International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Small Bowel Dose Parameters Predicting Grade ≥3 Acute Toxicity in Rectal Cancer Patients Treated With Neoadjuvant Chemoradiation: An Independent Validation Study Comparing Peritoneal Space Versus Small Bowel Loop Contouring Techniques

Robyn Banerjee, MD, Santam Chakraborty, MD, Ian Nygren, MSc, and Richie Sinha, MD

Department of Radiation Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada

Received Sep 22, 2012. Accepted for publication Sep 30, 2012

Summary

The peritoneal space has been proposed as a substitute for contouring individual small bowel loops to assess the risk of small bowel toxicity, yet it remains unvalidated. This study retrospectively examined 67 rectal cancer patients treated with neoadjuvant chemoradiation therapy to compare the association of both contouring techniques with acute small bowel toxicity. The results demonstrated a dose-volume relationship between peritoneal space volumes and small bowel toxicity, supporting the use of this volume in treatment planning. Dose constraints were extrapolated on the basis of peritoneal space and individual small bowel loop volumes.

Purpose: To determine whether volumes based on contours of the peritoneal space can be used instead of individual small bowel loops to predict for grade ≥3 acute small bowel toxicity in patients with rectal cancer treated with neoadjuvant chemoradiation therapy.

Methods and Materials: A standardized contouring method was developed for the peritoneal space and retrospectively applied to the radiation treatment plans of 67 patients treated with neoadjuvant chemoradiation therapy for rectal cancer. Dose-volume histogram (DVH) data were extracted and analyzed against patient toxicity. Receiver operating characteristic analysis and logistic regression were carried out for both contouring methods.

Results: Grade ≥3 small bowel toxicity occurred in 16% (11/67) of patients in the study. A highly significant dose-volume relationship between small bowel irradiation and acute small bowel toxicity was supported by the use of both small bowel loop and peritoneal space contouring techniques. Receiver operating characteristic analysis demonstrated that, for both contouring methods, the greatest sensitivity for predicting toxicity was associated with the volume receiving between 15 and 25 Gy.

Conclusion: DVH analysis of peritoneal space volumes accurately predicts grade ≥3 small bowel toxicity in patients with rectal cancer receiving neoadjuvant chemoradiation therapy, suggesting that the contours of the peritoneal space provide a reasonable surrogate for the contours of individual small bowel loops. The study finds that a small bowel V15 less than 275 cc and a peritoneal space V15 less than 830 cc are associated with a less than 10% risk of grade ≥3 acute toxicity. © 2012 Elsevier Inc.

Reprint requests to: Robyn Banerjee, MD, Tom Baker Cancer Centre, 1331 29th St NW, Calgary, Alberta, Canada T2N 4N2. Tel: (310) 592-5228; Fax: (310) 794-1984; E-mail: robynbanerjee@gmail.com

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–7, 2012
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2012.09.036

Introduction

The small bowel represents the dose-limiting structure in the treatment of rectal cancer with therapeutic radiation. Radiation-induced diarrhea is the most common side effect of bowel irradiation, with grade $\geq$3 toxicity associated with 12% to 38% of rectal cancer patients receiving neoadjuvant chemoradiation therapy (1-4). Prospective randomized trials have shown that up to 10% of such patients are unable to complete treatment because of bowel toxicity (1).

Before the 3-dimensional treatment planning era, a dose-volume relationship between radiation of the small bowel and acute toxicity had been assumed but had not been well characterized. Dosimetric studies relied on orthogonal projections and delineation of the small bowel based on oral contrast medium enhancement (5), which made it impossible to routinely account for inhomogenous dose within the field and to quantify the dose distribution beyond the field edge. More recently, dosimetric studies based on computed tomography (CT) have been able to more accurately quantify the amount of small bowel receiving significant dose during treatment. As a result, the dose-volume relationship for the small bowel has been confirmed and, to a lesser extent, quantified (6-11).

