Brachytherapy for rectal cancer

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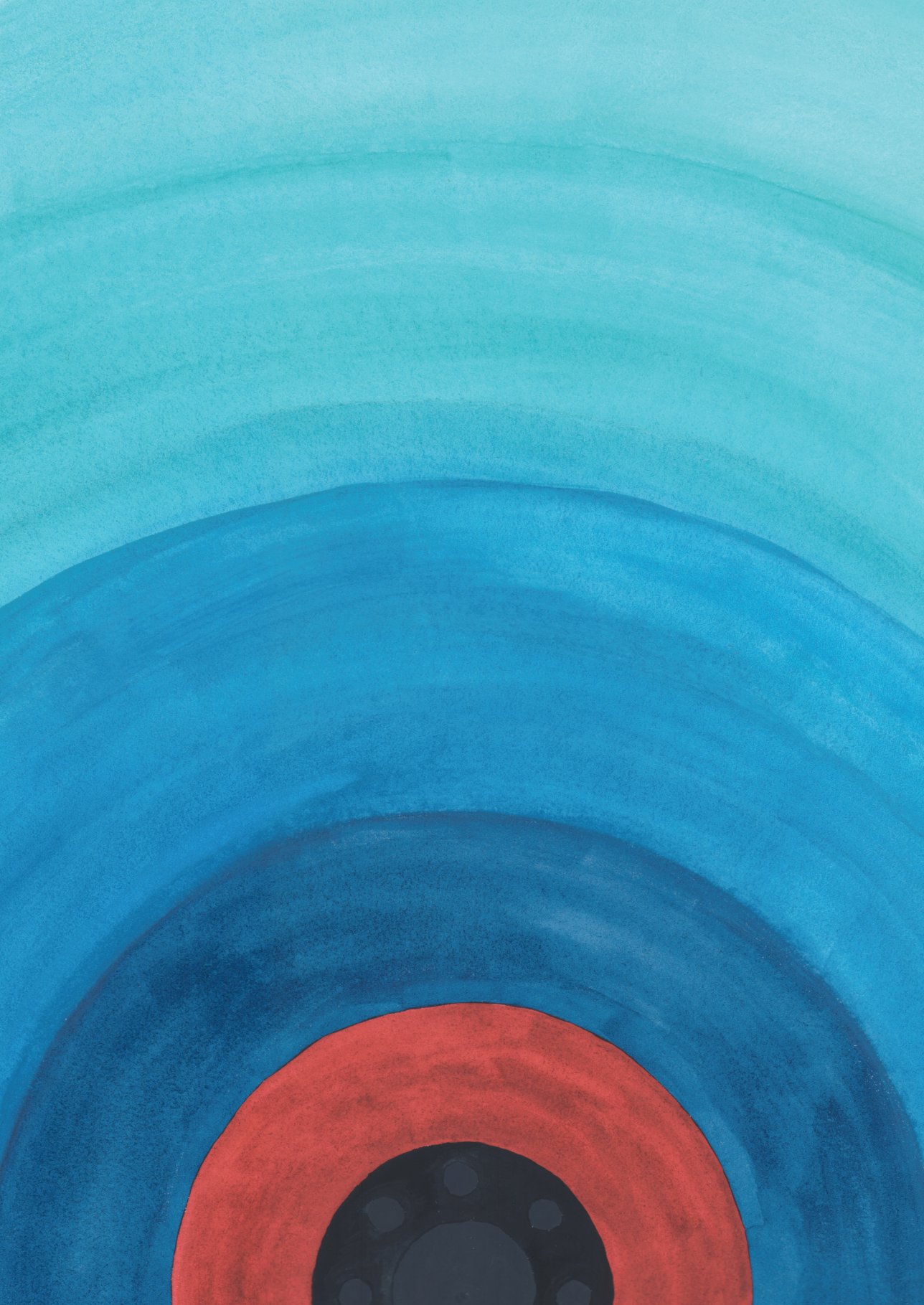

Chapter 4

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.

