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Scientific Article

The Influence of Pelvic Bone Dose-volume Parameters on Bone Marrow Suppression During Radiation Therapy in Patients With Stage I to III Rectal Cancer Based on Real-world Data

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Purpose: The aim of this study was to evaluate the effect of pelvic bone dose-volume parameters on bone marrow suppression during radiation therapy (RT) in patients with rectal cancer stage I to III disease receiving either neoadjuvant radiation therapy (neo-RT) or curative-intent radiation therapy (cur-RT).

Methods and Materials: This was a retrospective study with data mined from an electronic medical record review at a single institution. Between January 2016 and September 2022, patients with rectal cancer who consecutively received neo-RT or cur-RT in our department were included. The data collected included complete baseline peripheral blood counts and hematologic toxicity (HT) data collected during RT. The radiation dose-volume parameters of 3 pelvic bone marrow subsites (iliac bone marrow [IBM], lumbosacral bone marrow, and lower pelvis bone marrow) were collected. The primary endpoint was grade ≥ 2 HT (HT2+), including leukopenia, neutropenia, anemia, thrombocytopenia, and total HTs. Logistic regression was employed to analyze the associations of HT2+ with dosimetric parameters and clinicopathologic characteristics. Receiver operating characteristic curves and the area under the curve (AUC) were generated to verify the prediction efficacy of the pelvic bone dose-volume parameters combined with clinicopathologic indices.

Results: A total of 130 patients with stage I to III rectal cancer with complete clinical data were included. During neo-RT and cur-RT, 57 (43.8%) of these patients experienced HT2+. Multivariate analysis revealed that gender, the IBM-Dmean, the IBM-V15, and the IBM-V40 were significantly associated with grade 2+ leukopenia ($P < .05$), and the AUC of gender combined with the IBM-Dmean, the IBM-V15, and the IBM-V40 in predicting grade 2+ leukopenia was 0.834. The optimal cutoff values were an IBM-Dmean = 2692.75 cGy, an IBM-V15 = 86.65%, and an IBM-V40 = 20.75%. Patients who received oxaliplatin-containing concurrent chemotherapy (ChT) regimens were more likely to experience grade 2+ thrombocytopenia ($P = .054$). The AUC of concurrent ChT

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regimens in predicting grade 2+ thrombocytopenia was 0.678. Female gender was significantly associated with grade 2+ anemia and total HT2+ status.

Conclusions: Among patients with rectal cancer stage I to III disease who received neo-RT or cur-RT, female patients with higher IBM-Dmean, IBM-V15, and IBM-V40 were more likely to experience grade 2+ leukopenia, and oxaliplatin-containing concurrent ChT regimens were identified as a potential factor for increasing the incidence of grade 2+ thrombocytopenia.

Introduction

According to GLOBOCAN 2020 estimates, colorectal cancer is the third most common cancer. It is the second leading cause of cancer-related death.[1] Radiation therapy (RT) plays an important role in the treatment of patients with locally advanced rectal cancer (LARC).[2,3] Neoadjuvant chemoradiotherapy (neo-CRT) followed by total mesorectal excision surgery and adjuvant chemotherapy (ChT) is the standard treatment for patients with LARC .[4] For early-stage patients who are not suitable for surgical treatment (eg, those with severe cardiovascular disease), or who strongly desire to preserve the anus when the tumor is located in the lower rectum, curative-intent CRT may be required.[5]

RT kills tumor cells by using high-energy radiation, such as x-rays, which are produced by a linear medical accelerator. Although x-rays are most commonly used in clinical practice and can damage the DNA of tumor cells, they can also induce hematologic toxicity (HT) by damaging hematopoietic stem cells which possess self-renewal ability.[6] In the CAO/ARO/AIO-94 trial,[7] 27% of patients experienced grade 3+ toxicity in the neoadjuvant arm. Hence, RT could cause bone marrow suppression and HTs during RT, which can lead to ChT and RT dose reductions and/or delays.

The results of previous studies showed that pelvic bone marrow (PBM)-sparing RT could reduce the incidence of HTs, such as cervical cancer, rectal cancer, and anal cancer, in patients who received pelvic RT.[6,8-10] Corbeau et al[6] performed the first literature review including 17 articles to evaluate the correlation between bone marrow (BM) and HT for patients with locally advanced cervical cancer, and the results suggested that whole pelvic bone doses of V10 > 95% to 75%, V20 > 80% to 65%, and V40 > 37% to 28% were significantly associated with increased HTs. Arcadipane et al[11,12] conducted a prospective phase 2 trial to evaluate acute HTs in patients with anal cancer who received concurrent ChT and BM-sparing intensity modulated radiation therapy (IMRT), and they found that ^{18}FDG-PET (18-Fluoro-2-deoxy-glucose positron emission tomography)-guided BM-sparing IMRT could reduce acute HTs. However, a consensus on the specific dose constraints of PBM has not been documented in patients with LARC. This research aimed to investigate the influence of pelvic bone dose-volume parameters on bone marrow suppression during RT in patients with stage I to III rectal cancer based on real-world data from our department, and we hope to provide a reference for clinical work.

