Association between rectal bleeding and the absolute dose volume of the rectum following image-guided radiotherapy for patients with prostate cancer

KAZUKI KOTABE[1], HIDETSUGU NAKAYAMA[1], ARUGA TAKASHI[2], ATSUKO TAKAHASHI[3], TSUYOSHI TAJIMA[4] and HARUKI KUME[3]

[1]Department of Radiation Oncology, National Center for Global Health and Medicine; [2]Department of Radiation Oncology, Funabashi Municipal Medical Center; Departments of [3]Urology and [4]Radiology, National Center for Global Health and Medicine, Tokyo 162-8655, Japan

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Abstract. The association between rectal bleeding and the received dose relative to the volume of the rectum is well established in prostate cancer patients who have undergone radiotherapy. The relative volume of the rectum is affected by the rectal anatomical volume, which depends on the definition of rectal length. Compared with the relative rectal volume, the absolute volume of the rectum may be more associated with rectal bleeding. The present study investigated the absolute volume of the rectum that may be used to predict late rectal bleeding following intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). The cases of 82 patients of prostate cancer, who underwent IMRT and IGRT, were retrospectively evaluated by evaluating dose volume histograms. The median patient age was 73.4 years (range, 51.3-85.9 years). The median total prescribed dose was 76 Gy given in 38 fractions. The absolute and relative dose volumes of the rectum were evaluated by multivariate analysis, and the optimal dose to prevent rectal bleeding was determined. The actuarial ≥grade 1 rectal bleeding rate at 4 years was 4.5% (95% confidence interval, 1.5-13.4%) with a median observation period of 45.3 months. The absolute rectal volume (ml) treated with 60 Gy was the only significant risk factor for rectal bleeding ($P<0.05$), but the relative rectal volume (%) was not identified as a significant factor by the multivariate analysis. When the rectal volume of 5 or 10 ml received 60 Gy (D5cc and D10cc), rectal bleeding was expected to occur in 3.3 and 7.3% of the patients, respectively. Rectal D5cc ≤60 Gy is recommended to prevent late ≥grade 1 rectal bleeding in IGRT.

Correspondence to: Dr Hidetsugu Nakayama, Department of Radiation Oncology, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku, Tokyo 162-8655, Japan
E-mail: hnakayama@hosp.ncgm.go.jp

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Introduction

In a nationwide randomized trial in the United Kingdom, the prostate cancer-specific mortality and disease progression rates in patients with prostate cancer who have undergone external-beam radiotherapy at a dose of 74 Gy in 37 fractions were demonstrated to be comparable to those of surgery (1). Prior to that landmark trial, dose-escalation randomized studies reported that high-dose radiotherapy resulted in a lower incidence of biochemical disease progression compared with conventional doses (2-6). A meta-analysis (7) also reported improved biochemical disease free-progression rates, but an increased incidence of late gastrointestinal toxicities (3,4,6,8).

When the prostate is irradiated using conventional methods, a similar dose is irradiated to the rectum near the prostate. The development of intensity-modulated radiotherapy (IMRT) allows for reductions in the radiotherapy dose to the rectum. Incidences of late rectal bleeding in patients with prostate cancer has successfully reduced with the use of IMRT (9,10), but rectal bleeding remains a major concern, and even if grade 1 toxicity occurs, rectal bleeding reduces the quality of life of individuals (11). The ideal radiotherapy procedure for prostate cancer involves total tumor control without incurring rectal bleeding. The addition of image-guided radiotherapy (IGRT) to IMRT is expected to decrease the risk of rectal bleeding.

Numerous studies have examined the occurrence of rectal bleeding by analyzing the radiation dose to the rectum using dose volume histogram parameters (9,10,12-20). In the majority of these studies, the dose to the rectum is defined as a relative dose, and not the absolute dose. In addition, the anatomical definition of the rectum differs across the studies, making it difficult to compare the results of each study. We hypothesized that the absolute dose, which is less dependent on the volume of the delineated rectum, may have more reproducibility compared with the relative dose. The absolute dose

is also more easily compared among studies compared with the relative dose.

