Original Article

Dosimetry and Gastrointestinal Toxicity Relationships in a Phase II Trial of Pelvic Lymph Node Radiotherapy in Advanced Localised Prostate Cancer

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Abstract

Aims: Pelvic lymph node (PLN) radiotherapy for high-risk prostate cancer is limited by late gastrointestinal toxicity. Application of rectal and bowel constraints may reduce risks of side-effects. We evaluated associations between intensity-modulated radiotherapy (IMRT) dose-volume data and long-term gastrointestinal toxicity.

Materials and methods: Data from a single-centre dose-escalation trial of PLN-IMRT were analysed, including conventionally fractionated (CFRT) and hypo-fractionated (HFRT) radiotherapy schedules. Associations between volumes of rectum and bowel receiving specified doses and clinician- and patient-reported toxicity outcomes were investigated independently. A metric, δ median (δM), was defined as the difference in the medians of a volume between groups with and without toxicity at a specified dose and was used to test for statistically significant differences.

Results: Constraints were respected in most patients and, when exceeded, led to higher rates of gastrointestinal toxicity. Biologically relevant associations between rectum dose-points and toxicity were more numerous with both mild and moderate toxicity thresholds, but statistical significance was limited after correction for false discovery rate. Rectal V50Gy (CFRT) associated with grade 2+ bleeding; bowel V43Gy and V47 (HFRT/4 days/week schedule) associated with patient-reported loose stools and diarrhoea, respectively. Further investigation showed that CFRT patients with rectal bleeding had a mean rectal V50Gy above the treatment planning constraint.

Conclusions: When dose-volume parameters are kept below tight constraints, toxicity is low. Residual dosimetry loses much of its predictive power for gastrointestinal toxicity in the setting of PLN-IMRT for prostate cancer. We have benchmarked dose-volume constraints for safely delivering PLN-IMRT using CFRT or HFRT.

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Key words: Dose-volume constraints; dosimetry; IMRT; pelvic lymph nodes; prostate cancer; gastrointestinal side-effects

Introduction

Long-term side-effects can become major issues for patients in whom prostate cancer (PCa) is controlled or cured.

Late toxicity, starting 3 months to years after treatment, is of particular concern as pelvic lymph node (PLN) radiotherapy may increase gastrointestinal side-effects [1–4].

The risk of gastrointestinal toxicity is judged with dose-volume histograms. However, there is limited consensus regarding their prognostic value, particularly in the era of dose-volume constraint-based inverse-planned radiotherapy. Although concordant at higher doses, studies show different dose-volume histogram metrics as predictive of rectal bleeding and it is difficult to find consistent

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correlations with other gastrointestinal symptoms [5—8]. Treatment planning dose constraints have been developed to minimise risks. Although the QUANTEC meta-analyses on gastrointestinal dose constraints provided evidence-based guidance for radiotherapy planning, they were based on studies using three-dimensional conformal radiotherapy [5,9]. Intensity-modulated radiotherapy (IMRT) may have changed toxicity patterns and relationships with dosimetry [5,9]. Other proposed models of risk evaluation have not been introduced in the clinic [10—12].

We investigated relationships between dose-volume constraints and late gastrointestinal toxicity in patients prospectively treated with conventionally fractionated (CFRT) or hypofractionated (HFRT) prostate and pelvic IMRT for high-risk PCa in a phase I/II study [3].

Materials and methods

Patients and Data

Patients treated in a previously reported phase I/II study of prostate and pelvic IMRT for high-risk PCa (IMRT-PCa trial) were eligible [3]. The trial accrued 473 patients with high-risk PCa between August 2000 and September 2013. CFRT was delivered to the prostate and seminal vesicles (70—74 Gy in 35—37 fractions) and 50, 55 or 60 Gy to the PLN concomitantly over 7—7.4 weeks. Two further cohorts received HFRT, with 60 Gy (20 fractions) delivered to the prostate and seminal vesicles and 47 Gy to the PLN in either 4 (5 days/week, HFRT-5D) or 5 weeks (4 days/week, HFRT-4D). The change to a 5 week schedule (which is an extension of the 4 week schedule to 5 weeks by delivering four instead of five fractions/week) occurred because of documented increases in short-lasting acute gastrointestinal toxicity also observed in other studies [3,13,14]. All patients received long-course androgen deprivation therapy.

Only patients with both toxicity and complete dosimetric data were included. Patients with <2 years of follow-up data at the time of analysis were excluded.

Dosimetric Variables

Dosimetric data were obtained from prostate and pelvic node radiotherapy forms, used to assess the clinical suitability of radiotherapy plans according to defined dose constraints (see supplementary Table SUPP-1). Where unavailable, data were obtained from original treatment plans. Optimal and mandatory bowel constraints were derived from dose levels related to Radiation Therapy Oncology Group (RTOG) grade ≥ 1 and ≥ 2 in previous reports [15]. Rectal dose constraints were derived by pragmatically adapting available evidence at the time of study design [16,17]. Constraints were modified for HFRT in proportion to the prescribed dose.

