

**DOSIMETRY AND GASTROINTESTINAL TOXICITY RELATIONSHIPS IN A PHASE 2 TRIAL OF PELVIC
LYMPH NODE RADIOTHERAPY IN ADVANCED LOCALISED PROSTATE CANCER.**

- SUPPLEMENTARY MATERIAL -

Table SUPP-1: IMRT trial dose-volume constraints for rectum and bowel.

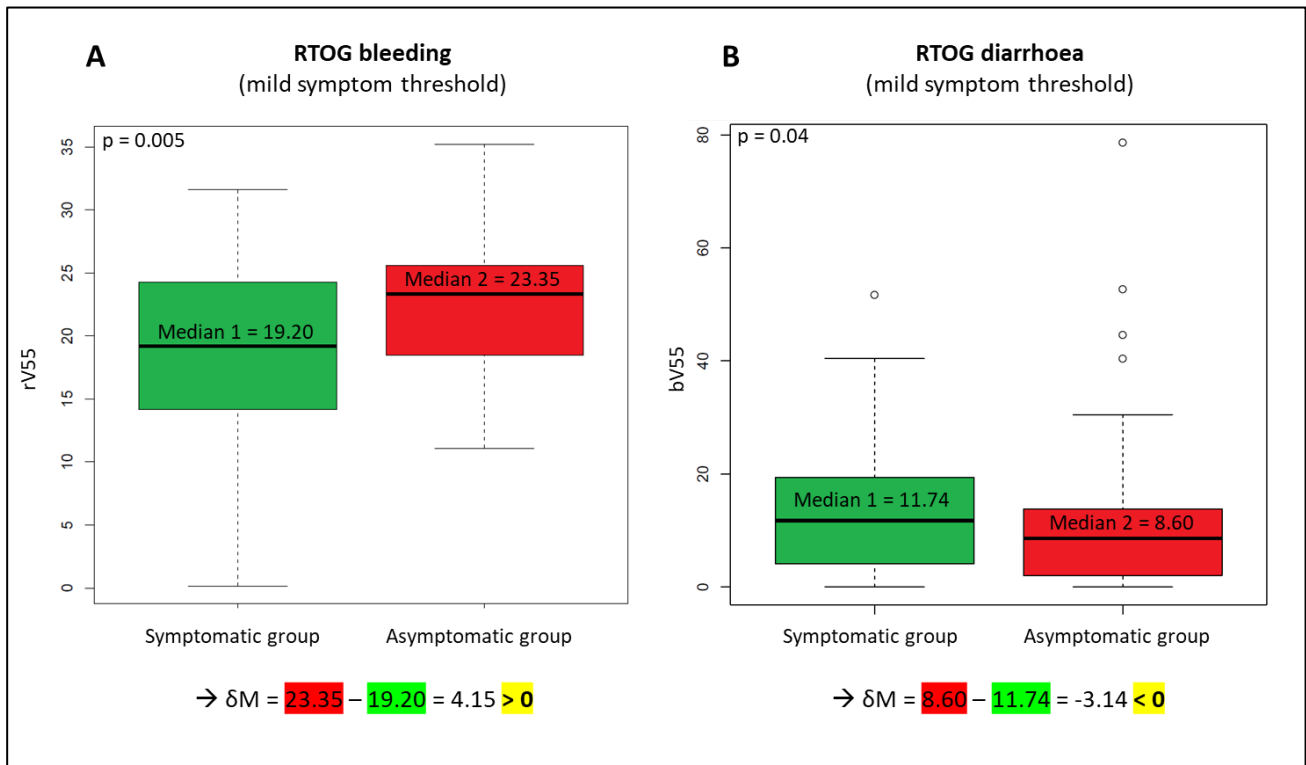
RECTUM				BOWEL			
2Gy/fraction		3Gy/fraction*		2Gy/fraction		3Gy/fraction*	
Dose constraint (Gy)	Volume required (%)	Dose constraint (Gy)	Volume required (%)	Dose constraint (Gy)	Volume required (cc) Mandatory (optimal)	Dose constraint (Gy)	Volume required (cc) Mandatory (optimal)
rV50	60	rV43	60	bV45	158 (78)	bV39	158 (78)
rV60	50	rV51	50	bV50	110 (17)	bV43	110 (17)
rV65	30	rV55	30	bV55	28 (14)	bV47	28 (14)
rV70	15	rV59	15	bV60	6 (0)	bV51	6 (0)
rV75	3	rV63	0	bV65	0 (0)	bV55	0 (0)

**Constraints for the 3Gy cohorts were simply extrapolated from the 2Gy cohort in a ratio of 60/70 (reflecting the initial prostate treatment dose of 70Gy) with no implicit radiobiological assumptions.*

Table SUPP-2: Toxicity thresholds for patient-reported outcomes.

CLINICIAN-REPORTED OUTCOMES			
Scale		Threshold	
		<i>Mild</i>	<i>Moderate/severe</i>
RTOG		NS: grade 0	NS: grade 0/1
		vs.	vs.
		S: grade 1+	S: grade 2+
LENT-SOM		NS: grade 0	NS: grade 0/1
		vs.	vs.
		S: grade 1+	S: grade 2+
PATIENT-REPORTED OUTCOMES			
Scale	Reported outcome (question number)	Threshold	
		<i>Mild</i>	<i>Moderate/severe</i>
UCLA-PCI	Rectal urgency (question 17)	NS: once a week or less	NS: more than once a week or less
		vs.	vs.
		S: at least more than once a week	S: at least once a day
	Loose/liquid stools (question 18)	NS: rarely or less	NS: about half the time or less
		vs.	vs.
		S: at least about half the time	S: at least usually
	Bowel distress (question 19)	NS: a little distress or less	NS: moderate distress or less
		vs.	vs.
		S: at least moderate distress	S: severe distress
	Crampy pain (question 20)	NS: about once a week or less	NS: several times a week or less
		vs.	vs.
		S: at least several times a week	S: at least about once a day
Bowel problem (question 21)	NS: very small problem or less	NS: small problem or less	
	vs.	vs.	
	S: at least small problem	S: at least moderate problem	

NS=Non-symptomatic group; S=Symptomatic group.