The present study focused on the absolute dose to the rectum to determine whether it is superior for predicting rectal bleeding compared with the relative dose. The findings also clarified the thresholds of rectal bleeding with the absolute dose, and a cut-off value of the absolute dose was presented that was obtained using a receiver operating characteristic curve and logistic regression analysis.

Patients and methods

Patients and follow-up. The present study was approved by the Institutional Review Board of the National Center for Global Health and Medicine Committee (approval no. NCGM-G-002165-00) with a waiver of informed consent due to the retrospective nature of this study. The cases of patients with prostate cancer who underwent definite radiotherapy between January 2007 and January 2016 at the National Center for Global Health and Medicine were retrospectively reviewed. Patients who underwent radiotherapy combined with brachytherapy were excluded.

Eighty-seven consecutive patients underwent definitive radiotherapy. Four patients were excluded as the treatment-planning computer was unavailable. One patient who had ulcerative colitis was excluded. The cases of the remaining 82 patients were evaluated. None had inflammatory bowel disease, Crohn's disease or ulcerative colitis. Patient characteristics are summarized in Table I.

All patients had clinical T1-T4N0M0 histologically proven prostate adenocarcinoma. The median age of patients was 73.4 years (range, 51.3-85.9 years). Thirty-eight (46.3%), 22 (26.8%) and 22 (26.8%) patients had serum prostate specific antigen (PSA) levels of <10, >10-20 and >20 ng/ml, respectively. The numbers of low-, intermediate- and high-risk patients, classified according to the system of D'Amico *et al* (21) were 30 (36.6%), 18 (22.0%) and 34 (41.5%), respectively. Twenty (24.4%) patients underwent adjuvant maximum anti-androgen therapy consisting of luteinizing hormone-releasing hormone and bicalutamide for a median period of 25 months (range, 2-74 months).

The median total dose was 76 Gy given in 38 fractions (range, 76.5 Gy given in 34 fractions-70 Gy given in 35 fractions). Four patients received the radiotherapy dose 2.5 Gy, and the remaining 78 patients received the radiotherapy dose 2.0 Gy, each at 5 times/week. All patients underwent IMRT for prostate and/or seminal vesicles. Prior to IMRT, 7 (8.5%) and 10 (12.2%) patients underwent pelvic lymph node radiotherapy at the dose 45 Gy given in 20 fractions and the dose 20 Gy given in 10 fractions using the four-field box technique, respectively. The patients were followed up every 3 months following the completion of radiotherapy for 3 years and then every 6 months thereafter.

Radiotherapy treatment. Simulation and treatment were performed with the patient in the supine position, with the use of an immobilized vacuum cushion. The patient had been instructed to have a comfortably full bladder and empty rectum for the treatment. The bladder, rectum, prostate and seminal vesicles were counted on a computed tomography imaging (CT) scan using a slice interval of ≤2 mm. Magnetic resonance imaging was used to confirm the position of the prostate and rectum. The clinical target volume (CTV) included the prostate and/or seminal vesicles. The volume of seminal vesicles was decided by the treating physician in reference to the T factor, serum PSA level and Gleason score of the patient. The planning target volume (PTV) comprised the CTV with a 0.3-1.0 cm margin posteriorly and 0.5-1.0 cm margins in all other directions. The median PTV volume for the prostate and/or seminal vesicles was 99.5 ml (49.0-291.7 ml). Cone beam CT (CBCT) imaging was applied every session prior to radiotherapy in all patients to observe the position of the target and organs. The patient drank 100-500 ml of water 30-60 min prior to the radiotherapy to fill the bladder. Rectal gas was deflated when there was too much air in the rectum as presented on the CBCT scan.

In each case, the rectum was defined from the anal verge or ischial tuberosities to the sacroiliac joint or rectosigmoid junction as a solid organ. The mean delineated rectal volume was 47.8±19.4 ml. The bladder was contoured from the apex to the dome as a solid organ. Radiotherapy was delivered using 10-15 MV photons via a 5- to 7-field IMRT technique. The PTV dose was typically prescribed to the 90-95% isodose lines in the IMRT plan.