However, the literature available to correlate small bowel toxicity with dose remains sparse compared with other organs (12). A literature review for the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) overview in 2010 found only 6 studies with quantitative dose-volume information for the small bowel. These include 4 studies of rectal cancer patients and 2 studies of gynecologic patients. Patients varied significantly in terms of the type and amount of chemotherapy received, preoperative versus postoperative status, and irradiated volumes. This heterogeneity in patient, tumor, and treatment factors confounds attempts to quantify a dose-volume relationship for the small bowel and to provide generalizable dose constraints.

Another key source of this variability is the lack of a standardized method for contouring and reporting dose to the small bowel. One method is to individually contour loops of small bowel, with or without contrast medium enhancement. The concept of contouring a "peritoneal space" or "potential bowel space" has recently been proposed as an alternative and has even been adopted in phase 2 and 3 randomized trials (13, 14). This volume can be considered as the region where the small or large bowel may lie at any point during treatment, although no detailed consensus definition of the "peritoneal space" has been established.

The small bowel is known to be mobile during a course of radiation (15). By accounting for any potential region that may be occupied by the small bowel, dose-volume histogram (DVH) analysis based on contours of the peritoneal space may better correlate with small bowel toxicity compared with volumes based on contours of individual small bowel loops. Yet, a consistent definition of the "peritoneal space" is lacking, and a dose-volume relationship between this volume and small bowel toxicity has not been established.

The purpose of this study was to directly compare contouring techniques for the small bowel in a homogenous group of rectal cancer patients treated with neoadjuvant radiation and 5-fluorouracil (5-FU) chemotherapy to determine whether DVH data based on contours of the peritoneal space can be used instead of individual small bowel loops to predict for grade $\geq$3 acute small bowel toxicity. Secondary aims were the establishment of dose constraints using both volumes and the development of reproducible criteria for contouring the peritoneal space.

Methods and Materials

Ethics approval for this study was granted by the Alberta Cancer Research Committee. Medical charts and radiation plans for patients treated with neoadjuvant chemoradiation therapy for rectal cancer at the Tom Baker Cancer Centre between 2008 and 2010 were screened for eligibility. To be included in the study, patients had to have a diagnosis of rectal adenocarcinoma treated with curative intent neoadjuvant chemoradiation therapy. Only patients receiving continuous infusional 5-FU chemotherapy were included. Patients were excluded if they received an alternative chemotherapy regimen, a radiation dose greater than 50.4 Gy, or treatment to nonstandard pelvic fields (ie, superior to the bifurcation of the distal common iliac vessels).

Sixty-seven patients were included. Collected chart data included pertinent demographic information and tumor characteristics. On-treatment notes, hospital charts, and treatment summary notes were reviewed to determine the maximal acute toxicity patients experienced while they were receiving treatment. Toxicity was scored according to the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria for the lower gastrointestinal tract.

All patients were planned for 3-dimensional conformal radiation therapy using Varian Eclipse treatment planning software. Typical treatment plans consisted of a 4-field arrangement treated to 45 Gy followed by a 5.4-Gy boost to a smaller volume in 1.8-Gy daily fractions. All treatment plans and contours were reviewed by 1 of the authors (R.B., S.C., R.S.) and double-checked by another author. Contours for the peritoneal space, small bowel, and large bowel, and a volume for peritoneal space minus large bowel, were added to pre-existing radiation treatment plans.

The small bowel contours were defined by outlining all individual loops of bowel as several discontinuous structures (Fig. 1). The contours extended from the inferiormost extent of small bowel to 5 slices (1.5 cm) above the field edge to encompass bowel treated by lower (<50%) but still potentially significant doses. The large bowel was contoured beginning at the peritonealized sigmoid colon. The descending, transverse, and ascending colon were contoured to 1.5 cm superior to the field edge.

The peritoneal space was defined anteriorly and laterally by the posterior aspect of the abdominal muscles. Posteriorly, it is bound by the vertebral bodies, sacrum, or the posterior aspect of peritonealized sigmoid colon. The inferior extent was defined 1 slice (3 mm) below the inferiormost extent of small bowel. Superiorly, the space was extended 5 slices (1.5 cm) superior to the field edge. The peritoneal space encompassed all contoured small and large bowel and excluded bladder, prostate, ovaries, and uterus (see Supplementary figure E1).

