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CLINICAL INVESTIGATION Prostate

DOSE–VOLUME CONSTRAINTS TO REDUCE RECTAL SIDE EFFECTS FROM PROSTATE RADIOTHERAPY: EVIDENCE FROM MRC RT01 TRIAL ISRCTN 47772397

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Purpose: Radical radiotherapy for prostate cancer is effective but dose limited because of the proximity of normal tissues. Comprehensive dose–volume analysis of the incidence of clinically relevant late rectal toxicities could indicate how the dose to the rectum should be constrained. Previous emphasis has been on constraining the mid-to-high dose range (≥50 Gy). Evidence is emerging that lower doses could also be important.

Methods and Materials: Data from a large multicenter randomized trial were used to investigate the correlation between seven clinically relevant rectal toxicity endpoints (including patient- and clinician-reported outcomes) and an absolute 5% increase in the volume of rectum receiving the specified doses. The results were quantified using odds ratios. Rectal dose–volume constraints were applied retrospectively to investigate the association of constraints with the incidence of late rectal toxicity.

Results: A statistically significant dose–volume response was observed for six of the seven endpoints for at least one of the dose levels tested in the range of 30–70 Gy. Statistically significant reductions in the incidence of these late rectal toxicities were observed for the group of patients whose treatment plans met specific proposed dose–volume constraints. The incidence of moderate/severe toxicity (any endpoint) decreased incrementally for patients whose treatment plans met increasing numbers of dose–volume constraints from the set of V30≤80%, V40≤65%, V50≤55%, V60≤40%, V65≤30%, V70≤15%, and V75≤3%.

Conclusion: Considering the entire dose distribution to the rectum by applying dose–volume constraints such as those tested here in the present will reduce the incidence of late rectal toxicity. © 2010 Elsevier Inc.

Prostate radiotherapy, rectal complications, late toxicity, dose–volume constraints.

INTRODUCTION

Late normal tissue effects limit the dose that can be safely delivered during radical prostate radiotherapy (RT), but Phase III dose-escalation trials have demonstrated an advantage in disease control using higher doses (1–4). Conformal and intensity-modulated RT techniques limit the volume of normal tissue treated; however, to take full advantage of these methods, accurate knowledge of the dose response of the normal tissues is required. The side effects of RT in the rectum significantly affect patients, and many attempts

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have been made to link dosimetric parameters to the risk of developing late rectal toxicity (5–10).

The Medical Research Council RT01 multicenter randomized controlled trial of conformal prostate RT, delivered either 64 or 74 Gy with neoadjuvant androgen suppression, accrued 843 patients (4, 11, 12) and showed improvement in early effectiveness outcome measures for escalated doses. In addition to the comprehensive data on late toxicity, which was collated, complete dosimetric data were available for 388 patients. This database provided an opportunity to examine the relationship between dose and volume and late effects in prostate RT using a variety of late rectal toxicity measures.

Most studies of dose–volume effects in rectal toxicity have concentrated on the outcome measure of late rectal bleeding (5–8, 10, 13–17). Although this endpoint is straightforward to record, other symptoms, such as urgency, frequency, loose stools, and anal continence, are at least as important to the patients (18, 19). As RT techniques improve target conformality, the incidence and severity of late rectal toxicity should decrease (20); therefore, it is increasingly important to consider all toxicity grades that concern patients. Studies have investigated the correlation between dosimetric parameters and both bleeding and nonbleeding endpoints (9, 21–25). The most up-to-date results from the Italian AIROPROS 01-02 trial (21) used self-reported questionnaire responses to measure the incidence of frequency/tenesmus/pain (as one indicator), incontinence, and bleeding and reported a number of statistically significant volume cutoffs for the different dose levels. The Dutch multicenter trial (9) used five specific symptom indicators. Vargas *et al.* (22) reported the correlations between the dosimetric parameters and the National Cancer Institute Common Toxicity Criteria, version 2.0, rectal endpoints. Another study (23, 24) pooled all Radiation Therapy Oncology Group/Late Effects of Normal Tissues (LENT) endpoints and presented the analysis according to the greatest grade of any toxicity type.

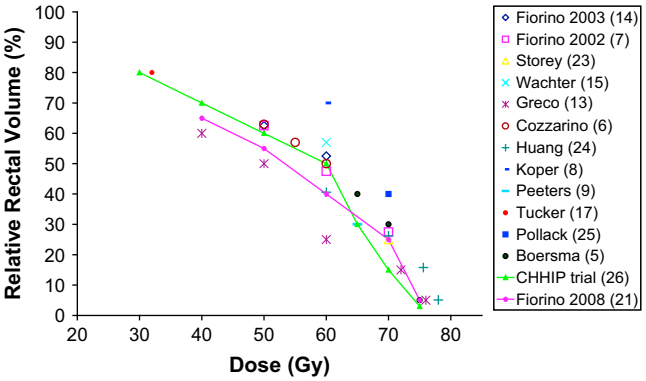

Fig. 1. Proposed dose–volume constraints for late rectal toxicity. Two constraint sets tested connected by lines.

