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Original Research Article

Refinement & validation of rectal wall dose volume objectives for prostate hypofractionation in 20 fractions

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ABSTRACT

Background and purpose: Dose-volume objectives for the rectum have been proposed to limit long term toxicity after moderately hypofractionated radiotherapy (MHRT) for localized prostate cancer. The purpose of the present study is to validate and possibly refine dose volume objective for the rectal wall after 20-fraction MHRT.

Materials and methods: All patients treated by 20-fraction MHRT at a single Institution were identified and relative rectal wall (%RW) DVH retrieved. The endpoint of the study is the development of grade 2 + late rectal bleeding (LRB) according to a modified RTOG scale. Clinical and dosimetric predictors of LRB were investigated at both uni- and multi-variable analysis.

Results: 293 patients were identified and analyzed. Of them, 35 (12%) developed the endpoint. At univariable analysis, antithrombotic drug usage (yes vs no), technique (3DCRT vs IMRT/VMAT) and several %RW DVH cut-points were significantly correlated with LRB. However, within patients treated by 3DCRT (N = 106), a bi-variable model including anti-thrombotic drug usage and selected %RW dose/volume metrics failed to identify independent dosimetric predictors of LRB. Conversely, within patients treated with intensity modulation (N = 187), the same model showed a progressively higher impact of the percent of RW receiving doses above 40 Gy. Based on this model, we were able to confirm (V32), refine (V60) and identify a novel (V50) cut-point for the %RW.

Conclusion: We recommend the following dose volume objectives for the %RW in order to minimize the risk of LRB after 20-fraction MHRT: V32 $\leq$ 50%; V50 $\leq$ 25.8% and V60 $\leq$ 10%.

1. Introduction

In the last decade, external beam radiotherapy (RT) for localized prostate cancer has leaned towards shorter schedules in order to decrease both patient logistic load and health care costs [1]. Several clinical trials support the use of moderately hypofractionated RT (MHRT) in 20–28 fractions over conventionally fractionated RT in 35–40 fractions [2–7].

It has been shown that the possibility to obtain concave dose distributions at planning through intensity modulation reduces the risk of long term rectal toxicity [8]. Recently, also image guidance has shown to be associated with decreased late rectal toxicity [9]. Moreover, since the α/β ratio of late responding tissues is considered to be higher than the one of prostate cancer [10,11], (moderate) hypofractionation is expected to be less toxic on late responding tissues than an isoeffective tumor dose at 2 Gy/fraction. However, despite technical improvements and a favorable radiobiological scenario, the rectum remains a dose-limiting organ for prostate external beam radiotherapy, including MHRT [2,6,12–15].

Dose-volume objectives are placed at planning on the rectum (or the rectal wall-RW) in order to control for (and possibly) limit its dosage. However, there are scarce data looking at the relationship between individual dose/volume metrics and late rectal toxicity in the setting of MHRT [9,16–18] particularly regarding the 20-fraction schedule that is widely supported by the available trials

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[2,3,6]. In the present paper we have analyzed our experience with MHRT in 20 fractions in order to validate and possibly refine dose volume objectives for late rectal bleeding (LRB).

2. Methods and materials

2.1. Patient selection

All patients treated with MHRT at a single Institution until December 2017 were considered. From 2003 to 2007, MHRT had been offered within a prospective trial to patients with NCCN intermediate to high risk disease as extensively reported before [2,10,19,20]. Afterwards, MHRT was considered for patients with localized prostate cancer in whom elective treatment of the pelvic lymph nodes was not planned and not fitting or refusing other research protocols regardless the risk group. For patients treated outside research protocols, the consent requirement was waived being a retrospective chart review with no more than minimal risks for the patients.

2.2. Treatment planning

The schedule consisted in 62 Gy delivered at 3.1 Gy per fraction over 5 weeks (4 times per week). As a rule, the clinical target volumes (CTV) included both the prostate and the entire seminal vesicles. In 9 patients (3.1%) with low risk disease, only the prostate was targeted. CTV was expanded to the planning target volume (PTV) by 10 mm isotropically except posteriorly (rectum) where it was reduced to 6 mm.

