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Thoracic Vertebral Body Irradiation Contributes to Acute Hematologic Toxicity During Chemoradiation Therapy for Non-Small Cell Lung Cancer

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Abstract

Purpose—To determine the relationships between radiation doses to the thoracic bone marrow and declines in blood cell counts in non-small cell lung cancer (NSCLC) patients treated with chemoradiation therapy (CRT).

Methods and Materials—We included 52 patients with NSCLC treated with definitive concurrent carboplatin/etoposide and RT. Dose-volume histogram (DVH) parameters for the thoracic vertebrae (TV), sternum, scapulae, clavicles, and ribs were assessed for associations with changes in blood counts during the course of CRT. Linear and logistic regression analyses were performed to identify associations between hematologic nadirs and DVH parameters. A DVH parameter of V_x was the percentage of the total organ volume exceeding $\times$ radiation dose.

Results—Grade 3 hematologic toxicity including neutropenia developed in 21% (n=11), leukopenia in 42% (n=22), anemia in 6% (n=3), and thrombocytopenia in 2% (n=1) of patients. Greater RT dose to the TV was associated with higher risk of grade 3 leukopenia across multiple DVH parameters, including TV V₂₀ (TVV) (odds ratio [OR] 1.06; $P=.025$), TVV₃₀ (OR 1.07; $P=.013$), and mean vertebral dose (MVD) (OR 1.13; $P=.026$). On multiple regression analysis, TVV₃₀ ($\beta = -0.004$; $P=.018$) and TVV₂₀ ($\beta = 0.003$; $P=.048$) were associated with white blood cell nadir. Additional bone marrow sites (scapulae, clavicles, and ribs) did not affect hematologic toxicity. A 20% chance of grade 3 leukopenia was associated with a MVD of 13.5 Gy and a TTV₃₀ of 28%.

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Cutoff values to avoid grade 3 leukopenia were MVD 23.9 Gy, TVV₂₀ 56.0%, and TVV₃₀ 52.1%.

Conclusions—Hematologic toxicity is associated with greater RT doses to the TV during CRT for NSCLC. Sparing of the TV using advanced radiation techniques may improve tolerance of CRT and result in improved tolerance of concurrent chemotherapy.

Introduction

Non-small cell lung cancer (NSCLC) continues to be a leading cause of cancer death in Americans each year, and approximately 30% of cases initially present as stage III, locally advanced disease (1–2). The standard of care for patients with unresectable lung cancer is concurrent radiation (RT) and chemotherapy, which results in better outcomes than sequential or either treatment alone (3–5). Although combined chemoradiation therapy (CRT) affords a better chance of cure, bone marrow (BM) suppression is a common toxicity that often necessitates interruptions in chemotherapy administration or reduction of chemotherapy doses. For example, grade 3 neutropenia occurred in 82% of patients in Radiation Therapy Oncology Group (RTOG) protocol 9410 and 24% of patients in RTOG 0617, and when grade 3 neutropenia did occur, the protocol for these trials mandated that chemotherapy be held or reduced until blood counts recovered (4–6).

Because of the radiosensitivity of BM stem cells (7), radiation oncologists have implemented efforts to mitigate the degree of hematologic toxicity (HT) during concurrent CRT for anal (8) and cervical (9) cancer by reducing doses to the pelvic BM using advanced radiation techniques, such as intensity modulated radiation therapy (IMRT). However, the relative impact of RT dose to the BM during CRT for NSCLC has remained poorly evaluated. Previous work has demonstrated correlations between lung dose-volume histogram (DVH) parameters and lymphocyte nadirs; however, no work has looked specifically at BM DVH parameters (10). Because approximately 35% of the functional BM is located in the thorax, irradiation of these thoracic structures could contribute to the HT experienced by NSCLC patients. Therefore we sought to determine the DVH constraints that correlate with HT due to thoracic BM irradiation during CRT.

