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Bone marrow sparing RapidArc treatment in locally advanced rectal cancer – can it reduce haematological toxicity?

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Original Article

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Abstract

Context: Haematological toxicities are seen in rectal cancer patients receiving concurrent chemoradiotherapy (CRT) with capecitabine.
Aims: To compare dose volume histogram (DVH) parameters and acute haematological toxicities using RapidArc with or without bone marrow constraints for rectal cancer patients receiving pelvic chemoradiation as part of curative treatment.
Setting and designs: This is a prospective randomised controlled study including patients with rectal cancer initiated on chemoradiation. Patients were stratified into two arms, bone marrow sparing (BMS) arm and non-bone marrow sparing arm (NBMS).
Materials and methods: DVH parameters and weekly toxicity data were collected. Grade 2 or more anaemia, leucopenia, neutropenia, or thrombocytopenia, any blood transfusions, colony-stimulating factor injection, platelet transfusions were considered as an event in acute haematological toxicity (HT).
Statistical analysis: Independent *t*-test was used to compare quantitative parameters, and Mann–Whitney *U*-test was used for ordinal parameters between groups.
Results: A total of 43 patients were enrolled. Bone marrow constraints were achieved without compromising the target coverage. There was a significant reduction in the bone marrow dose with BMS technique ($p < 0{\cdot}05$). A 16·7% reduction in the HT (33·3% versus 50%) and a 21·9% reduction in the grade 2 or more anaemia (19% versus 40·9%) were noted in the BMS arm when compared to NBMS arm, though not statistically significant. However, in the preoperative setting, a significant reduction in grade 2/more anaemia (7·1% versus 41·1%, $p = 0{\cdot}035$) was noticed in the BMS arm.
Conclusions: Pelvic BMS radiotherapy may benefit patients receiving chemoradiation for locally advanced carcinoma rectum as part of curative treatment.

Key Messages

Pelvic bone marrow sparing radiotherapy can significantly reduce dose to the bone marrow. Haematological toxicity in patients receiving preoperative chemoradiation for locally advanced carcinoma rectum may be reduced with bone marrow sparing radiotherapy.

Introduction

Chemoradiotherapy (CRT) for rectal cancer causes haematological, gastrointestinal, genitourinary toxicity and skin reactions.[1] Intensity-modulated radiotherapy (IMRT) has shown to reduce acute bowel toxicity, treatment breaks and hospitalisations.[2,3] The destruction of radiosensitive marrow cells by pelvic radiation causes acute myelosuppression. Studies on pelvic malignancies including rectal cancer concluded that radiation dose to pelvic bone marrow is a predictor of haematological toxicity (HT).[4–8] There were hardly any trials that assessed the benefit of bone marrow sparing (BMS) radiotherapy (RT) for rectal cancer. So, we aimed to determine the benefit of BMS RapidArc (RA) (volumetric-modulated arc treatment) on acute HT in patients with carcinoma rectum receiving CRT in neoadjuvant or adjuvant setting.

Materials and Methods

Forty-three patients who were undergoing pelvic CRT for locally advanced rectal cancer from August 2018 to December 2020, either preoperatively or postoperatively, were prospectively recruited in this single-centre randomised control trial.

Table 1. Patient characteristics in BMS and NBMS arm

	Characteristics		Total		BMS-VMAT		NBMS-VMAT		*p*
			No of pts	Percentage	No of pts	Percentage	No of pts	Percentage	
1	Age (years)	41–50	6	14·0%	5	23·8%	1	4·5%	0·45
		51–60	11	25·6%	4	19·0%	7	31·8%	
		61–70	20	46·5%	9	42·9%	11	50·0%	
		71–80	6	14·0%	3	14·3%	3	13·6%	
		Mean age (years)	62·5		61·4		63·5		
		Median age (years)	64		63		64		
2	Gender	Male	20	46·5%	12	57·1%	8	36·4%	0·17
		Female	23	53·5%	9	42·9%	14	63·6%	
3	Timing of chemoradiotherapy	NACRT	31	72·1%	14	66·7%	17	77·3%	0·43
		Adj CRT	12	27·9%	7	33·3%	5	22·7%	
4	AJCC clinical stage	IIA	8	18·6%	5	23·8%	3	13·6%	0·107
		IIIA	2	4·7%	1	4·8%	1	4·5%	
		IIIB	29	67·4%	15	71·4%	14	63·6%	
		IIIC	4	9·3%	0	0	4	18·2%	
5	Histological grade	Grade 1	7	16·3%	5	23·8%	2	9·1%	0·13
		Grade 2	35	81·4%	16	76·2%	19	86·4%	
		Grade 3	1	2·3%	0	0	1	4·5%	