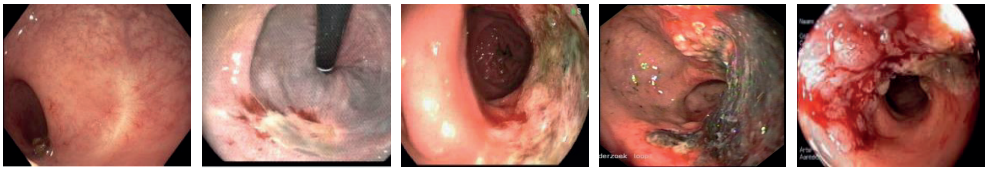
Questionnaires were sent to all patients at 13 time points; at baseline, weekly during EBRT, two and four weeks after EBRT, weekly during HDREBT and two weeks, two months, six months and one year after brachytherapy. The used questionnaire is based on the symptoms mentioned in the RTOG/EORTC GU and GI 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.

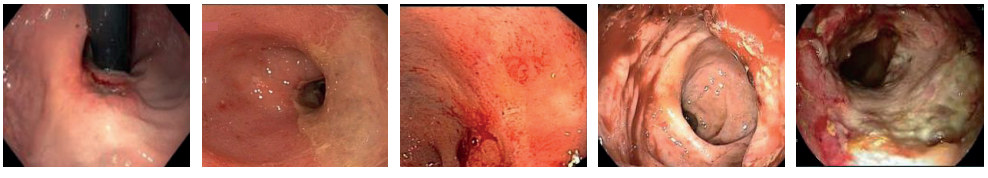
Endoscopic assessment at tumour site was scored by C.M. and E.R. in a 5 point scale; 0. erythema/scarring; 1. superficial ulcer; 2. deep ulcer; 3. very deep ulcer; 4. evident tumour mass (see Figure 1A). Endoscopic toxicity at the contralateral wall was scored using the endoscopic proctitis assessment 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.

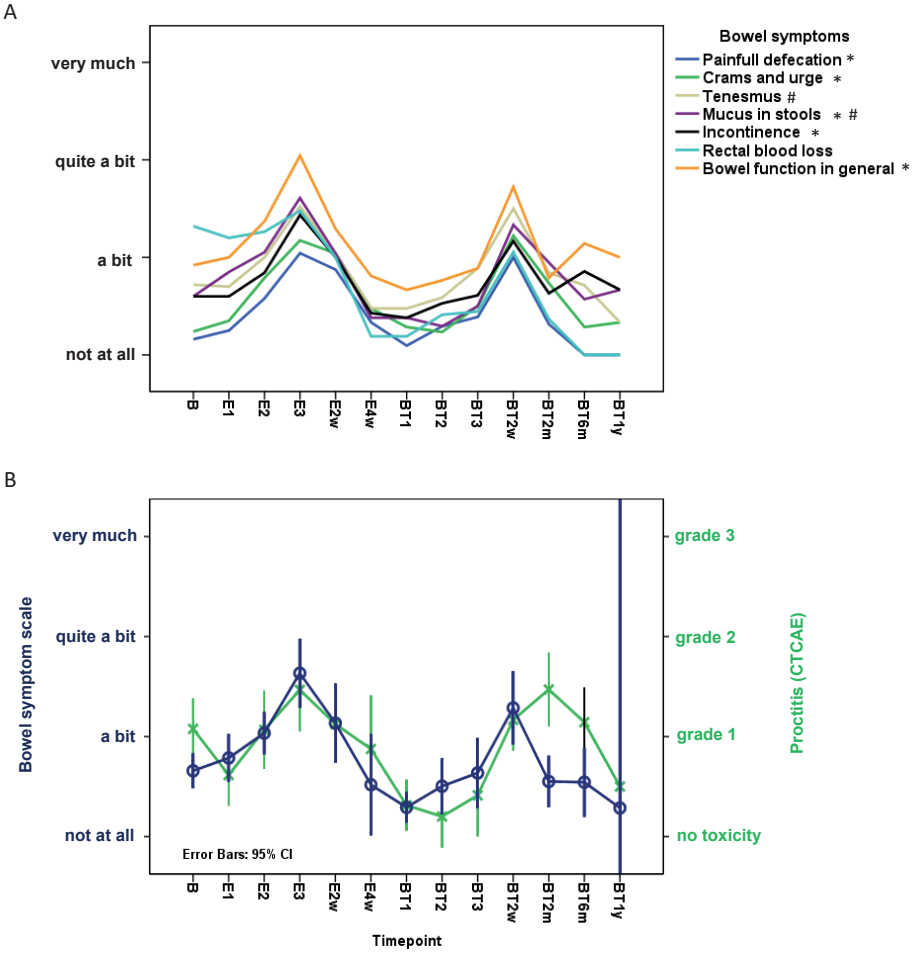


Figure 2. Patient reported bowel symptoms (A) and comparison of bowel symptoms with CTCAEv3 (B).

