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Clinical and dosimetric predictors of acute hematologic toxicity in rectal cancer patients undergoing chemoradiotherapy

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Abstract

Background and purpose—To identify clinical and dosimetric factors associated with hematologic toxicity (HT) during chemoradiotherapy for rectal cancer.

Materials and methods—We analyzed 120 rectal cancer patients treated with neoadjuvant pelvic radiotherapy (PRT) with concurrent 5-fluorouracil-based chemotherapy. The coxal (ilium, ischium, and pubis) bone marrow (BM), sacral BM, and femoral BM were contoured and dose-volume parameters were extracted. Associations between cell count trend and clinical predictors were tested using repeated-measures analysis of variance (ANOVA) test. Associations between clinical variables, V_x (percentage volume receiving x Gy), and cell count ratio at nadir were tested using linear regression models.

Results—Nadirs for white blood cell count (WBC), absolute neutrophil count (ANC), and platelets (PLT) occurred in the second week of PRT and the fifth week for hemoglobin and absolute lymphocyte count (ALC). Using cell count ratio, patients treated with 3DCRT had a lower WBC ratio trend during PRT compared to patients treated with IMRT ($p = 0.04$), and patients ≥ 59 years of age had a lower hemoglobin ratio trend during PRT ($p = 0.02$). Using absolute cell count, patients treated with 3DCRT had lower ANC cell count trend ($p = 0.03$), and women had lower hemoglobin cell count trend compared to men ($p = 0.03$). On univariate analysis, use of 3DCRT was associated with a lower WBC ratio at nadir ($p = 0.02$). On multiple regression analysis using dosimetric variables, coxal BM V₄₅ ($p = 0.03$) and sacral BM V₄₅ ($p = 0.03$) were associated with a lower WBC and ANC ratio at nadir, respectively.

Conclusions—HT trends during PRT revealed distinct patterns: WBC, ANC, and PLT cell counts reach nadirs early and recover, while hemoglobin and ALC decline steadily. Patients who were treated with 3DCRT and older patients experienced lower cell count ratio trend during PRT. Dosimetric constraints using coxal BM V₄₅ and sacral BM V₄₅ can be considered.

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Conflict of interest notification

The authors of this manuscript have no actual or potential conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2014.09.002>.

Keywords

Rectal cancer; Acute radiation toxicity; Clinical predictors; Dose constraint

Pelvic radiotherapy (RT) is an integral part of the multidisciplinary care for patients with locally advanced rectal cancer. The use of pre-operative RT with 5-fluorouracil (FU)-based chemotherapy has been shown to improve locoregional control in several randomized trials [1–5]. Despite the established therapeutic advantage of RT in rectal cancer management, there is paucity of data on the impact of pelvic RT on bone marrow (BM) suppression and incidence of acute hematologic toxicity (HT). Given that pelvic BM is routinely included in a pelvic field, and approximately 40% of the total-body BM reserves are located within the pelvic bones [6], the destruction of the radiosensitive marrow stem cells by RT can lead to acute myelosuppression [7]. Studies in patients with cervical and anal cancer have demonstrated associations between concurrent chemoradiotherapy (CRT) and an increased risk of Grade 2–4 anemia, neutropenia, and thrombocytopenia during treatment [8–11]. However, the timing of the development of acute HT during CRT remains unclear.

