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# Is the irradiated small bowel volume still a predictor for acute lower gastrointestinal toxicity during preoperative concurrent chemo-radiotherapy for rectal cancer when using intensity-modulated radiation therapy?

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## Abstract

**Background:** The small bowel (SB) represents the most important dose-limiting structure in pelvic radiotherapy (RT). However, we observed that the majority of rectal cancer patients who received preoperative pelvic intensity modulated RT (IMRT) developed acute tenesmus without watery diarrhea. The objective of this study is to determine if the RT dose to SB affects the acute lower gastrointestinal toxicity (ALGIT) in rectal cancer patients who received neoadjuvant concurrent chemotherapy-IMRT. We will also evaluate if patient and tumor factors affect the ALGIT.

**Methods:** We retrospectively analyzed 63 rectal cancer patients that consecutively received preoperative IMRT (45 Gy for pelvis and 50 Gy for gross tumor in 25 fractions) with concurrent chemotherapy (oxaliplatin 130 mg/m<sup>2</sup> on day 1 and capecitabine 825 mg/m<sup>2</sup>, twice per day from day 1 to day 14, week 1 and 4) between May 2012 and May 2013. The ALGIT was assessed with Common Terminology Criteria for Adverse Events version 3. The patients were stratified into two groups (with and without grade  $\geq 2$  ALGIT). The effect of SB volume receiving 5 to 40 Gy (V5 to V40) at a 5 Gy interval dose level on grade  $\geq 2$  ALGIT was evaluated. The volume of small bowel is defined as the volume of the small bowel loop. Other factors evaluated include patient's age and gender, tumor size and location and preexisting number of daily bowel movements.

**Results:** Overall, grade  $\geq 2$  ALGIT occurred in 57 % (36/63) patients. There was no significant difference between the two groups of patients (with and without grade  $\geq 2$  ALGIT) in SB V5 to V40, patient's age and gender, tumor location and preexisting number of daily bowel movements. There was a significant difference between the two groups of patients in tumor volume (with grade  $\geq 2$  ALGIT: 115.5  $\pm$  85.5 cm<sup>3</sup> versus without grade  $\geq 2$  ALGIT: 58.5  $\pm$  25.2 cm<sup>3</sup>,  $p = 0.0001$ ). Multivariate analysis revealed no association between the dose SB received (V5 to V40) and the grade  $\geq 2$  ALGIT after adjusting for the tumor volume.

**Conclusions:** With IMRT technique used in rectal cancer patients undergoing preoperative chemo-radiotherapy, the acute lower GI toxicity is not associated with small bowel V5 to V40; instead it is associated with rectal tumor size.

**Keywords:** Small bowel dose volume, Acute lower gastrointestinal toxicity, Chemo-radiotherapy, Rectal cancer, Intensity-modulated radiation therapy

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## Introduction

Radiation therapy plays an important role in preoperative and postoperative therapy for locally advanced rectal cancer [1–4]. Radiation-induced lower GI toxicity is the main concern. Serious acute lower GI toxicity was reported in 12 to 44 % of patients undergoing radiotherapy alone or with concurrent chemotherapy in multicenter randomized clinical trials [4, 5]. The small bowel represents the most important dose-limiting structure in the pelvic radiation therapy. Dosimetric studies revealed association between the lower GI toxicity and the irradiated small bowel volume [6, 7].

Since the German trial reported that preoperative chemo-radiotherapy improved local control and was associated with reduced toxicity as compared with postoperative chemo-radiotherapy, preoperative concurrent chemo-radiotherapy has become a standard of care for locally advanced rectal cancer (T<sub>3-4</sub> and/or N positive) [4, 8]. A study has shown that the small bowel volume irradiated could be reduced in patients undergoing preoperative radiotherapy as compared with those undergoing postoperative radiotherapy [9]. Intensity-modulated radiation therapy (IMRT) has been confirmed to be advantageous at protection of the organs at risk such as bladder, femoral head and small bowel, and widely accepted as a relatively safe and effective radiotherapy method in the treatment of rectal cancer [10, 11]. Using IMRT technique further decreases the small bowel in the radiation field as compared to those using 3D conformal radiotherapy. Hence, the acute lower GI toxicity could be decreased significantly when IMRT used in preoperative chemo-radiation therapy. In clinical practice, we noticed that most rectal cancer patients who received preoperative IMRT typically presented with tenesmus and a feeling of incomplete defecation without watery diarrhea and abdominal pain. It seems that such side effects were induced rather by rectal reaction to radiation than by small bowel inflammation.

