50 Gy in 25 fractions or 50.4 Gy in 28 fractions, five days a week. Treatment was usually combined with concurrent chemotherapy, which consisted mainly of bidaily capecitabine 825 mg/m2 (7 days/week), for some patients combined with oxaliplatin or bevacizumab. Surgery was performed after 5-8 weeks. In specific cases of LARC intra-operative radiotherapy with a single dose of 10 Gy was administered at the HMC.

Treatment planning consisted of a CT-based 3-7 field conformal technique and was performed in Pinnacle[3] version 9.0/9.2 Philips Medical Systems, Milpitas, CA, USA) for LUMC and HMC in 2010 and Helax TMS version 6.1B (Uppsala Sweden) for HMC up to 2010. The clinical target volume (CTV) consisted of the primary tumour, mesorectum and presacral, internal iliac and in distal tumours obturator nodes. The majority of patients from the HMC received a pre-operative stoma, while this was not customary in the LUMC. All patients were instructed to have a full bladder during radiotherapy.

Toxicity

Acute toxicity was assessed between the start of radiotherapy and date of surgery and was retrospectively collected using patient charts and scored according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0). A composite endpoint for gastrointestinal toxicity was composed of the highest score of any of the following symptoms: diarrhoea, nausea, vomiting, abdominal pain and obstipation (see Table 1A).

After a median follow-up time of 4.6 years, late toxicity was assessed in patients who were disease-free, using relevant items from the EORTC QLQ-C30 and a questionnaire from the TME trial on bowel and urinary function.[16,17] For reasons of logistic regression a dichotomised variable was created. In analogy with the CTCAE classification, all hospitalisations for gastrointestinal symptoms or interference of stools with activities of daily living were assessed as severe late GI toxicity. Questions on stoma-related problems, bowel frequency and stool consistency were also included in this combined endpoint. For a detailed description see the Supplementary files.

Delineation of organs at risk and DVH parameters

Delineations were performed by JVZ, BO, DT, ER and checked by a second observer (ER/FP). An experienced radiologist was consulted if needed. The bowel volume was delineated according to three different definitions (Figure 1): Individual small bowel loops (SBL), the bowelbag following EMBRACE guidelines (EMBRACE-BB) consisting of one structure determined by the outer contour of both small and large bowel loops, excluding the rectosigmoid [12], and the bowelbag according to RTOG guidelines (RTOG-BB) including all abdominal contents starting from the most inferior small or large bowel loop, excluding muscle, bones, bladder, prostate and uterocervix.

Table 1A. Acute GI toxicity

	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Acute GI toxicity*	35 (22.3)	50 (31.8)	44 (28.0)	24 (15.5)	2 (1.3)
Diarrhea	58 (36.9)	45 (28.7)	34 (21.7)	16 (10.2)	2 (1.3)
Nausea	120 (76.4)	18 (11.5)	13 (8.3)	4 (2.5)	0 (0.0)
Vomiting	141 (89.8)	5 (3.2)	5 (3.2)	4 (2.5)	0 (0.0)
Abdominal pain	117 (74.5)	26 (16.6)	7 (4.5)	4 (2.5)	0 (0.0)
Constipation	135 (86.0)	9 (5.7)	9 (5.7)	2 (1.3)	0 (0.0)

* "Acute GI toxicity" is the maximum score of diarrhea, nausea, vomiting, abdominal pain and obstipation.

Table 1B. Late GI toxicity

	No	Yes	Missing
Severe late GI toxicity	50 68.5%	23 31.5%	0 0.0%
No stoma (n=14)			
Stool frequency > 10/day (no stoma)	12 85.7%	2 14.3%	0 0.0%
Stool frequency night > 3/night (no stoma)	11 78.6%	3 21.4%	0 0.0%
Consistency: watery stools	13 92.9%	1 7.1%	0 0.0%
Stoma (n=59)			
Stool frequency ≥ 4 bags per day	54 91.5%	3 5.1%	2 3.4%
Consistency: watery stools	56 94.9%	1 1.7%	2 3.4%
Noisy stoma	52 88.1%	4 6.8%	3 5.1%
Smelly stoma	51 86.4%	4 6.8%	4 6.8%
All patients(n=73)			
Dissatisfaction with stools	67 91.8%	6 8.2%	0 0.0%
Often/always limited in activities of daily living by bowel			
Work or household	57 78.1%	13 17.8%	3 4.1%
Outside the house	56 76.7%	13 17.8%	4 5.5%
Social activities like theater	56 76.7%	11 15.1%	6 8.2%
Hospitalisation for bowel symptoms	60 82.2%	13 17.8%	0 0.0%

No modifications were made to exclude the target volume from the RTOG-BB.[13] Contouring was performed up to 3 cm cranial to the planning target volume. The absolute volumes for dose regions from 5 to 50 Gy with a 5 Gy interval were derived (V5Gy-V50Gy).

Literature search

The PubMed database was searched for articles reporting a dose-volume constraint for bowel using either of the above-mentioned delineation techniques. Search items included: bowel OR bowelbag OR bowelcavity AND normal tissue complication probability (NTCP) OR dose-volume OR dosimetric OR dose response AND radiotherapy OR chemoradiotherapy. The search was limited to full text articles in English published since the Quantec report on bowel toxicity in March 2010 up to March 5th 2020.[18] All studies of the Quantec review and studies published since on dose-volume constraints for SBL, EMBRACE-BB, RTOG-BB or bowelcavity corresponding to the same volume as the RTOG-BB, with a minimum of 30 patients were included. Also, the reference lists of included articles were checked for relevant studies. Studies without dose constraints or constraints for brachytherapy or stereotactic radiotherapy were excluded.

Statistical analysis

Statistical analyses were performed using SPSS v23.0 (IBM, Armonk, NY) and R v3.3.2 (R Foundation, Vienna, Austria). Pearson correlation was used to assess correlation between bowel contouring methods. Mann-Whitney U tests and logistic regression were performed for dose-response analyses. Chi-squared, linear-by-linear association test and logistic regression were used to compare patient and treatment characteristics with occurrence of acute or late toxicity.

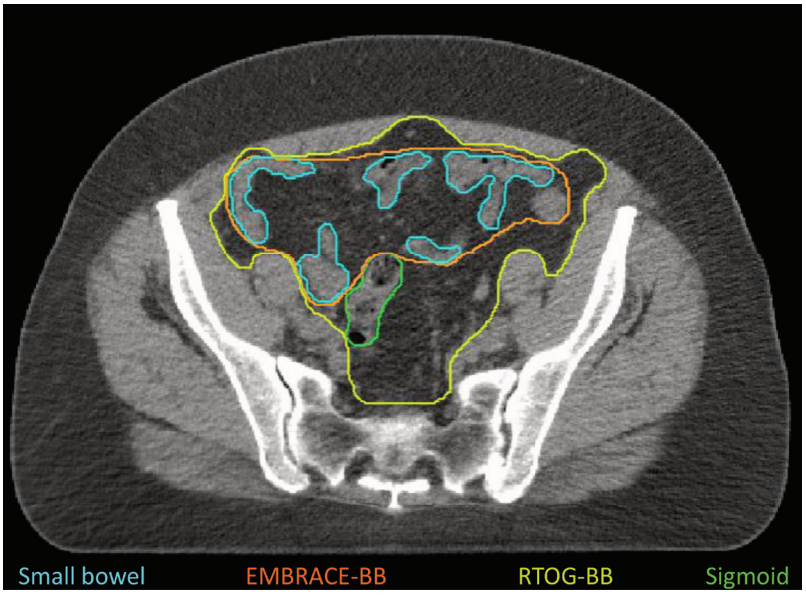

Figure 1. Example of different bowel contouring definitions:
- Small bowel (sky blue): Individual bowel loops.
- EMBRACE bowelbag (orange): Outer contour of small and large bowel, excluding rectosigmoid.
- RTOG bowelbag (yellow green): All abdominal contents starting from the most inferior axial slice with small or large bowel loops or above the rectum.
- Sigmoid (Green).

In case of separation, Firth regression with a likelihood ratio test was performed. To correct for multiple testing, a p-value of < 0.01 was considered statistically significant. A weighted mean of dose constraints for SBL in rectal cancer patients was created using number of patients included in the study as weight factor.

RESULTS

In total 157 patients with LARC treated between January 2003 and October 2010 met the inclusion criteria for the current analysis. Ninety-seven were treated at the LUMC and 60 at the HMC. Median age was 64 (range 25-92) and 55% was male. Sixty-six percent had a cT3-tumour and 80% had positive lymph nodes. Eighty-five percent of patients received chemotherapy; 74% capecitabine and 11% capecitabine with oxaliplatin or bevacizumab. One-third of patients received a pre-CRT stoma. During this procedure, the sigmoid was positioned in the small pelvis as a spacer for the small bowel. Detailed patient characteristics are provided in Supplementary Table S1.

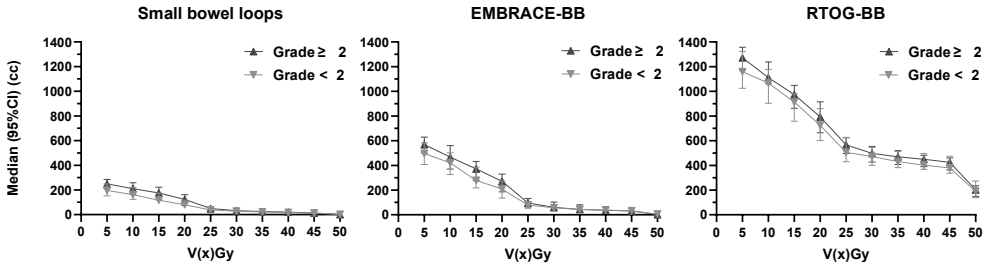

Figure 2. Relation of SBL, EMBRACE-BB and RTOG-BB with acute GI toxicity grade ≥ 2.

In June 2011, after a median follow-up time of 4.6 years (range 1.1-8.0 years), 96 patients were alive and disease free of whom 73 patients responded to the questionnaire. Baseline characteristics of the subgroup analysed for late toxicity were comparable to the total cohort except for sex (64% male). 59 patients had a stoma at time of the questionnaire.

Bowel contouring guidelines

The three guidelines for bowel delineation showed a large difference in volume, but were highly correlated to each other (see Figure 2). The V5Gy to V50Gy of EMBRACE-BB and of SBL had a correlation coefficient between 0.86 and 0.92 ($p<0.001$) while the correlation between RTOG-BB V5Gy-V50Gy and SBL V5Gy-V50Gy was between 0.52-0.71 ($p<0.001$). The correlations between SBL V15Gy and EMBRACE-BB V15Gy and RTOG-BB V15Gy are provided in Figure 3. Correlations for the other dose levels (V5Gy-V50Gy) are provided in Supplementary Table S2.

Toxicity

Acute and late GI toxicity scores are shown in Table 1A and 1B respectively. Acute GI toxicity grade ≥ 2 occurred in 44.8% and grade ≥ 3 in 16.8% of patients. Severe late GI toxicity occurred in 31.5%. None of the bowel DVH parameters showed a significant correlation with acute or

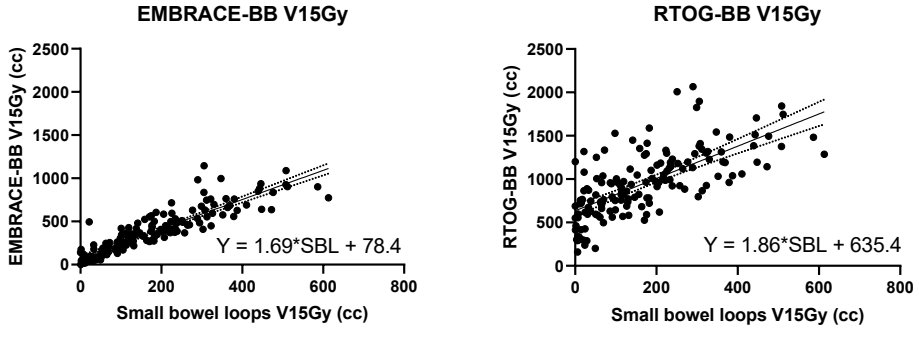

Figure 3. Pearson correlation of EMBRACE-BB V15 and RTOG-BB V15 with SBL V15.

late GI toxicity (See Figure 2 and Supplementary Tables S3/S4). For SBL and EMBRACE-BB, the V15Gy showed the largest difference in median volume for acute grade ≥ 2 toxicity (see Figure 2). For RTOG-BB the largest difference was observed for the V5Gy. These values were tested in multivariable analyses but remained insignificant (data not shown).
In a subanalysis, performed in patients with capecitabine based chemoradiotherapy only (n=116), the dose-response analyses remained insignificant (data not shown).

Risk factors for acute GI toxicity

Correlation of acute GI toxicity grade ≥ 2 with patient and tumour characteristics is shown in Table 2. Prior abdominal surgery (creating a stoma excluded) was significantly associated with increased occurrence of acute GI toxicity and a trend was observed for female sex and concurrent chemotherapy. Prior abdominal surgery increased the occurrence of grade ≥ 2 GI toxicity from 35.8% to 61.8% (p=0.002). Grade ≥ 2 GI toxicity was seen in 55.7% of women versus 36.5% in men (p=0.02) and in 48.5% of patients treated with CRT vs. 26.1% of patients treated with RT only (p=0.05). In multivariable analyses a trend remained for prior abdominal surgery and concurrent chemotherapy (Table 2).

Table 2. Logistic regression for acute GI toxicity grade ≥ 2

		Univariable analyses			Multivariable analyses		
		OR	95% CI	p-value	OR	95% CI	p-value
Institute	LUMC vs. HMC	0.93	0.49 1.79	0.83			
Sex	Female vs. male	2.19	1.15 4.18	*0.02*	2.08	0.96 4.48	0.06
Age	years	0.99	0.96 1.02	0.52			
Active smoker	yes vs. no	1.59	0.72 3.55	0.25	2.20	0.87 5.56	0.09
BMI	kg/m2	1.04	0.97 1.11	0.32	1.05	0.97 1.15	0.21
Clinical tumour stage	cT2	1.00		0.74			
	cT3	1.51	0.34 6.66	0.58			
	cT4	1.20	0.25 5.68	0.82			
Tumour level	> 10 cm	1.15	0.52 2.53	0.72			
EBRT fraction size	2.0 Gy vs. 1.8 Gy	0.72	0.30 1.75	0.47			
Concurrent chemotherapy	yes vs. no	2.67	0.99 7.19	*0.05*	4.52	1.12 18.25	*0.03*
Prior abdominal surgery	yes vs. no	2.90	1.46 5.77	**0.002**	2.50	1.14 5.46	*0.02*
Preoperative stoma	yes vs. no	0.81	0.41 1.62	0.56			

Abbrevations: OR, odds ratio; CI, confidence interval; BMI, Body Mass Index.
Trends (p=0.01-0.05) are displayed in italic and sigificant values (p<0.01) in bold.

Risk factors for late GI toxicity

Distance of the tumour > 10 cm from the anal verge, absence of a stoma at time of questionnaire and treatment with concurrent chemotherapy showed a trend for increased risk of severe late GI toxicity (Supplementary Table S5). Patients with a tumour more than 10 cm from the anal verge more often reported late GI toxicity compared with tumours < 10 cm (53.5% vs. 25.5%, p=0.04). Half of patients without a stoma experienced symptoms vs. 27.1% with a stoma (p=0.04) and

none of the 10 patients without concurrent chemotherapy experienced late GI toxicity (p=0.03). No difference was observed for sex, age, smoking status, BMI, fraction size, prior abdominal surgery or surgical complications.

Review of the literature

The search of the literature resulted in 351 articles between March 2010 and March 2020 of which 16 complied with the inclusion criteria. Fourteen studies from nine different groups reported on constraints for small bowel loops [8,19-30] and five studies on constraints for the RTOG bowelbag.[23,28,31-33] There were no studies reporting on constraints for the bowelbag following the EMBRACE definition. The results are displayed in Table 3.

Small bowel loops

For rectal cancer, most studies reported a constraint for V15Gy. Reis et al. and Gunnlaugsson et al. reported constraints for acute grade ≥ 2 toxicity while the group of Robertson et al. and Banerjee et al. focused on grade ≥ 3 toxicity.[8,19,20,23] Notably, the constraints for grade ≥ 2 were not higher than for grade ≥ 3. The V15Gy was reported most consistently and a weighted mean resulted in a constraint for V15Gy of 164.5 cc (95%CI 157.5-171.4). For gynaecologic malignancies constraints for V15Gy, V30Gy and V40Gy were frequently reported and also included constraints for late GI toxicity. The group of Chopra et al. reported more strict constraints in comparison to the group of Isohashi et al. with a constraint for V30Gy of 190 cc compared to 300 cc for late grade ≥ 3 GI toxicity.[28,31]

EMBRACE bowelbag

There are no studies yet reporting on constraints for the new definition of the EMBRACE group for bowelbag. The study by Roeske et al. which was already included in the Quantec paper, reports constraints of V33.8Gy < 396 cc and V45Gy < 195 cc for acute grade ≥ 2 diarrhea (0%) using a small bowelbag.[34] The definition used by Roeske et al. includes the outer contour of the small bowel loops and is therefore smaller than from EMBRACE bowelbag which also includes the large bowel loops. However, the constraints could still be used for the EMBRACE bowelbag and will be relatively safe because of a smaller volume.

RTOG bowelbag

Only one study reported a dose constraint for the RTOG-BB in patients with rectal cancer. Banerjee et al. advise a V15Gy < 830 cc for acute grade ≥ 3 diarrhea.[23] The suggested constraint for late GI toxicity in gynaecologic malignancies is more consistent for RTOG-BB than for small bowel loops and a V30Gy < 900-940 cc is advised by Chopra et al. and Isohashi et al.[28,31]

Table 3. Review table: constraints for Small bowel loops and RTOG bowelbag

Small bowel loops	N	Radiation technique	RT dose*	Concurrent chemotherapy	Toxicity endpoint (RA^)	Constraints (cc)									
						V5	V10	V15	V20	V25	V30	V35	V40	V45	V50
Rectal cancer															
Reis 2015[19]	45	3D CRT	50.4 Gy	Capecitabin, irinotecan and cetuximab	Acute diarrhea gr ≥ 2 (<30%)	292									
					Acute diarrhea gr ≥ 2 (ns)		322	125	97	14	10				
Gunnlaugsson 2007[20]	28	3D CRT	50 Gy	5FU/oxaliplatin	Acute diarrhea gr ≥ 2 (<10%)			150							
Robertson 2008[$, 22]	96	3D CRT	45 Gy	5FU	Acute diarrhea gr ≥ 3 (<10%)	425	265	120	112	105	92	85	71		
Robertson 2010[$, 8]	152	3D CRT	45 Gy	5FU	Acute diarrhea gr ≥ 3 (<10%)			130							
Banerjee 2012[23]	67	3D CRT	50.4 Gy	5FU	Acute diarrhea gr ≥ 3 (<10%)			275		190					
Gynecologic malignancies															
Lee 2014[24]	95	3D CRT	45-50.4 Gy ± VBT	66%(ns)	Acute diarrhea gr ≥ 2 (<10%)			290	Without PAS				75	With PAS	
Chopra 2014[$$, 25]	71	IMRT/3D CRT	50 Gy+VBT	Cisplatin	Late GI gr ≥ 2 (<10%)						190		150		
					Late GI gr ≥ 3 (<5%)			275			190		150		
Chopra 2015[$$, 31]	103	IMRT/3D CRT	50 Gy+VBT	Cisplatin	Late GI gr ≥ 3 (<5%)			275			190		150		
Isohashi 2013[$$$, 26]	97	IMRT/ 3D CRT/2D	50 Gy	Nedaplatin	Late GI gr ≥ 2 (<5%)								340		
					Late GI gr ≥ 2 (ns)			380			360			340	
Isohashi 2015[$$$, 27]	62	IMRT/3D CRT	50 Gy	Nedaplatin	Late GI gr ≥ 2 <5%								340		
Isohashi 2016[$$$, 28]	135	IMRT/ 3D CRT/2D	50 Gy/ 50.4 Gy	Nedaplatin	Late GI gr ≥ 3 <10%						300				
Anal cancer															
Olsen 2017[29]	52	IMRT	42-54 Gy	5FU+MMC	Acute GI gr ≥ 2 (ns)					186	155	41	30		
Prostate Cancer															
Sini 2017[30]	206	TOMO/ IMAT/IMRT	51.8 Gy (WPRT)	35% HT	Acute loose stools; PROM (<20%)				470		245		110		

Table 3. (continued) Review table: constraints for Small bowel loops and RTOG bowelbag

RTOG bowelbag	N	Radiation technique	RT dose*	Concurrent chemotherapy	Toxicity endpoint (RA^)		Constraints (cc)									
							V5	V10	V15	V20	V25	V30	V35	V40	V45	V50
Rectum																
Banerjee 2012[23]	67	3D CRT	50.4 Gy	5FU	Acute diarrhea	gr ≥ 3 (<10%)			830		650					
Gynecologic malignancies																
Chopra 2015[$$, 31]	103	IMRT/3D CRT	50 Gy+VBT	Cisplatin	Late GI	gr ≥ 3 (<5%)			1200			900		750		
Isohashi 2016[$$$, 28]	135	IMRT/ 3D CRT/2D	50-50.4 Gy	Nedaplatin	Late GI	gr ≥ 3 (ns)						940		850	800	
Bladder																
Søndergaard 2014[32]	116	IMRT/ 3D CRT/2D	60 Gy	ns	Acute diarrhea	gr ≥ 2 (<30%)									200	
					Acute diarrhea	gr ≥ 2 (<50%)									600	
Retroperitoneal sarcoma																
Mak 2016[33]	56	IMRT/3D CRT	21.6-58.1 Gy	18% ns	Acute GI	gr ≥ 2 (<50%)					650	430				

No studies were found that described constraints for EMBRACE-BB.

Abbreviations: 3D CRT, 3d conformal radiotherapy; IMRT, intensity modulated radiotherapy; TOMO, helical tomography; IMAT, intensity modulated arc therapy; WPRT, whole pelvis radiotherapy; HT, hormonal therapy; PROM, patient reported outcome measures; VBT, vaginal brachytherapy; RA, risk assessment; ns, not specified; PAS, prior abdominal surgery.

* prescribed physical in conventional fractions of 1.8 or 2 Gy per fraction.

^ Risk of toxicity was rouded to 5% intervals.

$/$$/$$$ Follow-up publications of the same cohort.

Three studies on anal cancer reported on the bowel cavity as defined by Devisetty et al. which is similar to the RTOG-BB. It includes the bowel cavity, limited by the abdominal wall ventrally and the maximum extent of bowel laterally and dorsally, including the sigmoid. A V30Gy of < 300/310 cc is advised to reduce the risk of acute grade ≥ 3 toxicity and of < 450 cc for grade ≥ 2 toxicity.[35-37]

DISCUSSION

This study evaluated different recommendations for bowel contouring and the dose-response relationship as well as clinical risk factors for gastrointestinal toxicity in locally advanced rectal cancer patients treated with neoadjuvant (chemo)radiotherapy and TME surgery. The main clinical risk factor for acute toxicity was prior abdominal surgery while concurrent chemotherapy was the only significant predictor for late GI toxicity. These factors have been previously reported.[18,24,31,38,39] Other known factors such as BMI or smoking could not be confirmed with our data.[40]

Prior abdominal surgery could influence the mobility of bowel loops and therefore have a great influence of dose to the bowel. This is also illustrated by the relatively strict dose constraint reported by Lee et al. for patients with prior abdominal surgery.[24] The group of Robertson et al. also recognised the difference between patients treated with preoperative and postoperative chemoradiotherapy in their cohort, whit a risk of 7% in pre-operative patients compared with 13% in postoperative patients with the same constraints.[8]

The observed toxicity and the range in SBL V5Gy-V50Gy in our study was similar to other studies, but a statistically significant dose-response effect for GI toxicity was not detected.[8,9,23] There are a number of reasons which could explain the absence of any dose response on our cohort: The influence of other risk factors could have overshadowed the dose-response relationship. Grade 2 toxicity might have been underreported in patients' charts and the size of the study population could still be too small to detect a significant association. Furthermore, gastrointestinal toxicity, partly originates from chemotherapy, the tumour itself and radiation proctitis. For late toxicity, the resection can cause symptoms as well, making it difficult to clearly distinguish the symptoms that have been caused by radiation.

We do believe that there is enough evidence in the literature to support a dose-response effect for bowel and we performed a review of the literature to update the current constraints reported by the Quantec group.[18] The review table provides constraints from different tumour sites for small bowel loops and the bowelbag contoured according to RTOG guidelines. Studies reporting both SBL and RTOG bowelbag demonstrated a superior discriminative ability for SBL.[9,18,23,26-28] Small bowel loop contouring is therefore still considered the gold standard. However, individual bowel loop contouring is time consuming and fails to take bowel motion into account. Previous studies have shown that only 20% of delineated bowel correlate with actual loops during treatment.[10,11]

A planning risk volume using an expansion of 1-3 cm to the small bowel loops could compensate for bowel mobility, but use of an alternative structure such as the bowelbag is a more attractive approach.[10,11]

We showed that both EMBRACE-BB and RTOG-BB are significantly correlated to dose to the small bowel loops and thus could be used as an alternative. The EMBRACE bowelbag has some advantages over the RTOG bowelbag in treatment of rectal cancer: (1) It DVHs show the strongest correlation with the SBL DVHs $\rho=0.9$ $p<0.001$; (2) It has no overlap with the CTV whereas RTOG bowelbag includes the proximal rectum and pre-sacral regions; (3) it excludes large areas which never contain bowel loops (especially retro-peritoneal) and (4) It will allow for comparison with toxicity data of the EMBRACE II which are expected to provide prospective dose-response data for a large cohort of cervical cancer patients. We therefore suggest to use the EMBRACE-BB in rectal cancer patients in future studies.

The correlation of small bowel loops with EMBRACE-BB and RTOG-BB allows us to roughly estimate constraints for EMBRACE-BB and RTOG-BB from SBL constraints. We tested the correlation equations (provided in Table S2) on three studies that reported constraints for SBL as well as RTOG-BB.[23,28,31] The constraints of Banerjee et al. for SBL V15Gy and V25Gy would correlate to a constraint for RTOG-BB V15Gy < 1147 cc and V25Gy < 337.8 cc. This shows that the equation results in an overestimation of V15Gy and an underestimation of V25Gy. This difference could be explained by the relatively large spread in RTOG-BB values around the fitted line (see Figure 3). In the gynaecologic studies (Chopra et al. and Isohashi et al.) the calculated constraints were more in concordance to the reported data. Because the EMBRACE bowelbag showed a very high correlation to SBL, we are fairly confident about the reported equations for EMBRACE-BB and prefer to use these rather than the RTOG-BB.

A recent review on small bowel toxicity concluded that all dose levels (V5Gy-V50Gy) are relevant for small bowel toxicity.[9] The V15Gy is most often reported in literature and has the largest discriminating potential for acute toxicity (see Table 3). When using these constraints in clinical practice it is however important to realise that these constraints arise mostly from 3D conformal radiotherapy studies. With implementation of intensity modulated and volumetric arc therapies the dose distributions have changed substantially with reduction of high dose regions at the cost of increase of low dose areas.

Based on the literature review we would advise a constraint for acute grade 2-3 GI toxicity for patients with rectal cancer for V15Gy of 165 cc for SBL. With the correlations found in the current study, this would lead to a V15Gy of 356 cc for delineations according to the EMBRACE-BB. These constraints need to be validated in future studies using modern radiotherapy techniques.

CONCLUSION

The bowelbag as defined by EMBRACE guidelines is highly suitable as a fast and practical bowel contouring alternative to small bowel loops. Also, our data confirms the influence of clinical risk factors such as chemotherapy and prior abdominal surgery on GI toxicity. Future research on NTCP models should include these risk factors and aim to validate the suggested dose constraint for EMRBACE bowelbag V15Gy of 350 cc using modern radiotherapy techniques.

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SUPPLEMENTARY MATERIAL

Supplementary file. TME questionnaire items

Items of the Questionnaire on Bowel and Urinary Function
Bowel function
Mean bowel frequency at day and night
Description stool
Anal blood and mucus loss
Faecal incontinence at day and night
Use of pads for faecal incontinence
Ability to delay bowel emptying
Stoma function
Peristomal skin irritation
Stoma smell
Stoma bleeding
Stoma leakage
Painful stoma
Noisy stoma
Blood and mucus loss from stump
Impact of bowel dysfunction on
Work or household activities
Activities outside the house like shopping
Social activities like theatre or cinema visiting
Hospitalisation for bowel related problems
Urinary function
Urinary frequency during the day
Frequency urinary incontinence
Relation of urinary incontinence to stress and urge
Use of pads for urinary incontinence
Urine-retention after miction
Need to urinate again within 2 hours
Stream hesitation
Difficulty postponing miction
Weak urinary stream
Difficult to start miction
Satisfaction with bowel and urinary function

Supplementary file. Definition of severe late GI toxicity

Symptom/question	Definition	Rational
Stool frequency	≥ 10 (no stoma) > 4 bags per day (stoma)	Severe CTCAE gr 3: more than 7 increased over baseline. Baseline is assumed to be 1-3 in rectal cancer patients
Stool frequency night	≥ 3 (no stoma)	
Stool consistency	Watery stools (stoma or no stoma) in combination with dissatisfaction or limitation of ADL	Watery stool was categorised as moderate to severe if patients reported problems in daily living of dissatisfaction.
Noisy stoma	Often / always in combination with dissatisfaction or limitation of ADL	Category 3-4 from 4-point Likert scale. (“not at all” / “sometimes” were considered not/mild)
Smelly stoma	Often / always in combination with dissatisfaction or limitation of ADL	Category 3-4 from 4-point Likert scale. (“not at all” / “sometimes” were considered not/mild)
Satisfaction with stools	Unsatisfied - Excluding proctitis related symptoms (urgency, rectal blood loss, incontinence)	Symptoms as urgency or incontinence were considered to have major impact on satisfaction but not related to bowel
Limited in activities of daily living (ADL) by bowel	Mostly / very much - Excluding proctitis related symptoms (urgency, rectal blood loss, incontinence)	Symptoms as urgency or incontinence were considered to have major impact on ADL but not related to bowel
Hospitalisation	Every hospitalisation for bowel related symptoms (severe diarrhoea, abscess, fistula, obstruction included; wound dehiscence, rectal blood loss etc. excluded)	Hospitalisation = grade 3

Table S1. Baseline characteristics

	n / mean	%* (range)
Total	157	100.0%
Center		
LUMC	97	61.8%
HMC	60	38.2%
Sex		
Male	86	54.8%
Female	71	45.2%
Age	64	(25 - 92)
BMI (kg/m2)	25.4	(17.0 - 44.4)
Active smoker		
yes	31	19.7%
no	111	70.7%
IBD		
yes	2	1.3%
no	154	98.1%
Prior abdominal surgery		
yes	56	35.7%
no	96	61.1%
cT-Stage		
cT2	8	5.1%
cT3	104	66.2%
cT4	44	28.0%
cN-stage		
cN0	31	19.7%
cN1	74	47.1%
cN2	45	28.7%
Distance from anal verge		
< 10 cm	114	72.6%
> 10 cm	32	20.4%
EBRT Dose (Gy)	49.9	(44.0 - 52.0)
EBRT fraction size		
1.8 Gy/fraction	24	15.3%
2.0 Gy/fraction	133	84.7%
Concurrent chemotherapy		
No chemotherapy	24	15.3%
Capecitabine	116	73.9%
Capecitabin + oxaliplatin/bevacizumab	17	10.9%
Stoma pre-CRT		
yes	49	31.2%
no	108	68.8%
Type of surgery		
LAR	24	15.3%
APR	102	65.0%
Hartmann	19	12.1%
Proctocolectomy	1	0.6%
No resection	8	5.1%
Intraoperative radiotherapy		
yes	8	5.1%
no	149	94.9%
Complications after resection		
yes	49	31.2%
no	89	56.7%

Table S1. Baseline characteristics

* Due to missing numbers, percentages do not add up to 100%.

Table S2. Correlation of EMBRACE-BB and RTOG-BB with SBL

Correlation of SBL(Vx) with EMBRACE-BB(Vx)

SBL(Vx)	pearson ρ	p-value	equation
V5Gy	0.86	<0.001	E-BB(Vx) = SBL(Vx) × 1.75 + 143
V10Gy	0.88	<0.001	E-BB(Vx) = SBL(Vx) × 1.69 + 117
V15Gy	0.90	<0.001	E-BB(Vx) = SBL(Vx) × 1.69 + 78.4
V20Gy	0.92	<0.001	E-BB(Vx) = SBL(Vx) × 1.66 + 53.1
V25Gy	0.92	<0.001	E-BB(Vx) = SBL(Vx) × 1.63 + 28.1
V30Gy	0.90	<0.001	E-BB(Vx) = SBL(Vx) × 1.66 + 18.6
V35Gy	0.90	<0.001	E-BB(Vx) = SBL(Vx) × 1.57 + 15.6
V40Gy	0.91	<0.001	E-BB(Vx) = SBL(Vx) × 1.51 + 13.9
V45Gy	0.91	<0.001	E-BB(Vx) = SBL(Vx) × 1.46 + 11.3
V50Gy	0.87	<0.001	E-BB(Vx) = SBL(Vx) × 1.41 + 4.3

Correlation of SBL(Vx) with RTOG-BB(Vx)

SBL(Vx)	pearson ρ	p-value	equation
V5Gy	0.65	<0.001	R-BB(Vx) = SBL(Vx) × 1.81 + 816
V10Gy	0.66	<0.001	R-BB(Vx) = SBL(Vx) × 1.74 + 742
V15Gy	0.69	<0.001	R-BB(Vx) = SBL(Vx) × 1.86 + 635
V20Gy	0.71	<0.001	R-BB(Vx) = SBL(Vx) × 2.00 + 547
V25Gy	0.68	<0.001	R-BB(Vx) = SBL(Vx) × 2.19 + 434
V30Gy	0.65	<0.001	R-BB(Vx) = SBL(Vx) × 2.44 + 389
V35Gy	0.63	<0.001	R-BB(Vx) = SBL(Vx) × 2.36 + 371
V40Gy	0.60	<0.001	R-BB(Vx) = SBL(Vx) × 2.33 + 358
V45Gy	0.58	<0.001	R-BB(Vx) = SBL(Vx) × 2.30 + 342
V50Gy	0.52	<0.001	R-BB(Vx) = SBL(Vx) × 3.47 + 177

Abbreveations: SBL, small bowel loops; BB, bowelbag; E-BB, Embrace-BB; R-BB, RTOG-BB.

Table S3. Dose response analyses for acute GI toxicity

	< grade 2 n=85		≥ grade 2 n=70			MW
	Median	**(IQ range)**	**Median**	**(IQ range)**	**Δ median**	**p-value**
Small Bowel loops						
V5Gy [cc]	196.1	(110.8 - 315.1)	249.2	(123.5 - 343.4)	53.2	0.20
V10Gy [cc]	161.8	(77.9 - 301.2)	210.3	(106.8 - 320.9)	48.4	0.25
V15Gy [cc]	117.0	(55.8 - 245.1)	176.1	(47.5 - 261.7)	59.1	0.35
V20Gy [cc]	79.5	(29.7 - 185.1)	123.1	(11.7 - 202.1)	43.6	0.56
V25Gy [cc]	38.0	(8.1 - 89.3)	49.7	(6.6 - 97.7)	11.8	0.68
V30Gy [cc]	27.2	(3.2 - 61.6)	31.6	(3.2 - 71.2)	4.4	0.81
V35Gy [cc]	21.6	(1.7 - 47.7)	24.7	(2.0 - 61.7)	3.2	0.80
V40Gy [cc]	17.0	(0.6 - 40.1)	20.2	(0.6 - 52.2)	3.2	0.71
V45Gy [cc]	12.2	(0.0 - 33.9)	13.1	(0.3 - 44.7)	0.8	0.60
V50Gy [cc]	1.3	(0.0 - 14.6)	0.2	(0.0 - 13.3)	-1.1	0.91
EMBRACE bowelbag						
V5Gy [cc]	496.9	(259.6 - 772.1)	568.3	(365.2 - 786.1)	71.3	0.23
V10Gy [cc]	421.0	(186.0 - 664.8)	466.8	(285.3 - 656.9)	45.8	0.24
V15Gy [cc]	278.0	(132.1 - 501.7)	371.5	(134.5 - 559.7)	93.6	0.24
V20Gy [cc]	208.4	(61.9 - 377.4)	271.0	(71.8 - 438.3)	62.6	0.39
V25Gy [cc]	78.3	(23.6 - 198.4)	95.8	(23.1 - 218.0)	17.5	0.60
V30Gy [cc]	56.1	(14.5 - 148.4)	59.6	(13.5 - 158.3)	3.5	0.67
V35Gy [cc]	44.0	(8.2 - 104.3)	43.9	(9.8 - 136.7)	-0.1	0.68
V40Gy [cc]	38.2	(4.8 - 78.5)	36.4	(6.0 - 119.9)	-1.8	0.65
V45Gy [cc]	32.5	(2.2 - 67.9)	30.6	(2.8 - 103.8)	-1.9	0.62
V50Gy [cc]	5.3	(0.0 - 24.0)	1.3	(0.0 - 17.6)	-4.0	0.53
RTOG bowelbag						
V5Gy [cc]	1158.8	(866.3 - 1536.2)	1272.6	(1018.8 - 1549.8)	113.8	0.16
V10Gy [cc]	1066.8	(708.0 - 1375.5)	1111.1	(879.0 - 1409.6)	44.3	0.17
V15Gy [cc]	912.6	(595.6 - 1197.4)	974.1	(737.5 - 1193.2)	61.5	0.21
V20Gy [cc]	724.9	(518.8 - 996.7)	793.0	(569.0 - 1067.8)	68.1	0.31
V25Gy [cc]	505.2	(368.2 - 725.6)	566.8	(423.2 - 712.3)	61.6	0.34
V30Gy [cc]	471.6	(302.8 - 653.9)	498.1	(368.8 - 626.8)	26.5	0.43
V35Gy [cc]	430.7	(280.9 - 612.3)	469.5	(352.5 - 557.6)	38.8	0.36
V40Gy [cc]	401.8	(260.4 - 572.2)	449.6	(342.9 - 525.5)	47.9	0.36
V45Gy [cc]	380.3	(230.7 - 532.8)	424.8	(319.2 - 501.1)	44.5	0.38
V50Gy [cc]	189.5	(89.7 - 308.5)	202.7	(102.7 - 272.3)	13.2	0.74

Abbreviations: MW, Mann Whitney; IQ-range, Inter quartile range.

Table S4. Dose response analyses for severe late GI toxicity

	No late GI toxicity n=50		Severe late GI toxicity n=23			MW
	Median	**(IQ-range)**	**Median**	**(IQ-range)**	**Δ median**	**p-value**
Small Bowel loops						
V5Gy [cc]	225.5	(86.7 - 365.5)	213.5	(115.7 - 366.8)	-12.0	0.80
V10Gy [cc]	199.3	(66.3 - 321.3)	176.0	(89.1 - 328.6)	-23.2	0.80
V15Gy [cc]	164.6	(34.3 - 280.3)	117.0	(65.2 - 251.0)	-47.6	0.80
V20Gy [cc]	103.4	(16.4 - 226.9)	81.1	(21.3 - 202.2)	-22.4	0.90
V25Gy [cc]	39.7	(4.6 - 98.6)	28.1	(10.4 - 95.2)	-11.6	1.00
V30Gy [cc]	27.1	(0.3 - 75.4)	25.4	(6.9 - 73.8)	-1.7	0.90
V35Gy [cc]	21.1	(0.0 - 66.1)	11.6	(3.9 - 51.3)	-9.5	0.90
V40Gy [cc]	18.6	(0.0 - 62.0)	10.4	(1.8 - 45.3)	-8.1	0.90
V45Gy [cc]	14.3	(0.0 - 56.8)	9.0	(0.2 - 37.0)	-5.3	0.80
V50Gy [cc]	0.8	(0.0 - 13.6)	0.0	(0.0 - 14.3)	-0.8	0.70
EMBRACE bowelbag						
V5Gy [cc]	560.7	(248.3 - 816.4)	547.5	(274.6 - 699.6)	-13.2	0.70
V10Gy [cc]	472.3	(169.2 - 723.3)	450.5	(220.4 - 611.5)	-21.7	0.60
V15Gy [cc]	370.1	(120.0 - 628.5)	334.4	(184.2 - 479.8)	-35.8	0.40
V20Gy [cc]	265.2	(68.1 - 451.7)	208.9	(69.5 - 391.7)	-56.2	0.80
V25Gy [cc]	95.8	(23.8 - 218.0)	55.6	(21.4 - 208.2)	-40.2	0.70
V30Gy [cc]	69.7	(12.8 - 165.0)	48.5	(13.4 - 151.3)	-21.2	0.80
V35Gy [cc]	57.7	(7.5 - 134.8)	42.4	(10.2 - 117.9)	-15.3	0.70
V40Gy [cc]	48.2	(3.7 - 119.2)	39.1	(6.8 - 86.1)	-9.1	0.80
V45Gy [cc]	37.6	(1.8 - 92.2)	32.8	(2.9 - 76.6)	-4.8	0.80
V50Gy [cc]	3.7	(0.0 - 41.7)	4.0	(0.0 - 20.5)	0.3	0.70
RTOG bowelbag						
V5Gy [cc]	1180.7	(871.8 - 1565.2)	1167.7	(892.8 - 1587.5)	-13.0	1.00
V10Gy [cc]	1089.1	(784.2 - 1419.6)	1036.0	(756.3 - 1418.7)	-53.1	0.90
V15Gy [cc]	951.0	(688.5 - 1217.3)	866.0	(644.8 - 1292.5)	-85.0	0.80
V20Gy [cc]	825.5	(510.8 - 1010.9)	724.9	(461.3 - 1169.7)	-100.5	1.00
V25Gy [cc]	536.5	(364.7 - 724.9)	566.4	(381.8 - 750.4)	29.9	0.90
V30Gy [cc]	482.6	(310.3 - 656.2)	531.5	(360.0 - 681.1)	48.9	0.70
V35Gy [cc]	460.5	(272.4 - 608.4)	424.2	(326.5 - 606.9)	-36.3	0.90
V40Gy [cc]	439.6	(259.1 - 571.0)	386.5	(296.5 - 579.1)	-53.2	0.90
V45Gy [cc]	411.6	(241.4 - 527.8)	377.4	(269.2 - 547.5)	-34.2	0.90
V50Gy [cc]	192.6	(87.7 - 354.4)	169.4	(89.1 - 275.7)	-23.2	0.60

Abbreviations: MW, Mann Whitney; IQ-range, Inter quartile range.