* 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.

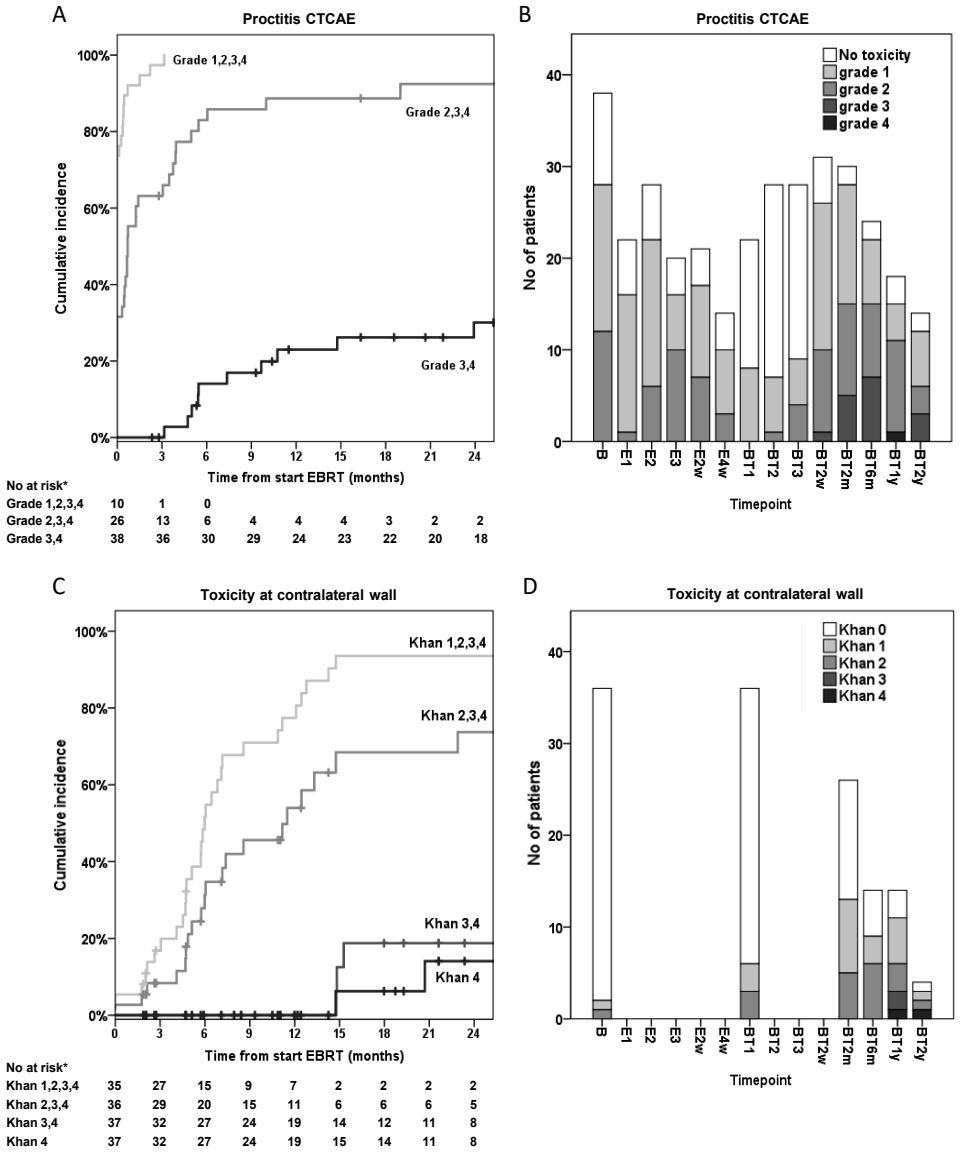


Figure 3. Proctitis (CTCAEv3) and endoscopic evaluation at the contralateral bowel wall.