To better understand these clinical presentations, we attempted to find out if the irradiated small bowel volume still is a predictor for acute lower GI toxicity during preoperative concurrent chemo-radiotherapy for locally advanced rectal cancer when IMRT is utilized. We also examined other potential predictors for acute lower GI toxicity in this patient population.

## Patients and methods

### Patient selection

The study population consisted of 63 patients with stage II or III pathologically confirmed adenocarcinoma of the rectum who were consecutively treated with preoperative IMRT and concurrent chemotherapy between May 2012 and May 2013 in our hospital. The clinical stage and the tumor location (distance from the anal edge) were

determined with physical examination and diagnostic studies, including digital rectal endoscopy, abdominal-pelvic contrast-enhanced MRI, endorectal ultrasound (EUS) and a chest CT scan. Factors recorded and analyzed include age, gender, pre-treatment number of daily bowel movements and number of daily bowel movements during the treatment (see Table 1). The study was approved by the institutional ethic committee (reference number: 2013KY011).

### Radiotherapy

All patients underwent a contrasted CT simulation with a supine position. Oral contrast was given 30 min prior to simulation in order to differentiate the small bowel from the large bowel. A planning CT scan of the lower abdomen and pelvis was obtained at 5-mm intervals from the inferior edge of the second lumbar vertebrae (L<sub>2</sub>) through the mid-thigh. The CT data was transferred to the Xio treatment planning system (CMS Xio Version4.6 and

**Table 1** Patient characteristics

	n (%)	Acute GI toxicity		P value
		Grade < 2	Grade ≥ 2	
	N = 63	N = 27	N = 36	
Age (years)				
Median (range)	55 (30–78)	55 (30–78)	57 (35–74)	
Mean (SD)	56 (10)	55 (11)	57 (10)	0.388 <sup>a</sup>
Gender				
Male	45 (71.4)	16	29	0.092 <sup>b</sup>
Female	18 (28.6)	11	7	
T stage				
T1	0	0	0	0.759 <sup>b</sup>
T2	3 (4.8)	2	1	
T3	33 (52.4)	14	19	
T4	27 (42.8)	11	16	
N stage				
Negative	4 (6.3)	2	2	1.000 <sup>b</sup>
Positive	59 (93.7)	25	34	
Tumor volume (cc)				
Median (range)	92 (20–318)	55 (20–135)	83 (26–318)	
Mean (SD)	91 (72)	59 (25)	116 (86)	0.0004 <sup>a</sup>
Tumor location (cm from the anal verge)				
Median (range)	6 (2–12)	5 (3–10)	6(2–12)	
Mean (SD)	6 (2)	6 (2)	6 (2)	0.738 <sup>a</sup>
Pre-existing number of daily bowel movements				
1	6 (9.5)	4	2	0.184 <sup>b</sup>
2–3	25 (39.7)	13	12	
4–6	25 (39.7)	9	16	
≥ 7	7 (11.1)	1	6	

<sup>a</sup>Independent T test; <sup>b</sup>Exact test

Monaco 3.2.0, Elekta CMS Software, Maryland Heights, MO) for delineating the target volume and organs at risk (OARs).

The gross tumor volume (GTV) was contoured based on clinical information, including digital rectal examination, endoscopy ultrasound and abdominopelvic MRI. The clinical target volume (CTV) included a minimum of a 3 cm craniocaudal margin to the GTV in addition to the entire mesorectum, presacral, and internal iliac lymph node drainage regions. The CTV was delineated per atlas at the RTOG web site <http://www.rtog.org/Corelab/ContouringAtlases/Anorectal.aspx>. Planning target volumes (PTVs) for GTV and CTV were generated with an additional 10-mm margin separately. Critical normal structures including the small bowel, bladder, femoral head, femoral neck, and pelvic bones (including sacrum, ilium, pubis and ischium) were contoured according to the pelvic normal tissue contouring guidelines of RTOG [11, 12]. The small bowel was outlined as loops containing contrast. The small bowel contouring stopped at least 2 cm above the PTV-CTV (see Fig. 1a).

