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Radiation Dose to the Thoracic Vertebral Bodies Is Associated With Acute Hematologic Toxicities in Patients Receiving Concurrent Chemoradiation for Lung Cancer: Results of a Single-Center Retrospective Analysis

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Abstract

Purpose: To test the hypothesis that increasing radiation therapy (RT) dose to the thoracic vertebral bodies (TVBs) contributes to the development of hematologic toxicities (HTs) in patients with lung cancer.

Methods and Materials: Cases of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) treated with definitive chemoradiation with concurrent platinum-based doublet chemotherapy at our institution from 2007 to 2016 were identified. Mean TVB dose and the volume of TVBs receiving at least 5 to 60 Gy (V_5 – V_{60}) were retrospectively recorded. Logistic regression was used to test associations between grade 3 HT (HT3+) and dosimetric/clinical parameters. Normal tissue complication probability was evaluated using the Lyman-Kutcher-Burman (LKB) model for HT3+, and receiver operating characteristics analysis was used to determine dosimetric cut-points.

Results: We identified 201 patients, the majority having NSCLC ($n = 162$, 81%) and stage III to IV disease ($n = 179$, 89%). All patients received either cisplatin/etoposide ($n = 107$, 53%) or carboplatin/paclitaxel ($n = 94$, 47%). Median RT dose was 60 Gy (range, 60–70 Gy). The rate of HT3+ was 49% ($n = 99$). Increasing mean TVB dose (per Gy) was associated with higher odds of developing HT3+ (odds ratio 1.041, 95% confidence interval 1.004–1.080, $P = .032$), as were increasing TVB V_5 to V_{20} . These dosimetric correlates to HT3+ persisted on multivariate analysis. Constrained optimization of the LKB model for HT3+ yielded the parameters: $n = 1$, $m = 1.79$, and $TD_{50} = 21.4$ Gy. Optimal cut-points identified were $V_5 = 65\%$, $V_{10} = 60\%$, $V_{20} = 50\%$, and

mean dose = 23.5 Gy. Patients with values above these cut-points had an approximately 2-fold increased risk of HT3+.

Conclusions: We found that mean TVB dose and low-dose parameters (V_5 - V_{20}) were associated with HT3+ in chemoradiation for lung cancer. Per the LKB model, bone marrow behaves like a parallel organ ($n = 1$), implying that mean TVB dose is a useful predictor for toxicity. These data suggest that efforts to spare dose to the TVBs may reduce rates of severe HT.

Summary

Hematologic toxicities are a common acute side effect of concurrent chemoradiation therapy in patients with lung cancer. This study demonstrates an association between radiation dose to the thoracic vertebral bodies and the development of acute hematologic toxicities, which suggests that bone marrow sparing radiation methods may be used to reduce the incidence of hematologic toxicities in these patients

Introduction

Lung cancer remains the leading cause of cancer death in the United States (1). The efficacy of definitive concurrent radiation therapy (RT) and chemotherapy for locally advanced non-small cell lung cancer (NSCLC) and limited-stage small cell lung cancer (SCLC) has been proven in previous randomized trials (2–7). Unfortunately, severe acute hematologic toxicities (HTs) during chemoradiation (CRT) remain problematic in this population. In the Radiation Therapy Oncology Group 0617 study, Bradley et al (3) reported grade 3 HT (HT3+) in 47.6% of NSCLC patients receiving RT plus combination carboplatin and paclitaxel with or without cetuximab. In patients with SCLC treated with once- or twice-daily RT with concurrent cisplatin and etoposide, the CONVERT study reported grade 3 neutropenia rates of 65.4% and 74.1%, respectively (8). Severe HT leads to increased rates of hospitalization, infections, and transfusion requirements, which can reduce quality of life and increase costs of care. Moreover, when severe HT leads to chemotherapy breaks and dose reductions it may negatively impact treatment efficacy (9, 10).