Absolute DVH data were exported from Eclipse. A customized Matlab software designed in house (I.N.) was used to determine the absolute volume of each study structure receiving a given dose and was tabulated in 5-Gy dose intervals (0-50 Gy). Statistical analysis was carried out with SPSS version 16.0. Categoric variables were tested for association with grade $\geq$3 toxicity by use of Pearson's χ^2 test. Small bowel and peritoneal space volumes were

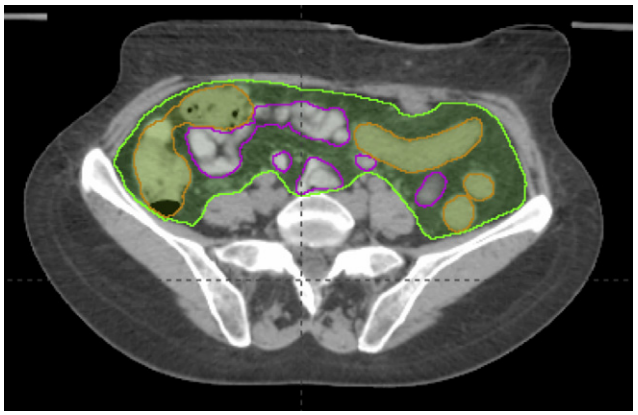

Fig. 1. Representative slice demonstrating contours for small bowel (purple), large bowel (orange), and peritoneal space (green).

tested for association with toxicity by use of the paired *t* test for the volumes at 5-Gy dose intervals to 45 Gy. Receiver operating characteristic (ROC) curves were generated for the small bowel and peritoneal space at the same 5-Gy intervals. Logistic regression was performed to determine the volumetric cutpoints for small bowel toxicity. The predicted probability of toxicity for each dose interval was plotted against the absolute volumes receiving the dose in scatterplots, with markers to indicate grade of toxicity (grade ≥3 vs grade 0-2) for each patient in the study.

Results

Acute grade ≥3 small bowel toxicity occurred in 16% (11/67) of patients. Acute small bowel toxicity was grade 0 in 5 patients (7.5%), grade 1 in 29 patients (43%), grade 2 in 22 patients (33%), grade 3 in 10 patients (15%), and grade 5 in 1 patient (1.5%). The patient's death was due to an acute small bowel obstruction immediately upon completion of treatment.

Factors tested for association with toxicity are shown in Table 1. All patients experiencing grade ≥3 toxicity were female. Patient age, position, T stage, and N stage were not significantly associated with small bowel toxicity.

Mean small bowel volumes and peritoneal space volumes demonstrated a significant association with grade ≥3 toxicity. The average small bowel volume for patients experiencing grade ≥3 toxicity was 658 cc, compared with 294 cc for patients with grade 0-2 toxicity ($P = .000$). The average peritoneal space volume was 1600 cc for patients with grade ≥3 toxicity versus 1142 cc for patients with grade 0-2 toxicity ($P = .003$). Initial analyses demonstrated the peritoneal space minus large bowel volume to be unrelated to toxicity; therefore, subsequent analyses using these volumes were foregone.

For the small bowel volume, the association maintained significance at each 5-Gy dose interval from 5 to 45 Gy (Table 2). The peritoneal space was significantly associated with toxicity at every 5-Gy dose interval except 45 Gy (Table 2). Figure 2 depicts the association of mean small bowel and peritoneal space volumes at 5-Gy dose intervals from 0 to 45 Gy.

ROC curves were generated for all dose intervals. As Table 3 shows, both methods of contouring showed good to excellent ability to discriminate between patients with grade ≥3 toxicity versus those with grade 0-2 toxicity. Among the various dose bins, V25 had the highest area under the curve or discriminant ability for both methods of contouring (0.964 for small bowel and 0.896 for peritoneal space).