The IMRT plan consisted of 5 coplanar beams with the isocenter set at the center of PTV-GTV, arranged at 55°, 115°, 180°, 245° and 310°. The dose prescribed to PTV-GTV was 50 Gy/25 fractions and to PTV-CTV was 45 Gy/25 fractions. The doses to OARs were limited as follows:  $V_{45} < 35\%$  for bladder,  $V_{30} < 15\%$  for femoral head, and  $V_{30} < 60\%$  and  $D_{max} < 45$  Gy for small bowel. All patients were irradiated with one fraction daily for five consecutive days per week. The prescription dose was to cover at least 95% volume of PTV.

A small bowel dose-volume histogram (DVH) was generated for each patient. The absolute and relative volumes of small bowel receiving doses between 5 Gy and 40 Gy were recorded from the DVH at 5-Gy interval ( $V_5$  to  $V_{40}$ ) according to the study of Baglan KL [6].

### Concurrent chemotherapy

The chemotherapy that patients received during the radiation therapy was per an institutional protocol [13]. All patients had two 3-week cycles of chemotherapy during the course of radiation therapy. The chemotherapy regimen included oxaliplatin (130 mg/m<sup>2</sup> on day-1) and capecitabine (825 mg/m<sup>2</sup>, twice per day from day-1 to day-14) every 3 weeks.

### Toxicity assessment

All patients received chemo-radiation therapy as inpatients. The patients were evaluated and the toxicities were recorded daily prospectively. For the purpose of this study, the daily progress notes and the final treatment summary note were reviewed to determine the lower GI toxicities during the radiation therapy course. Lower GI toxicity was assessed with Common Terminology Criteria for Adverse

Events (CTCAE) version 3. Because most patients had no watery diarrhea or abdominal pain, we assessed the lower GI toxicities by using only the number of daily bowel movements [14] (see Table 2). Patients were stratified into two groups: with grade <2 and grade  $\geq 2$  lower GI toxicity.

### Statistical analysis

The chi-squared test was used to compare the proportions of the two patient groups for the baseline patient characteristics and RT delivery parameters. The independent sample *T*-test was used to compare the treatment target volume, small bowel volume, the volumes of small bowel receiving doses between 5 Gy and 40 Gy between the two groups (patients with grade <2 and  $\geq 2$  lower GI toxicity). A *p* value of  $\leq .05$  was considered significant. Statistical analyses were conducted using the Statistical Analysis Systems software package, version 9.3 (SAS Institute, Cary, NC).

### Results

Overall, acute grade  $\geq 2$  lower GI toxicity during radiotherapy occurred in 57.1% (36/63) patients. Among them, 14 were grade 2, 22 grade 3 and 0 grade 4. Only 4 of 36 had watery diarrhea at the second, seventh, eleventh and sixteenth fraction of radiotherapy. The remaining 27 patients experienced grade 0 and 1 lower GI toxicities. The median age of the entire group of patients was 55 (range 30–78). Most patients were male (71.4%) and had a clinical stage of T3-4 (95.2%) or were N positive (93.7%). The tumor located 2–12 cm from the anal verge with a median of 6 cm. The tumor volume ranged from 20 cm<sup>3</sup> to 318 cm<sup>3</sup> with a median volume of 92 cm<sup>3</sup> (Table 1). Patients with a larger tumor volume had a significantly higher rate of grade  $\geq 2$  toxicity ( $59 \pm 25$  cm<sup>3</sup> vs  $116 \pm 86$  cm<sup>3</sup>,  $p = 0.0004$ ). Almost half of the patients (32/63) had pre-existing grade 2 or above frequent bowel movements secondary to rectal tumor (Table 1). It was found that 52.4% (33/63) patients had either stable symptoms or had various extents of improvement in symptoms during the radiotherapy.

The average total contoured small bowel volume for all patients was  $257 \pm 152$  cm<sup>3</sup> and was  $288 \pm 193$  cm<sup>3</sup> and  $234 \pm 108$  cm<sup>3</sup> for patients that had lower GI toxicities of grade <2 and  $\geq 2$  ( $p = 0.244$ ), respectively. Table 3 shows that small bowel  $V_5$  to  $V_{40}$  did not have significant differences in patients with or without  $\geq 2$  acute lower GI toxicity.