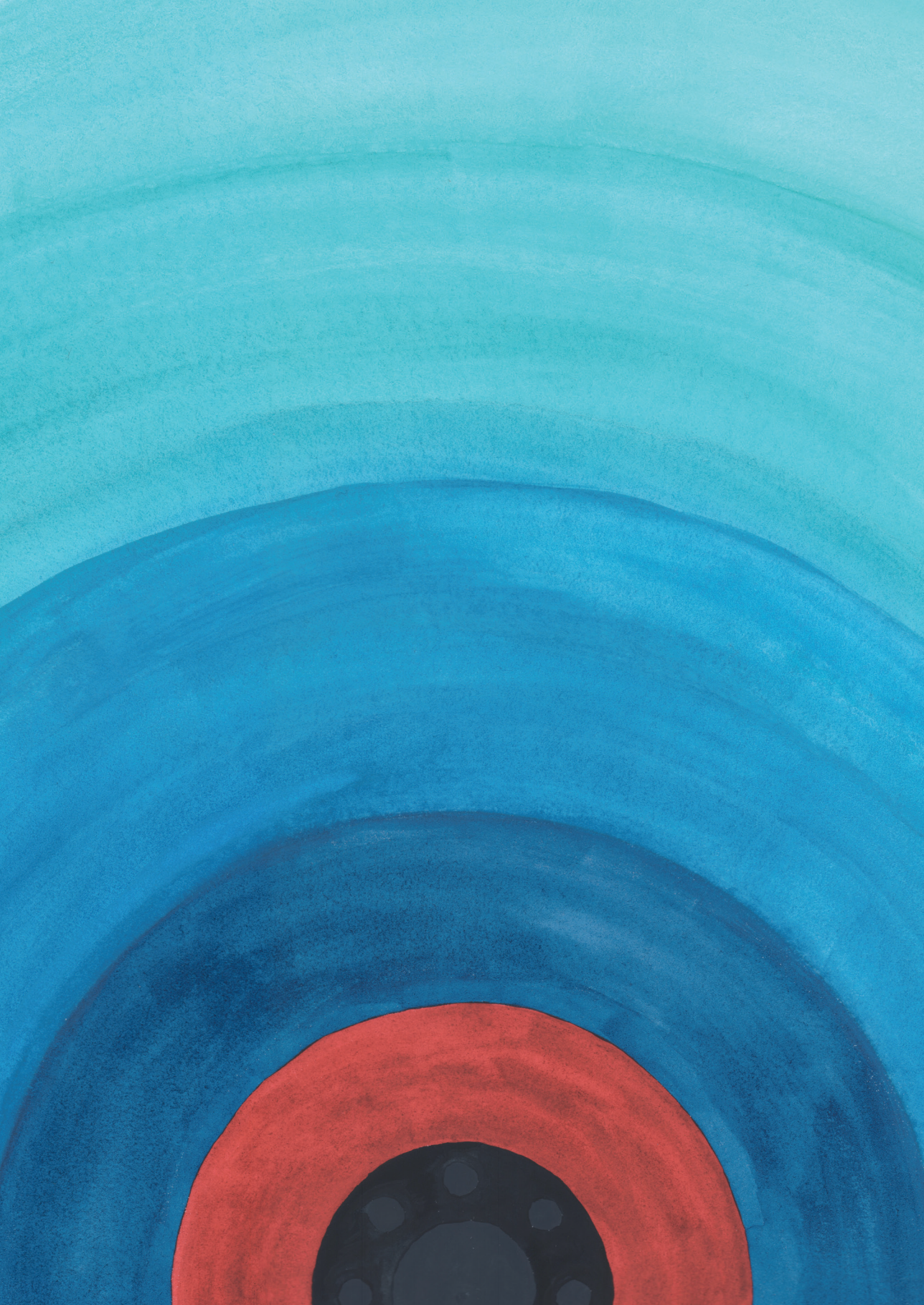
Table S5. Logistic regression for severe late GI toxicity

				Late GI toxicity		
		n/mean	**%/(range)**	**OR**	**(95% CI)**	**p-value**
Sex	Female vs. male	26	35.6%	0.71	(0.25 - 2.05)	0.53
Age	years	63	(25 - 83)	1.00	(0.95 - 1.05)	0.95
Active smoker	yes vs. no	13	19.1%	0.84	(0.23 - 3.10)	0.80
BMI	kg/m2	25.1	(17.7 - 36.2)	1.02	(0.90 - 1.16)	0.75
Tumour level	> 10 cm	15	20.5%	3.34	(1.01 - 11.02)	*0.05*
Concurrent chemotherapy	yes vs. no	63	86.3%	12.19	(1.45 - 1593.4)	*0.02**
Prior abdominal surgery	yes vs. no	29	39.7%	0.79	(0.28 - 2.22)	0.65
Type of resection	LAR	15	20.5%	1.00		0.12
	APR	46	63.0%	0.28	(0.08 - 0.93)	*0.04*
	Hartmann	12	16.4%	0.44	(0.09 - 2.11)	0.30
Complications after resection	yes vs. no	23	32.9%	2.67	(0.94 - 7.63)	0.07
Stoma	yes vs. no	59	80.8%	0.37	(0.11 - 1.23)	0.10
Acute GI toxicity	grade ≥ 2	31	42.4%	0.76	(0.28 - 2.09)	0.59

* Firth regression (likelihood ratio test).

Abbreveations: BMI, Body Mass Index.

Trends (p=0.01-0.05) are displayed in italic and sigificant values (p<0.01) in bold.



Chapter 3

Endorectal brachytherapy boost after external beam radiotherapy in elderly or medically inoperable patients with rectal cancer: Primary outcomes of the phase I HERBERT study

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ABSTRACT

Purpose

To evaluated toxicity and efficacy of the combination of external beam radiotherapy (EBRT) followed by high dose rate endorectal brachytherapy (HDREBT) boost in elderly and medically inoperable patients with rectal cancer.

Material and Methods

A phase I dose escalation study was performed. Treatment consisted of EBRT (13×3 Gy) followed by three weekly brachytherapy applications six weeks later. HDREBT dose started at 5 Gy per fraction, increasing with 1 Gy per fraction if dose limiting toxicity (DLT, defined as > grade 3 proctitis < 6 weeks after HDREBT) occurred in ≤ 2 patients per dose level. The primary endpoint was the maximum tolerated dose, defined as 1 dose-level below the dose were three patients experienced DLT. Secondary endpoints were toxicity, clinical tumour response, freedom from local progression and local progression free and overall survival (L-PFS and OS).

Results

Thirty-eight patients with a median age of 83 years were included in the study. Thirty-two were evaluable for DLT and late toxicity and 33 for response evaluation. Maximum delivered dose was 8 Gy per fraction resulting in a recommended dose of 7 Gy per fraction. Response occurred in 29 of 33 patients (87.9%) with 60.6% complete response (CR). L-PFS and OS were 42% and 63% at two years. Patients with CR showed a significant improved L-PFS (60% at 2 years, p=0.006) and a trend in improved OS (80% at 2 years, p=0.11). Severe late toxicity occurred in 10 of 32 patients.

Conclusion

We found that HDREBT after EBRT results in a high overall response rate, with improved L-PFS for patients with a CR. The high observed rate of severe late toxicity requires further evaluation of the risks and benefits of a HDREBT boost.

INTRODUCTION

The incidence of rectal cancer in elderly patients is increasing due to screening and aging of the population.[1,2] Although total mesorectal excision (TME surgery) with or without preoperative (chemo)radiation is the standard treatment for rectal cancer, the risk of surgical complications and postoperative mortality rises with increasing age and comorbidity. Postoperative complications occur in approximately 50% in patients older than 75 years and 1-month postoperative mortality in patients aged 75 to 95 with an American Society of Anaesthesiology classification of II to IV ranges from 5.4% to 28.0%. At 6 months this results in an overall mortality of 13.4% in patients aged 75 to 85, increasing to almost 30% in patients aged 85 to 95 years.[3] Because patients who are unfit for surgery are usually also unfit for chemotherapy, they are often offered palliative radiation therapy. However, there are indications that patients might benefit from a more radical approach using radiation therapy alone.[4]

To achieve local control with radiotherapy alone high doses are needed. With standard doses external beam chemoradiotherapy (EBRT, 45-50 Gy) a complete pathologic response is observed in approximately 16%.[5,6] Dose-response analyses indicate that doses as high as 92 Gy (equivalent dose in 2 Gy per fraction [EQD2]) are needed to achieve complete pathologic response in 50% of patients.[7]

Contact-X-ray radiation therapy, initially developed as monotherapy for small mobile tumours, can deliver high doses to the tumour surface and has been used in combination with EBRT in inoperable patients, with promising results.[8-11] An alternative to contact-X-ray is high-dose-rate endorectal brachytherapy (HDREBT), which was originally developed as preoperative treatment modality.[12,13] Endorectal brachytherapy combined with EBRT in inoperable patients has only been described in a few retrospective series.[14-16] Little is known regarding the optimal dose and toxicity profile, and various treatment schedules have been used. The HERBERT study was designed to evaluate the maximum tolerated endoluminal brachytherapy dose after EBRT in inoperable rectal cancer patients, with the aim to provide durable local tumour control. The aim of this analysis was to report both the primary outcome (maximum tolerated dose) and to evaluate tumour response, severe treatment related late toxicity and survival.

MATERIAL AND METHODS

This study was performed at the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, and the Leiden University Medical Center. Patients were treated with EBRT, followed by three weekly HDREBT applications six weeks after EBRT (Figure 1A). The primary outcome was the maximum tolerated HDREBT boost dose. A phase I dose escalation approach, based on an accelerated dose escalation design by Simon et al. was used.[17] Dose limiting toxicity (DLT) was specified as proctitis grade ≥ 3 occurring within 6 weeks after brachytherapy (CTCAE v3; 'stool incontinence or other symptoms interfering with ADL or operative intervention indicated').[18] Patients were entered in cohorts of six, starting at 5 Gy per fraction. Dose was increased with 1 Gy per fraction if no more than one patient experienced DLT. A dose level was expanded to nine patients if two patients experienced DLT. The maximum delivered dose was reached if three patients in 1 dose level experienced DLT. One dose level below this level is considered the maximum tolerated and recommended phase 2 dose. Additional patients were entered in this dose level to assure a safe toxicity profile.

Secondary endpoints were toxicity, clinical tumour response, freedom from local progression, local progression free survival (L-PFS) and overall survival (OS). The study was approved by the medical ethics committees and informed consent was obtained from all patients before treatment. The study was registered with the Dutch Central Committee on Research Involving Human Subjects; registration no. NL17037.031.07.[19]

Patient selection

Patients with histologically verified adenocarcinoma of the rectum, stage cT2-4N0-1M0-1, who were unfit for or refused surgical treatment were eligible. Pre-treatment evaluation included digital rectal examination, endoscopy, MRI or (if contra-indicated) CT of the pelvis, and endorectal ultrasound (EUS) on indication. To allow adequate insertion of the brachytherapy applicator, the tumour had to be within 15 cm of the anal verge and have a lumen of ≥ 2 cm. To avoid stenosis, tumour involvement of > 2/3 of the rectal circumference was not allowed. Exclusion criteria were; prior pelvic radiotherapy, chemotherapy or surgery for rectal cancer, WHO score ≥ 3, life-expectancy of < six months and inability to undergo rectoscopy.

External beam radiotherapy

Patients received 39 Gy EBRT (13×3 Gy, 4/wk) in the referring hospital. The clinical target volume (CTV) consisted of the gross tumour volume, rectum, mesorectum and internal iliac and presacral lymph nodes. The cranial border was at the level of S2 to S3 in low-lying tumours or the promontory. Margin from CTV to planning target volume was 1 cm. Treatment was planned and delivered according to institutional guidelines. A minimum of CT-based 3D-conformal radiotherapy was required, but more advanced techniques as intensity modulated radiotherapy

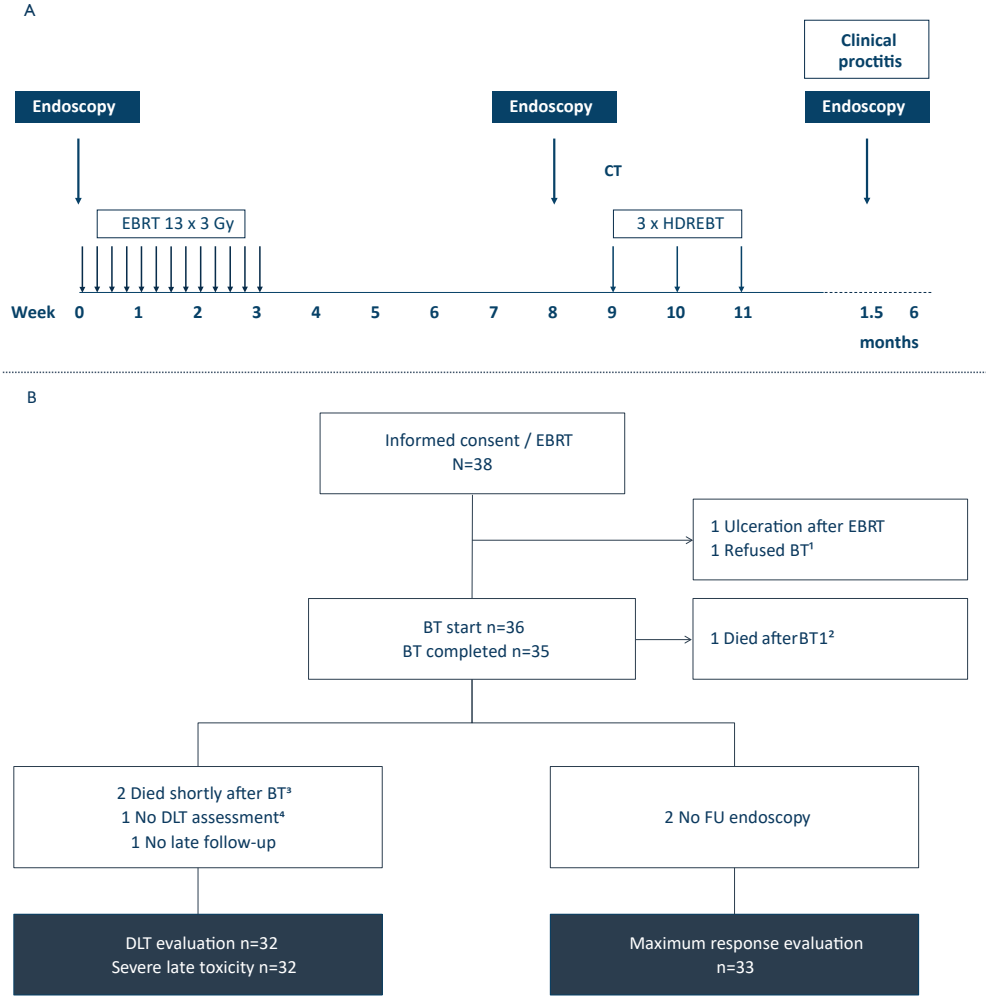

Figure 1. Study period (A) and flowchart (B).
(1) Patient refused brachytherapy after a period of dehydration and hospital admission after EBRT. (2) Patient died of cardiac arrest, not related to treatment. (3) Two other patients deceased of pulmonary causes (not related to treatment), both had cCR based on endoscopies during treatment or autopsy and were included in response evaluation. (4) Patient was included in analyses of late toxicity.
Abbreviations: HDREBT/BT, high-dose-rate brachytherapy; EBRT, external beam radiotherapy; FU, follow-up; DLT, dose limiting toxicity.

was allowed. Position verification could consist of either cone-beam-CT or megavolt/kilovolt orthogonal images. Dose distribution was in accordance to the recommendations of the International Commission on Radiation Units and Measurements report 62.

Brachytherapy

Brachytherapy equipment, treatment planning and positioning procedures were adapted from the McGill University Centre.[20] Prior to EBRT, endoluminal clips were inserted with a flexible rectosigmoidoscope at the proximal and distal end of the tumour for delineation and position verification purposes. A flexible applicator (Oncosmart®, Nucletron, Veenendaal, The Netherlands) of 2 cm diameter, with a central canal and 8 peripheral catheters, was inserted into the rectum. To fixate the applicator in the rectum and reduce dose to the contralateral wall, a semi-circular balloon was inflated over the applicator on the contralateral side. Delineation and treatment planning was performed on a planning CT with applicator in situ, acquired before the first application. The CTV was defined as residual macroscopic tumour or scarring after EBRT and was delineated by two radiation oncologists. In case of discrepancy, consensus was sought for the definitive CTV. Delineation was performed in Pinnacle3, version 9.0 (Philips Medical Systems, Fitchburg, Wisconsin U.S.A) and treatment planning with Oncentra Brachy (Elekta, Veenendaal, The Netherlands), using TG-43 dose calculation. The aim of treatment planning was complete coverage of the CTV by the 100% isodose, restricted to 2 cm from the applicator surface, avoiding hotspots in organs at risk (contralateral rectal wall, anal canal, vagina, bladder and bowel).
High-dose-rate endorectal brachytherapy was performed using a microSelectron HDR afterloader (Elekta) with an ^{192}Ir source. Verification of correct applicator positioning and determination of the indexer length was done by comparing the reference digitally reconstructed radiograph from the planning CT with anteroposterior and lateral radiographs, taken in treatment position.[20]

Follow up

Follow-up was done at two months, six months and yearly after HDREBT. Clinical tumour response was assessed on digital rectal examination and endoscopic evaluation and was classified in four categories; complete remission (CR), partial remission (PR; > 30% decrease), stable disease (SD) and progressive disease (PD; > 20% increase). Because of limited salvage options in this population, additional investigation such as MRI, biopsies or imaging for detection of distant metastases were not routinely performed but were left at the discretion of the treating physician. Toxicity was scored according to the CTCAE v3. Late treatment related toxicity was assessed in all patients with CR or PR > 90 days after treatment, with censoring in case of progression.

Statistical analyses

Statistical analyses were performed with SPSS v20.0 (IBM, Armonk,NY). Baseline characteristics between dose levels were compared using the one-way analysis of variance, χ^2 and Fisher's exact test. For reporting of DLT and severe late toxicity, descriptive statistics were used. The Kaplan Meier method and log-rank test were used for actuarial survival estimates. Freedom from local progression was defined as time from start of EBRT to local progression, with censuring at death or date of last follow-up. Local progression free survival and overall survival were defined as time from start of EBRT to local progression or death of any cause and death of any cause, respectively.

RESULTS

In total 38 patients were included between 2007 and 2013, of whom 32 were evaluable for toxicity endpoints and 33 for response analyses (Figure 1B). Patient, tumour and treatment characteristics are shown in Table 1. Nine patients were treated with 5 Gy per fraction, 5 with 6 Gy, 14 with 7 Gy and 10 with 8 Gy per fraction. Differences in number of patients per dose level arise from including additional patients in a dose level if the follow-up for the primary endpoint was not yet reached. Additional patients were entered in the 7-Gy dose level after 3 DLTs were observed in the 8-Gy dose level to assure safety. There were no statistically significant differences between patient characteristics in the different dose levels (Supplementary Table S1). Clinical target volume thickness at brachytherapy (median 1.0 cm) exceeded 2 cm in only two patients. A CTV D90 of > 97% of the prescribed dose was achieved in 78% of patients.

Table 1. Patient, tumour and treatment characteristics

Characteristics	**n**	**%**
Total	38	100%
Age (median range)	83	(57-94)
Gender		
Male	21	55.3%
Female	17	44.7%
WHO		
WHO 0	4	10.5%
WHO 1	15	39.5%
WHO 2	15	39.5%
Co-morbidities		
Cardiovascular co-morbidity	27	71.1%
Pulmonary co-morbidity	12	31.6%
Anticoagulant use	25	65.8%
TNM classification		
cT2N0M0	22	57.9%
cT2N1M0	1	2.6%
cT3N0M0	5	13.2%
cT3N1M0	8	21.1%
cT3N2M0	2	5.3%
Distance from anal verge		
0-5 cm	19	50.0%
5-10 cm	13	34.2%
10-15 cm	6	15.8%
Brachytherapy CTV	**median**	**range**
Thickness (cm)	1.0	(0.4-3.0)
Length (cm)	3.2	(1.8-6.4)
Volume (cc)	7.1	(2.0-25.0)
D90 (Gy)	7.1	(1.8-9.8)

Abbreviations: CTV, clinical target volume; WHO, World Health Organisation.

The population consisted mainly of elderly patients (31 of 38 patients ≥ 75 years), and/or patients assessed as medically inoperable (29 of 38). Most patients had severe comorbidity, with 31 of 38 patients classified as ASA III-IV. Almost all patients who were deemed medically operable but refused surgery were elderly (8 of 9 aged > 75 years).

One patient in the 5-Gy dose level and 3 in the 8-Gy dose level experienced a DLT. Maximum tolerated dose was set at 7 Gy. Details of DLT symptoms and subsequent course are summarised in Table 2.

Table 2. Dose limiting toxicity

Dose level	Dose limiting toxicity	Severe late toxicity
5 Gy	Proctitis limiting ADL; Pain, frequency and fatigue	Yes*
8 Gy	Rectal bleeding; Hospital admission; blood transfusion	Yes*
8 Gy	Proctitis limiting ADL: Pain (opioids needed); rectal bleeding gr 2.	Yes*
8 Gy	Proctitis limiting ADL. Pain, tenesmus and frequency.	Censored; PD

* acute proctitis did not resolve < 90 days and was also scored as severe late toxicity (Table 3).

Abbreviations: ADL, Activities of daily living; gr, grade; PD, progressive disease.

Response and Survival

At time of analysis 11 of 33 evaluable patients were alive with a median follow up of 30 months (range 21-86 months), of whom 8 were in complete remission at last follow-up. Clinical tumour response was observed in 29 of 33 patients (87.9%); 20 patients achieved CR and 9 PR. A recurrence developed in 6 of 20 patients with CR, while 6 of 9 patients with PR showed progression. Seventeen patients (51.5%) had a sustained response.

Median time to local progression was 9.3 months (range 4-32 months) and actuarial freedom from local progression at 1, 2 and 3 years was 71%, 55% and 44% respectively. Figure 2 shows the clinical tumour response and overall survival for evaluable patients (Supplementary Figure S1 shows all patients per dose level). Local progression free survival rates at 1, 2 and 3 years were 64%, 42% and 20%, and corresponding OS rates were 82%, 63% and 27%, respectively, with a median overall survival of 33.2 months (95% confidence interval 30.5-36.0 months).

For patients with a complete response, L-PFS was significantly improved in comparison to those with no or partial response, which corresponded with a trend in improved OS (Figure 3).

Late toxicity

In total 28 of 32 patients had a response to treatment and were evaluable for analyses of late severe toxicity. Nine patients (33%) experienced grade 3 toxicity and one patient (4%) experienced grade 4 toxicity, these toxicities are detailed in Table 3. In six patients, who all used anticoagulants, rectal bleeding grade 3 was observed. Four patients experienced severe rectal pain, which was caused by a deep ulcer at the tumour site.

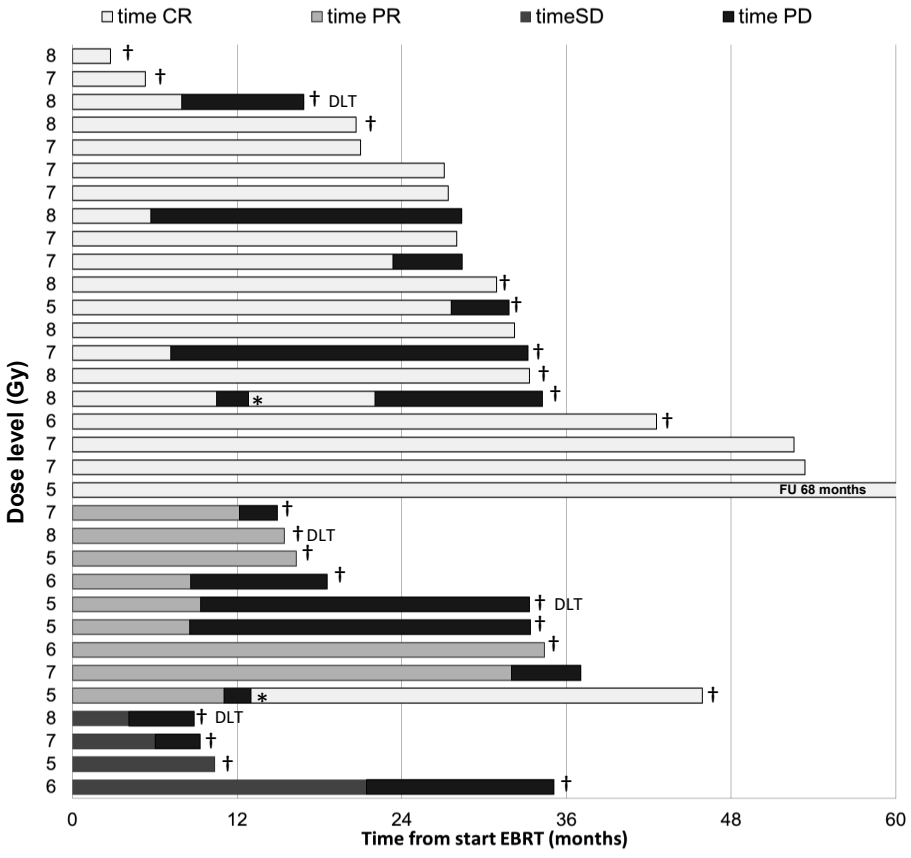

Figure 2. Response and overall survival.

* Two patients received salvage surgery. † Deceased.

Abbreviations: DLT, dose-limiting toxicity; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

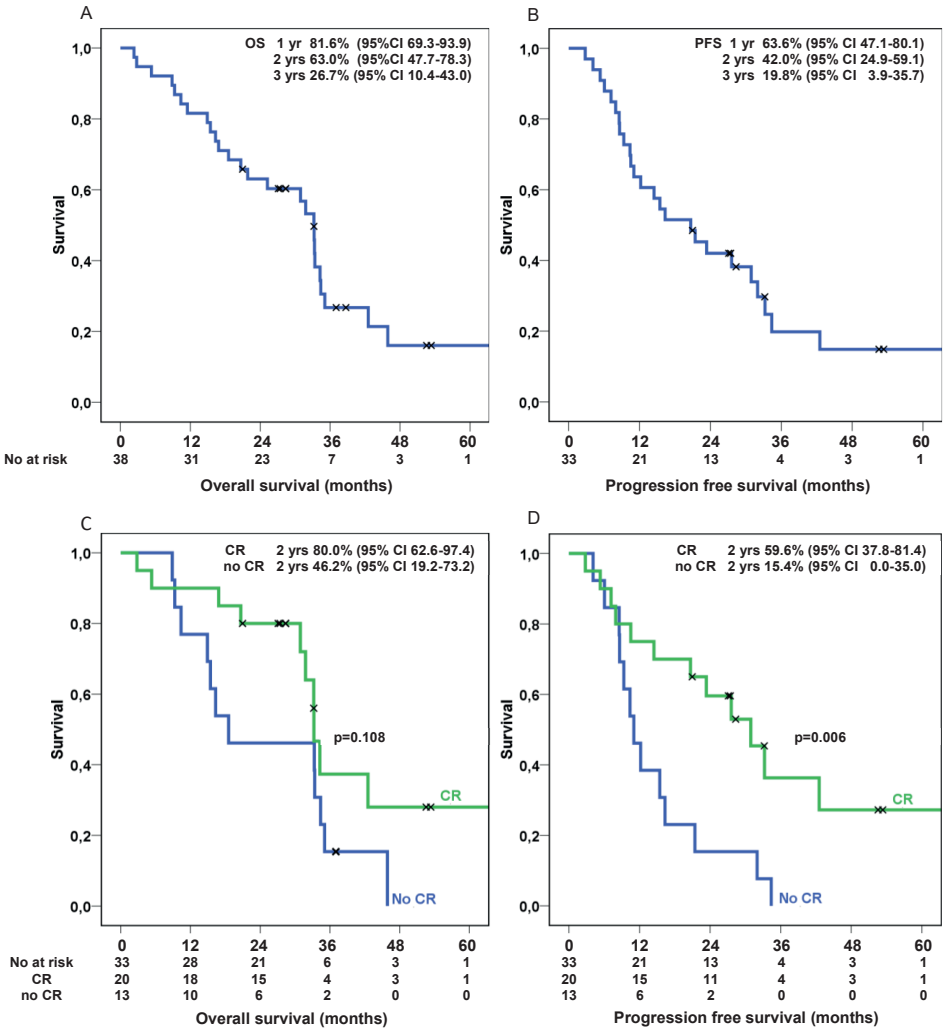

Figure 3. Overall survival (OS) and local progression-free survival (PFS) with subgroup analyses for patients with a complete response.

(A) Local progression-free survival (n=33). (B) Overall survival (n=38). (C) Local progression-free survival: comparison complete response versus no complete response (n=33). (D) Overall survival: comparison complete response versus no complete response (n=33).

Abbreviation: CI, confidence interval.

Table 3. Severe treatment-related late toxicity

Dose	Severe late toxicity (> 90 days, maximum score)	Proctitis grade 3 < 6 wks	Response	Time (months) *	Anti-coagulant use
5 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Pain, frequency and fatigue FU: PD at 7 months, proctitis grade 2.	yes	PR	1^	Aceno-coumarol
8 Gy	*Grade 3: Rectal bleeding* Symptoms: Hospital admission at 1 month; blood transfusion at 5 months. FU: PD at 9 months after HDREBT.	yes	CR	1^	Carbasalate calcium
8 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Pain; opioids needed and rectal bleeding. FU: Improvement at 7 months (gr 1-2 bleeding persisted)	yes	PR	1^	Carbasalate calcium
5 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Pain and incontinence FU: Salvage surgery at 8 months for PD.	no	PR	2^	-
7 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 5 months. FU: PD with severe rectal bleeding at 10 months.	no	PR	5	Phen-procoumon
7 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 6 months (Hb 3.1) FU: Grade 1-2 proctitis	no	CR	6	Carbasalate calcium
7 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Urgency, frequency and tenesmus Treatment: Multiple medical interventions. FU: Gr 2 proctitis; PD at 21 months for which a palliative stoma	no	CR	8	-
7 Gy	*Grade 4: Ulceration and rectocutaneous fistula* Symptoms: Pain, fatigue, rectal bleeding (transfusion) Treatment: Specialised wound care and HBOT. FU: Slight improvement, but fistula persisted (gr 3)	no	CR	12	-
7 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 19 months (Hb 3.5) FU: Grade 1 rectal bleeding	no	CR	19	Phen-procoumon
8 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 21 months (possible interference of coecum tumour (Hb3.5). FU: Grade 1-2 rectal bleeding	no	CR	21	Phen-procoumon

*All time points in this table were calculated from end of treatment.

^ Onset of grade 3 proctitis < 90 days, but symptoms persisted > 90 days.

Abbreviations: ADL, activities of daily living; CR, complete response; PR, partial response; PD, progressive disease; FU, follow-up.

DISCUSSION

The aim of this study was to evaluate tolerability and effectivity of HDREBT after EBRT in elderly or medically inoperable patients with rectal cancer. In this dose escalation study, the maximal tolerated and therefore recommended phase 2 dose was set at 7 Gy per fraction. Overall response rate was 88%, with 61% of patients achieving CR. A sustained response was obtained in 52% patients. Severe late toxicity was seen in 10 of 32 patients, of which rectal blood loss, associated with the use of anticoagulants, was most frequently observed. In this population of mainly elderly and medically inoperable patients, overall survival was 64% at two years, with a median OS of 33 months.

The HERBERT study is, to our knowledge, the first prospective dose-finding study evaluating toxicity, response and survival after a combination of HDREBT and EBRT. Results indicate that this treatment is feasible in medically inoperable patients with a T2-T3 tumour and can provide durable local progression free survival. Few retrospective series have used HDREBT or contact-X-ray therapy in combination with EBRT.[9-11,14,15,21]

Corner et al. described a cohort of 52 inoperable patients (median age, 82 years) treated with 6×6 Gy HDREBT or chemoradiation with a HDREBT boost of 2×6 Gy. HDREBT was prescribed at 1 cm from the applicator surface using a single channel applicator with optional shielding. Complete response was seen in 56% and PR in 27% of patients. Late toxicity occurred in six patients (three rectal ulcers, two strictures and one colovesical fistula). Median OS was 18 months.[15]

Aumock et al. reported the outcome of 199 patients with a T1-T3 tumour, treated with EBRT (45-48 Gy) and contact therapy (median surface dose: 60 Gy in 2 fractions; range 45-120). Excellent control was achieved in T1 (100%) and mobile T2 (85%) lesions, and a CR was seen in 58% of patients with a fixed T2 or T3 tumour. Transitory proctitis occurred in 19 patients of whom two patients required blood transfusion.[11]

A historical overview of all patients treated with contact-X-ray in France between 1980 and 2012 describes a subgroup of 120 patients with T2-T3 tumours treated with contact-X-ray followed by (chemo)radiation. Median contact-X-ray surface dose was 85 Gy in 3 fractions and EBRT schedules used were 39 Gy (13×3 Gy), with optional boost to 43 Gy, and 50 Gy (25×2 Gy). In case of incomplete response, additional interstitial brachytherapy or local resection was performed. Overall CR rate was 94% with a 3-year OS of 60%. Local recurrence occurred in 26 of 113 patients with a median time to recurrence of 16 to 17 months. Rectal bleeding was observed in 50 to 70% with grade 3 rectal bleeding in 10 patients.[10]

The first two studies show very similar response rates, in populations comparable to our study. The third study was performed in slightly younger patients and treatment was intensified when necessary, resulting in higher response rates.

In the last decade, dose escalation in rectal cancer has also been a topic of interest in patients with locally advanced rectal cancer and in organ-preservation strategies.[21-28] A recent study showed excellent results after combined EBRT (60 Gy; simultaneous integrated boost) with an endorectal brachytherapy boost (5 Gy) in patients with T2-3 rectal cancer. A CR rate of 78% was observed in 51 evaluable patients, with a sustained response of 52% at two years. Most common late toxicity was rectal bleeding (7% grade 3).[28] This study shows the high potential of a nonsurgical approach in well selected fit patients. This approach with intensified chemoradiotherapy and optional salvage surgery is however not feasible in our population.

All studies observed a lower rate in severe late toxicity compared to the present study. There are several possible explanations. First, the retrospective nature might have led to underreporting of toxicity. Second, favourable criteria for contact-X-ray include tumours with a limited diameter (< 3 cm), leading to smaller irradiated volumes. In addition, the high rate of co-morbidity, with 65% of patients using anticoagulants, might result in a higher risk of severe rectal bleeding. Furthermore, the total biologic equivalent doses differ between studies. In the HERBERT study, an EBRT schedule of 39 Gy in 13 fractions (EQD2 46.8 Gy, $\alpha/\beta=3$) was selected, which is somewhat higher in comparison to 45 Gy in 25 fractions (EQD2 43.2 Gy). On the other hand, this schedule appears safe in the extensive French experience.[10,29] The brachytherapy dose was higher in the present study compared to other HDR series and prescribed to the circumferential CTV margin, instead of 1 cm from the applicator. However, besides tumour thickness, air or faeces can increase the distance between the applicator and the circumferential margin of the CTV, hampering optimal coverage. During the course of the study, being aware of the high applicator surface dose when planning at 2 cm, an additional constraint of 400% at the applicator surface was added. In contact-X-ray, a dose of 30 Gy to the surface results in approximately 10 Gy at 1 cm depth,[30] which is more comparable to the HDR dose in this cohort. However, the treatment volume with contact therapy is often smaller and no dose is delivered to the contralateral wall. Future use of additional balloon spacing, shielding, daily image guidance, and MRI during brachytherapy can further improve conformal dose delivery, with increased sparing of organs at risk.[31-34]

Overall survival is difficult to interpret in this mainly elderly population with severe comorbidity. A median overall survival of 33 months was favourable compared with the series described by Corner et al. (median OS 18 months). A subgroup analysis excluding patients younger than 75 years found similar L-PFS and OS compared to the total population. When CR was achieved, a significant improvement was seen in L-PFS at two years (60% vs. 15%) and a trend in OS (80% vs. 46%). Overall survival was, however, not significantly improved due to other causes of death. The alternative treatment for our study population is palliative radiation therapy, which is effective for symptom palliation (56-100%), but with variable duration (1 to > 44 months).[35] Complete clinical response after 40 to 60 Gy is reported in 30%, ranging from 49% in mobile tumours to 9% in fixed tumours, whereas a sustained response is rare (78% recurrence after

CR).[36] However, the value of a more durable response with a brachytherapy boost has to be weighed against increased treatment burden and more toxicity in a population with limited overall survival.

A dose-escalation design in radiotherapy has clear limitations because evaluation of late toxicity requires long term follow-up. Acute proctitis was used as a surrogate for late toxicity.[37] Although all patients with DLT developed severe late toxicity, also patients with grade 1 to 2 acute toxicity experienced severe late toxicity, indicating the limitation of this surrogate endpoint.

Another limitation is the difficulty of predicting CR based on the basis of endoscopy and digital rectal examination.[38,39] Response assessment at first evaluation was often uncertain and additional assessments over time usually clarified the course of disease. Biopsies or MRI were only performed if there were clinical implications.

In conclusion, HDREBT after EBRT offers a high response rate of almost 90% with 60% CR and a significantly improved L-PFS in patients with a CR. However, a high rate of grade 3 toxicity was observed with a clear correlation to comorbidity. This suggests that patient selection might be at least as important in preventing severe toxicity as the delivered dose. Further correlation of patient, tumour and treatment characteristics with clinical outcomes will be performed to improve future patient selection and treatment objectives. Future studies should focus on weighing the risks and benefits of a brachytherapy boost in elderly and/or inoperable patients. A proposed study design would be to randomise patients between EBRT with or without HDREBT, with symptom relieve, patient-reported quality of life, and survival as the main endpoints.

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SUPPLEMENTARY MATERIAL

Table S1. Patient and tumour and treatment characteristics per dose level

		5 Gy n=9		6 Gy n=5		7 Gy n=14		8 Gy n=10		total n=38		
Patient characteristics		**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**p-value**
Age (median/range)		81	(57-93)	87	(69-94)	82	(63-91)	83	(72-91)	83	(57-94)	0.55
Gender												0.78
male		6	(66.7)	2	(40.0)	7	(50.0)	6	(60.0)	21	(55.3)	
female		3	(33.3)	3	(60.0)	7	(50.0)	4	(40.0)	17	(44.7)	
ASA-score												0.09
II		1	(11.1)	0	(0.0)	1	(7.1)	5	(50.0)	7	(18.4)	
III		8	(88.9)	5	(100)	12	(85.7)	5	(50.0)	30	(78.9)	
IV		0	(0.0)	0	(0.0)	1	(7.1)	0	(0.0)	1	(2.6)	
WHO performance												0.41
WHO 0		1	(16.7)	0	(0.0)	2	(15.4)	1	(10.0)	4	(11.8)	
WHO 1		1	(16.7)	3	(60.0)	8	(61.5)	3	(30.0)	15	(44.1)	
WHO 2		4	(66.7)	2	(40.0)	3	(23.1)	6	(60.0)	15	(44.1)	
Co-morbidities												
Cardio Vascular	no	2	(22.2)	1	(20.0)	5	(35.7)	3	(30.0)	11	(28.9)	0.87
	yes	7	(77.8)	4	(80.0)	9	(64.3)	7	(70.0)	27	(71.1)	
Pulmonary	no	7	(77.8)	4	(80.0)	8	(57.1)	7	(70.0)	26	(68.4)	0.68
	yes	2	(22.2)	1	(20.0)	6	(42.9)	3	(30.0)	12	(31.6)	
Anticoagulant use	no	4	(44.4)	2	(40.0)	4	(28.6)	3	(30.0)	13	(34.2)	0.86
	yes	5	(55.6)	3	(60.0)	10	(71.4)	7	(70.0)	25	(65.8)	
Tumour Characteristics		**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**p-value**
TNM classification												0.33
T2N0M0		7	(77.8)	1	(20.0)	7	(50.0)	7	(70.0)	22	(57.9)	
T2N1M0		0	(0.0)	0	(0.0)	1	(7.1)	0	(0.0)	1	(2.6)	
T3N0M0		0	(0.0)	2	(40.0)	1	(7.1)	2	(20.0)	5	(13.2)	
T3N1M0		2	(22.2)	2	(40.0)	3	(21.4)	1	(10.0)	8	(21.1)	
T3N2M0		0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)	2	(5.3)	
Distance from anal verge												0.20
0-5 cm		3	(33.3)	3	(60.0)	5	(35.7)	8	(80.0)	19	(50.0)	
5-10 cm		5	(55.6)	2	(40.0)	5	(35.7)	1	(10.0)	13	(34.2)	
10-15 cm		1	(11.1)	0	(0.0)	4	(28.6)	1	(10.0)	6	(15.8)	

Brachytherapy CTV	**Median (range)**	**Median (range)**	**Median (range)**	**Median (range)**	**Median (range)**	**p-value**
Volume (cc)	9.6 (2.0-25.0)	7.2 (4.7-9.6)	6.4 (2.0-20.0)	7.1 (3.6-14.8)	7.1 (2.0-25.0)	0.67
Max thickness (cm)	1.1 (0.7-3.0)	1.1 (0.8-1.4)	1.0 (0.4-1.7)	1.0 (0.7-1.6)	1.0 (0.4-3.0)	0.30
Length (cm)	3.4 (2.1-5.2)	3.6 (2.4-4.0)	2.8 (2.2-4.1)	2.9 (1.8-6.4)	3.1 (1.8-6.4)	0.72
D90 (Gy)	6.7 (1.8-8.3)	6.6 (4.7-9.8)	6.8 (4.3-8.7)	8.2 (5.0-9.8)	7.1 (1.8-9.8)	0.13

Abbreviations: ASA, American Society of Anesthesiology; CTV, clinical target volume; WHO, World Health Organisation.