(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.

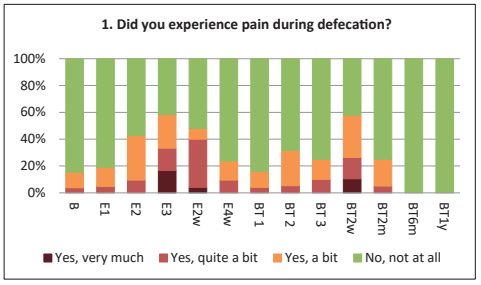
REFERENCES

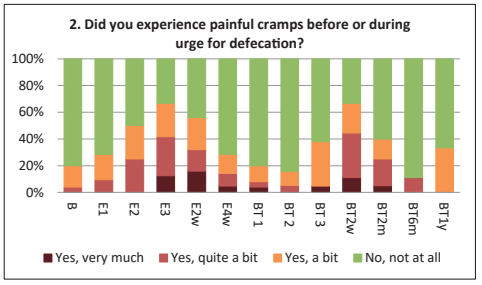
1. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol.* 2010;11(9):835-844.
2. Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol).* 2008;20(2):176-183.
3. Maas M, Lambregts DM, Nelemans PJ, et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. *Ann Surg Oncol.* 2015;22(12):3873-3880.
4. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *International journal of radiation oncology, biology, physics.* 2014;88(4):822-828.
5. Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *International journal of radiation oncology, biology, physics.* 2013;85(1):74-80.
6. Aumock A, Birnbaum EH, Fleshman JW, et al. Treatment of rectal adenocarcinoma with endocavitary and external beam radiotherapy: results for 199 patients with localized tumors. *International journal of radiation oncology, biology, physics.* 2001;51(2):363-370.
7. Gerard JP, Chapet O, Ortholan C, Benezery K, Barbet N, Romestaing P. French experience with contact X-ray endocavitary radiation for early rectal cancer. *Clin Oncol (R Coll Radiol).* 2007;19(9):661-673.
8. Coatmeur O, Truc G, Barillot I, Horiot JC, Maingon P. Treatment of T1-T2 rectal tumors by contact therapy and interstitial brachytherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2004;70(2):177-182.
9. Burbach JP, den Harder AM, Intven M, van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2014;113(1):1-9.
10. Gerard JP, Frin AC, Doyen J, et al. Organ preservation in rectal adenocarcinoma (T1) T2-T3 Nx M0. Historical overview of the Lyon Sud - nice experience using contact x-ray brachytherapy and external beam radiotherapy for 120 patients. *Acta Oncol.* 2015;54(4):545-551.
11. Marijnen CA. External beam radiotherapy and high dose rate brachytherapy for medically unfit and elderly patients. *Clin Oncol (R Coll Radiol).* 2007;19(9):706-710.
12. Corner C, Bryant L, Chapman C, Glynne-Jones R, Hoskin PJ. High-dose-rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. *Brachytherapy.* 2010;9(1):66-70.
13. Rijkmans EC, Cats A, Nout RA, et al. Endorectal Brachytherapy Boost After External Beam Radiation Therapy in Elderly or Medically Inoperable Patients With Rectal Cancer: Primary Outcomes of the Phase 1 HERBERT Study. *International journal of radiation oncology, biology, physics.* 2017;98(4):908-917.
14. Dutch Central Committee on Research Involving Human Subjects; registration no. NL17037.031.07. https://www.toetsingonline.nl/to/ccmo_search.nsf/fABRpop?readform&unids=C1257BA2002CC066C12572FF005D33C8. Accessed 06-01-2017.