Methods and Materials

Patient population

From November 1999 to September 2012, a cohort of 100 patients with histologically confirmed NSCLC were evaluated under an institutional review board–approved protocol for retrospective review. Inclusion criteria included treatment with definitive concurrent carboplatin–paclitaxel and RT. In total, 48 patients were excluded because of a chemotherapy regimen other than carboplatin–paclitaxel (n=30), use of colony-stimulating factors (n=8), or treatment with RT alone (n=10). Patients who received induction chemotherapy (32%) and had adequately recovered their blood counts before starting CRT were included on the basis of previous studies documenting blood cell counts during concurrent CRT to be similar to those treated with concurrent CRT alone (11–12). Patients with inoperable (owing to medical comorbidities) stage II (n=5) NSCLC treated with

definitive CRT were included. Patients with stage IV oligometastatic NSCLC, defined as a solitary extrathoracic metastasis, who received definitive CRT were included as well (13–15).

Pretreatment evaluation

Pre-CRT workup included a complete history and physical examination, complete blood count, serum chemistry profile, chest computed tomography scan, positron emission tomography scan, brain magnetic resonance imaging, and mass or nodal biopsy. Clinical staging was defined using the American Joint Committee on Cancer (6th edition) criteria (16).

Treatment planning

Patients were placed in a supine position with arms up in a large mold. RT was delivered using 3-dimensional conformal RT (3D-CRT) or IMRT first to 40 Gy in 1.8 or 2 Gy per fraction per day, followed by oblique fields to avoid the spinal cord for an additional 20 to 26 Gy. The analytic anisotropic algorithm was used with tissue inhomogeneity corrections, with 6- or 15-MV photons used to deliver the RT. The radiation dose for the spinal cord was <50 Gy. The mean lung dose was <20 Gy, lung V_5 <60% to 70%, and lung V_{20} <37%.

The typical chemotherapy regimen consisted of intravenous infusional drug delivery consisting of paclitaxel (45 mg/m²) and carboplatin (area under the curve = 2) on days 1, 8, 15, 22, 29, and 36 of RT. Chemotherapy was typically held or reduced in dose when absolute neutrophil count (ANC) dropped below 1.5 k/ μ L.

Evaluation

Weekly white blood cell (WBC), ANC, hemoglobin (Hgb), and platelet (Plt) counts were collected from the first day of treatment through 1 week after CRT for WBC count and ANC and 90 days after treatment completion for Hgb and Plts counts. These values were then scored using the Common Terminology Criteria for Adverse Events, version 4.0. For consistency, the thoracic vertebrae (TV) from T1 to T10, thoracic ribs (ribs 1-10), clavicles, scapulae, and sternum were contoured on planning 4-dimensional computed tomography simulation scans. The DVH data were collected for TV V_{10} - V_{60} (TVV), Ribs V_{10} - V_{60} (RV), Clavicle V_{10} - V_{60} (CV), Sternum V_{10} - V_{60} (STV), and Scapula V_{10} - V_{60} (SCV) in increments of 10. The TVV₅, RV₅, CV₅, STV₅, SCV₅, mean vertebral dose (MVD), mean rib dose (MRD), mean clavicle dose (MCD), mean sternum dose (MSTD), and mean scapula dose (MSCD) were also collected. A DVH parameter of V_x was defined as the percentage of organ receiving $\times$ Gy of radiation.

Statistical analysis

Summary statistics for DVH parameters were conducted on all patients. The Shapiro-Wilks test was performed to assess for normality of hematologic cell values, and non-normally distributed values were log transformed. Simple linear and logistic regression models were used to test for correlations between HT and DVH parameters. Simple logistic regression was also used to calculate the risk of HT for increasing DVH values. We performed separate multiple linear and logistic regression models including a single dosimetric parameter and

other variables with P values > 0.3 on univariate analysis. Multiple linear regression models that included each individual BM component at a given DVH level (ie, TVV₁₀, RV₁₀, CV₁₀, etc) were also performed. In these models, DVH parameters were adjusted using the equation $\text{newDVH} = \text{original DVH} \times (\% \text{ BM contained in structure} / \text{total \% of thoracic BM} \times 100) / 20$ to take into account the different relative amounts of cellular production in each thoracic BM structure (17). Receiver operating characteristic (ROC) curves were used to evaluate cutoff DVH values to avoid HT. These cutoffs were determined by finding the point closest to the upper left of the ROC graph, which represents the highest accuracy of predicting HT (18). The average number of TV that received $\times$ Gy of radiation was calculated by dividing volume of organ receiving $\times$ Gy by the average volume of a single TV for each individual patient. Logistic regression was then performed using average number of vertebrae receiving $\times$ Gy as a predictor to determine the impact RT to individual TV had on HT. All analyses were conducted using SAS v9.3 (SAS Institute, Cary, NC) at a significance level of .05.