Dosimetric analysis. The absolute (ml) and relative (%) volume doses of 60, 62, 64, 66, 68, 70, 72 and 74 Gy to the rectum in each of the 82 patients were reviewed using a treatment planning system (Eclipse; Varian Medical Systems, Palo Alto, CA). The equivalent dose delivered at 2.0 Gy/fraction was calculated using a linear-quadratic model with an α/β ratio of 10 (22).

Statistical analysis. The data are presented as the mean ± standard deviation. The Kaplan-Meier estimator method was used to examine the time point of rectal bleeding, calculated between the first day of radiotherapy and the date of rectal bleeding. The log-rank test was applied to compare the probability of rectal bleeding. Late rectal bleeding was evaluated according to the Common Terminology Criteria for Advanced Events (version 4.03) (23). The differences in continuous variables and categorical variables were examined by the Wilcoxon rank sum test and the chi-square test with Fisher's exact test, respectively. Welch's test was used to compare the doses in patients who underwent the four-field technique or not. Spearman's rank-order correlation was used to analyze dose volume parameters. The dose thresholds for rectal bleeding were assessed by determining the nonparametric area under the receiver operating characteristic curve (AUC). The cut-off value was defined as the point closest to the (0, 1) point. A Cox proportional hazards model was used to analyze independent variables. A logistic regression model was used for the estimation of the probability of a binary response based on dose volume variables. All statistical analyses were performed using STAT software (version 13.0; StataCorp LP, College Station, TX, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Rectal bleeding rate. The median observation period was 45.3 months (range, 14.3-118.7 months). Grade 2 and Grade 1

Table I. Patient characteristics (n=82).

Characteristic	Non-rectal bleeding (n=77)	Rectal bleeding (n=5)	P-value
Age, years	73.4±6.4	74.3±9.6	0.71
T factor			0.12
T1	40	4	
T2	21	0	
T3	14	0	
T4	2	1	
PSA			0.85
≤10	36	2	
10-20	21	1	
>20	20	2	
Gleason score			0.43
≤6	22	3	
7	27	1	
≥8	28	1	
Risk classification			0.99
Low	28	2	
Intermediate	17	1	
High	32	2	
Anti-androgen blockade therapy			0.65
Yes	19	1	
No	58	4	

PSA, prostate-specific antigen.

late rectal bleeding were observed in 3 (3.7%) and 2 (2.4%) patients, respectively. No patients experienced ≥grade 3 rectal bleeding. The patient characteristics did not significantly differ between the patients who had ≥grade 1 rectal bleeding and those without rectal bleeding as analyzed using the Wilcoxon rank sum test and the chi-square test (Table I). The actuarial ≥grade 2 rectal bleeding rates at 2 years and 4 years post-treatment were 1.5% [95% confidence interval (CI), 0.2-10.1] and 3.2% (95% CI, 0.8-12.4), respectively. The actuarial ≥grade 1 rectal bleeding rates at 2 and 4 years were 2.8% (95% CI, 0.7-10.1) and 4.5% (95% CI, 1.5-13.4), respectively.

Absolute and rectal volumes. The mean absolute volumes (ml) of 60 Gy received by the rectum (aV60), aV62, aV64, aV66, aV68 and aV70 in the patients with ≥Grade 1 late rectal bleeding were significantly larger compared with those in non-bleeding patients (Table II). The mean relative volumes (%) of 60 Gy received rectum (rV60), rV62, rV64 and rV66 in the patients with ≥grade 1 rectal bleeding were significantly larger than those in the non-bleeding patients by the Wilcoxon rank sum test (Table II). No significant difference in rectal dose was observed between patients who underwent the four-field technique prior to IMRT or not by Welch's t-test (Table III).

Receiving operator characteristic analysis. The areas under the absolute and relative rectal volume curves are presented in Table IV. The AUCs of aV60 to aV70 and rV60 to rV66 were all >0.80. Table V lists the Spearman's rank correlations among the dose volume parameters. All dosimetric parameters of rectum volume curves were significantly correlated with each other (P<0.001). The plain parameters aV60, rV60, aV70 and rV70 were chosen for further analysis.

