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SHORT COMMUNICATION

Predictors of late bowel toxicity using three different methods of contouring in patients undergoing post-operative radiation for cervical cancer

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Objective: This study investigates the correlation between dose-volume histogram derived from three bowel contouring methods and late toxicity in patients undergoing post-operative radiation therapy (PORT) for cervical cancer.

Methods: From June 2010 to May 2013, 103 patients undergoing PORT were included. Three different contouring methods were used: (a) individual small bowel (SB) and large bowel (LB) loops, (b) total bowel (TB; including SB and LB) and (c) peritoneal cavity (PC). The volume of SB, LB, TB and PC receiving 15, 30 and 40 Gy was calculated. Acute and late bowel toxicities were scored using Common Terminology Criteria for Adverse events v. 3.0. Receiver operating characteristic curve identified thresholds predicting late toxicity with the highest specificity. All data were dichotomized across these thresholds. Univariate and multivariate analyses were performed using SPSS[®] v. 20 (IBM Corporation, Armonk, NY; formerly SPSS Inc., Chicago, IL).

Results: On univariate analysis, $V_{30} \text{ PC} \geq 900 \text{ cm}^3$ ($p = 0.01$), $V_{40} \text{ PC} \geq 750 \text{ cm}^3$ ($p = 0.03$) and $V_{40} \text{ TB} \geq 280 \text{ cm}^3$ ($p = 0.03$) and use of concurrent chemotherapy ($p = 0.03$) predicted grade $\geq \text{II}$ acute toxicity. On multivariate analysis, use of

concurrent chemotherapy [odds ratio (OR) 3.5, 95% confidence interval (CI) 1.1–11.1, $p = 0.03$] and $V_{30} \text{ PC} \geq 900 \text{ cm}^3$ (OR 2.3, 95% CI 1–5.5, $p = 0.05$) predicted acute grade $\geq \text{II}$ toxicity. On univariate analysis for late toxicity, SB ($V_{30} \geq 190 \text{ cm}^3$, $p = 0.009$; $V_{40} \geq 150 \text{ cm}^3$, $p = 0.03$), LB ($V_{15} \geq 250 \text{ cm}^3$, $p = 0.04$), $V_{40} \text{ PC}$ ($V_{40} \geq 750 \text{ cm}^3$, $p = 0.001$) and presence of acute grade $\geq \text{III}$ toxicity ($p = 0.006$), treatment technique (three-dimensional conformal radiation or intensity modulated radiotherapy, $p = 0.02$) predicted more than or equal to grade II late bowel toxicity. On multivariate analysis, only body mass index $\geq 25 \text{ kg m}^{-2}$ (OR 7.3, 95% CI 1.6–31.6, $p = 0.008$) and presence of acute grade III toxicity predicted toxicity (OR 5.1, 95% CI 1.4–18.1, $p = 0.007$).

Conclusion: $V_{30} \text{ PC} \geq 900 \text{ cm}^3$ and use of concurrent chemotherapy independently predicts acute toxicity. Presence of acute grade $\geq \text{III}$ toxicity independently predicts late toxicity. Minimizing dose to PC subvolumes can therefore reduce both acute and late toxicities.

Advances in knowledge: Study establishes PC thresholds that can minimize both acute and late bowel toxicities.

INTRODUCTION

Adjuvant radiation is considered the standard of care in patients with cervical cancer with post-operative risk factors,¹ however, predisposes patients to bowel toxicity.² While various studies^{3–6} have evolved recommendations to limit acute toxicity, it is essentially based on patients with rectal cancer. Extrapolation of these data to patients with cervical cancer though intuitive is limited owing to the differences in the post-operative anatomy, chemotherapy and use of brachytherapy. Furthermore, the contouring methods and recommendations to limit bowel dose are

also not uniform. The recent organ at risk contouring guidelines by the Radiation Therapy Oncology Group (RTOG)⁷ suggests delineation of large bowel (LB) and small bowel (SB) separately for gastrointestinal (GI) tumours while peritoneal cavity (PC) for gynaecological malignancies. We recently reported strong correlation between dose-volume histogram (DVH) of SB and LB and grade $\geq \text{III}$ late bowel toxicity in patients receiving adjuvant radiation for cervical cancer.⁸ As the RTOG recommends contouring PC,⁷ we compared three methods of bowel contouring for the prediction of late toxicity.