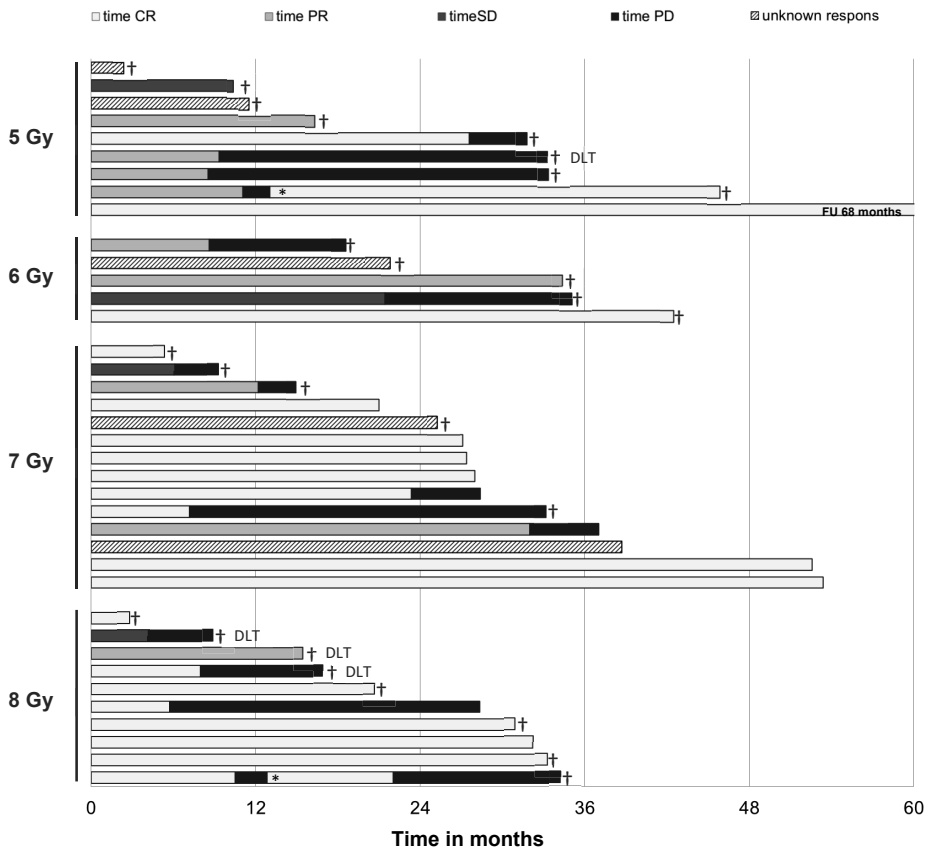
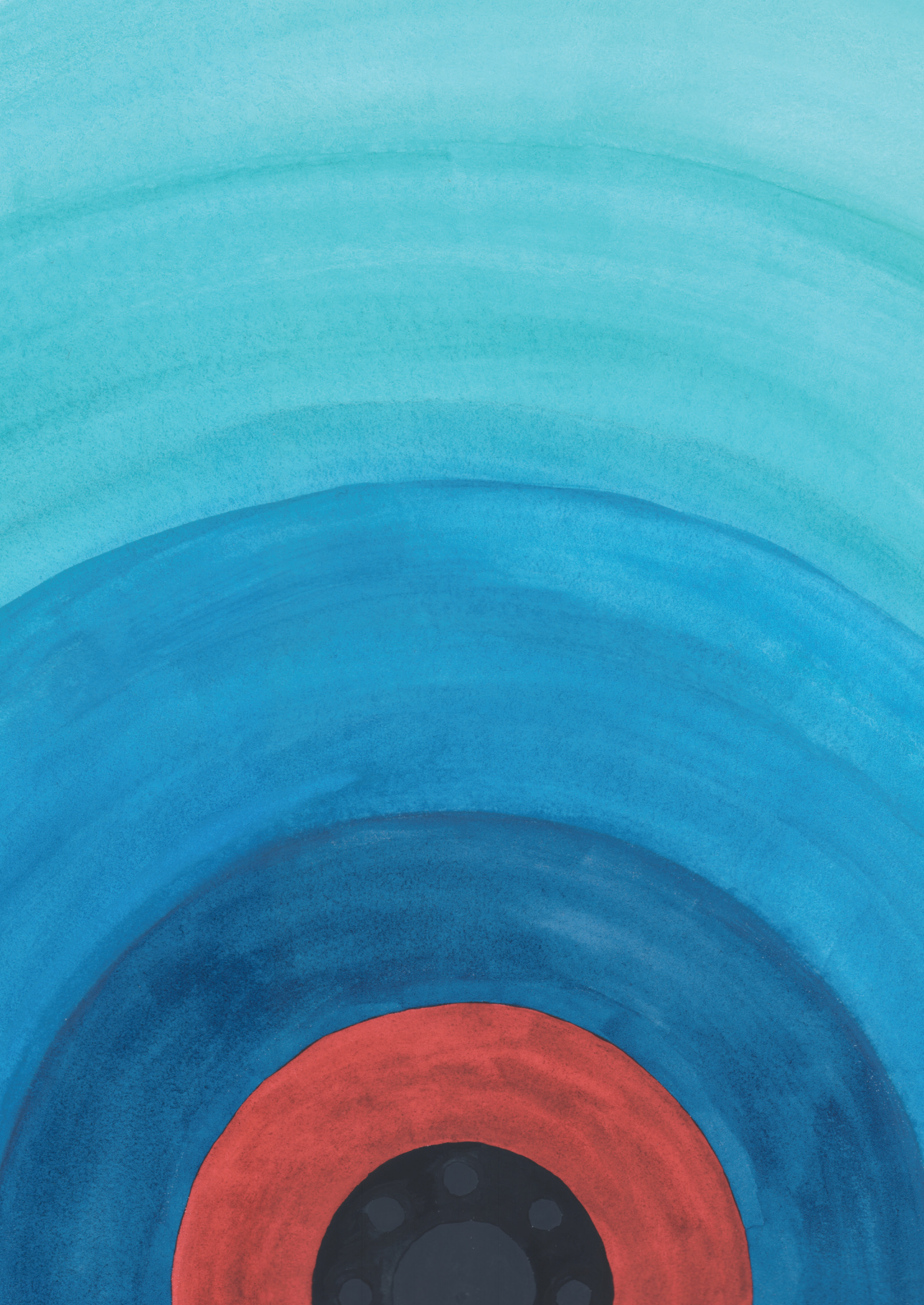


Figure S1. Response and overall survival arranged by dose level.
All 38 patients are included in this figure.
* Two patients received salvage surgery. † Deceased.
Abbreviations: DLT, dose-limiting toxicity; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.



Chapter 4

Evaluation of clinical and endoscopic toxicity after external beam radiotherapy and endorectal brachytherapy in elderly patients with rectal cancer treated in the HERBERT study

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ABSTRACT

Introduction

The HERBERT study evaluated a high-dose-rate endorectal brachytherapy boost (HDREBT) after EBRT in medically inoperable/elderly patients with rectal cancer. The response-rates are promising but not without risk of toxicity. The current analysis provides a comprehensive overview of patient reported, physician reported and endoscopically observed toxicity.

Material and Methods

A brachytherapy dose finding study was performed in 38 inoperable/elderly patients with T2-T4N0-1 rectal cancer. Patients received EBRT (13×3 Gy) followed by three weekly HDREBT applications (5-8 Gy). Toxicity was assessed via three methods: patient and physician (CTCAEv3) reported rectal symptoms and endoscopically. Wilcoxon signed rank test, paired t-test and Spearman's correlation were used.

Results

Patient reported bowel symptoms showed a marked increase at the end of EBRT and two weeks after HDREBT. Acute grade 2 and 3 proctitis occurred in 68.4% and 13.2% respectively while late grade 2 and ≥ 3 proctitis occurred in 48% and 40%. Endoscopic evaluation mainly showed erythema and telangiectasia. In three patients frank haemorrhage or ulceration occurred. Most severe toxicity was observed 12-18 months after treatment.

Conclusion

For elderly patients with rectal cancer, definitive radiotherapy can provide good tumour response but has a substantial risk of toxicity. The potential benefit and risks of a HDREBT boost above EBRT alone must be further evaluated.

INTRODUCTION

Radiotherapy for rectal cancer is mainly used as preoperative treatment in combination with total mesorectal excision (TME) with the aim of reducing the risk of local recurrence. Although rectal cancer has been regarded as relatively radio-resistant, complete pathologic response after standard neoadjuvant chemoradiotherapy is observed in approximately 16%.[1,2] In selected centres, with a dedicated watch and wait approach after chemoradiation, complete clinical response rates can be as high as 34-49% due to specific selection criteria.[3,4] Dose response analyses indicate that higher complete response rates can be achieved with increased radiation doses in rectal cancer.[5] As a result, there is increasing interest in organ preservation, avoiding radical TME-surgery altogether.

To increase the chance of a complete response, dose escalation is necessary. This can be achieved by combining external beam radiotherapy (EBRT) with either an EBRT boost or a more locally applied treatment like contact-X-ray or brachytherapy. The last two have been used for small T1/T2 tumours as definitive treatment [6-8] whereas an EBRT boost has mainly been investigated in the preoperative setting in more advanced tumours with the purpose of increasing radical resection rates and sphincter preservation.[9] A combination of EBRT with either contact-X-ray or high dose rate endoluminal brachytherapy (HDREBT) boost has been offered to patients who were medically unfit for surgery as an alternative to palliative treatment.[10-12] However, still little is known about the most optimal dose, and the toxicity profile of this combined external and internal radiotherapy approach.

The HERBERT study was designed to evaluate the feasibility of adding a HDREBT boost to external beam radiotherapy with the aim to provide durable local tumour control in elderly/medically inoperable patients with rectal cancer. Patients received 39 Gy EBRT in 13 fraction followed by three weekly HDREBT applications using a dose escalation design. The primary endpoint was acute dose limiting toxicity defined as physician reported proctitis grade 3 (CTCAEv3) within 6 weeks after brachytherapy; secondary endpoints included response, survival and toxicity. Although the primary results showed promising response rates of almost 90% and a safe acute toxicity profile in dose levels ≤ 7 Gy per fraction, there was considerable late toxicity with approximately one-third of patients experiencing proctitis grade 3 during follow up.[13] Little has been reported on toxicity of endorectal brachytherapy. The aim of the current analysis is to provide a comprehensive overview of the observed toxicity in the HERBERT study using patient and physician reported clinical toxicity and endoscopically observed toxicity.

MATERIAL AND METHODS

The HERBERT study, designed as a phase I dose escalation study, was performed at the Leiden University Medical Center and the Netherlands Cancer Institute. Patients with histologically verified adenocarcinoma of the rectum, stage cT2-4N0-1M0-1, who were unfit for or refused surgical treatment were eligible. Details of the study design and methods have been described previously.[13] The study was approved by the medical ethical committee in both centres and informed oral and written consent was obtained from all patients before treatment. The study was registered with the Dutch Central Committee on Research Involving Human Subjects; registration no. NL17037.031.07.[14]

Treatment

Patients were treated with 39 Gy EBRT, delivered in 13 fractions of 3 Gy, 4 days a week followed by three weekly HDREBT applications of 5-8 Gy per fraction. Details on EBRT and HDREBT were previously described.[13] In brief, for HDREBT, a flexible applicator (Oncosmart®, Elekta, Veenendaal, The Netherlands) of 2 cm diameter, with 8 peripheral catheters and an inflatable semi-circular balloon, was used. The clinical target volume (CTV) was defined as residual macroscopic tumour or scarring after EBRT which was delineated on a planning-CT scan with the applicator in situ prior to the first brachytherapy application. The aim of treatment planning was complete coverage of the CTV by the 100% isodose. The 100% isodose was restricted to 2 cm from the applicator surface with no hotspots allowed in the surrounding organs. During the course of the study an additional constraint of 400% isodose within the applicator surface was added. HDREBT was performed using a microSelectron HDR afterloader (Elekta, Veenendaal, the Netherlands) with an Iridium-192 source.

Endpoints

For this study, toxicity was assessed using three methods: patient reported symptoms as assessed with questionnaires, clinical proctitis scored by the treating physician according to NCI Common Toxicity Criteria of Adverse Events (CTCAE v3), and endoscopic images of the tumour site and the contralateral rectal wall.

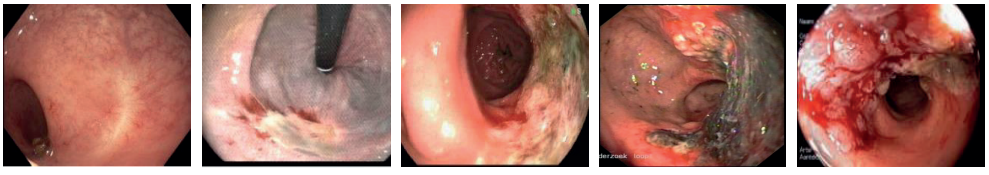
Questionnaires were sent to all patients at 13 time points; at baseline, weekly during EBRT, two and four weeks after EBRT, weekly during HDREBT and two weeks, two months, six months and one year after brachytherapy. The used questionnaire is based on the symptoms mentioned in the RTOG/EORTC GU and GI toxicity scoring systems and has been previously used in studies on toxicity after radiotherapy for prostate cancer (Supplementary Figure S1).[15,16] Symptoms concerning pain with stools, painful abdominal cramps/ urge, tenesmus, mucus discharge, faecal incontinence and bowel function as a general problem were scored in a four point Likert scale: 1. no, not at all; 2. yes, a little; 3. yes, quite a bit; 4. yes, very much. Use of pads for incontinence or soiling and rectal blood loss were scored as: 1. no, not at all; 2. yes, 1-2 days a week;

3. yes, more than 2 days a week; 4. yes, every day. Additional questions on bowel function included; faecal consistency, frequency of stools per day and use of medication or dietary changes for bowel symptoms.

Clinical acute dose limiting toxicity (proctitis grade 3 CTCAEv3 within 6 weeks after brachytherapy) was prospectively scored. Additional proctitis scores (CTCAEv3) were collected retrospectively from patient charts. Proctitis grade 1: rectal discomfort, intervention not indicated, grade 2; symptoms not interfering with activities of daily living (ADL); medical intervention indicated, grade 3; stool incontinence or other symptoms interfering with ADL; operative intervention indicated, grade 4; Life threatening consequences (e.g., perforation).[17] Scores were collected for all time points corresponding to the questionnaires and additionally yearly during further follow-up. The maximum score for each time point was used. The maximum score between 1 and 3 months was assigned to time point 2 months, the maximum score between 3 and 9 months for time point 6 months, the maximum score between 9 and 18 months the time point of 1 year etc. Late faecal incontinence, rectal bleeding and rectal pain were additionally scored as separate symptoms (CTCAEv3). Maximum score occurring more than 90 days after treatment was documented. Patients with progressive disease were excluded for late proctitis, incontinence, rectal bleeding and rectal pain.

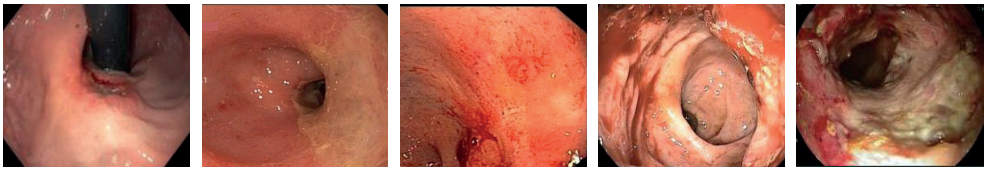
Endoscopic assessment at tumour site was scored by C.M. and E.R. in a 5 point scale; 0. erythema/scarring; 1. superficial ulcer; 2. deep ulcer; 3. very deep ulcer; 4. evident tumour mass (see Figure 1A). Endoscopic toxicity at the contralateral wall was scored using the endoscopic proctitis assessment scale by Khan et al; 0. normal mucosa; 1. mild erythema; 2. diffuse erythema and punctate haemorrhage; 3. frank haemorrhage and 4. ulceration (see Figure 1B).[18]

A: Endoscopic toxicity at tumoursite



0. Erythema/scarring | 1. Superficial ulcer | 2. Deep ulcer | 3. Very deep ulcer | 4. Evident tumour

B: Endoscopic toxicity at contralateral wall



0. Normal mucosa | 1. Mild erythema | 2. Diffuse erythema and punctate haemorrhage | 3. Frank haemorrhage | 4. Ulceration

Figure 1. Endoscopic assessment at tumour site (A) and contralateral wall (B).

Endoscopic assessment was done at baseline, prior to brachytherapy, 2 and 6 months after brachytherapy and yearly during follow-up. For correlation of CTCAE with endoscopic toxicity, the CTCAE score at time of endoscopy was used.

Statistical analyses

Statistical analyses were performed with SPSS version 23.0 (IBM, Armonk, NY) and R version 3.3.2 (R Foundation, Vienna, Austria). Median follow-up was calculated using the Kaplan-Meier method. Time was calculated from start of EBRT to last date of clinical follow-up. Descriptive statistics were used for reporting of observed toxicity. Wilcoxon's signed rank test and paired t-test were used for evaluation of patient reported outcomes at different time points. Correlation of patient reported bowel symptoms, proctitis (CTCAEv3) and endoscopic toxicity was assessed using Spearman's correlation. Patient level bootstrapping was applied to correct for multiple measurements per patient. For correlation with CTCAE proctitis with patient reported symptoms a scale was used including questions concerning painful defecation, cramps, tenesmus, mucus, incontinence, blood loss and bowel function as a general problem (Cronbach's alfa = 0.83). To correct for multiple testing, a p-value of < 0.01 was considered significant.
Patients who did not receive HDREBT were censored for all analyses from six weeks after EBRT. Patients with stable disease (SD) or progression (PD) were censored for late toxicity (≥ 90 days after brachytherapy), starting one month prior to documented SD or PD. For acute toxicity and endoscopic toxicity no censoring was applied for SD or PD.

RESULTS

In total, 38 patients entered the study of whom 35 completed treatment. Two patients did not receive brachytherapy (1 patient choice; 1 ulcer after EBRT) and one patient died one week after the first BT application due to cardiac arrest. Baseline characteristics are provided in Table 1. Median duration of clinical follow-up was 22 months (IQ range 11-37); while at time of database closure (January 2017) seven patients were still alive with a median follow-up of 43.7 months (range 38.8-107.4). Available toxicity scores for patient reported, physician reported toxicity and endoscopic assessment per time point are illustrated in Supplementary Figure S2.

Patient reported symptoms

A clear increase of patient reported bowel symptoms at the end of EBRT and 2 weeks after HDREBT was found (see Figure 2A). In addition, mean stool frequency increased from 3.2 per day at baseline to 7.7 in the third week of EBRT ($p<0.001$), and from 2.8 per day prior to HDREBT to 5.8 two weeks after HDREBT ($p = 0.03$). Six weeks after EBRT and two months after BT all symptoms were not significantly different from baseline. Scores of individual questions are provided in Supplementary Figure S1.

Table 1. Baseline characteristics

Total	**N=38**	**100%**
Age (median range)	83	(57-94)
Gender		
Male	21	55.3%
Female	17	44.7%
WHO		
WHO 0	4	11.8%
WHO 1	15	44.1%
WHO 2	15	44.1%
Co-morbidities		
Cardiovascular co-morbidity	27	71.1%
Pulmonary co-morbidity	12	31.6%
Anticoagulant use	25	65.8%
Incontinence	18	47.4%
cTNM classification		
cT2N0M0	22	57.9%
cT2N1M0	1	2.6%
cT3N0M0	5	13.2%
cT3N1M0	8	21.1%
cT3N2M0	2	5.3%
Distance from anal verge		
0-5 cm	19	50.0%
5-10 cm	13	34.2%
10-15 cm	6	15.8%
HDREBT treatment parameters	**median**	**range**
CTV volume (cm3)	7.1	(2.0-25.0)
CTV thickness (cm)	1.0	(0.4-3.0)
CTV length (cm)	3.1	(1.8-6.4)
CTV D90 (Gy)	7.1	(1.8-9.8)
Contralateral wall D2cc (Gy)	8.0	(3.7-14.2)
Anus D2cc (Gy)	1.2	(0.0-4.4)

Abbreviations: WHO, World Health Organisation performance status; HDREBT, High-dose rate endorectal brachytherapy; CTV, clinical target volume.

Physician reported toxicity

Physician reported toxicity is displayed in Table 2. Acute proctitis was correlated with late proctitis. In patients with grade 1 acute proctitis no severe late proctitis was reported, whereas in 6 out of 16 patients with acute grade 2 and in 3 out of 4 patients with acute grade 3 proctitis severe late proctitis occurred (Spearman's correlation = 0.43; 95%CI 0.05-0.70). Twelve patients received a clinical intervention for proctitis; 8 sucralfate enema/ mesalazine, 2 argon plasma coagulation and 6 blood transfusion. Rectal blood loss was in all cases associated with anticoagulants. There was no association between tumour distance to the anal verge and proctitis or incontinence.

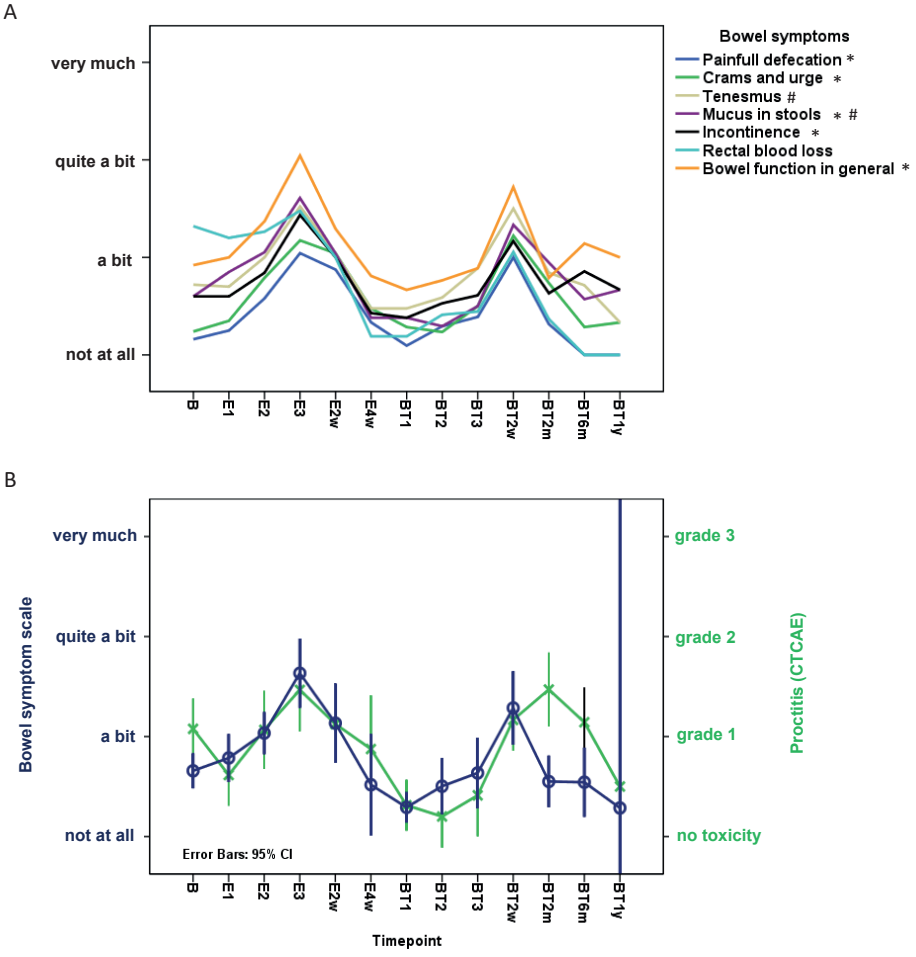


Figure 2. Patient reported bowel symptoms (A) and comparison of bowel symptoms with CTCAEv3 (B).

* Symptoms increased significantly from baseline to third week of EBRT ($p<0.01$).

\# Symptoms increased significantly from start of brachytherapy to 2 weeks after brachytherapy ($p<0.01$). Spearman's correlation between the first and second peak showed a trend for incontinence ($\rho=0.56$; 95% CI 0.01-0.83, $p=0.03$).

Abbreviations: B; Baseline; E1-3, EBRT week 1-3; BT1-3, Brachytherapy 1-3; w, weeks; m, months; y, years.

Cumulative incidence of proctitis at 1 year was 89% for grade 2 or higher and 23% for grade 3 and 4 (see Figure 3A). Prevalence of proctitis at different time points is illustrated in Figure 3B. Most severe toxicity was observed 1 year after treatment. Details concerning severe late proctitis (CTCAEv3) were previously reported (see Chapter 3 or Supplementary Table S1).[13]

Table 2. Physician reported toxicity

Proctitis (CTCAEv3)	**n**	**%**
*Acute proctitis < 90 Days**	38	
No toxicity	0	0.0%
Grade 1	7	18.4%
Grade 2	26	68.4%
Grade 3	5	13.2%
Grade 4	0	0.0%
*Late proctitis > 90 Days**	25	
No toxicity	0	0.0%
Grade 1	3	12.0%
Grade 2	12	48.0%
Grade 3	9	36.0%
Grade 4	1	4.0%
*Late toxicity > 90 Days^*	25	
*Incontinence for stools/mucus**		
No toxicity	7	28.0%
Grade 1	4	16.0%
Grade 2	12	48.0%
Grade 3	1	4.0%
Missing	1	4.0%
*Rectal pain**		
No toxicity	17	68.0%
Grade 1	2	8.0%
Grade 2	4	16.0%
Grade 3	2	8.0%
*Rectal bleeding**		
No toxicity	5	20.0%
Grade 1	7	28.0%
Grade 2	7	28.0%
Grade 3	6	24.0%
*Treatment for proctitis**	12	48.0%
Sucralfate/ mesalazine	8	32.0%
APC	2	8.0%
Blood transfusion	6	24.0%

* maximum score; ^ all symptoms are involved in the proctitis score but were also assessed separately.
Abbreviations: APC, Argon plasma coagulation.

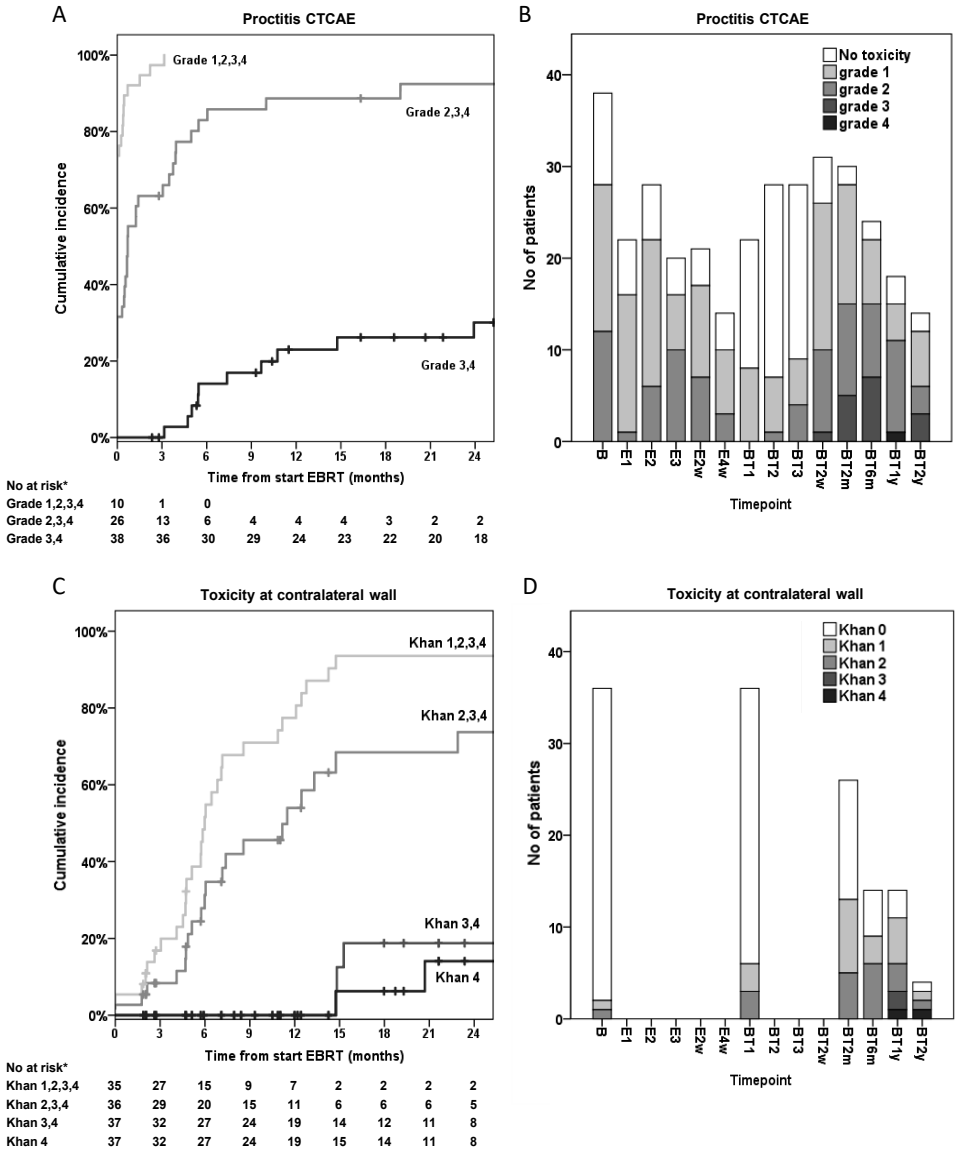


Figure 3. Proctitis (CTCAEv3) and endoscopic evaluation at the contralateral bowel wall.

(A) Cumulative incidence of proctitis CTCAEv3 (baseline symptoms included). (B) Prevalence of proctitis (CTCAEv3). (C) Cumulative incidence of endoscopic toxicity at the contralateral wall. (D) Prevalence of endoscopic toxicity at the contralateral wall.

* Patients who have experienced toxicity in there category are no longer at risk. Each category has a specific no at risk. Khan 1 = Mild erythema; Khan 2 = Diffuse erythema and punctate haemorrhage; Khan 3 = Frank Haemorrhage; Khan 4 = ulceration.

Abbreviations: B, Baseline; E1-3, EBRT week 1-3; BT1-3, Brachytherapy 1-3; w, weeks; m, months; y, years.

Endoscopic toxicity

Cumulative incidence and prevalence of endoscopic toxicity of the contralateral wall is shown in Figure 3CD. After EBRT alone, 86% of patients had a normal mucosa at the contralateral wall. Two months after HDREBT 46% of patients had a normal mucosa, 27% of patients showed mild erythema and 27% had diffuse erythema and punctate haemorrhage of the contralateral wall. Cumulative incidence of Khan's classification 2 or higher was 54% 1 year after treatment. Maximum Khan's classification during follow-up was mild in 12 patients (normal n = 4, mild erythema n = 8), moderate in 16 (diffuse erythema and punctate haemorrhage) and severe in three patients. One patient showed frank haemorrhage after 12 months and two patients developed an ulcer at 13 and 18 months.

In patients with progressive disease, endoscopic findings usually showed an ulcerative regrowth categorised as deep ulceration, which progressed to evident tumour over time. Therefore, we scored maximum endoscopic late toxicity at the tumour site in patients with a complete or partial response to treatment. Toxicity at tumour site was mild in 16/28 patients (normal n = 1; erythema/scarring n = 3; superficial ulcer n = 12) and more severe in 12/28 patients (deep ulcer n = 10 and very deep ulcer n = 2). Of the patients with a deep ulcer, seven were scored as a partial response and five as a complete response at the time of the endoscopy.

Correlation of different toxicity scoring methods

Proctitis (CTCAEv3) and patient reported symptoms show a similar pattern over time (see Figure 2B). Spearman's correlation of proctitis with the patient reported bowel symptom scale was 0.37 (95% CI 0.23-0.50). The relation between clinical proctitis (CTCAEv3) and endoscopic toxicity is displayed in Table 3 (Spearman's correlation = 0.37, 95% CI 0.18-0.56). Clinical proctitis score was higher than the Khan's classification in 36.8% and lower in 24.6% of measurements. No correlation was found between proctitis (CTCAEv3) and endoscopic toxicity at the tumour site.

Table 3. Relation between clinical proctitis and endoscopic toxicity

Toxicity at the contralateral wall	Proctitis (CTCAEv3) at time of endoscopy			
	No toxicity	Grade 1	Grade 2	Grade 3
0. Normal mucosa	24	15	12	1
1. Mild erythema	8	9	9	1
2. Diffuse erythema and punctate haemorrhage	4	8	11	4
3. Frank haemorrhage	1	0	4	0
4. Ulceration	0	0	2	1

DISCUSSION

The current analysis of the HERBERT study provides a detailed insight in the observed toxicity after EBRT and HDREBT for rectal cancer in elderly patients. The patient reported outcomes show a very clear pattern with increased symptoms at the end of EBRT and after HDREBT, resolving within weeks after treatment. During HDREBT bowel symptoms were mild and the severity of bowel symptoms after HDREBT did not exceed symptoms scores after EBRT. The proctitis (CTCAEv3) scores show that the majority of patients experience moderate to severe proctitis during follow-up.

Endoscopic toxicity ranged from only scarring at the tumour site with normal mucosa at the contralateral wall to severe ulceration of the entire circumference. Most severe endoscopic toxicity was observed between 12 and 18 months after treatment.

The rectal toxicity observed during EBRT shows a very predictable pattern comparable to other reports in the literature. A prospective cohort study on palliative radiotherapy for rectal cancer (13×3 Gy) also showed increased rectal toxicity at the end of EBRT reducing below baseline 6 and 12 weeks after EBRT.[19] The main question for this study is however how the addition of a HDREBT boost affects both acute and late clinical and endoscopic toxicity.

Limited data is available on toxicity after HDREBT for rectal cancer. The only prospective study was described by Appelt et al. and evaluated chemoradiotherapy with a HDREBT boost in a non-surgical treatment approach for patients with T2-3 rectal cancer.[20] Patient and physician reported toxicity was prospectively scored. Occurrence of rectal bleeding was comparable to the current study and was reported by 78% of patients and was most severe 12 months after treatment. Faecal incontinence was most common 6 months after treatment (40% of patients) and reduced to baseline levels with approximately 30% of patients reporting incontinence at one year. This appears less than our population, but can possibly be explained by the fact that we reported the total incidence of incontinence and our population consisted of more elderly patients with a higher prevalence of incontinence at baseline (53%).

A retrospective series of 52 patients, from the Mount Vernon Cancer Centre in the UK, treated with either definitive HDREBT or a combination of chemoradiotherapy with a HDREBT boost, describes limited acute toxicity and 8% late toxicity; 3 rectal ulcers, 2 strictures (occurring 3 and 21 months after treatment) and a colovesical fistula. While other symptoms associated with proctitis were not documented as late toxicity, a reported median symptom response of three months suggests that most patients did experience late proctitis-related symptoms.[12,21]

An alternative to HDREBT is contact X-ray therapy, which is most suitable for smaller, superficial tumours, but has been combined with EBRT in larger tumours. In series without EBRT, toxicity involves mild to moderate late haemorrhaging proctitis in 17-51% and severe haemorrhaging/ulceration in 0-3%. [8,22-24] The largest series of contact X-ray with EBRT consists of 120 patients and is reported by Gerard et al. In this series, 58% of patients received an additional interstitial Iridium boost. Rectal bleeding from radiation induced telangiectasia was observed in 50-70% although blood transfusion was exceptional and rectal bleeding diminished after 2-4 years.[10]

Ulceration occurred at the tumour site in 33% of patients with a T3 tumour, but most of these ulcers healed within 3-10 months.

Regretfully, no dose response data are available for proctitis in rectal cancer, but a dose-effect correlation for rectal morbidity has been well established in patients with prostate or cervical cancer.[25-27] While high doses are needed for maximum tumour control,[5] it is clearly not without risk. It must however also be considered that after standard treatment for rectal cancer consisting of radiotherapy and TME surgery, late morbidity is also a well-known problem. Forty-six percent of patients experienced major low anterior resection syndrome up to 14 years after treatment in the TME trial. The Polish trial comparing 5×5 Gy with chemoradiation described late anorectal function impairment in approximately two-thirds of patients.[28-30]

To our knowledge, this is the first study which systematically evaluated endoscopic toxicity after HDREBT. The scoring method used is straightforward, and was described by Khan et al. in a study for prostate cancer.[18] However, most data on endoscopic toxicity use the somewhat more complex Vienna Rectoscopy Score (VRS) limiting direct comparison of results.[31] A review in prostate cancer patients, reporting the VRS, shows that 72% of patients have telangiectasia and 33% congested mucosa (oedema or erythema).[32] This correlates with our results when “mild erythema” and “diffuse erythema and punctate haemorrhage” are grouped together (77%). Most severe toxicity was seen between one and two years after treatment which is consistent with our results.

While this study provides valuable insight in acute and late proctitis, it is subject to a number of limitations. The number of patients is small and follow-up information was limited in this elderly population. For late proctitis all patients with a partial or complete response were included in the analyses. Bowel symptoms could therefore partly originate from residual tumour in patients with a partial response. Also, high rates in co-morbidity and anticoagulant use might have influenced the rate of severe proctitis. Technical improvements to the brachytherapy application technique and use of repeated imaging will probably result in better tumour coverage with increased sparing of the normal rectal wall in future studies.[33-35]

Strengths of our study include the combination of three different scoring methods with reliable low grade toxicity provided by the patient reported outcome and correlation of late clinical proctitis with endoscopic findings. While this intensive follow-up schedule is not desirable outside a clinical trial, we advise to continue clinical follow-up (with endoscopic evaluation on indication) for at least 1.5 years because of the risk of late radiation proctitis. Although there is no consensus on the optimal treatment of radiation proctitis, a review by Vanneste et al. provides an overview of current conservative and invasive treatment options.[36]

For elderly patients with rectal cancer, definitive radiotherapy is an option with good tumour response rates but not without risk of severe toxicity. Increasing experience and future use of MRI and adaptive treatment for HDREBT will hopefully reduce the risk of toxicity and improve tumour response. The benefit of a HDREBT boost with regard to local control should be weighed against the increased risk of toxicity and must be further evaluated, ideally in a randomised setting between EBRT alone and EBRT with a HDREBT boost.

