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Predictors of Radiotherapy-related GI Toxicity from Anal Cancer DP-IMRT: Secondary Analysis of NRG Oncology RTOG 0529

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Abstract

Purpose—NRG Oncology RTOG 0529 assessed the feasibility of dose-painted intensity-modulated radiation therapy (DP-IMRT) to reduce the acute morbidity of chemoradiation with 5-fluorouracil (5FU) and mitomycin-C (MMC) for T2-4N0-3M0 anal cancer. This secondary analysis was performed to identify patient and treatment factors associated with acute and late gastrointestinal (GI) adverse events (AEs).

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Methods and Materials—NRG Oncology RTOG 0529 treatment plans were reviewed to extract dose-volume data for tightly contoured small bowel, loosely contoured anterior pelvic contents (APC), and uninvolved colon outside the target volume (UC). Univariate logistic regression was performed to evaluate association between volumes of each structure receiving doses ≥ 5 to 60 Gy (V5–V60) in 5 Gy increments between patients with and without ≥ grade (G) 2, acute and late GI AEs, and ≥G3 acute GI AEs. Additional patient and treatment factors were evaluated in multivariate (MV) logistic regression (acute AEs) or Cox proportional hazards models (late AEs).

Results—Among 52 evaluable patients, ≥G2 acute, ≥G2 late, and ≥G3 acute GI AEs were observed in 35, 17, and 10 patients, respectively. Trends ($p<0.05$) towards statistically significant associations were observed between: ≥G2 acute GI AEs and small bowel dose (V20–V40); ≥G2 late GI AEs and APC dose (V60); ≥G3 acute GI AEs and APC dose (V5–V25), increasing age, tumor size >4cm, and worse Zubrod. Small bowel volumes of 186.0 cc, 155.0 cc, 41.0 cc, and 30.4 cc receiving doses greater than 25, 30, 35, and 40 Gy, respectively, correlated with increased risk of acute ≥ grade 2 GI AEs.

Conclusions—Acute and late GI AEs from 5FU/MMC chemoradiation using DP-IMRT correlate with radiation dose to the small bowel and APC. Such associations will be incorporated in the dose-volume normal tissue constraint design for future NRG Oncology anal cancer studies.

Keywords

Anal; Cancer; IMRT; Gastrointestinal; Toxicity

Introduction

Definitive chemoradiotherapy (CRT) with 5-fluorouracil (5FU) and mitomycin-C (MMC) is the standard of care for non-metastatic squamous cell carcinoma of the anal canal (SCCA).[1–5] NRG Oncology RTOG 0529 demonstrated feasibility of dose-painted intensity-modulated radiation therapy (DP-IMRT) to reduce the acute morbidity of chemoradiation for T2-4N0-3M0 SCCA, with lower observed rates of grade ≥ 3 gastrointestinal (GI) adverse events (AEs) compared to the conventional radiation/5FU/MMC arm of Study RTOG 9811.[6]

While the observed rates of acute grade ≥ 3 GI AEs on NRG Oncology RTOG 0529 are encouraging, ideal dose-volume constraints to minimize GI toxicity for definitive SCCA CRT have not been well-quantified. Multiple series suggest a relationship between the radiation dose administered to an absolute volume of small bowel, and increased risk of acute toxicity in the neoadjuvant rectal cancer setting.[7–10] The addition of 5FU and MMC chemotherapy to definitive radiotherapy for the treatment of SCCA improves cause specific survival,[2] while both 5FU and MMC increase bowel radiosensitivity and GI toxicity.[2,4,11]

Treatment planning data collected under NRG Oncology RTOG 0529 present an opportunity to advance the understanding of bowel tolerance, and establish anal cancer specific constraints applicable both in general practice and for future cooperative group trials. This secondary analysis of NRG Oncology RTOG 0529 was performed to identify patient and treatment factors associated with acute and late GI AEs.

Patients and Methods

Patient Eligibility

This study was coordinated by the Radiation Therapy Oncology Group, now part of NRG Oncology and performed with the approval of the institutional review board for human research at each institution. Detailed criteria for patient eligibility and initial evaluation have been previously described.[6] In brief, patients with histologically documented squamous or basaloid carcinoma of the anal canal were eligible provided they were ≥ 18 years of age with Zubrod performance status ≤1, and documented 2002 American Joint Committee on Cancer clinical stage T2-4N0-3M0 disease. Exclusion criteria included severe comorbidity (including AIDS or other immunocompromised state), prior major malignancy within 3 years, and prior pelvic radiotherapy or chemotherapy.