Results

Patient characteristics

Baseline characteristics of the 52 patients are shown in Table 1. Median follow-up time was 13.7 months (range, 3.2–94.1 months). Median and mean age at diagnosis were 64.4 and 65.1 years (range, 40.5–82.8 years), and most patients were Caucasian (82.6%) and had stage III disease (82.7%).

Hematologic toxicity

Table 2 presents descriptive characteristics of key predictors and outcomes. Median and mean baseline blood cell values were WBC of 7.2 and 8.8 k/ μ L (range, 4.3–29.2 k/ μ L), ANC of 5.0 and 6.8 k/ μ L (range, 2.2–25.7 k/ μ L), Hgb of 12.2 and 12.0 g/dL (range, 7.8–15.0 g/dL), and Plts of 242 and 269 k/ μ L (range, 93–688 k/ μ L). Overall, 21% (n=11) of patients developed grade 3 neutropenia, 42% (n=22) developed grade 3 leukopenia, 6% (n=3) developed grade 3 anemia, and 2% (n=1) developed grade 3 thrombocytopenia (Table 3). Median and mean WBC and ANC nadir at 1 week after CRT were 2.2 and 2.5 k/ μ L (range, 0.9–5.5 k/ μ L) and 1.5 and 1.9 k/ μ L (range, 0.6–6.3 k/ μ L). Median and mean Hgb and Plts nadir at 3 months after CRT completion were 10.0 and 10.0 g/dL (range, 7.7–12.6 g/dL) and 132 and 141.7 k/ μ L, respectively (range, 19–351 k/ μ L). Median time to development of grade 3 neutropenia and leukopenia were 6 weeks (range for neutropenia, 2–7 weeks; range for leukopenia, 3–7 weeks).

DVH parameters associated with risk of HT

Grade 3 leukopenia was associated with increased radiation dose to the TV. Simple logistic regression analysis showed that increasing MVD ($P=.05$), TVV₂₀ ($P=.04$), and TVV₃₀ ($P=.021$) were associated with increased risk of grade 3 leukopenia. When adjusting for age and body mass index (BMI), multiple logistic regression analysis (Table 4) demonstrated that MVD ($P=.026$), TVV₂₀ ($P=.024$), and TVV₃₀ ($P=.014$) were associated with increased risk of grade 3 leukopenia. When using the median DVH values as a cutoff, Wilcoxon test

demonstrated that $TVV_{10} > 50.5\%$ resulted in a WBC nadir of 1.8 k/ μ L, compared with a $TVV_{10} \leq 50.5\%$, which resulted in a WBC nadir of 2.65 k/ μ L ($P = .02$).

Factors associated with hematologic nadir

On simple linear regression analysis, TVV_{30} ($\beta = -0.004$ [95% confidence interval (CI) -0.008 to -0.0008]; $P = .017$) was negatively correlated with log-transformed WBC nadir, on average. STV_{20} ($P = .056$) and STV_{30} ($P = .056$) trended toward significance. For other thoracic BM structures, including ribs, clavicles, and scapulae, DVH values were not significantly associated with hematologic nadir.

In the multiple regression analysis adjusted for age and BMI (Table 5), TVV_{20} ($\beta = -0.003$ [95% CI -0.007 to -0.00003]; $P = .048$) and TVV_{30} ($\beta = -0.004$ [95% CI -0.008 to -0.0007]; $P = .018$) were negatively associated with log-transformed WBC nadir, on average. Increasing age was associated with lower WBC nadir, whereas increasing BMI was associated with higher WBC nadir. For example, in the model including TVV_{20} , WBC nadir was negatively correlated with increasing age ($\beta = -0.006$ [95% CI -0.012 to BMI -0.0002]; $P = .044$), whereas higher ($\beta = 0.010$ [95% CI 0.0007 to 0.020]; $P = .036$) was positively correlated with WBC nadir. Adjusted R^2 was highest for the model containing TVV_{30} .