The present study systematically tested the relationship between the volume of rectum receiving a broad range of doses and the incidence of a number of different toxicities as scored by clinicians and reported by the patients. The translation of this dose–volume analysis into clinical practice was explored by applying two sets of suggested dose–volume constraints (21, 26) to investigate whether the incidence of rectal toxicity was reduced for treatment plans that adhered to the constraints. Figure 1 summarizes the proposed dose–volume constraints from the published data and the constraint sets tested.

METHODS AND MATERIALS

An analysis was undertaken of the correlation between the dose distribution to the rectum resulting from RT to the prostate and late rectal toxicity measured using a range of scores. Treatment

Table 1. Translation of late rectal toxicity scoring schemes to common grading scheme and baseline exclusion criteria

Variable	Scoring system	Baseline criteria	0, None	1, Mild	2, Moderate/severe
Rectal bleeding	RMH	Occasional or more often	None	Occasional	Simple outpatient management, transfusion, surgery
Proctitis	RTOG	Not recorded	No symptoms	Minor symptoms	Simple outpatient management, distressing symptoms, major surgical intervention or prolonged hospitalization, fatal complications
Subjective sphincter control	LENT	Occasional or more often	None	Occasional	Intermittent, persistent, refractory
Subjective stool frequency	LENT	≥2/d	<2/d	2–4/d	≥5/d
Management sphincter control	LENT	Use of incontinence pads	None	Dichotomize score	Use of incontinence pads
Loose stools	UCLA PCI	Half the time or more	Never/rarely	Half the time	Usually/always
Rectal urgency	UCLA PCI	≥1/wk	Never/rarely	≥1/wk	≥1/d

Abbreviations: RMH = Royal Marsden Hospital; RTOG = Radiation Therapy Oncology Group; LENT = Late Effects of Normal Tissues; UCLA = University of California, Los Angeles; QOL = quality of life.

Table 2. Patients who reported each grade of toxicity (common grading scheme)

	Rectal bleeding		Proctitis		Sphincter control (subjective)		Stool frequency (subjective)		Sphincter control (management)		Loose stools		Rectal urgency	
Toxicity grade	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
0	202	52.1	207	53.4	322	83.0	209	53.9	366	94.3	204	52.6	154	39.7
1	105	27.1	95	24.5	39	10.1	106	27.3	15	3.9	73	18.8	67	17.3
2	54	13.9	86	22.2	18	4.6	29	7.5	0	0.0	41	10.6	67	17.3
Excluded from analysis	27	7.0	0	0	9	2.3	44	11.3	7	1.8	70	18.0	100	25.8
Total included	361		388		379		344		381		318		288	

planning data were collected from participating RT01 centers and standardized using in-house software GUINESS (Graphical User Interface for the aNalysis and modElling of clinical StudieS) (27). The treatment planning data were imported, and the three-dimensional dose distribution was reconstructed and analyzed for each patient. Only patients with ≥2 years of follow-up and complete dosimetric data were included in the present study. For each patient, the maximal side effect recorded during follow-up for each toxicity was used. The present study used a subset of the main trial data set; frozen in November 2007 (median follow-up, 60 months).

Normal tissue contours were reviewed centrally by one of us (H.C.), and minor adjustments were undertaken as necessary to ensure consistency. The rectum was outlined from the anus taken at the level of the ischial tuberosities or 1 cm below the planning target volume, whichever was more inferior to the rectosigmoid junction. The conformal planning technique for the trial has been previously reported (11). In brief, the centers could use three or four fields in the treatment plan for the initial 64 Gy. The treatment plans of patients randomized to receive the additional 10 Gy to prostate only used four or six fields. The treatment plans of the patients who were prescribed 74 Gy with two separate phases were summed together to generate a combined dose–volume histogram. The only dose constraint placed on normal tissues in the trial protocol was that no area in the rectum or bladder outside the planning target volume could receive more than the randomized prescription dose.

Detailed follow-up data were available for the late rectal toxicity endpoints assessed using physician-completed Royal Marsden Hospital scores (12), Radiation Therapy Oncology Group questionnaires (28), and Late Effects of Normal Tissues/Subjective, Objective, Management, Analytic (LENT/SOMA) grading (29). Also, the patient-completed University of California, Los Angeles, Prostate Cancer Index (UCLA-PCI) questionnaire (30) was used to assess patients' quality of life. Seven late rectal toxicity endpoints were chosen to represent clinically relevant effects. These were (*1*) rectal bleeding (Royal Marsden Hospital scale), (*2*) proctitis (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer), (*3*) subjective assessment of sphincter control (LENT/SOMA), (*4*) subjective assessment of stool frequency (LENT/SOMA), (*5*) management of sphincter control (LENT/SOMA), (*6*) frequency of loose stools (UCLA-PCI), and (*7*) urgency (UCLA-PCI). Late toxicities were deemed to be those reported at or after the 6-month assessment.