Factors such as age, gender, T stage, N stage, tumor volume, tumor location, pre-existing number of daily bowel movement and small bowel  $V_5$ - $V_{40}$  were analyzed in the univariate logistic regression model (Table 4). All but tumor volume ( $p = 0.002$ ), pre-existing number of daily bowel movements ( $p = 0.06$ ) and gender ( $p = 0.07$ ) were not significantly correlated with grade  $\geq 2$  acute lower GI

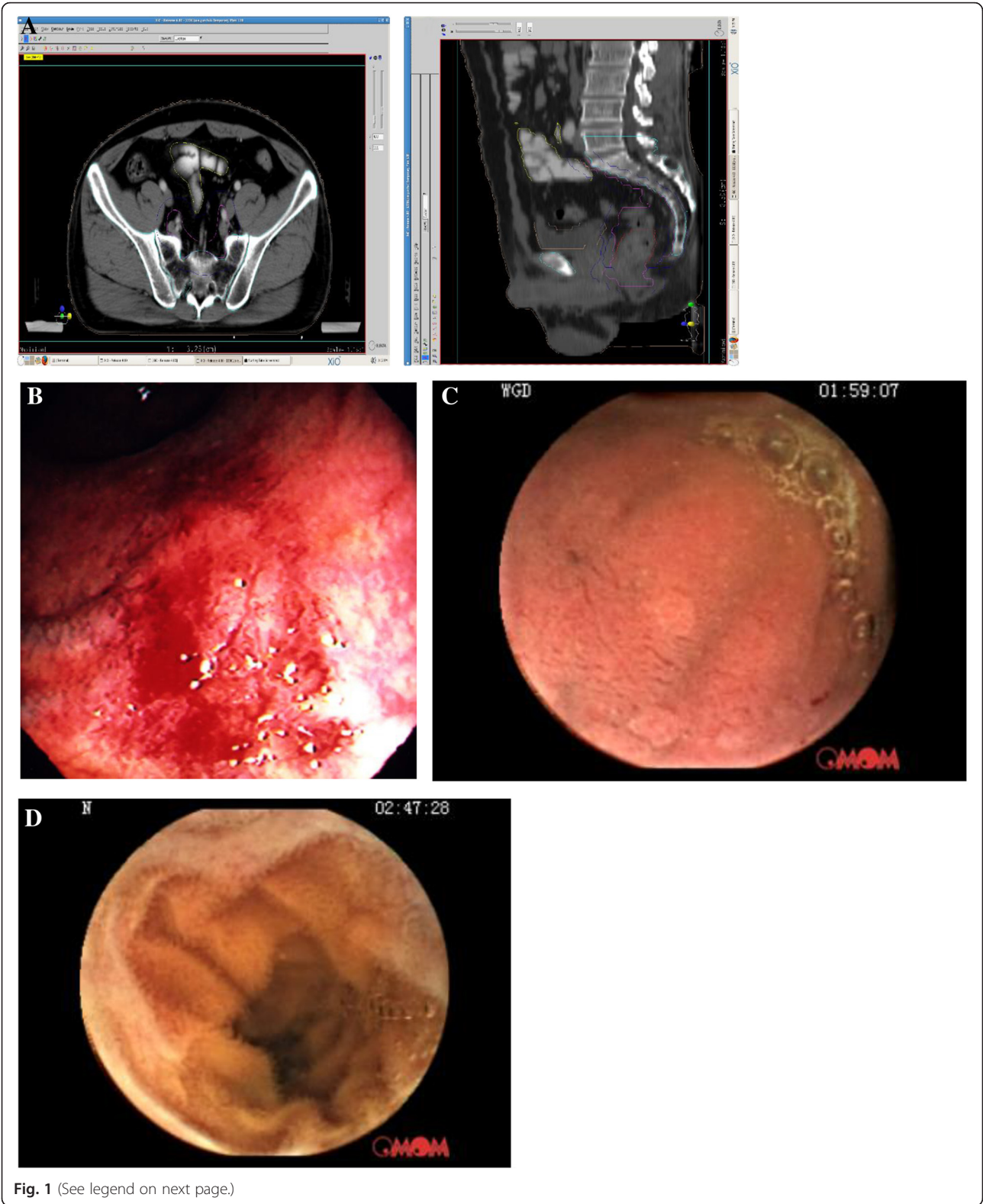


Fig. 1 (See legend on next page.)

