Brachytherapy for rectal cancer

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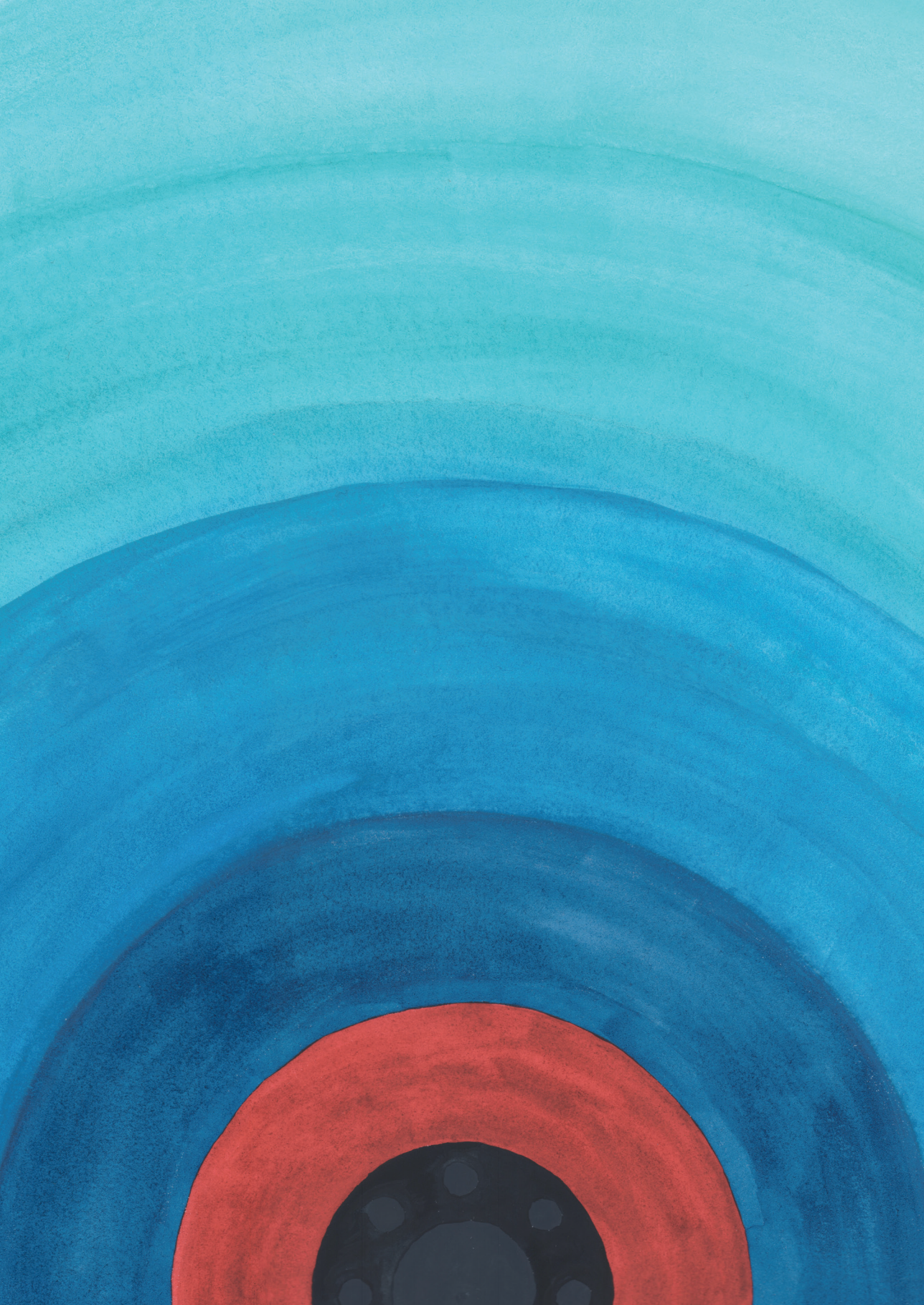

Chapter 2

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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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.