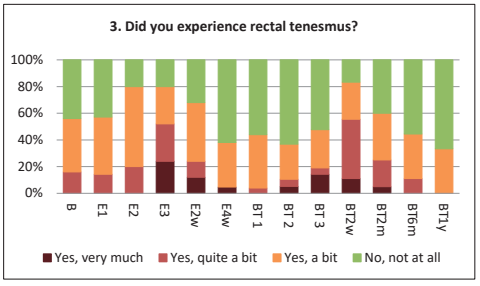
15. Heemsbergen WD, Peeters ST, Koper PC, Hoogeman MS, Lebesque JV. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. *International journal of radiation oncology, biology, physics.* 2006;66(1):3-10.
16. Goldner G, Wachter-Gerstner N, Wachter S, Dieckmann K, Janda M, Potter R. Acute side effects during 3-D-planned conformal radiotherapy of prostate cancer. Differences between patient's self-reported questionnaire and the corresponding doctor's report. *Strahlenther Onkol.* 2003;179(5):320-327.
17. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. March 31, 2003 (http://ctep.cancer.gov), Publish Date: August 9, 2006. Accessed 22-9-2016.
18. Khan AM, Birk JW, Anderson JC, et al. A prospective randomized placebo-controlled double-blinded pilot study of misoprostol rectal suppositories in the prevention of acute and chronic radiation proctitis symptoms in prostate cancer patients. *Am J Gastroenterol.* 2000;95(8):1961-1966.
19. Cameron MG, Kersten C, Vistad I, et al. Palliative pelvic radiotherapy for symptomatic rectal cancer - a prospective multicenter study. *Acta oncologica (Stockholm, Sweden).* 2016;55(12):1400-1407.
20. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol.* 2015;16(8):919-927.
21. Hoskin PJ, de Canha SM, Bownes P, Bryant L, Glynne Jones R. High dose rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2004;73(2):195-198.
22. Gerard JP, Ayzac L, Coquard R, et al. Endocavitary irradiation for early rectal carcinomas T1 (T2). A series of 101 patients treated with the Papillon's technique. *International journal of radiation oncology, biology, physics.* 1996;34(4):775-783.
23. Lavertu S, Schild SE, Gunderson LL, Haddock MG, Martenson JA. Endocavitary radiation therapy for rectal adenocarcinoma: 10-year results. *Am J Clin Oncol.* 2003;26(5):508-512.
24. Rauch P, Bey P, Peiffert D, Conroy T, Bresler L. Factors affecting local control and survival after treatment of carcinoma of the rectum by endocavitary radiation: a retrospective study of 97 cases. *International journal of radiation oncology, biology, physics.* 2001;49(1):117-124.
25. Schaake W, van der Schaaf A, van Dijk LV, Bongaerts AH, van den Bergh AC, Langendijk JA. Normal tissue complication probability (NTCP) models for late rectal bleeding, stool frequency and fecal incontinence after radiotherapy in prostate cancer patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2016;119(3):381-387.
26. Mazeron R, Fokdal LU, Kirchheiner K, et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2016;120(3):412-419.
27. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *International journal of radiation oncology, biology, physics.* 2010;76(3 Suppl):S123-129.
28. Chen TY, Wiltink LM, Nout RA, et al. Bowel function 14 years after preoperative short-course radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomized trial. *Clinical colorectal cancer.* 2015;14(2):106-114.
29. Pietrzak L, Bujko K, Nowacki MP, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2007;84(3):217-225.

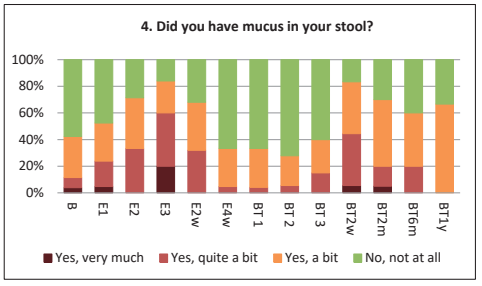
30. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *The British journal of surgery.* 2006;93(10):1215-1223.
31. Wachter S, Gerstner N, Goldner G, Potzi R, Wambersie A, Potter R. Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2000;54(1):11-19.
32. Krol R, Smeenk RJ, van Lin EN, Yeoh EE, Hopman WP. Systematic review: anal and rectal changes after radiotherapy for prostate cancer. *International journal of colorectal disease.* 2014;29(3):273-283.
33. Nout RA, Devic S, Niazi T, et al. CT-based adaptive high-dose-rate endorectal brachytherapy in the preoperative treatment of locally advanced rectal cancer: Technical and practical aspects. *Brachytherapy.* 2016;15(4):477-484.
34. Nout RA, Bekerat H, Devic S, Vuong T. Is Daily CT-Based Adaptive Endorectal Brachytherapy of Benefit Compared to Using a Single Treatment Plan for Preoperative Treatment of Locally Advanced Rectal Cancer? *Brachytherapy.*15:S83-S84.
35. Van den Ende RPJ, Rijkmans EC, Kerkhof EM, et al. OC-0280: Benefit of repeat CT in high-dose rate brachytherapy as radical treatment for rectal cancer. *Radiotherapy and Oncology.*123:S145-S146.
36. Vanneste BG, Van De Voorde L, de Ridder RJ, Van Limbergen EJ, Lambin P, van Lin EN. Chronic radiation proctitis: tricks to prevent and treat. *Int J Colorectal Dis.* 2015;30(10):1293-1303.