Rectum and bowel were contoured as solid organs according to a previously published protocol (see supplementary text) [3]. Data consisted of absolute rectum and bowel volumes (cm^3), and volumes of bowel (cm^3) and

rectum (% of volume) receiving the constraint dose or higher, henceforth referred to as $(a)V(x)$, where (x) is the respective dose (Gy) and (a) the identifier for rectum (r) or bowel (b).

Radiation-induced Gastrointestinal Toxicity Data

Clinical data were collected at 6-month intervals up to 5 years after radiotherapy and yearly thereafter. Only data collected ≥ 6 months after radiotherapy were used. In order to capture a comprehensive record of toxicity, three internationally accepted toxicity scales were used [18]. They were the European Organization for Research and Treatment of Cancer (EORTC)/RTOG and the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) clinician-reported late toxicity scales and the UCLA Prostate Cancer Index (UCLA-PCI) patient-reported outcomes scale—bowel subset (questions 17—21) [19—21].

Analysis was undertaken endpoint-by-endpoint. Patients with positive baseline side-effect scores were excluded from analysis for that specific endpoint only. For example, if a patient had rectal bleeding before radiotherapy, he was excluded from the rectal bleeding analysis but not from tenesmus and other endpoints. We also excluded toxicity endpoints that had an incidence of $\leq 5\%$ in the entire cohort.

Patients were divided by peak toxicity using mild and moderate/severe thresholds for each endpoint (see supplementary Table SUPP-2) [21].

Associations were studied between dose-points and all toxicity outcomes in three different scales by cohort. We do not report amalgamated results of all cohorts given that constraints were not equivalent radiobiologically and because this strategy enables the study of differential relationships between CFRT and HFRT schedules.

Statistical Considerations

Dose-volume metrics (dose-points) where $\geq 80\%$ of patients had a value of 0 were excluded. They were rV75/bV65 (CFRT) and rV63/bV55 (HFRT). Bowel metrics where the mean volume was <2 cm^3 were also excluded. They were bV60 (CFRT) and bV51 (HFRT).

To assess biological significance in this large dataset, a measure of inter-group difference was created. This metric, henceforth named 'δ median' (δM), is defined as:

$$\delta M = median\ V(x)\ (symptomatic\ group)$$
$$- median\ V(x)\ (non-symptomatic\ group)$$

where $V(x)$ is the dose-point of interest. Therefore, δM indicates if volumes appear greater in the group with or without toxicity (see supplementary Figure SUPP-1). Statistical significance was assessed using the Wilcoxon rank sum test.

Associations between dose-points and toxicity were sought by testing all dose-points against each endpoint in all toxicity scales, leading to the use of multiple statistical

tests (see supplementary Table SUPP-3). The Holm method was used to correct for false discovery rate (FDR) as per the following equation [22]:

$$Alpha\ level\ of\ significance = \frac{Target\ alpha\ level}{n - rank\ number\ of\ pair\ by\ degree\ of\ significance + 1}$$

where *n* is the number of tested hypotheses (number of tests done by toxicity scale per cohort, including both toxicity thresholds) and the target alpha level is 0.05. It follows that all *P* values reported in this article are 'uncorrected', as the Holm method uses the corrected alpha level of significance as a threshold to accept or reject the null hypothesis. A positive result is defined as a positive δM (>0) where statistical significance was reached.

Where positive associations resilient to FDR correction were found, new constraints were derived using receiver operating characteristic (ROC) curves [23]. Odds ratios of toxicity were calculated for protocol and new constraints and significance assessed with Fisher's exact test.

Analysis was carried out in Excel and R [24].

Results

Patient Characteristics

Of 473 patients recruited in the trial, 26 had been recruited <2 years before data lock and thus did not have long-term (≥2 years) toxicity data available and were excluded. Of the remaining 447 patients, 426 had been treated according to protocol and long-term toxicity data were available for 421. Dosimetric data were not retrievable for seven patients and thus 414 (98% of patients with ≥2 year toxicity follow-up data) were included for analysis. Proportions of patients with and without toxicity were comparable with those observed in the main analysis of the IMRT for Prostate Cancer trial, except for UCLA-PCI bowel problem (see supplementary Table SUPP-4). This discrepancy is explained by our methodology, as patients with a moderate/severe bowel problem at baseline (i.e. before the start of radiotherapy) were excluded in an endpoint-by-endpoint basis to obtain an accurate representation of gastrointestinal problems caused by radiotherapy. However, all patient- and clinician-reported gastrointestinal toxicity rates are comparable to previously reported analogous studies [25].

Groups were reported by prostate radiotherapy fractionation (Table 1) because dose-volume constraints were not equivalent radiobiologically [26]. This approach allows a comparison of differences between CFRT and HFRT in terms of relationships between dosimetry and toxicity, which was one of our objectives.