Methods and Materials

Patients

Between January 2016 and September 2022, patients with rectal cancer who consecutively received neoadjuvant radiation therapy (neo-RT) or curative-intent radiation therapy (cur-RT) at the RT department of the First Affiliated Hospital of Sun Yat-sen University were included. This was a retrospective study approved by our institutional medical ethics committee ([2023] 079). Written informed consent was obtained from all patients enrolled.

The inclusion criteria were as follows: (1) age, 18 to 75 years; (2) Eastern Cooperative Oncology Group Performance Status score 0 to 2; (3) pathologically confirmed diagnosis of adenocarcinoma; and (4) stage I to III disease according to the eighth edition American Joint Committee on Cancer Tumor-Node-Metastasis staging. Patients who met the following criteria were excluded: (1) had a prior history of other malignancies or (2) had serious medical conditions (eg, heart failure or psychiatric disease).

Computed tomography simulation

All enrolled patients were immobilized in the prone position using vacuum-lock bag with a Philips CT (Brilliance Big Bore). Subsequently, a 5-mm slice-thick computed tomography (CT) scan was performed from the inferior margin of the 12th thoracic vertebra to the middle femur. To minimize the exposure of the small bowel, patients were required to undergo CT simulation (CT-sim) with a full bladder by drinking 500 mL of water before CT-sim. Furthermore, oral contrast agent was administered before CT-sim, which helped doctors contour normal small bowel tissue more precisely.

Target volume delineation and RT dose

All patients received long-course RT with or without concurrent ChT. All patients underwent RT via volume-

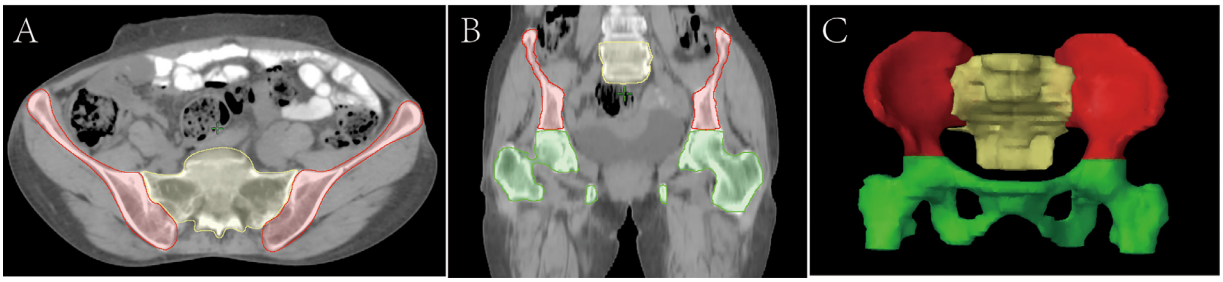

Figure 1 (A-C) Plane and 3-dimensional images of pelvic bone marrow. The red zones are ilial bone marrow, the green zones are lower pelvis bone marrow, and the yellow zone is lumbosacral bone marrow.

modulated arc therapy. The gross tumor volume (GTV) was defined as the primary tumor (GTVp) and positive lymph nodes (GTVn). The clinical target volume (CTV) included the GTV plus areas at risk with a 2 cm margin from the primary tumor and nodal areas at risk, including the mesorectal, presacral, and internal iliac nodes. For patients with T4 tumors, the external iliac nodes should also be included. Inguinal lymph nodes were covered electively in the following 2 situations: (1) there were positive lymph nodes in the inguinal lymphatic drainage area; and (2) the anal canal or perianal skin was involved. An 8 mm isotropic expansion of the GTVp, GTVn, and CTV was used to create the planning target volume (PTVp, PTVn, and PTV).

The prescribed doses delivered to the PTVp and PTVn for patients receiving neo-RT were 50 to 55 Gy, and for patients receiving cur-RT, they were 60 to 64 Gy. The doses delivered to the PTV ranged from 45 to 46 Gy, all of which were delivered in 25 daily fractions. RT was delivered using the 6 MV photon beams of modern linear accelerators. Treatment planning was calculated using the Monaco (Elekta AB) system or Eclipse (Varian Medical Systems, Inc).

Concurrent chemotherapy

During RT, concurrent ChT regimens included capecitabine (825 mg/m^2 twice daily for 5 days a week), CapeOx (oxaliplatin 130 mg/m^2 on day 1 + capecitabine 1000 mg/m^2 twice daily for 14 days, repeated for 3 weeks), and mFOLFOX (oxaliplatin 85 mg/m^2 on day 1, leucovorin 400 mg/m^2 on day 1, 5-Fu 400 mg/m^2 bolus on day 1, followed by 1200 mg/m^2/d for 2 days, over 46-48 hours of continuous infusion, repeated for 2 weeks). When patients were assessed as unsuitable for concurrent ChT by clinicians, RT alone was administered.

Delineation and dose constraints of organs at risk

When we contoured the organs at risk, the PBM was divided into 3 parts: (1) the iliac bone marrow (IBM), which was defined as the area from the iliac crest to the superior border of the femoral heads; (2) the lumbosacral bone marrow (LSBM), which was defined as the area from the superior border of the L5 vertebrae to the coccyx; and (3) the lower pelvis bone marrow (LPBM), which included the proximal femur, acetabula, pubis, and ischia from the superior border of the femoral heads to the inferior border of the ischial tuberosities (Fig. 1). The dosimetric evaluation indices of the target volumes included the total volume (cm^3), mean dose (Dmean), and Vx of the total (PBM) and the 3 subsections (IBM, LSBM, and LPBM). Vx represents the percentage of BM volume receiving X Gy (ie, IBM-V10 represents the percentage of IBM-volume receiving $\geq$ 10 Gy).