The toxicity scales were harmonized by taking the definitions of each point on each scale and classifying them as none (Grade 0), mild (Grade 1), or moderate/severe (Grade 2), in terms of the affect on the patient. In this harmonization, the management of sphincter control classified using the LENT/SOMA system was dichotomized, because it was thought that the requirement of any management intervention should be classified as Grade 2 (moderate/severe). Table 1 lists how the different scoring schemes were translated into a common scoring system. The worst recorded symptom level during the follow-up period was analyzed for each outcome.

Because some of the mild symptoms considered in the present study were already prevalent in the trial population before treatment, the patients who reported symptoms before RT were excluded from the analysis of that endpoint only, according to the criteria listed in Table 1.

To establish whether applying dose–volume constraints might reduce the incidence of late rectal toxicity, two sets of constraints were tested: those used in the current U.K. Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP ISRCTN97182923) trial (26) (derived from a published data review in 2000); and those recommended in the recent report by Fiorino *et al.* (21). We investigated the population effect

Table 3. Odds ratios for an increase in rectal volume of 5%. Rectal bleeding and proctitis

	Rectal Bleeding Grade 1 & 2			Rectal Bleeding Grade 2			Proctitis Grade 1 & 2			Proctitis Grade 2		
Volume receiving	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
20 Gy	1.03	0.93-1.13	0.587	1.11	0.96-1.28	0.162	1.06	0.97-1.16	0.224	0.99	0.89-1.11	0.917
30 Gy	1.06	1.00-1.13	0.052	***1.14***	***1.04-1.25***	***0.006***	***1.10***	***1.04-1.17***	***0.002***	1.08	1.01-1.16	0.032
40 Gy	*1.08*	*1.01-1.16*	*0.021*	***1.15***	***1.04-1.26***	***0.004***	*1.08*	*1.01-1.15*	*0.018*	*1.10*	*1.02-1.19*	*0.014*
50 Gy	*1.09*	*1.02-1.17*	*0.013*	***1.14***	***1.04-1.26***	***0.006***	*1.08*	*1.01-1.16*	*0.018*	***1.12***	***1.03-1.21***	***0.007***
60 Gy	***1.13***	***1.04-1.22***	***0.003***	***1.20***	***1.08-1.33***	***0.001***	***1.11***	***1.03-1.20***	***0.007***	***1.15***	***1.05-1.25***	***0.003***
65 Gy	***1.12***	***1.04-1.22***	***0.003***	***1.22***	***1.10-1.35***	***0.000***	***1.11***	***1.03-1.20***	***0.006***	***1.15***	***1.05-1.25***	***0.002***
70 Gy	***1.25***	***1.06-1.47***	***0.006***	***1.41***	***1.16-1.72***	***0.001***	***1.25***	***1.06-1.46***	***0.006***	***1.31***	***1.10-1.56***	***0.002***

Abbreviations: OR = odds ratio; CI = confidence interval.
***p* ≤ 0.01 (bold italics)**
p > 0.01, p < 0.05 (italics only)

Table 4. Odds ratios for an increase in rectal volume of 5%. Stool frequency and sphincter control

	Stool Frequency (subj) Grade 1 & 2			Stool Frequency (subj) Grade 2			Sphincter Control (subj) Grade 1 & 2			Sphincter Control (subj) Grade 2			Sphincter Control (mgmt)		
Volume receiving	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
20 Gy	1.04	0.94-1.14	0.494	0.93	0.79-1.10	0.407	1.14	0.99-1.32	0.078	1.17	0.90-1.52	0.236	0.99	0.79-1.25	0.951
30 Gy	1.05	0.99-1.12	0.111	0.97	0.87-1.08	0.582	1.09	1.00-1.19	0.055	1.11	0.96-1.29	0.171	1.05	0.90-1.23	0.538
40 Gy	1.07	1.00-1.15	0.065	0.99	0.88-1.12	0.883	1.09	1.00-1.20	0.056	1.06	0.91-1.23	0.489	0.96	0.82-1.13	0.645
50 Gy	*1.08*	*1.00-1.16*	*0.050*	0.98	0.86-1.11	0.711	1.09	0.99-1.20	0.065	1.05	0.90-1.23	0.550	0.95	0.79-1.13	0.547
60 Gy	*1.09*	*1.00-1.19*	*0.038*	0.97	0.84-1.13	0.717	*1.12*	*1.01-1.25*	*0.032*	1.10	0.93-1.31	0.280	0.98	0.80-1.19	0.802
65 Gy	1.00	0.93-1.09	0.927	0.95	0.82-1.10	0.480	1.09	0.99-1.20	0.096	***1.23***	***1.04-1.44***	***0.013***	1.14	0.95-1.36	0.156
70 Gy	1.11	0.94-1.31	0.224	0.95	0.70-1.29	0.728	1.20	0.98-1.47	0.082	1.34	0.98-1.83	0.070	1.21	0.85-1.73	0.290

Abbreviations as in Table 3.
p ≤ 0.01(bold italics)
p > 0.01, p < 0.05 (italics only)

on the incidence of the seven defined endpoints by comparing the incidence of complications for patients whose treatments plans failed each constraint compared with those whose treatment plan achieved the constraint.