Over the last decade, steps have been taken to reduce CRT-related toxicity in both NSCLC and SCLC in the forms of more conformal radiation fields, bone marrow (BM)-supporting agents, and use of less toxic systemic regimens. Although it is known that chemotherapeutic agents commonly given concurrently with RT for definitive treatment of lung cancers can cause HTs, the contribution of radiation to BM suppression in these patients is poorly understood. Recent data from a small cohort of NSCLC patients suggest a correlation between HT and radiation dose to the thoracic vertebral body (TVB) BM (11). Given these limited data, the TVBs are not typically included as an organ at risk in RT treatment planning, nor have proper TVB constraints been established. The purpose of this study is to identify TVB dosimetric parameters that correlate with HT (grade 3) in a large cohort of patients undergoing CRT for lung cancer and to determine potential dosimetric cut-points for organ-at-risk constraint utility that may be used for future validation in independent and/or prospective cohorts.

Methods and Materials

Patient selection

Two hundred thirty patients with histologically confirmed NSCLC and SCLC treated with curative CRT at our institution between April 2007 and February 2016 were reviewed in this institutional review board-approved retrospective study. Only patients who received standard fractionation RT and doublet platinum-based concurrent chemotherapy were included in our analysis, regardless of cancer stage. Induction chemotherapy was allowed when blood counts had sufficiently recovered before initiating CRT. Weekly complete blood count (CBC) laboratory draws were typically collected during and after CRT until counts recovered; patients with fewer than 4 documented CBC laboratory draws during CRT separated by at least 1 week were excluded ($n = 19$). Patients who received nonstandard chemotherapies ($n = 6$) and altered fractionation RT ($n = 2$) or who had CRT treatment truncated to proceed with surgical resection ($n = 2$) were also excluded. All remaining 201 patients had a documented history and physical examination and baseline CBC. Staging imaging included computed tomography of the chest and abdomen with or without positron emission tomography. Nodal sampling was performed when indicated. Clinical stage was determined using the TNM American Joint Committee on Cancer 7th Edition criteria.

Radiation therapy

A free-breathing, 4-dimensional computed tomography scan was used for patient simulation. Patients were placed in a supine position with arms over head, using an arm shuttle and vacuum bag molding for immobilization. Fusion of positron emission tomography imaging was used, when available, to help determine areas of active disease. Our current practice is to contour an internal gross tumor volume encompassing the primary tumor and nodal gross disease in all phases of the breath cycle. Sequential expansions of the internal gross tumor volume are made to form a clinical target volume and planning target volume to account for subclinical disease and intrafraction motion/setup error, respectively. Doses of 60 to 70 Gy were delivered to the planning target volume using intensity modulated radiation therapy (IMRT) or 3-dimensional conformal techniques.

Chemotherapy

Patients with NSCLC received either weekly combination carboplatin (area under the curve [AUC] = 2) and paclitaxel (50 mg/m²) or combination cisplatin (50 mg/m² on days 1, 8, 29, and 36) and etoposide (50 mg/m² on days 1–5 and 29–33) concurrent with RT. Combination cisplatin (80 mg/m² on day 1) and etoposide (100 mg/m² on days 1–3) was given every 3 weeks in all cases of SCLC.

Data collection

The TVBs from T1 to T10 were retrospectively contoured for all patients (Fig. E1; available online at www.redjournal.org). Vertebral bodies T11 to T12 were not included because their inferior location relative to lung cancer treatment fields keeps them from receiving meaningful low-dose radiation in the large majority of cases; we also wanted to be consistent with previously published data (11). The TVB mean dose and the volume of TVB

receiving at least 5 to 60 Gy (V_5 - V_{60}) were calculated from the dose-volume histogram. Weekly CBC data were recorded from the start of CRT to 2 weeks after RT completion. Hematologic toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 4, according to the nadir during treatment. The primary endpoint analyzed was grade ≥ 3 HT (HT3+), excluding lymphocytopenia.