The dose constraints for the organs at risk were as follows: maximum dose (Dmax) of the small intestine and colon $\leq$ 50 Gy, V50 of the bladder $\leq$ 50%, Dmean of the PBM $\leq$ 3000 cGy, and V50 of the femoral head $\leq$ 5%.

HT evaluation and treatment modifications

For all enrolled patients, complete peripheral blood, including the white blood cell (WBC) count, neutrophil (NEU) count, hemoglobin (HGB) level, and platelet (PLT) count, was collected at the time of diagnosis and on a weekly basis throughout the course of RT. HTs were graded according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE version 5.0).

The treatment plan continued when a patient experienced grade 1 or 2 HTs unless the patient could not tolerate treatment, but supportive care was provided. When a patient experienced any grade 3 or 4 HTs, all treatments were suspended, supportive care was provided, and treatment continued when the HTs decreased to grade 1 to 2 or all indices returned to normal. After grade 3 or 4 HTs, the ChT dose was reduced to 75%.

The criterion for packed red blood cell transfusions was HGB $\leq$ 60 g/L. When the PLT was $\leq 20 \times 10^9$/L, platelet transfusions were needed. When the WBC was $\leq 3.0 \times 10^9$/L, neupogen was needed.

Statistical analyses

The primary endpoint was the occurrence of grade ≥ 2 HT (HT2+) from baseline sample to the last day of RT. Univariate and multivariate analyses were conducted to identify significant clinical variables and dose-volume parameters for HTs by using regression analysis. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the model performance. Statistical analyses were carried out using IBM SPSS Statistics software, version 25.0 (IBM). $P < .05$ was considered to indicate statistical significance.

Results

Clinicopathologic characteristics

Between January 2016 and September 2022, 142 patients consecutively received neo-RT or cur-RT in our department, whereas 12 patients were excluded for the lack of complete clinical data or treatment interruption, and a total of 130 patients were included in this study finally. The mean age was 56 (range, 21-75) years, with 75.4% (n = 98) being males. Four patients were diagnosed with stage I disease, 5 patients with stage II disease, and 121 patients with stage III disease. The tumor locations were as follows: 5 patients in the upper rectum, 53 in the middle rectum, and 72 in the lower rectum. There were 84 patients with positive circumferential resection margin, 75 patients with positive extramural venous invasion, and 25 patients who were diagnosed with peritoneal reflection involvement, which were assessed by reading high-resolution pelvic magnetic resonance imaging at the time of diagnosis. The clinical and treatment characteristics of the patients are presented in Table 1.

The prescribed doses delivered to the GTVp and GTVn were 50 Gy for 81 patients, 50 to 55 Gy for 33 patients, and 60 to 64 Gy for 16 patients, and the doses delivered to the CTV were 45 Gy for 108 patients and 46 Gy for 22 patients, all of which were administered in 25 daily fractions. During RT, 125 patients received concurrent ChT, and 5 patients received RT only. Sixty-six patients received the capecitabine regimen ChT, 53 patients received the CapeOx regimen ChT, and 6 patients received the mFOLFOX regimen ChT.

HTs during RT

At the time of diagnosis, the median baseline peripheral blood counts were as follows: pre-WBC, 6.65 × 109/L (IQR: 5.46-7.85); pre-NEU, 3.82 × 109/L (IQR: 3.02-4.77); pre-HGB, 134 g/L (IQR: 119-143); and pre-PLT, 260 × 109/L (IQR: 211-305) (Table 2).

During RT with or without ChT, 39 patients experienced grade 2+ leukopenia, 22 patients experienced grade 2+ neutropenia, 23 patients experienced grade 2+ anemia, and 10 patients experienced grade 2+ thrombocytopenia. A total of 57 patients (43.8%) experienced HT2+ during the RT period, and no grade 5 HT occurred. All the data are summarized in Table 2 and Fig. 2.

Univariate and multivariate analysis

According to the univariate analysis, gender, the IBM-Dmean, the IBM-V15, the IBM-V40, and the PBM-Dmean were significantly associated with grade 2+ leukopenia ($P < .05$); female gender was significantly associated with grade 2+ anemia; concurrent ChT regimens, LSBM-V15, LSBM-V20, LSBM-V30, PBM-V30, and PBM-V40 were significantly associated with grade 2+ thrombocytopenia; and gender and IBM-V40 were significantly associated with total grade 2+ HTs (Table 3). However, no prognostic factor was found for grade 2+ neutropenia.

The clinicopathologic variables with $P \leq .05$ in the univariate analysis were included in the final multivariate model. According to multivariate analysis, gender, the IBM-Dmean, the IBM-V15, and the IBM-V40 remained independent prognostic factors for grade 2+ leukopenia ($P < .05$). Oxaliplatin-containing concurrent ChT regimens (CapeOx and mFOLFOX) tended to increase the incidence of grade 2+ thrombocytopenia ($P = .054$). Moreover, female gender was significantly associated with grade 2+ anemia and total grade 2+ HTs (Table 4).