Table 1
Patient demographics

	All cohorts	CFRT	HFRT-4D	HFRT-5D
No. patients with toxicity follow-up data ≥2 years (no. excluded due to follow-up data <2 years)	LENT-SOMA: 414 (54) RTOG: 414 (63) UCLA-PCI: 369 (73)	LENT-SOMA: 234 (42) RTOG:234 (51) UCLA-PCI: 213 (43)	LENT-SOMA: 122 (7) RTOG: 122 (7) UCLA-PCI: 103 (20)	LENT-SOMA: 58 (5) RTOG: 58 (5) UCLA-PCI: 53 (10)
No. patients analysed (no. excluded due to incomplete dosimetric data)	LENT-SOMA: 368 (46) RTOG: 368 (46) UCLA-PCI: 325 (44)	LENT-SOMA: 205 (29) RTOG: 205 (29) UCLA-PCI: 185 (28)	LENT-SOMA: 114 (8) RTOG: 114 (8) UCLA-PCI: 95 (8)	LENT-SOMA: 49 (9) RTOG: 49 (9) UCLA-PCI: 45 (8)
No. patients by prescription dose to the PLN n (%)	N/A	50 Gy: 15 (7.3%) 55 Gy: 52 (25.4%) 60 Gy: 138 (67.3%)	47 Gy: 103 (90.3%) 43 Gy*: 11 (9.7%)	47 Gy: 46 (93.9%) 43 Gy*: 3 (6.1%)
Age at treatment Mean (range)	65 (45–82)	64 (45–82)	67 (47–80)	67 (47–79)
Follow-up (years) Median (IQR)	5 (4–7)	7 (5–9)	4 (3–4)	5 (5–5.5)
Rectum volume (cm^3) Median (IQR)	66.7 (50.6–86.1)	64.7 (51.1–87.5)	63.5 (44.3–77.0)	72.9 (58.1–94.3)
Bowel volume (cm^3) Median (IQR)	478.2 (347.7–640.6)	463.2 (343.9–649.0)	478.3 (369.9–632.4)	519.1 (371.3–616.9)

CFRT, conventionally fractionated radiotherapy; HFRT-4D, hypofractionated radiotherapy (4 days/week); HFRT-5D, hypofractionated radiotherapy (5 days/week); RTOG, Radiation Therapy Oncology Group; PLN, pelvic lymph nodes; IQR, interquartile range.
LENT-SOMA.
UCLA-PCI.
* Patients had planned dose reductions due to difficulties in meeting dose-volume constraints.

Number of Patients Failing Constraints and Relationships with Toxicity

We previously published encouraging toxicity outcomes of dose-escalated and hypofractionated PLN-IMRT in the IMRT for Prostate Cancer trial [3]. The trial protocol used strict dose-volume constraints for rectum and bowel (see supplementary Table SUPP-1). Application of dose-volume constraints may reduce gastrointestinal toxicity [27]. We therefore first hypothesised that rates of patients failing constraints were low in our dataset. We also explored relationships between the number of failed constraints and RTOG-scored maximum peak toxicity.
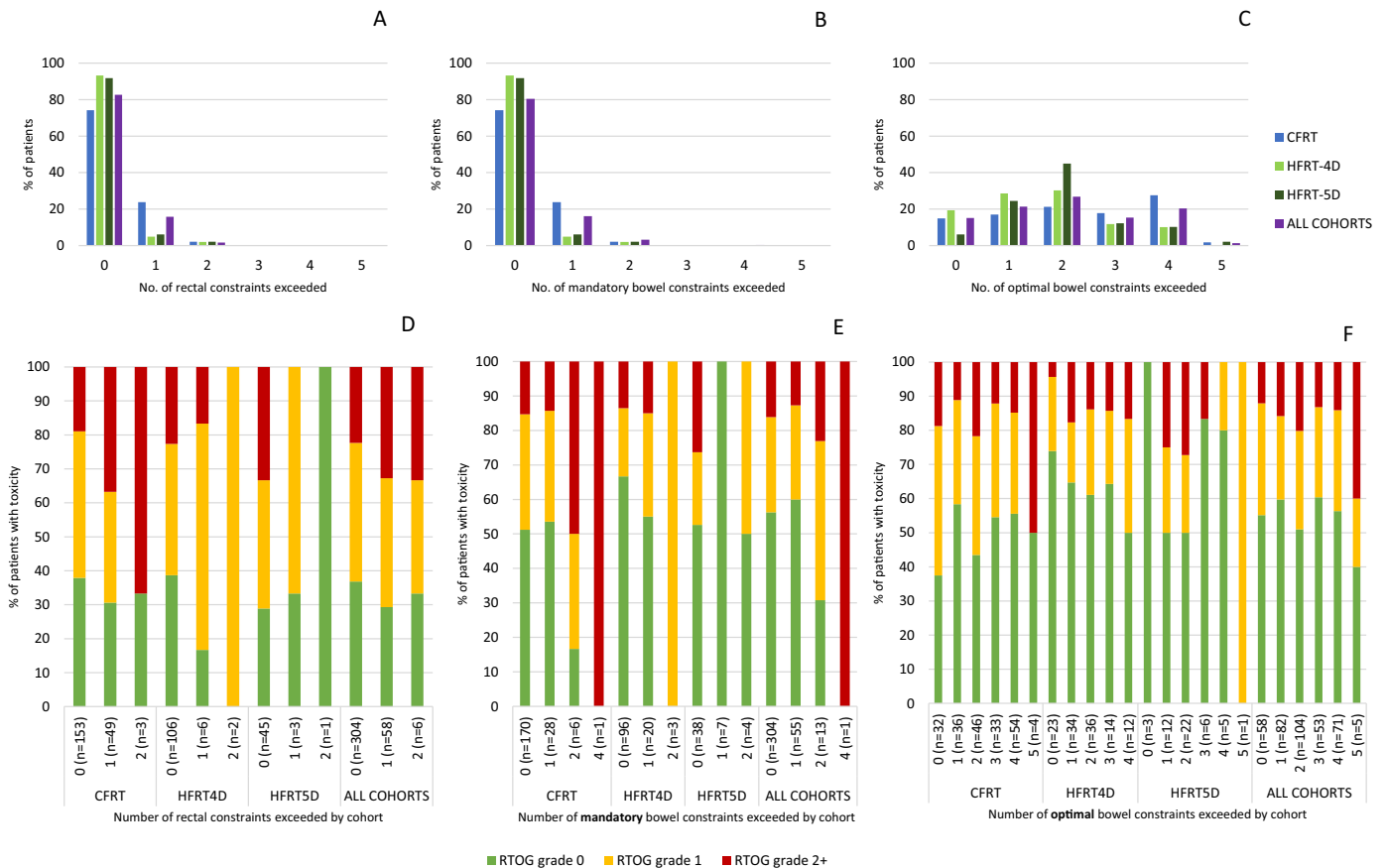
Rectum