Fig. 1 demonstrates the cut-off thresholds for ≥grade 1 rectal bleeding in the AUCs for aV60, aV70, rV60 and rV70 calculated using the nonparametric AUC. The optimal cut-off values to prevent rectal bleeding were determined as 10 ml at aV60 and 5 ml at aV70.

Kaplan-meier analysis. The ≥grade 1 rectal bleeding in the patients with a >10 ml rectal volume who received 60 Gy was significantly higher compared with the patients with a ≤10 ml rectal volume analyzed by the log-rank test (Fig. 2; P<0.001). The ≥grade 1 rectal bleeding in the patients with a >5 ml rectal volume who received 70 Gy was significantly higher compared with the patients with a ≤5 ml rectal volume (P=0.005; Fig. 2). None of the patients showing the values aV60 and aV70 at <5 ml and 2 ml, respectively, exhibited rectal bleeding.

Logistic plot. The Cox proportional hazards model revealed that aV60 was a significant risk factor for rectal bleeding, and that rV60 was not (P<0.05; Table VI). Fig. 3 presents a logistic plot, which used a logistic regression model to demonstrate the probability of ≥grade 1 rectal bleeding and absolute rectal

Table II. Comparison of ≥grade 1 rectal bleeding or non-bleeding by the absolute and relative volume of rectum.

A, Absolute volume of rectum

	Volume (ml)		
Parameters	Bleeding	No bleeding	P-value
aV60	12.2±1.0	6.6±0.5	<0.01
aV62	10.8±0.9	5.8±0.5	<0.01
aV64	9.8±0.9	5.2±0.5	<0.01
aV66	8.5±1.0	4.4±0.0	<0.01
aV68	7.1±1.1	3.8±0.4	0.02
aV70	5.9±1.2	3.1±0.3	0.02
aV72	4.1±1.4	2.4±0.3	0.12
aV74	2.8±1.3	1.6±0.3	0.33

B, Relative volume of rectum

	Volume (ml)		
Parameters	Bleeding	No bleeding	P-value
rV60	31.3±9.4	14.2±1.0	0.02
rV62	13.4±8.9	12.4±0.9	0.02
rV64	11.8±8.3	10.9±0.9	0.02
rV66	10.2±0.9	9.3±0.8	0.04
rV68	8.6±0.7	7.8±0.7	0.08
rV70	16.8±6.4	6.3±0.6	0.09
rV72	13.2±6.1	4.7±0.5	0.15
rV74	10.0±0.5	3.2±0.5	0.25

volume at the received doses of 70 and 60 Gy. When the rectal volumes of 2 ml (D2cc), 5 ml (D5cc) and 10 ml (D10cc) received ≤60 Gy, the expected ≥grade 1 rectal bleeding at 4 years post-treatment were 2.1, 3.3 and 7.3%, respectively. When the rectal volume of 2 (D2cc) and 5 (D5cc) ml received ≤70 Gy, the expected ≥grade 1 rectal bleeding at 4 years were 3.0 and 7.0%, respectively.

Discussion

Previous studies have reported rates of rectal bleeding that are lower than those reported in earlier investigations, as follows (9,10,14,24-26). Fonteyne *et al* (10) reported that the risk of ≥grade 2 rectal toxicity at 3 years post-treatment decreased by 16 to 5% following the restriction of dose constraints for the rectum using IMRT. Spratt *et al* (9) reported a 4.4% rate for late ≥grade 2 gastrointestinal toxicities at 7 years post-treatment, even though an increased dose of 86.4 Gy was prescribed to the prostate. At the same institute, Zelefsky *et al* (25) reported that IGRT, compared with non-IGRT, reduced rectal bleeding by 1.6-1.0%, but the difference was not significant. Three fiducial markers are placed at the prostate to ensure the position of the prostate to obtain orthogonal portal images using on board imaging. Guckenberger *et al* (27) reported 4% gastrointestinal toxicity at 2 years post-treatment using IMRT and IGRT with CBCT. In the present study, in which CBCT was used, the rate of ≥grade 2 rectal bleeding was 3.2% at 4 years post-treatment. The IGRT methods using CBCT (27) achieved rectal bleeding results that are comparable to those achieved with the use of prostate fiducial markers (25,28,29).