Statistical analysis

Logistic regression analysis was used retrospectively to investigate how each of the defined endpoints was influenced by the dose distribution to the rectum (regarded as a solid rectum). The two toxicity grades were dichotomized to consider the odds ratios (ORs) for experiencing any toxicity or moderate/severe (Grade 2 or greater) toxicity. The volume of rectum receiving at least a defined dose level was the independent variable in each model and was treated as continuous. The resulting ORs were defined as the change in the odds of reporting a specified toxicity, given a 5% absolute increase in the rectal volume receiving at least the defined dose. An OR >1 indicates an increased risk of reporting the specified late rectal toxicity. The ORs were calculated using Stata, version 10 (College Station, TX) for the discrete dose levels. The uncertainty of the ORs was summarized using 95% confidence intervals; $p < 0.05$ was taken as suggesting evidence of effect. ORs for the constraint analysis were defined as the odds of reporting a specified late rectal toxicity as a result of the treatment plan failing to meet a suggested constraint relative to the odds if the constraint had been met. ORs were calculated using the Statistical Program for Social Sciences, version 15 (SPSS, Chicago, IL).

RESULTS

Data from 388 patients were available for analysis. Table 2 summarizes the data of the patients who were excluded and the number of patients who experienced each grade of toxicity for each endpoint. By definition, no baseline assessment was done for proctitis; therefore, all 388 patients were included in the analysis.

The ORs calculated for a 5% increase in the volume of rectum receiving each specified dose are listed in Tables 3–5. The results are presented for any complication grade (Grades 1 and 2) and moderate or severe toxicity only (Grade 2).

The ORs for both rectal bleeding and proctitis (Table 3) increased progressively from 20 Gy to 70 Gy. For rectal bleeding (all grades), statistical significance was reached at 40 Gy (OR, 1.08) increasing to an OR of 1.25 at 70 Gy and for Grade 2 alone at 30 Gy (OR, 1.14) to 70 Gy (OR, 1.41). A generally similar pattern was seen for proctitis.

In contrast, the endpoints reporting stool frequency and sphincter control using the LENT/SOMA scheme showed little correlation with an increase in volume (Table 4). A 5% increase in volume at 50 and 60 Gy were statistically significant (OR, 1.08–1.09) for stool frequency; 60 Gy was the only statistically significant dose level for sphincter control (OR, 1.12; Grades 1 and 2). For Grade 2 toxicity only, 65 Gy

Table 5. Odds ratios for an increase in rectal volume of 5%. Rectal urgency and loose stools

	Rectal Urgency Grade 1 & 2			Rectal Urgency Grade 2			Loose Stools Grade 1 & 2			Loose Stools Grade 2		
Volume receiving	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
20 Gy	1.09	0.98-1.20	0.124	1.13	0.99-1.29	0.074	1.10	0.99-1.23	0.079	1.17	0.98-1.40	0.079
30 Gy	1.05	0.98-1.13	0.132	1.09	1.00-1.18	0.053	***1.10***	***1.03-1.18***	***0.008***	***1.18***	***1.06-1.32***	***0.004***
40 Gy	*1.10*	*1.02-1.18*	*0.016*	***1.12***	***1.03-1.22***	***0.012***	***1.13***	***1.05-1.22***	***0.002***	***1.16***	***1.04-1.30***	***0.007***
50 Gy	*1.10*	*1.02-1.19*	*0.019*	*1.11*	*1.02-1.22*	*0.022*	***1.14***	***1.05-1.23***	***0.001***	*1.13*	*1.02-1.26*	*0.022*
60 Gy	*1.12*	*1.02-1.22*	*0.015*	*1.11*	*1.01-1.23*	*0.038*	***1.15***	***1.05-1.26***	***0.002***	***1.17***	***1.04-1.32***	***0.009***
65 Gy	1.06	0.97-1.16	0.169	1.06	0.96-1.18	0.244	1.08	0.99-1.18	0.069	*1.14*	*1.02-1.28*	*0.025*
70 Gy	*1.21*	*1.00-1.45*	*0.045*	1.13	0.91-1.39	0.265	1.17	0.98-1.40	0.078	*1.28*	*1.01-1.62*	*0.037*