RT technique continuously evolved through years. Up to 2009, a 6-field 3D conformal technique (3DCRT) was used to include the PTV within the 90% prescription isodose. Afterwards, a 5-field IMRT technique was introduced, while VMAT (2 arcs) was implemented in 2014. Weekly portal films (with bone alignment) were taken until daily cone beam CT was introduced in 2014. Fiducials (N:3–4) were implanted to selected patients starting 2015.

The patient was instructed to undergo simulation/treatment with an empty rectum and a half full/half empty bladder. The outer rectal wall (including filling) was contoured on the planning CT according to Fiorino et al. [21]. The inner rectal wall was obtained by subtracting 3 mm to the outer rectal contour and the rectal wall obtained by subtracting the inner filling to the outer contour [22]. The rectal wall (RW) dose objectives at planning also changed throughout years with the amount of the RW receiving up to 38 Gy less than 50% (V38 $\leq$ 50%), V54 $\leq$ 30% and Dmax (0.035 cc) $\leq$ 62 Gy in the 3DCRT era [20], later refined to V32 $\leq$ 50%, V60 $\leq$ 15% and Dmax (0.035 cc) $\leq$ 63.5 Gy with intensity modulation.

2.3. Statistics

Patients were followed at 3-month intervals for 3 years and twice per year thereafter. Toxicity was prospectively recorded at each visit and rectal bleeding was scored according to a modified RTOG scale as previously reported [23]: Grade 1 (GR1), slight bleeding ($\leq$2/week); GR2, intermittent bleeding (>2/week); GR3, bleeding requiring surgery, coagulation procedure or transfusion; GR4, necrosis, perforation, fistula.

The endpoint of this study is the development of GR2 or higher late rectal bleeding (LRB) during the follow-up that would include any episode of bleeding graded 2 or more according to the above modified RTOG scale at least 3 months after treatment completion. Patients experiencing GR2+ LRB were referred for further evaluation that included a colonoscopy.

Individual relative RW cumulative DVH were extracted and compared between patients with and without LRB. Distribution of values between groups were compared with the chi-square and the Mann Whitney *U* test as appropriate. The time to LRB was estimated with the Kaplan Meier method and test of significance was based on the log-rank test. Hazard Ratios (HR) and their 95% confidence intervals were reported from Cox regression model; firstly we considered each variables separately (univariate analysis) then, in a multivariable approach, we tested all variables with a significance level <0.2 at univariate analysis. A stepwise forward selection based on Wald statistics with enter and remove limits set to 0.05 and 0.10 respectively, was carried out. A bootstrap validation based on 1000 samples was used to assess internal validation and HR/95% confidence intervals had been reported. Statistical significance was claimed for p values below 0.05. Statistical analyses were carried out using the SPSS software (IBM SPSS Statistic v. 21.0).

Median follow up is 45.3 months (3.0–195.7 months).

3. Results

3.1. Patients

Out of 299 consecutive patients, 6 did not have retrievable DVH for a final number of 293 analyzed patients.

Selected patient, tumor and treatment characteristics are reported in Table 1. All, but one patient treated with VMAT, had also daily IGRT with CBCT. None of the patients treated with 3DCRT had undergone CBCT during treatment.

3.2. RW DVH

The average relative cumulative rectal wall DVH by technique is reported in Fig. 1. Mann-Whitney *U* test shows statistically different average RW DVH between 3DCRT and IMRT/VMAT in the dose ranges from 11 to 54 Gy and from 62 to 65 Gy (Fig. 1). The number of patients not meeting the dose-volume objectives by technique are reported in Table 2. More patients treated with 3DCRT were unable to meet the intermediate dose volume objectives (V32 and V38) compared to those treated with intensity modulation; conversely the RW Dmax was more controlled with conformal over intensity modulated RT.

3.3. LRB incidence and predictors in the whole population

Grade 1, 2 and 3 late rectal bleeding was observed in 26 (8.9%), 28 (9.6%) and 7 (2.4%) patients, respectively. Grade 2 reactions had been recorded after a mean time of 12.9 months (SD: 7.0) after RT while GR3 ones after 17.8 (8.1) months (p = 0.111). All GR2-3 reactions had been observed within 33.9 months after treatment completion. The actuarial cumulative incidence of GR2-3 LRB at 3 yrs is 13.1 ± 2.0%. Mean duration of GR2-3 LRB was 9.7 months (SD: 8.8 mths) and similar for GR2 (9.5 months, SD: 9.1 mths) and GR3 (10.6 months, SD: 8.1 mths) reactions (p = 0.611). There was an inverse correlation between the time to onset of LRB and its duration with earlier events lasting longer than later ones (Spearman's rho: −0.395, p = 0.017). Patients whose onset of toxicity was within the median time of 12.6 months had a significantly longer duration of RB (mean: 12.64 months, SD: 9.74 mths) than those with a delayed onset (mean: 6.84 months, SD: 6.84 mths), p = 0.031.