There is no consensus regarding what level of toxicity is acceptable. The majority of the prior analyses were on patients with ≥grade 2 rectal bleeding being classed as acceptable toxicity. A number of studies describe grade 1 rectal bleeding. Kupelian *et al* (24) reported that 8% of their patients experienced ≥grade 1 rectal bleeding during a median observation period of 2 years. In this study, two-thirds of the patients underwent 3D conformal radiotherapy (24). Fellin *et al* (14) reported ≥grade 1 rectal bleeding in 7.8% of the patients who underwent 3D conformal radiotherapy. The advanced technology of IMRT together with IGRT may achieve reduced bleeding compared with these 3D reports, and thus more rigid evaluations for rectal bleeding are necessary. In the present study, the use of the novel IMRT and IGRT techniques successfully achieved a ≥grade 1 rectal bleeding rate at 4 years post-treatment of 4.5%, which is comparable to the outcomes described in several previous studies (25,27-29). The association between the rectal dose volume parameters and late rectal bleeding is well established (9,10,12-20). A number of these studies have reported that the relative volume of the rectum is associated with rectal bleeding, but the absolute volume of the rectum is not used to analyze rectal bleeding. The absolute volume of the rectum has been considered to be a better predictor of rectal bleeding theoretically, as the relative rectal volume is influenced by the delineated volume of the rectum and depends on the anatomical definition of the rectum. Chan *et al* (30) reported that the relative volume of the rectum is difficult to compare in dose volume analyses from study to study due to the different anatomical definitions of the rectum.

Several studies have examined the association between the absolute volume of the rectum and rectal bleeding. Vargas *et al* (31) reported that the absolute and relative rectal volumes were associated with rectal bleeding. It was noted that absolute and relative V60-V70 values were useful for predicting rectal bleeding (31). Huang *et al* (32) reported that not only the relative value, but also the absolute value of the rectal volume was associated with late rectal toxicities. They proposed that to avoid rectal toxicities, an absolute rectal volume <4 ml should be irradiated to 75.6 Gy and an absolute rectal volume <2 ml should be irradiated to 78 Gy. Kupelian *et al* (24) stated that, using multivariate analysis, the absolute rectal volume was the only significant factor of late rectal bleeding. They noted that a rectal volume of 15 ml irradiated at 78 Gy is associated with an increased likelihood of rectal bleeding (24). In the present study, the multivariate analysis indicated that the absolute dose volume, but not the relative dose volume, was a significant factor of late rectal bleeding, which is similar to the findings reported by Kupelian *et al* (24).

In contrast, Koper *et al* (33) reported that the absolute dose volume was less correlated with rectal bleeding compared with the relative dose volume. The radiation

Table III. Comparison of rectal dose between without (n=65) and with box irradiation (n=17).

Parameters	Without box irradiation, mean ± SD (Gy)	With box irradiation, mean ± SD (Gy)	P-value
aV60	6.8±0.5	7.8±1.7	0.41
aV62	6.4±0.5	6.4±1.6	0.76
aV64	5.4±0.4	5.5±1.4	0.96
aV66	4.8±0.4	4.3±1.1	0.63
aV68	4.2±0.4	3.3±1.0	0.36
aV70	3.5±0.4	2.4±0.8	0.20
aV72	2.7±0.3	1.6±0.7	0.14
aV74	1.9±0.3	0.7±0.3	0.06
rV60	15.0±1.2	16.0±3.5	0.75
rV62	13.0±1.1	13.0±3.1	0.86
rV64	12.0±1.1	11.0±2.9	0.68
rV66	10.6±1.0	8.6±2.2	0.39
rV68	9.1±0.9	6.7±2.0	0.24
rV70	7.6±0.8	4.8±1.6	0.14
rV72	5.8±0.8	3.3±1.2	0.12
rV74	4.1±0.7	1.5±0.7	0.06

SD, standard deviation.