Isolating clinical and dosimetric factors associated with pelvic radiotherapy-related hematologic toxicity is important as investigational agents are being combined with standard 5-FU-based chemoradiation for rectal cancer. Predictors of HT may help stratify patients who can tolerate intensification of therapy or guide dosimetric constraints that can reduce the risk of HT from the pelvic radiotherapy. In this study, we assessed HT in locally advanced rectal cancer patients receiving pelvic RT with concurrent FU-based chemotherapy. Given that infusional 5-FU or capecitabine chemotherapy functioned mainly as a radiosensitizer in patients undergoing neoadjuvant CRT for rectal cancer and had been reported to be associated with a low rate of myelosuppression [12,13–16], we felt that analyzing HT in this population would help us determine the myelosuppressive effect predominantly caused by pelvic RT. Our study aimed to establish the impact of standard long-course pelvic RT on BM suppression and to identify clinical and dosimetric predictors of HT. We tested the hypothesis that different hematologic cell types reach nadir at different time points during pelvic RT due to their distinct radiosensitivities, and that unique predictors for HT are associated with each cell type. Finally, we report potential dosimetric constraints for pelvic bony structures that can be used for pelvic RT planning, in particular IMRT planning, which has become more common in the treatment of rectal cancer.

Methods and materials

Patients and radiation planning and delivery

After obtaining approval of the Institutional Review Board, we retrospectively analyzed 120 consecutive rectal cancer patients treated with neoadjuvant pelvic RT with concurrent chemotherapy at our institution between 2007 and 2010. Patients who received induction chemotherapy prior to CRT or received CRT in the adjuvant setting were excluded. Concurrent chemotherapy was primarily continuous infusion 5-FU (225 mg/m²/day) (95%). Only 5% received concurrent capecitabine (875 mg/m² twice daily). Patient's clinical

information and weekly hematologic cell counts during pelvic RT were obtained through chart review.

All patients underwent computed tomography (CT) simulation in the prone position with marker placed at the anal verge. The gross tumor volume (GTV) consisted of the primary tumor and enlarged regional lymph nodes. For the standard pelvic fields, the clinical target volume (CTV) consisted of the GTV, rectum, and lymph node regions including mesorectum, pre-sacral nodes, internal iliac nodes, and the inferior rectal nodes. The initial planning target volume (PTV) is a 0.5 cm three-dimensional (3D) expansion of CTV. For the boost fields, CTV-boost consisted of the GTV, adjacent mesorectum, and presacral space, and PTV-boost is a 1.5 cm expansion and the CTV-boost. Normal tissues contoured at the time of RT planning included the bladder, rectum, small bowel, femoral heads, external genitalia, and vagina in female patients.

Patients underwent either 3DCRT or IMRT treatment planning with the in-house planning software, according to the treating physician's preference. 3DCRT was the RT delivery method for the majority (56%) of patients (Fig. 1). The median RT dose of the study cohort was 50 Gy in 25 fractions, and coverage of the PTV by at least 95% of the prescribed dose was required for all plans. 3DCRT plans consisted of three or four orthogonal beams for the pelvic fields and two lateral beams and one posterior–anterior beam for the boost fields. PTV was treated with 45 Gy in 1.8 Gy fractions followed by a 5.4 Gy boost to PTV-boost. IMRT plans consisted of seven to nine equally spaced coplanar fields. Dose homogeneity was assessed to minimize volume receiving more than 5% of the prescribed dose. The majority of patients treated with IMRT received 45 Gy in 1.8 Gy fractions to PTV and 50 Gy in 2 Gy fractions to the PTV-boost as an integrated boost.

Bone marrow delineation and dose calculation

Pelvic bone structures were contoured on the planning CT using bone windows. Pelvic BM was divided into three anatomic sites (Fig. 1): (1) sacral BM, extending from the L5-S1 junction to coccyx, (2) coxal BM, consisting of bilateral ilium, ischium, and pubis, and (3) proximal femoral BM, consisting of bilateral femoral heads and proximal femur. Doses to bony structures were calculated using the original treatment plan and dose-volume parameters were extracted for modeling using our in-house CERR (Computational Environment for Radiotherapy Research) [17] and DREES (Dose Response Explorer System) [18] software tools.