Logistic regression analysis was carried out for both volumes at the V25 and V15 dose intervals. The V25 level was chosen because it had the best discriminating ability on ROC analysis. The V15 was analyzed to facilitate comparison with related studies that report a V15 dose cutpoint and because the V15 was nearly as discriminating as V25 on ROC analysis (4, 11, 12). A less than 10% risk of acute grade ≥3 toxicity was associated with

Table 1 Patient characteristics and association with grade ≥3 acute small bowel toxicity in 67 patients

		RTOG lower GI acute toxicity				
		Grade 0-2		Grade ≥3		
Characteristic		n	%	n	%	*P* value
Sex	F	18	62.1%	11	38%	.000
	M	38	100%	0	0%	
Age (mean, y)		62.5		62.0		.879
5-FU dose (mean, mg/m^2/wk)		1467		1426		.635
T	1	1	100%	0	0%	.845
	2	1	100%	0	0%	
	3	45	82%	10	18%	
	4	9	90%	1	10%	
N	0	23	82%	5	18%	.961
	1	27	84%	5	16%	
	2	6	85%	1	15%	
Stage	II	23	82%	5	18%	.788
	III	33	85%	6	15%	
Bellyboard	Yes	19	83%	4	17%	.876
	No	37	84%	7	16%	
Position	Prone	31	84%	6	16%	.961
	Supine	25	83%	5	17%	

Abbreviations: 5-FU = 5-fluorouracil; GI = gastrointestinal; RTOG = Radiation Therapy Oncology Group.

Table 2 Association of small bowel and peritoneal space volumes with toxicity per 5 Gy dose increment

	RTOG lower GI acute toxicity	Mean volume (cc)	SD (cc)	*P* value		RTOG lower GI acute toxicity	Mean volume (cc)	SD (cc)	*P* value
SB V5	Grade 0-2	229	162	.000	PS V5	Grade 0-2	934	383	.000
	Grade ≥3	595	164			Grade ≥3	1452	289	
SB V10	Grade 0-2	184	145	.000	PS V10	Grade 0-2	790	339	.000
	Grade ≥3	540	153			Grade ≥3	1310	285	
SB V15	Grade 0-2	155	132	.000	PS V15	Grade 0-2	702	312	.000
	Grade ≥3	493	147			Grade ≥3	1196	297	
SB V20	Grade 0-2	132	125	.000	PS V20	Grade 0-2	637	298	.000
	Grade ≥3	470	146			Grade ≥3	1136	297	
SB V25	Grade 0-2	90	99	.000	PS V25	Grade 0-2	512	266	.000
	Grade ≥3	383	126			Grade ≥3	957	271	
SB V30	Grade 0-2	56	69	.000	PS V30	Grade 0-2	386	204	.000
	Grade ≥3	261	112			Grade ≥3	662	176	
SB V35	Grade 0-2	47	60	.000	PS V35	Grade 0-2	350	188	.000
	Grade ≥3	238	110			Grade ≥3	606	170	
SB V40	Grade 0-2	39	53	.000	PS V40	Grade 0-2	319	175	.000
	Grade ≥3	217	104			Grade ≥3	560	162	
SB V45	Grade 0-2	23	38	.003	PS V45	Grade 0-2	232	149	.515
	Grade ≥3	67	37			Grade ≥3	265	152	

Abbreviations: 5-FU = 5-fluorouracil; GI = gastrointestinal; PS = peritoneal space; RTOG = Radiation Therapy Oncology Group; SB = small bowel; SD = standard deviation.

a V25 of 190 cc for the small bowel and 650 cc for the peritoneal space. Regression at the V15 dose level demonstrated that a less than 10% risk of acute grade ≥3 toxicity was associated with a V15 of 275 cc for the small bowel and 830 cc for the peritoneal space (Fig. 3).