Results of uni-variable analysis on the risk of GR2-3 LRB are reported in Table 3. Among non-dosimetric covariates only antithrombotic drug usage (yes vs no) and technique (3DCRT vs IMRT/VMAT) were significantly correlated with LRB. Several RW

Table 1
Selected patient-, tumor- and treatment-characteristics.

Characteristic	Stratification	Mean/#	Interq range/%
Age (yrs)	Continuum	74	71–77
Antithrombotic drugs	None	185	63.1%
	Antiaggregants	88	30.0%
	Anticoagulants	20	6.9%
Diabetes	None	218	74.4%
	Yes	39	13.3%
	Missing	36	12.3%
Abdominal Surgery	None	154	52.6%
	Yes	77	26.3%
	Missing	62	21.2%
Hemorroids	None	164	56.0%
	Yes	48	16.4%
	Missing	81	27.4%
Androgen Deprivation	No	72	24.6%
	Yes	221	75.4%
T stage	T1	138	47.1%
	T2	133	45.4%
	T3	22	7.5%
Gleason Grade Group	I	66	22.5%
	II	127	43.3%
	III	65	22.2%
	IV	21	7.2%
	V	14	4.8%
iPSA (ng/ml)	Continuum	12.5	8.0–13.5
Risk	Low	51	17.4%
	Intermediate	167	57.0%
	High	75	25.6%
Treated Volume	P + SV	284	96.9%
	P only	9	3.1%
Treatment position	Supine	261	89.1%
	Prone	32	10.9%
Technique	3DCRT	106	36.2%
	IMRT	29	9.9%
	VMAT	158	53.9%
IGRT	PI	132	45.1%
	CBCT	161	54.9%
Fiducials	No	253	86.3%
	Yes	40	13.7%
Acute RB	None	257	87.7%
	Any	36	12.3%
Rectal Volume (cc)	Continuum	41.9	28.9–47.0

Abbreviations: SV: seminal vesicles; P: prostate; IGRT: image guided radiotherapy; PI: Portal Imaging; CBCT: cone beam CT; RB: rectal bleeding; iPSA: initial PSA

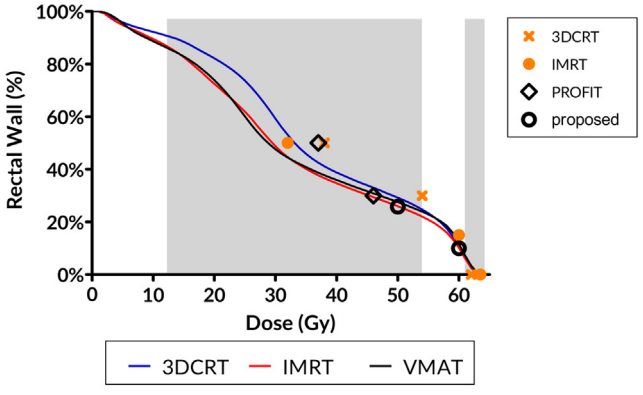

Fig. 1. Average RW cumulative DVH by technique. Rectal wall dose volume objectives for the PROFIT trial from Martin et al. [28].

dose/volume cut points (V25, V35, V40, V45) were significant at univariate analysis (Table 3).

At multivariable analysis, technique (IMRT/VMAT vs 3DCRT, HR: 0.414, 95%CI: 0.209–0.822, p = 0.012), antithrombotic drugs (yes vs no, HR: 3.830, 95%CI: 1.922–7.635, p < 0.0001) and RW V35 (>43.2% vs <43.2%, HR:2.156, 95%CI: 1.018–4.569, p = 0.045) were independently correlated with the endpoint. The model was confirmed at bootstrap analysis as it follows: technique (IMRT/VMAT vs 3DCRT, HR: 0.414, 95%CI: 0.213–0.788, p = 0.008), antithrombotic drugs (yes vs no, HR: 3.830, 95%CI: 1.837–8.499, p = 0.001) and RW V35 (>43.2% vs <43.2%, HR:2.156, 95%CI: 1.091–4.909, p = 0.029).