Toxicity and grading

All patients were monitored weekly during RT for acute toxicity including fatigue, dermatitis, mucositis, nausea, vomiting, diarrhea, proctitis, and cystitis. Weekly complete blood work with differentials was performed and documented: hemoglobin (g/dL), platelet count (K/mcL, PLT), white blood cell count (K/mcL, WBC), absolute neutrophil count (K/mcL, ANC), and absolute lymphocyte count (K/mcL, ALC). No patient required granulocyte–monocyte colony stimulating factor, or received packed red blood cell or platelet transfusion during CRT. HT was scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistical analysis

Blood cell counts were measured at pre-RT and at each week during the course of RT treatment. For statistical analysis, cell count ratios were calculated by dividing the cell counts at each week by pre-RT cell counts. One patient's cell counts were not obtained for week 2 of RT, 7 patients did not have cell counts for week 3, 1 patient did not have cell counts for week 4, and 20 patients for week 5. The missing data points were excluded from calculation of cell count ratios and analysis. A repeated-measures analysis of variance (ANOVA) was used to test cell count ratio trend and absolute cell count trend with dichotomous clinical and technical variables including: age (≥ 59 years, median age, vs. <59), stage (stage III, IV, or recurrent vs. stage I, II), patient sex (female vs. male), body mass index (BMI ≥ 27 kg/m², median BMI, vs. <27), and type of pelvic RT delivery (3DCRT vs. IMRT). Univariate linear regression models were used to test correlations between dichotomous clinical variables, BM (sacral, coxal, femoral) dosimetric V_x (percentage volume receiving x Gy) variables, and cell count ratios and absolute cell count at nadir. Using significant results from univariate analysis, multiple regression analysis was performed.

Results

The median age was 59 years. Forty-three patients (36%) were females. The majority of patients (76%) had advanced clinical stages (stage III or above) at the time of diagnosis. Table 1 provides an overview of patients' clinical characteristics. The mean baseline WBC, ANC, hemoglobin, ALC, and PLT were 7.0 K/mcL, 4.6 K/mcL, 13.1 g/dL, 1.7 K/mcL, and 257 K/mcL, respectively. Overall, 14 patients (11.7%), 5 patients (4.2%), and 12 patients (10.0%) experienced Grade 2+ leukopenia, neutropenia, and anemia respectively during pelvic RT. No patient experienced Grade 2+ thrombocytopenia. As expected, Grade 2+ lymphopenia was observed in almost all patients (117 patients, 97.5%). No patient experienced Grade 3+ leukopenia. Only 2 patients (1.7%) and 1 patient (0.8%) experienced Grade 3+ neutropenia and anemia, respectively, while the majority of patients (56.7%) had Grade 3+ lymphopenia.

Different cell types reached their nadirs at different time points: the nadirs for WBC, ANC, and PLT were observed during the second week of pelvic RT and recovered thereafter; conversely hemoglobin and ALC showed continuous decline during pelvic RT (Fig. 2). Given that no patient experienced clinically significant thrombocytopenia, and that almost all patients had Grade 2+ lymphopenia that has minimal clinical significance, we reported analyses on the effect of pelvic RT with concurrent chemotherapy on WBC, ANC, and hemoglobin.

Cell count trend

Clinical parameters and their association with cell count ratio were tested with repeated-measures ANOVA. The use of 3DCRT was associated with significantly lower WBC ratio trend during pelvic RT compared to patients treated with IMRT ($p = 0.04$). Patients treated with 3DCRT also showed lower ANC ratio trend during pelvic RT compared to patients treated with IMRT but did not reach statistical significance ($p = 0.07$). Patients ≥ 59 years of

age were found to have significantly lower hemoglobin cell count ratio trend compared to patients <59 years of age ($p = 0.02$, Fig. 2). Patient sex, BMI, and clinical stage did not predict for a significant difference in cell count ratio in WBC, ANC, or hemoglobin. Using absolute cell count, patients treated with 3DCRT had significantly lower ANC cell count trend ($p = 0.03$) compared to patients treated with IMRT, and women had significantly lower hemoglobin cell count trend during pelvic RT compared to men ($p = 0.03$).