**Figure SUPP-1: Example of δM in two results where $p < 0.05$ (A: HFRT-4D, B: CFRT). $\delta M = \text{Median 2} - \text{Median 1}$.
 A: $\delta M = 4.15$, indicating that median $rv55$ is higher in patients with (red) than in patients without (green) symptoms.
 B: $\delta M = -3.14$, indicating that median $bv55$ is higher in patients without (green) than in patients with (red) symptoms.**

Table SUPP-3: Number of statistical tests used per toxicity scale by cohort (analysis of dosepoints/toxicity relationships).

	Rectum			Bowel		
	RTOG	LENT-SOM	UCLA-PCI	RTOG	LENT-SOM	UCLA-PCI
CFRT	32	52	36	12	15	27
HFRT-4D	32	56	40	12	24	30
HFRT-5D	32	56	36	12	18	27

Some dosepoints and toxicity endpoints were excluded as per the criteria included in the materials and methods section (subsections: "Radiation-induced GI toxicity data" and "Statistical considerations"), explaining differences in the number of statistical tests between cohorts.

Table SUPP-4: Numbers and proportions of patients failing rectum constraints in the CFRT cohort.

RECTUM CFRT	rV50	rV60	rV65	rV70	rV75
CONSTRAINTS (% of rectal volume)	60	50	30	15	3
MEAN volume	55.19 %	27.73 %	17.73 %	3.27 %	0.02%
Standard Deviation	11.84%	8.32%	6.71%	2.94%	0.20%
Number of patients failing constraint (total number)	50 (193)	0 (193)	3 (198)	0 (197)	0 (190)

Means and standard deviations are reported for reference.

All N/A values were excluded for analysis in a dosimetric dose-point by dose-point basis.

Table SUPP-5: Numbers and proportions of patients failing rectum constraints in the HFRT-4D cohort.

RECTUM HFRT-4D	rV43	rV51	rV55	rV59	rV63
CONSTRAINTS (% of rectal volume)	60	50	30	15	0
MEAN volume	49.67%	28.17%	20.43%	9.11%	0%
Standard Deviation	6.70%	6.90%	6.45%	3.40%	0%
Number of patients failing constraint (total number)	5 (119)	0 (119)	3 (119)	2 (119)	0 (119)

Means and standard deviations are reported for reference. All N/A values were excluded for analysis in a dosimetric dose-point by dose-point basis.

Table SUPP-6: Numbers and proportions of patients failing rectum constraints in the HFRT-5D cohort.

RECTUM HFRT-5D	rV43	rV51	rV55	rV59	rV63
CONSTRAINTS (% of rectal volume)	60	50	30	15	0
MEAN volume	52.12 %	28.05 %	20.19 %	8.79 %	0.002 %
Standard Deviation	6.63 %	7.25 %	6.40 %	3.53 %	0.01 %
Number of patients failing constraint (total number)	2 (53)	0 (53)	2 (53)	1 (53)	1 (53)

Means and standard deviations are reported for reference.

All N/A values were excluded for analysis in a dosimetric dose-point by dose-point basis.

Table SUPP-7: Numbers and proportions of patients failing bowel constraints in the CFRT cohort.

BOWEL CFRT	bV45	bV50	bV55	bV60	bV65
Optimal CONSTRAINTS (cc)	78	17	14	0	0
Mandatory CONSTRAINTS (cc)	158	110	28	6	0
MEAN volume (cc)	84.03	41.72	12.51	0.96	0.08
Standard Deviation	42.34	25.42	11.68	1.87	0.45
Number of patients failing optimal constraint (total number)	118 (236)	192 (236)	83 (236)	137 (232)	16 (229)
Number of patients failing mandatory constraint (total number)	12 (236)	2 (236)	22 (236)	2 (232)	16 (229)

Means and standard deviations are reported for reference.

All N/A values were excluded for analysis in a dosimetric dose-point by dose-point basis.

Table SUPP-8: Numbers and proportions of patients failing bowel constraints in the HFRT-4D cohort.

BOWEL HFRT-4D	bV39	bV43	bV47	bV51	bV55
Optimal CONSTRAINTS (cc)	78	17	14	0	0
Mandatory CONSTRAINTS (cc)	158	110	28	6	0
MEAN volume (cc)	75.33	29.39	3.13	0.85	0.35
Standard Deviation	37.26	17.63	3.92	2.28	1.35
Number of patients failing optimal constraint (total number)	47 (119)	87 (119)	2 (119)	38 (119)	22 (119)
Number of patients failing mandatory constraint (total number)	0 (119)	0 (119)	0 (119)	4 (119)	22 (119)

Means and standard deviations are reported for reference.

All N/A values were excluded for analysis in a dosimetric dose-point by dose-point basis.

Table SUPP-9: Numbers and proportions of patients failing bowel constraints in the HFRT-5D cohort.

BOWEL HFRT-5D	bV39	bV43	bV47	bV51	bV55
Optimal CONSTRAINTS (cc)	78	17	14	0	0
Mandatory CONSTRAINTS (cc)	158	110	28	6	0
MEAN volume (cc)	90.74	38.24	4.38	0.65	0.20
Standard Deviation	38.10	19.41	4.11	1.52	0.62
Number of patients failing optimal constraint (total number)	28 (53)	48 (53)	2 (53)	17 (53)	9 (53)
Number of patients failing mandatory constraint (total number)	4 (53)	1 (53)	0 (53)	1 (53)	9 (53)

Means and standard deviations are reported for reference.

All N/A values were excluded for analysis in a dosimetric dose-point by dose-point basis.