3.4. LRB predictors by technique

Next we focused on patients treated with conformal radiotherapy or intensity modulated RT (IMRT or VMAT). Fig. 2 illustrates the hazard ratios of LRB by the percent of RW that receives a given dose of radiotherapy in a bi-variable model including antithrombotic usage (yes vs no) after stratification by RT technique. Within patients treated by 3DCRT (Fig. 2a), the bi-variable model failed to show a significant correlation between selected RW dose/volume metrics and LRB. Conversely, after adjusting for drug usage, hazard ratios of LRB progressively increased with dose for IMRT/VMAT plans becoming statistically significant at 60 Gy (Fig. 2b). Hazard ratios were confirmed at bootstrap analysis for both groups. However, within the group of patients treated with IMRT/VMAT, HR in the range V40-V55 were significant (V40: 1.083, 95%CI: 1.010–1.202; V45: 1.098, 95%CI: 1.019–1.219; V50: 1.101, 95%CI: 1.022–1.204; V55: 1.096, 95%CI: 1.013–1.221), while V60 was borderline significant (HR: 1.119, 95%CI: 0.992–1.257, p = 0.054).

Within patients treated with IMRT/VMAT, we then explored novel cut-offs at the lower tertile for RW V40 (≤34.5% vs >34.5%), V50 (≤25.8% vs >25.8%) and V60 (≤10.0% vs >10.0%). Hazard ratios on the risk of GR2-3 LRB were 2.314 (95%CI: 0.659–8.132, p = 0.191), 8.246 (95%CI: 1.088–64.481, p = 0.041) and 4.325 (95%CI: 0.978–19.125, p = 0.054) for V40, V50 and V60, respectively. The proposed dose volume objectives for V50 and V60 are illustrated in Fig. 1, while the one on V40 was disregarded due to the lack of statistical significance.

Fig. 3 shows the cumulative incidence of LRB by RW V50/V60 and anticoagulant usage in patients treated with IMRT/VMAT only.

4. Discussion

In our 16-yr experience with 20-fraction MHRT, the treatment technique has evolved and the dose volume objectives at planning have been progressively refined [10]. For example, in the 3DCRT era, 50% of the RW was allowed to receive less than 38 Gy [10], while switching to IMRT/VMAT the dose limit was tightened at 32 Gy (Table 2). As a consequence of both technique improvement and dose-objective refinement, the average cumulative RW% DVH became significantly better for IMRT/VMAT over 3DCRT plans in a wide dose range interval as shown in Fig. 1.

We also found that, in a slightly narrower but fully overlapping dose interval (35–40 Gy, Table 3), the risk of GR2-3 LRB was correlated to the percent of rectal wall being irradiated, suggesting a clinical benefit as well. The fact that, within a mixed population of patients treated at different Institutions (and with different techniques), intermediate to low rectal dose levels (rather than higher dose levels) are predictive of LRB is not a novel finding [24]. The issue is whether this represents the region of the RW DVH that needs to be (further) constrained in order to improve clinical outcomes.

Table 2
Number of patients exceeding the dose/volume objectives on the RW by technique.

Dose/volume objective	Threshold	Applies to	Technique				p value	Overall N = 293	
Metric			3DCRT N = 106		IMRT/VMAT N = 187				
			N	%	N	%		N	%
V32	>50%	**IMRT**	60	56.6%	**23**	**12.3%**	<0.001	83	28.3%
V38	>50%	**3DCRT**	**5**	**4.7%**	2	1.1%	0.050	7	2.4%
V54	>30%	**3DCRT**	**10**	**9.4%**	24	12.8%	0.383	34	11.6%
V60	>15%	**IMRT**	29	27.4%	**34**	**18.2%**	0.067	63	21.5%
V62	>0*	**3DCRT**	**56**	**52.8%**	151	80.7%	<0.001	207	70.6%
V63.5	>0*	**IMRT**	18	17.0%	**79**	**42.2%**	<0.001	97	33.1%