Most patients met all constraints in all cohorts (Figure 1A, supplementary Figure SUPP-2A, Tables SUPP-5—SUPP-7). However, the rV50 constraint was exceeded in 26% in the CFRT cohort. Patients exceeding rectal constraints experienced more toxicity, particularly with CFRT, but this pattern was also reproduced in other cohorts (Figure 1D).

Bowel

Optimal/mandatory bowel constraints were defined by average volumes correlating with no/mild diarrhoea, respectively, in previous reports [15]. Although optimal constraints were exceeded frequently, mandatory constraints were generally respected (Figure 1B, C, supplementary Figure SUPP-2B, Tables SUPP-8—SUPP-10). As with rectum, a pattern whereby patients exceeding bowel constraints experience more toxicity was observed. This pattern was most evident in the CFRT cohort and mandatory constraints (Figure 1E, F).

Associations between Dosimetric Parameters and Toxicity

We used the δM measure to assess differences in volumes between groups of patients with and without toxicity and assessed their statistical significance stringently. For most endpoints, δM was small: 79% and 74.6% of δM were $\leq \pm 3\%$ of rectum or ≤ 10 cm^3 of bowel volumes, respectively (supplementary Table SUPP-11), reflecting small differences in median dose-point values between patients with and without toxicity. Five of 63 (8%) relationships suggested had negative δM values, but were not robust to FDR correction.

Fig 1. Rectum and bowel constraints exceeded and relationships with gastrointestinal toxicity. (A—C) Proportion of patients by number of exceeded rectal (A), bowel mandatory (B) and optimal (C) constraints; by cohort. (D—F) Proportions of patients with toxicity by number of rectal (D), bowel mandatory (E) and optimal (F) constraints exceeded; by cohort. Gastrointestinal toxicity was scored with maximum peak cumulative Radiation Therapy Oncology Group (RTOG) grade (rectum: maximum score of bowel frequency, bleeding, diarrhoea, proctitis, rectal stricture, rectal ulcer; bowel: maximum score of bowel frequency, diarrhoea, bowel obstruction).

All relevant results are described in Table 2 (rectum) and 3 (bowel). Supplementary Tables R1−9 (rectum) and B1−9 (bowel) summarise all findings.

Rectum

In the CFRT cohort, rV50 was higher in patients with moderate/severe (grade 2+) rectal bleeding in both RTOG ($P = 0.00008$) and LENT-SOMA ($P = 0.00004$) scales. These were the only results for rectum that were resilient to Holm correction (Table 2). rV50 was also higher in patients with mild (grade 1+) LENT-SOMA bleeding and bowel problem, albeit non-significantly. In HFRT cohorts, rV51/rV55 (HFRT-4D) and rV59 (HFRT-5D) associated with bleeding, albeit non-significantly.

Bowel

In the HFRT-4D cohort, bV43 and bV47 were higher in patients with mild self-reported loose stools ($P = 0.0005$) and RTOG-scored diarrhoea ($P = 0.002$), respectively. These were the only results resilient to FDR correction (Table 3). However, bV39 also associated non-significantly with mild self-reported loose stools and bV43 also associated non-significantly with diarrhoea-related toxicity endpoints, as did bV39/bV43 and bV45/bV55/bV60 in the HFRT-5D and CFRT cohorts, respectively.

Relationships between Significant Associations and Dose-volume Constraints

Three significant associations were detected in our dataset: rV50 (CFRT) and rectal bleeding, as well as bV43/bV47 (HFRT4D) with loose stools/diarrhoea. We examined if relationships with constraints were present and explored whether different constraints could be derived from our dataset.