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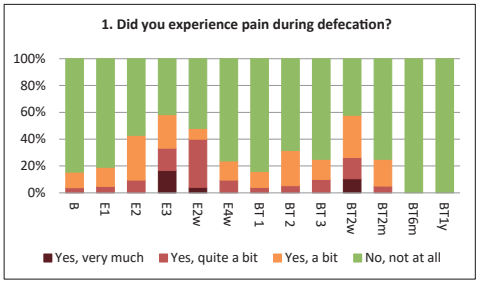
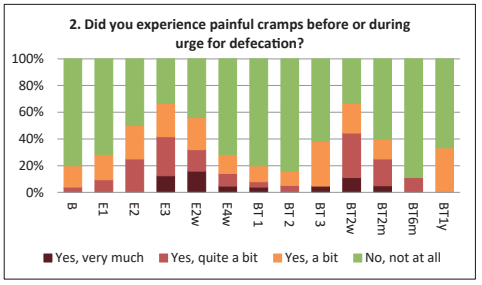
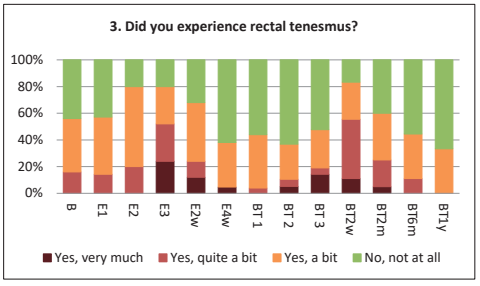
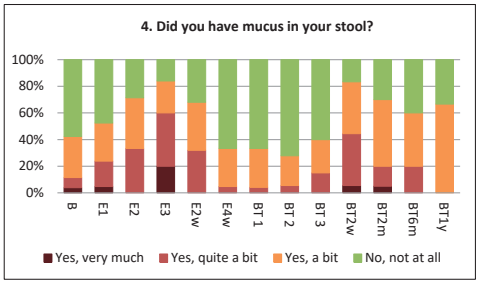
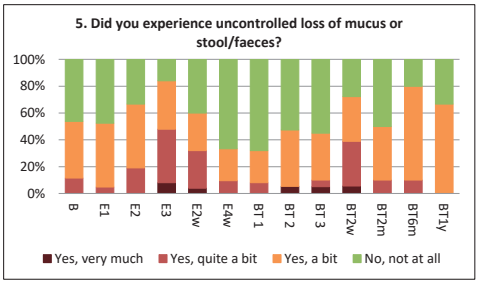
SUPPLEMENTARY MATERIAL

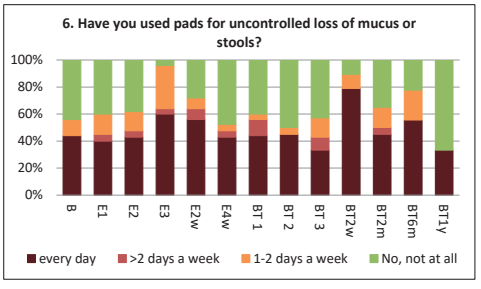


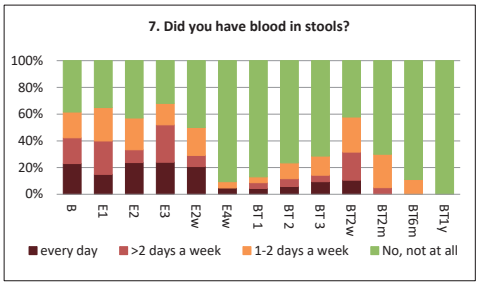


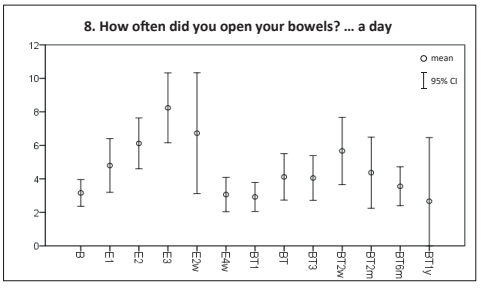












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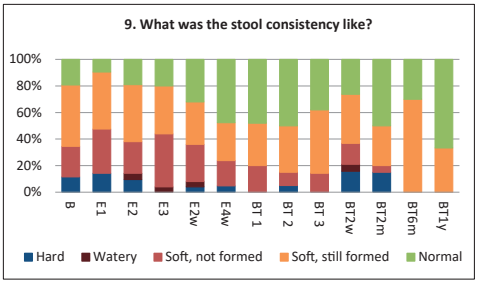

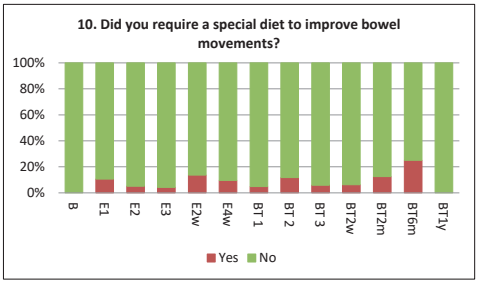

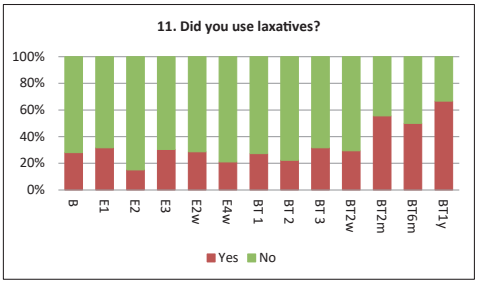

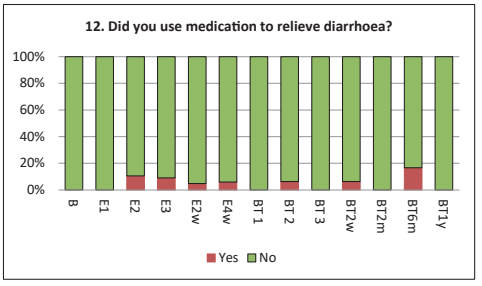

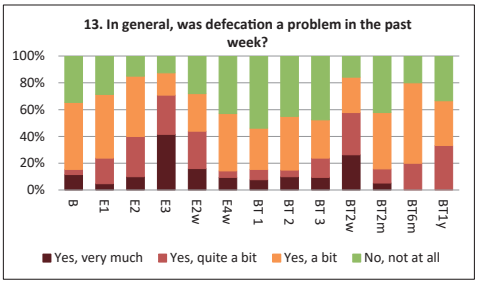

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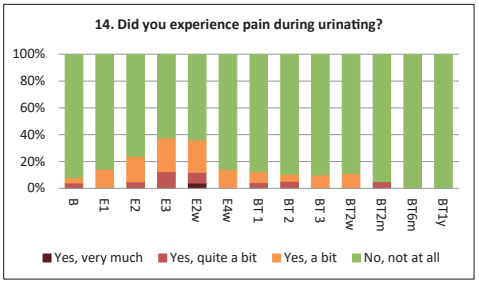
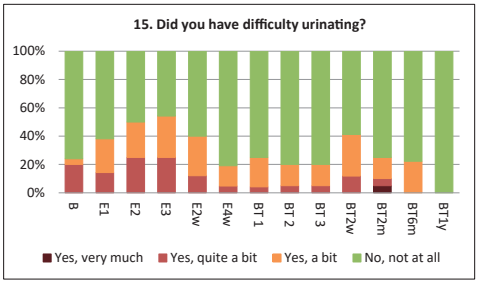
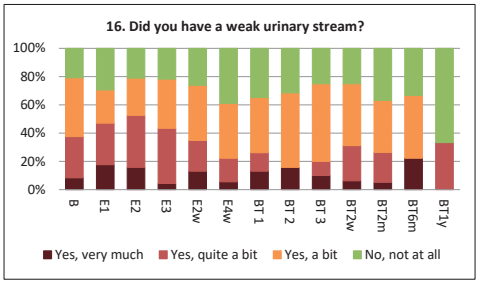
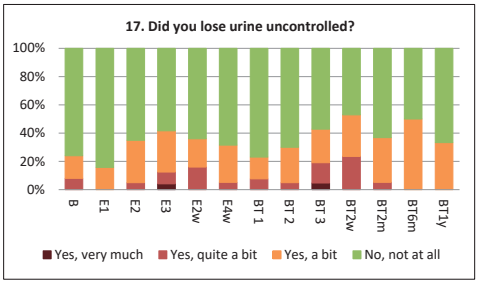
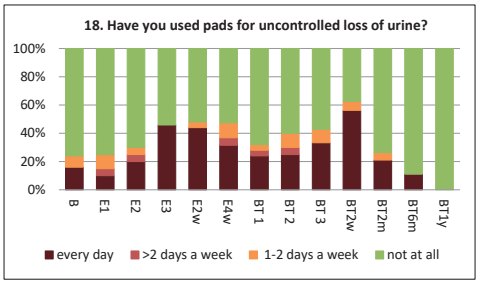
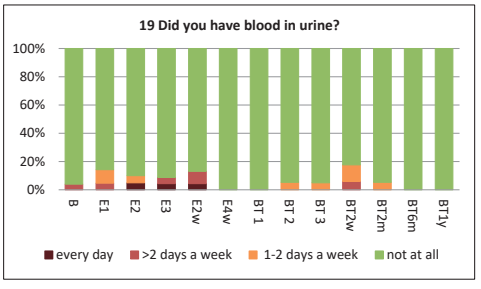


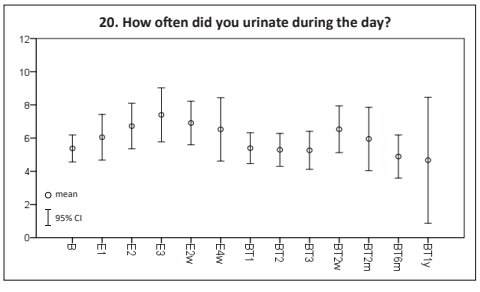












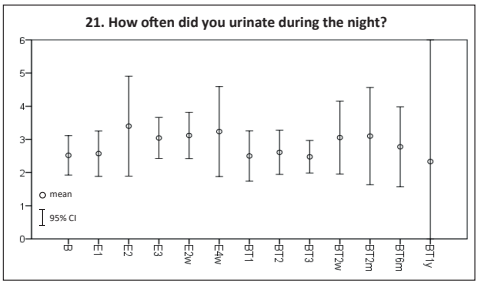


Figure S1. Patient reported outcome (continued): urinary symptoms.

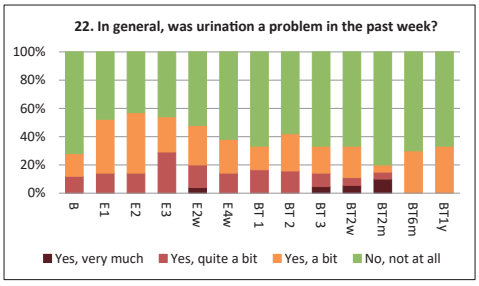
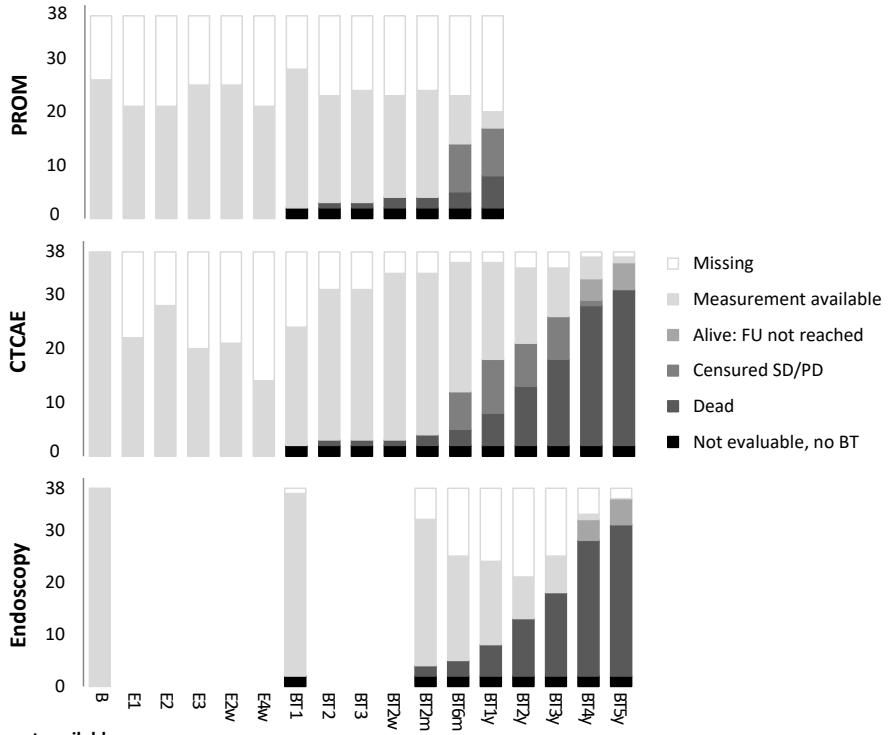


Figure S1. Patient reported outcome (continued): urinary symptoms.



Measurement available

PROM	26	21	21	25	25	21	26	20	21	19	20	9	3				
CTCAE	38	22	28	20	21	14	22	28	28	31	30	24	18	14	9	4	1
Endoscopy	36						36				26	14	14	4	7	1	0

Figure S2. Available toxicity scores for patient reported, physician reported and endoscopic toxicity.
Abbreviations: B, baseline; E1-3, EBRT week 1-3; BT1-3, brachytherapy 1-3; w, weeks; m, months; y, years; PROM, patient reported outcome measurement; CTCAEv3, common toxicology criteria for adverse events; FU, follow-up; SD, stable disease; PD, progressive disease; BT, brachytherapy.

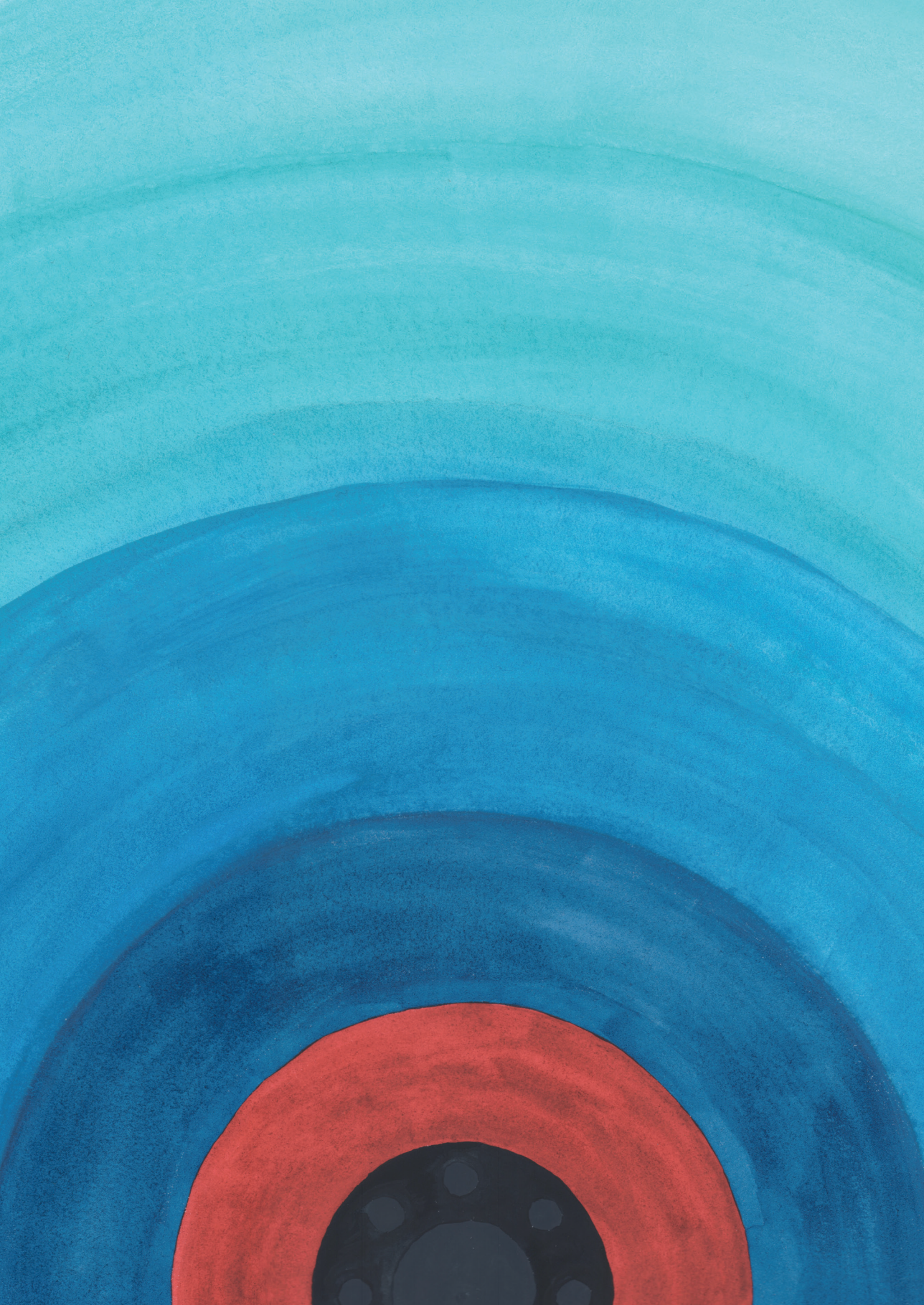
Table S1. Severe treatment-related late toxicity

Dose	Severe late toxicity (> 90 days, maximum score)	Proctitis grade 3 < 6 wks	Response	Time (months) *	Anti-coagulant use
5 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Pain, frequency and fatigue FU: PD at 7 months, proctitis grade 2.	yes	PR	1^	Aceno-coumarol
8 Gy	*Grade 3: Rectal bleeding* Symptoms: Hospital admission at 1 month; blood transfusion at 5 months. FU: PD at 9 months after HDREBT.	yes	CR	1^	Carbasalate calcium
8 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Pain; opioids needed and rectal bleeding. FU: Improvement at 7 months (gr 1-2 bleeding persisted)	yes	PR	1^	Carbasalate calcium
5 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Pain and incontinence FU: Salvage surgery at 8 months for PD.	no	PR	2^	-
7 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 5 months. FU: PD with severe rectal bleeding at 10 months.	no	PR	5	Phen-procoumon
7 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 6 months (Hb 3.1) FU: Grade 1-2 proctitis	no	CR	6	Carbasalate calcium
7 Gy	*Grade 3: Proctitis limiting ADL* Symptoms: Urgency, frequency and tenesmus Treatment: Multiple medical interventions. FU: Gr 2 proctitis; PD at 21 months for which a palliative stoma	no	CR	8	-
7 Gy	*Grade 4: Ulceration and rectocutaneous fistula* Symptoms: Pain, fatigue, rectal bleeding (transfusion) Treatment: Specialised wound care and HBOT. FU: Slight improvement, but fistula persisted (gr 3)	no	CR	12	-
7 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 19 months (Hb 3.5) FU: Grade 1 rectal bleeding	no	CR	19	Phen-procoumon
8 Gy	*Grade 3: Rectal bleeding* Symptoms: Blood transfusion at 21 months (possible interference of coecum tumour (Hb3.5). FU: Grade 1-2 rectal bleeding	no	CR	21	Phen-procoumon

*All time points in this table were calculated from end of treatment.

^ Onset of grade 3 proctitis < 90 days, but symptoms persisted > 90 days.

Abbreviations: ADL, activities of daily living; CR, complete response; PR, partial response; PD, progressive disease; FU, follow-up.



Chapter 5

Predictive factors for response and toxicity after brachytherapy for rectal cancer; results from the HERBERT study

Eva C. Rijkmans, Corrie A.M. Marijnen, Baukelien van Triest, Martijn Ketelaars, Annemieke Cats, Akin Inderson, Roy P.J. van den Ende, Mirjam S. Laman, Ellen M. Kerkhof, Remi A. Nout

Radiotherapy and oncology 2019;133:176-182

ABSTRACT

Purpose

The HERBERT study was a dose-finding feasibility study of a high-dose rate endorectal brachytherapy (HDREBT) boost after external beam radiotherapy (EBRT) in elderly patients with rectal cancer who were unfit for surgery. This analysis evaluates the association of patient, tumour and dosimetric parameters with tumour response and toxicity after HDREBT in definitive radiotherapy for rectal cancer.

Patients and methods

The HERBERT study included 38 inoperable patients with T2-3N0-1 rectal cancer. Thirteen fractions of 3 Gy EBRT were followed by three weekly HDREBT applications of 5-8 Gy per fraction. Clinical and dosimetric parameters were tested for correlation with clinical complete response (cCR), sustained partial/complete response (SR), patient reported bowel symptoms, physician reported acute and late proctitis (CTCAE v3) and endoscopically scored toxicity.

Results

Thirty-five patients completed treatment and were included in the current analyses. Twenty of 33 evaluable patients achieved a cCR, the median duration of a sustained response was 32 months. Tumour volume at diagnosis showed a strong association with clinical complete response (OR 1.15; $p = 0.005$). No dose-response correlation was observed in this cohort. Prescribed dose to the brachytherapy CTV (D90) correlated with acute and late physician reported proctitis while CTV volume, CTV width and high dose regions in the CTV (D1cc/D2cc) were associated with endoscopic toxicity at the tumour site.

Conclusion

Tumour volume is the most important predictive factor for tumour response and a higher dose to the brachytherapy CTV increases the risk of severe clinically and endoscopically observed proctitis after definitive radiotherapy in elderly patients with rectal cancer.

INTRODUCTION

Over the last decades, radiotherapy for rectal cancer has developed substantially. While total mesorectal excision (TME) with or without neoadjuvant (chemo)radiotherapy remains the gold standard, risk of surgical morbidity and mortality and the possibility of a clinical or pathologic complete response after neoadjuvant treatment have led to increasing interest in organ preservation strategies.[1,2] Especially in elderly fragile patients with multiple comorbidities, surgical risks might outweigh the possible improved long-term oncological outcome.[3] With rising awareness for organ preservation, it is important to understand which factors are associated with a complete response. Previous studies describe a radiotherapy dose-effect relationship for rectal cancer.[4,5] A possible option for dose escalation is the use of high-dose rate endorectal brachytherapy (HDREBT), which allows for high doses to the tumour with sparing of the surrounding organs.

The HERBERT study was a dose escalation study, performed to evaluate the feasibility of a HDREBT boost after external beam radiotherapy (EBRT) in elderly patients with T2-3N0-2 rectal cancer who were unfit for standard TME surgery. The primary endpoint was the maximum tolerated brachytherapy boost dose after 13×3 Gy external beam radiotherapy. This was set at 3×7 Gy after three patients in the dose level with 8 Gy per fraction experienced acute grade 3 proctitis.[6]

Of the 38 patients included in the study, 35 completed brachytherapy treatment and 33 had endoscopic follow-up and were therefore evaluable for response analyses. Overall response was high (90% complete or partial response) and 60% achieved a clinical complete response. Severe toxicity was however not uncommon and occurred in approximately one third of patients.[6]

Few other studies have used HDREBT in treatment of rectal cancer. Treatment schedules between these studies vary widely and no consensus exists on dose prescription, fractionation or constraints for organs at risk.[7] Therefore it is of importance to better understand which patient, tumour and treatment characteristics have predictive value for tumour response and toxicity. This will aid in selection of patients who are most likely to benefit from a HDREBT boost. The aim of the current analyses is to evaluate patient-, tumour- and treatment parameters in relation with tumour response and toxicity in the HERBERT study.

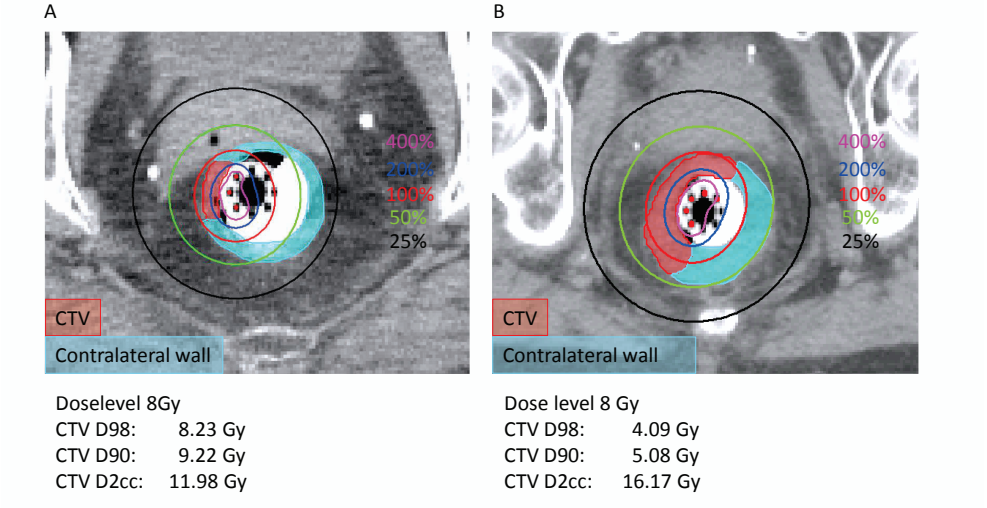
MATERIALS AND METHODS

A dose finding feasibility study was performed from 2007 to 2013 in elderly or medically inoperable patients with cT2-3N0-2 rectal cancer. Patients received 13 fractions of 3 Gy EBRT followed by three weekly HDREBT applications of 5, 6, 7 or 8 Gy per fraction six weeks after EBRT. Details of the study design and methods have been described previously.[6,8]

Endorectal Brachytherapy

For HDREBT a flexible applicator with a central canal and 8 peripheral catheters (Intracavitary Mold Applicator, ELEKTA, Veenendaal, The Netherlands) was used in combination with an inflatable semi-circular balloon to fixate the applicator and push away the normal rectal wall. HDREBT was performed with an Iridium-192 source using a microSelectron HDR after loader (Elekta, Veenendaal, the Netherlands). Treatment planning was performed with Oncentra Brachy (Elekta, Veenendaal, the Netherlands) on a planning-CT with applicator in situ acquired prior to the first brachytherapy application.

The aim of treatment planning was complete coverage of the clinical target volume (CTV) by the 100% isodose with no hotspots in the surrounding organs. The CTV was defined as the area suspicious for residual tumour and/or scarring at time of brachytherapy. Delineated was performed on the planning-CT by two observers using information of the diagnostic MRI, endoluminal clips at the proximal and distal border of the tumour, and rectoscopy images with a clinical drawing acquired prior to EBRT and during the first brachytherapy session. In case of discrepancy between observers, consensus was sought for the definitive CTV.[6,9] The 100% isodose was restricted to 2 cm from the applicator surface and during the course of the study an additional constraint of 400% at the applicator surface was added. The brachytherapy treatment plan of the first fraction was used for the 2nd and 3rd fraction. Orthogonal x-rays, visualizing endoluminal clips that were placed at the borders of the tumour, allowed for position verification at time of each brachytherapy fraction.[10]



Doselevel 8Gy
CTV D98: 8.23 Gy
CTV D90: 9.22 Gy
CTV D2cc: 11.98 Gy

Dose level 8 Gy
CTV D98: 4.09 Gy
CTV D90: 5.08 Gy
CTV D2cc: 16.17 Gy

Figure 1. Example of brachytherapy treatment planning in a patient with a small tumour (A) and with a larger tumour (B). To achieve acceptable tumour coverage in the larger tumour, dose to the HDREBT CTV D2cc is increased. As a result, tumour volume and the CTV D2cc are correlated.

Tumour characteristics and DVH parameters

The tumour was delineated on the diagnostic MRI to assess the baseline tumour volume. The HDREBT CTV, contralateral rectal wall and anal canal were delineated on the HDREBT planning-CT. The contralateral rectal wall was defined as the rectal wall, excluding lumen and CTV, extending 3 cm proximal and distal to the CTV. Figure 1 shows two examples of contoured structures and HDREBT planning. Dose-volume histogram (DVH) parameters were collected from the initial planning-CT for CTV coverage: CTV D98 and CTV D90 and for high dose regions in the CTV; D1cc, D2cc and D5cc and dose in the contralateral wall and the anal canal: D2cc and D5cc. A point dose on the lumen side of the contralateral wall directly opposing the centre of the CTV was also collected. All doses are described as physical dose per HDREBT fraction (Gy/#). In addition, the isodose volumes, including applicator and lumen, corresponding to a cumulative total 2 Gy equivalent total dose (EQD2) of 60 Gy and 75 Gy were acquired using an $\alpha/\beta = 3$ for late toxicity endpoints and $\alpha/\beta = 10$ for tumour control [4] and acute toxicity.

Endpoints

Clinical tumour response evaluation was based on digital rectal examination and endoscopy and was performed prior to brachytherapy, at two and six months and yearly after brachytherapy. Maximum response was determined, including information of multiple endoscopic evaluations if needed, and was categorised as clinical complete response (cCR), partial response (PR; > 30% decrease of tumour bulk on endoscopy images), stable disease (SD; ≤ 30% decrease or ≤ 20% increase) or progressive disease (PD; > 20% increase in tumour bulk on endoscopy images). Complete responders (cCR) were compared to non-complete responders (no cCR). Sustained response was defined as complete or partial response with time calculated from start of EBRT to progression. Patients were censored at time of death or loss of follow-up.

Evaluation of clinical and endoscopic toxicity has been previously reported.[8] In summary, toxicity was assessed via three methods: (1) Patient reported bowel symptoms (PROM), assessed by questionnaires acquired from start of HDREBT to 2 months after HDREBT. Symptoms concerning pain with stools, painful abdominal cramps/urge, tenesmus, mucus discharge, faecal incontinence and bowel function in general were scaled; (2) Clinical toxicity (CTCAE v3): acute and late clinical proctitis and late ≥grade 2 rectal bleeding and incontinence; and (3) Endoscopic evaluation: endoscopically scored toxicity at the tumour site was categorised as 0. erythema or scarring, 1. superficial ulcer and 2. (very) deep ulcer, and toxicity at the contralateral wall as 0. normal mucosa; 1. mild erythema; 2. diffuse erythema and punctate haemorrhage; 3. frank haemorrhage and 4. ulceration.[11] Patients with SD or PD were excluded for late toxicity and evaluation of endoscopically scored toxicity at the tumour site.

Statistical analyses

Statistical analyses were performed with SPSS version 23.0 (IBM, Armonk, NY). Correlation of factors was assessed using Spearman's correlation. Further analyses for association were performed with the Armitage test for trend for ordinal variables and the Kruskal-Wallis H and Mann-Whitney *U* test for continuous variables. Logistic regression and cox-regression were used for uni- and multivariable analyses. Due to small sample size, multivariable analyses were only performed for binary outcome measures with a maximum of 2 variables. A p-value < 0.01 was considered significant to correct for multiple testing.

Table 1. Tumour and treatment parameters

Clinical tumour stage	n	%
cT2	20	57.1%
cT3	15	42.9%
cN1-2	11	31.4%
Baseline tumour measurements	median	range
Tumour volume (cc)*	11.3	2.1 - 39.8
Tumour thickness (mm)*	16	5 - 34
Tumour length (cm)^	4.0	1.5 - 6.0
Distance from anal verge (cm)^	6.0	2.0 - 15.0
Tumour circumference (%)^	40	15 - 90
HDREBT CTV characteristics$		
CTV volume (cc)$	7.2	2.0 - 25.0
CTV max thickness (mm)$	10	4 - 30
CTV length (cm)$	3.1	1.8 - 6.4
CTV width (cm)$	3.8	1.0 - 7.9
CTV circumference (%)$	30	20 - 80
HDREBT DVH parameters per fraction		
CTV D98 (Gy/#)	6.0	1.2 - 8.8
CTV D90 (Gy/#)	7.2	1.8 - 9.8
CTV D1cc (Gy/#)	14.9	7.9 - 28.4
CTV D2cc (Gy/#)	12.9	5.3 - 22.5
CTV D5cc (Gy/#)	9.2	3.6 - 15.0
Contralateral rectal wall		
Contralateral wall D2cc (Gy/#)	8.1	3.7 - 14.2
Contralateral wall D5cc (Gy/#)	5.9	2.6 - 11.6
Point dose contralateral wall (Gy/#)	5.0	1.7 - 18.7
Anal canal		
Anal canal D2cc (Gy/#)	1.2	0.0 - 4.4
Anal canal D5cc (Gy/#)	1.0	0.0 - 3.2
Volume cumulative dose#		
Volume EQD2 60 Gy α/β =3 (cc)	102.9	26.2 - 203.1
Volume EQD2 60 Gy α/β =10 (cc)	61.9	16.9 - 123.6
Volume EQD2 75 Gy α/β =3 (cc)	50.0	13.7 - 104.4
Volume EQD2 75 Gy α/β =10 (cc)	33.0	9.0 - 70.3

* Based on delineation on diagnostic MRI, ^ Based on diagnostic endoscopy and MRI, $ Based on HDREBT planning-CT, # Volume derived from isodose lines (including applicator) corresponding to a cumulative dose of 60 and 75 Gy.

Abbreviations: HDREBT, High dose rate endorectal brachytherapy; EQD2, equivalent dose in 2 Gy fractions; Gy/#, Gy per brachytherapy fraction.

RESULTS

Thirty-five of 38 patients included in the study completed treatment and were included in the current analyses. All 35 patients were available for evaluation of acute toxicity, 26 for late toxicity and 33 for response evaluation. Baseline patient characteristics have been previously reported.[6] Patients were mainly elderly with a median age of 83 years and most patients had severe comorbidity, with 80% classified as American Society of Anaesthesiology III to IV and 69% anticoagulant use. Twenty patients had a cT2 tumour and fifteen a cT3 tumour. Of these fifteen, five had a tumour with > 5 mm fat infiltration (cT3c/d). MRI showed positive nodes in 11 patients; N1 in 9 patients and N2 in 2 patients. Baseline tumour characteristics and brachytherapy dose-volume histogram (DVH) parameters are listed in Table 1.

Clinical tumour response

After full treatment, clinical complete response was achieved in 20 of 33 evaluable patients. Seven of these patients already had a cCR after EBRT alone. A sustained partial or complete response (SR) was seen in 61.8% at one year, 54.7% at two years and 46.5% at three years, with a median SR of 32 months. Table 2 shows the results of the univariable analyses for cCR and for SR. Volume at baseline was the only significant predictive factor for clinical complete response; OR 1.15 (cc) p = 0.005. Median volume of patients with a complete response was 10.8 cc vs. 27.3 cc in patients without cCR (see Figure 2A).

Table 2. Univariable analyses for clinical complete response and sustained response

	Complete response			**Sustained response (CR/PR)**		
	OR	**(95% CI)**	**p**	**HR**	**(95% CI)**	**p**
Baseline		*n=33*			*n=33*	
cT-stage (cT3 vs. cT2)	1.75	(0.43-7.17)	0.44	1.32	(0.50-3.53)	0.58
cN-stage (N1-2 vs. N0)	4.67	(0.99-21.9)	0.05	2.15	(0.80-5.79)	0.13
Volume at baseline (cc)	1.15	(1.04-1.27)	0.005	1.05	(1.01-1.09)	0.02
Circumference at baseline (per 10%)	1.49	(0.99-2.26)	0.06	1.33	(1.04-1.68)	0.02
Thickness at baseline (mm)	1.16	(1.02-1.33)	0.02	1.08	(1.01-1.16)	0.03
Length at baseline (cm)	1.23	(0.72-2.10)	0.45	1.06	(0.75-1.51)	0.73
Distance to anal verge (cm)	0.99	(0.81-1.21)	0.91	0.98	(0.85-1.13)	0.78
HDREBT		*n=26**			*n=33*	
CTV volume (cc)	1.29	(0.98-1.69)	0.07	1.11	(1.01-1.21)	0.03
CTV circumference (per 10%)	2.21	(1.09-4.47)	0.03	1.36	(1.04-1.78)	0.03
CTV thickness (mm)	1.23	(0.96-1.56)	0.10	1.05	(0.96-1.15)	0.31
CTV length (cm)	1.64	(0.57-4.73)	0.36	1.64	(1.02-2.63)	0.04
CTV width (cm)	1.59	(0.76-3.34)	0.22	1.34	(0.96-1.87)	0.08
CTV D98 (Gy)	1.02	(0.62-1.69)	0.93	1.22	(0.82-1.80)	0.33
CTV D90 (Gy)	0.98	(0.62-1.55)	0.93	1.2	(0.84-1.73)	0.32
CTV D1cc (Gy)	1.16	(0.93-1.43)	0.19	1.13	(1.02-1.26)	0.03
CTV D2cc (Gy)	1.28	(0.94-1.74)	0.12	1.19	(1.03-1.38)	0.02

* Effect of HDREBT variables on cCR were tested in patients with PR/SD at time of brachytherapy.

Abbreviations: HDREBT, high-dose rate endorectal brachytherapy; CTV, clinical target volume.

Significant results (p<0.01) in bold and trends (p=0.01-0.05) in italics.

Clinical nodal stage, response to EBRT, tumour thickness at baseline and HDREBT CTV circumference all showed a trend for association with cCR. In patients with positive lymph nodes, complete tumour response rate was 36% compared to 73% in cN0 patients (p = 0.05). Thirteen of twenty-one patients with a partial response after EBRT achieved a cCR after HDREBT, while none of five patients with stable disease achieved a cCR (p = 0.01). For sustained response a trend was observed for tumour volume, circumferential involvement and thickness at baseline and for HDREBT CTV volume, length and circumferential involvement (see Table 2). The effect of tumour volume at time of diagnosis and at time of brachytherapy on complete and sustained response is illustrated in Figure 2. Patients with a baseline tumour volume < 20 cc had a 2 year sustained response rate of 74% compared to only 25% for patients with baseline tumour volume > 20 cc (p = 0.007).

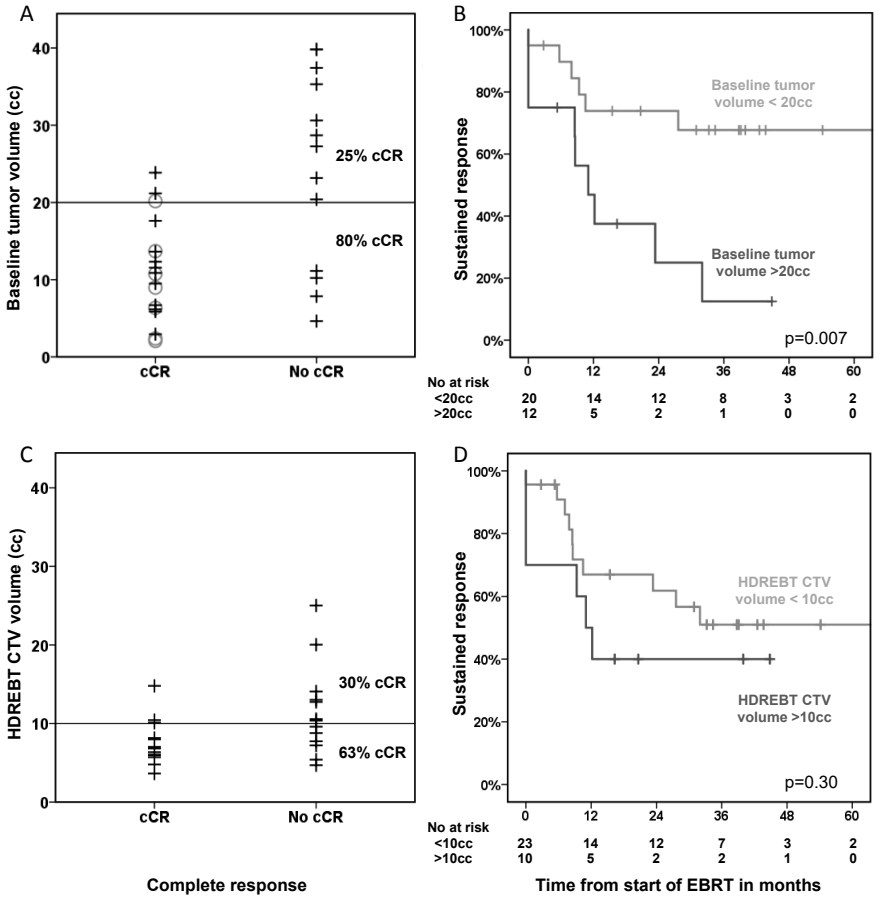


Figure 2. Correlation of tumour volume with clinical complete response and sustained partial/complete response. (A) Correlation of baseline volume with clinical complete response* (B) Sustained response according to baseline tumour volume. (C) Correlation of HDREBT CTV volume with clinical complete response* (D) Sustained response according to HDREBT CTV volume.

*Patients with a cCR after EBRT are displayed in grey circles in Figure A and are excluded in Figure C.

Table 3. Factors associated with toxicity

	ρ	p-value	Explained variance
PROM acute proctitis scale			
CTV D98 (Gy/#)	0.43	*0.03*	18.2
CTV D90 (Gy/#)	0.46	*0.02*	20.7
CTV D1cc (Gy/#)	0.56	**0.003**	31.4
CTV D2cc (Gy/#)	0.51	**0.007**	25.9
CTV D5cc (Gy/#)	0.50	*0.03*	24.5
CTCAE acute proctitis			
Tumour thickness at baseline (mm)	0.44	**0.005**	19.5
CTV D98 (Gy/#)	0.43	*0.01*	18.4
CTV D90 (Gy/#)	0.46	**0.006**	21.0
CTCAE severe late proctitis			
CTV D90 (Gy/#)	0.43	*0.03*	18.5
Endoscopic toxicity at the tumour site			
CTV volume (cc)	0.44	*0.03*	19.4
CTV width (cm)	0.53	**0.006**	28.1
CTV D1cc (Gy/#)	0.42	*0.03*	21.0
CTV D2cc (Gy/#)	0.59	**0.001**	41.7
Volume EQD2 60 Gy (cc)	0.55	**0.004**	26.2
Volume EQD2 75 Gy (cc)	0.57	**0.003**	26.6

Abbreviations: PROM, patient reported outcome measure; CTV, clinical target volume; Gy/#, Gy per brachytherapy fraction.

Only factors with a trend or significant correlation are listed. Results of the complete analyses are in the supplementary material. Statistics: Spearman correlation; significant results ($p<0.01$) in bold and trends ($p=0.01$-0.05) in italics.

No dose-response correlation was observed for HDREBT CTV dose coverage (D98/D90). After correction for CTV volume in multivariable analyses still no association could be established. In univariable analyses HDREBT CTV high dose regions (D1cc/D2cc) showed a negative association with cCR and SR. CTV D2cc was however correlated to CTV volume ($\rho = 0.63$; $p<0.001$), illustrated in Figure 1) and after correction for CTV volume in multivariable analyses this association was no longer detected.