*0.035 cc

IMRT has several dosimetric advantages over 3DCRT particularly in the intermediate dose region [25]. Moreover, it has been associated with a more favorable GI toxicity profile than 3DCRT after conventionally fractionated RT [8]. However, our data clearly show that the effect of technique on LRB cannot be explained only in terms of percent of RW exposed to a given dose of radiation. In a matched group of patients treated with either 3DCRT or IMRT at the dose of 1.8 Gy per fraction, Troeller et al found significantly different average RW DVH by technique across the majority of dose bins, but the differences were relatively small and inconsistent to the larger difference in GR2+ CTCAE GI toxicity rates between patients treated with conformal or intensity modulated RT [26]. After an elegant and exhaustive discussion on all possible causes for this discrepancy, the Authors concluded that the reason for the superiority of IMRT over 3DCRT remains unclear and that dosimetric parameters should be specific for each treatment modality [26]. It should be also noted that the recent ASTRO, ASCO and AUA Evidence-based guideline on hypofractionated RT does not recommend non modulated 3DCRT techniques when delivering MHRT [27]. Therefore, unlike other Authors [9,17], we focused on patients treated with IMRT/VMAT only.

The bi-variable analysis in this subgroup of patients showed that below 40 Gy there is poor correlation between individual % RW V_{DOSE} and LRB (Fig. 2b); of note, the vast majority of patients had met the V32 dose volume objective (Table 2), and all but 6 (96.8%) would have met the one at V37 <50% (Fig. 1) of the PROFIT trial [6]. Unfortunately, in the CHHiP trial, the rectum was contoured as a solid organ [3] and no direct comparison with our experience can be made. Therefore, within this dose range, we conclude that the current dose/volume objective for V32 ($\leq$50%) is adequate.

Conversely, the bi-variable model showed a progressively higher impact of the percent of RW receiving doses above 40 Gy. (Fig. 2b). Using the lower tertile threshold we were able to define a novel RW dose volume objective (V50 $\leq$25.8%) that may further reduce the risk of LRB for patients treated with intensity modulated 20-fraction MHRT. Of note, in the 45–50 Gy dose range, we did not have any RW dose objective. Moreover, only 37.4% of our patients would have satisfied a slightly relaxed objective at 46 Gy ($\leq$30%) that was mandatory in order to be eligible for randomization within the PROFIT trial [28].

Finally, in the higher dose range, our data suggest that a refinement of the %RW dose objective at V60 from $\leq$15% to $\leq$10% may help to limit LRB as well.

Antithrombotic drugs are known to be associated with an increased risk of LRB [15,29]. Active anticoagulant therapy was an exclusion criterion for the CHHiP trial [3] but not the PROFIT or NRG Oncology 0415 ones [6,7]. Our data caution on the higher risk of LRB in case of anticoagulant/antiaggregant usage, especially when the %RW V50/V60 objectives are not met (Fig. 3). However, the same figure suggests that in patients with favorable RW dosimetry the risk of LRB is mitigated despite anticoagulants and thus acceptable.

The present study has several peculiarities and few limitations.

First, despite our earlier studies on the α/β for rectal toxicity [10], we did not attempt to express the dose at 2 Gy fraction but we reported nominal doses. Since the 20-fraction schedule is the one with the most robust evidence base to date [2,3,6], and is currently recommended by treatment guidelines, systematic reviews and cooperative groups [27,30,31] this approach would help to implement dose volume objectives without the inherent approximations and uncertainties of the linear quadratic transformation [32,33].

Second, this is the largest single-Institution series on MHRT which allowed us to analyze dosimetric predictors of LRC after correcting for clinical potential confounders in order to refine/validate dose volume objectives [29,34].

Third, in the vast majority of patients we treated both the prostate and the entire seminal vesicles to the prescription dose. The inclusion of (at least part of) the SV in the target obviously depends on the risk of their involvement [35]. However, when included, most Authors would agree on either covering only their proximal part [36] or on under-dosing their distal portion [3]. Moreover, we prescribed a slightly higher dose to the target, 62 Gy, as opposed to 60 Gy in both the PROFIT and the CHHiP trials [3,6]. Therefore, it is likely that the average %RW DVH reported here (Fig. 1) is to be considered on the upper end side of 20-fraction MHRT and that both prescribing a slightly lower total dose and excluding part of the SV from the prescription dose would provide, on average, more favorable RW DVH.