CFRT/rV50 and rectal bleeding

Mean rV50 was 65%/54% and 66%/54% for patients treated with CFRT with/without grade 2+ RTOG and LENT-SOMA bleeding, respectively. Interestingly, in both cases, mean rV50 for patients with bleeding was above the rV50 constraint (Figure 2A−F). Such a relationship was not observed for any other rectal endpoint in relation to bleeding in any cohort. The rV50-CFRT constraint derived using this dataset was 59% (AUC: 0.79; 95% confidence interval 0.69−0.89; supplementary Table SUPP-12). Odds ratios for toxicity using protocol or new constraints were similar (supplementary Table SUPP-13), indicating that the protocol constraint was adequate for preventing toxicity if respected.

HFRT-4D/bV43 and loose stools

Although mean bV43 was higher in patients with mild self-reported loose stools (36.9 cm^3) than in patients without loose stools (34.3 cm^3), they were both under the mandatory (110 cm^3) and over the optimal (17 cm^3) constraints (Figure 2G−I). bV39 was non-significantly higher than mandatory constraints in patients with loose stools, unlike patients without loose stools. Mean volumes for

bV47−bV55 overlapped between groups, similar to the HFRT-5D cohort. With CFRT, there were no differences between groups. The bV43-HFRT constraint derived using this dataset was 24 cm^3 (AUC: 0.73; 95% confidence interval 0.62−0.84; see supplementary Table SUPP-12). Odds ratios using protocol constraints could not be calculated, as all patients met the constraint. However, for the new constraint, the odds ratio was 3.81 (1.59−9.80), indicating that it may be useful (see supplementary Table SUPP-13).

HFRT-4D/bV47 and diarrhoea

With HFRT-4D, the mean bV47 was 4.49 cm^3 in patients with and 2.80 cm^3 in patients without mild (grade 1+) RTOG diarrhoea. These values are below the mandatory (28 cm^3) and optimal (14 cm^3) constraints for bV47 (Figure 2J−L). Similar differences between these groups were also detected for bV39 and bV43, albeit non-significantly. Such patterns were not observed in other cohorts. The bV47 constraint derived using this dataset was 2.15 cm^3 (AUC: 0.69; 95% confidence interval 0.59−0.79; see supplementary Table SUPP-12). Odds ratios using protocol and new constraints were 5.51 (1.79−21.49) and 9.40 (3.24−32.59). This result indicates that failing to meet either constraint predicts for higher toxicity levels, although the new constraint may be more robust (see supplementary Table SUPP-13).

Discussion

Late gastrointestinal toxicity limits high-dose pelvic radiotherapy. Rectum and bowel dose-volume constraints, designed to minimise gastrointestinal side-effects, are increasingly important as inverse-planned IMRT becomes the primary radiotherapy technique for PCa. Several efforts have been made to detect thresholds below which probabilities of gastrointestinal toxicity are low [5,9,16,17,27−29].

We acknowledge limitations in our study. Planning computed tomography is a snapshot of a moving organ, especially for non-rectal bowel. By contouring bowel loops proximal to the rectum, different organs are included (sigmoid, colon, jejunum/ileum). However, although segmented bowel outlining is increasingly used in research and has been adopted by some centres, RTOG guidelines recommend that whole bowel (i.e. unsegmented) should be outlined for genitourinary tumours, reflecting general clinical practice [30]. We also recognise that the pelvic doses studied are non-standard, as we used data derived from an IMRT dose-escalation trial [3]. However, PLN-IMRT may become a standard option pending definitive results of ongoing phase III trials. Irrespective of this, our analysis allows an understanding of modern relationships between dosimetry and toxicity in a mature dataset.

Our approach makes comparisons between fractionation schedules possible, which was one of our objectives. However, in practice, it would be imprecise to pool all cohorts into a single dose-equivalent dataset, due to three factors: (1) α/β ratios are not available for most of the symptoms we studied, (2) there could be imprecisions related to time

Table 2
Positive associations between rectum dosimetry/toxicity

Clinician-reported toxicity						
Cohort	Threshold	LENT-SOMA		% patients with toxicity	RTOG	% of patients with toxicity
CFRT	M	**rV60 and mucosal loss ($P = 0.005$, δM = 3.3)**		21%	rV60 and bowel frequency ($P = 0.01$, δM = 3.85)	38%
		rV65 and mucosal loss ($P = 0.003$, δM = 4.3)		21%		
		rV50 and bleeding ($P = 0.04$, δM = 20.25)		22%		
		rV60 and sphincter control ($P = 0.008$, δM = 3.21)		18%		
		rV65 and sphincter control ($P = 0.04$, δM = 4.1)		18%		
	MS	*rV50 and bleeding ($P = 0.00004$, δM = 8.5)*		8%	*rV50 and rectal bleeding ($P = 0.00008$, δM = 7.1)*	10%
		rV60 and mucosal loss ($P = 0.003$, δM = 4.95)		6%		
		rV65 and mucosal loss ($P = 0.007$, δM = 5.54)		6%		
		rV60 and bleeding ($P = 0.04$, δM = 5.23)		8%		
HFRT-4D	M	rV51 and mucosal loss ($P = 0.04$, δM = 2.83)		22%	rV51 and rectal bleeding ($P = 0.02$, δM = 3.13)	44%
		rV55 and mucosal loss ($P = 0.03$, δM = 3.9)		22%	**rV55 and rectal bleeding ($P = 0.005$, δM = 4.15)**	44%
		rV59 and bleeding management ($P = 0.03$, δM = 2.43)		14%		
	MS	N/A			N/A	
HFRT-5D	M	rV51 and tenesmus ($P = 0.01$, δM = 5.91)		39%	**rV59 and proctitis ($P = 0.002$, δM = 2.3)**	55%
		rV55 and tenesmus ($P = 0.01$, δM = 3.74)		39%		
		rV59 and tenesmus ($P = 0.01$, δM = 2.25)		39%		
		rV59 and frequency ($P = 0.05$, δM = 1.86)		41%		
	MS	rV59 and bleeding ($P = 0.04$, δM = 2.66)		26%	N/A	
		rV59 and mucosal loss ($P = 0.02$, δM = 3.9)		6%		