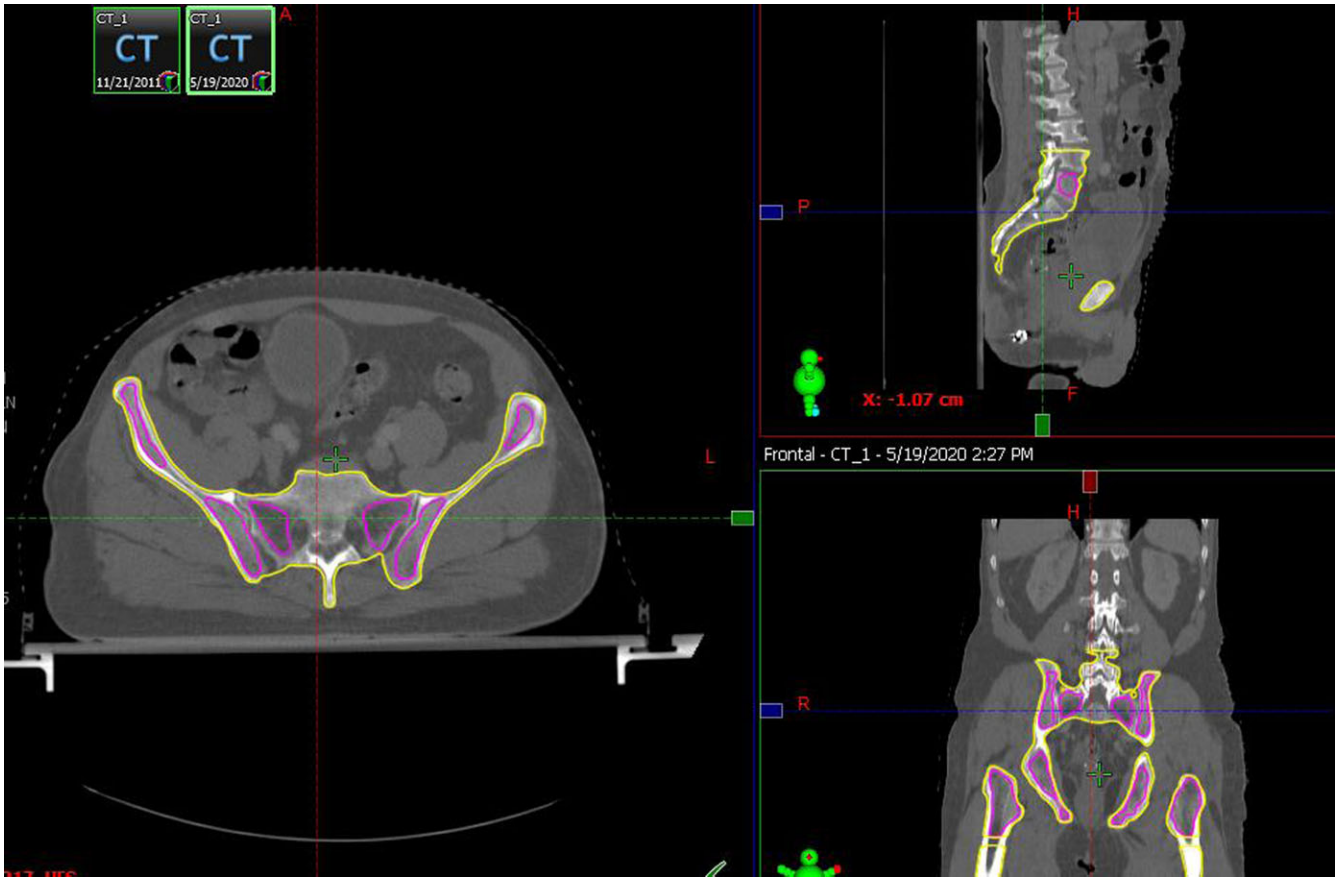

Figure 1. Bone marrow contouring: CT sections showing whole bone (yellow line) and freehand cavity contours (purple line).