METHODS AND MATERIALS

From January 2010 to May 2013, patients undergoing adjuvant or salvage pelvic chemoradiation within context of ongoing institutional trials were included.

Simulation and treatment planning

The details of patient simulation, target delineation and planning have been previously described.⁸ All patients received 50 Gy/25 fractions/5 weeks with concomitant weekly cisplatin (40 mg m^{-2}). This was followed by vaginal brachytherapy. For the purpose of this study, planning CT scans were retrieved and total bowel (TB) was contoured as outer wall for both SB and LB (individual loops beyond sigmoid up to 2 cm above planning target volume) and PC as per RTOG guidelines (Figure 1). No editing of clinical target volume or planning target volume was performed in the regions of overlap. The absolute volumes receiving 15 Gy (V_{15}), 30 Gy (V_{30}) and 40 Gy (V_{40}) were derived.

Toxicity recording

All patients completed the Common Terminology Criteria for Adverse Events at baseline, during treatment and subsequently at follow-up. The highest grade of GI toxicity within 3 months of treatment was recorded as acute toxicity. Thereafter, the worst score during follow-up was recorded as late toxicity. Proctitis was not considered as a bowel event.

Statistical analyses

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS®, v. 20.0.1; IBM Corporation, Armonk, NY; formerly SPSS Inc., Chicago, IL). The grade of acute and late bowel toxicities was categorized as grade $\leq$ II and grade $\geq$ III. Receiver operating characteristic (ROC) curve was used to identify the thresholds of SB, LB, TB and PC that predict late grade $\geq$ II toxicity with the highest specificity and were used to dichotomize data for statistical analysis. Predictive probability of grade $\geq$ II late bowel toxicity was derived using actual event data. Using a cut-off value of 5% late toxicity, bowel dose-volume thresholds were determined and predictive probability plots were generated such that restricting dose below the proposed area under the curve would minimize incidence of late toxicity to $<5\%$. Univariate analysis for predictors of acute and late

bowel toxicities was performed using Fisher's exact test. Patient- and treatment-related factors with p -value <0.05 were included in multivariate analysis using binary logistic regression with backward conditional method. Parameters with odds ratio (OR) of >1 and $p \leq 0.05$ were considered as significant predictors of toxicity.

RESULTS

Baseline characteristics

A total of 103 patients with median age of 48 years (35–65 years) were included. While 72 patients received upfront adjuvant radiation, 31 patients received radiation for post-operative central or parametrial recurrence. The median body mass index was 24.6 kg m^{-2} ($15.8\text{--}37.7 \text{ kg m}^{-2}$). Only 5 (4.8%) patients had history of abdominal surgeries, and 12 (11.7%) patients had pre-existing diabetes or hypertension. The surgical procedure was hysterectomy with or without salpingo-oophorectomy in 64 (72.1%) patients and Wertheim's hysterectomy in 39 (37.9%) patients. Intensity-modulated radiotherapy (IMRT) was used in 60 (58.2%) patients and three-dimensional conformal radiation (3D CRT) in 43 (41.8%) patients; 87 of 103 (84.5%) patients received weekly cisplatin.

Toxicity

Acute grade I, II, III bowel toxicity was observed in 38 (36.9%), 42 (40.8%) and 21 (20.4%) of patients, respectively, acute toxicity grade was not known for two patients. No grade IV toxicity was observed. Overall, 2 of 21 patients developed severe emesis within the first week of chemoradiation necessitating hospitalization. This was attributed to concurrent chemotherapy. Other common acute toxicities were diarrhoea and abdominal cramps and were managed with oral medications without any treatment breaks or radiation dose modifications.