Toxicity

Clinically relevant correlations between patient, tumour and DVH-parameters with toxicity endpoints are shown in Table 3. Full analyses are provided in Supplementary Table S1.

Acute toxicity

For patient reported bowel symptoms, a dose-response association was found for all DVH parameters of the HDREBT CTV, with the strongest correlation of $\rho = 0.56$ for CTV D1cc. Acute physician reported toxicity (CTCAE v3) was correlated to tumour thickness at baseline and HDREBT CTV D90 and D98. Median HDREBT CTV D90 was 6.6 Gy/# (range 4.7-9.3 Gy) for grade ≤1; 7.8 Gy/# (range 1.8-9.8 Gy) for grade 2 and 8.7 Gy/# (range 7.2- 9.8 Gy) for grade 3 acute proctitis ($p = 0.04$; see Figure 3A).

Late proctitis

Severe late proctitis (≥ grade 3 proctitis CTCAE v3) occurred in 10/25 patients who achieved a cCR or cPR. Only HDREBT CTV D90 showed a correlation (see Table 3 and Figure 3). Severe late proctitis occurred in 0/5 (0%) patients with a CTV D90 < 6 Gy/#, in 5/13 (38%) patients with a CTV D90 between 6 and 8 Gy/# and in 5/7 (71%) patients with a CTV D90 exceeding 8 Gy/# (p = 0.02). In multivariable analyses the effect of CTV D90 remained correlated to severe late proctitis after correction for tumour volume (CTV D90 OR 3.1 (Gy) p = 0.03 and CTV volume OR 1.3 p = 0.08). For late rectal bleeding, a trend was observed for use of anticoagulants: grade ≥ 2 rectal bleeding occurred in 1/6 patients without anticoagulants and in 12/19 patients with anticoagulant use (p = 0.05). Late incontinence was not associated with any of the clinical or dosimetric parameters (data not shown).

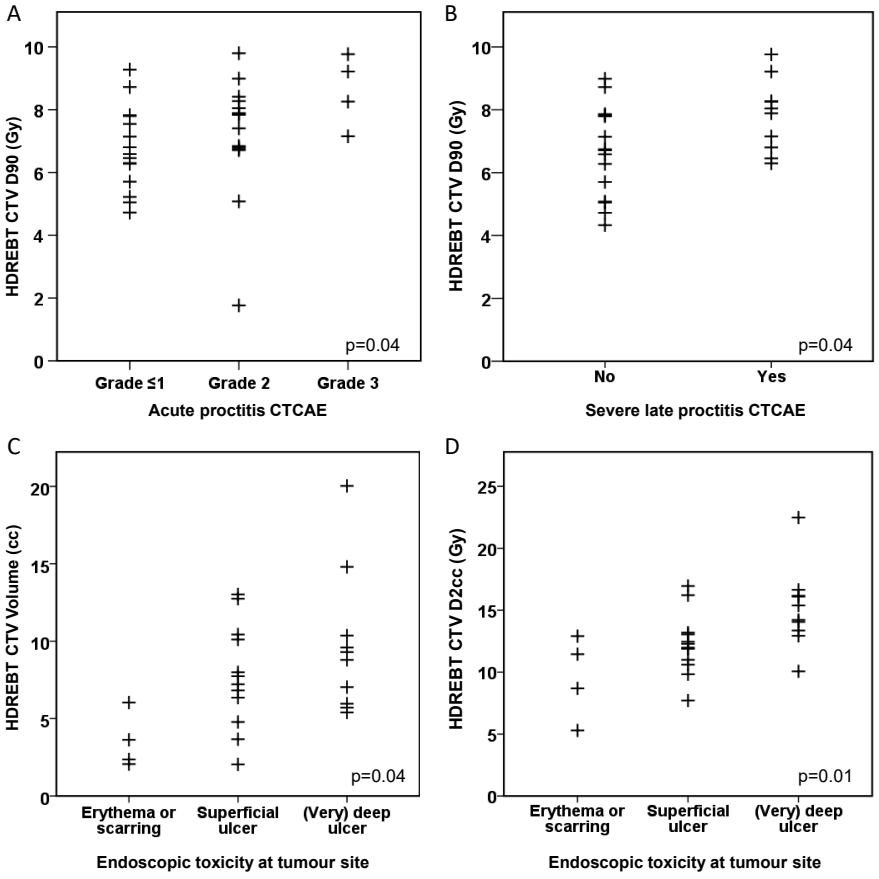


Figure 3. Factors associated with rectal toxicity.

(A) Correlation of HDREBT CTV D90 (Gy) with acute proctitis CTCAE. (B) Correlation of HDREBT CTV D90 (Gy) with severe late proctitis CTCAE. (C) Correlation of HDREBT CTV volume (cc) with endoscopic toxicity at the tumour site. (D) Correlation of HDREBT CTV D2cc (Gy) with endoscopic toxicity at the tumour site.

Abbreviations: HDREBT, high-dose rate endorectal brachytherapy; CTV, clinical target volume.

Endoscopic toxicity

Endoscopic toxicity at the contralateral wall showed no correlation with clinical or dosimetric parameters (see Supplementary Table S1). Endoscopic toxicity at the tumour site was correlated with HDREBT CTV volume and width, CTV D1cc and D2cc and volumes of 60 and 75 Gy ($EQD2_{\alpha/\beta 3}$), showing the strongest correlation of ρ = 0.59 for CTV D2cc. Median CTV D2cc was 10.1 Gy/# (5.3-12.9) in patients with erythema or scarring, 12.1 Gy/# (7.7-17.0) in patients with a superficial ulcer and 14.8 Gy/# (10.1-22.5) in patients with a deep or very deep ulcer (see Figure 3D). Deep ulceration occurred in 7/9 (78%) of patients with a CTV D2cc > 14 Gy/# and in 3/18 (17%) patients with a CTV D2cc < 14 Gy/# (p = 0.002).

DISCUSSION

This sub-analysis of the HERBERT study evaluated factors associated with tumour response and toxicity after a combination of EBRT and a brachytherapy boost in patients with rectal cancer. The results show that the most important predictor for a clinical complete response is tumour volume at baseline. Other factors that were associated with cCR included limited tumour thickness at baseline, a good response to EBRT and limited circumferential involvement at time of brachytherapy. Tumour volume, thickness and circumference at baseline were associated with a sustained partial/complete response. While we could not demonstrate a relation between brachytherapy dose and tumour response, a dose-effect relationship was observed for most toxicity endpoints. Prescribed dose to the brachytherapy CTV (D90) correlated best with acute and late physician reported proctitis and high dose regions in the CTV (D1cc/D2cc) were associated with patient reported toxicity and endoscopic toxicity at the tumour site.

The current analysis provides unique data on factors associated with response and toxicity after HDREBT for rectal cancer. While reports on HDREBT are limited, previous studies on definitive radiotherapy using contact-X-ray have demonstrated that T-stage, tumour size, mobility/depth of invasion and early response to radiotherapy are strong prognostic factors for complete clinical tumour response.[12-16] Studies evaluating pathologic complete response after preoperative (chemo)radiotherapy have further shown a correlation with cT-, cN- and cM-stage, histological subtype (in favour of adenocarcinoma), differentiation grade, presence of vascular or lymphatic invasion (LVSI), the addition of neoadjuvant chemotherapy, radiotherapy dose escalation and timing from CRT to surgery.[4,17-21]

Factors associated with tumour response in the current study were tumour volume, thickness, circumferential involvement, cN-stage and response to EBRT. cT-stage showed no correlation, but it has long been recognised that tumour volume is a stronger predictor than cT-stage.[22,23] While there was substantial variation in total cumulative CTV D90, with a median $EQD2_{\alpha/\beta 10}$ of 72.9 Gy (IQ-range: 68-80 Gy) we did not observe a dose-response correlation. This can probably mainly be contributed to the limited number of 35 patients. The effect of dose escalation could also have

been overshadowed by other factors such as tumour volume. Also, the use of one planning-CT scan for 3 fractions could have resulted in a different dose coverage at the 2nd and 3rd fraction limiting the dose-response analyses.[9,24] In addition, while aided by clips, MRI and endoscopy, soft tissue resolution on CT is poor and residual uncertainty in delineation may occur.[25,26] A negative correlation was observed for high dose regions to the brachytherapy CTV, which was interpreted, and confirmed by multivariable analysis, as an indirect effect of tumour volume.

Rectal morbidity after radiotherapy is a well-known problem and is especially challenging in definitive radiotherapy for rectal cancer given that the tumour is incorporated in the organ at risk. Only one study has prospectively evaluated toxicity after chemoradiation and a HDR boost. Cumulative EQD2 was 66 Gy and although overall functional outcome was good, rectal bleeding was present in approximately 80% > 1 year after treatment.[27] This study is the first to evaluate prognostic factors for radiation proctitis in patients with rectal cancer. From previous studies in patients with prostate and gynaecological malignancies we know that radiation dose and co-morbidity including diabetes mellitus and haemorrhoids have been associated with increased risk of acute and late rectal toxicity.[28] Additional risk factors for late rectal morbidity include age, history of abdominal surgery, presence of cardiovascular disease, use of anticoagulants, smoking and the presence of acute rectal toxicity.[28-33]

In our study, a higher dose to the brachytherapy CTV (D90) was associated with patient and physician reported proctitis and brachytherapy CTV volume and CTV D1cc and D2cc were correlated with ulceration at the tumour site. No association was observed for patient comorbidities or dose to the normal rectal wall. Our study population however existed entirely of elderly/frail patients with comorbidity who were therefore all at increased risk of rectal toxicity. Despite the absence of a clear dose-response correlation, it is advisable to limit the dose in the normal mucosa as much as possible.

Limitations of this study are the small number of patients and multiple tests performed, making it on the one hand difficult to distinguish between real effects and random variations, whereas on the other hand real effects might remain undetected. Also, we included patients with a partial response in the toxicity analyses and have to consider the following in the interpretation of the results. Firstly, proctitis could partly be caused by residual tumour limiting the correlation with other parameters, and secondly, both toxicity and tumour regression can result in ulceration. We observed a correlation for both volume and CTV D2cc with ulceration at the tumour site, which is likely a combined result of regression in large tumours and ulceration after high doses to the mucosa.

The HDREBT technique has evolved since the HERBERT study and the current findings have to be validated in future studies using optimal brachytherapy treatment planning with incorporation of repeated CT-scanning before every fraction.[9,24] The use of spacing balloon(s) to improve applicator positioning, together with optional use of shielding in the central canal, contribute to decreasing dose to organs at risk.[24] Use of MRI with applicator in situ, has the advantage of visualisation of the residual GTV at time of brachytherapy, and has been shown to improve the

reproducibility of target delineation in other sites.[25,26] MRI would also allow the use of an adaptive target concept that takes tumour regression during treatment into account and can further direct dose optimisation for areas at risk of macroscopic residual tumour and at risk for microscopic disease. Consensus on target definition and dose reporting are needed to further improve the understanding of dose-effect relationships for HDREBT from an international perspective.

The findings of the current study can be useful in selection of patients for definitive radiotherapy. It seems that patients with a baseline tumour volume < 20 cc and at least a partial response to EBRT are good candidates for a brachytherapy boost. Use of anticoagulants increases the risk of late rectal blood loss and this should be considered when counseling patients for this treatment. As previously reported, the recommended brachytherapy boost dose after 13×3 Gy EBRT was determined to be 7 Gy per fraction.[6] Based on the current analyses we advise to aim for a maximum CTV/rectal wall D2cc of 200% (14 Gy/#) to limit the risk of deep ulceration. While some of the patients that were treated with 7 Gy per fraction did experience severe late proctitis, we expect that with improved patient selection, technique and the suggested additional constraint we will observe less severe toxicity. Further research on the added value and risks of a HDREBT boost in elderly patients with limited treatment options is necessary. A proposed follow-up study for medically inoperable rectal cancer patients (HERBERT II) will randomise between EBRT alone and EBRT followed by a HDREBT boost in using these treatment planning aims.

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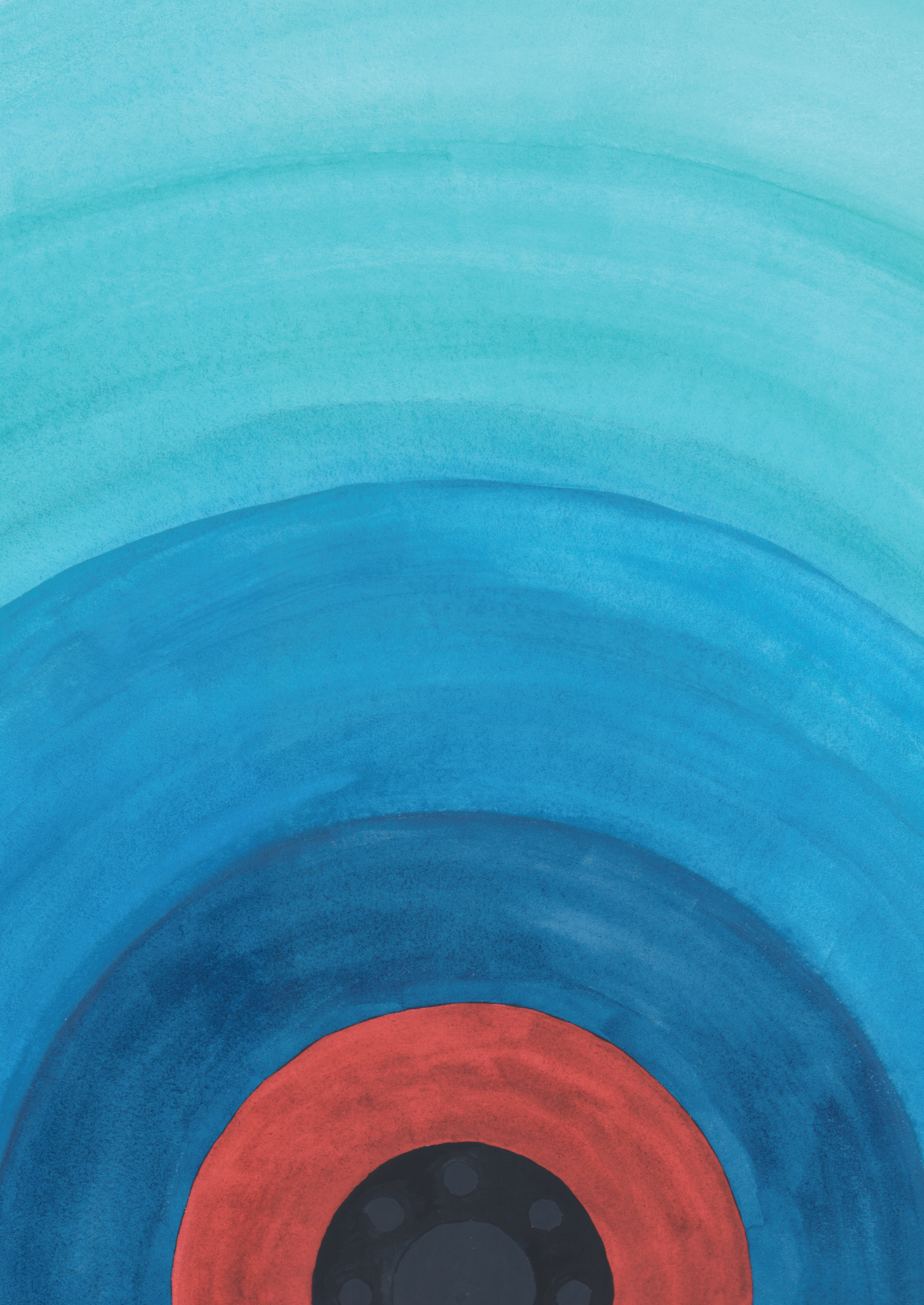
SUPPLEMENTARY MATERIAL

Table S1. Spearman correlation for toxicity analyses

	PROM Bowel scale		Acute proctitis CTCAE		Severe late proctitis CTCAE		Endoscopic toxicity at contralateral wall		Endoscopic toxicity at tumour site	
Characteristics	**ρ**	**p-value**	**ρ**	**p-value**	**ρ**	**p-value**	**ρ**	**p-value**	**ρ**	**p-value**
T-stage	-0.005	0.98	-0.17	0.32	-0.44	*0.03*	0.02	0.93	0.21	0.3
N-positive	0.14	0.51	-0.03	0.84	-0.2	0.33	0.04	0.84	0.15	0.46
Tumour length at baseline (cm)	0.22	0.27	-0.08	0.65	0.11	0.61	0.01	0.94	0.27	0.19
Tumour distance from anal ring (cm)	-0.25	0.22	-0.23	0.19	-0.21	0.32	-0.24	0.19	0.02	0.91
Tumour thickness at baseline (mm)	-0.04	0.84	0.44	*0.01*	0.23	0.26	-0.28	0.13	0.16	0.45
Tumour volume at baseline (cc)	0.03	0.89	0.1	0.57	0.15	0.48	-0.23	0.21	0.34	0.09
Tumour circumference at baseline (%)	0.11	0.58	0.07	0.7	0.12	0.57	-0.05	0.8	0.34	0.09
HDREBT CTV volume (cc)	0.09	0.67	0.09	0.61	0.11	0.59	0.15	0.41	0.44	*0.03*
HDREBT CTV max thickness	-0.15	0.47	0.1	0.59	0.11	0.59	0.09	0.63	0.14	0.5
HDREBT CTV length (cm)	-0.07	0.75	0.23	0.18	-0.04	0.85	-0.21	0.25	0.11	0.6
HDREBT CTV width	0.08	0.69	0.13	0.47	0.22	0.29	0.2	0.28	0.53	**0.006**
HDREBT CTV circumference (%)	-0.03	0.9	0.17	0.33	0.21	0.31	0.08	0.65	0.33	0.1
HDREBT CTV D98 (Gy)	0.43	*0.03*	0.38	*0.02*	0.38	0.06	-0.18	0.33	-0.12	0.57
HDREBT CTV D90 (Gy)	0.45	*0.02*	0.42	*0.01*	0.43	*0.03*	-0.16	0.38	-0.1	0.63
HDREBT CTV D1cc (Gy)	0.56	**0.003**	0.28	0.11	0.17	0.42	0.15	0.42	0.42	*0.03*
HDREBT CTV D2cc (Gy)	0.5	*0.01*	0.22	0.21	0.29	0.15	0.31	0.09	0.59	**0.001**
HDREBT CTV D5cc (Gy)	0.5	*0.03*	0.31	0.12	0.35	0.13	0.23	0.28	0.22	0.34
Contralateral rectal wall D2cc (Gy)	0.3	0.14	0.12	0.5	-0.05	0.83	0.29	0.11	0.38	0.05
Contralateral rectal wall D5cc (Gy)	0.3	0.13	0.02	0.91	-0.12	0.55	0.27	0.15	0.42	*0.03*
Contralateral rectal wall point dose (Gy)	0.11	0.61	0.2	0.26	0.2	0.33	0.19	0.31	0.41	*0.04*
Anus D2cc (Gy)	0.13	0.54	0.1	0.57	0.15	0.48	0.21	0.26	0.04	0.86
Anus D5cc (Gy)	0.03	0.9	-0.07	0.7	0.04	0.86	0.33	0.09	0.23	0.29
V60Gy (EQD2 a/b=10) (cc)	0.38	0.05	0.12	0.5						
V75Gy (EQD2 a/b=10) (cc)	0.37	0.06	0.16	0.35						
V60Gy (EQD2 a/b=3) (cc)					-0.02	0.91	0.13	0.46	0.55	**0.004**
V75Gy (EQD2 a/b=3) (cc)					-0.02	0.91	0.14	0.43	0.57	**0.003**

Abbreviations: PROM, patient reported outcome measure; CTV, clinical target volume; Gy/#, Gy per brachytherapy fraction.

Significant results (p<0.01) in bold and trends (p=0.01-0.05) in italics.



Chapter 6

Benefit of adaptive CT-based treatment planning in high-dose-rate endorectal brachytherapy for rectal cancer

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ABSTRACT

Purpose

In this planning study, we investigated the dosimetric benefit of repeat CT-based treatment planning at each fraction versus the use of a single CT-based treatment plan for all fractions for high-dose rate endorectal brachytherapy (HDREBT) for rectal cancer.

Materials and methods

We included eleven patients that received a CT scan with applicator in situ for all three fractions. The treatment plan of the first fraction was projected on the repeat CT scans to simulate the use of a single treatment plan. Additionally, replanning was performed on the repeat CT scans and these were compared to the corresponding projected treatment plans.

Results

Repeat CT-based treatment planning resulted on average in a 21% higher ($p=0.01$) conformity index compared to single CT-based treatment planning. Projecting the initial treatment plan to the repeat CT scans of fraction two and three, 12/22 fractions reached a CTV D98 of 85% of the prescribed dose of 7 Gy, which increased to 14/22 using replanning. For the remaining fractions, median CTV D98 was 4.2 Gy and an intervention would be necessary to correct applicator balloon setup or to remove remaining air and/or feces between the CTV and the applicator.

Conclusions

Using a single CT-based treatment plan for all fractions may result in a suboptimal treatment at later fractions. Therefore, repeat CT imaging should be the minimal standard practice in HDREBT for rectal cancer to determine whether an intervention would be necessary. Replanning based on repeat CT imaging resulted in more conformal treatment plans and is therefore recommended.

INTRODUCTION

Total mesorectal excision is the mainstay in the treatment of rectal cancer. For more advanced cases, the addition of neoadjuvant (chemo)radiotherapy has resulted in lower local recurrence rates, but none of the recent trials has demonstrated a benefit in overall survival.[1-4] Unfortunately, (chemo)radiotherapy is associated with an increased risk of side effects such as bowel and sexual dysfunction.[5] Vuong et al. introduced high-dose rate endorectal brachytherapy (HDREBT) as a replacement of neoadjuvant external beam radiation therapy (EBRT) with promising results in local control.[6,7] For patients unfit or unwilling to undergo surgery, definitive or palliative radiotherapy are alternatives. Rijkmans et al. demonstrated the feasibility of a HDREBT boost after EBRT in inoperable patients.[8] Compared to EBRT, HDREBT can deliver high doses to the tumour while sparing surrounding organs due to a steeper dose gradient.[7] As a consequence, HDREBT has the potential to decrease morbidity and reduce the risk of side effects.[9] However, the steeper dose gradient means that an anatomical inter-fraction variation of millimetres can have a high impact on the delivered dose to the target volume or surrounding organs. Therefore, high precision is required in imaging, contouring and treatment planning.

For HDREBT treatment planning, the conventional approach is to use the treatment plan generated at the first fraction, for all later fractions.[10,11] Alternatively, an adaptive approach could be used by creating a new treatment plan based on new imaging acquired at each fraction, taking into account inter-fraction anatomical variation.[12,13] For cervical cancer, several studies on image-guided brachytherapy compared the use of one treatment plan for all fractions to an adaptive approach using a newly generated treatment plan at each fraction.[14,15] The treatment plan for the first fraction was simulated on the imaging of the later fractions. The results showed that the treatment plan based on imaging of the first fraction did not lead to comparable target volume coverage and dose to organs at risk at later fractions.[14,15] Nowadays, repeat MR imaging is therefore recommended in brachytherapy for cervical cancer.[16]

Most studies on the use of HDREBT for rectal cancer focus on oncological outcome and treatment related toxicity in the pre-operative setting, with limited detail on treatment planning. They do not address the question of using a non-adaptive or adaptive approach.[9,17-19] Vuong *et al.* initially reported a non-adaptive approach using one planning CT scan with applicator in situ on which a treatment plan is generated and used for all later fractions.[10,11] Recent publications by the same group describe an adaptive approach generating a new treatment plan based on a new CT scan for each fraction.[12,13] A recent abstract concludes that an adaptive approach resulted in a more conformal dose distribution.[20]

In our study, we further investigated the comparison between a non-adaptive and an adaptive approach and added a quantification of conformity. Additionally, we analysed the repeat CT scans and reported causes of insufficient target volume coverage. The aim of this study was to determine the differences regarding treatment plan conformity, target volume coverage and dose to organs at risk between using a single treatment plan for all fractions versus a new treatment plan at each fraction in HDREBT for rectal cancer.

MATERIAL AND METHODS

Patient selection

For the current study, we selected eleven patients from the HERBERT trial in whom repeat CT scans with applicator in situ were available at each fraction (the HERBERT trial, registered with the Dutch Central Committee on Research Involving Human Subjects; registration no. NL17037.031.07).[8,21]

Treatment

All patients were treated with 13×3 Gy EBRT at four fractions per week, followed by three weekly fractions of HDREBT using a prescription dose of 5-8 Gy starting six weeks after conclusion of EBRT. We adapted the brachytherapy equipment, application and positioning procedures from Devic *et al*. as described in Rijkmans *et al.*[8,11] Patients received an enema prior to the CT scan with applicator in situ at each fraction.

We acquired a planning CT scan with applicator in situ prior to the first fraction. An inflatable balloon around the applicator on the opposite side of the clinical target volume (CTV) was used to fixate the applicator and to decrease the dose to the normal rectal wall. Treatment planning was performed using Oncentra Brachy (Elekta, Veenendaal, The Netherlands). The aim for treatment planning was to cover the CTV with the 100% isodose while containing the 400% isodose within the applicator. Repeat CT scans with applicator in situ were acquired for research purposes. In case of obvious differences compared to the CT scan of the first fraction, the treatment plan was adapted accordingly. These adapted treatment plans were not used in this study.

Delineation

The CTV was defined as residual macroscopic tumour and scarring after EBRT. CTV, anus, mesorectum and healthy rectal wall were delineated by two observers with help of diagnostic MRI, rectoscopy images and inserted endoluminal clips at the proximal and distal border of the tumour. The rectoscopy images were acquired before EBRT and before the first brachytherapy fraction. Comparing CTV delineations between fractions of the same patient was allowed to check for consistency. In case of discrepancy between delineations, consensus was sought.

Projection and replanning

To determine the differences in conformity, CTV coverage and dose to organs at risk between the use of a single treatment plan for all fractions and a new treatment plan at each fraction, the treatment plan of the first fraction and the new treatment plan were compared for each repeat CT scan. In order to obtain the dose distribution of the initial treatment plan on the repeat CT scans, the treatment plan of the first fraction was projected on the repeat CT scans. For this

purpose, the most cranial activated dwell position was identified on the repeat CT scans in the same location with respect to the most cranial slice of the CTV delineation as on the CT scan of the first fraction. Subsequently, the dwell position pattern and dwell times were copied.
An experienced radiation treatment technologist created new treatment plans based on the repeat CT scans. As a result, for each repeat CT scan we thus obtained both a projected treatment plan of the first fraction and a new treatment plan.

Analysis

To quantify dose conformity, the COnformal INdex (COIN) parameter was used, as defined by Baltas *et al.* in the following equation:[22]

$$COIN = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \times \prod_{i=1}^{N_{CO}} \left[1 - \frac{V_{COref,i}}{V_{CO,i}}\right]$$

With TV_{RI} the tumour volume covered by the reference isodose, TV the tumour volume, V_{RI} the reference isodose volume, N_{CO} the number of critical organs, $V_{COref,i}$ the volume of the critical organ with index i covered by the reference isodose and $V_{CO,i}$ the volume of the critical organ with index i (Figure 1). The healthy rectal wall, mesorectum and anus were considered critical organs. The COIN parameter ranges from 0-1, with 0 representing no conformity and 1 representing full conformity.

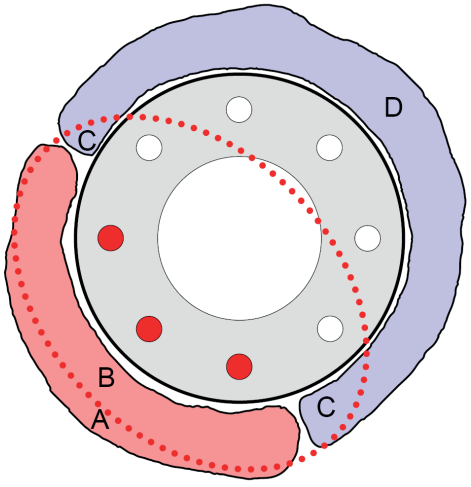

Figure 1. Schematic representation of the parameters of the COIN equation: tumour volume $(TV, A + B)$, tumour volume covered by the 100% isodose (TV_{RI}, B), healthy rectal wall $(V_{CO}, C + D)$, and healthy rectal wall covered by the 100% isodose (V_{COref}, C). VRI is the volume encompassed by the 100% reference isodose, represented by the dotted line. The three filled dots on the lower left side of the applicator represent activated dwell positions.

The HERBERT trial was a dose escalation study and patients were treated with a prescription dose of 5-8 Gy.[8] Therefore, for reporting of dose parameters, we chose to scale the dose distributions to a prescription dose of 7 Gy. To quantify CTV coverage, the CTV D98 parameter (i.e. the minimal dose to 98% of the CTV volume) was collected for each treatment plan. For the dose to organs at risk, the D2cc (i.e. the minimal dose to the 2 cc of the organ at risk that receives the highest dose) for mesorectum and anus were collected. Additionally, a point dose on the healthy rectal wall directly opposing the delineated CTV within the center slice of the CTV was chosen to quantify dose to the healthy rectal wall.
We visually analysed all CT scans and if a suboptimal applicator balloon orientation or air and/or feces between the CTV and the applicator were observed, an intervention would be required to correct applicator balloon orientation or to remove air and/or feces.

Statistics
We used SPSS Statistics 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) for statistical analysis. The Friedman test was used to test for volume differences of the CTV delineations between the three CT scans. A univariate analysis of variance was performed for each dependent variable (COIN, CTV D98, healthy rectal wall dose and D2cc of the mesorectum and anus). Included independent variables were *plan type* (projection or replanning), *intervention required* (yes or no), *timepoint* (fraction two or three) and *patient* (one through eleven). All tests were two-sided and the significance threshold was set at 0.05.

RESULTS

CTV delineation
The average delineated CTV volume for all CT scans was 6.8 cc (range 2.4-13.0). Delineated CTV volumes did not differ significantly between the three CT scans for each patient (p=0.31).

Initial treatment planning
Table 1 shows the results for COIN and CTV D98 for the treatment plan of the first fraction, all projections and all new treatment plans. Results are presented as median (range).
The median COIN for treatment plans of the first fraction was 0.14 (0.04-0.20) and the median CTV D98 was 5.8 Gy (3.6-7.3). On four of the eleven CT scans, air and/or feces was seen between the CTV and the applicator. As a result of this, combined with the constraint of the 400% isodose within the applicator, the CTV coverage and conformity were lower in the corresponding four treatment plans (Figure 2). The median COIN and CTV D98 were 0.09 (0.04-0.13) and 5.6 Gy (3.6-5.8), respectively. An intervention would be necessary to remove air and/or feces before creating a more conformal treatment plan with higher CTV coverage. The median COIN and CTV D98 for the seven remaining treatment plans was 0.15 (0.13-0.20) and 6.3 Gy (4.6-7.3), respectively.

Table 1. Conformity (COIN) and target volume coverage (CTV D98) for the initial treatment plan of the first CT scan and the projection and replanning for the repeat CT scans of all patients

Parameter	Initial treatment plan	Projections	Replanning	Mean difference projections and replanning (mean (range))	Effect of plan type (p-value)	Mean ratio (projection vs. re-planning)
Number of CT scans						
All	11	22	22			
Only interventions	4	8	8			
Excl. interventions	7	14	14			
COIN (-)						
All	0.14 (0.04 - 0.20)	0.13 (0.01 - 0.18)	0.15 (0.02 - 0.19)	0.02 (-0.02 - 0.08)	0.01	1.21
Only interventions	0.09 (0.04 - 0.13)	0.08 (0.01 - 0.15)	0.11 (0.02 - 0.16)	0.02 (-0.02 - 0.08)	0.17	1.31
Excl. interventions	0.15 (0.13 - 0.20)	0.14 (0.07 - 0.18)	0.15 (0.11 - 0.19)	0.02 (-0.01 - 0.04)	< 0.001	1.15
CTV D98 (Gy)						
All	5.8 (3.6 - 7.3)	6.4 (3.3 - 7.8)	6.6 (2.8 - 7.6)	0.3 (-1.0 - 2.4)	0.11	1.07
Only interventions	5.6 (3.6 - 5.8)	4.2 (3.3 - 6.9)	5.0 (2.8 - 5.9)	0.1 (-1.0 - 1.7)	0.89	1.03
Excl. interventions	6.3 (4.6 - 7.3)	6.9 (3.7 - 7.8)	7.0 (6.1 - 7.6)	0.5 (-0.8 - 2.4)	0.06	1.10

Result are presented as median (range) unless indicated differently.

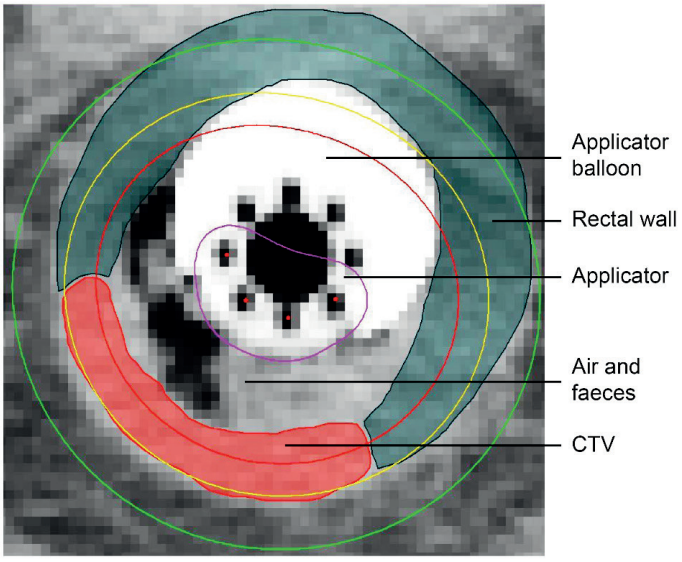

Figure 2. Example of a CT scan in which full coverage of the CTV was not possible considering the constraint of the 400% isodose within the applicator. Air and faeces are seen between the CTV and the applicator. The 400%, 100%, 75% and 50% isodoses are shown. CTV, clinical target volume.

Projection

The treatment plan of the first fraction was projected on the repeat CT scans of the second and third fraction for each patient, resulting in 22 projections. The median COIN and CTV D98 of all projections were 0.13 (0.01-0.18) and 6.4 Gy (3.3-7.8), respectively. In some of the 22 repeat CT scans, air and/or feces was seen between the CTV and the applicator (5/22), a suboptimal orientation of the applicator balloon was observed (2/22) or the applicator balloon was not inflated (1/22). For the projections on these eight repeat CT scans (from six patients), the median COIN and CTV D98 were 0.08 (0.01-0.15) and 4.2 Gy (3.3-6.9), respectively. An intervention would be necessary to remove air and/or feces or to correct applicator balloon orientation before creating a more conformal treatment plan with higher CTV coverage. For the remaining 14 projections (from nine patients), the median COIN and CTV D98 were 0.14 (0.07-0.18) and 6.9 Gy (3.7-7.8), respectively. Figure 3 shows an example of a patient in which the projections lead to similar conformity and CTV coverage as the initial treatment plan and a patient in which air and feces is seen on the CT scan of the third fraction leading to lower conformity and CTV coverage.

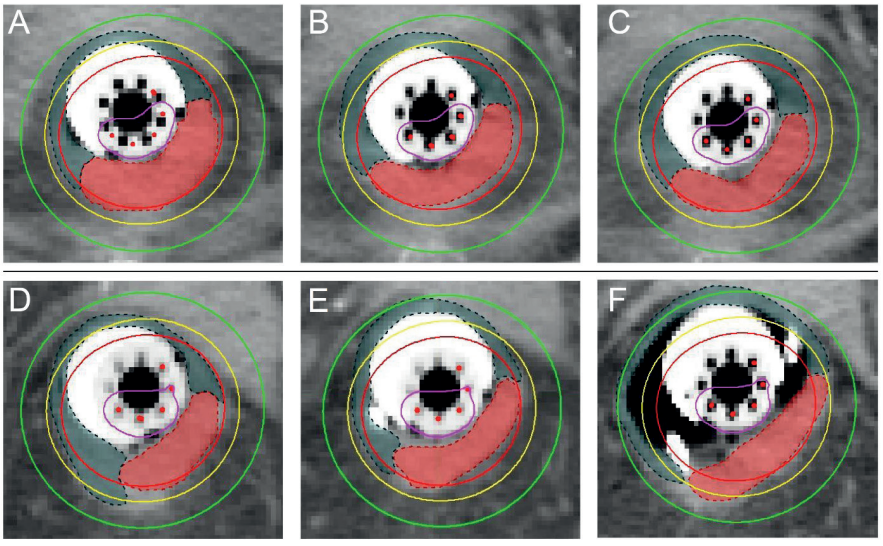

Figure 3. An example of a patient in which the projections (B+C) lead to similar conformity and CTV coverage as the initial treatment plan (A), and a patient in which the projections lead to similar conformity and CTV coverage (E) and lower conformity and CTV coverage (F, due to air and faeces) compared to the initial treatment plan (D). The 400%, 100%, 75% and 50% isodoses are shown. CTV, clinical target volume.

Replanning

New treatment plans were generated based on the repeat CT scans for each patient, resulting in 22 new treatment plans. The median COIN and CTV D98 were 0.15 (0.02-0.19) and 6.6 Gy (2.8-7.6), respectively. For the new treatment plans based on the eight repeat CT scans that required an intervention, the median COIN and CTV D98 were 0.11 (0.02-0.16) and 5.0 Gy (2.8-5.9), respectively. For the remaining 14 new treatment plans, the median COIN and CTV D98 were 0.15 (0.11-0.19) and 7.0 Gy (6.1-7.6), respectively.

Projection versus replanning

There was a statistically significant effect of *plan type* (p=0.01) and *intervention required* (p=0.002) on the COIN parameter considering all cases. The COIN was on average 21% higher after replanning compared to the projected treatment plans. Considering the cases that did not require an intervention, COIN was on average 15% higher after replanning (Table 1).

There was a statistically significant effect of *intervention required* (p=0.001) on CTV D98, considering all cases. Only borderline significance was reached on the effect of *plan type* in the subgroup of cases that did not require an intervention (p=0.06). In those cases, CTV D98 was on average 10% higher after replanning. One case showed an increase of CTV D98 of 2.4 Gy (66%, from 3.7 Gy to 6.1 Gy) after replanning and another case showed an increase of CTV D98 of 1.7 Gy (42%, from 4.0 Gy to 5.7 Gy). In one case, replanning resulted in a CTV D98 decrease of 1.0 Gy (-15%, from 6.9 to 5.9 Gy). All other differences in CTV D98 were smaller than 1.0 Gy.

When considering a plan acceptable when the CTV D98 is at least 85% of the prescribed dose and at least 90% of the initial treatment plan at the first fraction, 12/22 projections were considered acceptable versus 14/22 new treatment plans. In the eight remaining unacceptable treatment plans, an intervention would have been necessary to achieve an acceptable treatment plan.

Dose to organs at risk

The dose to organs at risk is presented in Table 2. There was a statistically significant effect of *intervention required* on D2cc of the mesorectum considering all cases (p<0.001). No other significant effects were observed. In one case, after replanning, a reduction of the rectal wall point dose larger than 1 Gy (3.1 Gy) was observed. In another case, a decrease of mesorectum D2cc of more than 1 Gy (1.3 Gy) was observed. In another patient with a very distal tumour, an increase of the anus D2cc of 2.3 Gy and 2.1 Gy for fraction two and three was observed. All other differences in anus D2cc were smaller than 1 Gy.

Table 2. Dose to organs at risk (rectal wall point dose and D2cc of mesorectum and anus) for the initial treatment plan of the first CT scan and the projection and replanning for the repeat CT scans of all patients

Parameter	Initial treatment plan	Projection	Replanning	Mean difference projection and replanning (mean (range))	Effect of plan type (p-value)	Mean ratio (projection vs. replanning)
Number of CT scans						
All	11	22	22			
Only interventions	4	8	8			
Excl. interventions	7	14	14			
Rectal wall point dose (Gy)						
All	5.2 (2.7 - 6.9)	4.8 (2.8 - 10.6)	5.1 (3.0 - 7.5)	-0.2 (-3.1 - 0.9)	0.28	0.98
Only interventions	5.0 (3.6 - 6.4)	5.1 (4.5 - 10.6)	5.2 (4.0 - 7.5)	-0.5 (-3.1 - 0.8)	0.24	0.95
Excl. interventions	5.3 (2.7 - 6.9)	4.5 (2.8 - 6.5)	4.9 (3.0 - 6.2)	-0.1 (-0.8 - 0.9)	0.66	1.00
Mesorectum D2cc (Gy)						
All	6.1 (4.8 - 7.2)	6.1 (4.0 - 8.0)	5.8 (3.9 - 7.7)	-0.2 (-1.3 - 0.7)	0.15	0.98
Only interventions	5.2 (4.8 - 7.2)	5.5 (4.0 - 8.0)	5.2 (3.9 - 7.7)	-0.4 (-1.3 - 0.6)	0.08	0.94
Excl. interventions	6.4 (5.8 - 6.8)	6.2 (4.4 - 7.5)	5.9 (4.4 - 7.2)	-0.1 (-0.8 - 0.7)	0.65	1.00
Anus D2cc (Gy)						
All	1.7 (0.5 - 3.6)	2.7 (0.4 - 4.5)	3.0 (0.4 - 6.1)	0.2 (-0.8 - 2.3)	0.34	1.07
Only interventions	2.1 (0.9 - 2.6)	3.2 (0.9 - 4.3)	3.1 (0.9 - 6.1)	0.2 (-0.8 - 2.3)	0.66	1.05
Excl. interventions	0.9 (0.5 - 2.6)	2.3 (0.4 - 4.5)	2.7 (0.4 - 4.7)	0.2 (-0.6 - 2.1)	0.37	1.08

Results are presented as median (range) unless indicated differently.