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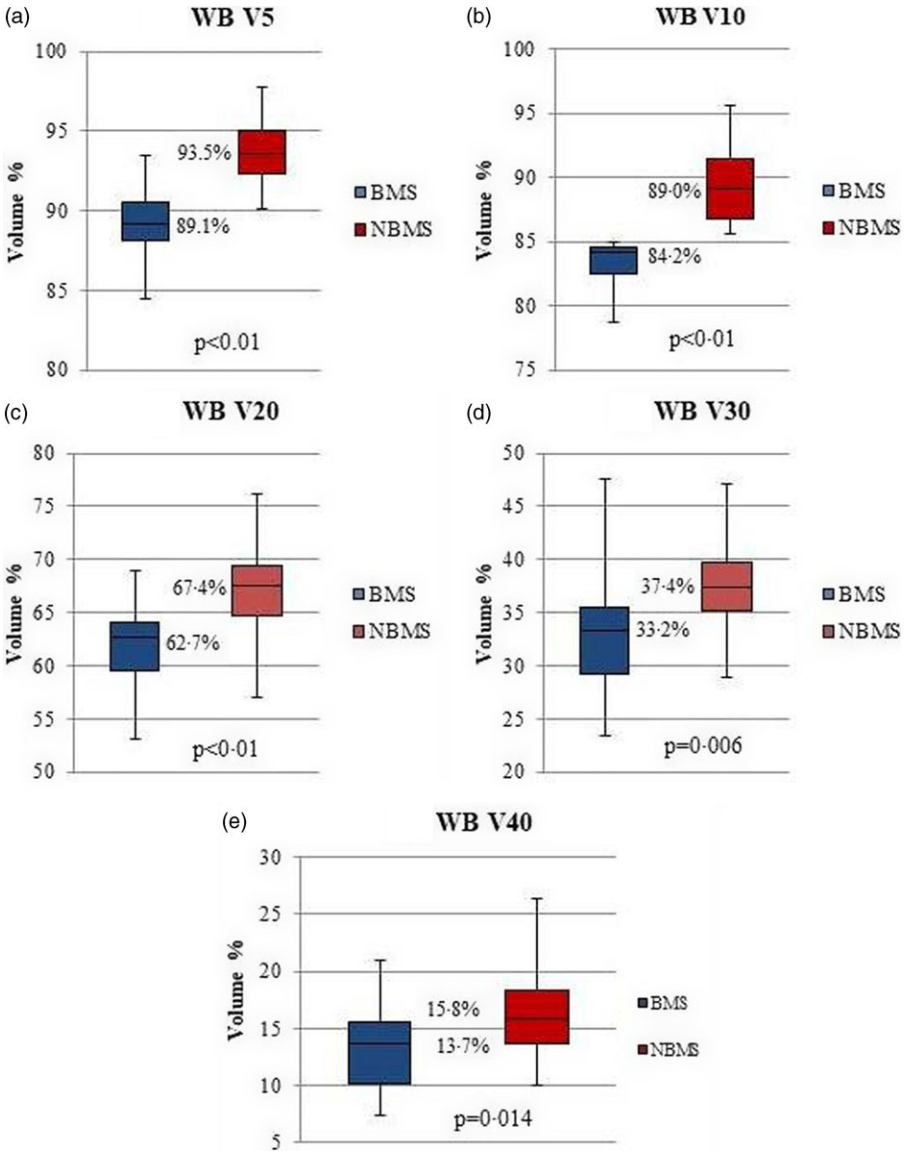

Figure 2. Dosimetric parameters of whole bone marrow (WB) in BMS and NBMS arms.

Major inclusion criteria were as follows: (1) biopsy-proven, non-metastatic adenocarcinoma rectum of T stage 3–4 or N stage 1–2 with tumours located within 15 cm of the anal verge; (2) ECOG performance status ≤ 2; (3) age 18–80 years; and (4) adequate liver and renal function. Exclusion criteria were as follows: (1) recurrent disease; (2) history of previous pelvic irradiation; (3) synchronous malignancies; and (4) presence of any active collagen vascular diseases or gastrointestinal diseases like inflammatory bowel disease and coeliac disease. Eligible patients were stratified into two arms by block randomisation: (1) BMS arm: receiving BMS RA; (2) NBMS arm: receiving non-bone marrow sparing (NBMS) RA.

Radiation simulation, planning and delivery

Patients were immobilised using a six-point thermoplastic mask in the supine position with arms above the head. CT simulation was done with the patient in the treatment position, of 3 mm slice thickness from L2 vertebrae to 3 cm below the pelvic floor, using oral and intravenous non-ionic contrast in full bladder. CT and diagnostic MRI images were then imported into the Eclipse treatment planning system (Varian Medical Systems), and both the datasets were fused. Targets were delineated as per radiation therapy oncology group (RTOG) consensus panel contouring atlas.[9] Bowel, bladder and femoral heads were defined as organs at risk for all patients. In patients allotted to BMS-RA arm, two sets of bone marrow were contoured, whole bone (WB) and freehand (FH) contours of low-density regions inside the bone. The WB volume started 3 cm above the upper border of PTV and ended 3 cm below the lower border of PTV. FH cavity volume was created in the LS spine from L5 to the entire sacrum, lower pelvis including pubes, ischia, acetabula and ilium (Fig. 1). RA plan was created on the Eclipse treatment planning system and calculated using an anisotropic analytical algorithm version 13.6.23. The optimisation priority was CTV> small bowel> bladder> femoral heads> WB marrow. Plan evaluation was done by assessing the D mean, D98% (near-minimum dose), D2% (near-maximum dose) received by CTV, conformity index, homogeneity index and organs at risk (OARs) constraints. All patients received RT dose of 45 Gy in 25 fractions to pelvis (tumour and pelvic lymph nodal regions) followed by 5·4 Gy in 3 fractions to tumour boost, by RA technique using 6-MV