At the median follow-up of 26 months (2–46 months), the grade I, II, III, IV and V late bowel toxicity was observed in 37 (35.9%), 47 (45.6%), 12 (11.7%), 5 (4.8%) and 2 (1.9%) patients, respectively. The most common late grade II toxicity was lower abdominal pain followed by anorexia, haemorrhage, diarrhoea and distention of the abdomen. The late grade III toxicity included diarrhoea ($n = 3$) and obstruction ($n = 2$); grade V toxicity was seen in two patients with SB perforation leading to death after 5 and 9 months of chemoradiation. Both patients had no pre-existing risk factors, and however, were treated with 3D CRT with LB doses more than the previously recommended threshold (V_{15} SB, 68 and 167 cm^3 , and V_{15} LB, 309 and 337 cm^3 , respectively). One patient underwent emergency exploration following acute abdomen however succumbed to intestinal perforation within 24 h of surgery. Another patient refused medical intervention following diagnosis of subacute obstruction and died within 2 weeks of presenting with subacute bowel obstruction.

Dose-volume histogram parameters and toxicity

On ROC analysis, the dose cut-off values with the highest specificity for V_{15} , V_{30} and V_{40} of SB, LB, TB and PC for the prediction of late toxicity were 275, 190 and 150 cm^3 (SB); 250, 100 and 90 cm^3 (LB); 450, 330 and 280 cm^3 (TB) and 1200, 900 and 750 cm^3 (PC), respectively.

Acute toxicity

Univariate and multivariate analyses

Univariate analysis for acute grade $\geq$ II and $\geq$ III toxicity is depicted in Table 1. On multivariate analysis, use of concurrent chemotherapy

Figure 1. CT showing contours of small bowel (SB; white arrows), large bowel (LB; dotted arrows), total bowel (SB + LB) and peritoneal cavity (black arrow).

Table 1. Univariate analysis of treatment-related parameters predicting acute bowel toxicity

Variables	Strata (n)	Grade $\geq$ II, absent	Grade $\geq$ II, present	<i>p</i> -value	Grade $\geq$ III, absent	Grade $\geq$ III, present	<i>p</i> -value
Age (years)	<48	20	31	0.93	38	13	0.12
	$\geq$ 48	20	32		45	7	
Type of hysterectomy	Wertheim's	15	24	0.95	32	7	0.76
	Simple	35	45		66	14	
Type of RT	IMRT	25	34	0.52	51	8	0.03
	3D CRT	14	25		27	12	
Concurrent chemotherapy	No	10	6	0.03	15	1	0.14
	Yes	30	57		68	19	
Body mass index (kg m ⁻²)	<25	25	31	0.18	47	9	0.34
	$\geq$ 25	15	32		36	11	
Abdominal surgery	Single	22	50	0.33	54	18	0.30
	Multiple	3	2		5	0	
Co-morbidities	Yes	7	5	0.14	9	3	0.60
	No	33	58		74	17	
Tobacco use	Yes	8	7	0.21	13	2	0.51
	No	32	56		70	18	
<i>V</i> ₁₅ SB (cm ³)	$\geq$ 275	7	14	0.56	16	5	0.56
	<275	33	49		67	15	
<i>V</i> ₃₀ SB (cm ³)	$\geq$ 190	7	18	0.20	19	6	0.50
	<190	33	45		64	14	
<i>V</i> ₄₀ SB (cm ³)	$\geq$ 150	7	17	0.26	18	6	0.43
	<150	33	46		65	14	
<i>V</i> ₁₅ LB (cm ³)	$\geq$ 250	2	11	0.06	9	4	0.26
	<250	38	52		74	16	
<i>V</i> ₃₀ LB (cm ³)	$\geq$ 100	9	25	0.07	27	7	0.83
	<100	31	38		56	13	
<i>V</i> ₄₀ LB (cm ³)	$\geq$ 90	7	21	0.07	21	7	0.38
	<90	33	42		62	13	
<i>V</i> ₁₅ TB (cm ³)	$\geq$ 450	7	18	0.20	20	5	0.93
	<450	33	45		63	15	
<i>V</i> ₃₀ TB (cm ³)	$\geq$ 330	4	15	0.07	16	3	0.65
	<330	36	48		67	17	
<i>V</i> ₄₀ TB (cm ³)	$\geq$ 280	3	15	0.03	13	5	0.32
	<280	37	48		70	15	
<i>V</i> ₁₅ PC (cm ³)	$\geq$ 1200	14	28	0.34	35	7	0.55
	<1200	26	35		48	13	
<i>V</i> ₃₀ PC (cm ³)	$\geq$ 900	6	24	0.01	22	8	0.23
	<900	34	39		61	12	
<i>V</i> ₄₀ PC (cm ³)	$\geq$ 750	4	17	0.03	15	6	0.23
	<750	36	46		68	14	