DVH toxicity threshold for HT

To evaluate parameters that may guide oncologists on prevention of HT, we calculated the probability of developing grade 3 leukopenia at continuously higher RT doses. A 20% chance of grade 3 leukopenia was associated with an MVD of 13.5 Gy, and each 2-Gy increase in MVD corresponded with a 22% increase in the risk of developing grade 3 leukopenia. A 20% risk of grade 3 leukopenia was associated with a TTV_{30} of 28%, and each 2% increase in TTV_{30} corresponded with a 12% increased risk of development of grade 3 leukopenia.

To identify thresholds for dosimetric planning, we analyzed the ROC curves for grade 3 leukopenia for MVD, TVV_{20} , and TVV_{30} (Fig. 1). Cutoffs to avoid grade 3 leukopenia were MVD 23.9 Gy, $TVV_{20} \leq 56\%$, and $TVV_{30} \leq 52.1\%$. These represent DVH values with the highest accuracy of predicting grade 3 leukopenia. Patients receiving $TTV_{30} > 52.1\%$ were more likely to develop grade 3 leukopenia (61.1%) than those receiving $\leq 52.1\%$ (32.4%; $P = .046$). Additionally, patients receiving $TTV_{20} > 56\%$ were also more likely to develop grade 3 leukopenia (57.9%) than those receiving $\leq 56\%$ (33.3%; $P = .084$). For every additional vertebra that received 5 Gy of RT, the odds of grade > 3 leukopenia were increased by 37% (odds ratio 1.37 [95% CI 0.92-2.04]; $P = .082$). For every additional vertebra that received 20 Gy of RT, the odds of grade > 3 leukopenia was increased by 60% (odds ratio 1.60 [95% CI 1.03-2.50]; $P = .025$).

Discussion

Increasing RT dose to the TV was associated with increased risk of leukopenia but not anemia or thrombocytopenia. Other thoracic BM structures, including the scapulae, ribs, and clavicles, did not have an association with HT. Increasing TVV_{20} and TVV_{30} had the

strongest association with WBC nadir. The cutoffs to avoid grade 3 leukopenia were MVD 23.9 Gy, TVV₂₀ 56.0%, and TVV₃₀ 52.1%.

The radiosensitivity of the BM is well understood to occur clinically (7,19) and modifications of BM doses to the pelvis in cervical (8–9) and anal (20) cancers and the cervical vertebrae in head and neck cancers (21) have been previously studied. Lymphocytes are the most radiosensitive cell line and can reach nadirs within hours to days of irradiation. Granulocytes and Plts have intermediate radiosensitivity and reach their nadirs between 2 and 5 weeks, whereas Hgb is the least radiosensitive and may not reach a nadir for 8 to 12 weeks after RT (22). In pelvic malignancies, techniques such as IMRT demonstrate the ability to reduce HT through knowledge of specific dose constraints of the BM that can be incorporated into treatment planning (23).

Multiple regression models that included each individual BM component were not significantly correlated with hematologic nadir. Therefore, the TV seems to be the best structure to assess for the risk of HT during CRT. The TV likely had the greatest impact on HT during thoracic irradiation due to its larger contribution to the overall BM function (19.9%) compared with the sternum (2.9%), scapula (3.8%), and ribs and clavicles (8.8%) (24). Thus it is likely that the TV have a greater contribution to peripheral blood counts. We found no significant contribution to the development of HT from irradiation of the scapulae, ribs, and clavicles, mostly likely because of their limited BM producing capacity. We also did not identify any association between DVH parameters and Hgb or Plts nadirs, despite 90-day follow-up after RT. These findings are similar to studies of HT in cervical cancer, which also have not documented correlations between RT and Hgb and Plts nadirs within 2 months of treatment completion (8–9). However, these results could also be confounded by the fact that some patients received a transfusion of packed red blood cells during treatment, which would have kept nadirs artificially higher. One weakness of the regression analysis is that each DVH variable was correlated with multiple different outcomes of interest, so it is possible that on multiple hypotheses testing borderline significant *P* values could become nonsignificant. For this reason, we believe it is important to validate these findings in an external and larger scale study.