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Table 2. Acute HT in whole study group

	Total ($n = 43$)		BMS ($n = 21$)		NBMS ($n = 22$)		
Toxicity	No. of pts	%	No. of pts	%	No. of pts	%	$p^{\#}$
Haematological toxicity	18	41·9	7	33·3	11	50	0·21
Anaemia	13	30·2	4	19	9	40·9	0·11
Leucopenia	9	20·9	5	23·8	4	18·2	0·46
Neutropenia	5	11·6	4	19	1	4·5	0·15
Thrombocytopenia	1	2·3	1	4·8	0	0	0·48

[#]Fisher's exact test.

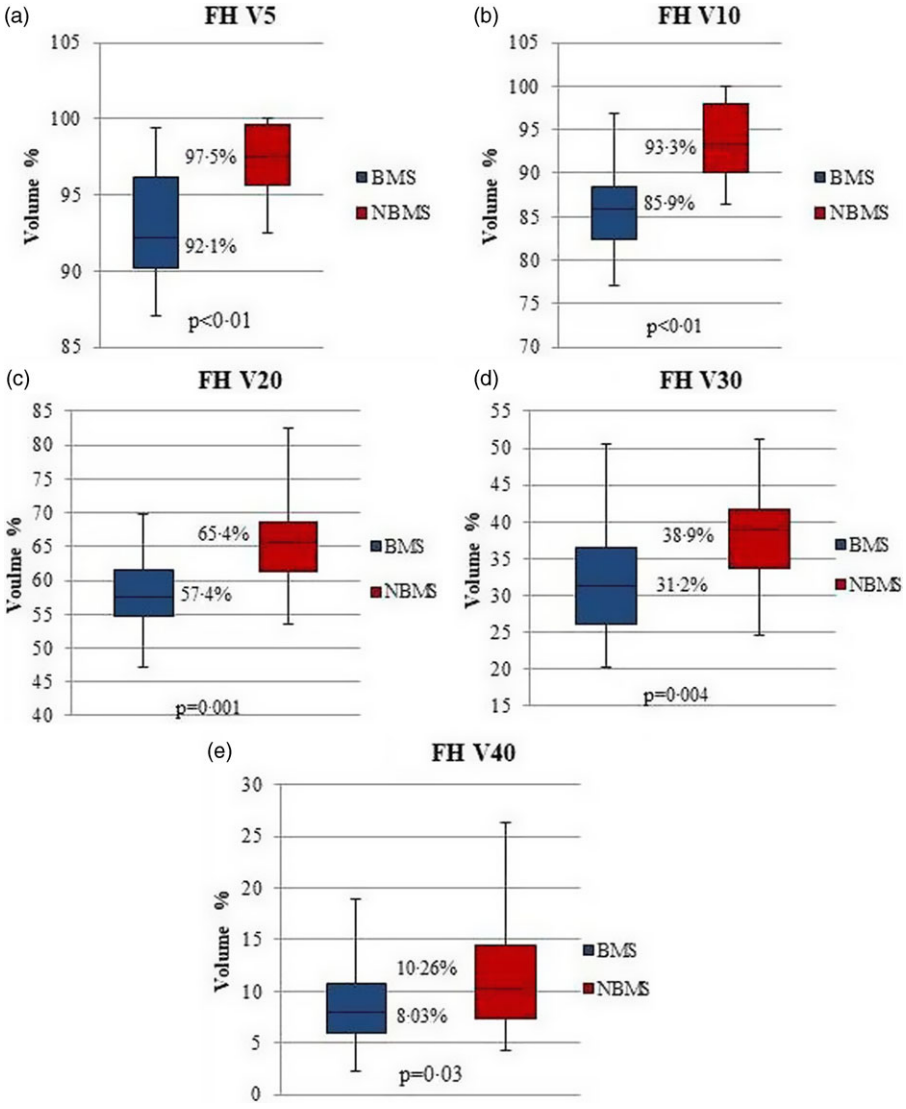

Figure 3. Dosimetric parameters of free hand bone marrow (FH) in BMS and NBMS arms.

photons by Varian Unique performance Linear Accelerator with a dose rate of 600 MU/MIN.