Patient-reported toxicity										
	Urgency		Loose stools		Distress		Crampy pain		Problem	
Threshold →	M	MS	M	MS	M	MS	M	MS	M	MS
Cohort ↓										
CFRT	rV50 ($P = 0.003$, δM = 4.5)	rV50 ($P = 0.04$, δM = 2.75)	N/A	N/A	N/A	N/A	rV50 ($P = 0.03$, δM = 3.2)	N/A	rV50 ($P = 0.03$, δM = 2.35)	N/A
% patients with toxicity	38%	27%	—	—	—	—	19%	—	44%	—
HFRT-4D	N/A	N/A	rV43 ($P = 0.03$, δM = 4.56)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% patients with toxicity	—	—	43%	—	—	—	—	—	—	—
HFRT-5D	N/A	N/A	N/A	rV59 ($P = 0.04$, δM = 4)	N/A	N/A	N/A	rV43 ($P = 0.01$, δM = 5.2)	N/A	N/A
% patients with toxicity	—	—	—	20%	—	—	—	15%	—	—

Where N/A is reported, no positive associations were found. Where $P ≤ 0.01$, results are in bold. Where results were significant after Holm correction, results are bold and italicized. M = mild threshold (symptomatic patients are defined as having mild or worse symptoms). MS = moderate/severe (symptomatic patients are defined as having moderate or worse symptoms). % of patients with toxicity events excludes patients where data was unavailable (for full results see supplementary Tables R1–R9).

factors related to repair/recovery, (3) dose-points were not radiobiologically equivalent if using a 'one-fits-all' late effect α/β ratio of 3 Gy [31].

Numbers of patients with late grade 2+ toxicity were low. For completeness, comparisons using mild toxicity thresholds were carried out in parallel. Multiple statistical tes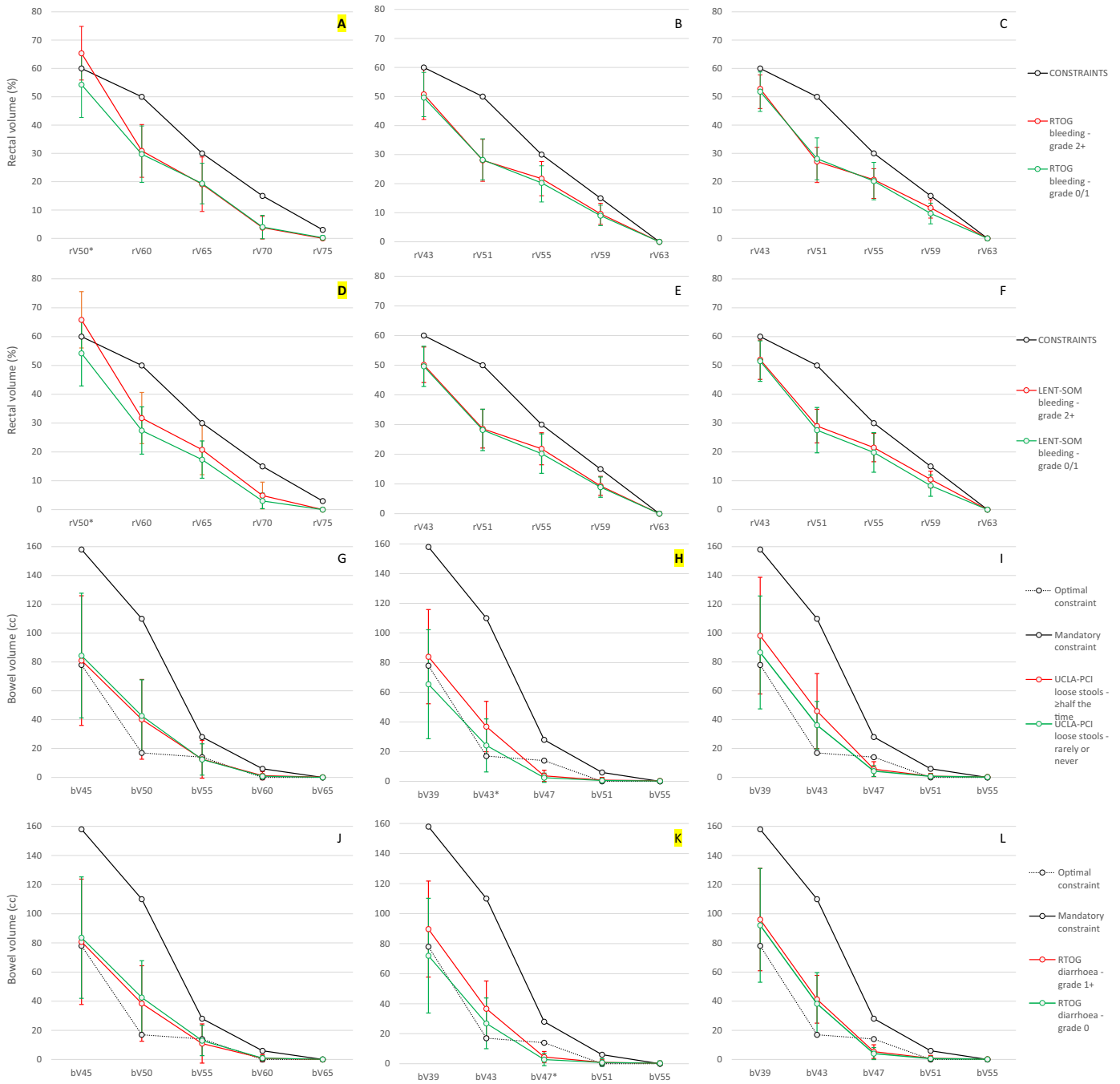ts were used, therefore requiring FDR correction. Holm correction was chosen for its robustness. We nevertheless pragmatically report different levels of significance. Overall, few results were found to be robustly significant.