Abbreviations as in Table 3.
p ≤ 0.01(bold italics)
p > 0.01, p < 0.05 (italics only)

Table 6. Dose–volume constraints tested and number of patients who failed each constraint

Constraint	Dose (Gy)	Volume (%)	Patients who failed constraint (*n*)
CHHiP30	30	80	153 (39.3)
CHHiP40	40	70	96 (24.7)
CHHiP50	50	60	81 (20.8)
CHHiP60	60	50	50 (12.9)
CHHiP65	65	30	46 (11.8)
CHHiP70	70	15	36 (9.3)
CHHiP75	75	3	2 (0.5)
Fiorino40	40	65	139 (35.7)
Fiorino50	50	55	126 (32.4)
Fiorino60	60	40	124 (31.9)
Fiorino70	70	25	4 (1.0)
Fiorino75	75	5	0 (0.0)

Data in parentheses are percentages.

was statistically significant for sphincter control. No statistically significant results were found for stool frequency (Grade 2) or management of sphincter control for any of the dose levels tested.

In contrast to these results, the patient-reported endpoints from the UCLA-PCI questionnaire (Table 5) indicated a consistently strong volume response for Grades 1 and 2 and Grade 2 only, for doses of 30–40 Gy, respectively, to 60 Gy for loose stools (OR, 1.10–1.15) and rectal urgency (OR, 1.1–1.12), with less-consistent results as the dose increased to the prescription dose level.

Dose–volume constraint analysis

Table 6 summarizes the dose–volume constraints mandated for the CHHiP trial (26) and those proposed by Fiorino *et al*. (21). Also listed are the number of patients from the available RT01 data set whose rectal dose–volume histogram failed each constraint. None of the treatment plans of the 388 patients failed the 75 Gy constraint proposed by Fiorino *et al*. (21). The ORs calculated by applying the dose–volume constraints retrospectively to the dose–volume histograms are presented in Tables 7–9.

Statistically significant ORs were observed for rectal bleeding (all grades) for the CHIiP trial constraints of 50–65 Gy (Table 7). For Grade 2 toxicity, the range of statistically significant CHHiP constraints shifted upward to 60–70 Gy (OR, >2.5). Only the 40 Gy Fiorino constraint was statistically significant (Grades 1 and 2; OR, 1.57). When considering all grades of proctitis, the 30 and 65 Gy CHHiP constraints were statistically significant. For Grade 2 proctitis, the CHHiP 50–70 Gy constraints and the 40–60 Gy constraints proposed by Fiorino *et al*. (21) were statistically significant (ORs, 1.64–2.05).

In keeping with the results for a volume increase of 5% at a specified dose, few of the proposed dose–volume constraints were statistically significant for endpoints defined using the LENT/SOMA criteria (Table 8). No significant results were found when considering Grade 2 toxicity only.

Table 9 presents the results of applying the constraints for the patient-reported endpoints of rectal urgency and loose stools. The ORs for rectal urgency (Grades 1 and 2) were statistically significant for the Fiorino constraints for 40–60 Gy (ORs, 1.7–1.9). For Grade 2 toxicity, the same constraints were statistically significant with ORs >2. The 40 Gy CHHiP constraint was statistically significant for both Grades 1 and 2 and Grade 2 only. The results for loose stools (all grades) were statistically significant for the 30–60 Gy CHHiP constraints (ORs, 1.67–2.48) and extended to 65 Gy for Grade 2 only (OR, ≥2.4). The 40–60 Gy Fiorino constraints were statistically significant for Grades 1 and 2 (OR, 1.88–2.24). However, only the 40 Gy constraint remained significant for Grade 2 toxicity.

The overall effect of applying dose–volume constraints on the incidence of rectal toxicity is summarized in Fig. 2. The tightest set of constraints (*i.e.,* the lowest allowed volume from either CHHiP or Fiorino constraints at each dose level) was applied to the patient cohorts. They were volume receiving 30 Gy of ≤80%, 40 Gy of ≤65%, 50 Gy of ≤55%, 60 Gy

Table 7. Odds ratios for the retrospective application of dose volume constraints. Rectal bleeding and proctitis