Chemotherapy delivery and toxicity assessment

Chemotherapy consisted of capecitabine (825 mg/m^2) twice daily concurrently on the days of radiation. Capecitabine dose adjustment was done in case of grade 3 or more toxicity. Patients were assessed weekly during RT, and in the first week, sixth week and third month after RT for toxicities (haematological, gastrointestinal, genitourinary and skin), and they were graded using RTOG/EORTC acute radiation morbidity grading criteria.

Primary end point was acute HT. Grade 2 or higher anaemia, leucopenia, neutropenia or thrombocytopenia, any blood transfusions, colony-stimulating factor injection and platelet transfusions were considered as an event in acute HT.

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Table 3. Acute HT in patients who received preoperative CRT

	Total ($n = 31$)		BMS ($n = 14$)		NBMS ($n = 17$)		
Toxicity	Count	%	Count	%	Count	%	$p^{\#}$
Haematological toxicity	12	38·7	3	21·4	9	52·9	0·063
Anaemia	8	25·8	1	7·1	7	41·1	0·035
Leucopenia	6	19·3	2	14·2	4	23·5	0·294
Neutropenia	4	12·9	2	14·2	2	11·7	0·393
Thrombocytopenia	0	0	0	0	0	0	–

[#]Fisher's exact test.

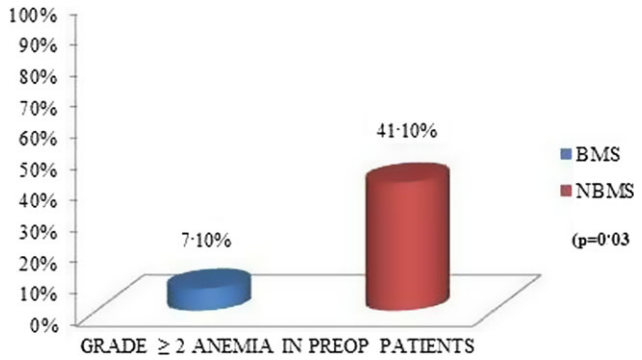

Figure 4. Comparison in incidence of grade 2 or more anaemia in patients who received preoperative CRT, between BMS and NBMS arms.

Statistical analysis

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± standard deviation, respectively. An independent *t*-test was used to compare quantitative parameters between categories. Mann–Whitney *U*-test was used to compare ordinal parameters between groups. Wilcoxon signed-rank test was carried out to compare ordinal parameters between two intervals of time. Chi-square test and Fisher's exact test were used to find an association between categorical variables. For all statistical interpretations, $p < 0{\cdot}05$ was considered the threshold for statistical significance. Statistical analyses were performed by using a statistical software package SPSS, version 20.0.

Results

Patient and treatment characteristics

Between August 2018 and December 2020, 43 patients consented to the study, out of which 21 patients were in the BMS arm and 22 patients were in the NBMS arm. Most patients belong to the age group of 61–70 years. Gender distribution was equal in our study group. In the total 43 patients, 31 patients received neoadjuvant CRT and 12 patients received adjuvant CRT. This distribution was similar in both arms (Table 1).

Dosimetric parameters

The bone marrow dosimetric parameters were significantly different between the BMS arm and NBMS arm ($p < 0{\cdot}01$), favouring the BMS arm. The difference was seen in both WB marrow and FH bone marrow, presented as box plots (Figs. 2 and 3).

Acute toxicity

In the whole study group, overall HT occurred in 41·9% of patients (Table 2). Acute HT was seen in 33% of patients in the BMS arm and 50% of patients in the NBMS arms; however, the difference was not statistically significant ($p = 0{\cdot}213$).

The incidence of grade 2 or more anaemia was 19% and 40% in BMS and NBMS arm, respectively ($p = 0{\cdot}109$). Grade 2 or more leucopenia was seen in 23·8% and 18·1% in the BMS and NBMS arms, respectively, not statistically significant. Only one patient (2·3%) in the BMS arm developed grade 2 or more thrombocytopenia.

Out of the 31 patients who received preoperative CRT, 38·7% developed HT (Table 3). The incidence of HT was more in the NBMS arm than the BMS arm, 52·9% versus 21·4% ($p = 0{\cdot}063$). Grade 2 or more anaemia was seen in 7·1% versus 41·1% in BMS and NBMS arms, respectively. This was statistically significant ($p = 0{\cdot}035$), as shown in Fig. 4. Grade 2 or more leucopenia was seen in 23·5% and 14·2% in NBMS and BMS arms, respectively ($p = 0{\cdot}29$).

Among patients who received postoperative CRT, 45% of the patients had HT, as described in Table 4. The incidence of grade 2 or more anaemia, leucopenia or neutropenia in both arms were similar in the postoperative setting. No patients had grade 2 or more thrombocytopenia.