We found no differences in WBC nadirs among patients treated with 3D-CRT (2.4 k/ μ L), IMRT (2.8 k/ μ L), or 3D-CRT/IMRT (2.5 k/ μ L; *P*=.70). Thoracic cancers treated with IMRT and concurrent chemotherapy (25–27) have not shown higher rates of HT compared with those found in studies such as RTOG 9410, in which only 3D-CRT was used. However, we do not believe our study population is an ideal one to look for differences between 3D-CRT and IMRT. First, our population had a mixed sample of patients treated with 3D-CRT, IMRT, and combined 3D-CRT/IMRT, making it difficult to discern differences between modalities. Second, BM DVH values for patients treated with IMRT did not always follow the expected distributions of large volumes receiving low doses of RT. This finding could be due to the fact that doses were constrained for the lung rather than the BM because there were no specific BM constraints to follow. These dose findings may have been driven by tumor location as well. As an example, in early reports of proton therapy for lung cancer, where BM constraints were also probably not used, there were no differences between proton therapy and IMRT in terms of HT (28). However, it is known that when taken into account

during treatment planning, proton therapy can reduce radiation doses to the BM (29) compared with IMRT. Thus, we can only account for thresholds of BM toxicity in this report, rather than comparing outcomes among radiation techniques.

Heylmann et al hypothesized that blood irradiation could be a cause of declines in blood counts during chemo-radiation (30). This is plausible, but there is strong evidence that BM irradiation contributes to HT. To begin with, use of IMRT has lowered rates of HT compared with 3D-CRT in anal cancer (31). Additional compelling evidence comes from Rose et al (32), who demonstrated that WBC nadir correlated specifically with radiation dose to active BM but not inactive BM. Furthermore, multiple studies have shown that WBC counts may not reach baseline levels until 10 years after RT (33, 34). Such long-term suppression of cell counts indicates radiation injury to the BM. Thus radiation to the blood may contribute to HT, but it is likely BM irradiation plays a large role as well.

Here we document an optimal MVD cutoff of 23.9 Gy to avoid developing grade 3 leukopenia. Rose et al recommended an MVD of < 26.8 Gy to the lumbar vertebrae, sacrum, and pelvis to avoid grade 3 leukopenia in cervical cancer (32). The lumbar vertebrae, sacrum, and pelvis may be able to tolerate a larger RT dose because they contain more BM (51.1%) than the TV (19.9%), and thus similar amounts of radiation will impact peripheral counts less (24). The optimal V_{20} to avoid grade 3 leukopenia for cervical cancer was 76% (35), compared with 56% in this study. However, rates of grade 3 leukopenia above and below these cutoffs were similar when comparing rates in cervical cancer (57.7% vs 21.8%) with rates in NSCLC from our study (57.9% vs 33.3%) and different chemotherapy regimens may impact HT.

The exact contribution of RT to development of HT is not known. Early studies by Le Chevalier et al (36) documented HT to occur in 7% of patients receiving RT alone, compared with 33% in patients receiving CRT. Mitigating the contribution of RT to HT becomes important when considering that if neutropenia occurs, most treatment protocols specify that chemotherapy be held to allow for BM recovery. Some clinicians may also impose interruptions in RT in the setting of neutropenia. Treatment interruptions can result in failure to complete the prescribed course of CRT in a timely duration, which has been shown to negatively impact overall survival and can contribute to repopulation and reduced local control in NSCLC, anal cancer, and cervical cancer (37–41). HT caused a significant portion (36%) of our patient population to miss at least one dose of concurrent chemotherapy. Thus, improved TV sparing can likely decrease HT and increase the likelihood of full administration of chemotherapy, possibly resulting in improved outcomes. Additionally, given the future potential for immunotherapy to use a patient's own immune system in the treatment of cancer, maximum preservation of BM function is necessary (42) and may be aided by better TV sparing.

Conclusions

Higher doses of radiation to the TV during CRT are associated with increased risk of HT. Optimizing treatment plans through BM sparing may reduce treatment interruptions and

improve outcomes in NSCLC patients treated with CRT. Further prospective studies to identify appropriate dosimetric constraints are necessary.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

Greater radiation dose to the thoracic vertebrae (TV) contributes to hematologic toxicity during chemoradiation (CRT) for non-small cell lung cancer. Thoracic vertebrae V_{20} (TVV₂₀) ($\beta = -0.003$; $P=.048$) and TVV₃₀ ($\beta = -0.004$; $P=.018$) were associated with leukocyte nadir. Cutoffs to avoid grade 3 leukopenia were mean vertebral dose 23.9 Gy, TVV₂₀ 56%, and TVV₃₀ 52.1%. Sparing the TV using advanced radiation techniques may improve tolerance of CRT and reduce missed doses of concurrent chemotherapy.