DISCUSSION

The aim of this study was to determine the differences regarding treatment plan conformity, target volume coverage and dose to organs at risk between using a single treatment plan for all fractions versus a new treatment plan at each fraction in HDREBT for rectal cancer. In this study of eleven patients, replanning for each fraction resulted in a significantly more conformal treatment plan and in some cases a substantially higher CTV D98 (Table 1). This study shows that for 12/22 repeat CT scans, the projected treatment plans met the coverage criteria of CTV D98 being at least 85% of the prescribed dose and at least 90% of the CTV D98 of the first fraction. This improved to 14/22 after replanning. An important value of repeat CT at each fraction lies in verifying applicator balloon setup and absence of air and/or feces in the rectum. This is underlined by the significant effect of *intervention required* on COIN and CTV D98. Although replanning resulted on average in a 31% increase in COIN in the cases that needed an intervention, COIN and CTV D98 remain low and demonstrate the limited value of replanning in these cases (Table 1). If interventions would have been performed where needed, we expect that treatment plan conformity and target volume coverage would have been similar to those cases that did not need an intervention. After an intervention, a new repeat CT scan should always be acquired to verify its effect.

Adding repeat CT planning before each fraction adds approximately one hour per fraction. This includes acquiring the CT scan, delineation of target volume and organs at risk and treatment planning. We realise that this adaptive approach is labour intensive and may therefore be difficult to implement. Therefore, we report on the benefit of an adaptive approach in terms of treatment plan quality to aid in the decision whether to implement it or not. Even without replanning, acquiring a repeat CT scan is valuable to verify applicator balloon setup and absence of air and/or feces.

As reported, two cases show an increase of CTV D98 of 2.4 Gy and 1.7 Gy after replanning. In the first case, this was due to a different insertion angle of the applicator, which led to a different orientation of the CTV. In the second case, this was due to a suboptimal balloon orientation and a different insertion angle of the applicator, which led to a different orientation of the CTV on the repeat CT scan. Therefore, in these two cases, the projected treatment plan partly missed the CTV. Consequently, after replanning, the new treatment plan was adapted to the CTV on the repeat CT scan and this resulted in a higher CTV D98. One case showed a decrease of CTV D98 of 1.0 Gy and a reduction of the rectal wall point dose of 3.1 Gy because the applicator balloon was not inflated on the repeat CT scan, which resulted in a more conservative treatment planning for the new treatment plan. In another case, after replanning, a decrease of mesorectum D2cc of 1.3 Gy was observed because the CTV orientation was slightly different on the repeat CT scan. This resulted in the projected treatment plan partly missing the CTV and covering a part of the mesorectum instead. After replanning, the new treatment plan was adapted to the CTV on the repeat CT scan, resulting in a lower mesorectum D2cc. An increase of the anus D2cc of 2.3 Gy and 2.1 Gy for fraction two and three was observed in a patient with a distal tumour. For this specific patient, the most caudal slice of the CTV was larger on the repeat CT scans compared to the CTV on the CT scan of the first fraction, resulting in lower CTV coverage of the projected treatment plan. Consequently, after replanning, the new treatment plan was adapted to the larger CTV and this resulted in a higher anus D2cc.

Our conclusions are consistent with a congress abstract of Nout *et al.* on a cohort of 16 patients.[20] Additionally, we report on treatment plan conformity and causes of decreased target volume coverage. Similar studies have been performed for image-guided brachytherapy for cervical cancer, which conclude that an adaptive approach is necessary to correct for possible changes in applicator and anatomy geometry.[14,15]

One paper by Devic *et al.* describes the distribution of the corrections in craniocaudal direction for a cohort of 62 patients and shows for one patient what effect it would have on the CTV dose if these corrections were not applied [11]. Our study did not evaluate variations in dose as a result of uncertainties in applicator positioning correction using X-rays.

Baltas *et al.* describe the COIN parameter for evaluation of implant quality and dose specification in brachytherapy.[22] With HDREBT using an endorectal applicator no implants are involved. As the radiation source is brought next to the tumour instead of into the tumour, the reference isodose volume (V_{RI}) will always be substantially larger than the volume of the CTV that is covered by

the reference isodose (TV_{RI}). The (TV_{RI}/V_{RI}) component of the COIN equation is therefore very low, resulting in low COIN values. This explains the low COIN values reported in this study, compared to the values mentioned in Baltas *et al*.[22] In our opinion, rather than the absolute value, the ratio of the COIN between projection and replanning is informative and a good measure for treatment plan conformity.

Two factors of the COIN equation are dependent on the absolute delineated volume of the tumour (TV) and organs at risk $(V_{CO,i})$. However, as comparisons are made between the projection and the replanning on the same CT scan, the delineated volumes of the tumour and organs at risk are the same for projection and replanning.

There are some limitations in this study. First, the number of patients was small. Secondly, the delineations of the CTV are difficult to perform on CT, even with the provided diagnostic MRI scan, rectoscopy images, digital rectal examination and inserted endoluminal clips at the proximal and distal border of the tumour. No MRI with applicator in situ was available because the endoluminal clips cause large artefacts on MRI. Consequently, there may be delineation variation among the CT scans of the three fractions. Third, we did not report cumulative dose in this study because only four patients did not require an intervention at all three fractions, on which no reliable conclusions can be drawn. Finally, it would be difficult to show the clinical benefit for patients in terms of local control or reduction in toxicity. However, our results show that without additional imaging, patients would have received a suboptimal treatment with substantial underdosage.

CONCLUSION

The results of this study show that using a single CT-based treatment plan for all fractions in HDREBT for rectal cancer may result in a suboptimal treatment at later fractions. Therefore, repeat CT imaging should be the minimal standard practice in HDREBT for rectal cancer to determine whether an intervention would be necessary. Replanning based on repeat CT imaging resulted in more conformal treatment plans and is therefore recommended.

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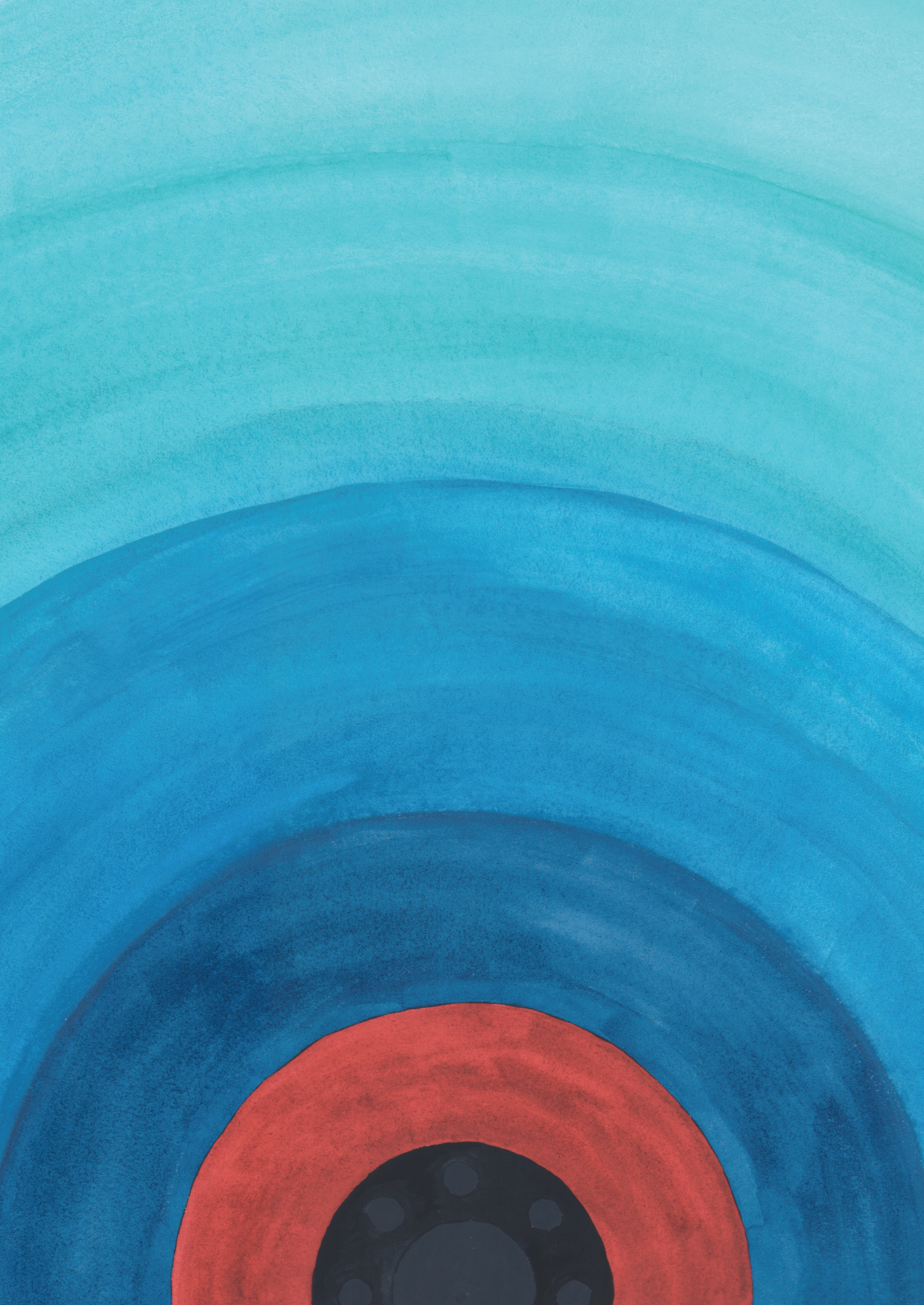

Chapter 7

EUS-guided fiducial marker placement for radiotherapy in rectal cancer: feasibility of two placement strategies and four fiducial types

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ABSTRACT

Background and study aims

To facilitate image guidance during radiotherapy of rectal cancer, we investigated the feasibility of fiducial marker placement. This study aimed to evaluate technical success rate and safety of two endoscopic ultrasound (EUS)-guided placement strategies and four fiducial types for rectal cancer patients.

Patients and methods

This prospective multicentre study included 20 participants who were scheduled to undergo rectal cancer treatment with neoadjuvant short-course radiotherapy or chemoradiation. EUS-guided endoscopy was used for fiducial placement at the tumour site (n = 10) or in the mesorectal fat and in the tumour (n = 10). Four fiducial types were used (Visicoil 0.75mm, Visicoil 0.50mm, Cook, Gold Anchor). The endpoints were technical success rate and retention of fiducials, the latter of which was evaluated on cone-beam computed tomography scans during the first five radiotherapy fractions.

Results

A total of 64 fiducials were placed in 20 patients. For each fiducial type, at least three fiducials were successfully placed in all patients. Technical failure consisted of fiducial blockage within the needle (n = 2) and ejection of two preloaded fiducials at once (n = 4). No serious adverse events were reported. In three patients, one of the fiducials was misplaced without clinical consequences; two in the prostate and one in the intraperitoneal cavity. After a median time of 17 days after placement (range 7-47 days), a total of 42/64 (66%) fiducials were still present (24/44 intratumoral vs. 18/20 mesorectal fiducials, P = 0.009).

Conclusions

Placement of fiducials in rectal cancer patients is feasible, however, retention rates for intratumoral fiducials were lower (55%) than for mesorectal fiducials (90%).

INTRODUCTION

Neoadjuvant (chemo)radiotherapy, in addition to total mesorectal excision (TME), improves local control of rectal cancer.[1,2,3,4] However, patients experience long-term side effects after neoadjuvant (chemo)radiotherapy, including faecal incontinence and impaired sexual functioning.[5,6,7,8] A reduction in target volume may reduce these side effects. However, precise irradiation of the target remains difficult for rectal cancer due to tumour motion and poor visibility of the tumour area on cone-beam CT (CBCT). Fiducial markers may improve radiotherapy position verification, not only for external beam radiotherapy, but more importantly for brachytherapy.

Prior studies evaluated endoluminal clips for this purpose, demonstrating limited usefulness due to poor long-term retention rates ranging from 50% to 75% 1 week after placement.[9,10] Preferably at least two clips should remain present in a patient during the full course of radiotherapy. In addition, these endoluminal clips create large artefacts on magnetic resonance imaging (MRI). As an alternative, MRI-compatible fiducials may be used, since they have adequate retention rates after implantation in many solid cancers, such as prostate, oesophageal, and pancreatic cancer.[11,12,13] Three previous studies described successful placement of fiducials in rectal cancers, in 54, 11, and 9 patients, respectively.[13,14,15] In these studies, different placement techniques and different fiducial types were used. One of these studies evaluated postprocedural loss of intratumoral fiducials, resulting in loss of 10 of 39 fiducials during radiotherapy.[14] The optimal placement technique and fiducial type have thus not been identified.

Usefulness of rectal cancer fiducials is strongly dependent on the rate of retention of the fiducials, on visibility on images used for target delineation and treatment planning, and on visibility on CBCT scans.

This pilot study aimed to evaluate technical feasibility and safety of EUS-guided fiducial placement at the tumour site in patients with rectal cancer, and fiducial loss after placement, comparing two fiducial placement strategies and four different fiducial types.

PATIENTS AND METHODS

Study design and population

In this prospective interventional pilot study we included 20 rectal cancer patients in the Netherlands Cancer Institute (NKI) and Leiden University Medical Center (LUMC). Participants were to be treated for rectal cancer with short-course radiotherapy (5×5 Gy) or chemoradiation consisting of 25×2 Gy combined with capecitabine 825 mg/m2 twice daily, followed by total mesorectal excision. Exclusion criteria were coagulopathy, use of anticoagulants (vitamin K antagonists, direct oral anticoagulants), prior pelvic irradiation or surgery, World Health Organisation performance status 3-4, pregnancy, prior hip replacement, or a contraindication for MRI.

The study procedure included an endoscopic ultrasound (EUS)-guided endoscopy with placement of fiducials. If no clear EUS view could be obtained, a forward-looking endoscope was used and fiducials were placed under direct view into the tumour.
The study protocol was approved by the medical ethics committee of the Netherlands Cancer Institute and the study was registered at the Dutch Trial Registry (trial ID NTR4606). All participating patients provided written informed consent.

Fiducial marker placement

At least 1 day before the first fraction of radiotherapy, all patients received a phosphate enema followed by EUS-guided endoscopy of the rectum with placement of three fiducials. Fiducial placement was performed by four experienced gastroenterologists, two in each study centre. Four types of fiducials were used in this study (Visicoil 0.75 mm × 5 mm and Visicoil 0.50 mm × 5 mm FIBA Dosimetry GmbH, Germany), Cook 0.64 mm × 3.4 mm (Cook Medical, Limerick, Ireland) and Gold Anchor 0.28 mm × 20 mm (unfolded length, Naslund Medical AB, Sweden). All fiducials were certified by the European Conformity (CE). Attribution of a fiducial type to a participant in each study centre was performed randomly.
EUS was performed using a linear-array endoechoscope (Pentax, EG-3270UK, Pentax, EG-3870UTK, Olympus GIF-Q180, Olympus GIF-H180, or Fujinon, EG-580UT). The target lesion was visualised and absence of intervening vascular structures was ascertained. A fine-needle aspiration EUS needle (19 gauge or 22 gauge, Cobra Medical or Cook EchoTip Ultra) was inserted into the target area under EUS guidance or direct endoscopic view. The EUS needle was loaded with one of the fiducials and the tip was sealed with sterile bone wax. The Cook EchoTip Ultra Fiducial Needle was pre-loaded with four fiducials.
Two strategies for fiducial placement were evaluated. In the first 10 patients, defined as group 1, three fiducials were placed into the tumour (one proximal, one central and one distal). In the second 10 patients, defined as group 2, we aimed to place at least two fiducials in the mesorectal fat (one proximal and one distal from the tumour) and one fiducial in the centre of the tumour.

Periprocedural care

Periprocedural medication was not administered in participating patients (no sedatives, analgesia or prophylactic antibiotics were given). Patients were instructed to contact the radiation oncologist at any sign of fever, a change in pain or other unexpected adverse reactions. Patients were monitored by the radiation oncologist during regular outpatient clinic appointments during and after (chemo)radiotherapy.

Outcome measures

Technical success was defined as placement of three fiducials at the desired location in the rectum. Technical feasibility also included technical failure and technical difficulty of the EUS procedure, and second fiducial loss during radiotherapy. “Technical failure” comprised fiducial

loading or unloading problems, whereas "technical difficulty" included problems with identifying tumour and surrounding tissue, which limits obtainment of a safe window for fiducial placement at the desired location, or inability to visualise the fiducials after insertion by EUS. Fiducial loss was evaluated by planning CT scans (when available) and over the course of radiotherapy by assessing the fiducials on CBCTs.

Adverse events (AEs) included any undesirable experience that occurred to a patient during the study, defined as the period between placement of the fiducials and TME or a maximum of 30 days follow-up, whether or not considered related to the experimental intervention.

Statistical analyses

Data were analysed in IBM SPSS Statistics 22. Patient and tumour characteristics and differences in fiducial retention were compared between groups using Chi Square or Fishers Exact tests.

RESULTS

Patient and tumour characteristics

Participants were included between June 2015 and September 2016. Rectal cancer treatment consisted of neoadjuvant short-course radiotherapy in 11 patients and chemoradiation in nine patients. In one patient, a complete response was seen after chemoradiation and a wait and see policy was adopted. Median age at diagnosis was 62 years (range 51-82 years). Two of 20 patients used a platelet aggregation inhibitor, which was continued during fiducial placement.

In the first 10 patients (group 1), fiducials were only placed at the tumour site. In the second 10 patients (group 2), fiducials were aimed to be placed in both the mesorectal fat and the tumour. No clear differences were found in baseline characteristics of these two patient groups, including age, gender, or TNM stage (Table 1). Patients in group 2, with fiducials aimed for the mesorectum (and tumour), appeared to receive more frequent treatment with chemoradiation.

Feasibility of EUS-guided fiducial placement

Technical success

A total of 64 fiducials were placed in 20 patients (Table 2). In group 1, at least three fiducials were successfully placed in the tumour of each patient.

In nine of 10 patients in group 2, fiducials were placed in the mesorectal fat, including eight patients with at least two fiducials in mesorectal fat (Table 1). In one tumour, only one fiducial could be placed in the mesorectal fat, because surrounding tissues limited the options for a safe window of placement of a second fiducial in the mesorectal fat. Placement of a fiducial in the mesorectal fat both proximal and distal from the tumour was feasible in only three of 10 patients. Placement of fiducials in the mesorectal fat was limited to proximal from the tumour in another

three of 10 patients, because the tumour was close to the anal verge. In the final three of 10 patients, the tumour could not be passed by the endoscope and the fiducials in the mesorectal fat were placed only distal from the tumour.

Technical failure

Unloading problems occurred during placement of six fiducials. During placement of Cook fiducials, two fiducials were ejected at once in four patients. In one other patient, two of three Gold Anchors inserted in 19G needles consecutively blocked within the sheet of the needle and could not be removed. All other Gold Anchor fiducials were placed with a 22G needle without any problems.

Table 1. Characteristics of two patient groups with different fiducial placement strategies

Baseline characteristics	**Group 1: Patients with fiducials aimed for the tumour (N)**	**Group 2: Patients with fiducials aimed for mesorectum (and tumour) (N)**
Age (median, range in years)	65 (57 - 82)	60 (51 - 65)
Gender		
Male	8	7
Female	2	3
T stage		
T2	2	2
T3	8	8
N stage		
N0	4	3
N+	6	7
Endoscopic distance from anal verge (median, range in cm)	8 (0 - 15)	6 (1 - 16)
Treatment		
5×5	7	4
CRT	3	6
Fiducial placement characteristics		
Fiducial type		
Visicoil 0.50	3	2
Visicoil 0.75	5	1
Cook	3	2
Gold Anchor	0	5
Fiducial location		
Intratumoral only	10	1
Mesorectal fiducials: number		
1		1
≥ 2		8
Mesorectal fiducials: location in relation to tumour		
Proximal (≥ 1) & distal (≥ 1)		3
Proximal (≥ 1, not distal)		3
Distal (≥ 1, not proximal)		3

All differences were not statistically significant based on Fishers' exact tests.

Technical difficulty

The overview obtained by EUS was limited in seven patients. In five of them with intratumoral fiducials, it was not feasible to obtain clear delineation of the small tumour by EUS for all fiducials and at least one fiducial in these five patients was placed under direct vision with forward-looking endoscopy into the tumour. In another patient with the aim of placing fiducials in the mesorectal fat, it was not feasible to create a safe window for fiducial placement into this area, resulting in placement of three fiducials at the tumour site. In the third patient with a limited overview by EUS, the endoscopist noted that identification of the prostate and surrounding tissues was unclear. Indeed, one of the fiducials was placed in the prostate in this patient. In two additional patients, CBCT displayed a location of one of the fiducials outside the mesorectum. This included one patient with a fiducial in the prostate. The other patient had a proximal rectal cancer, and a fiducial was present in the peritoneal cavity which was not observed during EUS. None of these patients showed any signs or symptoms that had a probable relation to the procedure, and treatment was completed as planned.

EUS visualisation of the placed fiducial was evaluated in 10 of 20 patients (Figure 1). In five of 10 evaluated patients, not all three fiducials were visible by EUS.

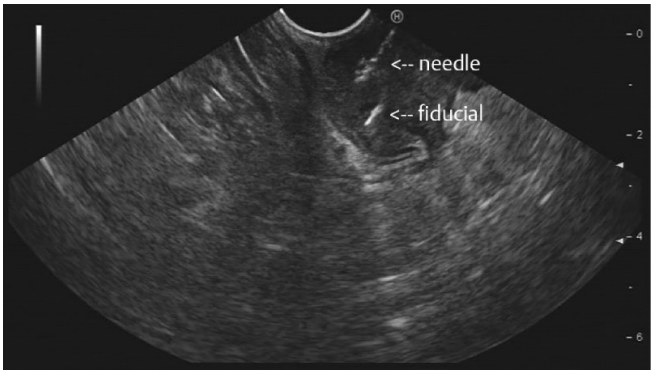


Figure 1. Fiducial placed under EUS-guidance.

Fiducial loss evaluated on CBCTs

CBCT scans for radiotherapy treatment planning and positioning were used for evaluation of fiducial loss.

Median time between fiducial placement and the first fraction of radiotherapy was 6 days (range 1-18 days). On the first CBCT, 43 of 64 (67%) of the presumably successfully placed fiducials were visible (Figure 2). Only one additional fiducial was lost during radiotherapy. Median time between fiducial placement and the last CBCT was 17 days (range 7-47 days), after which 42 of 64 (66%) fiducials were detected. In all patients, at least one fiducial was present at the end of follow-up.

Table 2. Rectal cancer patient and EUS-guided fiducial placement characteristics

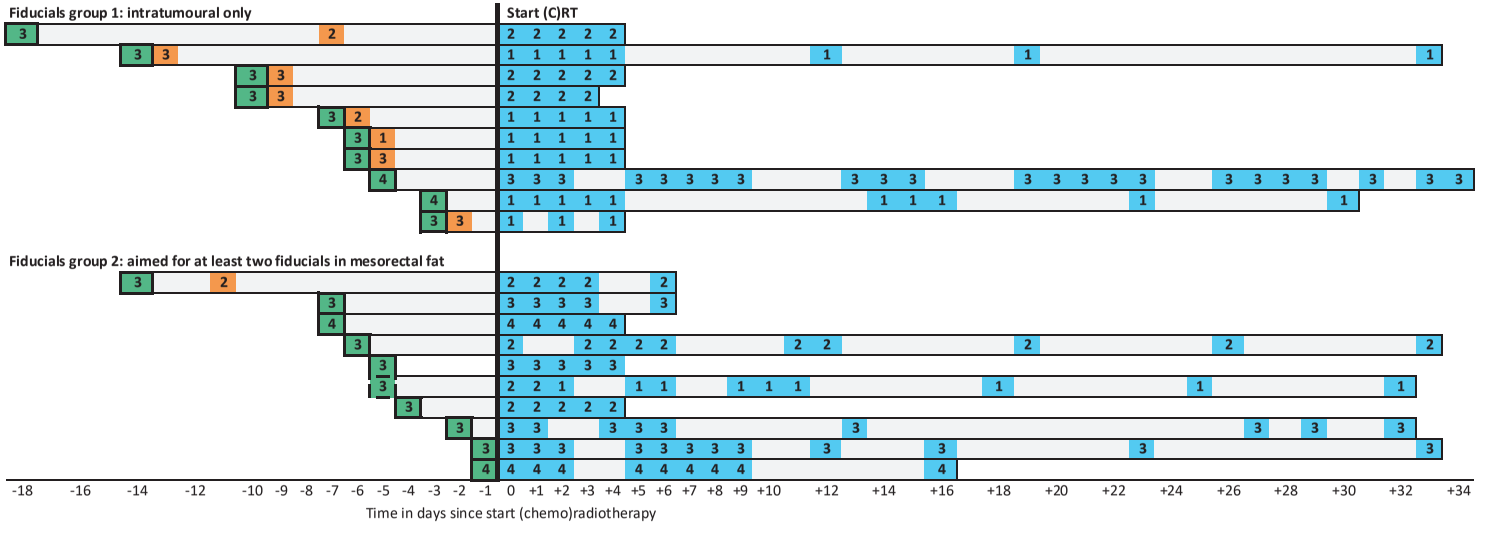
ID	Gender	Age	cTNM	cm from anal verge	Tx	Fiducial type	Needle (Gauge)	Placed fiducials (n)	Aimed location (n) intratumour/ mesorectum	Failure fiducial unloading*	Difficulty placement window^	Undesired placement location	(n) EUS visualisation placed fiducial
Group 1: aimed for placement of three intratumoral fiducials													
1	F	60	T3N1M0	2	5×5	Visicoil 0.50	19	3	3/0		1		NE
2	M	75	T3N0M0	10	5×5	Visicoil 0.75	19	3	3/0		1		NE
3	M	82	T2N1M0	15	5×5	Visicoil 0.75	19	3	3/0		1		NE
4	M	71	T3N0M0	5	5×5	Visicoil 0.50	22	3	3/0		1		NA
5	M	63	T3N1M0	15	5×5	Visicoil 0.75	19	3	3/0		1		NE
6	M	82	T3N0M0	0	5×5	Visicoil 0.50	22	3	3/0				1
7	M	67	T3N2M0	8	CRT	Visicoil 0.75	19	3	3/0				3
8	F	62	T2N1M0	11	5×5	Cook	22	3	3/0				3
9	M	58	T3N0M0	1	CRT	Cook	22	4	4/0	1			3
10	M	57	T3N2M0	7	CRT	Cook	22	4	4/0	1			1
Group 2: aimed for placement of at least two fiducials in the mesorectal fat (and one in the center of the tumour)													
11	M	63	T2N0M0	2	CRT$^{\$}$	Visicoil 0.50	19	3	2-Jan			prostate (n = 1)	2
12	M	60	T3N1M0	8	CRT	Visicoil 0.50	22	3	1-Feb				2
13	F	52	T3N1M0	8	5×5	Visicoil 0.75	19	3	1-Feb				3
14	M	63	T3N0M0	1	CRT	Gold Anchor	22	3	1-Feb		1	prostate (n = 1)	3
15	M	65	T3N2M0	2	CRT	Gold Anchor	19/22	3	3/0	2	1		3
16	M	59	T2N1M0	16	5×5	Gold Anchor	22	3	0/3			intraperitoneal (n = 1)	NE
17	F	60	T3N1M0	2	5×5	Cook	22	4	0/4	1			NE
18	M	59	T3N2M0	8	CRT	Cook	22	4	2-Feb	1			NE
19	F	61	T3N1M0	10	5×5	Gold Anchor	22	3	1-Feb				NE
20	M	51	T3N0M0	2	CRT	Gold Anchor	22	3	1-Feb				NE

* Defined as fiducial blockage in the needle or ejection (blockage (ID 15) and two fiducials at once (ID 9, 10, 17, 18).

^ Limited overview by EUS, noted by endoscopist (Patient ID 1 - 5: switch to endoscopic placement under direct view with forward looking endoscope for at least 1 marker, ID 14: difficulty identifying prostate and surrounding structures, ID 15: no window for placement in mesorectum).

$ Wait and see policy.

Abbreviations: Tx, radiotherapy treatment schedule; CRT, chemoradiotherapy; NE, not evaluated; NA, not applicable.



Days since fiducial placement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-34
Σ fiducials lost	3	3	9	10	12	15	17	17	17	19	20	20	20	22	22
N intratumoural fiducials lost	3		5		2	3	2			2	1			2	
N mesorectal fiducials lost			1	1											

Figure 2. Fiducial detection by CBCTs after placement.

Each bar represents a patient. Patients with +5 days of follow-up recieved short-course (5x5 Gy) radiotherapy, whereas patients with longer follow-up recieved chemoradiotherapy.

- Number of placed fiducials
- Intratumoural fiducials only
- Number of fiducials visualised on planning CT
- Number of fiducials visualised in CBCT

When comparing fiducial retention rates based on placement location per fiducial, 55% of intratumoral fiducials were still detected on the final CBCT (detected in group 1 and group 2, retention rates ranged from 46% to 67% between fiducial types) compared with 90% in mesorectal fiducials (group 2 only, Fishers' exact P = 0.009, which ranged from 50% to 100% between fiducial types) (Table 3).
Additional comparison of placement strategies between groups demonstrated a retention rate of 15 of 32 (47%) fiducials in group 1 (intratumoral fiducials only) and 27 of 32 (84%) fiducials in group 2 (both in the mesorectal fat and intratumoral, P = 0.002).

Patient safety
No serious AEs were reported. During approximately 1 week post-fiducial placement, symptoms consisted of an increase in blood loss in stool (n = 3) and in flatulence (n = 5).

Table 3. Fiducial characteristics: description of four fiducial types

Characteristic	Total	Visicoil 0.50	Visicoil 0.75	Cook	Gold Anchor
	N (%)	N (%)	N (%)	N (%)	N (%)
Placed fiducials	64	15	15	19	15
Retained at end of follow-up	42 (66)	9 (60)	7 (47)	14 (74)	12 (80)
Intratumoral fiducials	44 (69)	12 (80)	13 (87)	13 (68)	6 (40)
Retained at end of follow-up	24 (55)	6 (50)	6 (46)	8 (62)	4 (67)
Mesorectal fiducials	20 (31)	3 (10)	2 (13)	6 (32)	9 (60)
Retained at end of follow-up	18 (90)	3 (100)	1 (50)	6 (100)	8 (89)

DISCUSSION

This prospective multicentre study was the first to compare two fiducial placement strategies for rectal cancer to evaluate technical feasibility and fiducial retention rates. We demonstrated that fiducial retention rates are higher when fiducials are placed in the mesorectal fat instead of in the tumour. Because of the higher retention rate of mesorectal fiducials, this strategy appears more useful for position verification in image-guided radiotherapy or brachytherapy. Intratumoral fiducial placement was considered especially difficult in smaller tumours with limited volume for fiducial placement. Placement of all four investigated fiducial types was feasible.
Prior studies on endoluminal clips in rectal cancer were disappointing, due to intraluminal movement of the clips, poor long-term retention rates (ranging from 50% to 75% 1 week after placement) and MRI artefacts caused by the clips.[9,10] This led to exploration of the feasibility of fiducials, as they are more frequently compatible with MRI and appear to stay in place in other organs. A first report by Vorwerk et al. on rigid rectoscopy for placement of fiducials in the mesorectal tissue of nine patients with rectal cancer demonstrated 100% retention rates in

the first 5 weeks after placementt.[15] A consecutive study of EUS-guided endoscopic placement of intratumoral fiducials in 11 patients resulted in a fiducial retention rate of 74% at the time of surgery.[14]

In our study, only 55% of intratumoral fiducials were present on CBCT after a median follow-up of 17 days, in comparison with 90% of fiducials placed in the mesorectal fat. In seven patients with intratumoral fiducials, only one fiducial was present at the end of the first week of radiotherapy. This limits the usefulness of the fiducials, as the presence of at least two fiducials is necessary for interpretation of the location of fiducials in relation to the tumour, especially when taking rectal motion into account.

Intratumoral placement of fiducials was challenged by the small volume and the soft consistency of the tumour. In addition, placement of fiducials in the mesorectal fat was associated with some technical challenges. It was considered difficult to obtain a safe window for mesorectal fiducial placement, due to surrounding tissues such as the prostate, seminal vesicles, bladder, vessels, and lymph nodes. This limited window may have led placement of three fiducials outside the mesorectal fat. Unfortunately, not all fiducials were visible by EUS after insertion, which limited confirmation of placement locations. No other AEs were described.

In the study by Vorwerk et al., who described fiducial placement in the mesorectum in nine patients, a fiducial located in the peritoneum was detected in one of nine patients.[15] In another study using EUS-guided endoscopy for intratumoral fiducial placement, one minor bleed and one undefined technical difficulty were described in a total of 54 patients.[13] The oncologic and non-oncologic health risks of fiducial placement in (or migration to) other tissues than the (meso)rectum appear low, as no symptoms were reported and treatment was finalised as planned. No evidence exists for routine administration of prophylactic antibiotics, as were given in the study by Moningi et al.[14]

We evaluated four different types of fiducials, which were all successfully inserted at the desired location. There was no clear difference between the feasibility of the four types, however, use of Cook fiducials more frequently led to simultaneous insertion of two fiducials at once, and Gold Anchor fiducials blocked twice within the 19G needle. EUS visibility of fiducials after placement appeared more difficult when using smaller fiducials. We did not find a clear difference in retention rates between fiducial types, as this appeared more likely related to the location of fiducial placement. Future studies may explore the option of MRI-guided brachytherapy, which may lead to a preference of a fiducial depending on MRI visibility and migration properties.

In other gastrointestinal tumour locations, such as the oesophagus and the pancreas, fiducials are more widely investigated and used.[13,16-19] Retention rates for fiducials placed in the tumour or surrounding tissue in oesophageal and pancreatic cancer are 66% to 94% and 93% to 100%, respectively.[17,20-24] The relatively high rate of intratumoral fiducial loss in rectal cancer may be due to a small tumour volume, rectal motion or the passing of stool.[25]

CONCLUSION

In conclusion, EUS-guided placement of fiducials for rectal cancer is feasible and safe, but adequate positioning remains a challenge. Placement of fiducials in the mesorectal fat leads to a higher rate of retention of fiducials, however, these results could be influenced by other factors (e.g. fiducial type) and should be confirmed in a larger study.

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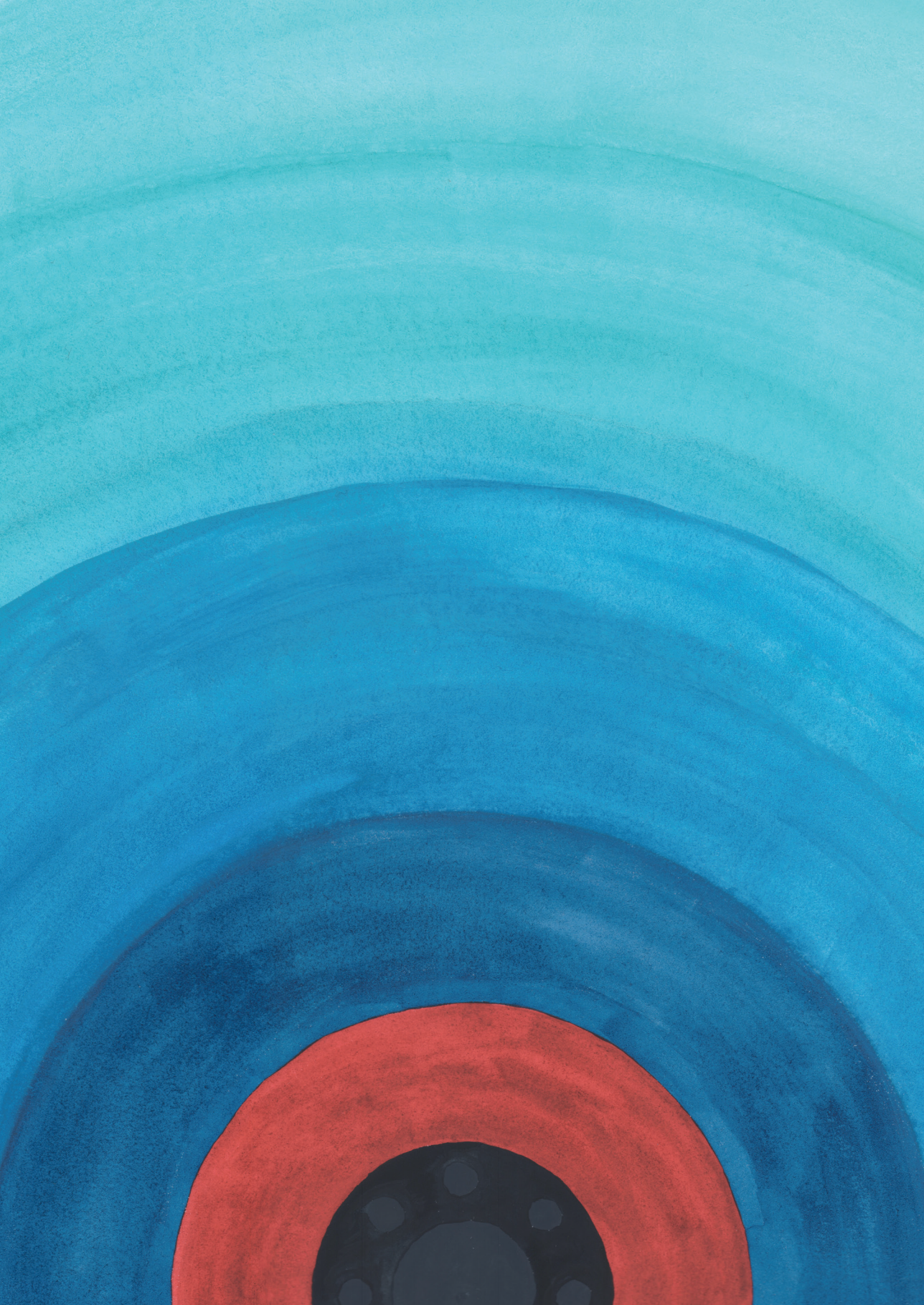


Chapter 8

Summary

8. SUMMARY

In this thesis, radical radiotherapy as an alternative to standard TME resection for elderly patients with rectal cancer is explored. As the population is aging, the incidence of rectal cancer is rising. And with increasing age, the burden of morbidity and postoperative mortality, associated with TME surgery, rises. Alternative treatment options for elderly patients are therefore urgently needed.

Because not every elderly patient is frail and not every frail patient is elderly, a one-size-fits-all approach does not suffice. Multiple factors have to be considered and it is therefore strongly advised to consult the geriatric department for a comprehensive geriatric assessment. Generally, patients can then be divided into four categories: (1) fit patients; (2) medium-fit patients, at surgical risk; (3) frail patients, in whom radical surgery is contraindicated and (4) very frail patients, in whom only palliative care is indicated. In fit patients, standard treatment is advised, but adjustments to the standard treatment can be made to minimise the toxicity. For example, the use of short course radiotherapy instead of chemoradiotherapy or reduction of the electively treated volume in external beam radiotherapy to lower toxicity. In medium-fit patients, further adjustments can be made to reduce treatment morbidity and in case of a clinical (near) complete response, a watch-and-wait strategy or local excision could be favoured to TME surgery. The group at high surgical risk might benefit from radical radiotherapy. And the last group, for which there is no curative intent, should be treated with a short palliative radiotherapy schedule in an attempt to alleviate symptoms.

As is clear from the above, understanding and predicting toxicity in these frail patients is extremely important. Therefore, a better understanding of dose-response effects for toxicity in external beam radiotherapy (Chapter 2) and for brachytherapy (Chapter 4 and 5) is needed. Knowing the chances of a complete response and associated risk of toxicity of a brachytherapy boost (Chapter 3 and 5) would allow us to discuss the risks and benefits with patients in shared decision making. Further improvements in the brachytherapy technique (Chapter 6 and 7) will increase the efficacy and reduce toxicity, optimising both response and tolerability of a HDREBT boost in rectal cancer.

CHAPTER 2

The bowel or small bowel have always been considered to be the main limiting organs at risk for external beam radiotherapy in rectal cancer and reliable and practical dose constraints are therefore needed. Contouring of individual small bowel loops (SBL) is often regarded as the gold standard for dose-response analyses, but is very time consuming and disregards the day-to-day variation. Two widely used less time consuming and more motion-robust alternatives are the bowelbag following EMBRACE guidelines (EMBRACE-BB) and bowelbag following RTOG

guidelines (RTOG-BB). In Chapter 2, these contouring methods were compared in a cohort of 157 locally advanced rectal cancer patients treated with chemoradiotherapy and factors associated with acute and late gastrointestinal toxicity were evaluated.
A statistically significant dose-response correlation could not be detected for any of the defined bowel delineations. Risk of acute toxicity was, however, clearly increased in patients with prior abdominal surgery, whereas concurrent chemoradiotherapy was the single most important risk factor for severe late gastrointestinal toxicity.
The volume of the EMBRACE-BB was approximately 2-3 times the volume of the small bowel loops and showed a strong linear correlation to the volume of SBL (rho = 0.9). The volume of the RTOG-BB was approximately a factor of 6 larger with a lower correlation (rho = 0.5-0.7).
Based on a literature review, a dose constraint for the volume of individual small bowel loops receiving 15 Gy (SBL V15) of 164 cc is proposed for acute grade 2-3 gastrointestinal toxicity. Using the correlation of SBL with EMBRACE-BB from the current analysis (EMBRACE-BB (V15) = SBL(V15) x 1.69 + 78.4), a constraint of 350 cc for EMBRACE-BB V15 is suggested as an alternative.