(See figure on previous page.)

**Fig. 1 a.** Axial (left) and sagittal (right) views of small bowel contour in a 46 year-old male patient with a stage cT3 cN+ cM0 rectal cancer treated with preoperative IMRT concurrent with chemotherapy. **b.** Reference video capsule endoscopy image for radiation induced small bowel injury: Friability and oozing blood from atrophic-appearing mucosa. (Authorization by Medscape Drugs & Diseases). **c.** Case1: A 60 year-old female patient with a stage cT3 cN+ cM0 rectal adenocarcinoma who presented with grade 2 tenesmus without watery stools on the day 13 of the radiotherapy which was resolved in 2 days after symptomatic treatment. Video capsule endoscopy showed normal mucosa throughout the small bowel. **d.** Case 2: A 60 year-old male patient with a stage cT2 cN+ cM0 rectal adenocarcinoma who did not experienced significant lower GI toxicity during the treatment course. Video capsule endoscopy showed normal mucosa throughout the small bowel

toxicity. Therefore, only tumor volume, pre-existing number of daily bowel movements and gender were included in the multivariate logistic regression analysis. Multivariate analysis (Table 4) revealed that tumor volume (OR 0.147, 95 % CI 0.043–0.499) and pre-existing number of daily bowel movements (OR 0.272, 95 % CI 0.080–0.922) but not gender were significantly correlated with grade  $\geq 2$  acute lower GI toxicity. Forcing V5-V40 into the model showed that small bowel V5-V40 was not significantly correlated with grade  $\geq 2$  acute lower GI toxicity.

**Discussion**

The most interesting finding of this study is no correlations between the dose-volume parameters of small bowel (V<sub>5</sub> to V<sub>40</sub>) and the acute lower GI toxicity during preoperative concurrent chemo-radiotherapy for rectal cancer when IMRT is used. This study also revealed that the rectal tumor volume is a predictor of grade  $\geq 2$  lower GI toxicity. To our knowledge, this is the first study to report that with IMRT, the acute lower GI toxicity in this patient population is mainly influenced by rectal tumor volume but not small bowel dose-volume parameters.

**Preoperative radiotherapy with IMRT decreased small bowel volume in the pelvic radiation field**

Minsky et al. showed a dramatic decrease of small bowel volume in the radiation field for patients that received preoperative radiotherapy when compared with postoperative radiotherapy (212 ± 44 cm<sup>3</sup> versus 462 ± 129 cm<sup>3</sup>, p = 0.002) [9]. Sauer et al. found that  $\geq$  grade 3 diarrhea occurred in patients treated preoperatively significantly

less frequent than those treated postoperatively (12 % vs. 18 %, p = 0.04) [4]. To further reduce small bowel volume in the radiation field, IMRT has been used in several studies in the preoperative chemo-radiation therapy for rectal cancer [15, 16]. Two dosimetric studies showed that the small bowel volume was reduced significantly in the radiation field with IMRT [17, 18]. In the study by Arbea L et al., the small bowel V<sub>40</sub> with IMRT was only one third of the V<sub>40</sub> treated with conventional 3-field technique (68.9 cc vs. 178.3 cc, p < 0.01) [19]. In our study, all patients received preoperative radiotherapy with IMRT technique. The small bowel V<sub>40</sub> in the current study was only 23–30 cc which is smaller than the small bowel V<sub>40</sub> (68.9 cc) in patients treated with IMRT in the study of Arbea et al. Our study suggests that the small bowel V<sub>5</sub>-V<sub>20</sub> are no longer predictors for grade  $\geq 2$  lower GI toxicity when an irradiated small bowel volume is reduced to a very low level by using modern radiotherapy technique such as IMRT.