Cell count at nadir

On univariate linear regression analysis, use of 3DCRT was the only parameter significantly associated with a lower WBC ratio at nadir ($p = 0.02$), which occurred during the second week of pelvic RT (Table 2). Patient sex, stage, age, and BMI were not associated with a difference in WBC ratio at nadir.

Table 3 details the dose–volume parameters for the pelvic BM and its subsites. Dosimetrically, sacral BM V35 (mean = 80.7%, standard deviation (SD) = 17.8%, $p = 0.05$), V45 (mean = 50.9%, SD = 23.8%, $p = 0.03$), V50 (mean = 9.3%, SD = 11.8%, $p = 0.05$) and coxal BM V45 (mean = 13.1%, SD = 8.9%, $p = 0.03$) were associated with a lower WBC ratio at nadir. However, the dosimetric parameters R^2 values were low (<0.05) for these. Based on the significant univariate regression dosimetric variables (sacral BM V35, V45, V50, and coxal BM V45), multiple regression was performed and coxal BM V45 ($p = 0.03$) was associated with a lower WBC ratio at nadir. Using absolute WBC count, no significant clinical and dosimetric factors were found to be associated with a lower WBC count at nadir. When only including patients treated with 3DCRT in the dosimetric analysis, coxal BM V45's association with a lower WBC ratio at nadir increased ($R^2 = 0.10$).

On univariate analysis, no significant clinical parameter was found to be associated with a lower ANC ratio at nadir, which occurred during the second week of pelvic RT. Using absolute ANC count, female gender was found to be predictive of lower ANC count at nadir on univariate analysis ($p = 0.01$). Dosimetrically, sacral BM V45 ($p = 0.09$) and V50 ($p = 0.06$) showed association with a lower ANC ratio at nadir but did not reach statistical significance. On multiple regression analysis including sacral BM V45 and V50, sacral BM V45 was found to be significantly associated with a lower ANC ratio at nadir ($p = 0.03$). No dosimetric variable was found to be significantly associated with a lower absolute ANC count at nadir.

Age, both as a continuous ($p = 0.06$) or binary (< 59 vs. ≥ 59 years) ($p = 0.07$) variable, showed association with lower hemoglobin ratio at nadir during pelvic RT with univariate analysis but did not reach statistical significance. No other clinical variables including patient sex, stage, treatment type, or BMI were associated with a lower hemoglobin ratio at nadir during the fifth week of pelvic RT. Using absolute hemoglobin count, female gender ($p < 0.0001$) and age ≥ 59 ($p = 0.03$) were significantly associated with a lower hemoglobin count at nadir on univariate analysis. Dosimetrically, sacral BM V45 was found to be significantly associated with a lower hemoglobin ratio at nadir ($R^2 = 0.04$, $p = 0.05$). When only including patients ≥ 59 years of age in the dosimetric analysis, sacral BM V45's association with a lower hemoglobin ratio at nadir increased ($R^2 = 0.11$). Given that no other dosimetric variable showed or approached statistical significance, no multiple regression

analysis was performed. No dosimetric variable was found to be significantly associated with a lower absolute Hgb count at nadir.

Discussion

While prior studies have shown both clinical and modifiable dosimetric predictors for hematologic toxicity in patients undergoing pelvic RT [8–10], it is unclear when the acute toxicity occurred. In this analysis, we demonstrated that various cell types reach nadir at different time points and are influenced by different clinical and dosimetric predictors. To identify the myelosuppressive effect caused predominantly by RT, we investigated patients undergoing neoadjuvant CRT for rectal cancer, as 5-FU-based chemotherapy has been associated with lesser myelosuppressive properties [12–14]. Acute hematologic toxicity associated with pelvic RT with continuous infusion 5-FU for rectal cancer has been reported up to 8% [5,19–22], and pelvic RT with capecitabine was found to cause less HT in a randomized phase III trial comparing oral capecitabine and intravenous 5-FU chemotherapy (2% vs. 8% with Grade 3 neutropenia) [13]. Excluding lymphopenia, the overall Grade 3+ hematologic toxicity is low in our patient cohort (1%); nevertheless, 12% of our patients experienced Grade 2+ neutropenia, and 10% of the patients had Grade 2+ anemia. This is significantly lower than the reported HT findings in anal cancer patients (50% with Grade 3+ HT) [10], and cervical cancer patients (68% with Grade 2+ HT) [8,9]. While chemotherapy may have contributed some myelosuppressive effect in our patient population, the marrow-toxic chemotherapy in patients with anal and cervical cancers undergoing CRT contributed significantly to the development of acute HT during pelvic CRT.