Treatment

Patients were treated definitively with DP-IMRT and concurrent 5FU and MMC, the techniques of which have been previously described.[6] CT-based treatment planning was performed for all patients with oral and IV contrast recommended to allow better visualization of target and normal structures. Patients were positioned either supine in a frog-legged position using custom immobilization or prone with bowel displacement.

The gross tumor volume (GTV_A) and involved nodal volumes ($GTVN_{50–54}$) were contoured using all available exams, imaging, and endoscopy findings. A 2.5 cm and 1 cm expansion was added to the primary and nodal GTVs, respectively, to create CTVs. Manual editing was allowed to avoid overlap into natural barriers to tumor infiltration, and also to avoid overlap into non-target small and large bowel. Such editing was not allowed at the expense of sacrificed coverage to the primary tumor or rectum. A 1 cm expansion was added to all CTVs to create the planning target volume (PTVs). Dose prescriptions for PTVs varied according to stage; T2N0: 42 Gy elective nodal and 50.4 Gy anal tumor PTVs in 28 fractions, T3-4N0-3: 45 Gy elective nodal, 50.4 Gy ≤ 3 cm or 54 Gy > 3 cm regional nodal and 54 Gy anal tumor PTVs in 30 fractions. Elective nodal CTVs included the mesorectum, presacrum, bilateral internal and external iliac, and bilateral inguinal regions as previously described.[12] DP-IMRT treatments were delivered once daily, 5 fractions per week, with daily image guidance (IGRT) recommended for prone delivery. Two cycles of 5FU (1000 $mg/m^2/d$ as a 96 hour infusion, days 1–5 and 29–33) and MMC (10mg/m^2 bolus, days 1 and 29) were administered with dose modifications as previously described.[6]

Toxicity Assessment

Adverse events (AEs) were assessed per the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3 weekly during chemoradiation and in follow-up (4 and 8 weeks post-treatment, then every 3 months during year 1, every 6 months during year 2, then annually). The incidence of the worst grade toxicity sustained up to 90 days from DP-IMRT initiation is defined as an acute toxicity event. AEs occurring after 90 days are defined as late. Since the primary purpose of this analysis was to determine predictors of GI AEs during DP-IMRT, GI AEs were excluded from analysis when clearly unrelated to radiotherapy bowel dose (stomatitis, dysgeusia, hemorrhoids).

Analysis of Patient and Dose Factors Correlating with GI Toxicity

All treatment plans were exported to third-party commercial software (MimVista, Mim Software Inc. Cleveland, OH) to allow review of small and large bowel contours. Per the original protocol, normal tissue contouring included “tight” contouring of any loops of small and large bowel that lay within treated axial planes. All small and large bowel contours were verified and amended if required for accuracy. Large bowel contours were amended to exclude overlap with the CTV to create a structure representative of the uninvolved colon outside the target volume (UC). Additionally, an anterior pelvic contents (APC) contour was generated to include any peritoneal space occupied or potentially occupied by bowel, large or small, as previously described to account for variability in bowel motion.[13] Bladder and gynecologic structures were excluded from APC contours. A representative image of small bowel, UC, and APC contours relative to the elective nodal volume is shown in Figure 1A.

Statistical Considerations

To adjust for multiple comparisons in this exploratory analysis, a p-value < 0.001 was considered statistically significant, and a p-value between 0.001 and 0.05 was considered as showing a trend towards statistical significance. Univariate logistic regression models were performed to find associations between the organs at risk (OARs) receiving doses ≥5 to ≥60 Gy (V5–V60, analyzed as continuous variables) and (i) patients with grade < 2 vs. grade ≥ 2 acute gastrointestinal GI AEs, (ii) patients with grade < 3 vs. grade ≥ 3 acute GI AEs, and (iii) patients who had a radiation treatment (RT) position of supine vs. prone. Cox proportional hazards models[14] were performed to find associations between OARs receiving doses ≥5 to ≥60 Gy and patients with grade < 2 vs. grade ≥ 2 late GI AEs. Analysis of factors correlated with ≥ grade 3 late GI AEs was not performed due to low incidence of late ≥ grade 3 GI morbidity.