3D CRT, three-dimensional conformal radiation; IMRT, intensity-modulated radiotherapy; LB, large bowel; PC, peritoneal cavity; RT, radiotherapy, SB, small bowel; TB, total bowel; *V*₁₅–*V*₄₀, volume of bowel getting the specified dose in gray.

Table 2. Univariate analysis for acute bowel toxicity in patients receiving concurrent chemoradiation ($n = 87$)

Variables	Strata (n)	Grade $\geq$ II, absent	Grade $\geq$ II, present	p-value	Grade $\geq$ III, absent	Grade $\geq$ III, present	p-value
Age (years)	<48	15	30	0.81	32	13	0.09
	$\geq$ 48	15	27		36	6	
Type of hysterectomy	Wertheim's	9	21	0.52	23	7	0.80
	Simple	21	36		45	12	
Type of RT	IMRT	18	31	0.75	41	8	0.07
	3D CRT	11	22		22	11	
Concurrent chemotherapy	No	12	4	0.46	15	1	0.92
	Yes	72	15		81	6	
Body mass index (kg m^{-2})	<25	19	29	0.26	40	8	0.19
	$\geq$ 25	11	28		28	11	
Abdominal surgery	Single	17	45	0.08	45	17	0.32
	Multiple	3	2		5	0	
Co-morbidities	Yes	3	4	0.62	4	3	0.16
	No	27	53		64	16	
Tobacco use	Yes	6	6	0.22	10	2	0.64
	No	24	51		58	17	
V_{15} SB (cm^3)	$\geq$ 275	5	12	0.62	12	5	0.40
	<275	25	45		56	14	
V_{30} SB (cm^3)	$\geq$ 190	6	14	0.63	15	5	0.69
	<190	24	43		53	14	
V_{40} SB (cm^3)	$\geq$ 150	6	14	0.63	15	5	0.69
	<150	24	43		53	14	
V_{15} LB (cm^3)	$\geq$ 250	2	10	0.16	9	3	0.77
	<250	28	47		59	16	
V_{30} LB (cm^3)	$\geq$ 100	8	22	0.26	24	6	0.76
	<100	22	35		44	13	
V_{40} LB (cm^3)	$\geq$ 90	6	18	0.25	18	6	0.66
	<90	24	39		50	13	
V_{15} TB (cm^3)	$\geq$ 450	5	15	0.30	16	4	0.82
	<450	25	42		52	15	
V_{30} TB (cm^3)	$\geq$ 330	3	12	0.19	13	2	0.38
	<330	27	45		55	17	
V_{40} TB (cm^3)	$\geq$ 280	3	12	0.19	11	4	0.61
	<280	27	45		57	15	
V_{15} PC (cm^3)	$\geq$ 1200	9	25	0.20	27	7	0.82
	<1200	21	32		41	12	
V_{30} PC (cm^3)	$\geq$ 900	5	20	0.07	18	7	0.37
	<900	25	37		50	12	
V_{40} PC (cm^3)	$\geq$ 750	4	15	0.16	14	5	0.59
	<750	26	42		54	14	

3D CRT, three-dimensional conformal radiation; IMRT, intensity-modulated radiotherapy; LB, large bowel; PC, peritoneal cavity; RT, radiotherapy; SB, small bowel; TB, total bowel; V_{15} – V_{40} , volume of bowel getting the specified dose in gray.