Modeling dosimetric predictors of HTs

Based on the results of multivariate analysis, ROC curves were generated to identify the optimal cutoff values of IBM-Dmean, IBM-V15, and IBM-V40 for predicting grade 2+ leukopenia. The optimal cutoff values for predicting grade 2+ leukopenia were an IBM-Dmean < 2692.75 cGy, an IBM-V15 < 86.65% and an IBM-V40 < 20.75%. Gender combined with an IBM-Dmean < 2692.75 cGy, an IBM-V15 < 86.65% and an IBM-V40 < 20.75% showed a satisfactory predictive ability for a greater incidence of grade 2+ leukopenia (AUC = 0.834, 95% CI, 0.757-0.911) (Fig. 3A). Oxaliplatin-containing concurrent ChT regimens showed relatively satisfactory predictive ability for a higher incidence of grade 2+ thrombocytopenia (AUC = 0.678, 95% CI, 0.540-0.817) (Fig. 3B).

Discussion

The present study explored the correlation between PBM radiation dosimetric parameters and HTs during

Table 1 Clinical characteristics of the 130 patients at baseline and univariate logistic regression analysis for grade 2+ HTs during RT

		Grade 2+ leukopenia		Grade 2+ anemia		Grade 2+ thrombocytopenia		Total grade 2+ HTs	
Patient characteristics	**Patient number (%)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age, y									
≥60	51 (39.2)	0.697 (0.318-1.529)	.368	0.995 (0.395-2.504)	.991	0.000 (0.000-infinite)	.997	0.954 (0.469-1.940)	.896
<60	79 (60.8)								
Gender									
Female	32 (24.6)	16.600 (6.287-43.829)	<.001	6.021 (2.301-15.757)	<.001	2.190 (0.577-8.315)	.249	12.240 (4.298-34.855)	<.001
Male	98 (75.4)								
BMI (kg/m^2)*									
≥23	64 (49.2)	0.985 (0.456-2.127)	.970	0.655 (0.254-1.687)	.380	1.966 (0.469-8.240)	.355	0.733 (0.359, 1.496)	.393
<23	60 (46.2)								
History of DM									
Yes	14 (10.8)	0.606 (0.159-2.305)	.462	2.042 (0.580-7.196)	.267	0.000 (0.000-infinite)	.999	0.956 (0.312-2.930)	.937
No	116 (89.2)								
History of CAD									
Yes	25 (19.2)	1.406 (0.560-3.528)	.468	0.862 (0.265-2.803)	.805	1.054 (0.210-5.300)	.949	1.231 (0.513-2.951)	.642
No	105 (80.8)								
Tumor location (distance from anal verge)									
≤5 cm	72 (55.4)	1.011 (0.525-1.948)	.973	1.556 (0.727-3.330)	.255	1.438 (0.490-4.220)	.508	1.255 (0.684-2.300)	.463
>5 to ≤10 cm	53 (40.8)								
>10 cm	5 (3.8)								
Clinical T stage									
T2	6 (4.6)	1.467 (0.752-2.862)	.261	1.340 (0.602-2.985)	.474	2.026 (0.593-6.921)	.260	1.493 (0.809-2.753)	.200
T3	66 (50.8)								
T4	58 (44.6)								
Clinical N stage									
N0	9 (6.9)	1.167 (0.632-2.155)	.622	0.844 (0.414-1.720)	.641	1.168 (0.401-3.406)	.776	0.966 (0.553-1.686)	.902
N1	54 (41.5)								
N2	67 (51.5)								

(*continued on next page*)

Table 1 (*Continued*)

Patient characteristics	Patient number (%)	Grade 2+ leukopenia		Grade 2+ anemia		Grade 2+ thrombocytopenia		Total grade 2+ HTs	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CRM[†]									
Positive	84 (71.2)	1.343 (0.691-2.607)	.384	1.156 (0.524-2.550)	.719	1.260 (0.406-3.914)	.690	1.172 (0.6372.155)	.610
Negative	34 (28.8)								
EMVI[‡]									
Positive	72 (64.9)	0.892 (0.592-1.343)	.583	0.779 (0.459-1.320)	.353	0.888 (0.431-1.830)	.747	0.913 (0.630-1.324)	.631
Negative	39 (35.1)								
Peritoneal reflection involved[§]									
Yes	25 (21.0)	1.404 (0.796-2.478)	.242	1.543 (0.811-2.938)	.187	1.392 (0.562-3.446)	.475	1.407 (0.812-2.437)	.223
No	94 (79.0)								
Concurrent ChT regimens[‖]									
Capecitabine	66 (52.8)	1.175 (0.548-2.520)	.679	1.286 (0.502-3.283)	.603	5.020 (1.021-24.678)	.047	1.219 (0.600-2.477)	.585
CapeOx/mFOLFOX	59 (42.7)								
RT dose (Gy)									
>45 to ≤50	81 (62.3)	0.826 (0.476-1.434)	.498	0.750 (0.375-1.502)	.417	0.789 (0.292-2.136)	.642	0.653 (0.390-1.095)	.106
>50 to ≤55	33 (25.4)								
>55	16 (12.3)								

Abbreviations: BMI = body mass index; CAD = coronary artery disease; Capecitabine = 825 mg/m^2 twice daily for 5 days a week; CapeOx = Oxaliplatin 130 mg/m^2 on day 1 + Capecitabine 1000 mg/m^2 twice daily for 14 days, repeated for 3 weeks; ChT = chemotherapy; CRM = circumferential resection margin; DM = diabetes mellitus; EMVI = extramural venous invasion; HT = hematologic toxicity; mFOLFOX = Oxaliplatin 85 mg/m^2 on day 1, leucovorin 400 mg/m^2 on day 1, 5-Fu 400 mg/m^2 bolus on day 1, followed by 1200 mg/m^2/d for 2 days, over 46 to 48 hours continuous infusion, repeated for 2 weeks; OR = odds ratio; RT = radiation therapy.