**Lower GI toxicity is the consequence of rectal irradiation**

It is well known that the symptoms of small bowel and rectal injury are different. The symptoms from acute small bowel injury include watery diarrhea, colicky abdominal pain, bloating, loss of appetite, nausea and dehydration [20]. On the other hand, the symptoms from rectal injury typically include soft or diarrhea-like stools, rectal pain and tenesmus (a sense of rectal distention with cramping and frequency) [21]. Studies have shown that patients treated with chemotherapy alone had a risk

**Table 3** Comparison of small bowel dose-volume in patients with grade < 2 to grade  $\geq 2$  acute lower GI toxicity

Dose level (Gy)	Small bowel volume(mean ± SD, cm <sup>3</sup> )		P value
	Grade 0–1	Grade $\geq 2$	
5	268 ± 173	217 ± 107	0.156
10	230 ± 154	189 ± 99	0.196
15	203 ± 138	169 ± 95	0.242
20	174 ± 124	143 ± 86	0.247
25	127 ± 105	103 ± 68	0.272
30	75 ± 78	60 ± 49	0.367
35	47 ± 63	37 ± 37	0.445
40	30 ± 49	23 ± 24	0.429

**Table 2** Scale for acute GI toxicity based on common toxicity criteria v3.0

Grade	Symptom
0	None
1	Increase of <4 stools per day over pretreatment
2	Increase of 4–6 stools per day or nocturnal stools
3	Increase of $\geq 7$ stools per day or incontinence or need for parenteral support for dehydration
4	Physiologic consequences requiring intensive care of hemodynamic collapse

**Table 4** Factors associated with grade  $\geq 2$  lower GI toxicity

Factors	Median	Univariate		Multivariate	
		OR (95 % CL)	P value	OR (95 % CL)	P value
Age (years)	$\leq 55 / > 55$	0.716 (0.259–1.946)	0.513		
Gender	Female/Male	0.351 (0.114–1.084)	0.069	0.376 0.108 1.308	0.124
T stage	$\leq T3 / > T3$	0.859 (0.313–2.361)	0.769		
N stage	N-/N+	0.735 (0.097–5.581)	0.766		
Tumor volume (cc)	$\leq 64 / > 64$	0.185 (0.062–0.550)	0.002	0.147 0.043 0.499	0.002
Tumor location <sup>a</sup>	$\leq 6 / > 6$	0.700 (0.248–1.978)	0.501		
Pre-existing BM <sup>b</sup>	$< 4 / \geq 4$	0.374 (0.134–1.048)	0.061	0.272 0.080 0.922	0.036
Small bowel V5 (cc)	$\leq 213 / > 213$	1.562 (0.572–4.265)	0.384		
Small bowel V10 (cc)	$\leq 191 / > 191$	1.562 (0.572–4.265)	0.384		
Small bowel V15 (cc)	$\leq 174 / > 174$	1.818 (0.662–4.995)	0.246		
Small bowel V20 (cc)	$\leq 146 / > 146$	1.818 (0.662–4.995)	0.246		
Small bowel V25 (cc)	$\leq 100 / > 100$	1.626 (0.593–4.458)	0.345		
Small bowel V30 (cc)	$\leq 53 / > 53$	1.818 (0.662–4.995)	0.246		
Small bowel V35 (cc)	$\leq 23 / > 23$	0.550 (0.200–1.511)	0.246		
Small bowel V40 (cc)	$\leq 11 / > 11$	0.640 (0.234–1.747)	0.384		

<sup>a</sup>Distance from the anal verge; <sup>b</sup>pre-existing number of daily bowel movement

of around 20 % in developing  $\geq$  grade 3 treatment-related diarrhea [22] and adding chemotherapy concurrently to radiotherapy increased the frequency and severity of diarrhea [23]. In theory, diarrhea caused by chemotherapy should occur in the course of chemotherapy and could be cured in a short duration. In our study, most patients presented tenesmus. We believe that the occasional watery diarrhea of 4 patients in our study was caused by concurrent chemotherapy since they only occurred during the week of receiving chemotherapy and was cured in a week.

**Primary tumor volume influences the lower GI toxicity**

Another finding in this study was that the most common acute lower GI toxicity was tenesmus. The gross tumor volume was the only independent influencing factor for the acute lower GI toxicity. The larger the tumor volume

the more frequent bowel movements ( $115.5 \pm 85.5 \text{ cm}^3$  versus  $58.5 \pm 25.2 \text{ cm}^3$  for grade  $\geq 2$  and grade 0–1,  $p = 0.000$ ). Given that most patients had no watery diarrhea, we believe that the named lower GI acute toxicity is a rectal reaction to the tumor and to the radiation injury. In the study of Myerson RJ et al., although they used the 3D-CRT technique, they also found that proctitis was the most common acute toxicity (5/37) during preoperative chemo-radiotherapy and associated with large tumors (PTV  $\geq 500 \text{ cc}$ ). There was only one patient who had enteritis during the treatment course [24].