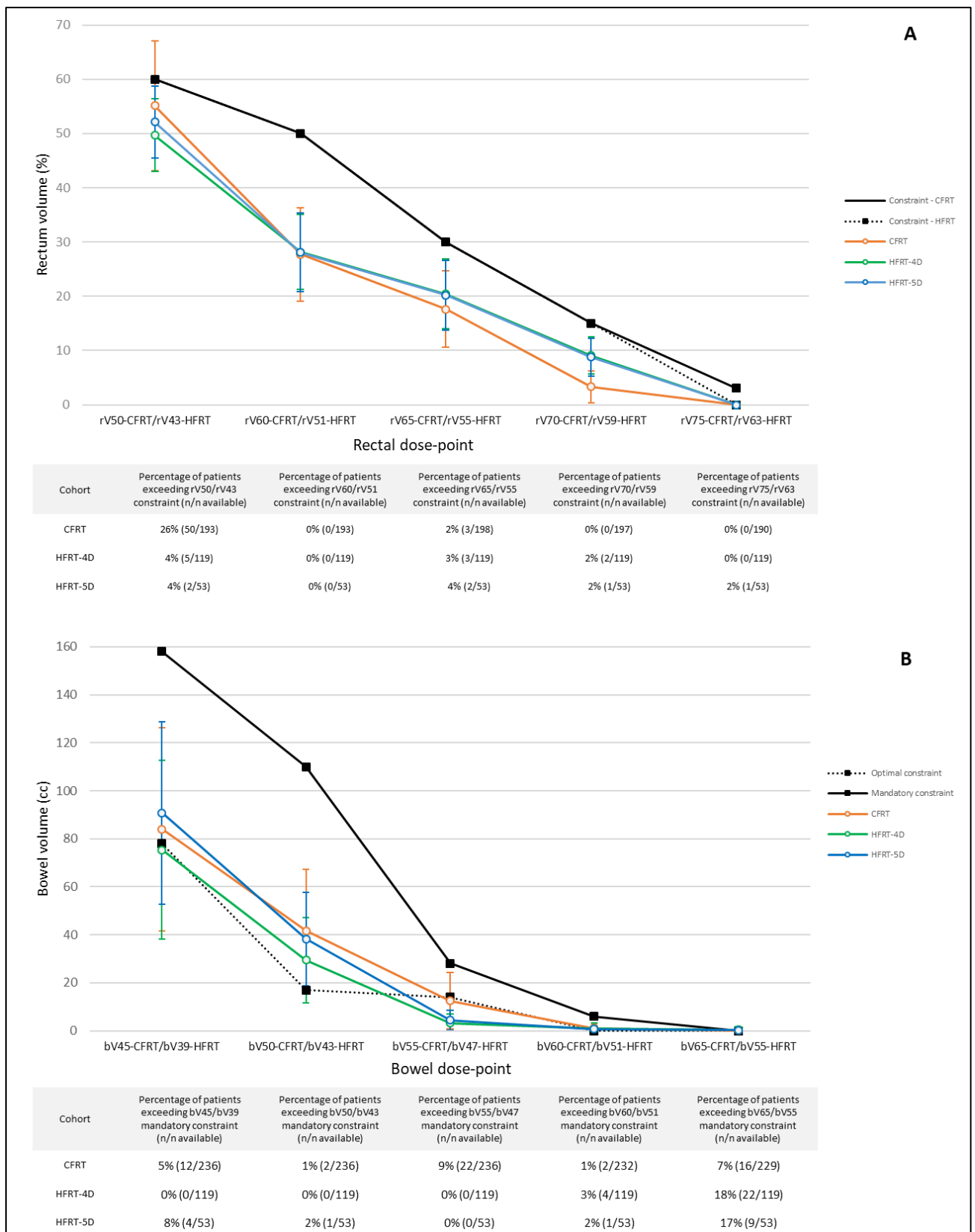


Figure SUPP-2: Mean volumes per dose-point by cohort and relationship with dose-volume constraints for rectum (A) and bowel (B). Error bars represent standard deviations. Constraint curves (black) are illustrative.

Table SUPP-10: Proportions of δM by organ and toxicity scale.

RECTUM									
δM	RTOG			LENT-SOM			UCLA-PCI		
	CFRT	HFRT4D	HFRT5D	CFRT	HFRT4D	HFRT5D	CFRT	HFRT4D	HFRT5D
$\delta M < -5\%$	0.0	0.0	3.1	0.0	8.9	0.0	0.0	0.0	0.0
$-5 < \delta M \leq -4\%$	0.0	0.0	0.0	0.0	1.8	0.0	0.0	0.0	0.0
$-4 < \delta M \leq -3\%$	0.0	0.0	0.0	1.9	0.0	5.4	0.0	2.5	2.8
$-3 < \delta M \leq -2\%$	3.1	6.3	0.0	3.8	5.4	1.8	0.0	10.0	8.3
$-2 < \delta M \leq -1\%$	3.1	9.4	3.1	3.8	8.9	3.6	2.8	22.5	8.3
$-1 < \delta M \leq 0\%$	25.0	25.0	12.5	17.3	10.7	3.6	33.3	12.5	8.3
$0 < \delta M \leq 1\%$	25.0	9.4	18.8	25.0	23.2	14.3	8.3	12.5	13.9
$1 < \delta M \leq 2\%$	21.9	28.1	25.0	17.3	17.9	21.4	27.8	17.5	11.1
$2 < \delta M \leq 3\%$	12.5	6.3	12.5	5.8	17.9	14.3	16.7	12.5	19.4
$3 < \delta M \leq 4\%$	6.3	12.5	12.5	9.6	5.4	17.9	5.6	5.0	13.9
$4 < \delta M \leq 5\%$	0.0	3.1	9.4	5.8	0.0	7.1	5.6	5.0	0.0
$5 < \delta M \leq 6\%$	0.0	0.0	3.1	7.7	0.0	10.7	0.0	0.0	5.6
$\delta M > 6\%$	3.1	0.0	0.0	1.9	0.0	0.0	0.0	0.0	8.3