*The BMI data of 6 patients were not available.

†The status of CRM of 12 patients was not available.

‡The status of EMVI of 19 patients was not available.

§The status of peritoneal reflection involved or not of 11 patients was not available.

‖There were 5 patients received RT only without concurrent ChT.

Table 2 Baseline of peripheral blood counts and HTs during RT

		HTs during RT				
Blood cell	Pretreatment Median (IQR)	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
WBC	6.65×10^9/L (5.46, 7.85)	45 (34.6)	46 (35.4)	36 (27.7)	3 (2.3)	0 (0)
ANC	3.82×10^9/L (3.02, 4.77)	95 (73.1)	13 (1.0)	19 (14.6)	3 (2.3)	0 (0)
HGB	134 g/L (119, 143)	50 (38.5)	57 (43.8)	19 (14.6)	3 (2.3)	1 (0.8)
PLT	260×10^9/L (211, 305)	98 (75.4)	22 (16.9)	9 (6.9)	1 (0.8)	0 (0)
Total HTs	-	14 (10.8)	59 (45.4)	49 (37.7)	7 (5.4)	1 (0.8)

Abbreviations: ANC = absolute neutrophil count; HGB = hemoglobin; HT = hematologic toxicity; PLT = platelet; RT = radiation therapy; WBC = white blood cell.

RT in patients with stage I to III rectal cancer. The results demonstrated that female patients were more likely to experience grade 2+ anemia and total grade 2+ HTs during the RT period. In addition, female patients with higher IBM-Dmean, IBM-V15, and IBM-V40 were more likely to experience grade 2+ leukopenia, and oxaliplatin combined with concurrent ChT regimens tended to increase the incidence of grade 2+ thrombocytopenia.