We analysed different variables like age, gender, preoperative or postoperative CRT, nodal status, TNM stage, AJCC composite stage group, prior chemotherapy received or not, the dose of capecitabine, and body surface area (BSA) as predictors of HT and found that only female gender was related to HT (Tables 5 and 6). Sixty-one percentage of women developed HT compared to 20% of men who received CRT ($p = 0{\cdot}007$). We could find no association between the mean WB marrow dose and FH bone marrow dose with HT (Fig. 5)

Disease response evaluation

Thirty-one patients received preoperative CRT and 20 of them underwent surgery at our institution. These patients were taken for response evaluation. The post-neoadjuvant CRT surgical histopathology report revealed that 45% of patients were down-staged to T3N0 stage and only 15% of patients were above stage T3N0. Four patients have had pathological complete response, three in BMS

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Table 4. Acute HT in patients who received postop CRT

	Total ($n=9$)		BMS ($n=5$)		BMNS ($n=4$)		
Toxicity	Count	%	Count	%	Count	%	$p^{\#}$
Haematological toxicity	4	44·4	2	40	2	50	0·476
Anaemia	4	44·4	2	40	2	50	0·476
Leucopenia	3	33·3	2	40	1	25	0·476
Neutropenia	2	22·2	2	40	0	0	0·278
Thrombocytopenia	0	0	0	0	0	0	–

Table 5. Association of HT with selected variables in whole study group

		Haematological toxicity					
		No		Yes			
Variables		Count	Percent	Count	Percent	χ^2	p
Age	≤60	8	47·1	9	52·9	1·42	0·234
	>60	17	65·4	9	34·6		
Sex	Male	16	80·0	4	20·0	7·34	0·007
	Female	9	39·1	14	60·9		
Timing of CRT	Preoperative chemoradiotherapy	19	61·3	12	38·7	0·45	0·501
	Postoperative chemoradiotherapy	6	50·0	6	50·0		
N stage	No	7	70·0	3	30·0	1·7	0·427
	N1a/1b	9	47·4	10	52·6		
	N2a/2b	9	64·3	5	35·7		
TNM stage	T0 N0–T1 N2a	6	60·0	4	40·0	1·22	0·545
	T3 N1–T2 N2a	10	50·0	10	50·0		
	Others	9	69·2	4	30·8		
Prior chemotherapy	No	21	63·6	12	36·4	1·76	0·184
	Yes	4	40·0	6	60·0		
Composite stage group	0 – IIIA	6	60·0	4	40·0	0·02	0·892
	IIIB/IIIC	19	57·6	14	42·4		
Dose of capecitabine (500mg)	1–0–1; 2–0–1; 2–0–2	6	40·0	9	60·0	3·11	0·078
	3–0–2; 3–0–3	19	67·9	9	32·1		

χ^2 – Chi-square test.

Table 6. Association of BSA as a predictor for haematological toxicity in whole study group

	Haematological toxicity							
	No			Yes				
BSA	Mean	SD	*N*	Mean	SD	*N*	*t*	*p*
	1·6	0·2	25	1·6	0·2	18	0·63	0·532

t – Independent *t*-test.

and one in the NBMS arm. The partial response had occurred in four patients in BMS and seven patients in the NBMS arm. The disease was progressed in one patient in each arm even with neoadjuvant therapy. And hence as shown in Table 7, response to RT was statistically similar in both arms, with or without BMS RT.

Discussion

The standard of care in locally advanced rectal cancer is CRT followed by radical resection and adjuvant chemotherapy as indicated. But the acute toxicities associated with CRT cause treatment interruptions frequently, thereby dampening treatment efficacy. Newer techniques like IMRT or RA can reduce the frequency of these acute toxicities, such as gastrointestinal toxicity than conventional treatments.[2,10–12] RA has the added benefit of faster treatment with lesser intrafraction error probability. Recently, the concept of BMS RT used in gynecological cancers resulted in reduction of acute HT. We know that it is possible to reduce the pelvic bone marrow dose without increasing the dose to other OARs or compromising dose to target with the help of BMS IMRT/RA.