BOWEL									
δM	RTOG			LENT-SOM			UCLA-PCI		
	CFRT	HFRT4D	HFRT5D	CFRT	HFRT4D	HFRT5D	CFRT	HFRT4D	HFRT5D
$\delta M \leq -25\text{cc}$	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
$-25 < \delta M \leq -20\text{ cc}$	0.0	0.0	0.0	0.0	0.0	0.0	3.7	0.0	0.0
$-20 < \delta M \leq -15\text{ cc}$	0.0	0.0	0.0	0.0	0.0	0.0	3.7	0.0	14.8
$-15 < \delta M \leq -10\text{ cc}$	8.3	0.0	0.0	13.3	0.0	0.0	14.8	0.0	3.7
$-10 < \delta M \leq -5\text{ cc}$	16.7	0.0	8.3	26.7	8.3	0.0	18.5	0.0	18.5
$-5 < \delta M \leq 0\text{ cc}$	41.7	16.7	41.7	20.0	12.5	33.3	29.6	0.0	37.0
$0 < \delta M \leq 5\text{ cc}$	25.0	25.0	16.7	26.7	37.5	33.3	25.9	44.4	3.7
$5 < \delta M \leq 10\text{ cc}$	0.0	16.7	25.0	0.0	20.8	0.0	3.7	25.9	11.1
$10 < \delta M \leq 15\text{ cc}$	0.0	8.3	8.3	0.0	4.2	11.1	0.0	14.8	11.1
$15 < \delta M \leq 20\text{ cc}$	8.3	8.3	0.0	6.7	4.2	11.1	0.0	3.7	0.0
$20 < \delta M \leq 25\text{ cc}$	0.0	8.3	0.0	0.0	8.3	0.0	0.0	7.4	0.0
$\geq 25\text{ cc}$	0.0	16.7	0.0	6.7	4.2	11.1	0.0	3.7	0.0

All results are % unless otherwise indicated.

1 – DOSE-VOLUME ASSOCIATIONS - RECTUM

A - Rectum RTOG (TABLES R1-3)

		RTOG item ->	Bowel frequency		Rectal bleeding		Diarrhoea		Proctitis		
		Symptom threshold ->	MS	M	MS	M	MS	M	MS	M	
TABLE R1 CFRT	N	Symptomatic patients (n)	19	76	18	62	27	67	20	66	
		Non-symptomatic patients (n)	179	122	172	128	178	138	185	139	
		NA patients	7	7	15	15	0	0	0	0	
		TOTAL	205	205	205	205	205	205	205	205	
		rV50	p	0.90	0.09	0.00	0.15	0.90	0.59	0.31	0.36
			δM	-0.60	1.20	7.10	0.90	-1.10	-2.40	1.90	-0.10
		rV60	p	0.25	0.01	0.18	0.49	0.94	1.00	0.48	0.82
			δM	2.60	3.85	1.85	0.80	-0.31	-0.05	1.40	0.60
		rV65	p	0.24	0.06	0.35	0.42	0.94	0.96	0.48	0.99
	δM		2.10	2.56	3.10	2.80	1.45	1.45	1.90	0.15	
	rV70	p	0.71	0.88	1.00	0.80	0.82	0.57	0.64	0.97	
		δM	0.40	0.24	0.00	-0.20	0.28	0.00	0.70	-0.15	

LEGEND FOR ALL TABLES:

Symptom thresholds:

- M = mild threshold
- MS = moderate/severe threshold

Where highlighted in green, a positive association ($\delta M > 0$ and $p \leq 0.05$) was found.

Where highlighted in yellow, $p \leq 0.05$ but $\delta M = 0.00$ (minimal difference between groups).

Where highlighted in red, $p \leq 0.05$ but $\delta M < 0$ (defined as non-biologically plausible).

TABLE R2 HFRT-4D	RTOG item ->		Bowel frequency		Rectal bleeding		Diarrhoea		Proctitis	
	Symptom threshold ->		MS	M	MS	M	MS	M	MS	M
	N	Symptomatic patients (n)	12	30	8	46	10	29	13	36
Non-symptomatic patients (n)		95	77	97	59	103	84	100	77	
NA patients		7	7	9	9	1	1	1	1	
TOTAL		114	114	114	114	114	114	114	114	
rV43	p	0.77	0.71	0.56	0.10	0.78	0.22	0.60	0.46	
	δM	0.32	-0.40	3.48	3.13	-0.68	1.80	1.80	2.06	
rV51	p	0.16	0.80	1.00	0.02	0.73	0.98	1.00	0.81	
	δM	0.32	-0.40	3.48	3.13	-0.68	1.80	1.80	2.06	
rV55	p	0.41	0.50	0.55	0.00	0.79	0.72	0.60	0.92	
	δM	-2.40	1.64	1.56	4.15	-2.55	1.60	1.35	0.95	
rV59	p	0.64	0.49	0.94	0.09	0.79	0.22	0.54	0.33	
	δM	-0.75	-0.52	-0.50	1.34	-1.45	-1.85	-0.88	-1.13	

RTOG item ->	Bowel frequency		Rectal bleeding		Diarrhoea		Proctitis			
	Symptom threshold ->		MS	M	MS	M	MS	M		
	N	Symptomatic patients (n)	7	15	4	22	6	15	3	27
Non-symptomatic patients (n)		41	33	42	24	43	34	46	22	
NA patients		1	1	3	3	0	0	0	0	
TOTAL		49	49	49	49	49	49	49	49	
TABLE R3 HFRT-5D	rV43	p	0.84	0.56	0.84	0.68	0.21	0.69	0.53	0.34
		δM	-0.27	1.35	-0.37	0.17	4.30	1.45	1.45	3.05
	rV51	p	0.73	0.18	0.86	0.23	0.82	0.57	0.16	0.13
		δM	1.06	4.56	-1.70	3.10	1.10	-0.35	5.10	4.90
	rV55	p	0.45	0.23	0.81	0.12	0.65	0.91	0.37	0.15
		δM	3.50	2.85	1.70	2.88	-1.34	0.68	2.38	3.23
	rV59	p	0.56	0.20	0.30	0.12	0.92	0.58	0.48	0.00
		δM	0.55	1.50	0.65	1.85	-0.21	0.40	0.42	2.30