Fourth, we decided to focus only on a particular aspect of rectal toxicity, bleeding, because it is an objective sign, not prone to misinterpretation and easily recalled by the patient [37]. Since the prevalence of RB in normal adults is between 14% and 19% [38], and since the RTOG scoring criterion is somewhat vague in differentiating between grades 1 and 2 ('slight' vs 'intermittent' RB)[37], we used a modified RTOG scale that introduces the number of episodes per week [39,40]. In analyzing the endpoint we decided to estimate the survival function and not just the crude incidence, because earlier events usually last longer (as shown here) and thus have a potential higher impact than later ones.

Finally, since the radiobiology of gastrointestinal toxicity may be different among the various clinical scenarios [29,34], dose-volume objectives herein are intended to be used for LRB only.

Table 3
Univariable analysis on the risk of GR2+ late rectal bleeding.

Covariate	Stratification	GR2+ LRB at 3 yrs	HR (95% CI)	p value
Antithrombotic drugs	No	17.4 ± 2.0%	1	
	Yes	23.0 ± 4.2%	3.346 (1.694–6.609)	0.001
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	None	17.4 ± 2.0%	1	
	Antiaggregants	11.9 ± 4.6%	3.181 (1.558–6.496)	0.001
	Anticoagulants	17.8 ± 10.6%	4.114 (1.466–11.543)	0.007
Diabetes	No	12.2 ± 2.3%	1	
	Yes	16.6 ± 6.2%	1.385 (0.568–3.377)	0.473
Age	<74 yrs/old	14.4 ± 3.2%	1	
	≥74 yrs/old	12.0 ± 2.6%	0.791 (0.411–1.522)	0.483
Abdominal Surgery	No	13.4 ± 2.9%	1	
	Yes	12.2 ± 3.8%	0.925 (0.418–2.044)	0.846
Hemorroids	No	14.6 ± 2.8%	1	
	Yes	13.1 ± 5.5%	0.727 (0.276–1.913)	0.519
Tmt position	SUPINE	14.6 ± 2.3%	1	
	PRONE	0	0.042 (0–3.976)	0.172
Treated Volume	P	0	1	
	P + SV	13.7 ± 2.1%	4.653 (0.158–136.615)	0.373
Androgen Dep	No	11.4 ± 4.2%	1	
	Yes	13.8 ± 2.4%	1.407 (0.616–3.212)	0.418
Technique	3DCRT	19.4 ± 3.9%	1	
	IMRT/VMAT	9.5 ± 2.3%	0.659 (0.474–0.915)	0.013
IGRT	PI	15.7 ± 3.2%	1	
	CBCT	10.2 ± 2.5%	0.644 (0.333–1.243)	0.189
Fiducials	No	12.9 ± 2.2%	1	
	Yes	15.4 ± 6.7%	1.049 (0.407–2.701)	0.921
Acute RB	No	12.0 ± 2.1%	1	
	Yes	20.2 ± 6.9%	1.735 (0.760–3.960)	0.191
Rectal volume	≤35.2 cc	11.8 ± 2.8%	1	
	>35.2 cc	14.3 ± 3.0%	1.230 (0.637–2.374)	0.537
D5%	≤61.25 Gy	11.4 ± 2.7%	1	
	>61.25 Gy	14.7 ± 3.1%	1.280 (0.663–2.470)	0.462
RW V15	≤86.6%	14.1 ± 3.0%	1	
	>86.6%	12.0 ± 2.7%	0.853 (0.443–1.641)	0.634
RW V20	≤78.8%	11.4 ± 2.8%	1	
	>78.8%	14.8 ± 3.0%	1.390 (0.717–2.697)	0.330
RW V25	≤64.3%	17.5 ± 2.3%	1	
	>64.3%	17.6 ± 3.2%	2.345 (1.154–4.767)	0.019
RW V30	≤50.3%	18.8 ± 2.4%	1	
	>50.3%	16.2 ± 3.1%	1.755 (0.889–3.465)	0.105
RW V35	≤43.2%	17.4 ± 2.3%	1	
	>43.2%	17.6 ± 3.2%	2.684 (1.294–5.565)	0.008
RW V40	≤37.7%	8.1 ± 2.4%	1	
	>37.7%	16.8 ± 3.1%	2.254 (1.109–4.581)	0.025
RW V45	≤32.8%	8.1 ± 2.3%	1	
	>32.8%	17.9 ± 3.3%	2.326 (1.144–4.727)	0.020
RW V50	≤28.5%	9.5 ± 2.5%	1	
	>28.5%	15.6 ± 3.1%	1.787 (0.905–3.527)	0.095
RW V55	≤23.2%	12.4 ± 2.8%	1	
	>23.2%	12.8 ± 2.8%	1.125 (0.585–2.166)	0.723
RW V60	≤11.9%	12.3 ± 2.8%	1	
	>11.9%	13.8 ± 3.0%	1.138 (0.591–2.198)	0.698
RW V38	≤50.0%	13.0 ± 2.1%	1	
	>50.0%	14.3 ± 3.2%	1.086 (0.149–7.926)	0.935
RW V54	≤30.0%	14.0 ± 2.2%	1	
	>30.0%	5.1 ± 4.2%	0.422 (0.101–1.757)	0.236
RW V62	0	12.3 ± 3.7%	1	
	>0	13.4 ± 2.4%	1.067 (0.515–2.214)	0.861
RW V32	≤50.0%	10.9 ± 2.2%	1	
	>50%	17.1 ± 4.2%	1.624 (0.831–3.174)	0.156
RW V60	≤15.0%	11.1 ± 2.1%	1	
	>15.0%	19.9 ± 5.2%	1.901 (0.950–3.802)	0.069
RW V63.5	0	13.5 ± 2.5%	1	
	>0	12.1 ± 3.4%	0.888 (0.437–1.805)	0.744