Fig. 1.
(A-C) Receiver operating characteristic curves for grade 3 leukopenia as a function of thoracic vertebral V₂₀ (A), thoracic vertebral V₃₀ (B), and mean vertebral dose (C). Arrows indicate the cutoff value that represents the highest accuracy of predicting grade 3 leukopenia.

Table 1

Baseline characteristics of patients with non-small cell lung cancer

Characteristic	n	%
Total	52	100
Gender		
Female	28	53.9
Male	24	46.1
Ethnicity		
Caucasian	43	82.6
African American	5	9.6
Hispanic	2	2.9
Asian	2	3.9
Clinical stage		
N/A	1	1.9
II	5	9.6
III	43	82.7
IV	3	5.8
T stage		
N/A	2	3.9
Tx	1	1.9
T0	1	1.9
T1	9	17.3
T2	19	36.5
T3	8	15.4
T4	12	23.1
T/N stage		
TxN2	2	3.8
T0N3	1	1.9
T1T2N0	1	1.9
T1T2N1	5	9.5
T1T2N2	9	17.4
T1T2N3	15	28.8
T3T4N0	2	3.8
T3T4N1	2	3.8
T3T4N2	9	17.4
T3T4N3	6	11.7

Table 2

Descriptive characteristics of predictors and outcomes

Parameter	Mean	Standard deviation
Age (y)	65.1	8.7
Tumor volume (mL)	200.2	187.0
Baseline blood count		
WBC (k/ μ L)	8.8	5.2
ANC (k/ μ L)	6.8	5.2
Hgb (g/dL)	12.0	1.5
Plts (k/ μ L)	269.0	112.3
Blood cell nadir		
WBC (k/ μ L)	2.5	1.1
ANC (k/ μ L)	1.9	1.1
Hgb (g/dL)	10.0	1.2
Plts (k/ μ L)	141.7	58.7
Vert DVH		
Thoracic vertebrae V60 (%)	2.0	2.4
Thoracic vertebrae V50 (%)	10.4	7.2
Thoracic vertebrae V40 (%)	36.1	16.3
Thoracic vertebrae V30 (%)	45.6	14.3
Thoracic vertebrae V20 (%)	50.7	14.7
Thoracic vertebrae V10 (%)	56.4	15.3
Thoracic vertebrae V5 (%)	61.1	15.4
Mean vertebrae dose (Gy)	23.9	6.4
Ribs DVH		
Ribs V60 (%)	5.2	4.5
Ribs V50 (%)	10.5	6.8
Ribs V40 (%)	15.7	7.8
Ribs V30 (%)	19.8	8.1
Ribs V20 (%)	24.3	8.8
Ribs V10 (%)	31.7	10.2
Ribs V5 (%)	39.7	12.9
Mean rib dose (Gy)	13.8	4.3
Sternum DVH		
Sternum V60 (%)	24.1	24.4
Sternum V50 (%)	43.7	27.4
Sternum V40 (%)	58.8	24.6
Sternum V30 (%)	66.8	21.2
Sternum V20 (%)	73.3	19.7
Sternum V10 (%)	82.3	15.1
Sternum V5 (%)	88.1	12.5
Mean sternum dose (Gy)	39.8	11.1

Parameter	Mean	Standard deviation
Clavicle DVH		
Clavicle V60 (%)	8.2	10.6
Clavicle V50 (%)	16.4	18.1
Clavicle V40 (%)	23.7	23.5
Clavicle V30 (%)	28.6	26.3
Clavicle V20 (%)	32.5	28.1
Clavicle V10 (%)	37.5	28.8
Clavicle V5 (%)	42.7	30.4
Mean clavicle dose (Gy)	17.8	14.2
Scapula DVH		
Scapula V60 (%)	2.0	3.5
Scapula V50 (%)	3.3	5.0
Scapula V40 (%)	5.0	6.4
Scapula V30 (%)	8.1	9.1
Scapula V20 (%)	12.8	12.2
Scapula V10 (%)	21.0	14.4
Scapula V5 (%)	27.8	18.6
Mean scapula dose (Gy)	7.6	5.2

Abbreviations: ANC = absolute neutrophil count; DVH = dose-volume histogram; Hgb = hemoglobin; Plts = platelets; WBC = white blood cell.