	Rectal Bleeding Grade 1 & 2			Rectal Bleeding Grade 2			Proctitis Grade 1 & 2			Proctitis Grade 2		
constraint	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
CHHiP30	1.50	0.98-2.29	0.060	1.72	0.96-3.08	0.064	*1.59*	*1.05-2.39*	*0.027*	1.29	0.79-2.09	0.307
CHHiP40	1.46	0.91-2.35	0.115	1.57	0.84-2.94	0.151	1.34	0.84-2.12	0.219	1.55	0.91-2.62	0.105
CHHiP50	*1.66*	*1.00-2.74*	*0.049*	1.66	0.87-3.18	0.120	1.39	0.85-2.26	0.192	*1.80*	*1.04-3.12*	*0.034*
CHHiP60	***2.53***	***1.34-4.78***	***0.003***	***2.55***	***1.24-5.22***	***0.009***	1.69	0.93-2.08	0.085	*2.01*	*1.06-3.82*	*0.031*
CHHiP65	*2.13*	*1.11-4.08*	*0.021*	***2.54***	***1.21-5.34***	***0.011***	*2.13*	*1.13-4.03*	*0.018*	*2.07*	*1.07-4.01*	*0.028*
CHHiP70	1.79	0.89-3.63	0.100	*2.56*	*1.15-5.70*	*0.017*	1.48	0.74-2.96	0.261	***2.47***	***1.21-5.08***	***0.011***
CHHiP75	1.27	0.08-20.5	0.865	0.85	0.81-0.89	0.552	0.53	0.48-0.58	0.185	0.78	0.74-0.82	0.449
Fiorino40	*1.57*	*1.02-2.42*	*0.040*	1.63	0.91-2.93	0.097	1.38	0.91-2.91	0.129	***1.90***	***1.17-3.09***	***0.009***
Fiorino50	1.51	0.97-2.34	0.067	1.61	0.89-2.90	0.114	1.28	0.84-1.96	0.256	***2.05***	***1.25-3.35***	***0.004***
Fiorino60	1.47	0.94-2.28	0.087	1.63	0.90-2.94	0.103	1.41	0.92-2.16	0.118	*1.64*	*1.00-2.70*	*0.049*
Fiorino70	3.87	0.40-37.5	0.210	1.91	0.20-18.7	0.571	0.38	0.04-3.66	0.383	1.17	0.12-11.4	0.891

Abbreviations as in Table 3.
p ≤ 0.01(bold italics)
p > 0.01, p < 0.05 (italics only)

Table 8. Odds ratios for the retrospective application of dose volume constraints. Sphincter control and stool frequency

	Stool Frequency (subj) Grade 1 & 2			Stool Frequency (subj) Grade 2			Sphincter Control (subj) Grade 1 & 2			Sphincter Control (subj) Grade 2			Sphincter Control (mgmt)		
constraint	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
CHHiP30	1.23	0.79-1.92	0.364	0.6	0.26-1.40	0.236	1.36	0.77-2.39	0.291	1.58	0.61-4.07	0.342	1.04	0.36-2.98	0.942
CHHiP40	1.56	0.94-2.58	0.084	0.85	0.33-2.17	0.732	1.71	0.93-3.14	0.084	1.6	0.58-4.39	0.358	0.47	0.10-2.13	0.318
CHHiP50	***1.94***	***1.14-3.30***	***0.014***	0.82	0.30-2.23	0.692	1.34	0.69-2.60	0.388	1.13	0.36-3.53	0.837	0.27	0.04-2.11	0.183
CHHiP60	*1.95*	*1.00-3.82*	*0.047*	0.89	0.26-3.10	0.86	1.64	0.76-3.52	0.201	1.44	0.4-5.18	0.574	0.50	0.06-3.87	0.496
CHHiP65	1.04	0.53-2.03	0.917	0.54	0.12-2.36	0.406	1.49	0.67-3.29	0.321	2.23	0.70-7.10	0.164	0.52	0.07-4.07	0.529
CHHiP70	1.62	0.78-3.36	0.191	0.70	0.16-3.11	0.641	2.13	0.94-4.83	0.064	3.04	0.94-9.81	0.051	0.70	0.09-5.47	0.73
CHHiP75	0.61	0.56-0.66	0.254	0.92	0.89-0.95	0.667	0.85	0.81-0.89	0.551	0.95	0.93-0.97	0.752	0.96	0.94-0.98	0.774
Fiorino40	1.52	0.97-2.39	0.067	0.98	0.44-2.18	0.962	*1.78*	*1.01-3.15*	*0.044*	1.47	0.57-3.83	0.423	0.65	0.20-2.09	0.469
Fiorino50	1.54	0.97-2.45	0.064	0.95	0.42-2.17	0.909	1.69	0.95-3.00	0.074	1.38	0.52-3.65	0.516	0.53	0.15-1.90	0.318
Fiorino60	*1.74*	*1.09-2.78*	*0.019*	1.03	0.45-2.34	0.95	***2.10***	***1.18-3.72***	***0.01***	2.31	0.89-5.98	0.077	0.79	0.25-2.55	0.697
Fiorino70	1.55	0.10-25.0	0.755	0.92	0.89-0.95	0.667	2.86	0.25-32.0	0.373	0.95	0.93-0.97	0.698	0.96	0.94-0.98	0.725

Abbreviations as in Table 3.
p ≤ 0.01(bold italics)
p > 0.01, p < 0.05 (italics only)

of ≤40%, 65 Gy of ≤30%, 70 Gy of ≤15%, and 75 of ≤3%. Fig. 2 presents the maximal toxicity grade experienced (from any of the seven endpoints) relative to the number of constraints which the treatment plan failed. It can be clearly observed that the number of patients experiencing Grade 2 toxicity increases as more constraints are failed.