Abbreviations: SV: seminal vesicles; P: prostate; IGRT: image guided radiotherapy; PI: Portal Imaging; CBCT: cone beam CT; RB: rectal bleeding; RW: rectal wall; D5%: dose to 5% of RW.

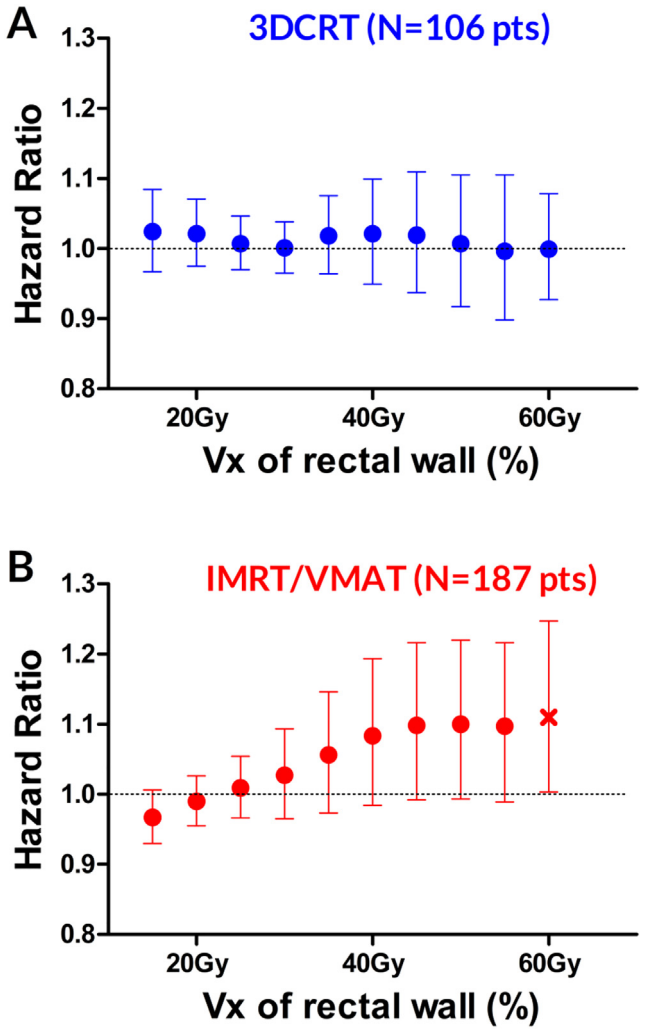

Fig. 2. Hazard ratios of GR2-3 LRB by technique and percent RW that receives a given dose of radiotherapy. (A) 3DCRT patients; (B) IMRT/VMAT patients. • not statistically significant Hazard Ratio; × statistically significant Hazard Ratio.