In addition to toxicity, we also reported that hematologic cell count nadir took place at different time points during pelvic RT according to cell types, indicating variation in intrinsic radiosensitivity. While studies examining hematologic toxicity in anal and cervical cancer patients correlated predictors to hematologic cell counts at nadirs, it is unclear when the nadirs occurred in these studies [8,10]. In our investigation, we found that WBC, ANC, and PLT nadirs occurred during the second week of RT and recovered thereafter. While ANC and PLT returned to baseline at the end of RT, WBC demonstrated a slower recovery, most likely due to ALC, a component of WBC, exhibiting a continuous decrease during pelvic RT. These results differed from a previous report by Yang et al. [23], in which the authors observed a continuous decrease in leukocyte count during RT. However, the authors included heterogeneous patients treated for different primary malignancies with variable use of types of chemotherapy, which could cause the differences in outcomes. This hypothesis is supported by Zachariah et al. [24], where the authors showed a difference in cell count trends in patients treated with RT for head and neck, lung, and pelvic malignancies. The authors showed that WBC, ANC, and platelets nadired at the third week of RT in patients treated for pelvic malignancies, while ALC demonstrated a continuous decline during RT, which echoes our finding. The cell-count patterns for WBC, ANC, and PLT are indicative of an initial RT insult followed by BM recovery. Further biological studies are warranted to determine if this is due to an inflammatory mediated process or an intrinsic radiobiological property of the cell types. ALC showed exponential decline early and continued throughout pelvic RT, an expected model for extremely radiosensitive lymphocytes.

While no patient in this study experienced clinically significant Grade 2+ thrombocytopenia, almost all patients experienced Grade 2+ lymphopenia. The clinical relevance of Grade 2+ lymphopenia during pelvic RT, however, is limited, and no patient in our study experienced significant viral infection, such as zoster reactivation. Therefore, we only examined clinical and dosimetric factors associated with decrease in WBC, ANC, and hemoglobin during pelvic RT. To do so, we used both absolute cell count and cell count ratio, defined as weekly cell count divided by baseline cell count. In examining associated clinical factors for HT in patients undergoing chemoradiotherapy for anal cancer, Mell et al. showed that female patients and patients with decreased body mass index had a lower WBC and ANC at nadir during treatment [10]. Similar to Mell et al., we found that female patients had lower absolute ANC cell count at nadir; however, we did not find these clinical variables significantly predicted for lower WBC or ANC ratio at nadir in our study. Using univariate linear regression analysis, we found that the use of 3DCRT is associated with a lower WBC ratio at nadir. The theoretic benefit of bone marrow sparing effect of IMRT has been reported through dosimetric analysis [25], and we observed that patients treated with IMRT had significantly less BM exposed to high dose RT (coxal BM V45–50: IMRT = 10.1% vs. 3DCRT = 25.1%, $p < 0.0001$ using Wilcoxon test). Our study included balanced proportions of patients who were treated with 3DCRT and IMRT, allowing us to demonstrate the hematologic effect caused by different treatment modalities. While age was not found to be a significant predictor for hematologic toxicity in both anal and cervical cancer patients [8–10], we found that older patients in our study had a lower hemoglobin ratio and absolute hemoglobin cell count at nadir. This could be due to decreased hematopoietic response to decrease in red blood cells in older patients.