Table IV. Area under absolute and relative rectal volume curve.

A, Absolute rectal volume curve

Volume (ml)	AUC	95% CI
aV60	0.882	0.809-0.954
aV62	0.887	0.814-0.960
aV64	0.883	0.808-0.958
aV66	0.863	0.777-0.948
aV68	0.817	0.689-0.944
aV70	0.802	0.679-0.924
aV72	0.711	0.521-0.900
aV74	0.628	0.372-0.884

B, Relative rectal volume curve

Volume (%)	AUC	95% CI
rV60	0.830	0.635-1.024
rV62	0.821	0.621-1.022
rV64	0.815	0.610-1.020
rV66	0.803	0.562-1.043
rV68	0.775	0.514-1.036
rV70	0.771	0.567-1.035
rV72	0.750	0.472-1.028
rV74	0.678	0.333-1.023

AUC, area under curve; CI, confidence interval.

technique in their study was partly 3D conformal radiotherapy and partly 2D radiotherapy, which is different from the treatment provided in the present study. In addition, the use of the electronic portal imaging to assure precise positioning was necessary to evaluate the association between rectal bleeding and the dose administered to the rectum in the dose volume analysis.

Whether multiple dose volume parameters are required to prevent rectal bleeding (13,17,20) or a few parameters are enough remains unknown. Certain authors have proposed that receiving a lower dose may also contribute to the development of late effects (31,34). The association among various dose volume metrics in the present dataset was significant, and thus we hypothesized that certain dose parameters may be used as a surrogate for other doses; these findings also indicate that a rectal volume <10 ml treated at 60 Gy is an important metric to prevent late rectal bleeding, as it was demonstrated to be significant in the uni- and multivariate analyses.

In the current study, the rectal dose of patients who underwent box irradiation prior to IMRT was not high. The possible reason is that rectal dose was more limited by an IMRT plan following box irradiation. These data included analysis to increase statistical robustness.

Another limitation concerns volume, there is uncertainty regarding whether to define the rectum as a total volume (solid) or as a wall. In the cases of a dilated rectum, the absolute volume is large. A dilated rectum is reported to be associated with poor outcome (35), and thus the air in the rectum is eliminated to empty the rectum prior to radiotherapy. Delineation of the rectum as a rectal wall is ideal, but the difference between the solid and the wall was minimalized due to the elimination of air in the rectum.

Other variables have been reported to be associated with late rectal bleeding (17,26,36), but in the present study, the multivariate analysis revealed that anti-androgen therapy (36), patient age (17), and T stage (26) were not significant variables;

Table V. Spearman's rank correlation among various dose volume parameters of the rectum.