Factors showing significance or a trend towards significance on univariate analysis were evaluated in conjunction with other patient and treatment factors using multivariate logistic regression or Cox proportional hazards models. Time to late GI AEs were estimated by the cumulative incidence method.[15] Time to late GI AEs were measured from the date of randomization to the date of the earliest worst grade GI AE occurring after 90 days from DP-IMRT initiation. Patients with no late grade ≥ 2 GI AEs were censored at death or last follow-up. In addition to dose-volume parameters, the following variables were assessed in the Cox and logistic models: increasing age (continuous), increasing distance from the anal verge (continuous), gender, race (white vs. other), Zubrod (0 vs.1), differentiation (other vs. high grade), tumor size (≤ 4 vs. > 4cm), T stage (T2 vs. T3/T4), N stage (N0 vs. N1–3), AJCC stage (II vs. IIIA/IIIB), and RT position (supine vs. prone). A hazard ratio (HR) or odds ratio (OR) > 1 indicates an increased risk or odds of having the higher grade toxicity. Given the small number of events, only two-variable logistic models were constructed to avoid overfitting.

Receiver Operating Characteristic Analyses

Receiver operating characteristic (ROC) analyses were also used to identify the usefulness of each volume of small bowel getting a certain dose (V5–V60) in classifying patients with and without acute grade ≥ 2 GI AEs. If there was no classification value, the area under the curve

(AUC) would be 0.5. Each volume of small bowel getting a certain dose (V5–V60) was compared to chance: H_0 (Null Hypothesis): AUC_{VX}-AUC_{chance} = 0. If p-value > 0.05 then H_0 could not be rejected so the AUC of the volume of small bowel getting a certain dose (V5–V60) was not considered statistically significantly different than chance in its ability to classify patients as having acute grade ≥ 2 GI AEs. The AUCs and 95% confidence intervals (CIs) were determined for each VX (V5–V60).

For those VX that were statistically significantly different than chance, a ROC curve was created in order to determine threshold dose/volume points. Threshold dose/volume points were identified using the Youden Index,[16] which was the difference between the true positive rate and the false positive rate. The maximum of the Youden Index indicates an optimal threshold dose/volume point. A p-value of < 0.05 was considered statistically significant. These threshold dose/volume points were then used to dichotomize each VX variable (≤ threshold dose/volume point vs. > threshold dose/volume point). Logistic regression models were used to determine if there was any association between the dichotomized VX variables and having acute grade ≥ 2 GI AEs.

For those VX variables (using the threshold dose/volume points) that showed a trend toward being (<0.05) associated with having acute grade ≥ 2 GI AEs, two-variable logistic models were constructed using the other characteristics that showed an association with having acute grade ≥ 2 GI AEs in univariate analyses (OR: < 0.5 or > 2.0). Since RT position (prone vs. supine) was of particular interest, it was included in these two-variable models even if not statistically significantly in univariate analysis.

Results

Patients

NRG Oncology RTOG 0529 opened December 21, 2006 and closed March 21, 2008, after accruing a total of 63 patients, of which 52 were evaluable. Reasons for patient exclusion have been previously described[6]. Patient and tumor characteristics for NRG Oncology RTOG 0529 are shown in Table 1. The majority of evaluable patients were female (81%), had Zubrod 0 performance status (77%), T2 disease (62%), and no nodal involvement (56%). Thirty-nine patients (75.0%) were treated in a supine position and 13 (25.0%) were treated prone. The median follow-up was 4.8 years among all patients, and 5.0 years among living patients.

Acute and Late GI AEs

Thirty-five patients (67.3%) had acute grade ≥ 2 GI AEs and 10 (19.2%) had acute grade ≥ 3 GI AEs (Table 2). Seventeen patients (32.7%) had late grade ≥ 2 GI AEs and one patient had a late grade ≥ 3 GI AE, consisting of both diarrhea and enteritis. The most frequently observed acute grade ≥ 2 GI AEs included diarrhea (n=18), dehydration (n=10), anorexia (n=8), and nausea (n=8). The most frequently observed late grade ≥ 2 GI AEs included constipation (n=6), anorexia (n=4), and diarrhea (n=4). Composite frequencies of individual acute and late GI AEs are shown in Table 3 (Supplemental data).