We show a relationship between the number of exceeded rectal constraints and late toxicity. Our results confirm previous reports showing rV50 to predict grade 2+ rectal bleeding. However, robust relationships of higher doses

Table 3
Positive associations between bowel dosimetry/toxicity

Clinician-reported toxicity

Cohort	Threshold	LENT-SOMA	% patients with toxicity	RTOG	% patients with toxicity
CFRT	M	N/A		N/A	
	MS	bV45 and consistency/frequency management ($P = 0.01$, $\delta M = 52.7$)	6%	bV45 and bowel frequency ($P = 0.04$, $\delta M = 16.96$)	10%
				bV55 and bowel frequency ($P = 0.03$, $\delta M = 3.8$)	10%
HFRT-4D	M	bV39 and frequency ($P = 0.03$, $\delta M = 17.66$)	30%	bV39 and diarrhoea ($P = 0.03$, $\delta M = 17.32$)	25%
				bV43 and diarrhoea ($P = 0.01$, $\delta M = 7.39$)	25%
				bV47 and diarrhoea ($P = 0.002$, $\delta M = 2.15$)	25%
	MS	bV39 and frequency ($P = 0.02$, $\delta M = 27.5$)	13%	bV39 and bowel frequency ($P = 0.04$, $\delta M = 27.17$)	11%
		bV43 and consistency ($P = 0.04$, $\delta M = 8.33$)	10%	bV43 and diarrhoea ($P = 0.03$, $\delta M = 24.50$)	9%
HFRT-5D	M	bV39 and consistency ($P = 0.05$, $\delta M = 32.59$)	26%	N/A	
		bV43 and consistency ($P = 0.03$, $\delta M = 15.99$)	26%		
		bV43 and frequency ($P = 0.05$, $\delta M = 13.48$)	31%		
	MS	bV43 and consistency ($P = 0.04$, $\delta M = 18.76$)	17%	N/A	

Patient-reported toxicity

	Urgency		Loose stools		Distress		Crampy pain		Problem	
Threshold →	M	MS	M	MS	M	MS	M	MS	M	MS
Cohort ↓										
CFRT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% patients with toxicity	—	—	—	—	—	—	—	—	—	—
HFRT-4D	**bV43 ($P = 0.006$, $\delta M = 7.04$)**	**bV43 ($P = 0.009$, $\delta M = 8.8$)** bV47 ($P = 0.03$, $\delta M = 1.55$)	**bV39 ($P = 0.009$, $\delta M = 24.78$)** ***bV43 ($P = 0.0005$, $\delta M = 11.74$)*** bV47 ($P = 0.05$, $\delta M = 0.07$)	N/A	bV43 ($P = 0.04$, $\delta M = 4.10$)	N/A	N/A	N/A	bV39 ($P = 0.04$, $\delta M = 10.50$) **bV43 ($P = 0.002$, $\delta M = 11.37$)**	bV39 ($P = 0.04$, $\delta M = 14.20$) **bV43 ($P = 0.003$, $\delta M = 12.22$)** bV47 ($P = 0.03$, $\delta M = 2.01$)
% patients with toxicity	41%	33%	43%	—	34%	—	—	—	54%	39%
HFRT-5D	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
% patients with toxicity	—	—	—	—	—	—	—	—	—	—

Where N/A is reported, no positive associations were found. Where $P \leq 0.01$, results are in bold. Where results were significant after Holm correction, results are bold and italicized. M = mild threshold (symptomatic patients are defined as having mild or worse symptoms). MS = moderate/severe (symptomatic patients are defined as having moderate or worse symptoms). % of patients with toxicity events excludes patients where data was unavailable (for full results see supplementary Tables R1–R9).