In investigating dosimetric factors associated with HT, we found that coxal BM V45 and sacral BM V45 have significant associations with a lower WBC, ANC, and hemoglobin cell count ratio at nadirs. This is different from the low-dose radiation effect reported in anal cancer patients [10]. We speculate that by removing the effect of heavily marrow-toxic chemotherapy use as such in anal cancer, a higher RT dose threshold was therefore determined through our analysis. From our results, dose constraints of sacral V45 <51% and coxal V45 <13% can be considered using IMRT planning, especially in high-risk patients, such as those who are 59 years of age. Interestingly, no significant dosimetric predictor was derived when absolute cell count at nadir was used for analysis. By using cell count ratio at nadir and accounting for patient's baseline hematologic characteristics, we believe it may be a more sensitive model in assessing hematologic toxicity.

A limitation of our study is that given the nature of neoadjuvant rectal cancer treatment utilizing concurrent chemoradiotherapy, we are unable to definitively separate out the myelosuppressive effect of chemotherapy and RT in this study. While 5-FU-based chemotherapy is associated with less marrow toxicity, it can contribute to the development of acute HT during PRT [7]. Due to the nature of the study requiring many dosimetric variables to be included in the analysis, it is possible that significant association was influenced by the multiple analyses.

Leukopenia, specifically neutropenia, can lead to serious complications such as severe infections, and anemia can lead to treatment limiting symptoms, such as fatigue and

shortness of breath. The purpose of this study was to identify patients with clinical characteristics that correlated less BM reserve and at higher risks of developing complications, and potentially to utilize the modifiable dosimetric variables identified in this study to prevent HT in these patients. Even though the number of patients who experienced serious toxicity during neoadjuvant CRT for rectal cancer is low, it is still clinically significant to be able to further reduce these incidences in this patient population. Moreover, our study demonstrates fundamental effects of pelvic bone marrow radiation on peripheral cell counts in the setting of minimally myelotoxic chemotherapy. These results will provide guidance in designing chemotherapy intensification clinical trials by providing an understanding of the expected myelotoxicity primarily caused by radiation therapy.

In conclusion, hematologic toxicity, though uncommon, is identified in patients undergoing neoadjuvant CRT for rectal cancer. Different cell types reach nadir at different time points during pelvic RT: WBC, ANC, and PLT at the second week, recovering thereafter, while ALC and hemoglobin demonstrate a continuous decline throughout during RT. Unique predictors are associated with toxicity of different cell types. We found that the use of 3DCRT is associated with increased WBC toxicity, and older patients experienced worse anemia during pelvic RT. Through detailed dosimetric investigations, coxal BM V45 and sacral BM V45 emerged as significant predictors for lower WBC, ANC, and hemoglobin cell count ratio at nadirs. Dose constraint utilizing these variables can be considered using IMRT planning, especially in high-risk patients, such as those who are 59 years of age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Pelvic bone marrow subsites (A), and a comparison of dose distribution of intensity modulated radiation therapy rectal cancer treatment (B) versus three-dimensional conformal radiation therapy rectal cancer treatment (C). These snapshots were captured using our in-house software (Computational Environment for Radiotherapy Research).

Fig. 2. Cell count ratio trend (mean and 95% confidence interval plotted): (A) weekly cell count ratio for all cell types; (B) treatment type versus weekly WBC count ratio; (C) age versus weekly hemoglobin count ratio during pelvic radiotherapy.

Table 1

Patient characteristics.