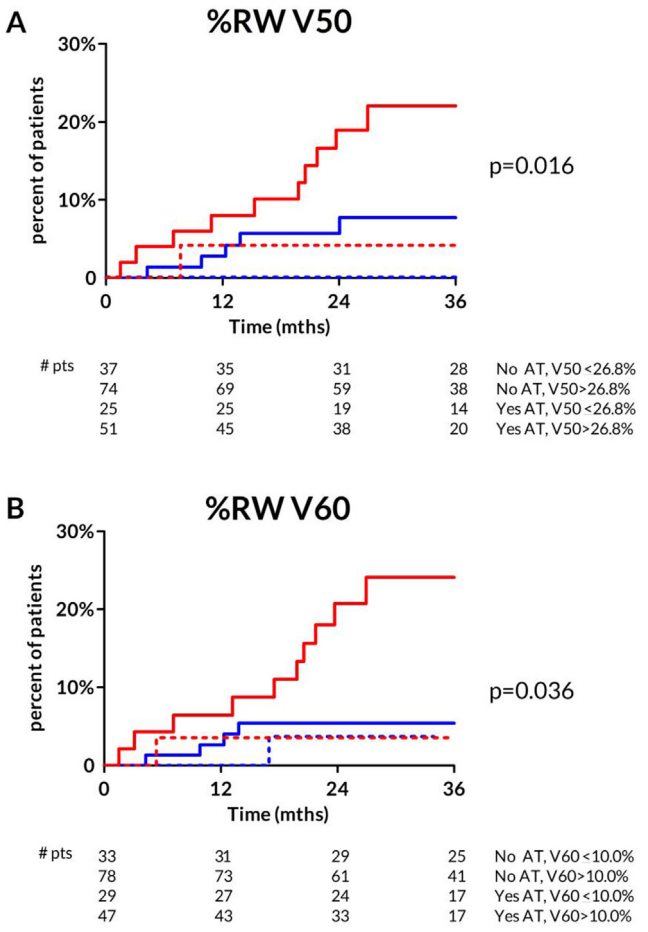

Fig. 3. Cumulative incidence of LRB by Antithrombotic drug usage (Yes vs No) and % RW V50 (≤25.8% vs > 25.8%) (A) or V60 (B) (≤10.0% vs >10.0%) after selecting only patients treated with intensity modulation. The overall p value (4 strata) is shown. Blue lines: No antithrombotic (AT) drug usage; Red lines: Yes AT drug usage; Solid lines: %RW > tertile value (25.8% and 10% for V50 and V60, respectively); Dashed lines: %RW ≤ tertile value. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Among other limitations, the present study suffers from those related to any retrospective analysis, even if a significant part of the patients were treated within a prospective controlled study and toxicity was always scored pro-actively at each visit [2]. Moreover, unlike others [9], we were unable to tease out a significant benefit for IGRT on LRB, since the majority of patients treated with intensity modulated underwent daily CBCT (Table 1). Therefore, our results are to be used in the context of intensity modulation with daily IGRT [12]. This also implies that the deterioration of the dose distribution during the course of treatment is not accounted for, though the improvement in the accuracy to predict LRB between the planned and delivered dose in prostate radiotherapy seems quite modest [41]. Moreover, we have shown in a previous study on a group of similar patients treated with conventional fractionation (otherwise identical in target volume and RW delineation as well as PTV margins) that rectal wall DVHs randomly change during treatment, but this does not have a significant impact on the probability of side effects [42]. Finally, the present study did not account for either biological markers for rectal toxicity such as calprotectin [43] or genetic predisposition for LRB such as reduced gene expression [44], though their role in clinical practice is unclear.

In conclusion, based on the results of the present study, we recommend the following dose volume objectives for the RW in order to minimize the risk of LRB after 20-fraction MHRT delivered through intensity modulation: V32 ≤ 50%; V50 ≤ 25.8% and V60 ≤ 10%. Patients undergoing antithrombotic therapy are at higher risk of LRB and, in them, dose volume objectives on the % RW (particularly at V50 and V60) should be strictly enforced.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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