Table 3. Univariate analysis of treatment-related parameters predicting late bowel toxicity

Variables	Strata (n)	Grade $\geq$ II, absent	Grade $\geq$ II, present	<i>p</i> -value	Grade $\geq$ III, absent	Grade $\geq$ III, present	<i>p</i> -value
Age (years)	<48	36	9	0.45	42	3	1.0
	$\geq$ 48	36	6		39	3	
Type of hysterectomy	Wertheim's	33	6	0.60	60	4	1.0
	Simple	51	13		36	3	
Type of RT	IMRT	44	5	0.02	49	0	0.002
	3D CRT	23	10		27	6	
Concurrent chemotherapy	Yes	72	15	0.48	81	6	1.0
	No	12	4		15	1	
Body mass index (kg m^{-2})	<25	37	11	0.07	45	3	1.0
	$\geq$ 25	35	4		36	3	
Abdominal surgery	Single	59	13	0.25	66	6	0.72
	Multiple	3	2		5	0	
Co-morbidities	Yes	9	3	0.69	10	2	0.18
	No	75	16		86	5	
Tobacco use	Yes	14	1	0.29	14	1	0.98
	No	70	18		82	6	
Acute grade II	Yes	48	15	0.11	56	7	0.04
	No	36	4		40	0	
Acute grade III	Yes	12	8	0.01	14	6	0.0001
	No	72	11		82	1	
V_{15} SB (cm^3)	$\geq$ 275	15	6	0.21	18	3	0.14
	<275	69	13		78	4	
V_{30} SB (cm^3)	$\geq$ 190	16	9	0.01	21	4	0.05
	<190	68	10		75	3	
V_{40} SB (cm^3)	$\geq$ 150	16	8	0.06	19	5	0.07
	<150	68	11		77	2	
V_{15} LB (cm^3)	$\geq$ 250	8	5	0.06	9	4	0.005
	<250	76	14		87	3	
V_{30} LB (cm^3)	$\geq$ 100	25	9	0.17	30	4	0.21
	<100	59	10		66	3	
V_{40} LB (cm^3)	$\geq$ 90	20	8	0.15	24	4	0.08
	<90	64	11		72	3	
V_{15} TB (cm^3)	$\geq$ 450	18	7	0.23	22	3	0.35
	<450	66	12		74	4	
V_{30} TB (cm^3)	$\geq$ 330	13	6	0.11	16	3	0.11
	<330	71	13		80	4	
V_{40} TB (cm^3)	$\geq$ 280	12	6	0.09	14	4	0.01
	<280	72	13		82	3	

(Continued)

Table 3. (Continued)

Variables	Strata (n)	Grade $\geq$ II, absent	Grade $\geq$ II, present	p-value	Grade $\geq$ III, absent	Grade $\geq$ III, present	p-value
V_{15} PC (cm^3)	≥ 1200	33	9	0.60	40	2	0.69
	< 1200	51	10		56	5	
V_{30} PC (cm^3)	≥ 900	21	9	0.05	25	5	0.02
	< 900	63	10		71	2	
V_{40} PC (cm^3)	≥ 750	12	9	0.003	16	5	0.004
	< 750	72	10		80	2	

3D CRT, three-dimensional conformal radiation; IMRT, intensity-modulated radiotherapy; LB, large bowel; PC, peritoneal cavity; RT, radiotherapy; SB, small bowel; TB, total bowel; V_{15} – V_{40} , volume of bowel getting the specified dose in gray.