DISCUSSION

It has been shown that the incidence of late rectal toxicity correlates with an increase in volume at specific dose levels. The results for rectal bleeding, proctitis, loose stools, and rectal urgency have demonstrated compelling evidence of volume effects for dose ranging from 30–40 Gy upward to the prescription dose. These results are consistent for mild and moderate/severe toxicities reported by the clinician and patients. The trend of increasing ORs with an increasing dose for rectal bleeding and proctitis suggests that although a volume effect exists for a broad range of doses, the volume receiving the highest doses is particularly important. (It is important to consider the size of the OR rather than the size of the *p* value when assessing the effect of these results on clinical practice.) However, for rectal urgency and loose stools, our data suggest similar weight should be given to rectal volumes receiving ≥30 Gy. The variation in response between toxicity endpoints demonstrated that different aspects of the dose distribution to the rectum manifest in different functional and anatomic responses. This challenges the concept that the rectum is a serial structure (31) for which a maximal dose is the only consideration when avoiding toxicity.

Previous studies investigating late rectal toxicity have mainly focused on rectal bleeding and the rectal volume receiving high radiation doses approaching the prescribed dose. Thus, the dose–volume constraints investigated, and consequentially recommended, have tended to be in the dose range >60 Gy (5, 7, 8, 10, 14, 15, 17, 23). The constraints for the CHHiP trial were determined from the

Table 9. Odds ratios for the retrospective application of dose volume constraints. Rectal urgency and loose stools

	Rectal Urgency Grade 1 & 2			Rectal Urgency Grade 2			Loose Stools Grade 1 & 2			Loose Stools Grade 2		
constraint	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
CHHiP30	1.28	0.79-2.08	0.309	1.58	0.9-2.75	0.106	*1.67*	*1.05-2.67*	*0.030*	***2.64***	***1.35-5.17***	***0.004***
CHHiP40	*1.86*	*1.06-3.26*	*0.028*	***2.23***	***1.22-4.08***	***0.009***	***2.13***	***1.27-3.58***	***0.004***	***2.77***	***1.41-5.47***	***0.002***
CHHiP50	1.79	0.99-3.24	0.054	1.83	0.96-3.48	0.065	***2.48***	***1.44-4.28***	***0.001***	***2.44***	***1.21-4.92***	***0.011***
CHHiP60	1.35	0.64-2.81	0.427	1.34	0.59-3.05	0.49	***2.47***	***1.26-4.83***	***0.007***	*2.66*	*1.18-5.95*	*0.015*
CHHiP65	1.79	0.85-3.78	0.122	1.59	0.71-3.54	0.257	1.5	0.74-3.03	0.253	*2.6*	*1.12-6.03*	*0.021*
CHHiP70	1.64	0.73-3.70	0.231	1.24	0.50-3.09	0.643	1.29	0.59-2.82	0.515	1.89	0.72-4.97	0.189
CHHiP75	0.46	0.41-0.52	0.283	0.23	0.19-0.28	0.069	0.64	0.59-0.70	0.454	0.87	0.83-0.91	0.700
Fiorino40	*1.74*	*1.06-2.85*	*0.027*	***2.02***	***1.16-3.54***	***0.013***	***2.24***	***1.39-3.60***	***0.001***	***2.57***	***1.32-5.00***	***0.004***
Fiorino50	*1.82*	*1.09-3.04*	*0.020*	*2.02*	*1.14-3.57*	*0.015*	***2.02***	***1.24-3.28***	***0.004***	1.8	0.92-3.51	0.082
Fiorino60	*1.81*	*1.10-3.00*	*0.020*	*2.00*	*1.14-3.53*	*0.015*	***1.88***	***1.16-3.04***	***0.010***	1.92	0.99-3.73	0.052
Fiorino70	0.46	0.41-0.52	0.128	***0.23***	***0.18-0.28***	***0.010***	0.64	0.59-0.69	0.289	0.87	0.83-0.91	0.585

Abbreviations as in Table 3.
p ≤ 0.01(bold italics)
p > 0.01, p < 0.05 (italics only)