B - Rectum LENT/SOM (TABLES R 4-6)

	LENT SOM item ->		Tenesmus (subjective)		Mucosal loss (subjective)		Frequency (subjective)		Sphincter control (subjective)		Pain (subjective)	Bleeding (objective)		Tenesmus and frequency (management)	
	Symptom threshold ->		MS	M	MS	M	MS	M	MS	M	M	MS	M	MS	M
TABLE R4 CFRT	N	Symptomatic patients (n)	18	56	12	43	13	64	11	37	13	16	42	12	23
		Non-symptomatic patients (n)	184	146	192	161	183	132	193	167	191	178	152	192	181
		NA patients	3	3	1	1	9	9	1	1	1	11	11	1	1
		TOTAL	205	205	205	205	205	205	205	205	205	205	205	205	205
TABLE R4 CFRT	rV50	p	0.74	0.58	0.18	0.10	0.96	0.84	0.32	0.44	0.81	0.00	0.04	0.81	0.26
		δM	-2.15	-0.70	1.15	0.15	-2.25	0.10	5.25	-0.25	-0.45	8.50	1.75	-1.60	-3.80
	rV60	p	0.52	0.13	0.00	0.00	0.80	0.38	0.22	0.01	0.91	0.04	0.26	0.41	0.62
		δM	0.75	2.25	4.95	3.30	0.90	1.26	3.30	3.21	-0.10	5.23	1.11	1.20	0.75
	rV65	p	0.65	0.29	0.01	0.00	0.82	0.77	0.47	0.04	0.75	0.05	0.14	0.48	0.80
		δM	0.74	2.73	5.54	4.30	1.40	1.05	3.20	4.10	-1.00	5.69	3.45	2.50	1.50
	rV70	p	0.66	0.68	0.17	0.23	0.47	0.30	0.60	0.54	0.28	0.22	0.48	0.95	0.77
		δM	-0.10	-0.30	0.60	0.61	0.50	-0.67	0.80	0.55	-0.60	1.20	0.67	-0.35	0.28

LENT SOM item ->		Tenesmus (subjective)		Mucosal loss (subjective)		Frequency (subjective)		Sphincter control (subjective)		Pain (subjective)	Bleeding (objective)		Tenesmus and frequency (management)		Bleeding (management)
		MS	M	MS	M	MS	M	MS	M	M	MS	M	MS	M	M
N	Symptomatic patients (n)	11	36	6	25	13	36	7	28	11	17	33	11	21	16
	Non-symptomatic patients (n)	103	78	108	89	97	74	107	86	100	92	76	103	93	98
	NA patients	0	0	0	0	4	4	0	0	3	5	5	0	0	0
	TOTAL	114	114	114	114	114	114	114	114	114	114	114	114	114	114
rV43	p	0.70	0.34	0.76	0.07	0.76	0.13	0.18	0.47	0.27	0.83	0.79	0.78	0.94	0.72
	δM	-0.30	1.91	-1.23	2.60	2.05	2.74	-2.15	1.00	3.60	0.19	0.29	-0.06	-0.80	-1.45
rV51	p	0.19	0.76	0.32	0.04	0.42	0.42	0.89	0.58	0.30	0.65	0.86	0.19	0.20	0.34
	δM	-7.10	0.10	2.02	2.83	0.80	2.85	1.10	-0.15	0.70	1.60	1.27	-7.00	-4.20	0.23
rV55	p	0.23	0.49	0.20	0.03	0.78	0.21	0.98	0.84	0.38	0.34	0.45	0.37	0.40	0.10
	δM	-6.45	1.26	2.90	3.90	1.40	3.30	1.40	0.51	1.11	2.00	1.45	-6.10	-5.60	0.98
rV59	p	0.12	0.67	0.89	0.21	0.73	0.56	0.27	0.33	0.45	0.71	0.57	0.21	0.42	0.03
	δM	-1.80	-0.73	0.50	2.05	-0.40	0.86	-2.27	-1.23	1.84	0.17	0.17	-2.70	-1.80	2.43

LENT SOM item ->		Tenesmus (subjective)		Mucosal loss (subjective)		Frequency (subjective)		Sphincter control (subjective)		Pain (subjective)	Bleeding (objective)		Tenesmus and frequency (management)		Bleeding (management)	
		MS	M	MS	M	MS	M	MS	M	M	MS	M	MS	M	M	
N	Symptomatic patients (n)	10	19	3	14	4	20	5	10	3	12	18	6	8	5	
	Non-symptomatic patients (n)	39	30	46	35	45	29	44	39	46	34	28	42	40	44	
	NA patients	0	0	0	0	0	0	0	0	0	3	3	1	1	0	
	TOTAL	49	49	49	49	49	49	49	49	49	49	49	49	49	49	49
rV43	p	0.24	0.58	0.88	0.55	0.41	0.40	0.34	0.43	0.27	0.70	0.57	0.17	0.26	0.68	
	δM	1.15	1.05	0.79	-0.38	4.20	1.35	1.35	1.45	5.99	1.75	-0.70	2.50	2.50	0.65	
rV51	p	0.18	0.01	0.95	0.20	0.62	0.06	0.13	0.26	0.45	0.53	0.19	0.53	0.14	0.17	
	δM	4.07	5.92	0.70	4.15	-3.15	5.91	5.90	4.00	-3.75	3.11	4.69	2.26	5.17	5.30	
rV55	p	0.31	0.01	0.40	0.10	0.61	0.19	0.42	0.46	0.26	0.32	0.10	0.93	0.33	0.53	
	δM	2.65	3.74	3.88	3.55	-1.34	3.10	3.88	0.76	-2.92	2.70	3.38	0.23	3.40	1.98	
rV59	p	0.13	0.01	0.02	0.07	0.24	0.05	0.11	0.39	0.42	0.04	0.25	0.25	0.18	0.73	
	δM	1.36	2.25	3.90	2.39	-3.25	1.86	0.90	0.45	-1.48	2.66	1.91	1.16	1.26	0.52	