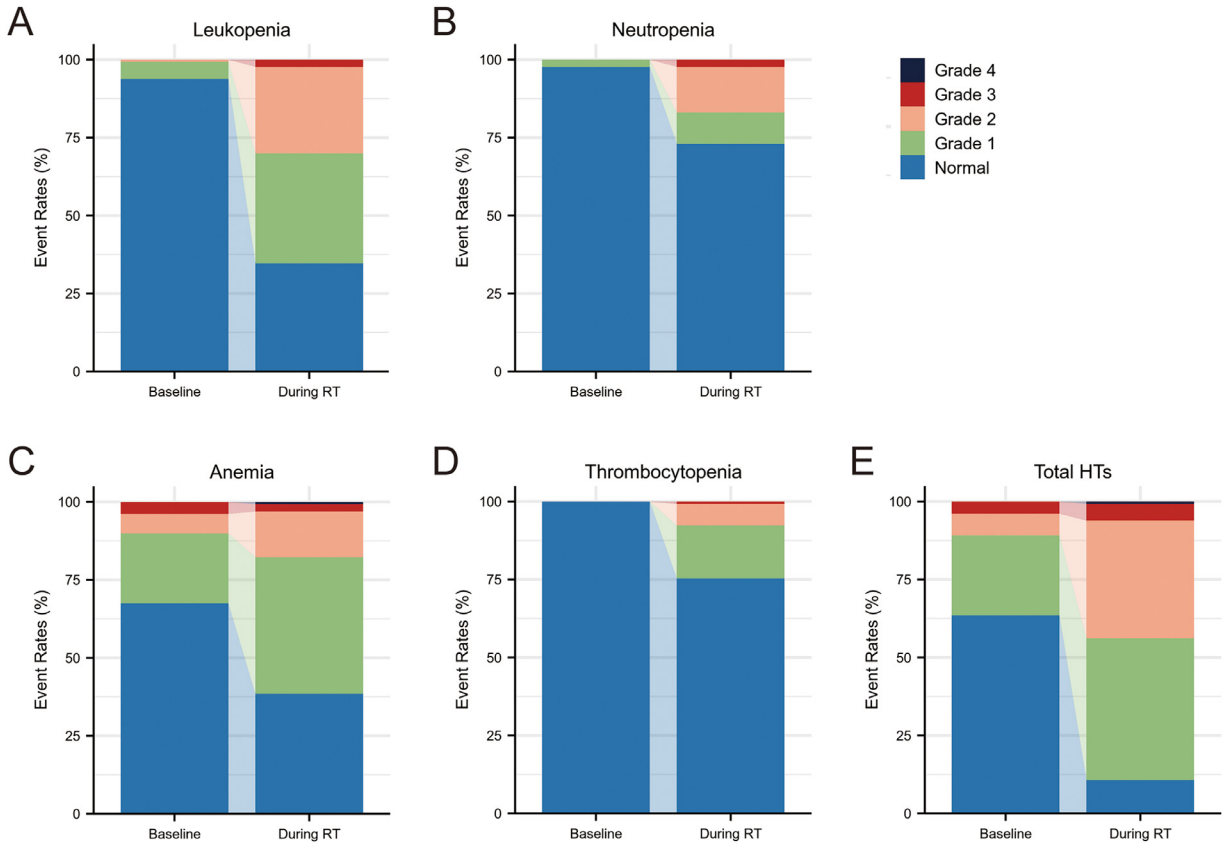

Figure 2 Peripheral blood counts at baseline and HTs during RT. (A) White blood cell counts at baseline and leukopenia during RT. (B) Neutrophil and neutropenia during RT. (C) Hemoglobin counts at baseline and anemia during RT. (D) Platelet counts at baseline and thrombocytopenia during RT. (E) Total HTs at baseline and during RT.
Abbreviations: HT = hematologic toxicity; RT = radiation therapy.

Table 3 Summary statistics of pelvic bone marrow dose-volume parameters and univariable analysis of dosimetric predictors for HT2+ events

			Grade 2+ leukopenia		Grade 2+ thrombocytopenia		Grade 2+ HTs	
Bone marrow region	**Dosimetric valuess**	**Median (IQR)**	**OR* (95% CI)**	***P***	**OR* (95% CI)**	***P***	**OR* (95% CI)**	***P***
Ilial bone marrow (IBM)	IBM-volume (cm^3)	397.69 (348.31, 466.06)	-	-	-	-	-	-
	IBM-Dmean (cGy)	2618 (2413, 2819)	1.002 (1.000-1.003)	.006	0.999 (0.997-1.001)	.500	1.001 (1.000-1.002)	.068
	IBM-V10 (%)	90.18 (85.24, 95.14)	1.038 (0.986-1.092)	.156	1.035 (0.945-1.133)	.461	1.020 (0.976-1.066)	.368
	IBM-V15 (%)	79.30 (72.32, 86.61)	1.044 (1.002-1.087)	.040	1.011 (0.947-1.079)	.744	1.022 (0.987-1.059)	.224
	IBM-V20 (%)	65.24 (55.09, 71.75)	1.026 (0.993-1.059)	.122	0.986 (0.937-1.037)	.575	1.015 (0.987-1.045)	.293
	IBM-V30 (%)	38.74 (30.68, 46.34)	1.009 (0.988-1.031)	.408	0.960 (0.903-1.022)	.201	1.002 (0.982-1.023)	.848
	IBM-V40 (%)	18.07 (13.25, 23.69)	1.096 (1.038-1.157)	.001	0.966 (0.879-1.062)	.478	1.059 (1.008-1.111)	.022
Lumbosacral bone marrow (LSBM)	LSBM-volume (cm^3)	336.05 (303.09, 382.94)	-	-	-	-	-	-
	LSBM-Dmean (cGy)	4030 (3744, 4312)	1.000 (1.000-1.001)	.310	0.999 (0.998-1.000)	.157	1.000 (0.999-1.001)	.484
	LSBM-V10 (%)	99.83 (91.52, 100)	0.998 (0.948-1.051)	.949	0.959 (0.889-1.034)	.279	1.003 (0.956-1.052)	.917
	LSBM-V15 (%)	97.57 (89.02, 100)	0.988 (0.947-1.030)	.565	0.963 (0.902-1.027)	.252	0.998 (0.958-1.039)	.906
	LSBM-V20 (%)	94.65 (85.47, 99.66)	0.987 (0.950-1.026)	.512	0.940 (0.887-0.997)	.038	0.984 (0.949-1.021)	.393
	LSBM-V30 (%)	85.08 (76.78, 93.50)	0.996 (0.964-1.028)	.796	0.929 (0.880-0.980)	.007	0.989 (0.960-1.019)	.477
	LSBM-V40 (%)	65.61 (56.61, 75.69)	1.015 (0.986-1.044)	.318	0.971 (0.931-1.013)	.171	1.000 (0.975-1.025)	.996
Lower pelvic bone marrow (LPBM)	LPBM-volume (cm^3)	604.25 (510.23, 659.36)	-	-	-	-	-	-
	LPBM-Dmean (cGy)	2349 (2096, 2697)	1.000 (1.000-1.001)	.228	0.999 (0.997-1.000)	.139	1.000 (0.999-1.001)	.761
	LPBM-V10 (%)	83.53 (72.20, 91.16)	1.011 (0.981-1.042)	.475	0.970 (0.924-1.019)	.222	1.009 (0.981-1.037)	.529
	LPBM-V15 (%)	68.63 (59.90, 77.26)	1.015 (0.987-1.044)	.289	0.970 (0.922-1.021)	.248	1.006 (0.981-1.033)	.628
	LPBM-V20 (%)	57.79 (49.32, 66.05)	1.020 (0.994-1.047)	.127	1.000 (0.956-1.045)	.985	1.009 (0.985-1.033)	.478
	LPBM-V30 (%)	30.60 (23.08, 44.24)	1.016 (0.990-1.042)	.232	0.968 (0.920-1.018)	.207	1.002 (0.979-1.026)	.837
	LPBM-V40 (%)	13.57 (8.71, 23.45)	1.023 (0.990-1.057)	.174	0.938 (0.859-1.024)	.151	1.005 (0.974-1.036)	.775
Pelvic bone marrow (PBM)	PBM-volume (cm^3)	1389.60 (1185.62, 1550.08)	-	-	-	-	-	-
	PBM-Dmean (cGy)	2859 (2670, 3064)	1.001 (1.000-1.003)	.022	0.999 (0.998-1.001)	.232	1.001 (1.000-1.002)	.116
	PBM-V10 (%)	87.56 (83.10, 92.63)	1.039 (0.979-1.102)	.208	0.941 (0.856-1.035)	.211	1.029 (0.975-1.086)	.298
	PBM-V15 (%)	78.19 (73.08, 83.37)	1.041 (0.988-1.096)	.132	0.944 (0.861-1.036)	.225	1.017 (0.969-1.066)	.498
	PBM-V20 (%)	68.37 (62.24, 73.06)	1.040 (0.994-1.087)	.087	0.953 (0.880-1.032)	.234	1.012 (0.973-1.054)	.546
	PBM-V30 (%)	48.21 (41.55, 55.14)	1.037 (0.996-1.080)	.074	0.926 (0.861-0.996)	.038	1.009 (0.973-1.046)	.637
	PBM-V40 (%)	28.97 (24.39, 34.72)	1.045 (0.996-1.097)	.071	0.897 (0.819-0.983)	.020	1.014 (0.971-1.059)	.537