Discussion

To our knowledge, this is the first study to correlate small bowel loop and peritoneal space contouring techniques with acute toxicity in a homogenous population of rectal cancer patients. The data further confirm the relationship between small bowel dose-volume and grade ≥3 acute small bowel toxicity—an association that is maintained whether the contoured volume is composed of individual small bowel loops or the peritoneal space. Compared with the peritoneal space, contouring individual small bowel loops results in greater correlation with grade ≥3 toxicity at all 5-Gy dose increments from 5 to 45 Gy, with the greatest discriminative ability associated with the volume receiving 25 Gy.

Use of the peritoneal space volume in place of individual small bowel loops offers several advantages. The space is easier to identify and much faster to contour than individual loops of bowel, especially when contrast medium is lacking and when the mobile large bowel is interspersed with the small bowel. Conceptually, the peritoneal space is satisfying because it incorporates the

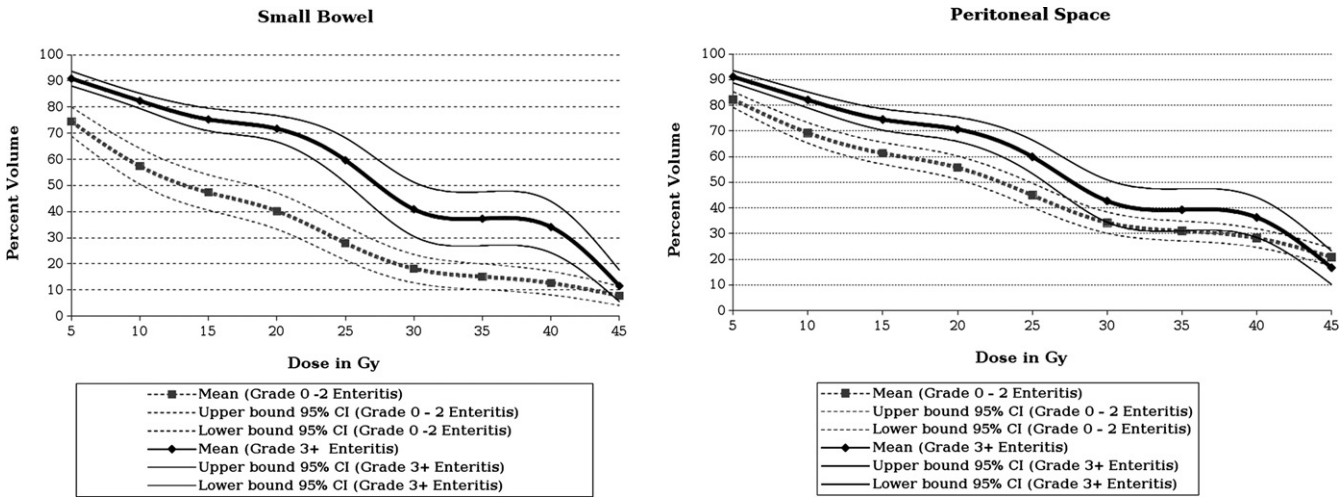

Fig. 2. Mean small bowel and peritoneal space volumes versus dose for patients experiencing grade ≥3 acute small bowel toxicity compared with patients experiencing grade 0-2 toxicity. For small bowel contours, grade ≥3 toxicity was associated with a greater volume irradiated for each 5-Gy dose increment from 0 to 45 Gy. For peritoneal space contours, grade ≥3 toxicity was associated with a greater volume irradiated for each 5-Gy dose increment from 0 to 40 Gy.