C - Rectum UCLA-PCI (TABLES R7-9)

UCLA item ->	Bowel urgency		Loose stools		Bowel distress	Crampy abdominal pain		Bowel problem			
	MS	M	MS	M	M	MS	M	MS	M		
N	Symptomatic patients (n)	43	61	29	63	42	15	32	41	81	
	Non-symptomatic patients (n)	118	100	134	100	137	155	138	143	103	
	NA patients	23	23	21	21	5	14	14	0	0	
	TOTAL	184	184	184	184	184	184	184	184	184	
TABLE R7 CFRT	rV50	p	0.04	0.00	0.40	0.81	0.17	0.06	0.02	0.20	0.03
		δM	2.75	4.50	-1.75	-0.05	1.00	4.35	3.20	1.80	2.35
	rV60	p	0.33	0.28	0.56	0.94	0.34	0.95	0.24	0.73	0.28
		δM	2.00	2.30	1.06	1.55	2.30	0.15	2.15	1.50	3.35
	rV65	p	0.49	0.23	0.66	0.54	0.73	0.66	0.40	0.77	0.53
		δM	1.75	2.80	0.00	1.50	1.70	-0.40	1.68	1.00	1.70
	rV70	p	0.34	0.67	0.18	0.19	0.88	0.45	0.56	0.52	0.44
		δM	-0.46	-0.25	-0.65	-0.79	-0.10	-0.20	-0.28	-0.10	-0.20

UCLA item ->	Bowel urgency		Loose stools		Bowel distress		Crampy abdominal pain		Bowel problem			
	MS	M	MS	M	MS	M	MS	M	MS	M		
N	Symptomatic patients (n)	47	34	12	34	6	32	12	20	37	51	
	Non-symptomatic patients (n)	37	50	68	46	87	61	71	63	58	44	
	NA patients	11	11	15	15	2	2	12	12	0	0	
	TOTAL	95	95	95	95	95	95	95	95	95	95	
TABLE R8 HFRT-4D	rV43	p	0.33	0.33	0.99	0.03	0.71	0.95	0.96	0.71	0.71	0.40
		δM	-2.29	-2.84	-2.24	4.56	-2.65	-0.86	-1.31	-1.06	-1.74	1.62
	rV51	p	0.47	0.29	0.50	0.24	0.85	0.96	0.93	0.34	0.76	0.80
		δM	-1.09	-1.85	3.12	2.90	-3.10	1.36	0.95	2.75	1.68	1.04
	rV55	p	0.40	0.16	0.28	0.28	0.98	0.76	0.95	0.34	0.81	0.96
		δM	0.84	-1.10	4.49	3.62	-1.40	1.28	2.15	2.84	2.97	1.54
	rV59	p	0.17	0.03	0.66	0.82	0.70	0.05	0.84	0.80	0.34	0.49
		δM	-0.60	-1.64	1.92	0.57	0.41	-1.68	-0.22	0.55	-0.25	-0.55

UCLA item ->		Bowel urgency		Loose stools		Bowel distress	Crampy abdominal pain		Bowel problem		
		MS	M	MS	M	M	MS	M	MS	M	
N	Symptomatic patients (n)	24	20	8	16	13	6	14	15	25	
	Non-symptomatic patients (n)	16	20	32	24	32	35	27	30	20	
	NA patients	5	5	5	5	0	4	4	0	0	
	TOTAL	45	45	45	45	45	45	45	45	45	
TABLE R9 HFRT-5D	rV43	p	0.63	0.31	0.50	0.67	0.97	0.01	0.13	0.95	0.45
		δM	0.99	2.05	2.40	-0.91	0.44	5.20	3.10	0.44	-1.35
	rV51	p	0.57	0.95	0.11	0.47	0.18	0.75	0.60	0.37	0.49
		δM	-3.39	-0.65	7.15	5.03	6.51	1.10	3.50	6.21	-2.99
	rV55	p	0.35	0.54	0.24	0.71	0.24	0.73	0.89	0.48	0.27
		δM	-2.12	0.08	3.50	3.10	3.00	2.85	1.70	2.60	-2.60
	rV59	p	0.46	0.42	0.04	0.50	0.06	0.87	0.96	0.12	0.40
		δM	-1.70	0.45	4.00	1.25	2.67	-1.00	0.00	2.15	1.55

2 - DOSE-VOLUME ASSOCIATIONS - BOWEL

A - Bowel RTOG (TABLES B1-3)

RTOG item ->	Bowel frequency		Diarrhoea		
	MS	M	MS	M	
Symptom threshold ->					
N	Symptomatic patients (n)	19	76	27	67
	Non-symptomatic patients (n)	179	122	178	138
	NA patients	7	7	0	0
	TOTAL	205	205	205	205
bV45	p	0.04	0.83	0.25	0.77
	δM	16.96	-0.95	-14.20	1.28
bV50	p	0.08	0.62	0.19	0.33
	δM	3.29	-4.39	-8.51	-6.50
bV55	p	0.03	0.30	0.36	0.04
	δM	3.80	-1.60	-0.80	-3.14

LEGEND FOR ALL TABLES:

Symptom thresholds:

- M = mild threshold
- MS = moderate/severe threshold

Where highlighted in **green**, a positive association ($\delta M > 0$ and $p \leq 0.05$) was found.