Abbreviations: Dmean = median dose; HT2+ = ≥ grade 2 hematologic toxicity; OR = odds ratio.

Table 4 Univariate and multivariate logistic regression analysis for grade 2+ hematologic toxicity

	Univariate analysis		Multivariate analysis	
Characteristics	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Grade 2+ leukopenia				
Gender	16.600 (6.287-43.829)	**<.001**	16.032 (5.441-47.240)	**<.001**
IBM-Dmean	1.002 (1.000-1.003)	**.006**	0.994 (0.989-0.999)	**.017**
IBM-V15 (%)	1.044 (1.002-1.087)	**.040**	1.130 (1.035-1.233)	**.006**
IBM-V40 (%)	1.096 (1.038-1.157)	**.001**	1.198 (1.036-1.385)	**.015**
PBM-Dmean	1.001 (1.000-1.003)	**.022**	1.001 (0.998-1.003)	.599
Grade 2+ anemia				
Gender	6.021 (2.301-15.757)	**<.001**	6.021 (2.301-15.757)	**<.001**
Grade 2+ thrombocytopenia				
Concurrent ChT regimens	5.020 (1.021-24.678)	**.047**	0.192 (0.036-1.032)	**.054**
LSBM-V20 (%)	0.940 (0.887-0.997)	**.038**	1.035 (0.890-1.203)	.657
LSBM-V30 (%)	0.929 (0.880-0.980)	**.007**	0.922 (0.804-1.056)	.241
PBM-V30 (%)	0.926 (0.861-0.996)	**.038**	1.048 (0.873-1.257)	.617
PBM-V40 (%)	0.897 (0.819-0.983)	**.020**	0.872 (0.688-1.105)	.257
Total grade 2+ HTs				
Gender	12.240 (4.298-34.855)	**<.001**	11.472 (3.784-34.781)	**<.001**
IBM-V40 (%)	1.059 (1.008-1.111)	**.022**	1.010 (0.952-1.071)	.743

Abbreviations: ChT = chemotherapy; Dmean = median dose; HT = hematologic toxicity; IBM: iliac bone marrow; LSBM: lumbosacral bone marrow; OR = odds ratio; PBM: pelvic bone marrow.
$P < .05$ was considered to indicate statistical significance.