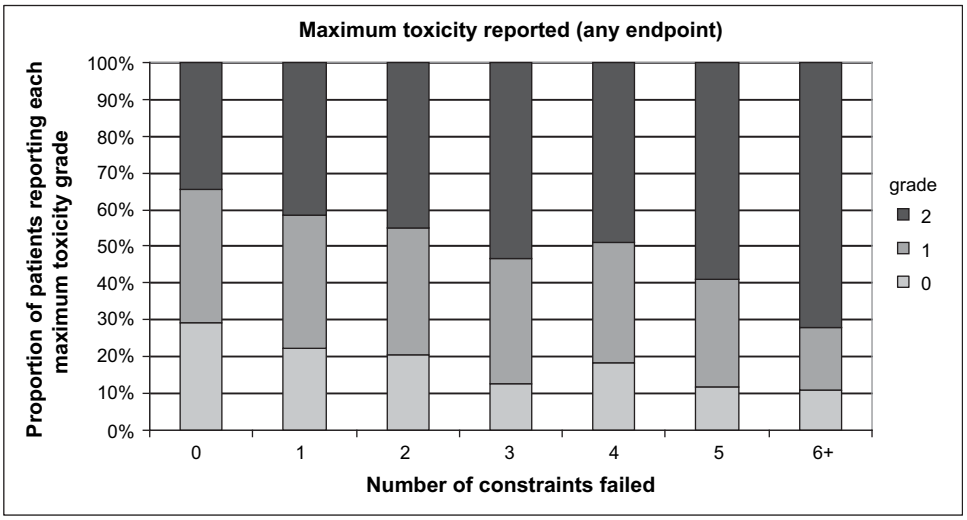

Fig. 2. Summary of maximal toxicity grade reported (any endpoint) relative to number of constraints failed. Lowest volume constraint taken at each dose level.

available published data (circa 2000) and are, therefore, most relevant to rectal bleeding. More recently, an understanding has emerged that volumes receiving lower doses might also contribute to the development of late effects (9, 13, 16, 21, 22). The recent Fiorino constraints are not just determined from rectal bleeding, for example, the constraint at 40 Gy is implicitly defined for rectal incontinence.

The CHHiP constraints relate well to rectal bleeding. Proctitis, which is a composite endpoint combining rectal bleeding with urgency, tenesmus, and other factors, was predicted by the stricter dose constraints for CHHiP at 65 and 70 Gy and the Fiorino constraints at 50 and 60 Gy. The Fiorino constraints related well to rectal urgency and subjective sphincter control. Both Fiorino and CHHiP constraints predicted loose stools and stool frequency but for doses of ≤60 Gy. These two pairs of endpoints could obviously be linked and have a different pathophysiology. Both constraint sets showed considerable merit; however, neither can be regarded as definitive.

The results we have presented have indicated that the entire dose distribution to the rectum should be considered carefully during treatment planning. This is particularly pertinent to inverse planning in which optimization constraints concentrating on doses close to the prescription might result in large rectal volumes at lower doses that have been shown in the present study to correlate with several measures of late rectal toxicity. Obviously, the volumes receiving the different dose levels are interrelated, and it might be that the reason that large volumes receiving intermediate doses correlate with late toxicity is a ''dose bath effect'' in which the functionality of the epithelial cells is impaired, reducing the ability to facilitate repair of higher dose neighboring regions.

A broad concordance has been reached in the published data that the application of dose–volume constraints can reduce late rectal toxicity (5, 10, 13, 14, 17). However, the proposed dose–volume constraints have varied (Fig. 1). A number of explanations are possible for this variability, including RT technique, volume definition, choice of endpoint, and method of scoring toxicity. It is clear from the published data that no global scoring system has been adopted, and many of the cited studies refer to modified versions of the classic grading scales, the Radiation Therapy Oncology Group/European Organization for Research and Treatment Cancer and LENT/SOMA. Without detailed information on how the scoring has been modified, it is difficult to directly compare the results. The work of Fiorino *et al.* (14) and subsequent correspondence with Bauman and Rodrigues (32) highlights many of the issues and summarizes the relevant published data.

A strength of our analysis was the validation of previously proposed, in contrast to data-derived, constraints on an independent population of patients treated without predetermined dose–volume histogram restrictions. Nevertheless, it is acknowledged that the number of statistical tests performed on our data might have resulted in some chance findings. In addition, the dose levels tested are interrelated parameters of the planned dose distributions. The interrelation was partly negated by the variety of different planning techniques used by participating centers within the trial protocol. It is also acknowledged that the treatment plan is determined from a snapshot of the patient's anatomy at the computed tomography planning scan, it has been assumed for the present study that the snapshot is representative of the volumes treated on a daily basis. However, these limitations could well contribute to our observation that one-third of patients experienced moderate/severe toxicity of some type despite meeting all dose constraints. An additional factor might be individual variations in radiosensitivity, which is the subject of additional study (33). We also acknowledge that coincidental comorbidities might have contributed to the toxicities recorded.

CONCLUSION

The comprehensive analysis of dose–volume effects and constraints presented in the present study has provided substantial evidence that considering only the maximal or high-dose region of the rectal dose distribution from a prostate RT plan

might not minimize the risk of patients experiencing late rectal toxicity. It is recommended that appropriate rectal dose–volume constraints using the currently available data should be introduced into routine treatment planning for prostate RT.

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