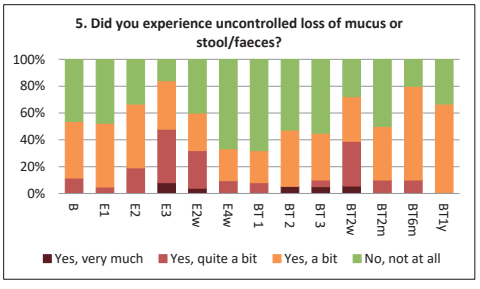
SUPPLEMENTARY MATERIAL

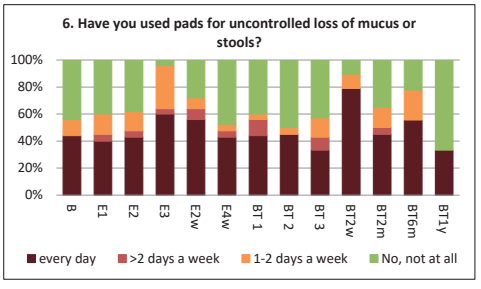


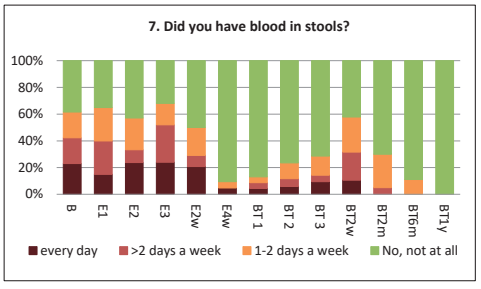












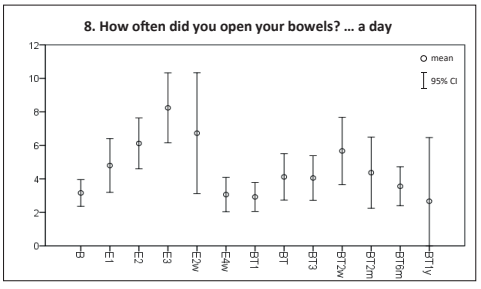
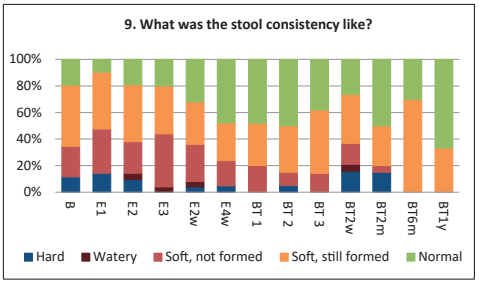
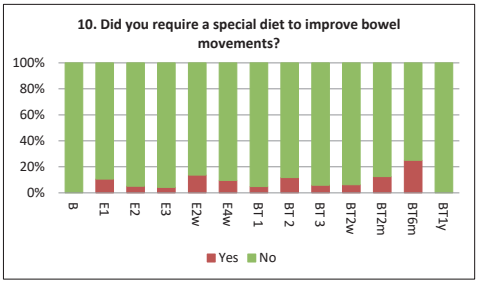
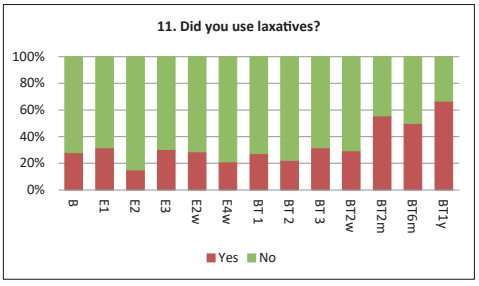
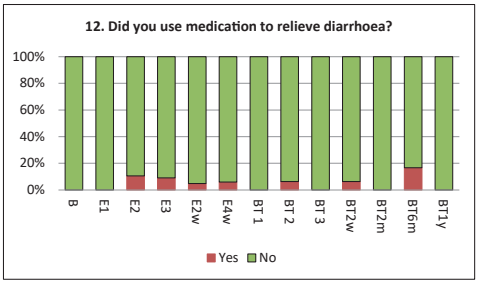