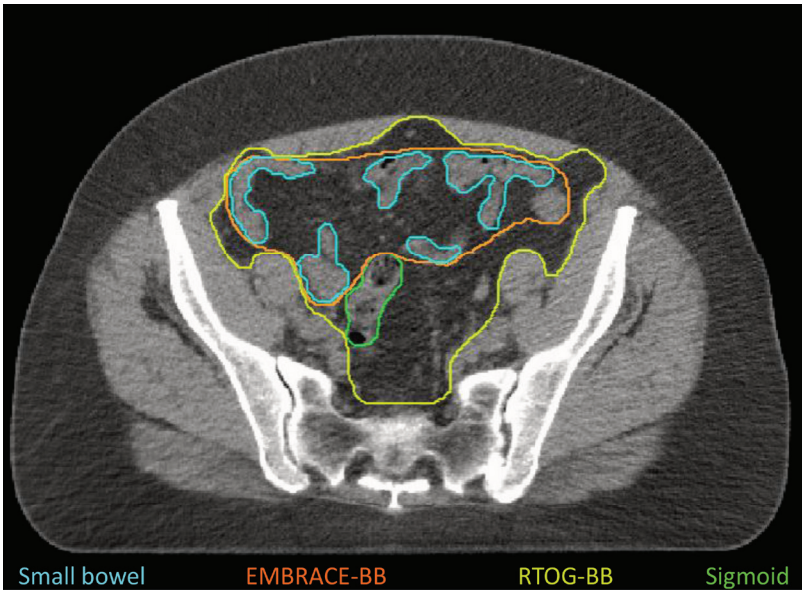

Figure 1. Example of different bowel contouring definitions:
- Small bowel (sky blue): Individual bowel loops.
- EMBRACE bowelbag (orange): Outer contour of small and large bowel, excluding rectosigmoid.
- RTOG bowelbag (yellow green): All abdominal contents starting from the most inferior axial slice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

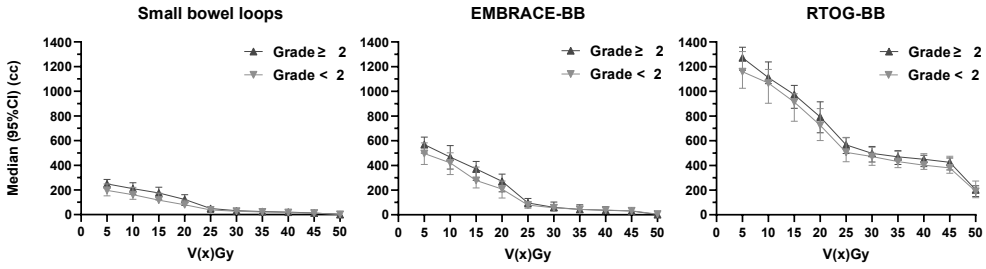

Figure 2. Relation of SBL, EMBRACE-BB and RTOG-BB with acute GI toxicity grade ≥ 2.

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

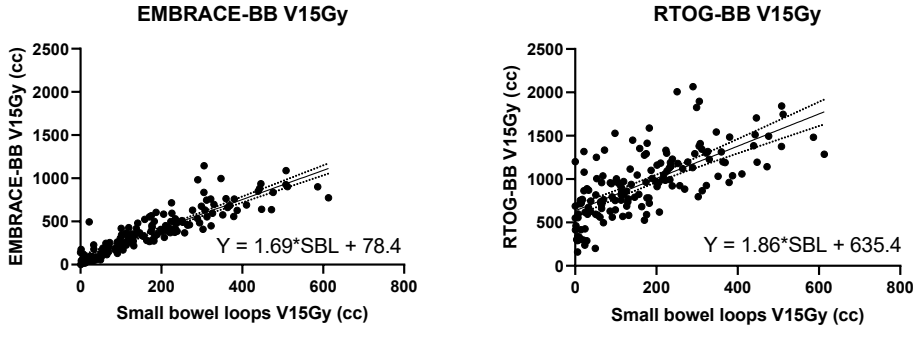

Figure 3. Pearson correlation of EMBRACE-BB V15 and RTOG-BB V15 with SBL V15.

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.