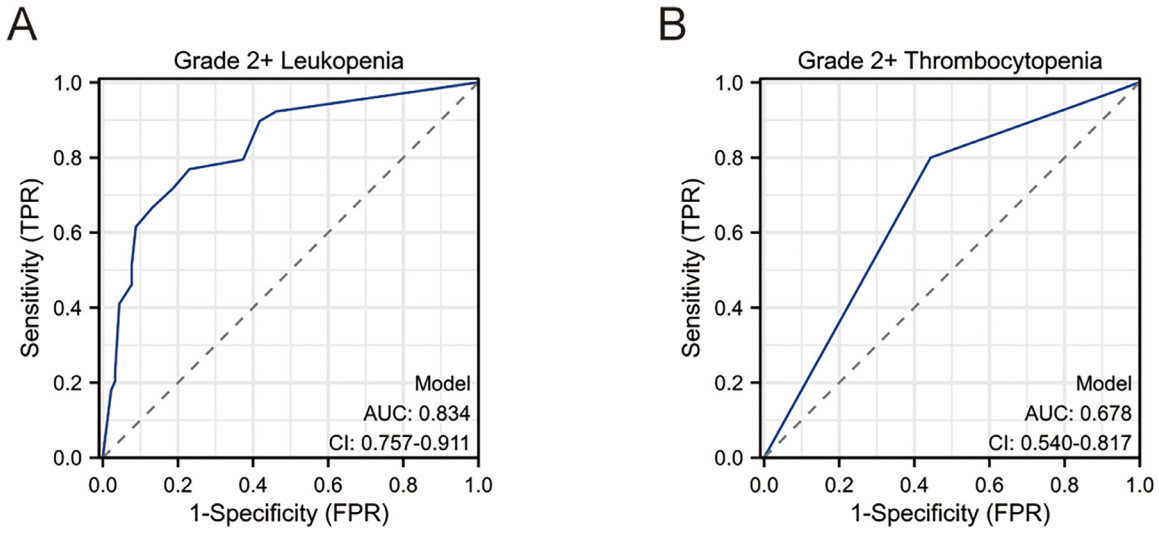

Figure 3 Receiver operating characteristic (ROC) curves for hematologic toxicities during radiation therapy based on the multivariate analysis results. (A) The area under the curve (AUC) of ROC curve of gender combined with iliac bone marrow (IBM)-Dmean, IBM-V15, and IBM-V40 for predicting grade 2+ leukopenia was 0.834 (95% CI, 0.757-0.911). (B) The AUC of ROC curve of oxaliplatin-containing concurrent chemotherapy regimens for predicting grade 2+ thrombocytopenia was 0.678 (95% CI, 0.540-0.817).
Abbreviations: FPR = false positive rate; TPR = true positive rate.

In this study, female patients were more likely to experience anemia. The main reasons included the following: (1) menstruation in premenopausal women and (2) compared with male patients with cancer, female patients were more likely to experience nausea and vomiting induced by chemoradiotherapy, which may decrease appetite and decrease iron absorption.[13] Previous studies have demonstrated that anemia is an adverse factor for tumor regression and prognosis for patients with cancer.[14-16] Anemia-induced tumor hypoxia can increase resistance to chemotherapy and RT .[15] Therefore, we should pay more attention to female patients with rectal cancer and anemia during CRT, and appropriate supportive care should be adopted.

The results of previous studies[17,18] have demonstrated that the RT dose of BM was closely associated with HTs during CRT for rectal patients, which was similar to our study findings. Jianyang et al[17] conducted a prospective phase 2 clinical trial, and they contoured the active BM by magnetic resonance as a normal tissue for 35 patients with LARC enrolled. The results of this study showed that increased BM-V5 was significantly associated with HTs (including decreased WBC, absolute neutrophil count, and PLT nadirs) during concurrent CRT. Franco et al[19] used the Lyman-Kutcher-Burman model to evaluate the probability of complication in normal tissue, and the results suggested that an LSBM-mean dose below 32 Gy could be used to minimize ≥ G3 HT in patients with anal cancer treated with IMRT. Li et al[18] reported that the low dose-volume parameters of the IBM, LSBM, and PBM were significant predictors of acute bone marrow suppression during concurrent CRT. Yang et al[20] analyzed 120 patients with rectal cancer treated with neo-RT with concurrent 5-Fu ChT and found that coxal BM V45 and sacral BM V45 were associated with a lower WBC and absolute neutrophil count ratio at nadir. Huang et al[21] conducted a clinical trial to compare patients with LARC who received PBM sparing IMRT and non-PBM sparing IMRT, and the results showed that patients treated with PBM-sparing IMRT had a lower incidence of acute HT. In addition to acute HTs, Newman et al[10] reported that BM-sparing preoperative RT could also reduce HTs for patients with LARC during postoperative ChT. Therefore, BM-sparing RT was an effective way to reduce HTs during and after RT.

In patients with anal cancer treated with pelvic RT, similar results were found according to previous literature. The results of previous studies[11,12,22-24] suggested that ^{18}FDG-PET is an effective means to define active bone marrow that may predict decreased blood cell counts, and they suggested that ^{18}FDG-PET-guided BM-sparing IMRT could significantly reduce acute HTs.

Concurrent ChT was another cause of the HTs. Cheng et al[9] compared the differences in HTs between patients who received FOLFOX or 5-FU concurrent ChT in the FOWARC study.[25] The results showed that 65.7% of patients in the FOLFOX group and 37.9% of patients in the 5-FU group experienced HT2+ ($P < .001$). Results of our study showed that oxaliplatin-containing concurrent ChT regimens (CapeOx and mFOLFOX) tended to increase the incidence of grade 2+ thrombocytopenia ($P = .054$). Oxaliplatin kills tumor cells by inhibiting DNA synthesis,[26] and thrombocytopenia was one of the most common adverse effects.[27] The main mechanisms by which oxaliplatin causes thrombocytopenia include myelosuppression, oxaliplatin-induced sinusoidal injury and immune thrombocytopenia.[28,29]

Although our study has yielded valuable insights, it is not without its limitations. As this was a retrospective, single-center analysis, the sample size was modest, warranting external validation in a larger cohort. Therefore, prospective randomized controlled trials are imperative to confirm our findings.

Conclusions

In conclusion, this study revealed that female patients with higher IBM-Dmean, IBM-V15, and IBM-V40 among stage I to III patients who received neo-RT or cur-RT were more likely to experience grade 2+ leukopenia. Concurrent oxaliplatin-containing ChT regimens were potential factors for increasing the incidence of grade 2+ thrombocytopenia. In our future clinical work, PBM-sparing RT should be recommended for patients with rectal cancer to reduce the incidence of HTs.

Disclosures

None.

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