Fig 2. Mean volumes per dose-point by cohort and relationship with dose-volume constraints for Radiation Therapy Oncology Group (RTOG) (A−C) and LENT-SOMA (D−F) bleeding − moderate/severe threshold (rectum); UCLA-PCI loose stools − mild threshold (G−I; bowel); and RTOG diarrhoea − mild threshold (J−L; bowel). Significant results are marked with asterisks and their curve identifier is highlighted. Error bars represent standard deviations.

(≥rV65) with bleeding were not found, as might have been expected from previous reports [16,27,29]. Rectal dosimetry was mostly kept under constraints and specific attention was given to higher dose-points, reflecting QUANTEC guidance [5]. The fact that the lower rectal constraint (rV50) was exceeded more often with CFRT is probably due to the superior rectum receiving dose from pelvic irradiation, which was 60 Gy for the majority (67%) of patients. HFRT cohorts received 47 Gy to the PLN, which is equivalent to 55

Gy for an α/β ratio typical of late reactions (3 Gy). This aspect may also explain lower incidences of patients failing constraints with HFRT.

bV43 and bV47 were significantly predictive of diarrhoeal endpoints in the HFRT-4D cohort. Although non-significant after FDR correction, similar trends were observed in other cohorts with clinician-reported diarrhoea. The number of mandatory and/or optimal bowel constraints exceeded showed a relationship with toxicity. A

Table 4
Proposed dose-volume constraints for rectum and bowel

Rectum				Bowel			
2 Gy/fraction		3 Gy/fraction*		2 Gy/fraction		3 Gy/fraction*	
Dose constraint (Gy)	Volume required (%)	Dose constraint (Gy)	Volume required (%)	Dose constraint (Gy)	Volume required (cm^3) Mandatory (target)	Dose constraint (Gy)	Volume required (cm^3) Mandatory (target)
rV50	60	rV43	60	bV45	158 (78)	bV39	158 (78)
rV60	50	rV51	50	bV50	110 (24)	bV43	110 (24)
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.

study analysing the prognostic value of bowel dose-volume metrics for acute bowel toxicity in patients undergoing prostate and pelvic radiotherapy for high-risk PCa showed bV40-bV50 to be predictive with CFRT, whereas higher (bV55) and lower (bV15) dose-points were less predictive. Interestingly, derived constraints were similar to the ones we propose, although a whole intestinal cavity contouring method was used [32]. Other studies also showed similar results [33,34]. Robust dosimetric relationships with late toxicity have proved more elusive, but, to our knowledge, we report the largest prospectively collected patient series to date [35,36]. Taken together, these data support the mandatory threshold as a relevant dose limit when planning pelvic radiotherapy to avoid grade 2+ diarrhoea. However, we also observed a relationship between exceeding optimal constraints and toxicity. We therefore recommend using optimal constraints as target doses and planning objectives for pelvic IMRT to ensure minimal gastrointestinal toxicity and that mandatory constraints should not be compromised to ensure acceptable gastro-intestinal side-effect rates. We propose that the optimal bV50-CFRT/bV43-HFRT constraint should be updated to 24 cm^3 instead of 17 cm^3 given our results showing this level to be more appropriate for predicting gastrointestinal side-effects. These new findings may usefully inform clinical trials and non-trial clinical practice.

We previously showed that moderate/severe gastro-intestinal toxicity was reported in about a third of patients meeting rectal constraints, whereas no gastrointestinal side-effects were reported in 10% of patients failing six or more constraints [27]. We observed similar relationships in this dataset. In addition to uncertainties in reporting dosimetry and toxicity, this result may be attributed to patient-related and environmental factors [37–41]. More-over, as many as 50% of patients have multiple gastro-intestinal diagnoses when symptoms, which may be misattributed to radiotherapy, are investigated [18].

Our data support that, when dose-volume parameters are kept below tight constraints, gastrointestinal toxicity is low and planning dosimetry loses predictive power for re-sidual moderate/severe gastrointestinal toxicities in the setting of PLN-IMRT. This conclusion suggests that if not

escalating radiation dose, further technical development of radiotherapy for PCa may only achieve marginal improve-ments in gastrointestinal toxicity outcomes unless it re-duces the rates of patients where constraints are exceeded. Future research needs to also incorporate contributing biological mechanisms of radiation-induced toxicity, which may help achieve superior clinical stratification of patients at risk of significant side-effects, as suggested by other authors.

To conclude, we provide an evidence base for safely delivering PLN-IMRT using CFRT or HFRT. We propose the constraints summarised in Table 4 as benchmarks for CFRT and HFRT and that the planning goal should be to achieve the target (optimal) bowel constraints whenever possible.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.02.012.

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