Optimal dose or volume constraints are not well defined in the literature nor is there a clarity on the anatomical subsite of pelvic

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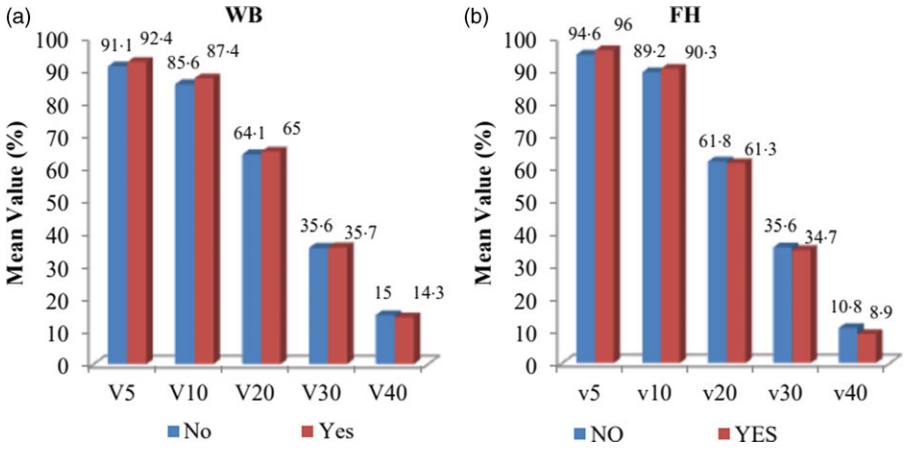

Figure 5. Association of whole bone marrow (WB) and freehand bone marrow (FH) mean dose as predictors of haematological toxicity in patients who received preoperative CRT.

Table 7. Comparison of response to chemoradiotherapy between the BMS and NBMS arm

	BMS (11pts)		NBMS (9 pts)		
Response	Count	%	Count	%	$p^{\#}$
pCR	3	27·27	1	11·11	0·93
Partial response	4	36·36	7	77·77	0·17
No response	3	27·27	0	0	1
Progression	1	9·09	1	11·11	0·71

[#]Fisher's exact test.

bone to be spared in treatment. Different techniques of delineation of bone marrow have been adopted in several studies. In RTOG 0418, the external surface of pelvic bones was contoured using autosegmentation through the whole length of PTV as bone marrow.[13] In some other studies, active bone marrow, that is, the low-density inner cavity of pelvic bone was spared.[8,14,15] Recently, functional imaging has been used to assess the extent of active bone marrow (FDG-PET or FLT-PET).[16,17] Various trials have also tried to find the relationship between HT and radiation dose to different anatomical subsites of the pelvis like the lumbosacral region, iliac crests, or lower pelvis.[18]

In our study, we created two sets of bone marrow contouring, first one with bone autosegmentation and the second one as the low-intensity active inner cavity of pelvic bones. We defined constraints for WB marrow as V5 < 95%, V10 < 85%, V20 < 80%, V30 < 65% and V40 < 45%. Significant reduction in the irradiated volume of both whole pelvic bone marrow and FH inner cavity bone marrow (V5, V10, V20, V30, V40) were achieved with the BMS RA ($p < 0·05$) when compared to NBMS RA. Along with this the right proximal femur dose max, V10, V40 and left proximal femur V5, V10 and V20 were also reduced ($p < 0·05$).

A recent study published in 2019 by Huang et al comparing pelvic BMS IMRT against NBMS IMRT in CRT with oral capecitabine for rectal cancer showed significant reduction in dose to bone marrow and bilateral femoral heads ($p \leq 0·05$) with BMS IMRT, and these patients had lower incidence of grade 2 or more acute HT (31% versus 57·1%, $p = 0·027$). A 26·1% reduction in HT with BMS IMRT was achieved in this trial.[13]

In our trial, we were able to achieve a 17% reduction in acute HT with BMS RA technique when compared to NBMS RA, though not statistically significant ($p = 0·21$). When we analysed, the HT in patients who received preoperative CRT alone, there was 31·5% reduction ($p = 0·063$) and 34% reduction in grade 2 or more anaemia which was statistically significant ($p = 0·035$), favouring BMS arm. This is similar to the aforementioned Huang et al trial.

Since most of the previous studies on HT and BMS pelvic radiation has been done using IMRT, it is possible that RA itself results in lower HT. However, evidence comparing volumetric-modulated arc therapy (VMAT) and IMRT in terms of HT showed no difference in the incidence of HT events, but the VMAT arm had lower bone marrow high-dose volumes.[19] We know from Albuquerque et al study on CRT in cervical cancer patient using 3DCRT, that volume of bone marrow receiving 20 Gy was a predictor of grade 2 or more HT. If V20 > 80%, the risk of grade 2 or more HT increases by a factor of 4·5 ($p < 0·05$).[4] In our study, V20 was less than 80% in all patients (both BMS and NBMS arms) because of the utilisation of RA. This is may be the reason why there was no statistical difference in HT between both arms.

Reduction in HT with the use of BMS CRT for pelvic malignancies seen in the literature was compared to our trial results (RA technique), and we found that grade 2 HT was similar. Interestingly, grade 3 HT seems to be completely reduced (to near zero) with the use of BMS technique, except in anal canal cancers where mitomycin (known for its HT) is used, described in Table 8.