CHAPTER 3 - 5

In chapters 3, 4 and 5 the results of the HERBERT study are presented. The HERBERT study was a feasibility study, evaluating the efficacy and tolerability of an HDR endorectal brachytherapy boost after external beam radiotherapy in elderly frail patients with rectal cancer. The study was designed as a brachytherapy boost dose escalation study which started with 3×5 Gy, six weeks after EBRT (13×3 Gy, 4/wk) and increased with 1 Gy per fraction in every next dose level. Dose-limiting toxicity was defined as proctitis grade 3 (CTCAEv3) occurring within six weeks after brachytherapy. Secondary endpoints were toxicity, clinical tumour response, freedom from local progression, local progression free survival (L-PFS) and overall survival (OS). Brachytherapy was performed with a flexible applicator with eight channels and treatment planning was based on a planning CT acquired prior to the first brachytherapy application. The clinical target volume was defined as the residual tumour or scarring at time of brachytherapy and delineation on the CT was assisted by the baseline MRI, endoscopy images and clips positioned at the proximal and distal end of the tumour. The 100% isodose was prescribed to the radial margin of the CTV with a restriction of 400% within the applicator.
In total, 38 patients with cT2-3N0-1 rectal cancer were included between 2007 and 2013. Thirty-two were evaluable for toxicity endpoints and 33 for response analyses. Patients were elderly with a median age of 83 and most had severe co-morbidity: 76% of patients were deemed medically inoperable. Dose-limiting toxicity occurred in the 8 Gy dose level, resulting in a maximum tolerated dose of 7 Gy per fraction. Almost 90% of patients had a response to treatment with a complete response (cCR) in 61%. After a median FU of 30 months, 52% had a sustained response to treatment. Median time to local progression was 9.3 months and actuarial freedom from local

progression at 1, 2 and 3 years was 71%, 55% and 44% respectively. Survival was limited due to the nature of the population, but in patients with a complete response to treatment, a significant benefit in local progression free survival and trend for overall survival was observed. At two years the local progression free survival was 60% vs. 15% (p=0.006) and the overall survival was 80% vs. 46% in cCR vs. non-cCR patients (p=0.11) After an update with a median FU of 43.7 months, the overall survival benefit also was significant (p=0.01) (unpublished).

Chapter 4 describes a comprehensive overview of patient-reported, physician-reported and endoscopically observed toxicity. The endoscopy images were assessed for changes to the normal rectal wall and to the tumour site, which were analysed separately. Both physician- and patient-reported toxicity showed a clear increase in the third week of EBRT and two weeks after brachytherapy reducing to baseline values between EBRT and brachytherapy and two months after brachytherapy. Maximum proctitis score during this period was grade 2 in 68% and grade 3 in 13%. The patients with grade 3 acute proctitis showed ongoing toxicity for more than three months and experienced severe late proctitis as well. In total, severe late proctitis was observed in 10 patients (crude risk in evaluable patients 40%, actuarial risk at one year 23%).

Endoscopic evaluation of the normal rectal wall mainly showed erythema and telangiectasia. In three patients, frank haemorrhage or ulceration occurred 12-18 months after treatment. At the tumour site, deep ulceration occurred in 42% of patients with a complete or partial response.

Chapter 5 evaluates the association of patient-, tumour- and dosimetric parameters with tumour response and toxicity. Tumour volume at diagnosis showed a strong association with clinical complete response. Patients with a baseline tumour volume < 20 cc had a 2-year sustained response rate of 74% compared to only 25% for patients with baseline tumour volume > 20 cc ($p = 0.007$). Also, tumours that showed no volume reduction after external beam radiotherapy (n=4) had a poor response to the brachytherapy boost. No dose-response correlation was observed between prescribed dose to the CTV (D90/D98) and clinical tumour response.

Brachytherapy CTV (D90/98) was however correlated with acute and late proctitis. In addition, CTV volume, CTV width and high dose regions in the CTV (D1cc/D2cc) were associated with ulceration at the tumour site. Deep ulceration occurred in 7/9 (78%) of patients with a CTV D2cc > 14 Gy per fraction and in 3/18 (17%) patients with a CTV D2cc < 14 Gy per fraction ($p = 0.002$).

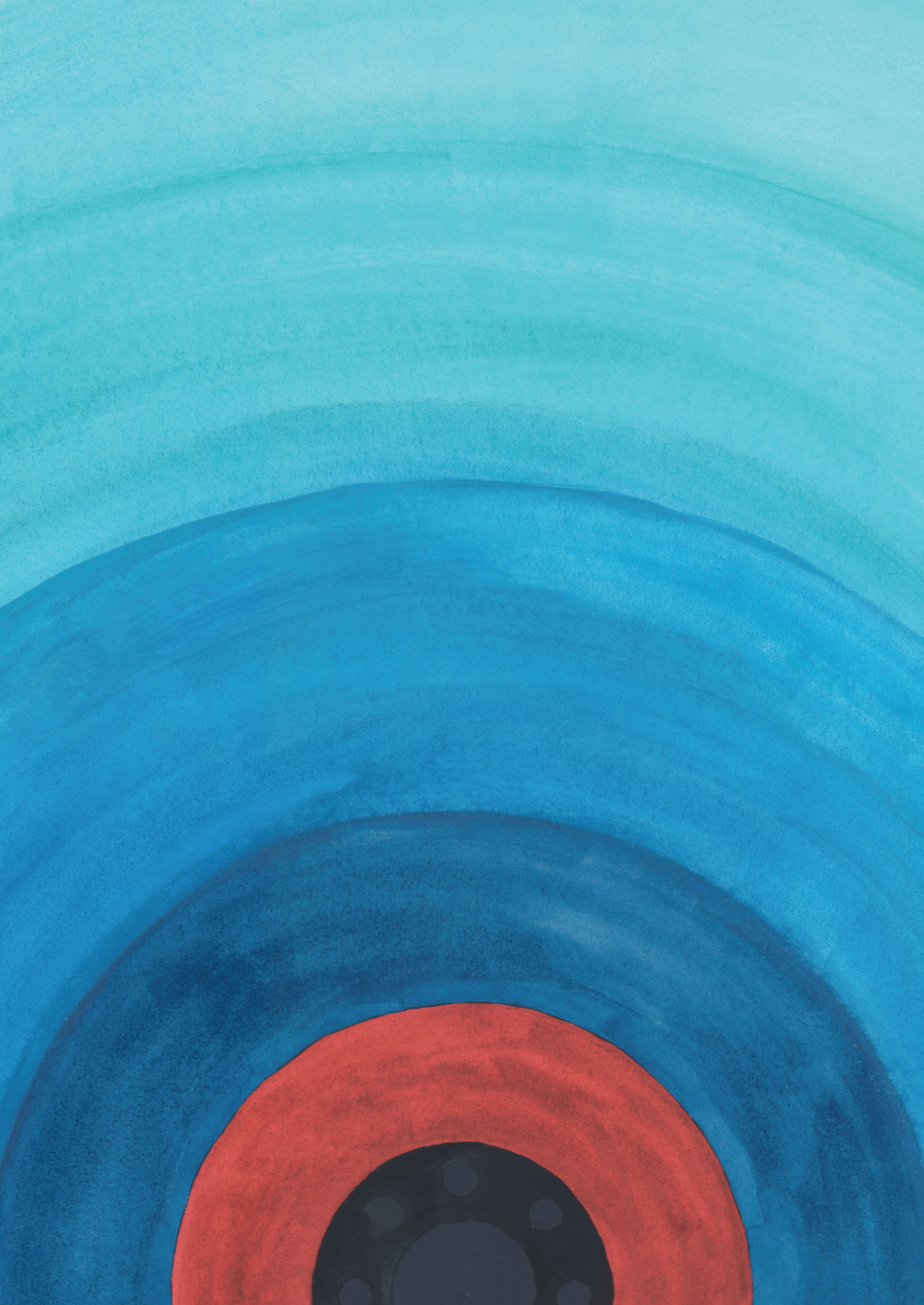
In conclusion, the HERBERT study shows that HDREBT is feasible in elderly rectal cancer patients with promising responses, but with considerable risk of toxicity. Patients with tumours < 20 cc at baseline, who respond well to EBRT are the best candidates for a brachytherapy boost. To limit the risk of toxicity a D2cc < 14 Gy per fraction is advised.

CHAPTER 6

A side study of the HERBERT study, the Repeat CT study, is reported in Chapter 6. In 11 patients, treated with an endorectal brachytherapy boost, additional CT scans were made at time of the second and third brachytherapy application. The treatment plan used for the brachytherapy boost (based on the planning CT scan acquired prior to the first brachytherapy application) was projected on the CT scans of the 2nd and 3rd application. A sufficient dose coverage was observed with the use of the first treatment plan in only 12/22 scans. In two cases, a significant improvement could be made by replanning, but in the remaining eight of 22 situations an intervention would have been necessary to correct applicator-balloon setup or to remove remaining air and/or faeces between the CTV and the applicator. This demonstrates that a single treatment plan, as was used in the HERBERT study, results in suboptimal dose distributions. Repeat CT scanning should therefore be the minimal standard of practice in HDREBT.

CHAPTER 7

The preferred imaging modality for contouring a rectal tumour is MRI. In the HERBERT study, MR imaging was not feasible because of artefacts caused by the endoluminal clips. Further improvement in the HDREBT technique could be facilitated by replacing the clips used in the HERBERT study with gold fiducials. The REMARK study was therefore initiated as part of a larger project for MRI-guided brachytherapy for rectal cancer. In this study, technical success rate and safety of four fiducial types were evaluated (Visicoil 0.5/0.75; Cook and Gold Anchor). Two endoscopic ultrasound (EUS)-guided placement strategies were used (in the tumour/rectal wall vs. in the mesorectum around the tumour). Twenty patients undergoing neoadjuvant external beam radiotherapy participated and in total, 64 fiducials were placed. After a median time of 17 days after placement (range 7-47 days), a total of 42/64 (66%) fiducials were still present (55% intratumoral vs. 90% mesorectal fiducials, P=0.009). There was no relevant difference in technical success rate of the different fiducial types. Based on the current analyses, placement of fiducials in the mesorectum is preferred.



Chapter 9

General discussion

9. GENERAL DISCUSSION

In this thesis, radical radiotherapy for frail or elderly patients with rectal cancer is evaluated in the HERBERT study. The results demonstrate that a combination of external beam radiotherapy and high-dose-rate endorectal brachytherapy (HDREBT) is both feasible and effective in rectal cancer patients unfit to undergo surgery. The results show promising tumour responses with almost 90% overall response and 61% complete response. Severe late toxicity, however, was observed in 40% of evaluable patients, which is unacceptable. As the HERBERT study represents the initial experience with HDREBT in the Netherlands, the high rate of toxicity can partly be explained by a learning curve. As was shown by the results of the repeat CT side study, there is much room for improvement of the technique. With developments in both external beam radiotherapy techniques and brachytherapy techniques, toxicity can be substantially reduced. Optimising the HDREBT technique and development of image-guided adaptive brachytherapy (IGABT) concepts for rectal cancer will allow for increased target coverage while minimising dose to normal tissue. As there is increasing interest in organ preservation for rectal cancer, HDREBT could have great potential, not only in elderly, but also fit patients who wish to avoid surgery.
In this general discussion, the HERBERT trial is compared to current literature on radical radiotherapy in elderly patients and a follow-up trial, the HERBERT II, is introduced. Furthermore, suggestions are made to improve the HDREBT technique for rectal cancer and a target concept for image-guided adaptive brachytherapy for rectal cancer is introduced. Finally, the potential role of HDREBT in neoadjuvant and definitive radiotherapy is described and the current status of primary organ preservation and several options for treatment intensification including HDREBT are discussed.

9.1 Radical radiotherapy in elderly patients

The results of the HERBERT study are compared to three recently published cohort studies on radical radiotherapy in elderly patients with rectal cancer in Table 1.[1-4] The studies by Gerard et al. and Myint et al. describe the use of contact X-ray (CXB) as a boost to chemoradiotherapy and the study by Garant et al. uses HDREBT after external beam radiotherapy alone. These studies show that dose escalation up to 90-100 Gy $EQD2_{\alpha\beta 10}$ is possible when using an intraluminal radiotherapy boost and is associated with a complete response rate between 61% and 86% in cT2-3 tumours.
Compared to the other studies in Table 1, the complete response rate in the HERBERT study is relatively low and the regrowth rate high. More importantly, the toxicity was unacceptably high. These differences can be explained by differences in patient selection and technique. In the contact X-ray cohorts young patients refusing standard surgery were also included and concurrent chemotherapy was prescribed, which might increase the chance of a complete response. Possibly, elderly or frail patients could have increased risk of toxicity due to reduced regenerative

Table 1. Comparison of the HERBERT study with recent publications of combined EBRT with intraluminal radiotherapy in elderly patients

	n	age	TNM-stage	Treatment					Outcome			
Study		**median (range)**		**EBRT**	**Chemo-therapy**	**CXB**	**HDREBT**	**EQD2***	**cCR**	**Regrowth^**	**Late tox.**	**Definition of toxicity**
HERBERT	38	83 (57-94)	cT2-3	13×3 Gy	no		3×5-8 Gy	61-78.2	61%	30%	40%	Proctitis grade 3
Garant 2019	94	81 (60-97)	cT1-4	16×2.5 Gy	no		3×10 Gy	91.7	86.2%	13.6%	19%	Grade not specified
Gerard 2019	74	74 (39-93)	cT2-3 < 5 cm	25×2 Gy	CAP	3×30 Gy		100	86%	10%	11%	Grade 3 bleeding/ incontinence
Myint 2018[$]	83	72 (36-87)	cT2-3 (RV < 3 cm)	25×1.8 Gy	CAP/5FU (n=71)	3×30 Gy		94.2	63.8%	13.2%	6%	gr 2; APC for rectal bleeding, no gr 3
Myint 2017[$]	200	74 (32-94)	cT1-4 (RV < 3 cm)	25×1.8 Gy	CAP/5FU (n=144)	3×30 Gy		94.2	72%	11%	11%	gr 2; APC for rectal bleeding, no gr 3

* Total EQD2 was calculated at 1 cm depth for contact X-ray (≈3×10 Gy).

^ regrowth is calculated as proportion of complete responders.

$ Myint 2018 is a selection of Myint 2017: cT1, small T2, T4, CXB< 4wkns after EBRT, missing data were excluded.

Abbreviations: EQD2, equivalent dose in fractions of 2 Gy, α/β=10; RV, residual volume after EBRT; CAP, capecitabin; 5FU, 5-fluorouracil.

ability. Moreover, CXB requires a small residual tumour volume (< 5 cc) and only patients with a tumour < 5 cm (Gerard et al.) or a residual tumour volume < 3 cm (Myint et al.) were included.[1-3] Furthermore, the contralateral wall is spared during CXB by the rigid proctoscope resulting in a very small irradiated volume. In the HERBERT trial, tumours were larger with a median residual diameter of 3 cm and median brachytherapy clinical target volume (CTV) of 7 cc.

The cohort described by Garant et al. is more comparable to the HERBERT study with a median age of 81 and no use of chemotherapy.[4] The prescribed HDREBT boost dose was higher with 3×10 Gy instead of 3×7 Gy resulting in a total EQD2 of 91.7 Gy. The clinical complete response rate of 86% is very promising and superior to the 61% observed in the HERBERT study. While the prescribed dose was higher, the long-term complication rates were lower: 12.8% rectal bleeding, 3.2% symptomatic ulceration, 2% proctitis and 1% perforation. Further, major low anterior resection syndrome (LARS) was seen in only 1 of 14 evaluable patients after two years.[4] These differences might be explained by the extensive experience with the technique at the McGill University Health Centre and further developments in the HDREBT technique compared to the technique used in the HERBERT study. These include use of central shielding, an ipsilateral balloon to reduce the surface dose to < 200% (i.e. 20 Gy) and adaptive CT-based image-guided brachytherapy.[5]

Overall, these studies show very promising complete response rates and prove the concept of radical radiotherapy for rectal cancer. While the studies using contact X-ray show minimal toxicity of very high doses to a small volume (3×30 Gy surface dose to < 3 cm), the toxicity analyses described in Chapter 4 and 5 show the risk of a HDREBT boost to larger volumes. In the dose-toxicity analyses described in Chapter 5, CTV D2cc and CTV volume were both strongly correlated with deep ulceration after brachytherapy. Improvements in brachytherapy technique, focussing on better target coverage in large tumours and reduction of very high dose regions, will likely result in improved tolerability. Further research on the risks and benefits of a brachytherapy boost is however warranted before implementing the use of a HDREBT boost as a standard treatment option for elderly patients.

Rationale for the HERBERT II study

In frail elderly patients with rectal cancer, unfit for standard surgery, the main aim of treatment should be to maximise tumour control while maintaining quality of life. While definitive radiotherapy is a possible curative option in cT2-3 tumours as illustrated by the cohort studies in Table 1, it is still associated with moderate to severe toxicity reducing quality of life in patients with a limited life expectancy. Palliative radiotherapy focussed on durable symptom control is currently still considered the standard of care in inoperable patients and the value of an endoluminal brachytherapy boost should be further evaluated in a randomised phase III trial.

The HERBERT II study will be performed to evaluate the added value of an intraluminal brachytherapy boost after external beam radiotherapy in cT2-3N0-1 rectal cancer patients, who are unfit for surgery.[6] An important part of the study is a geriatric assessment which is aimed at

selection of patients who are deemed medically inoperable but in whom radical treatment is desirable. Initial screening on functional and cognitive status will be done using the Geriatric-8 [7] and the six-item cognitive impairment test.[8] In case of abnormalities, patients will be referred for a comprehensive geriatric assessment. Treatment options, including the HERBERT II study, will then be discussed in a shared decision-making process.

The treatment schedule of the HERBERT II study is illustrated in Figure 1. Patients will receive 13×3 Gy external beam radiotherapy and, after response assessment, patients will be randomised to either a brachytherapy boost or further follow-up. The primary endpoint will be clinical complete response at six months after brachytherapy. Secondary endpoints include health-related quality of life, acute and late patient- and physician-reported toxicity and freedom from regrowth and overall survival at two years.

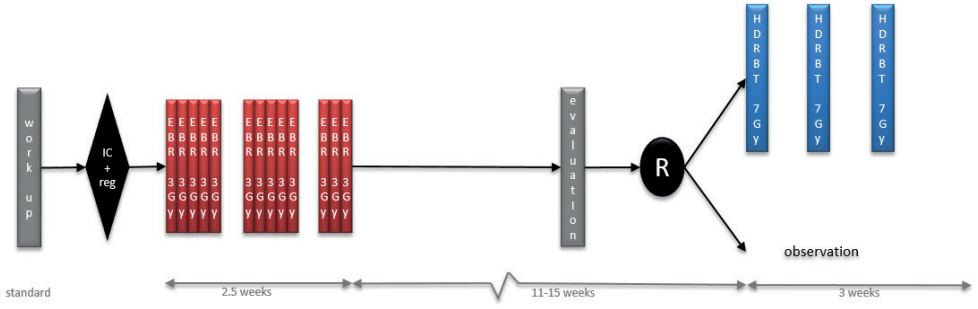


Figure 1. HERBERT II trial schedule.

9.2 Optimising HDR endorectal brachytherapy

To improve the outcome of HDREBT, further optimisation of the technique is needed, with the aim of improving target coverage while minimising dose to normal tissue. In Chapter 6, the benefit of CT-based adaptive brachytherapy was shown and this is now considered standard of care.[9,10] Several aspects of HDREBT can however be further improved, working towards an image-guided adaptive brachytherapy workflow:

1. Imaging
2. Target definition
3. Dose prescription
4. Shielding of normal tissue
5. Position verification

9.2.1 Imaging

Soft tissue contrast on CT is poor and although a diagnostic MRI, endoscopy images and clips were used to aid in CTV delineation in the HERBERT study, there was still a high level of uncertainty. The residual tumour volume is best evaluated using a combination of digital rectal examination (DRE), endoscopy and MRI.[11-13] Information of DRE and endoscopy at time of diagnosis and at time of brachytherapy is essential and can be summarised in a clinical drawing (see Figure 2).[10] Additional use of MRI has the potential to reduce interobserver variability and target volume compared to CT-based delineation.[14,15] T2-weighted MRI is currently considered the standard in evaluation of rectal cancer.[11] Functional imaging such as diffusion-weighted MRI and FDG-PET are helpful in identifying pathologic areas but might result in smaller volumes and are less reliable in geometric accuracy.[16,17]

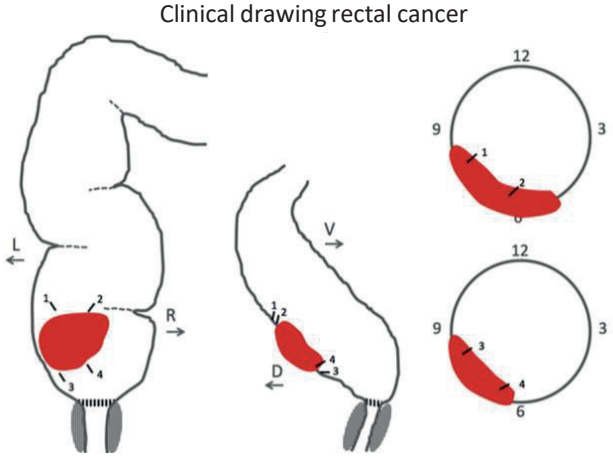


Figure 2. Clinical drawing for IGABT in rectal cancer.*

To allow for MRI evaluation after EBRT and MRI-guided brachytherapy, MRI compatible markers are needed. The clips used in the HERBERT study are not MRI compatible and gold fiducials were therefore tested as an alternative in the REMARK study. Visibility analyses selected the T1 3D GRE MRI sequence as the best sequence for marker detection and the Gold Anchor as the preferred marker because of superior visibility.[18] The use of MRI for HDR endorectal brachytherapy was evaluated in the OPPER-BT trial. Intermediate risk rectal cancer patients were treated with neoadjuvant HDREBT (4×6.5 Gy on four consecutive days), followed by total mesorectal excision. The benefit of MRI-guided delineation is clearly illustrated in Figure 3. Better discrimination

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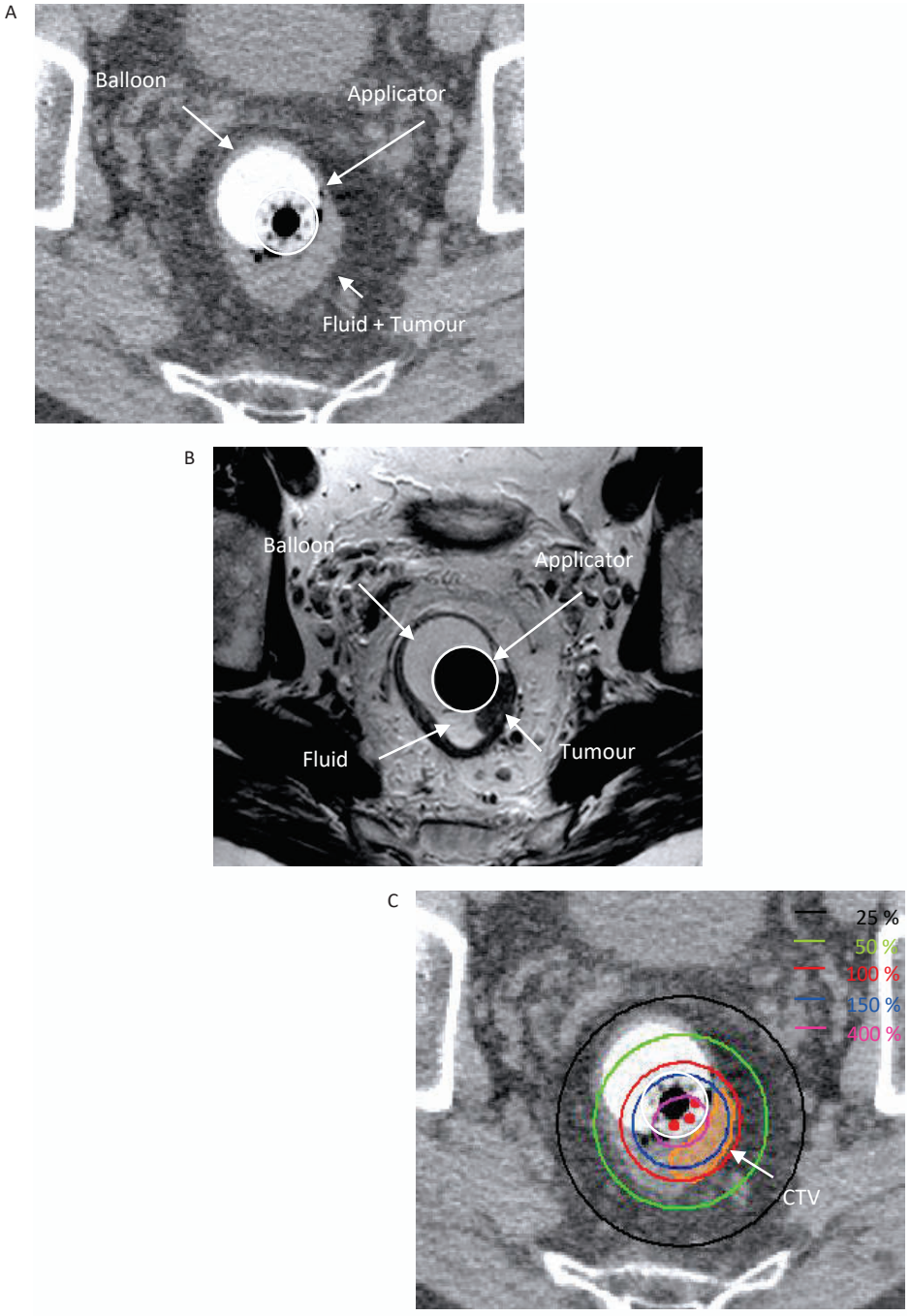

Figure 3. Example of MRI and planning CT of a patient in the OPPER-BT trial.
(A) Planning CT. (B) Planning MRI. (C) Planning CT with CTV delineation and dose distribution. The fluid could be excluded from the CTV due to superior soft tissue contrast of MRI.

between fluid, faeces and tumour will allow for increased accuracy in delineation and therefore reduction in the total irradiated volume, increasing conformity and limiting toxicity. The trial has been closed prematurely because of poor inclusion, most likely due to organ-sparing alternative treatment options in these patients. However, the MR-guided brachytherapy workflow is very promising and will be further developed in the HERBERT II trial.

9.2.2 Target definition

The target definition for external beam radiotherapy in rectal cancer is mainly related to the risk of lymphatic spread based on the initial tumour stage. A consensus paper published in 2016 provides recommendations for elective lymph node areas to be included in the external beam radiotherapy fields of intermediate and high risk rectal cancer.[19] With the introduction of radiotherapy in low risk tumours in organ-preservation studies, the size of the radiotherapy fields have been adjusted accordingly and include only the mesorectum.[20,21]

The target definition for a brachytherapy boost is related to the primary tumour and requires differentiation between macroscopic and microscopic spread around the macroscopic tumour. Currently, widespread accepted definitions and terminology for target volumes in brachytherapy for rectal cancer are lacking. In order to understand and compare results obtained and to perform future multicentre research, this is of utmost importance.

Differences between rectal brachytherapy modalities challenge the development of robust target definitions. In CXB, usually no imaging is performed and most HDR-brachytherapy applications are still CT-based which, as stated above, provides poor soft tissue contrast.

With the implementation of MRI, the tumour can be better visualised, which allows for development of image-guided adaptive brachytherapy (IGABT). This concept has been developed by the Gynaecological GEC-ESTRO group in cervical and recently also vaginal cancer, and has been adopted in ICRU-89.[22-25] These adaptive target concepts differentiate between target volumes at time of diagnosis (initial) and following response assessment during treatment (residual). Based on the expected cancer cell densities (decreasing with distance from the gross tumour volume (GTV)) and routes of microscopic tumour extension, different target volumes can be defined. In this paragraph, suggestions are made for a target concept for IGABT for rectal cancer (see Table 2).

Suggested target concept for IGABT in rectal cancer

Gross tumour volume for the primary tumour (GTV-T) is defined as macroscopic disease assessed through digital rectal examination, endoscopy and available imaging modalities. The initial GTV at diagnosis (GTV-T_{init}) will change during treatment and at every brachytherapy application a residual GTV (GTV-T_{res}) is defined. The clinical target volume is divided into CTV-T for direct spread of the primary tumour and CTV-N for potential lymph node spread. In IGABT, the CTV-T is further divided into three risk categories: high risk CTV-T, intermediate risk CTV-T and low risk CTV-T.

Table 2. Suggested target volumes for image-guided adaptive brachytherapy in rectal cancer

Target	Definition	Description
GTV-T_{init}	The initial gross macroscopic tumour volume at time of diagnosis.	The volume should be assessed using the information of DRE and endoscopy (clinical drawing) and the T2 weighted MRI. Areas with diffusion restriction should always be included in the GTV-T_{init}.
GTV-T_{res}	The gross macroscopic tumour volume at time of diagnosis as described by DRE, endoscopy and MRI.	The volume should be assessed using the information of DRE and endoscopy (clinical drawing) and the T2 weighted MRI. Areas with diffusion restriction should always be included in the GTV-T_{res}.
CTV-T_{HR}	The high risk CTV includes the GTV-T_{res} and if present the fibrotic scar	This includes the GTV-T_{res} and surrounding areas with hypo-isointense signal intensity on T2-weighted MRI (fibrotic scarring) occurring within the initial tumour extension in the rectal wall, and possible 'grey zones' in the mesorectum within the initial tumour extension.
CTV-T_{IR}	The intermediate risk CTV should include all areas with significant microscopic tumour extension.	This should minimally include a 0.5 cm lateral safety margin around the CTV-T_{HR}, and in addition should include the original tumour extension at diagnosis (GTV-T_{init}), taking previous unaffected anatomical borders into account.

The high risk CTV (CTV-T_{HR}) is the area at highest risk of recurrence and the highest tumour cell density. It is suggested to include the GTV-T_{res} and all areas with residual mucosal abnormalities on endoscopy and abnormal signal intensity on MRI. In rectal cancer, usually a hypointense scar is seen on the T2 weighted image.[11] If brachytherapy is the first treatment modality, CTV-T_{HR} resembles the GTV-T_{init} at the first fraction.

The intermediate risk (CTV-T_{IR}) includes the CTV-T_{HR} with margins to include areas with significant potential for direct microscopic extension. This area is dependant of initial tumour extension (stage) and regression to EBRT. Lateral margins should include the submucosal microscopic spread within the rectal wall, and deep margins the microscopic spread into the mesorectum. Currently there is insufficient evidence to support an exact evidence-based margin for mesorectal spread, but it is advised to minimally include the initial tumour extension (GTV-T_{init}) into the CTV-T_{IR}, taking previous unaffected anatomical boundaries into account.

Several surgical studies do provide some evidence for the lateral microscopic extension. A study by Smith et al. showed that the lateral microscopic extension within the rectal wall was largely dependent on ypT-stage. They observed microscopic tumour spread lateral to the residual mucosal abnormalities in 32 of 45 (71%) patients. In ypT1 tumours the median spread was 0 mm and maximally 4 mm, in ypT2 tumours median spread was 2.5 mm and maximally 9 mm and in ypT3 tumours the median spread was 4 and maximally 9 mm. All ypT2/3 tumours were originally staged as cT3.[26] A meta-analysis including four studies evaluating microscopic intramural extension after neoadjuvant chemoradiotherapy also confirmed the relation between ypT-stage and lateral microscopic extension. Interestingly, there was a large group with no microscopic tumour extension (80%). The remaining 20% showed lateral extension between 1-10 mm, with one outlier to 20 mm. The authors conclude that a GTV to CTV margin of 5.5 mm would be sufficient to encompass all microscopic tumour extension in 95% of patients after neoadjuvant treatment.[27]

These large differences in lateral microscopic extension can be explained by different patterns of tumour response: shrinkage, fragmentation and mucin pool formation (see Figure 4).[28] Inclusion of the GTV-T_{init} will account for microscopic spread in both fragmentation and mucin pool formation patterns, but might not be necessary in tumours that show a shrinkage regression pattern. Further research is necessary to assess if these regression patterns can be identified on MRI or endoscopy.

A clear translation from these data into exact margin prescriptions for CTV-T_{IR} is difficult, but a safety margin from CTV-T_{HR} to CTV-T_{IR} of 5 mm seems reasonable.

Areas at low risk of microscopic spread are referred to as the low risk CTV (CTV-T_{LR}). Areas at risk of lymph node spread are referred to as CTV-N. These CTVs can either be treated with (chemo)radiotherapy or surgery or both. A mesorectal excision after neoadjuvant brachytherapy is an example of surgical treatment of the CTV-T_{LR} and CTV-N.

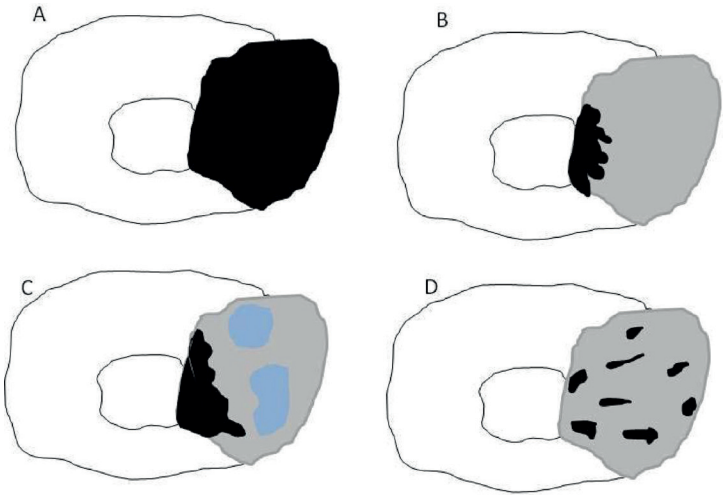

Figure 4. Schematic representation of response patterns. Adapted from Nagtegaal et al. 2020. [28,29]
A shows the tumour at diagnosis and B-D show different regression patterns. Residual GTV is shown in black and initial GTV in grey.
(A) Tumour at diagnosis (initial GTV).
(B) Tumour shrinkage scenario.
(C) Mucin pool formation (blue).
(D) Tumour fragmentation scenario in which scattered groups of tumour cells spread throughout the whole fibrotic area.

Target definitions for brachytherapy alone in cT1 tumours

The target definition as described above can be used in patients with cT1-4 rectal cancer in combination with EBRT. In low risk cT1 rectal cancer, the risk of lymph node metastasis is very low and standard treatment is local excision. Alternatively, these patients could be treated with brachytherapy alone. Extensive experience is described with contact X-ray by professor Papillon and professor Gerard in the era prior to local excision.[30,31] Because the risk of distant microscopic spread and lymph node spread is very low in these patients, the CTV-T_{LR} and CTV-N are disregarded and the tumour is treated locally (as with local excision). The CTV-T_{HR} is equal to the GTV-T_{init} at the first fraction, and resembles the definition in Table 2 in the following fractions. The CTV-T_{IR} should resemble the lateral microscopic tumour spread. A Japanese study showed that in stage I tumours, distal intramural spread is very rare and occurs only in 2.7%.[32] A review on microscopic spread in pT2 tumours showed no microscopic spread in 90.2% of patients and a spread of > 5 mm in only 4.7% of patients. It can be assumed that the risk in cT1 tumours is very low and probably no margin is needed in the majority of patients, but for now a safety margin of 5 mm is suggested to avoid potential undertreatment (see Table 2).

Finally, this is a suggested target concept, which should be discussed in a broader context allowing adoption by a larger number of centres to allow prospective clinical validation in such a setting.

9.2.3 Dose prescription

Currently, a wide variety of treatment schedules are used for an intraluminal boost after (chemo)radiotherapy. Dose prescription for the boost is usually performed at a fixed distance from the applicator surface (0 cm, 0.5 cm or 1.0 cm) or the radial margin of the delineated CTV (see Figure 3).[1,4,33-37] As dose prescription at a fixed distance will lead to overtreatment in superficial tumours and undertreatment in large tumours, prescription to the delineated CTV volume is preferred. However, prescribing to a delineated volume will also result in large differences in total irradiated volumes between patients with large and small tumours. Use of uniform terminology and reporting of the volumes of CTVs will allow for comparison between studies. In addition, registration of DVH parameters such as D98 and D90 and equivalent cumulative doses (EQD2$_{\alpha/\beta 10}$) rather than physical doses will allow for dose-response analyses.

Based on the results of the studies presented in Table 1 and a study on dose-response in patients with locally advanced tumours, an EQD2$_{\alpha/\beta 10}$ of at least 90 Gy for the CTV-T_{HR} is suggested, but needs confirmation in larger prospective trials.[1-4,38] For microscopic tumour included in the CTV-T_{IR}, an EQD2$_{\alpha/\beta 10}$ of 60 Gy is usually assumed to be sufficient.[25,39]

Planning aims for organs at risk

There are no reliable data to suggest evidence-based constraints in CXB or HDREBT treatment planning for rectal cancer.[40] In rectal cancer brachytherapy, the main organ at risk is the rectal wall, which overlaps with the clinical target volume. The CTV is therefore a target, but also an organ at risk. In contact X-ray, a surface dose of 3×30 Gy on the tumour after different schedules

of (chemo)radiotherapy (13×3 Gy/ 5×5 Gy/ 25×1.8-2 Gy) appears safe.[41] Series on contact therapy after local excision however have used a lower dose of 3×20 Gy or 2×15 Gy combined with CRT. Both schedules appear safe and it can therefore be assumed that 3×20 Gy surface dose is well tolerated in a small area < 3 cm.[42] In HDREBT, a constraint of 3×20 Gy on the surface is used in the study by Garant et al. and is associated with acceptable toxicity. From the HERBERT study, a CTV D2cc < 14 Gy/fraction is advised to minimise the risk of deep ulceration.

Organs at risk outside of the clinical target volume are the rectal wall surrounding the CTV (normal rectal wall), anal canal, the vagina and low-lying bowel loops. In the HERBERT study, no hotspots were allowed in the surrounding organs (D0.1cc < 100%) and no toxicity of the anal canal, vagina or small bowel was observed. The observed toxicity of the normal rectal wall illustrates the need for shielding, and reducing the dose as much as possible without compromising target coverage is currently advised. For the anal canal, dose constraints are needed to avoid painful ulceration in very low tumours. From experience in anal brachytherapy, a boost dose of 4×4 Gy interstitial brachytherapy seems safe after a dose of 45 Gy (EBRT+BT EQD2$_{\alpha/\beta 3}$ = 65.6 Gy).[43] In the HERBERT I study, the EQD2$_{\alpha/\beta 3}$ did not exceed 66 Gy and no anal toxicity was observed. From these data it can be assumed that a cumulative EQD2$_{\alpha/\beta 3}$ D2cc of < 66 Gy for the anal canal will be safe in IGABT for rectal cancer. For all other organs at risk, constraints from experience in gynaecological cancer can be applied.[39,44] However, registration of DVH parameters is advised to allow for dose-response analyses specifically for rectal cancer.

9.2.4 Shielding of normal tissue

In the HERBERT study, deep ulceration was seen in patients with very high surface dose at the tumour site. Due to the inverse-square law, dose reduction can be achieved by increasing the distance from the source to the organ at risk. This has led to the introduction of an ipsilateral semi-circular balloon. The surface dose and D2cc of the CTV can thereby be reduced while maintaining adequate tumour coverage. A volume of 20-30 cc is usually sufficient. Figure 5 illustrates reduction of the surface dose by use of an ipsilateral balloon.