Figure S1. Patient reported outcome: bowel symptoms.









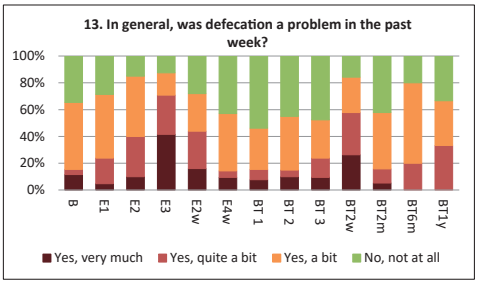
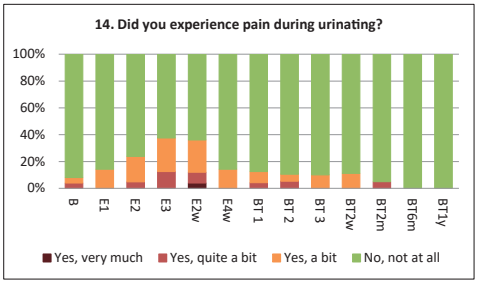
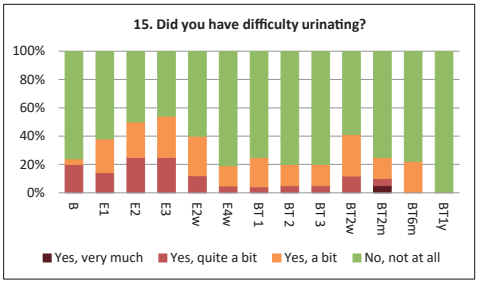
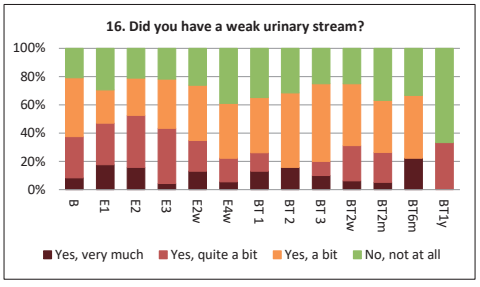
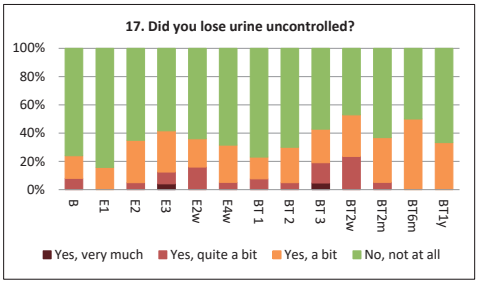


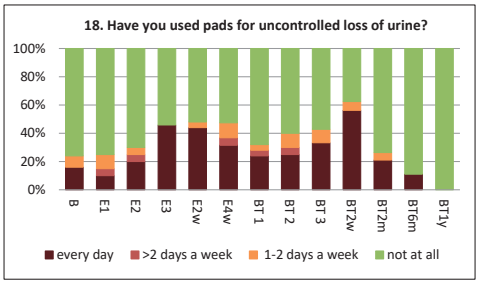
Figure S1. Patient reported outcome (continued): bowel symptoms.