HT was correlated with various factors, and we found that female gender was a predictor ($p = 0·007$), as seen in literature.[22] However, we could not identify the relation of bone marrow dosimetry to HT. In RTOG 0418, postoperative CRT of cervical cancer patients with IMRT found that V40 > 37% is related to grade 2 or more HT.[12] We were able to achieve V40 less than 37% in all our patients (both BMS and NBMS arms). Umesh Mahantshetty et al found that whole pelvis FH V40 ≥ 40% was associated with grade ≥ 2 HT in cervical cancer patients treated with chemoradiation using IMRT.[24] In our study, none of the patients in either of the arms received more than this dose. These may be the reasons for not identifying the correlation between dosimetric values of bone marrow and HT.

Twenty percentage of patients had pCR, and 75% had downstaging in patients who received preoperative BMS RA, which is slightly higher than in other studies may be due to the small sample size.[23] This confirms that BMS RA is not detrimental to disease outcome.

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Table 8. Clinical trials comparing acute HT in patients who received BMS versus NBMS CRT for pelvic malignancies

Sl. no.	Author (year)	Site (pts no.)	RT dose/ chemotherapy	Technique	BM definition	Constraints	HT grading	*HT2+	†HT3+
1	Liang Y et al.[20] (2012)	Cervix, Anal canal (21)	45 Gy/weekly cisplatin 50·4 Gy/‡5FU/§MMC	BMS-IMRT	FDG-PET + MRI based WB & active BM contour	Total and functional BM V10 ≤ 90% V20 ≤ 75%	‖RTOG	–	30% versus 47% (IMRT versus off protocol treatment)
2	Rattan et al.[21] (2016)	Anal canal [16]	45 Gy/ cisplatin + 5FU	BMS-IMRT versus 3DCRT	CT-based WB contour	V10 < 90%	RTOG	30% versus 40%	0 versus 20%
3	Huang et al.[19] (2019)	Rectum (84)	50·4 Gy/ capecitabine	BMS-IMRT versus IMRT	CT-based WB contour	V10 ≤ 85%; V20 ≤ 65%; V30 ≤ 45%	RTOG	31% versus 57·1% ($p = 0·027$)	–
4	Huang et al.[22] (2020)	Cervix (164)	50·4 Gy/weekly cisplatin	PBMS-IMRT versus IMRT	CT-based WB contour	LSS V10 < 85%, LSS mean < 30 Gy; **PBM V10 < 80%, PBM V20 < 70%, PBM V40 < 30%, and PBM mean < 30Gy.	RTOG	50% versus 69·5% ($p = 0·02$)	–
5	Arcadipane F et al.[23] (2020)	Anal canal [17]	54 Gy/5FU/ MMC	BMS-VMAT	FDG-PET-based active bone marrow	Active PBM V10 < 90%, active PBM V20 < 75%; active ††LSBM V40 < 41%, active LSBM Dmean < 32Gy	¶CTCAE V.4·0	-–	19% (compared with RTOG 0529, where HT3+ was 58%)
6	Our study (2021)	Rectum (43)	50·4 Gy/ capecitabine	BMS-RA versus NBMS-RA	CT-based WB and FH contour	Whole pelvis V5 < 95%; V10 < 85%; V20 < 80%; V30 < 65%; V40 < 45%.	RTOG	33% versus 50% (p = 0 213) Preop: 21·4% versus 52·9% ($p = 0·063$)	9·5% versus 0 Preop: 0 versus 0

*HT2+ – Grade 2 or more haematological toxicity.
†HT3+ – Grade 3 or more haematological toxicity.
‡5FU – 5-fluorouracil.
§MMC – mitomycin C.
‖RTOG – radiation therapy oncology group.
¶CTCAE – common toxicity criteria for acute events.
**PBM – pelvic bone marrow.
††LSSBM – lumbosacral spine bone marrow.

Conclusion

Dose to the bone marrow, both WB and active bone marrow, can be significantly reduced by BMS RA. A 17% reduction in acute HT was attained by this technique. The non-significance of this difference may be due to an inadequate sample size or the superiority of RA technique itself. In the preoperative setting, 31·5% reduction in the occurrence of acute HT ($p = 0{\cdot}06$) and 34% reduction in grade 2 or more anaemia ($p = 0{\cdot}035$) were achieved. The disease response to RT was similar in both arms. Hence, we can conclude that BMS RA definitely reduces bone marrow dose and shows a trend towards lower HT. It may benefit patients receiving chemoradiation for carcinoma rectum, especially in the preoperative setting as multimodality treatment such as surgery and adjuvant chemotherapy which will further depress bone marrow reserve awaits them.[25–27].

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Competing interests. None.

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