Table 3 ROC analysis for small bowel and peritoneal space volumes and association with grade ≥3 acute small bowel toxicity

Small bowel	AUC	SE	*P* value	Peritoneal space	AUC	SE	*P* value
SB V5	.937	.033	.000	PS V5	.865	.046	.000
SB V10	.946	.031	.000	PS V10	.883	.043	.000
SB V15	.951	.026	.000	PS V15	.883	.050	.000
SB V20	.955	.025	.000	PS V20	.881	.053	.000
SB V25	.964	.021	.000	PS V25	.896	.045	.000
SB V30	.948	.028	.000	PS V30	.839	.062	.000
SB V35	.943	.030	.000	PS V35	.847	.061	.000
SB V40	.950	.028	.000	PS V40	.844	.062	.000
SB V45	.812	.073	.001	PS V45	.567	.094	.488

Abbreviations: AUC = area under the curve; SB = small bowel; SE = standard error; PS = peritoneal space.

irradiated large bowel, whose contribution to radiation enteritis is suspected but remains undetermined, and also accounts for the mobility of the small bowel. A study using serial CT scans demonstrated that during a course of treatment for prostate cancer, an average of approximately 280 cc of small bowel fell outside the volume of bowel segments defined on the planning CT scan. Only 20% of the small bowel was observed in the same place throughout treatment (15).

Despite the inability of small bowel loop volumes to account for mobility, this contouring method was a more sensitive predictor of toxicity for each dose level than the peritoneal space. This points to inherent limitations in the peritoneal space volumes with respect to predicting toxicity. Compared with contours of individual small bowel loops, the peritoneal space volumes are both much larger and more variable between patients, which could have reduced the ability to predict small bowel toxicity and may make defining future toxicity cutpoints using the peritoneal space volume all the more challenging. However, the peritoneal space volumes still display a strong association with toxicity and offer a significant convenience compared with contouring individual small bowel loops.

The QUANTEC review of small bowel toxicity lists a peritoneal space constraint of V45 <195 cc for a less than 10% chance of developing acute grade ≥3 toxicity (12, 16). This parameter is based on 1 study of 50 patients with mixed gynecologic cancers treated with intensity modulated radiation therapy (IMRT), in which the volume analyzed was constructed by contouring the outermost loops of contrast medium-enhanced small bowel (9). Using this definition of the peritoneal space, the resultant volume would invariably be much smaller than the peritoneal space volume used in this study or ongoing clinical trials, which incorporate the noncontrast-medium-enhancing small bowel, the large bowel, and the remainder of the potential bowel space (13, 14). Moreover, inasmuch as no patients in that study experienced grade 3 small bowel toxicity, grade 2 toxicity was subdivided on the basis of frequency of medication use, and this "clinically significant" toxicity was correlated to small bowel dose and volume. On multivariate analysis, only the volume of small bowel receiving at least 45 Gy significantly correlated with toxicity. Thus, the peritoneal space parameter given in QUANTEC must be kept in the context of the single study from which it was derived, and it is unlikely to be generalizable.

The only other study to investigate small bowel toxicity using a volume analogous to the peritoneal space examined 28 patients with locally advanced and metastatic rectal cancer receiving concurrent 5-FU and oxaliplatinum with radiation therapy (11). Those authors defined a "whole abdomen" volume, which seems similar to our peritoneal space volume but extends superiorly to the diaphragm to encompass the whole abdomen (11). Larger irradiated volumes were associated with greater toxicity, although the relationship was not statistically significant.