Patients (<i>n</i>)		120
Age at RT initiation (years)	Median, Mean (Range, SD)	59, 60 (25–94, 13)
Patient sex (<i>n</i> , %)	Female	43 (36)
	Male	77 (64)
BMI (kg/m ²)	Median, Mean (Range, SD)	27, 27 (18–51, 5)
Clinical stage (<i>n</i> , %)	I	10 (8)
	II	19 (16)
	III	81 (68)
	IV	1 (1)
	Recurrent	9 (7)
cTN stage (<i>n</i> , %)	T1N1	1 (1)
	T2N0	10 (8)
	T2N1	9 (7)
	T2N2	2 (2)
	T3N0	18 (15)
	T3N1	56 (47)
	T3N2	10 (8)
	T4N0	6 (5)
	T4N1	5 (4)
	T4N2	3 (3)
Chemotherapy agent used (<i>n</i> , %)	5-FU	114 (95)
	Capecitabine	6 (5)
Mode of radiation therapy (<i>n</i> , %)	IMRT	53 (44)
	3DCRT	67 (56)
Radiation therapy dose (Gy)	Median, Mean (Range, SD)	50, 50 (30–56, 2)

Abbreviations: 3DCRT: three-dimensional conformal radiation therapy; 5-FU: fluorouracil; BMI: body mass index; cTN: clinical tumor and node stage; IMRT: intensity-modulated radiation therapy; SD: standard deviation.

Table 2

Univariate analysis of clinical factors associated with lower white blood cell count ratio nadir.

Variables	β	SE	<i>p</i>
Clinical variables			
Sex (male vs. female)	−0.006	0.030	0.84
Stage (<III vs. III)	−0.039	0.033	0.25
Age (<59 vs. 59 years)	0.014	0.029	0.64
Age (continuous)	0.002	0.001	0.85
Treatment type (3DCRT vs. IMRT)	−0.068	0.028	0.02
BMI (<27 vs. 27 kg/m ²)	−0.011	0.029	0.70
BMI (continuous)	−0.004	0.003	0.20

Abbreviations: β : linear regression coefficient; SE = standard error; other abbreviations are the same as Tables 1 and 2. Statistically significant values are bolded.

Table 3

Dose–volume parameters for pelvic bone marrow and univariate analysis of clinical factors associated with lower white blood cell count nadir.

BM dose–volume parameter	Mean cc (%)	β	SE	<i>p</i>
Coxal BM				
V10	583 (83.4)	−0.067	0.246	0.79
V15	549 (78.3)	−0.043	0.219	0.85
V20	501 (71.4)	−0.087	0.188	0.64
V25	414 (59.0)	−0.206	0.132	0.12
V30	313 (44.6)	−0.219	0.116	0.06
V35	227 (32.4)	−0.214	0.126	0.09
V40	160 (23.0)	−0.274	0.142	0.06
V45	91 (13.1)	−0.356	0.164	0.03†
V50	6 (0.8)	−0.513	0.632	0.42
Sacral BM				
V10	232 (98.4)	0.057	0.270	0.84
V15	230 (97.4)	−0.017	0.211	0.94
V20	226 (95.9)	−0.076	0.178	0.67
V25	219 (92.7)	−0.180	0.133	0.18
V30	206 (87.4)	−0.195	0.101	0.06
V35	190 (80.7)	−0.155	0.080	0.05
V40	170 (72.2)	−0.121	0.065	0.06
V45	120 (50.9)	−0.129	0.060	0.03
V50	22 (9.3)	−0.238	0.122	0.05
Proximal femoral BM				
V10	236 (65.4)	−0.047	0.075	0.53
V15	206 (57.4)	−0.051	0.073	0.49
V20	168 (47.1)	−0.104	0.068	0.13
V25	117 (33.2)	−0.107	0.062	0.09
V30	68 (19.3)	−0.111	0.073	0.13
V35	29 (8.1)	−0.248	0.133	0.06
V40	11 (3.1)	−0.311	0.313	0.32
V45	3 (0.9)	−0.449	0.712	0.53
V50	0.2 (0.1)	1.137	2.330	0.63

Abbreviations: BM: bone marrow; Vx: volume receiving x Gy; β : linear regression coefficient; SE = standard error.

Statistically significant values are bolded. Statistically significant value on multiple regression analysis is represented by †.