Univariate Analysis of Patient/Treatment Factors and GI AEs

No correlation was observed between any patient/tumor factors and incidence of acute or late grade ≥ 2 GI AEs. A significant correlation was observed between several patient factors (increasing age, Zubrod status, tumor size) and the incidence of acute ≥ 3 GI AEs on univariate logistic regression, as shown in Table 4.

Among dose-volume parameters (analyzed as continuous variables), Table 5 illustrates trends (p-values ranging from 0.016 to <0.05) towards statistically significant associations that were observed between ≥ grade 2 acute GI AEs and small bowel dose (V20–V40. A statistically significant association was also observed between ≥ grade 2 late GI AEs and APC dose (V60) ($p<0.0001$). No correlation was observed between ≥ grade 3 acute GI AEs and small bowel dose. No correlation was observed between ≥ grade 2 or ≥ grade 3 acute or late GI AEs and dose to UC.

A trend was observed for correlation between reduced small bowel V10Gy–V35Gy for treatment in the prone compared to supine position (p-values ranging from 0.025 to 0.05), but there was no statistically significant association between treatment position and the incidence of acute or late GI AEs. Figure 1B illustrates of the impact of treatment position on bowel displacement from the pelvic radiotherapy field for a patient treated prone with bowel compression compared to a different patient treated supine.

Multivariate Analysis of Patient/Treatment Factors and GI AEs

Two-variable logistic regression models were utilized to evaluate association between small bowel dose and toxicity in the context of other patient and treatment factors. On multivariate analysis, a trend towards significant association was observed between small bowel V25–V35 Gy and acute ≥ grade 2 GI AEs when also accounting for one of the previously described patient and treatment factors (p-values ranging from 0.015 to 0.036). Additionally, a trend ($p<0.05$) towards association between both variables and ≥ grade 3 acute GI AEs was observed for the following: APC V5–V15 and Zubrod status; APC V5–V25 and tumor size; APC V15–V25 and increasing distance from the anal verge. The correlation between ≥ grade 2 late GI AEs and APC V60 remained significant (p-values ranging from 0.0043 to 0.019) in the two-variable Cox regression models.

ROC Analysis of Significant Dose-Volume Parameters

Initial ROC analysis indicated usefulness of the absolute volume of small bowel at the V20–40 Gy dose levels in classifying patients with and without acute ≥ grade 2 GI AEs (p-values ranging from 0.0026 to 0.032). Univariate logistic regression confirmed a trend towards significance of each dichotomized V25–40 Gy threshold dose/volume point for detection of acute ≥ grade 2 GI AEs (p-values ranging from 0.0037 to 0.043). The greatest significance on logistic regression was observed for the absolute volume of small bowel >41.0 cc receiving greater than 35 Gy, with associated odds ratio of 9.48 for risk of acute ≥ grade 2 GI AEs ($p=0.0037$). On two-variable logistic regression modeling, the absolute volume of small bowel receiving 30, 35, and 40 Gy showed trends toward being statistically significantly associated with acute grade ≥ 2 GI AEs after adjusting for the other variable in the model (Table 6), but none of the other patient and tumor variables showed an

association. No ROC analysis was undertaken for acute grade ≥ 3 GI AEs since there were only ten events. For time to late grade ≥ 2 GI AEs, there was no AUC for volume of APC getting a certain dose (V5–V60) that was statistically significantly different than chance (0.5).