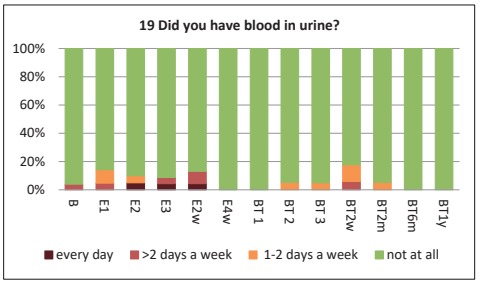


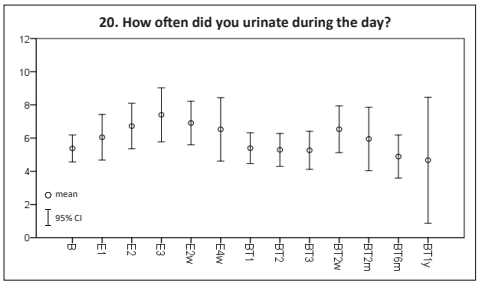












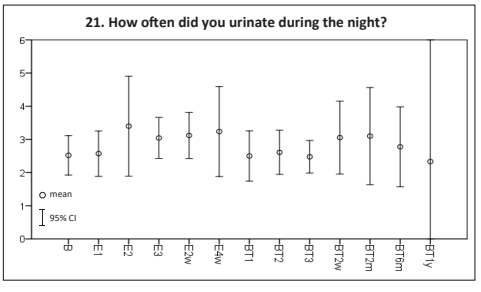


Figure S1. Patient reported outcome (continued): urinary symptoms.

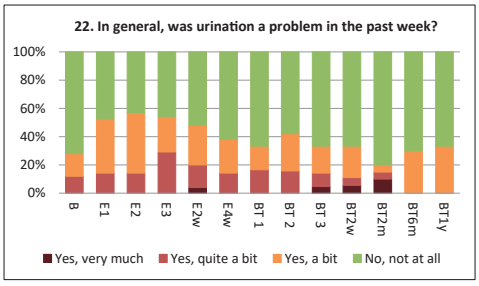
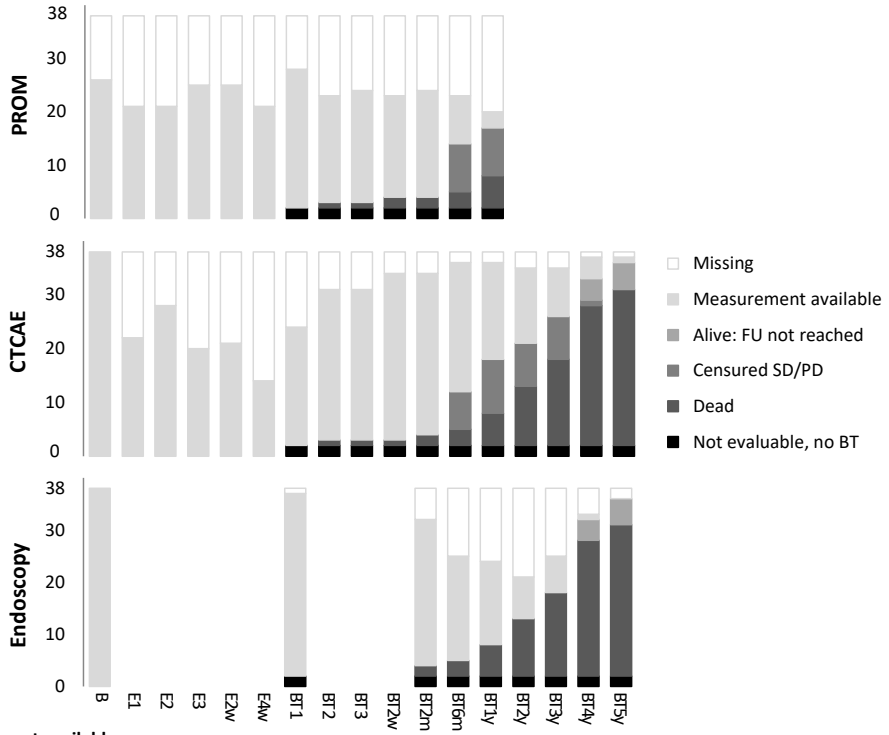


Figure S1. Patient reported outcome (continued): urinary symptoms.



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.