Filling of the contralateral balloon will reduce the risk of telangiectasia and erythema of the normal rectal wall. Filling is limited by the comfort of the patient and a volume of 40-80 cc can usually be achieved.[5]

In addition, reduction of dose to the contralateral rectal wall can be achieved by shielding. Several studies performed at the medical physics unit of McGill University have evaluated the dosimetric effect of a lead or tungsten rod in the central canal. Unfortunately, such shielding effects cannot be calculated in the most commonly used TG-43 planning systems. However, when only three channels are used, the dose at the side of the tumour is unaffected while the dose to the contralateral wall is reduced by an average of 24% (see Figure 6).[5,45,46]

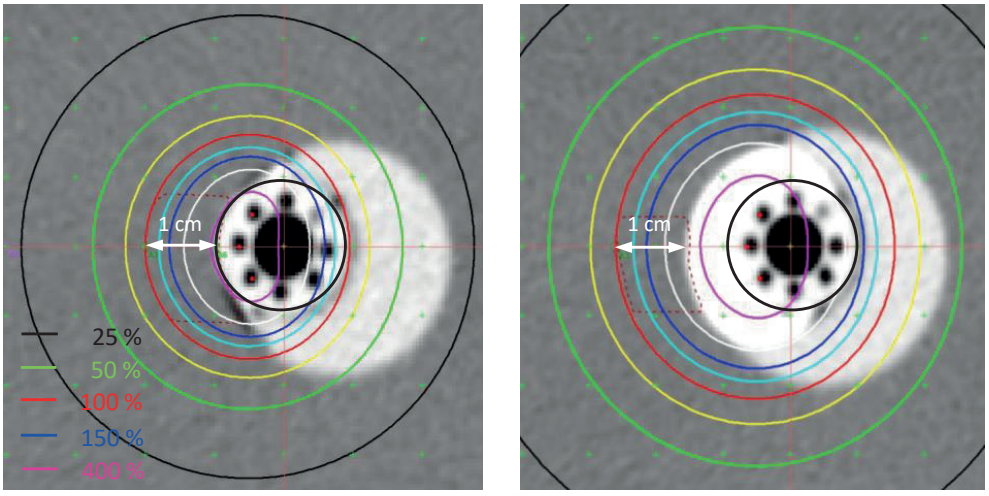

Figure 5. Simulation of the effect of an ipsilateral balloon on surface dose. 100% isodose is prescribed at 1 cm from the applicator/balloon surface. Surface dose is 450% without filling of the ipsilateral balloon and 275% after filling of the ipsilateral balloon with 20 cc contrast enhanced NaCl. The contralateral balloon is filled with 40 cc.

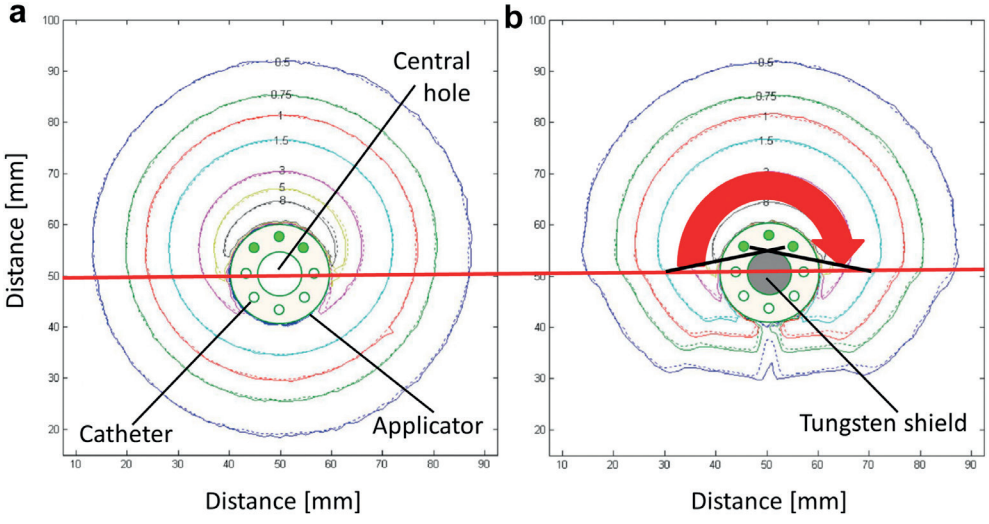

Figure 6. Absolute isodose distributions around the flexible multichannel applicator with sources loaded into three channels without (a) and with (b) tungsten shielding.*

* Reprint with permission of Elsevier from: Devic S, Bekerat H, Garant A, Vuong T. "Optimization of HDRBT boost dose delivery for patients with rectal cancer." Brachytherapy. 2019;18(4):559-63. Copyright Elsevier (2019).

Shielding possibilities of alternative applicators.

Several alternative applicators can be considered for HDREBT. Rigid cylinders and balloon-type applicators are currently in use and provide specific advantages and disadvantages compared to the flexible multichannel applicator.[47] Rigid cylinders with a central canal have a lower surface dose due to the increased distance from the source to the mucosa and shielding of 25-75% of the circumference allows for increased sparing of the contralateral rectal wall. Optimisation with one channel is however very limited and use of shielding induces a risk of shielding a part of the tumour in case of rotation of the rectal wall. Without shielding, the dose to the contralateral wall will be unacceptably high and a multichannel applicator is therefore preferred.

Balloon-type applicators use the concept of increasing the distance to the normal tissue by use of a balloon.[33,48] When both contralateral and ipsilateral balloons are used with a multichannel applicator this will have a similar effect. The advantage of the multichannel applicator is that the reconstruction of the source channels is more straightforward.

Two other applicator types are under development: The Flower applicator and a shielded dynamic/grooved applicator. The Flower applicator is an initiation of the MAASTRO clinic in the Netherlands.[49] It aims to mimic the dose distribution of contact X-ray therapy with an HDR iridium afterloader. The advantages and disadvantages of CXB compared with HDREBT therefore apply. The difference with CXB is the increased treatment time (13 min vs. 3 min), which introduces possible issues with intrafraction movement of the rectal wall. However, if online position verification can be achieved, this method will be a good alternative to CXB or HDREBT with a multichannel applicator in small tumours.

The shielded dynamic/grooved applicator is being developed by the physics group of the McGill University in Canada.[50,51] Two prototypes evaluate the use of a robot which steers the source to the correct positions in a fully shielded applicator and a fully shielded rigid applicator with multiple grooves for the sources. In theory, both applicators show increased sparing of normal tissue, but no reports on clinical testing have been published so far. Possible clinical limitations are the rigidity of the applicator, position verification and substantial increase in treatment time.

9.2.5 Position verification

Displacement of the applicator in between CT scanning and irradiation is a realistic risk in patients who will be transferred between imaging modalities and the treatment couch. This is currently overcome by correcting for depth and rotation, based on orthogonal X-rays in the brachytherapy suite.[10,52] An in-room 3D imaging modality will prevent transfers, whereas rapid replanning based on the latest image will be possible. Ideally, the imaging modality would be an MRI, given the superior soft tissue characteristics as compared to CT scanning. However, given the logistical challenges of an MRI-based brachytherapy procedure and current need for a CT for applicator reconstruction, most institutes opt for CT-based. At present, an MRI-compatible afterloader is

being developed in UMCU.[53] In addition, in our group MRI-based applicator reconstruction is being investigated. Given these developments, an MRI-only workflow will probably be available within 3-5 years from now.

9.3 The role of HDREBT in curative treatment of rectal cancer

HDREBT can also be used as an alternative to neoadjuvant CRT, as has been demonstrated at the McGill University Hospital in Canada over the last two decades.[54] The obvious advantage of neoadjuvant HDREBT compared to neoadjuvant CRT is the reduction in irradiated volume and, as a consequence, in associated toxicity. Concerns of inferior oncological outcome due to insufficient dose to the elective lymph nodes are contradicted by the excellent local control. In a cohort of 483 patients with cT3/lowT2 tumours, only 4.8% local recurrences occurred after 4×6.5 Gy (daily) HDREBT with delayed surgery.[55] A comparison of patients with cT3 tumours treated with neoadjuvant HDREBT in Canada and patients with cT3 tumours treated with neoadjuvant (C)RT in the Netherlands showed no significant differences in oncological outcome.[56]

The Correct trial is currently investigating both modalities in a randomised fashion and results are expected in 2021.[57] Comparable to the RAPIDO trial, this trial also implements the concept of total neoadjuvant treatment and prescribes full dose chemotherapy prior to TME surgery. In the RAPIDO trial, 5×5 Gy (SCRT) followed by 6-9 cycles of CAPOX/FOLFOX4 resulted in a higher compliance to chemotherapy and a reduced risk of locoregional and distant failure at three years.[58,59] Acute preoperative toxicity ≥ grade 3 was however increased from 25% with standard chemoradiotherapy to 48% in the experimental arm.[58] Replacing neoadjuvant SCRT (5×5 Gy) with HDREBT (4×6.5 Gy) might improve tolerability of total neoadjuvant treatment.

HDREBT has also been evaluated as a boost strategy in addition to standard neoadjuvant chemoradiotherapy in locally advanced rectal cancer. A randomised trial reported by Jakobsen et al, showed an increase in major pathologic response from 29% to 44% after addition of 2×5 Gy HDREBT in patients with a cT3/4 tumour, but this did not translate into increased progression free or overall survival. It was therefore concluded that a HDREBT boost currently is not advised in neoadjuvant treatment of locally advanced rectal cancer.[35,60]

However, if the aim of intensifying neoadjuvant treatment is to increase the chance of a watch-and-wait strategy, a HDREBT boost has been shown to be very effective in a phase II study by Appelt et al.[34] Fit patients with a cT2/3N0 tumour received a HDREBT boost of 5 Gy after high dose chemoradiotherapy (60 Gy). This resulted in a complete response rate of 78% and after a median follow-up of 23 months, 60% had successful organ preservation. Long-term follow-up showed excellent quality of life and local symptom scores.[61]

9.4 Organ preservation for rectal cancer

Shared decision making is the new standard in oncological care. In rectal cancer, a large group of patients have a clear desire for alternative treatment strategies to avoid a permanent stoma. In addition, the improved functional outcomes after a successful organ-preservation approach compared to neoadjuvant chemoradiotherapy followed by surgery further increases the interest in organ preservation.[61-64] Several options, such as intensifying radiotherapy or chemotherapy and selection of patients with earlier stages, are being explored to increase the chance of achieving a complete response. The downside of treatment intensification is the increased risk of toxicity in patients who do not achieve a complete response and require a completion TME. The GRECCAR-2 study clearly demonstrated that salvage TME after CRT and local excision is associated with increased morbidity compared to TME alone.[65] Moreover, the CARTS study reminded us that, although rare, chemoradiotherapy can even cause mortality itself.[66] While some patients therefore still prefer standard surgery, approximately 50% of patients are willing to risk extra toxicity in order to have a chance of organ preservation.[63,64,67] Careful discussions of the advantages and disadvantages of organ preservation strategies should therefore be standard practice.

9.4.1 Challenges in organ preservation

Selection of patients is one of the most important challenges in organ preservation. Although volume and stage are important factors, large tumours may be very radiosensitive, whereas small tumours might exhibit intrinsic radioresistance. Many studies are currently investigating the potential use of biomarkers and radiomics in prediction of good responders.[68-70] Clinical implementation of these markers will help in patient selection for organ preservation.

Another important challenge is response assessment. The current gold standard for response assessment is based on three diagnostic modalities: Digital Rectal Examination (DRE), white light endoscopy and multiparametric MRI.[12,13]

Criteria for a clinical complete response (cCR) are:

1. DRE: absence of any palpable tumour or irregularity.
2. Endoscopy: flat scar, whitening of the mucosa with or without telangiectasia.
3. MRI: normalised rectal wall or homogeneous fibrosis without diffusion restriction.

A combination of these three factors is associated with a chance of a true complete response of 98%.[12,13] Very few patients however present with the perfect complete response, but still might have a pathologic complete response.[12,71,72] From surgical studies it is clear that a longer waiting period increases the pCR rate and that response can be ongoing for several weeks and maybe months. In patients with minor residual abnormalities (near complete response), a watch-and-wait strategy can be discussed and reassessment every 6-8 weeks is advised to evaluate if there is an ongoing response.[11,73,74] In case of residual abnormalities after several

evaluations, a completion TME is advised. Data from salvage surgery however show that still approximately 20% of salvage resections show a pCR.[3,12,71,72,75-77] Response assessment after an intraluminal radiotherapy boost is possibly even more difficult than after EBRT alone because ulceration will be observed more frequently.[78] Techniques to diagnose a complete response therefore have to be improved to avoid unnecessary TME surgery with possible long-term morbidity. Use of big-data and radiomics could reduce the variability between radiologists and increase the positive predictive value of multiparametric MRI.[69] Another promising technique is the use of fluorescence during endoscopy. A novel EpCAM-targeting agent seems promising for the detection of rectal cancer, and could potentially be combined with white light endoscopy during response assessment.[79,80]

9.4.2 Treatment intensification

Early stages, currently treated with surgery alone, might be treated with (chemo)radiotherapy with standard doses, but to increase the chance of a complete response in more advanced stages, intensification of treatment is required in the majority of patients. Moderate radiotherapy dose escalation to the tumour and lymph nodes can be achieved with a simultaneous integrated boost using intensity modulated or volumetric arc radiotherapy.[34,61,81] While approximately 20% will achieve a complete response after moderate dose escalation, additional treatment of the residual tumour will be necessary in most patients.[81] Local excision, CXB, HDREBT and stereotactic radiotherapy are all possible options.

Local excision

Developments in endoscopic and transanal surgical techniques for early rectal cancer have made local excision very attractive and a widely available option. Several phase 2 studies evaluated the use of local excision after (chemo)radiotherapy in cT2-3 tumours.[82-85] The main advantage compared to other strategies is that response is confirmed by pathology. Further, in tumours which respond poorly to radiotherapy, a change in treatment modality may be logical and, in these patients, local excision could be preferred to HDREBT. The main disadvantages, however, are the need for general anaesthesia, a very high rate of severe acute toxicity including pain, and the risk of an incomplete resection or ypT2-3 stage requiring a completion TME. [66,82]

Contact X-ray

Contact X-ray, delivers a very high dose to the rectal mucosa by use of an X-ray tube with 50kV which is guided through a rigid rectoscope. Its use is limited by the availability of the contact X-ray machine, size of the tumour (< 3 cm) and accessibility of the tumour with rigid proctoscopy.[86] When all these requirements are met, contact X-ray is preferred to local excision, HDREBT or EBRT because of a favourable toxicity profile due to the small irradiated volume.

HDREBT

As described in this thesis, high-dose-rate endorectal brachytherapy can achieve a very high dose without the limitations of CXB. In small tumours, however, it does result in a larger irradiated volume than CXB. Patients with a large residual tumour are therefore good candidates for a HDREBT boost. The use of image-guided HDREBT will enable adjustment of the dose distribution on the residual tumour volume, preventing over or under treatment. No anaesthesia is required and treatment is well tolerated.

Stereotactic radiotherapy

Developments in precision in external beam radiotherapy with the use of MR-guided radiotherapy allows for dose escalation to the tumour with external beam radiotherapy.[87,88] The rectal boost trial evaluated dose escalation up to 65 Gy and showed that toxicity was acceptable.[89] To be able to achieve doses as high as 90 Gy EQD2, however, stereotactic radiotherapy techniques are required, which are currently not available for rectal cancer. Online MR-guided radiotherapy with an MRI-linac may facilitate the development of these techniques.[88] The main challenges will be sparing of the contralateral wall and compensation for intrafraction mobility. It remains to be determined whether similar high dose distributions can be achieved as in HDREBT or CXB.

9.4.3 Ongoing studies for primary organ preservation

Primary organ preservation is associated with possible increased toxicity and is therefore only advised within clinical trials. Table 3 shows a list of ongoing studies on primary organ preservation.[90-99]

Most trials focus on early stage rectal cancer. Use of chemotherapy is mainly seen in studies from the US, Canada, Germany, China and France, whereas intensification of radiotherapy is more common in the UK, France, Denmark and the Netherlands. Almost all studies opt for local excision for small residual disease. Only one study currently uses an intraluminal radiotherapy boost (the OPERA trial). Local excision, HDREBT, CXB or an external beam radiotherapy boost are however all possible treatment options for residual disease and have specific advantages and disadvantages. Therefore, all these methods should be evaluated in future organ-preservation studies.

Table 3. Ongoing primary organ preservation-studies

Study	Country	Stage	Treatment arms		Primary outcome	Accrual
			Standard	Experimental		
Single arm trials						
GI-116[90]	US	cT1-3N0 (cT1 high risk/T3 low risk)	NA	FOLFOX 6x + LE + CRT	Successful Local excision (R0)	2018-2022
NEO[91]	US/ Canada	cT1-T3bN0 (high risk excl.)	NA	FOLFOX 6x / CAPOX 4x + LE	3 yr. Organ preservation	2017-2020
NOM low risk rectal cancer[92]	China	cT2-3bN0-1	NA	CRT (concurrent CAPOX) ± LE	3 yr. Organ preservation	2016-2019
CAO/ARO/AIO-16[93]	Germany	cT1-2N+/ cT3N0	NA	CRT (3x 5FU/ OX) + CT (3x FOLFOX)	cCR rate	2018-2020
NO-CUT[94]	Italy	cT3-4 N0/ cT1-4, N1-3	NA	CAPOX + CRT	Distant Relapse-Free Survival	2018-2022
Randomised trials						
TESAR[95]	NL	ypT1,2, intermediate risk after LE	TME	CRT (45 Gy) ± LE	3 yr. Local recurrence	2015-2022
STAR-TREC Phase II[96]	NL/UK/ Denmark	cT2-3N0	TME	CRT (45 Gy) / SCRT ± LE	Accrual rate	2017-?
STAR-TREC Phase III[96]	NL/UK/ Denmark	cT2-3N0	TME	CRT (45 Gy) / SCRT ± LE	Organ preservation	2020-?
OPERA[97]	UK/ France/ Denmark	cT2-3bN0-1 (< 8 mm)	CRT (45 Gy) EBRT(9 Gy) ± LE	CRT (45 Gy) XCB (90 Gy) ± LE	3 yr. Organ preservation	2015-?
GRECCAR12[98]	France	cT2-3bN0-1 (< 8 mm)	CRT (50 Gy) + LE	Folfirinox 4x + CRT (50 Gy) + LE	1 yr. Organ preservation + absence of stoma	2016-2023
Watchful Waiting 3 Trial[99]	Denmark	cT1-3	CRT (50.4 Gy)	CRT (50.4 Gy + SIB 62 Gy)	2 yr. Organ preservation	2020-?

Studies published online at clinicaltrials.gov in April 2020. Search terms: “organ preservation” and “rectal cancer”. Abbreviations: NA, not applicable; cCR, clinical complete response; CRT, standard 5FU/capecitabin based chemoradiotherapy; yr., year; TME, total mesorectal excision; LE, Local excision; FOLFOX, 5FU+Folinic acid+ Oxaliplatin; CAPOX, Capecitabin + oxaliplatin; Folfirinox, 5Fu + Folinic acid + Irinotecan + Oxaliplatin.

CONCLUSION

In conclusion, HDREBT is a very promising technique for treatment in rectal cancer. Neoadjuvant HDREBT will likely improve quality of life without compromising oncological outcome in patients who prefer or are in need of surgical treatment. In organ preservation, a HDREBT boost can be applied in both fit and frail patients and allows for dose escalation to 90 Gy EQD2. Technical developments in image (MRI) guided adaptive brachytherapy provide the opportunity to increase treatment efficacy and limit the risk of toxicity. International consensus on image-guided adaptive brachytherapy concepts and training programs for brachytherapy teams are needed to facilitate a more widespread implementation of HDREBT for rectal cancer.

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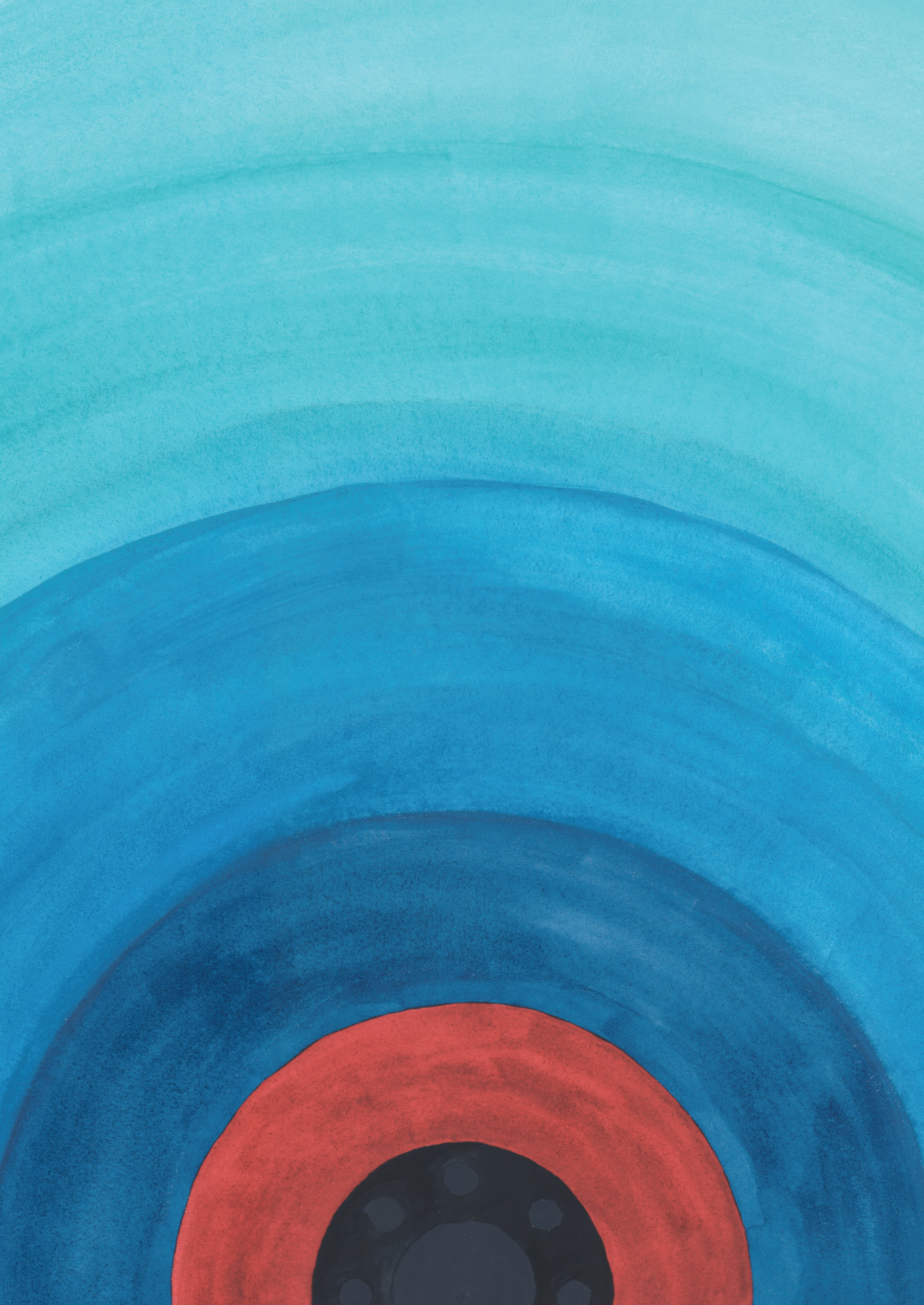

Appendices

NEDERLANDSE SAMENVATTING

Introductie

In dit proefschrift wordt radicale radiotherapie door middel van uitwendige radiotherapie met een brachytherapie boost (inwendige bestraling) onderzocht in oudere patiënten met endeldarmkanker. Door de vergrijzende populatie, neemt de incidentie van endeldarmkanker toe. Met een toenemende leeftijd neemt de kans op complicaties en risico op overlijden van een standaard chirurgische behandeling toe. Alternatieve behandelingsmogelijkheden voor oudere patiënten met endeldarmkanker zijn daarom dringend nodig.

Omdat er grote verschillen zijn in de belastbaarheid van oudere patiënten met endeldarmkanker kan een geriatrische screening ondersteunen in de keuze voor een behandeling. Over het algemeen kunnen patiënten worden onderverdeeld in vier categorieën: (1) fitte patiënten; (2) medium fitte patiënten met een licht verhoogd operatie risico; (3) kwetsbare patiënten met een hoog operatie risico en (4) zeer kwetsbare patiënten, voor wie alleen palliatieve (ondersteunende) zorg wordt geadviseerd. Bij fitte patiënten kan een standaardbehandeling worden geadviseerd, maar kunnen aanpassingen aan de standaardbehandeling worden gemaakt om de toxiciteit te minimaliseren. Voorbeelden hiervan zijn het gebruik van kortdurende radiotherapie in plaats van chemoradiotherapie of het verkleinen van het bestraalde volume bij uitwendige radiotherapie. Bij medium fitte patiënten kunnen verdere aanpassingen worden doorgevoerd om de morbiditeit van de behandeling te verminderen. In geval van een klinische (bijna) volledige respons kan een watch-and-wait-strategie of lokale excisie worden verkozen boven standaard TME-chirurgie. De groep met een hoog operatierisico kan baat hebben bij een intensiever radiotherapie schema (radicale radiotherapie) als alternatief voor een operatie. In de zeer kwetsbare groep wordt alleen een kort palliatief radiotherapie schema geadviseerd om de tumor-gerelateerde klachten te verlichten.

Om een goed advies te kunnen geven aan kwetsbare patiënten met endeldarmkanker is het belangrijk om beter te begrijpen wie een hoog risico loopt op het optreden van ernstige bijwerkingen en hoe we de kans op bijwerkingen kunnen beperken. In hoofdstuk 2 wordt gekeken naar de dosis-respons relatie voor darmtoxiciteit bij uitwendige radiotherapie. In hoofdstuk 3, 4 en 5 worden de uitkomsten van een dosisescalatie studie, de HERBERT studie, beschreven. Twee aspecten die een rol kunnen spelen in het optimaliseren van de brachytherapie techniek worden vervolgens beschreven in hoofdstuk 6 en 7.

Hoofdstuk 2

In dit hoofdstuk wordt gekeken naar de dosis-respons relatie tussen dosis op de darmen en acute en late toxiciteit in een cohort van 157 patiënten met endeldarmkanker. Tevens zijn drie intekenmethoden voor de definitie van “darmen” met elkaar vergeleken; individuele dunne darmlissen, een darmvolume gedefinieerd door de EMBRACE studiegroep (EMBRACE bowelbag) en een darmvolume gedefinieerd door de RTOG studiegroep (RTOG bowelbag). Er werd geen

dosis-respons relatie gevonden met toxiciteit. Wel werd een duidelijke verhoogd risico op toxiciteit gevonden bij patiënten die eerdere buikoperaties hadden ondergaan en bij patiënten die gelijktijdig chemotherapie kregen.
Het verschil tussen de verschillende intekenmethoden was groot. Het volume van de EMBRACE bowelbag was ongeveer 2-3 zo groot als het volume van losse dunne darmlissen en het volume van de RTOG bowelbag was ongeveer 6 keer zo groot. De dosis-volume histogram parameters van beide bowelbags waren sterk gecorreleerd aan die van de losse dunne darm intekening en kunnen daarom worden gebruikt als alternatief. De sterkste correlatie werd gevonden voor de EMBRACE bowelbag en er wordt voorgesteld om deze definitie te gebruiken voor toekomstig onderzoek.
Op basis van literatuuronderzoek wordt voorgesteld om het volume van dunne darmlissen dat 15 Gy krijgt zo mogelijk te beperken tot minder dan 165 cc om het risico op graad 2-3 acute gastro-intestinale toxiciteit te minimaliseren. Met een omrekenfactor, gebaseerd op de correlatie, wordt een beperking van 350 cc voor het volume van 15 Gy op de EMBRACE bowelbag voorgesteld als meer praktisch alternatief.

Hoofdstuk 3-5

In de hoofdstukken 3, 4 en 5 worden de resultaten van de HERBERT studie gepresenteerd. De HERBERT studie was een dosisescalatie studie naar de effectiviteit en veiligheid van een brachytherapie boost na uitwendige radiotherapie (EBRT) bij oudere kwetsbare patiënten met endeldarmkanker. Er werd gestart met een boost van 3x5 Gy, 6 weken na EBRT (13x3 Gy, 4/week). Bij uitblijven van ernstige toxiciteit werd de boost dosis met 1 Gy per inwendige bestraling verhoogd. Bij 8 Gy per fractie werd bij 3 van 6 patiënten graad 3 acute proctitis vastgesteld waardoor de maximum getolereerde brachytherapie boost dosis werd vastgesteld op 7 Gy per fractie.
In totaal werden tussen 2007 en 2013 38 patiënten met cT2-3N0-1 endeldarmkanker bestraald in deze studie. De mediane leeftijd was 83 jaar en de meesten hadden ernstige comorbiditeit waarbij 76% van de patiënten medisch niet-operabel werd geacht.
Van alle patiënten die vervolg endoscopieën ondergingen (33) hadden 29 patiënten een gedeeltelijke of complete respons (88%) waarvan 20 een complete respons (61%). Na een mediane follow-up van 30 maanden had 52% een aanhoudende respons. De kans op een aanhoudende response na 1, 2 en 3 jaar was respectievelijk 71%, 55% en 44%.
De overleving werd vooral door de leeftijd en comorbiditeit bepaald en was beperkt tot 63% na 2 jaar. Wel werd een verschil gezien tussen de patiënten met en zonder een complete respons. Na twee jaar was de lokale progressievrije overleving 60% in patiënten met een complete respons (cCR) en slechts 15% in patiënten zonder een complete respons (niet-cCR) ($p = 0,006$). De algehele overleving was 80% vs. 46% bij cCR vs. niet-cCR-patiënten ($p = 0,11$). Na een update met een langere follow-up van 43,7 maanden was dit verschil significant ($p = 0,01$) (niet gepubliceerd).

Patiënt-gerapporteerde, arts-gerapporteerde en endoscopisch waargenomen toxiciteit worden beschreven in hoofdstuk 4. Zowel door de arts als door de patiënt gerapporteerde toxiciteit liet een duidelijke toename zien van bijwerkingen in de derde week van de uitwendige bestraling en twee weken na brachytherapie. Deze bijwerkingen herstelden zich binnen twee maanden na brachytherapie. De meest patiënten (68%) hadden in de acute periode graad 2 proctitis klachten (matige klachten passend bij irritatie van de endeldarm). Een klein deel (13%) had graad 3 (ernstige) proctitis. Ernstige acute klachten waren geassocieerd met ernstige late toxiciteit. In totaal werd ernstige late proctitis klachten waargenomen bij 10 patiënten.
Endoscopische evaluatie van de normale rectumwand toonde voornamelijk erytheem en telangiëctasieën. Bij drie patiënten trad ernstig bloedverlies of ulceratie op tussen 12 en 18 maanden na de behandeling. Ter plaatse van de tumor werd vaak een ulcus waargenomen, variërend van een vlak ulcus tot diepe ulceratie. Deze toxiciteit werd alleen gescoord in de 28 patiënten met een respons. Een vlak ulcus (zonder opstaande rand) is typerend voor een complete response en werd waargenomen in 42%. Diepe ulceratie (42%) kan zowel passen bij een rest van de tumor als bij toxiciteit na radiotherapie of een combinatie van beiden. In de overige 14% werd alleen erytheem of een litteken gezien (complete response).
Hoofdstuk 5 evalueert de associatie van patiënt-, tumor- en dosimetrische parameters met respons en toxiciteit. Het tumorvolume bij diagnose was de beste voorspeller voor een klinische complete respons. In 74% van de patiënten met een tumorvolume kleiner dan 20 cc werd na 2 jaar geen groei/terugkeer van de tumor gezien, terwijl slechts 25% van de patiënten met een tumor groter dan 20 cc een aanhoudende response vertoonden ($p = 0,007$). Er werd tevens een relatie gezien tussen de respons op uitwendige radiotherapie en response op brachytherapie.
Een correlatie tussen de voorgeschreven dosis op het ingetekende tumorvolume (CTV D90 / D98) en de klinische tumor respons kon niet worden aangetoond. Wel was CTV D90/D98 gecorreleerd aan acute en late proctitis. Bovendien waren CTV-volume, CTV-breedte en hoge dosisregio's in het CTV (D1cc / D2cc) geassocieerd met ulceratie ter plaatse van de tumor. Diepe ulceratie trad op bij 7 van 9 patiënten met een CTV D2cc groter dan 14 Gy per fractie en bij 3 van 18 patiënten met een CTV D2cc kleiner dan 14 Gy per fractie ($p = 0,002$).
Uit bovenstaande gegevens kunnen we concluderen dat een brachytherapie boost haalbaar is bij oudere patiënten met endeldarmkanker met een redelijk hoge kans op een complete respons, maar ook een aanzienlijk risico op toxiciteit. Patiënten met tumoren kleiner dan 20 cc bij aanvang die goed reageren op uitwendige radiotherapie lijken de beste kandidaten voor een brachytherapie boost.

Hoofdstuk 6

Een apart onderdeel van de HERBERT-studie is de repeat CT-studie. Hierbij werd bij 11 patiënten een aanvullende CT-scan gemaakt op het moment van de tweede en derde brachytherapie-applicatie. Het doel van deze studie was te onderzoeken of herhaalde beeldvorming beter is dan de gebruikte techniek in de HERBERT studie. In de HERBERT studie werd het behandelplan

voor de brachytherapie boost gemaakt op een scan die verkregen was voorafgaand aan of bij de eerste bestraling. In de repeat CT studie werd dit plan geprojecteerd op de CT-scan van de 2e en 3e applicatie. In slechts 12/22 scans werd een acceptabele dosisverdeling waargenomen bij het gebruik van het eerste behandelplan. In twee gevallen zou een aanzienlijke verbetering kunnen worden bereikt door herplanning, maar in de overige acht van de 22 situaties zou een interventie nodig zijn geweest om de positie van de applicator of de ballon aan te passen en/of lucht of ontlasting te verwijderen. Dit toont aan dat een enkelvoudig behandelplan, zoals gebruikt in de HERBERT-studie, resulteert in suboptimale dosisverdelingen.

Hoofdstuk 7

De beste methode voor het afbeelden van endeldarmkanker is MRI. Bij endorectale brachytherapie worden echter clips gebruikt die een artefact veroorzaken op MRI en daarom wordt een CT-scan gebruikt om het behandelplan op te berekenen. Gebruik van MRI tijdens endorectale brachytherapie zou mogelijk gemaakt kunnen worden als de clips kunnen worden vervangen door gouden markers. De REMARK-studie is daarom gestart als onderdeel van een groter project voor MRI-geleide brachytherapie bij endeldarmkanker. In deze studie werden vier type goudmarkers getest. Deze goudmarkers werd geplaats via endoscopie. Twee methoden werden vergeleken: (1) in de tumor of rectumwand; (2) in het mesorectum rond de tumor. Twintig patiënten die neo-adjuvante uitwendige radiotherapie ondergingen werden geïncludeerd en in totaal werden 64 goudmarkers geplaatst. Alle typen konden met succes worden geïmplanteerd. Na een mediane tijd van 17 dagen na plaatsing (spreiding 7 - 47 dagen) waren in totaal 42 (66%) van de markers nog steeds aanwezig (55% in de tumor vs. 90% in het mesorectum, p=0,009). Om verlies van markers te voorkomen heeft mesorectale plaatsing derhalve de voorkeur.

Discussie

In de discussie worden allereerst de uitkomsten van de HERBERT studie vergeleken met recente publicaties van radicale radiotherapie schema's en wordt een vervolgstudie voorgesteld. Vervolgens worden suggesties gegeven voor het optimaliseren van de brachytherapie techniek en de mogelijke toepassingen in neo-adjuvante en orgaansparende behandeling van endeldarmkanker.

Er zijn drie belangrijke onderzoeksgroepen die uitwendige radiotherapie combineren met een inwendige boost. Twee hiervan gebruiken contact-X-ray en één brachytherapie. Contact-X-ray is een vorm van inwendige bestraling waarbij een röntgenbuis direct tegen de tumor wordt geplaatst, terwijl brachytherapie gebruikt maakt van een radioactieve bron die door middel van een applicator naar de tumor wordt gebracht. De cumulatieve equivalente dosis die in deze studies wordt gegeven op de tumor varieert van 61 tot 100 Gy en de kans op een complete response van 61% tot 86%. De kans op significante late toxiciteit in de HERBERT studie was met 40% echter

een stuk hoger dan in de andere series (6-19%). De oorzaak hiervan kan worden verklaard door verschillen in patiënt selectie (bijvoorbeeld kleinere tumoren of minder comorbiditeit) en de techniek van de inwendige boost.
Voordat een brachytherapie boost als standaardbehandeling kan worden aangeboden moet eerst worden onderzocht wat de meerwaarde is ten opzichte van uitwendige radiotherapie alleen. Dit is de rationale voor de HERBERT II studie. Hierin zullen kwetsbare patiënten met endeldarmkanker worden gerandomiseerd tussen 13x3 Gy uitwendige radiotherapie met of zonder een brachytherapie boost van 3x7 Gy.

Optimalisatie van de brachytherapie techniek
Technische verbeteringen van high-dose-rate (HDR) brachytherapie kunnen door betere dekking van de tumor en betere sparing van het normale weefsel zorgen voor een hogere kans op tumor controle en een lagere kans op toxiciteit. Het uiteindelijke streven is om een MRI-gestuurde adaptieve brachytherapie werkwijze te ontwikkelen. Door het implementeren van MRI kan de tumor beter worden gevisualiseerd en zal daardoor nauwkeuriger en conformeler bestraald worden. Afspraken rondom de definities van het doelgebied en de voorgeschreven dosis kunnen de kwaliteit van de brachytherapie verder verbeteren en kan vergelijking tussen instituten of verschillende boost technieken mogelijk maken. Er worden suggesties gedaan voor definities die de principes volgen van beeldgestuurde adaptieve brachytherapie die zijn ontwikkeld voor gynecologische brachytherapie.
Het beperken van de dosis op de normale rectumwand zou naast een conformeler bestralingsplan ook door afscherming kunnen worden bereikt. In de huidige applicator kan in het centrale kanaal een loden of wolfraam staaf worden ingebracht waardoor de dosis grotendeels wordt tegengehouden. Ook het vergroten van de afstand tot de normale rectumwand door optimaal gebruik van de ballon zal tot een aanzienlijke dosis reductie kunnen leiden.

Toepassing van brachytherapie in de curatieve behandeling van endeldarmkanker
Brachytherapie kan ook gebruikt worden als neo-adjuvante techniek, als alternatief voor neo-adjuvante uitwendige radiotherapie. Doordat er een veel kleiner volume bestraald wordt en het bestraalde volume wordt verwijderd bij de operatie is het risico op lange termijn bestralingseffecten zeer gering. Een prospectieve serie toont een vergelijkbare lokale controle als neo-adjuvante uitwendige radiotherapie met maar 4,8% lokale recidieven bij cT2-3 tumoren. Er is echter steeds meer interesse in het vermijden van een operatie en derhalve is de combinatie van uitwendige bestraling of chemoradiotherapie met een brachytherapie boost zeer interessant, niet alleen voor ouderen, maar ook voor jonge fitte patiënten. Er worden veel manieren onderzocht om de niet-chirurgische behandeling te intensiveren om de kans op een complete response zo groot mogelijk te maken. Zo wordt bijvoorbeeld gekeken of chemotherapie kan bijdragen aan een orgaansparende behandeling en wordt lokale excisie of hoge dosis radiotherapie onderzocht als alternatief voor een totale mesorectale excisie (TME)

na neo-adjuvante (chemo)radiotherapie. Een radiotherapie boost kan, zoals in dit proefschrift beschreven, worden gegeven met brachytherapie, maar ook door middel van contact-x-ray of stereotactische uitwendige radiotherapie. Indien deze opties niet leiden tot een complete response zal alsnog een TME-operatie moeten volgen. Daarmee bestaat dus het risico op extra toxiciteit in het geval van een onsuccesvolle orgaansparende behandeling. De potentiële voordelen en risico's van een in opzet orgaansparende behandeling moeten door middel van gezamenlijke besluitvorming met de patiënt worden besproken.

Concluderend is brachytherapie voor endeldarmkanker een veelbelovende techniek, waarbij dosisescalatie mogelijk is tot wel 90 Gy. Verdere ontwikkeling van MRI-gestuurde adaptieve brachytherapie en training van brachytherapie teams is nodig om deze techniek op grotere schaal mogelijk te maken.

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CURRICULUM VITAE

Eva Cornelia Rijkmans werd geboren in Amsterdam op 19 maart 1988. In 2006 behaalde zij het VWO diploma op het Coornhert Lyceum in Haarlem. In dat jaar begon zij met de studie geneeskunde aan de Leidse faculteit. Tijdens haar studie trokken de vakken “irradiation” en “imaging technologies” al vroeg haar aandacht en was de eerste interesse in de radiotherapie gewekt. Enige twijfels over een carrière in de urologie waren na een wetenschapsstage over de ontwikkeling van image-guided brachytherapie voor het cervixcarcinoom bij de afdeling radiotherapie verdwenen. Na deze stage onder leiding van prof. Dr. C.L Creutzberg en Dr. R.A. Nout was het haar duidelijk dat de radiotherapie het meest uitdagende en interessante specialisme is binnen de geneeskunde en de fascinatie voor brachytherapie in het bijzonder is nooit meer weg gegaan.

Na het behalen van het artsexamen in augustus 2013 (cum laude) werkte zij als ANIOS urologie in het Kennemer Gasthuis te Haarlem. Hierna startte zij in 2014 aan de opleiding tot radiotherapeut-oncoloog in het LUMC. Per 1 januari 2015 combineerde zij haar opleiding met een promotieonderzoek naar brachytherapie bij oudere patiënten met endeldarmkanker onder begeleiding van prof. dr. C.A.M Marijnen en later ook dr. R.A. Nout. Ze presenteerde meerdere malen de resultaten van haar onderzoek op de ESTRO en won een prijs voor beste poster in de “young clinical track” met de resultaten van hoofdstuk 5.

Per 1 mei 2020 heeft zij haar opleiding tot radiotherapeut-oncoloog afgerond en heeft zij haar carrière voortgezet als fellow radiotherapie in het Antoni van Leeuwenhoek ziekenhuis. Binnen dit fellowship verdiept zij zich in de gynaecologische en urologische radiotherapie waarbij veel aandacht is voor brachytherapie.