Discussion

In this analysis, patient and tumor factors from NRG Oncology RTOG 0529 were correlated with observed AEs, to determine factors correlated with acute and late GI morbidity. A correlation was observed on univariate and multivariate analyses between multiple small bowel and APC dose-volume parameters and GI morbidity. In particular, small bowel absolute volumes of 186 cc, 155 cc, 41 cc, and 30 cc receiving doses greater than 25, 30, 35, and 40 Gy, respectively, were found to correlate with increased risk of acute ≥ grade 2 GI AEs. These dose volume cut-points are more conservative than the initially proposed optimization parameters from NRG Oncology RTOG 0529, which suggested no more than 200 cc, 150 cc, 20 cc, and 0 cc of small bowel receive greater than 30 Gy, 35 Gy, 45 Gy, and 50 Gy. Since all treatment plans on the current study were subject to the above pre-determined protocol constraints, it is possible that these pre-determined threshold values influenced the study results. This potentially could cause the suggested parameters to be overly conservative, and limit analysis of ≥ grade 3 GI AEs, which were of lower incidence in the study. These results, however, remain clinically applicable, since these suggested conservative dose-volume parameters were achievable for many cases, and may have contributed to the observed low incidence of ≥ grade 3 AEs. These updated small bowel optimization parameters are proposed as useful to guide subsequent anal cancer DP-IMRT treatment planning, but will require validation in future studies, and must be interpreted with caution given priority for delivery of sufficient dose to the target.

Several prior studies have evaluated predictors of GI morbidity during anal cancer chemoradiotherapy. A retrospective analysis of 58 patients treated with definitive chemoradiotherapy for anal cancer by Defoe et al. suggested a correlation between acute ≥ grade 3 GI AEs and increased bowel doses with dose-volume cutpoints of APC V30Gy >310 cc and V40Gy > 70cc, with bowel delineated using the APC (bowel bag) method.[17] A prior study by Devisetty et al. also suggested correlation between acute ≥ grade 2 GI AEs and APC V30Gy >450 cc.[18] Both studies utilized the supine position for treatment. Compared to these prior studies, the respective V30Gy and V40Gy dose-volume cutpoints of 155 cc and 30 cc, suggested by the current analysis appear more conservative. This could be due to multiple factors between studies. First, plans in the current study were already subject to protocol constraints with no more than 200 cc, 150 cc, 20 cc, and 0 cc of small bowel receive greater than 30 Gy, 35 Gy, 45 Gy, and 50 Gy. These baseline constraints potentially could have reduced the overall incidence of GI AEs, and resulted in determination of more conservative dose-volume thresholds. Additionally, for the current analysis, ROC was performed on tightly contoured small bowel loops, which will invariably be of less volume than a loosely contoured APC (bowel bag) used in the above noted prior studies. While we appreciate that the current analysis is not of sufficient power or intended to compare these two methods, as contouring of individual small bowel loops remains the standard practice

for cooperative group normal tissue contouring for GI malignancies, the results provide potentially useful cut-points for plan optimization in future trials.

Although no correlation was observed between prone versus supine patient position and incidence of GI AEs, the dose delivered to small bowel (V10–V35) was lower for patients treated prone compared to supine. This suggests that even with application of IMRT, prone positioning remains useful to reduce small bowel dose. Limitations in sample size/events may have prevented an observed statistically significant clinical correlation between treatment position and incidence of GI AEs, suggesting that further study is warranted to determine if a correlation between treatment position and toxicity risk exists.

While this report represents the first dose-volume analysis of GI AEs in a prospective anal cancer study, there are several limitations that should be noted. Use of physician reported GI AEs rather than patient reported outcomes may have been a confounding factor in the analysis, since significant variability is known to exist between toxicity assessment methods.[19–20] While moderate correlation between physician and patient reported outcomes is known to exist,[19] use of patient reported data is imperative for incorporation in future studies.

Since this work was performed post-hoc it should be considered hypothesis generating with further validation required. Limitations in sample size resulted in large confidence intervals during determination of the V20–V40 Gy threshold dose/volume point odds ratios. Analyses of a high number of dose-volume parameters increases the likelihood of a type I statistical error, although p-value adjustment was performed in the analysis to adjust for multiple comparisons. Finally, the significant dose-volume parameters observed to correlate with GI AEs in this study should be cautiously applied in any extrapolation for routine treatment planning. While useful for plan optimization, it would be inappropriate to apply such dose-volume parameters as hard treatment planning constraints, given priority for cancer cure.

Conclusions

Acute and late GI AEs from 5FU/MMC chemoradiation using DP-IMRT correlate with RT dose to the small bowel and APC. Such associations will be incorporated in the dose-volume normal tissue constraint design for future NRG Oncology anal cancer studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary

In this secondary analysis of NRG Oncology RTOG 0529, acute and late gastrointestinal adverse events from 5FU/MMC chemoradiation using DP-IMRT for anal cancer treatment were found to correlate with radiation dose to the small bowel and anterior pelvic contents. Specific small bowel threshold-doses are of interest for IMRT optimization in future studies to reduce the risk of gastrointestinal adverse events.