Table 3

Frequency of hematologic toxicity

Toxicity	CTCAE grade, n (%)				
	0	1	2	3	4
Leukopenia	3 (5.8)	13 (25)	14 (26.9)	21 (40.4)	1 (1.9)
Neutropenia	20 (38.5)	6 (11.5)	15 (28.8)	11 (21.2)	0 (0)
Anemia	0 (0)	26 (50)	23 (44.2)	3 (5.8)	0 (0)
Thrombocytopenia	19 (36.5)	29 (55.8)	3 (5.8)	0 (0)	1 (1.9)

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events. Grade 0 represents normal counts.

Table 4

Multiple logistic regression for factors associated with grade 3 leukopenia

Variable	OR (95% CI)	P	HL test
Grade 3 WBC			
Thoracic vertebrae V60	1.02 (0.79, 1.33)	.87	0.55
Thoracic vertebrae V50	1.03 (0.95, 1.13)	.44	0.46
Thoracic vertebrae V40	1.03 (0.99, 1.08)	.11	0.07
Thoracic vertebrae V30	1.07 (1.01, 1.12)	.014	0.65
Thoracic vertebrae V20	1.06 (1.01, 1.11)	.024	0.04
Thoracic vertebrae V10	1.05 (1.0, 1.09)	.052	0.67
Thoracic vertebrae V5	1.04 (0.988, 1.09)	.06	0.80
Mean vertebrae dose	1.13 (1.02, 1.26)	.026	0.28

Abbreviations: CI = confidence interval; HL = Hosmer-Lemeshow; OR = odds ratio; WBC = white blood cell.

Models included dosimetric parameters, age, and body mass index.

Table 5

Multiple linear regression of factors associated with hematologic toxicity

Variable	β (95% CI)	P	Adjusted R^2
ANC nadir			
Thoracic vertebrae V60	0.011 (−0.018 to 0.968)	.14	0.08
Thoracic vertebrae V50	0.0002 (−0.009 to 0.009)	.96	0.07
Thoracic vertebrae V40	−0.003 (−0.007 to 0.0009)	.13	0.12
Thoracic vertebrae V30	−0.005 (−0.009 to −0.0005)	.031	0.16
Thoracic vertebrae V20	−0.004 (−0.008 to 0.0003)	.068	0.14
Thoracic vertebrae V10	−0.003 (−0.007 to 0.001)	.14	0.11
Thoracic vertebrae V5	−0.003 (−0.007 to 0.001)	.18	0.11
Mean vertebrae dose	−0.009 (−0.019 to 0.0009)	.07	0.13
Age *	−0.009 (−0.016 to −0.001)	.085	
BMI *	0.011 (−0.001 to 0.023)	.052	
WBC nadir			
Thoracic vertebrae V60	0.007 (−0.017 to 0.030)	.58	0.08
Thoracic vertebrae V50	−0.001 (−0.009 to 0.006)	.71	0.08
Thoracic vertebrae V40	−0.003 (−0.006 to 0.0007)	.12	0.12
Thoracic vertebrae V30	−0.004 (−0.008 to −0.0007)	.018	0.18
Thoracic vertebrae V20	−0.003 (−0.007 to −0.00003)	.048	0.15
Thoracic vertebrae V10	−0.003 (−0.006 to 0.0006)	.10	0.13
Thoracic vertebrae V5	−0.003 (−0.006 to 0.0007)	.13	0.12
Mean vertebrae dose	−0.008 (−0.016 to −0.00007)	.048	0.15
Age *	−0.006 (−0.012 to −0.0002)	.044	
BMI *	0.010 (0.0007–0.020)	.036	

Abbreviations: ANC = absolute neutrophil count; BMI = body mass index; CI = confidence interval; WBC = white blood cell. Models included 1 dosimetric parameter, age, and body mass index.

* Results for model including TVV20.