Where highlighted in **yellow**, $p \leq 0.05$ but $\delta M = 0.00$ (minimal difference between groups).

Where highlighted in **red**, $p \leq 0.05$ but $\delta M < 0$ (defined as non-biologically plausible).

	RTOG item ->		Bowel frequency		Diarrhoea	
	Symptom threshold ->		MS	M	MS	M
TABLE B2 HFRT-4D	N	Symptomatic patients (n)	12	31	10	30
		Non-symptomatic patients (n)	100	81	108	88
		NA patients	7	7	1	1
		TOTAL	119	119	119	119
	bV39	p	0.04	0.48	0.09	0.03
		δM	27.17	6.68	28.20	17.32
	bV43	p	0.11	0.59	0.03	0.01
		δM	11.60	-2.50	24.50	7.39
	bV47	p	0.76	0.62	0.34	0.00
		δM	1.07	-0.70	1.71	2.15

	RTOG item ->		Bowel frequency		Diarrhoea	
	Symptom threshold ->		MS	M	MS	M
TABLE B3 HFRT-5D	N	Symptomatic patients (n)	7	15	6	15
		Non-symptomatic patients (n)	41	33	43	34
		NA patients	1	1	0	0
		TOTAL	49	49	49	49
	bV39	p	0.89	1.00	0.73	0.76
		δM	-6.40	-4.00	5.60	3.07
	bV43	p	0.33	0.23	0.64	0.63
		δM	12.90	5.20	6.11	1.34
	bV47	p	0.53	0.51	0.31	0.29
		δM	-1.70	-2.27	-1.55	-0.31

B - Bowel LENT/SOM (TABLES B4-6)

	LENT SOM item ->		Frequency (subjective)	Consistency (subjective)		Consistency and frequency (management)	
	Symptom threshold ->		M	MS	M	MS	M
TABLE B4 CFRT	N	Symptomatic patients (n)	57	30	45	12	19
		Non-symptomatic patients (n)	139	171	156	192	185
		NA patients	9	4	4	1	1
		TOTAL	205	205	205	205	205
	bV45	p	0.90	0.34	0.11	0.02	0.19
		δM	-8.78	-10.95	-12.85	52.70	-4.50
	bV50	p	1.00	0.26	0.17	0.10	0.37
		δM	-5.90	-6.80	-9.25	15.20	-0.60
	bV55	p	0.35	0.96	0.50	0.35	0.40
		δM	1.60	1.30	-2.10	3.39	3.37

	LENT SOM item ->		Frequency (subjective)		Consistency (subjective)		Pain (subjective)	Constipation (subjective)	Consistency and frequency (management)	
	Symptom threshold ->		MS	M	MS	M	M	M	MS	M
TABLE B5 HFRT-4D	N	Symptomatic patients (n)	15	34	11	28	7	13	12	19
		Non-symptomatic patients (n)	97	78	102	85	107	100	102	95
		NA patients	2	2	1	1	0	1	0	0
		TOTAL	114	114	114	114	114	114	114	114
	bV39	p	0.02	0.03	0.28	0.14	0.59	0.72	0.06	0.15
		δM	27.50	17.66	23.40	14.51	-7.84	-8.77	24.82	5.84
	bV43	p	0.07	0.29	0.04	0.06	0.80	0.95	0.27	0.30
		δM	9.06	2.58	8.33	6.41	-0.90	5.12	1.15	1.10
	bV47	p	0.35	0.23	0.41	0.28	0.67	0.54	0.74	0.42
		δM	0.83	0.78	-0.45	0.60	-0.40	1.85	0.77	0.89

	LENT SOM item ->		Frequency (subjective)		Consistency (subjective)		Consistency and frequency (management)	
	Symptom threshold ->		MS	M	MS	M	MS	M
TABLE B6 HFRT-5D	N	Symptomatic patients (n)	5	14	8	12	7	9
		Non-symptomatic patients (n)	40	31	38	34	41	39
		NA patients	4	4	3	3	1	1
		TOTAL	49	49	49	49	49	49
	bV39	p	0.69	0.31	0.06	0.05	0.67	0.53
		δM	3.04	2.18	29.90	32.59	3.60	3.60
	bV43	p	0.33	0.05	0.04	0.03	0.61	0.47
		δM	12.85	13.48	18.76	15.99	1.90	1.90
	bV47	p	0.93	0.62	0.70	0.65	0.30	0.45
		δM	-0.81	-2.07	-2.19	-1.89	-2.17	-2.17

C - Bowel UCLA-PCI (TABLES B7-9)

UCLA item ->	Bowel urgency		Loose stools		Bowel distress	Crampy abdominal pain		Bowel problem			
	MS	M	MS	M	M	MS	M	MS	M		
N	Symptomatic patients (n)	43	61	29	63	42	15	32	41	81	
	Non-symptomatic patients (n)	118	100	134	100	137	155	138	143	103	
	NA patients	23	23	21	21	5	14	14	0	0	
	TOTAL	184	184	184	184	184	184	184	184	184	
TABLE B7 CFRT	bV45	p	0.55	0.87	0.86	0.56	0.32	0.09	0.34	0.88	0.23
		δM	-1.24	7.30	3.94	-11.28	-10.50	-20.00	-11.40	-9.18	-15.20
	bV50	p	0.73	0.86	0.54	0.39	0.23	0.20	0.49	0.63	0.14
		δM	0.60	0.60	-3.27	-6.03	-8.35	-7.60	-3.86	-5.47	-11.70
	bV55	p	0.51	0.97	0.84	0.85	0.94	0.70	0.79	0.40	0.46
		δM	-1.20	1.00	-0.10	0.70	0.45	-1.00	-1.53	1.20	-0.50