Normal tissue complication probability modeling

Normal tissue complication probability (NTCP) was evaluated using a simplified Lyman-Kutcher-Burman (LKB) model for HT3+. In this model the dose-volume histogram for the organ at risk, in this case the TVBs T1 to T10, is reduced to a single value called the equivalent uniform dose, which is the single uniform dose to the organ at risk that results in the same NTCP. The methods for modeling NTCP as a function of equivalent uniform dose have been previously described (12) and used (13). Maximum likelihood estimations were used to determine optimal values for the 3 parameters defined by the LKB model; specifically, n , the volume parameter; m , the slope parameter; and TD_{50} , the uniform organ at risk dose which results in a 50% complication risk.

Statistics

Differences in the median values of dosimetric parameters between 2 groups were evaluated by the Wilcoxon test. Univariate and multivariate analyses were performed using logistic regression to determine the correlation of TVB V_5 to V_{60} and TVB mean dose with HT3+. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. All clinical and dosimetric parameters with P values of $\leq .10$ on univariate analysis were included in the multivariate model, with each dosimetric parameter being evaluated independently. Age was also included in the multivariate model given the known fact that BM activity decreases with increasing age. A P value $< .05$ was considered statistically significant. Receiver operating characteristic analysis was used to determine the optimal cut-point for dosimetric parameters. MATLAB version 9.0 (The MathWorks, Natick, MA) and R version 3.3.1 (R Foundation for Statistical Computing, Vienna) optimization routines were used to maximize likelihood for NTCP parameters. All other statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics

Patient, tumor, and treatment characteristics are described in Table 1. Of the 201 eligible patients, 162 had a diagnosis of NSCLC. The cohort was gender balanced and had a median age at diagnosis of 63 years. The majority of patients had stage III disease ($n = 154$) and were of good to excellent performance status (89%). Of those with NSCLC, 58% received carboplatin plus paclitaxel, whereas the rest received cisplatin plus etoposide. Median RT dose was 60 Gy (range, 60–70 Gy). Induction chemotherapy was given in 42 patients (21%), and 41 patients (20%) went on to receive consolidation chemotherapy.

BM dosimetric parameters

A summary of TVB dose–volume parameters is listed in Table 2. The median TVB mean dose was 20.0 Gy. When compared with 3-dimensional conformal RT, the use of IMRT was associated with an increase in median V_5 (63.0% vs 56.5%, $P = .007$), median V_{10} (56.2% vs 48.3%, $P < .001$), and median V_{20} (46.2% vs 38.3%, $P = .003$). Intensity modulated radiation therapy also resulted in a trend toward increased median TVB mean dose (20.8 Gy vs 18.2 Gy, $P = .060$). Although a numerically higher proportion of NSCLC versus SCLC patients were treated with IMRT (79% vs 69%, $P = .192$), median TVB dose–volume parameters tended to be higher in the SCLC patients (Table E1; available online at www.redjournal.org).

Hematologic toxicities

Acute HTs are shown in Table 3. Grade 3 hematologic toxicities occurred in 49% of patients ($n = 99$), with leukopenia and neutropenia being the most common. The SCLC patients had a higher HT3+ rate compared with NSCLC patients (64% vs 46%, $P = .039$). Mean and median time to blood count nadir values were 34.5 and 36 days (range, 7–65 days) for leukopenia, 33.5 and 35 days (range, 0–65 days) for neutropenia, 32.9 and 35 days (range, 4–64 days) for thrombocytopenia, and 33.7 and 38 days (range, 0–65 days) for anemia. Chemotherapy delays and/or dose reductions were required in 80 patients (40%), 61 (76%) of which were due to severe HT. Ultimately, concurrent chemotherapy was stopped early owing to intolerance/toxicity in 31 patients; of these, 19 (61%) had severe HT cited as the cause for cessation. Six patients (3%) required platelet transfusion during CRT, whereas 44 patients (22%) required packed red blood cell transfusion from the time of CRT initiation to 2 months after completing treatment. Granulocyte colony-stimulating factor was not given during CRT for lung cancer at our institution.