**Wireless whole gastrointestinal video capsule endoscopy**

The acute toxicity of the small bowel is to a large extent a result of clonogenic and apoptotic cell death in the crypt epithelium, resulting in insufficient replacement of the villus epithelium, breakdown of the mucosal barrier, mucositis, and prominent compensatory and proliferative reactions (see Fig. 1b) [25]. The best way to observe the small bowel reaction to radiation is to use the wireless whole gastrointestinal video capsule endoscopy (VCE). Video capsule endoscopy enables excellent visualization of the small bowel mucosa [26]. Only a pilot study and a case report demonstrated the usefulness of VCE for radiation-induced late small bowel injury [27, 28]. We elected 2 patients, one had grade 2 and the other had grade 0 lower GI toxicity, to undergo VCE (Model of JS-ME-II, Chongqing Jinshan Science and Technology (group) Co.,Ltd) examination in 2 to 3 days after the completion of preoperative chemo-radiotherapy in order to observe the changes in the small bowel mucosa. The

**Table 5** Small bowel dose-volume for the two patients who underwent VCE examination

Dose level (Gy)	Small bowel volume (cm <sup>3</sup> )	
	Case 1	Case 2
5	330	183
10	295	159
15	281	142
20	254	116
25	192	90
30	108	44
35	64	18
40	40	9

duration of both VCE examinations were around 9 h and both showed normal small bowel mucosa (see Fig. 1c and d). The small bowel  $V_5$ - $V_{40}$  of these two patients are shown in Table 5. These findings directly confirmed our results that clinical lower GI toxicity in pelvic IMRT is not associated with the dose-volume parameters of small bowel.

### Quantifying the lower GI toxicity

Although there were many reports concerning the acute and chronic small bowel toxicity in pelvic radiation therapy, little data has been published quantifying the details of the toxicity such as extent, timing, duration, correlation with chemotherapy, etc. It is very hard to evaluate the lower GI toxicity via the status of stools for rectal cancer, because for most patients, the most common symptom at the time of diagnosis is increasing frequency of stools with or without mixed blood. Among the 63 patients in our study, the number of pre-existing daily bowel movements was found to be 1 time in 6 (9.5 %) patients, 2–3 times in 25 (39.7 %) patient, 4–6 times in 25 (39.7 %) patients and  $\geq 7$  stools in 7 patients (11.1 %) (see Table 1). Almost half of these patients presented with grade  $\geq 2$  bowel toxicity before initiating radiotherapy treatment. Moreover, both RTOG [29] and CTCAE [14] toxicity scales for lower GI toxicity are simple and rapidly assessable, but provide limited information. For example, they do not assess the development of anorectal symptoms such as tenesmus which is the most common symptom during the pelvic irradiation, especially for rectal cancer treated with IMRT technique. A modified questionnaire from the Inflammatory Bowel Disease Questionnaire (IBDQ) and Vaizey Incontinence questionnaire may be more sensitive and useful for toxicity data collection during the treatment and follow-up [30, 31]. Such questionnaires include much more information when compared to RTOG and CTCAE scales.

Limitations of this study include its retrospective nature, a lack of information on total small bowel volume and details of toxicity.

### Conclusion

When small bowel volume in the radiation field was reduced to a low level with IMRT, it was no longer as an influencing factor for acute lower GI toxicity. The radiation-induced lower GI symptoms such as tenesmus without watery diarrhea during pelvic IMRT may be caused by the rectal tumor itself and rectal reaction to radiotherapy. A future prospective study is warranted to investigate the details of lower GI toxicity during treatment and early follow-up, by using a real-time recorded clinical note, modified questionnaire and whole gastrointestinal wireless capsule endoscopy.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

BX conceived of the study, and participated in its design and coordination and helped to draft the manuscript. YG, TT, YC and HL performed data collection. ZY, GG and PC participated in the design of the study. CL participated in the design of the study, performed the statistical analysis and the manuscript revision. All authors read and approved the final manuscript.

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