Rectal dosimetric parameters	aV60	aV62	aV64	aV66	aV68	aV70	aV72	aV74	rV60	rV62	rV64	rV66	rV68	rV70	rV72
aV60															
aV62	0.992[a]														
aV64	0.980[a]	0.995[a]													
aV66	0.952[a]	0.976[a]	0.991[a]												
aV68	0.911[a]	0.942[a]	0.962[a]	0.984[a]											
aV70	0.870[a]	0.907[a]	0.933[a]	0.962[a]	0.990[a]										
aV72	0.792[a]	0.934[a]	0.862[a]	0.902[a]	0.954[a]	0.977[a]									
aV74	0.658[a]	0.701[a]	0.734[a]	0.783[a]	0.853[a]	0.894[a]	0.945[a]								
rV60	0.781[a]	0.784[a]	0.777[a]	0.759[a]	0.744[a]	0.723[a]	0.667[a]	0.595[a]							
rV62	0.781[a]	0.808[a]	0.806[a]	0.798[a]	0.791[a]	0.774[a]	0.724[a]	0.651[a]	0.989[a]						
rV64	0.783[a]	0.816[a]	0.821[a]	0.822[a]	0.823[a]	0.812[a]	0.766[a]	0.699[a]	0.971[a]	0.992[a]					
rV66	0.775[a]	0.814[a]	0.826[a]	0.841[a]	0.851[a]	0.846[a]	0.810[a]	0.751[a]	0.944[a]	0.974[a]	0.992[a]				
rV68	0.741[a]	0.789[a]	0.812[a]	0.840[a]	0.877[a]	0.888[a]	0.873[a]	0.827[a]	0.880[a]	0.923[a]	0.954[a]	0.977[a]			
rV70	0.735[a]	0.786[a]	0.815[a]	0.849[a]	0.896[a]	0.919[a]	0.917[a]	0.878[a]	0.829[a]	0.877[a]	0.915[a]	0.947[a]	0.987[a]		
rV72	0.714[a]	0.765[a]	0.764[a]	0.836[a]	0.896[a]	0.927[a]	0.966[a]	0.933[a]	0.735[a]	0.788[a]	0.828[a]	0.869[a]	0.927[a]	0.960[a]	
rV74	0.614[a]	0.663[a]	0.695[a]	0.744[a]	0.819[a]	0.864[a]	0.914[a]	0.980[a]	0.650[a]	0.703[a]	0.751[a]	0.800[a]	0.868[a]	0.910[a]	0.942[a]

rVn, relative volume of the rectum receiving n Gy. [a]P<0.001.

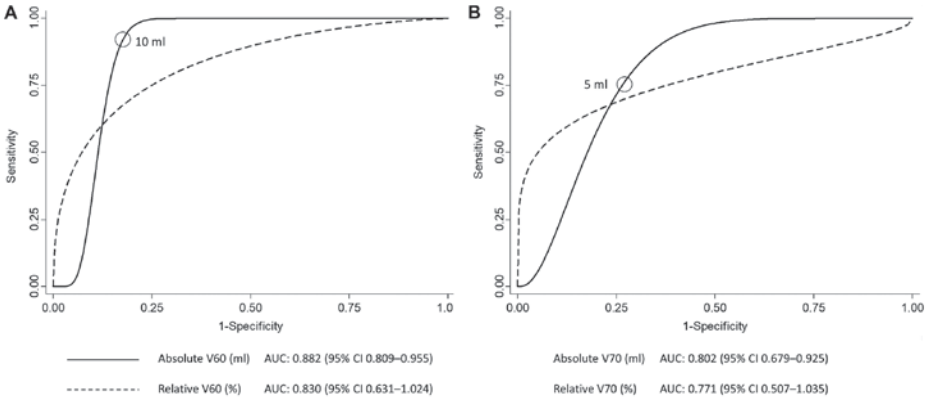

Figure 1. Receiver operating curve for ≥grade 1 rectal bleeding of the absolute and relative volumes at (A) 60 Gy and (B) 70 Gy. The optimal cut-off values (○) are presented as 10 ml at aV60 and 5 ml at aV70. AUC, area under the curve.

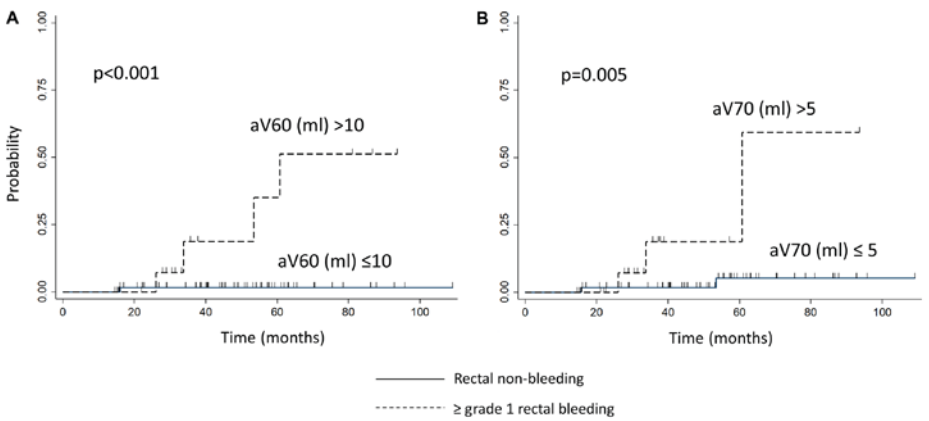

Figure 2. Kaplan-Meier curves for rectal bleeding in (A) the patients with a rectal volume >10 and ≤10 ml treated with 60 Gy and in (B) the patients with a rectal volume >5 ml and ≤5 ml treated with 70 Gy.