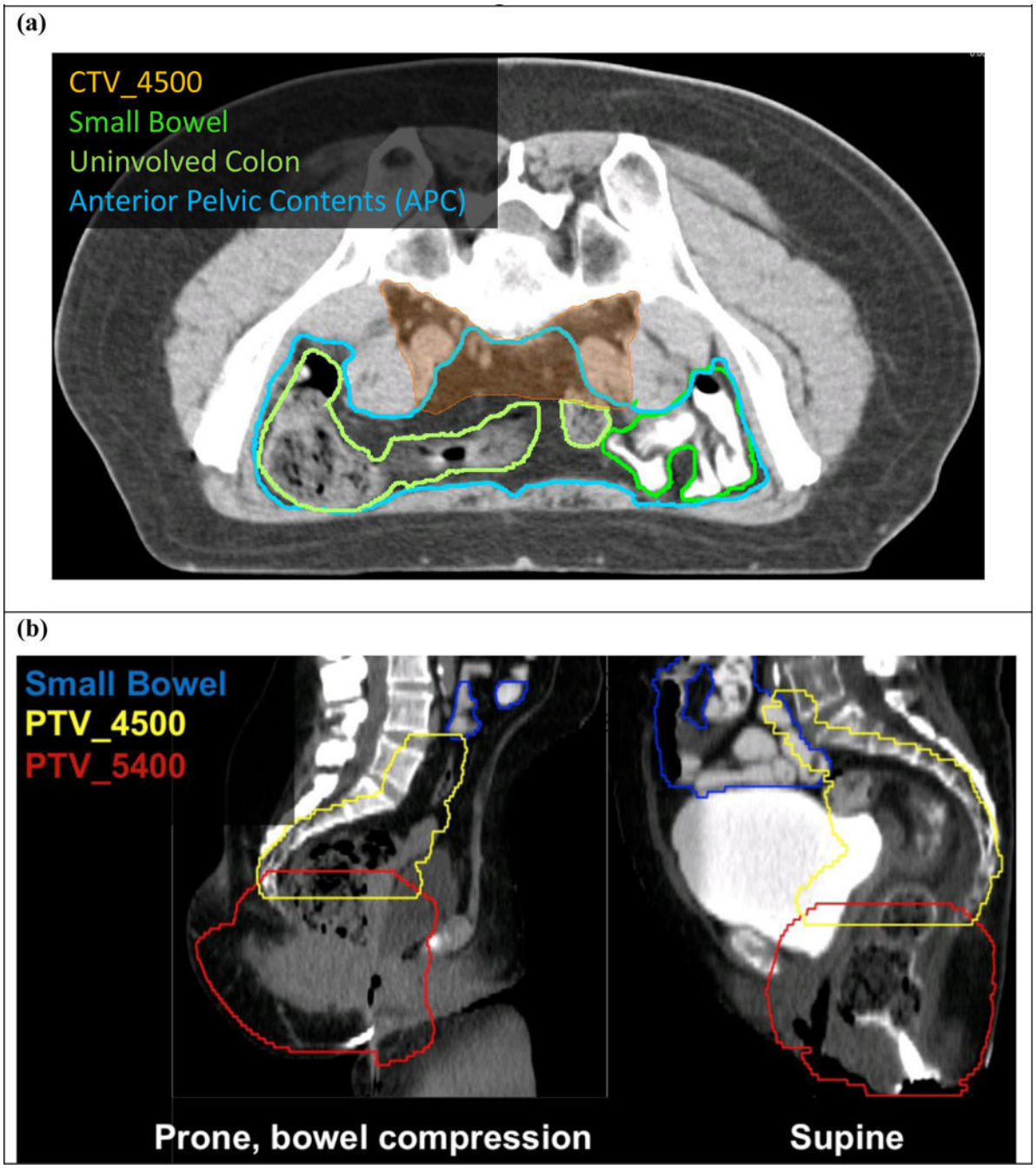

Figure 1.