UCLA item ->		Bowel urgency		Loose stools		Bowel distress		Crampy abdominal pain		Bowel problem		
		MS	M	MS	M	MS	M	MS	M	MS	M	
TABLE B8 HFRT-4D	N	Symptom threshold ->										
		Symptomatic patients (n)	28	34	12	34	6	32	12	20	37	51
		Non-symptomatic patients (n)	56	50	68	46	87	61	71	63	58	44
		NA patients	11	11	15	15	2	2	12	12	0	0
	TOTAL	95	95	95	95	95	95	95	95	95	95	95
	bV39	p	0.15	0.24	0.28	0.01	0.70	0.34	0.10	0.41	0.04	0.04
		δM	18.47	8.27	20.85	24.78	7.45	4.59	28.55	6.13	14.21	10.50
	bV43	p	0.01	0.01	0.06	0.00	0.22	0.04	0.09	0.08	0.00	0.00
		δM	8.80	7.04	9.90	11.74	1.19	4.10	11.15	6.80	12.22	11.37
	bV47	p	0.03	0.07	0.36	0.05	0.14	0.11	0.30	0.35	0.02	0.15
		δM	1.54	1.29	0.60	0.07	3.63	1.33	1.89	1.33	2.01	0.66

	UCLA item ->		Bowel urgency		Loose stools		Bowel distress	Crampy abdominal pain		Bowel problem	
	Symptom threshold ->		MS	M	MS	M	M	MS	M	MS	M
TABLE B9 HFRT-5D	N	Symptomatic patients (n)	15	20	8	16	13	6	14	15	25
		Non-symptomatic patients (n)	25	20	32	24	32	35	27	30	20
		NA patients	5	5	5	5	0	4	4	0	0
		TOTAL	45	45	45	45	45	45	45	45	45
	bV39	p	0.11	0.30	0.38	0.26	0.99	0.73	0.58	0.78	0.74
		δM	-19.90	-15.95	-16.37	13.62	5.42	5.35	13.63	-11.78	-16.12
	bV43	p	0.08	0.23	0.43	0.30	0.19	0.58	0.90	0.19	0.15
		δM	-6.27	-8.29	-5.53	10.95	-4.48	8.73	-1.95	-5.13	-8.54
	bV47	p	0.02	0.04	0.18	0.33	0.89	0.41	0.68	0.73	0.67
		δM	-3.40	-3.50	-3.03	1.12	-1.61	-2.10	-1.05	-0.41	-0.98

Table SUPP-11: Results of ROC analysis: new constraints derived using the IMRT for Prostate Cancer Study dataset.

CONSTRAINT	ENDPOINT	COHORT	AUC	CI (lower-upper)	Constraint	Specificity	Sensitivity
rV50	RTOG bleeding (moderate/severe threshold)	CFRT	0.79	0.69-0.89	58.9%	0.72	0.78
bV43	UCLA loose stools (mild threshold)	HFRT-4D	0.66	0.55-0.77	31.11cc	0.72	0.57
bV47	RTOG diarrhoea (mild threshold)	HFRT-4D	0.69	0.60-0.79	2.15cc	0.63	0.70

AUC = area under the curve. CI = confidence interval.

Table SUPP-12: Odds ratios for toxicity using protocol or new (data-derived) constraints.

Item	Constraint	OR	95% CI	P value	Interpretation
rV50 and MS RTOG bleeding (CFRT)	Protocol constraint 60% of rectal volume	7.09	2.54-22.05	0.0002	The odds of MS RTOG bleeding are 7.09 higher when the rV50 protocol constraint is exceeded.
	Data-derived constraint 59% of rectal volume	6.84	2.40-22.85	0.0002	The odds of MS RTOG bleeding are 6.84 higher when the rV50 data-derived constraint is exceeded.
rV50 and MS LENT-SOM bleeding (CFRT)	Protocol constraint 60% of rectal volume	7.14	2.42-24.36	0.0003	The odds of MS LENT-SOM bleeding are 7.14 higher when the rV50 protocol constraint is exceeded.
	Data-derived constraint 59% of rectal volume	7.41	2.42-28.39	0.0003	The odds of MS LENT-SOM bleeding are 7.41 higher when the rV50 data-derived constraint is exceeded.
bV43 and M UCLA-PCI loose stools (HFRT-4D)	Protocol optimal constraint 17cc of bowel	0.00	0.00-1.96	0.07	The odds of M UCLA-PCI loose stools can not be calculated because all patients met the protocol constraint.
	Data-derived constraint 24cc of bowel	3.81	1.59-9.80	0.003	The odds of M UCLA-PCI loose stools are 3.81 higher when the bV43 data-derived constraint is exceeded.
bV47 and M RTOG diarrhoea (HFRT-4D)	Protocol optimal constraint 14cc of bowel	5.51	1.79-21.49	0.003	The odds of M RTOG diarrhoea are 5.51 higher when the bV47 protocol constraint is exceeded.
	Data-derived constraint 2.15cc of bowel	9.40	3.24-32.59	0.000001	The odds of M RTOG diarrhoea are 9.40 higher when the bV47 data-derived constraint is exceeded.

M = mild toxicity threshold. MS = moderate/severe toxicity threshold. OR = odds ratio. CI = confidence interval. cc = cubic centimetres. P values were obtained with Fisher's exact test. No patients exceeded the mandatory bowel constraints for bV43 or bV47 so OR were not calculated.

SUPPLEMENTARY TEXT

Contouring guidelines for bowel and rectum:

- **Rectum:** The rectum was contoured as a solid organ from the anus (usually at the level of the ischial tuberosities or 1cm below the lower margin of the PTV, whichever was more inferior) to the recto-sigmoid junction.
- **Bowel:** Bowel was outlined separately by outlining bowel loops as a solid organ, excluding rectum and extending 2cm above the superior extent of PTV2. PTV2 included pelvic lymph nodes and uninvolved seminal vesicles with a further 0.5 cm margin.