[OR 3.5, 95% confidence interval (CI) 1.1–11.1, $p = 0.03$] and V_{30} PC $\geq 900 \text{ cm}^3$ (OR 2.3, 95% CI 1–5.5, $p = 0.05$) predicted acute grade $\geq$ II toxicity. On restricting the statistical analysis to patients receiving concurrent chemoradiation, none of the parameters predicted acute toxicity (Table 2).

Late toxicity

On univariate analysis, SB ($V_{30} \geq 190 \text{ cm}^3$, $p = 0.009$; $V_{40} \geq 150 \text{ cm}^3$, $p = 0.03$), LB ($V_{15} \geq 250 \text{ cm}^3$, $p = 0.04$), V_{40} PC ($V_{40} \geq 750 \text{ cm}^3$, $p = 0.001$) and presence of acute more than or equal to grade II late bowel toxicity ($p = 0.006$), treatment technique (3D CRT or IMRT, $p = 0.02$) predicted late grade $\geq$ bowel toxicity. In addition, presence of acute grade II/III toxicity ($p = 0.02$ and $p = 0.0001$), V_{40} TB $\geq 280 \text{ cm}^3$ ($p = 0.004$) and V_{30} PC $\geq 900 \text{ cm}^3$ ($p = 0.01$), treatment technique (3D CRT or IMRT, $p = 0.0002$) predicted grade late toxicity (Table 3). On multivariate analysis, only body mass index $\geq 25 \text{ kg m}^{-2}$ (OR 7.3, 95% CI 1.6–31.6, $p < 0.008$) and presence of acute grade $\geq$ III toxicity predicted late grade $\geq$ II toxicity (OR 5.1, 95% CI 1.4–18.1, $p = 0.007$). Using actual event data and binary logistic regression, predictive probability plots for various dose–

volume thresholds were generated. Restricting bowel doses below the proposed thresholds could restrict late toxicity $\leq 5\%$ (Figure 2).

Patients receiving concurrent chemoradiation

Univariate analysis for patients receiving concurrent chemoradiation ($n = 87$) is depicted in Table 4. On multivariate analysis, presence of acute grade $\geq$ III toxicity was identified as independent predictors of grade $\geq$ II late bowel toxicity (OR 4.1, 95% CI 1.2–13.1, $p < 0.01$).

DISCUSSION

In an earlier study⁸ from our group, we identified V_{15} SB and V_{15} LB to be important independent predictors of late toxicity. A recent study⁹ on 97 patients undergoing adjuvant radiation identified V_{15} – V_{45} SB dose and identified smoking as an independent risk factor for chronic GI toxicity. Contouring PC is more convenient method of delineating bowel than for SB and LB as their differentiation can be difficult. There is also an inherent delineation inaccuracy of SB and LB which can reach up to 17%.¹⁰ Theoretically, PC may also be more representative of the actual bowel dose as it includes all possible volume of internal motion.

Figure 2. Recommended dose–volume histogram for restricting late bowel toxicity $\geq$ grade III within 5%. x-axis, volume receiving 15, 30 and 40 Gy; y-axis, absolute bowel volume (in cubic centimetres).

Table 4. Univariate analysis of treatment-related parameters predicting late bowel toxicity in patients undergoing chemoradiation ($n = 87$)