(a) Representative image of small bowel, uninvolved colon, and APC contours relative to the elective nodal volume (CTV_4500). (b) Illustration of the impact of treatment position on bowel displacement for a patient treated prone with bowel compression (left), and a different patient treated supine. For supine positioning, increased small bowel was present in the treatment field, even in the presence bladder distension.

Table 1

Patient and Tumor Characteristics (n=52)

Age (years)	
Median (Min-Max)	58 (34–82)
Gender	
Male	10 (19.2%)
Female	42 (80.8%)
Race	
American Indian or Alaskan Native	1 (1.9%)
Black or African American	5 (9.6%)
White	44 (84.6%)
Unknown	2 (3.8%)
Zubrod Performance Status	
0	40 (76.9%)
1	12 (23.1%)
Differentiation	
Low grade	5 (9.6%)
Intermediate	22 (42.3%)
High grade	14 (26.9%)
Unknown	11 (21.2%)
T Stage (clinical)	
T2	32 (61.5%)
T3	16 (30.8%)
T4	4 (7.7%)
N Stage (clinical)	
N0	29 (55.8%)
N1	13 (25.0%)
N2	5 (9.6%)
N3	5 (9.6%)
AJCC Stage (6th Edition)	
Stage II	28 (53.8%)
Stage IIIA	13 (25.0%)
Stage IIIB	11 (21.2%)
RT Position	
Supine	39 (75.0%)
Prone	13 (25.0%)

Table 2

Acute and Late GI AEs

	Acute [≤ 90 days]	Late [> 90 days]
Grade < 2 (0–1)	17 (32.7%)	35 (67.3%)
Grade ≥ 2	35 (67.3%)	17 (32.7%)
Grade < 3 (0–2)	42 (80.8%)	51 (98.1%)
Grade ≥ 3	10 (19.2%)	1 (1.9%)

Table 4

Univariate Logistic Regression of Patient Factors Correlating with Acute ≥ G3 GI AEs

Variable	Comparison	n	Yes – Grade ≥ 3 Acute GI AE	OR*	95% C.I. LL	95% C.I. UL	p-value†	AUC (95% C.I.)
Increasing age	Continuous	–	–	1.12	1.03	1.22	0.0072	0.776 (0.617, 0.936)
Increasing distance from anal verge	Continuous	–	–	0.43	0.17	1.08	0.072	0.767 (0.621, 0.913)
Gender	Female	42	8	1.00	–	–	–	
	Male	10	2	1.06	0.19	6.00	0.95	0.505 (0.361, 0.649)
Zubrod	0	40	5	1.00	–	–	–	
	1	12	5	5.00	1.14	22.00	0.033	0.667 (0.494, 0.840)
Differentiation	Other	38	6	1.00	–	–	–	
	High grade	14	4	2.13	0.50	9.10	0.31	0.581 (0.408, 0.754)
Tumor size	≤ 4 cm	28	2	1.00	–	–	–	
	> 4 cm	24	8	6.50	1.22	34.53	0.028	0.710 (0.559, 0.860)
T stage (clinical)	T2	32	4	1.00	–	–	–	
	T3/T4	20	6	3.00	0.73	12.39	0.13	0.633 (0.458, 0.809)
N stage (clinical)	N0	29	3	1.00	–	–	–	
	N1/N2/N3	23	7	3.79	0.86	16.81	0.079	0.660 (0.492, 0.827)
AJCC stage (6th ed.)	II	28	3	1.00	–	–	–	
	IIIA/IIIB	24	7	3.43	0.78	15.17	0.10	0.648 (0.480, 0.815)
RT position	Supine	39	9	1.00	–	–	–	

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Variable	Comparison	n	Yes – Grade ≥ 3 Acute GI AE	OR*	95% C.I. LL	95% C.I. UL	p-value†	AUC (95% C.I.)
	Prone	13	1	0.28	0.03	2.44	0.25	0.407 (0.287, 0.527)

Abbreviations: C.I. confidence interval; AUC, area under the ROC curve

*Odds Ratio: An odds ratio of 1 indicates no difference between the two subgroups OR a 95% C.I. which includes 1 indicates no statistically significant difference between the subgroups. The variables were coded such that a OR > 1 indicates a greater chance of having an acute grade ≥ 3 GI AE.