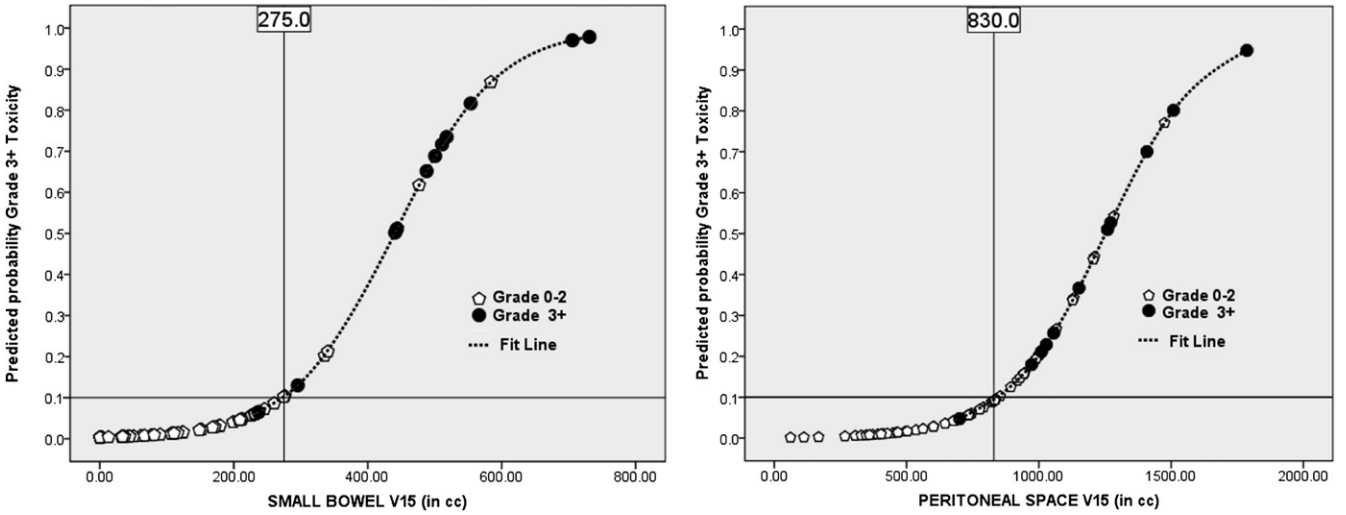

Fig. 3. Logistic regression curves for small bowel and peritoneal space V15. A less than 10% risk of grade ≥3 toxicity was associated with a small bowel V15 <275 cc and a peritoneal space V15 <830 cc.

There is discordance in the literature regarding whether small bowel toxicity is more dependent on the volume of small bowel receiving lower doses versus higher doses. In this study, the dose most strongly associated with toxicity for both small bowel contours and peritoneal space contours was the V25. Successive predictive models developed by Robertson et al in a combination of pre- and postoperative rectal cancer patients showed the volume of small bowel receiving 15 Gy was most strongly associated with toxicity (4, 7). The 20-Gy and 25-Gy regions were found to be nearly as predictive (4). Similar to our results, and in general agreement with the models of Robertson et al, Tho et al found a significant association for small bowel volume at all dose levels, with the strongest association between 5 and 30 Gy (8).

Huang et al evaluated the importance of prior abdominal surgery on acute small bowel toxicity in gynecologic cancer patients. In the group without prior surgery, small bowel toxicity was most strongly associated with the V40% (in this case, the volume of small bowel receiving at least 40% of the 39.6 Gy, or approximately 15 Gy). Toxicity was more strongly associated with the V100% in the prior surgery group (10). On balance, the existing evidence in rectal cancer patients supports the assertion that the volume of small bowel receiving low doses (15-25 Gy) is more predictive of acute toxicity than the volume receiving high doses.

The small bowel volume constraints derived in this study are larger than those previously published. A 10% risk of grade $\geq$3 toxicity was found at a V15 of 275 cc, compared with previously reported V15 cutoffs of 120 to 150 cc (4, 11, 12). One possible explanation for this observation is that our study was exclusively composed of preoperative patients. Patients with prior abdominal surgery are known to experience greater rates of radiation-induced enteritis (5, 10, 17). The larger volume constraints in our study may also have been caused in part by the extension of contours 1.5 cm superior to the field edge. As well, this study excluded patients treated with capecitabine or oxaliplatin, agents associated with higher rates of diarrhea (18, 19).

Patient, tumor, and treatment characteristics were not found to significantly correlate with toxicity, apart from female sex. Sex is not known to be associated with higher rates of radiation-induced enteritis. This finding can be partially explained by prior hysterectomies in some of these women (4/11), which typically results in more bowel falling in the radiation field. The overall significance of more women experiencing greater toxicity is questionable, given that our study was retrospective and nonrandomized.

The increasing use of IMRT will further confound the complex task of defining dose-volume constraints for the small bowel. IMRT optimization based on contours of the peritoneal space can result in greater bowel sparing than plans using individual bowel segments (15). Yet, IMRT is also known to spare high-dose regions at the expense of larger volumes receiving lower doses. For the small bowel, where the lower dose regions are of prime importance in predicting toxicity, this may be particularly significant.