Variables	Strata (n)	Grade $\geq$ II, absent	Grade $\geq$ II, present	<i>p</i> -value	Grade $\geq$ III, absent	Grade $\geq$ III, present	<i>p</i> -value
Age (years)	<48	36	9	0.48	42	3	0.93
	$\geq$ 48	36	6		39	3	
Type of hysterectomy	Wertheim's	26	4	0.48	54	3	0.40
	Simple	46	11		27	3	
Type of RT	IMRT	44	5	0.02	49	0	0.002
	3D CRT	23	10		27	6	
Body mass index (kg m^{-2})	<25	37	11	0.12	45	3	0.79
	$\geq$ 25	35	4		36	3	
Abdominal surgery	Single	53	9	0.30	57	5	0.76
	Multiple	3	2		5	0	
Co-morbidities	Yes	5	2	0.40	5	2	0.01
	No	67	13		76	4	
Tobacco use	Yes	11	1	0.37	11	1	0.83
	No	61	14		70	6	
Acute grade II	Yes	45	12	0.19	51	6	0.06
	No	27	3		30	0	
Acute grade III	Yes	12	7	0.01	14	5	0.0001
	No	60	8		67		
V_{15} SB (cm^3)	$\geq$ 275	13	4	0.44	14	3	0.05
	<275	59	11		67	3	
V_{30} SB (cm^3)	$\geq$ 190	14	6	0.08	17	3	0.10
	<190	58	9		64	3	
V_{40} SB (cm^3)	$\geq$ 150	14	6	0.08	16	4	0.008
	<150	58	9		65	2	
V_{15} LB (cm^3)	$\geq$ 250	8	4	0.11	9	3	0.008
	<250	64	11		72	3	
V_{30} LB (cm^3)	$\geq$ 100	23	7	0.27	27	3	0.40
	<100	49	8		54	3	
V_{40} LB (cm^3)	$\geq$ 90	18	6	0.23	21	3	0.20
	<90	54	9		60	3	
V_{15} TB (cm^3)	$\geq$ 450	16	4	0.71	18	2	0.53
	<450	56	11		63	4	
V_{30} TB (cm^3)	$\geq$ 330	11	4	0.28	13	2	0.27
	<330	61	11		68	4	
V_{40} TB (cm^3)	$\geq$ 280	11	4	0.28	12	3	0.02
	<280	61	11		69	3	
V_{15} PC (cm^3)	$\geq$ 1200	28	6	0.93	32	2	0.76
	<1200	44	9		49	4	

(Continued)

Table 4. (Continued)

Variables	Strata (n)	Grade $\geq$ II, absent	Grade $\geq$ II, present	p-value	Grade $\geq$ III, absent	Grade $\geq$ III, present	p-value
V_{30} PC (cm ³)	≥ 900	18	7	0.09	21	4	0.03
	< 900	54	8		60	2	
V_{40} PC (cm ³)	≥ 750	12	7	0.01	15	4	0.006
	< 750	60	8		66	2	

3D CRT, three-dimensional conformal radiation; IMRT, intensity-modulated radiotherapy; LB, large bowel; PC, peritoneal cavity; RT, radiotherapy; SB, small bowel; TB, total bowel; V_{15} – V_{40} , volume of bowel getting the specified dose in gray.

The results of the present study verified the predictive ability of V_{15} SB and V_{15} LB reported in our earlier study on univariate analysis.⁸ While the present study also verified the ability of V_{40} SB to predict acute and late toxicities,⁹ PC doses only independently predicted acute grade $\geq$ II toxicity, and acute toxicity was the only significant predictor of late toxicity. This is also the first study that conclusively confirms the predictive value of acute toxicity as an independent predictor of late toxicity in patients undergoing adjuvant pelvic radiation. Though our study has limited number of patients, we demonstrated that use of concurrent chemotherapy or treatment technique (IMRT) does not impact late outcomes. None of these factors predicted late toxicity.

The PC dose–volume thresholds identified to be predictive of late toxicity within our study are also more generous than that proposed by Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)^{3,8} and an earlier study in patients with rectal cancer.⁵ This difference could possibly be attributed to amount of intrapelvic

bowel in patients with cervical and rectal cancer or type of chemotherapy. It may also be noted that patients with rectal cancer may have inherent bowel symptoms which may attribute to increased bowel toxicity and thereby lowering the dose–volume thresholds. The thresholds identified in this study are derived from actual event data in cervical cancer and may be more applicable in this patient subset.

CONCLUSION

PC doses and acute GI toxicity are independent predictors of late grade $\geq$ III bowel toxicity. The data presented in this study can be used to restrict late bowel injury in patients undergoing adjuvant chemoradiation for cervical cancer and also identify patients who are at risk of developing serious late bowel injury.

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