†p-value from the Logistic regression model

Table 5

Univariate Logistic Models of Acute Grade ≥ 2 GI AEs: Absolute Volume of Small Bowel (V20–V40)

Variable		OR*	95% C.I. LL	95% C.I. UL	p-value†	AUC (95% C.I.)
Absolute V20	Continuous (u.i.=100)	1.63	1.02	2.61	0.042	0.671 (0.515, 0.826)
Absolute V25	Continuous (u.i.=100)	2.14	1.14	4.02	0.018	0.701 (0.554, 0.847)
Absolute V30	Continuous (u.i.=100)	2.86	1.22	6.70	0.016	0.729 (0.580, 0.879)
Absolute V35	Continuous (u.i.=100)	3.79	1.20	11.98	0.023	0.698 (0.537, 0.858)
Absolute V40	Continuous (u.i.=100)	5.56	1.09	28.34	0.039	0.692 (0.531, 0.854)

Abbreviations: OR, odds ratio; C.I. confidence interval; u.i. unit increase; AUC, area under the ROC curve,

†p-value from the Logistic regression model

Table 6

Two-variable Logistic Regression Modeling of Acute Grade ≥ 2 GI AEs (Absolute Volume of Small Bowel (cc) Receiving 30–40Gy [V30–V40], Dichotomized Using the Threshold Dose/volume Point)

	Comparison	OR*	95% C.I. LL	95% C.I. UL	p-value†
Absolute V30	≤155.0	1.00	–	–	–
	>155.0	5.35	1.43	20.04	0.013
Gender	Female	1.00	–	–	–
	Male	1.99	0.34	11.69	0.45
Absolute V30	≤155.0	1.00	–	–	–
	>155.0	5.14	1.36	19.48	0.016
Race	White	1.00	–	–	–
	Other	0.61	0.12	3.16	0.56
Absolute V30	≤155.0	1.00	–	–	–
	>155.0	4.88	1.27	18.69	0.021
Zubrod	0	1.00	–	–	–
	1	1.93	0.33	11.20	0.46
Absolute V30	≤155.0	1.00	–	–	–
	>155.0	5.57	1.45	21.33	0.012
RT position	Supine	1.00	–	–	–
	Prone	1.06	0.26	4.41	0.93
Absolute V35	≤41.0	1.00	–	–	–
	>41.0	10.01	2.11	47.55	0.0038
Gender	Female	1.00	–	–	–
	Male	2.61	0.40	17.23	0.32
Absolute V35	≤41.0	1.00	–	–	–
	>41.0	9.05	1.86	43.93	0.0063
Race	White	1.00	–	–	–
	Other	0.83	0.14	5.12	0.84
Absolute V35	≤41.0	1.00	–	–	–

	Comparison	OR*	95% C.I. LL	95% C.I. UL	p-value†
	>41.0	9.84	2.05	47.20	0.0043
Zubrod	0	1.00	–	–	–
	1	3.25	0.52	20.30	0.21
Absolute V35	≤41.0	1.00	–	–	–
	>41.0	10.17	2.06	50.20	0.0044
RT position	Supine	1.00	–	–	–
	Prone	1.28	0.27	6.18	0.76
Absolute V40	≤30.4	1.00	–	–	–
	>30.4	5.29	1.36	20.54	0.016
Gender	Female	1.00	–	–	–
	Male	2.17	0.37	12.75	0.39
Absolute V40	≤30.4	1.00	–	–	–
	>30.4	5.04	1.20	21.22	0.027
Race	White	1.00	–	–	–
	Other	0.83	0.14	4.79	0.83
Absolute V40	≤30.4	1.00	–	–	–
	>30.4	5.11	1.31	19.98	0.019
Zubrod	0	1.00	–	–	–
	1	2.74	0.49	15.42	0.25
Absolute V40	≤30.4	1.00	–	–	–
	>30.4	5.30	1.35	20.75	0.017
RT position	Supine	1.00	–	–	–
	Prone	0.96	0.23	4.02	0.96

*Odds Ratio: An odds ratio of 1 indicates no difference between the two subgroups OR a 95% C.I. which includes 1 indicates no statistically significant difference between the variable levels. The variables were coded such that an OR > 1 indicates a greater chance of having an acute grade ≥ 2 GI.

†p-value from the Logistic regression model