Table VI. Hazard ratio for absolute and relative volumes of the rectum by multivariate analysis.

A, Hazard ratio for volume dose of 60 Gy to the rectum

Factor	HR	95% CI		P-value
aV60				
≤10 ml vs. >10 ml	14.1	1.11	176	0.04
rV60				
≤15% vs. >15%	3.8	0.26	56.4	0.97
Age, years				
≤75 vs. >75	1.35	0.18	10.2	0.77
T factor				
T1 and 2 vs. T3 and 4	0.16	0.01	4.42	0.28
Anti-androgen therapy				
Yes vs. No	1.59	0.06	41.9	0.78

B, Hazard ratio for volume dose of 70 Gy to the rectum

Factor	HR	95% CI		P-value
aV70				
≤ 5 ml vs. >5 ml	6.75	0.34	134	0.21
rV70				
≤15% vs. >15%	3.35	0.18	63.8	0.42
Age, years				
≤75 vs. >75	0.52	0.05	4.97	0.57
T factor				
T1 and 2 vs. T3 and 4	0.31	0.01	14.2	0.55
Anti-androgen therapy +/-	0.76	0.02	31.8	0.89

aV60, absolute volume of the rectum receiving 60 Gy; rV60, relative volume of the rectum receiving 60 Gy; aV70, absolute volume of the rectum receiving 70 Gy; rV70, relative volume of the rectum receiving 70 Gy; HR, hazard ratio; CI, confidence interval.

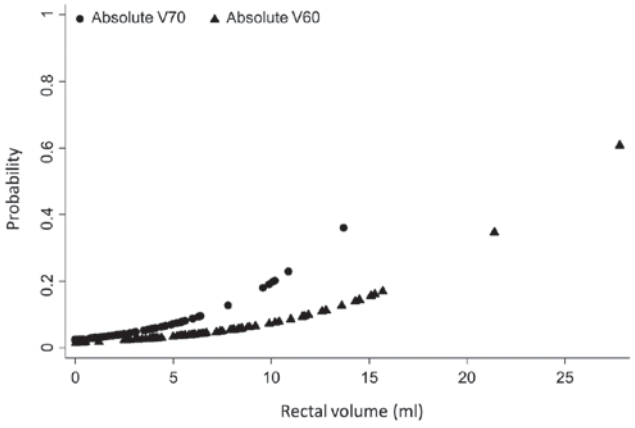

Figure 3. Logistic regression fit for the probability of ≥grade 1 rectal bleeding.

only the absolute volume of the rectum was a significant risk factor for rectal bleeding.

IMRT plus IGRT for patients with prostate cancer has achieved a low rate of late rectal bleeding. The findings of the present study demonstrate that the absolute rectal volume treated with 60 Gy is more important compared with the relative rectal volume. A rectal D5cc treated with ≤60 Gy is recommended to prevent ≥grade 1 late rectal bleeding.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KK was involved in the acquisition and interpretation of patient data regarding the dosimetric parameters from the treatment planning system. HN performed statistical analysis

and was a major contributor in writing the manuscript and the conception and design of the study. AT interpreted the association between dosimetric parameters and rectal bleeding and contributed to the conception and design of the study. AT performed the acquisition and assembly of the clinical data. TT was a contributor in analysis and interpretation of clinical data, and writing the manuscript. HK contributed to the conception of the study, the acquisition of clinical data and was involved in revising the manuscript critically. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Review Board of the National Center for Global Health and Medicine Committee (approval no. NCGM-G-002165-00).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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