Conclusion

Our data demonstrate for the first time a dose-volume relationship between peritoneal space contours and small bowel toxicity, suggesting that contouring the peritoneal space is a reasonable substitute for contouring individual small bowel loops. However, the small bowel loop contouring method demonstrated a better discriminative ability for predicting toxicity at each 5-Gy dose interval. For rectal cancer patients receiving neoadjuvant chemoradiation, a small bowel V15 less than 275 cc and peritoneal space V15 less than 830 cc was associated with a less than 10% risk of grade $\geq$3 acute toxicity. These dose constraints require prospective validation in future studies.

References

1. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351:1731-1740.
2. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;355:1114-1123.
3. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008;26: 3687-3694.
4. Robertson JM, Sohn M, Yan D. Predicting grade 3 acute diarrhea during radiation therapy for rectal cancer using a cutoff-dose logistic regression normal tissue complication probability model. *Int J Radiat Oncol Biol Phys* 2010;77:66-72.
5. Gallagher MJ, Brereton HD, Rostock RA, et al. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. *Int J Radiat Oncol Biol Phys* 1986;12:1565-1573.
6. Baglan KL, Frazier RC, Yan D, et al. The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation therapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2002;52:176-183.
7. Robertson JM, Lockman D, Yan D, et al. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2008;70:413-418.
8. Tho LM, Glegg M, Paterson J, et al. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. *Int J Radiat Oncol Biol Phys* 2006;66:505-513.
9. Roeske JC, Bonta D, Mell LK, et al. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. *Radiother Oncol* 2003; 69:201-207.
10. Huang EY, Sung CC, Ko SF, et al. The different volume effects of small-bowel toxicity during pelvic irradiation between gynecologic patients with and without abdominal surgery: a prospective study with computed tomography-based dosimetry. *Int J Radiat Oncol Biol Phys* 2007;69:732-739.
11. Gunnlaugsson A, Kjellen E, Nilsson P, et al. Dose-volume relationships between enteritis and irradiated bowel volumes during 5-fluorouracil and oxaliplatin based chemoradiotherapy in locally advanced rectal cancer. *Acta Oncol* 2007;46:937-944.
12. Kavanagh BD, Pan CC, Dawson LA, et al. Radiation dose-volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S101-S107.
13. Jhingran A, Miller B, Portelance L, et al. Radiation Therapy Oncology Group RTOG 0418: A phase II study of intensity modulated radiation therapy (IMRT) to the pelvis $\pm$ chemotherapy for post-operative patients with either endometrial or cervical carcinoma. Protocol. Broadcast date August 25, 2011.
14. Pollack A, Low D, Watkins-Bruner D, et al. Radiation Therapy Oncology Group RTOG 0534: A phase III trial of short term androgen deprivation with pelvic lymph node or prostate bed only radiotherapy (SPPORT) in prostate cancer patients with a rising

PSA after radical prostatectomy. Protocol. Broadcast date January 11, 2011.
15. Sanguineti G, Little M, Endres EJ, et al. Comparison of three strategies to delineate the bowel for whole pelvis IMRT of prostate cancer. *Radiother Oncol* 2008;88:95-101.
16. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S10-S19.
17. Minsky BD, Conti JA, Huang Y, et al. Relationship of acute gastrointestinal toxicity and the volume of irradiated small bowel in patients receiving combined modality therapy for rectal cancer. *J Clin Oncol* 1995;13:1409-1416.
18. Hofheinz R, Wenz FK, Post S, et al. Capecitabine versus 5-fluorouracil based neoadjuvant chemoradiotherapy for locally advanced rectal cancer: Long-term results of a randomized phase III trial. *J Clin Oncol* 2011;29(suppl). abstr 3504.
19. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04. *J Clin Oncol* 2011; 29(suppl). abst 3503.