On univariate analysis (Table 4), increasing TVB mean dose was associated with increased odds of developing HT3+ (OR 1.041 [95% CI 1.004–1.080]; $P = .032$), as were low-dose parameters V_5 (OR 1.023 [95% CI 1.005–1.042]; $P = .012$), V_{10} (OR 1.025 [95% CI 1.007–1.043]; $P = .008$), and V_{20} (OR 1.019 [95% CI 1.003–1.036]; $P = .022$). Table 4 demonstrates that higher TVB V_{30} to V_{50} were associated with a nonsignificantly increased risk of HT3+. Increasing body mass index (BMI) trended toward being protective (OR 0.961 [95% CI 0.921–1.002]; $P = .064$). Initial baseline blood counts were not significantly associated with HT3+, though a higher initial WBC was marginally protective (OR 0.948, $P = .092$). Intensity modulated radiation therapy was associated with a nonsignificantly increased risk of HT3+ (OR 1.703 [95% CI 0.871–3.330]; $P = .120$). The use cisplatin/etoposide versus carboplatin/paclitaxel did not significantly correlate with HT3+ (OR 1.411, $P = .225$), although the use of induction chemotherapy trended toward significance (OR 1.914 [95% CI 0.954–3.842]; $P = .068$). A sensitivity analysis, excluding the 39 patients with SCLC, showed that low-dose RT remained significantly associated with increased odds of developing HT3+, whereas TVB mean dose was marginally associated with HT3+ (Table E2; available online at www.redjournal.org).

Multivariate analysis was performed for each dosimetric parameter separately while including age, BMI, induction chemotherapy, and initial WBC as covariates. When adjusting

for these confounders, increasing TVB mean dose (OR 1.042 [95% CI 1.002–1.083]; $P = .039$), V_5 (OR 1.023 [95% CI 1.004–1.042]; $P = .027$), V_{10} (OR 1.025 [95% CI 1.006–1.044]; $P = .016$), and V_{20} (OR 1.019 [95% CI 1.002–1.037]; $P = .031$) were independently associated with HT3+ (Table 5). Body mass index, age, induction chemotherapy, and initial WBC remained marginally associated with HT3+ (Table 5).

We further performed an exploratory analysis of TVB dose and grade 4 HT. Applying the same methods of analysis, all TVB dose parameters were significantly associated with grade 4 HT on both univariate (Table E3; available online at www.redjournal.org) and multivariate analyses (Table E4; available online at www.redjournal.org). In addition, older age, use of induction chemotherapy, and use of cisplatin/etoposide were all independently associated with the development of grade 4 HT.

LKB NTCP modeling

Constrained optimization ($0 < n < 1$, with m and TD_{50} being unrestricted) of the LKB model for HT3+ generated the maximum likelihood values of $n = 1$, $m = 1.79$, and $TD_{50} = 21.4$ Gy. The LKB NTCP model for HT3+ is shown in Figure 1.

Optimal dosimetric cut-points for HT3+

To dichotomize the dosimetric parameters, optimal cut-points were identified on receiver operating characteristic curve analysis for TVB mean dose and V_5 to V_{20} for organ at risk constraint utility during RT treatment planning. The AUC for each parameter ranged from 0.58 to 0.61 (Fig. E2; available online at www.redjournal.org). The most accurate predictors to avoid HT3+ were TVB mean dose 23.5 Gy, V_5 65%, V_{10} 60%, and V_{20} 50%. Odds of developing HT3+ increased by 83.2% when TVB mean dose was 23.5 Gy (OR 1.832 [95% CI 1.027–3.269]; $P = .040$) and 96.8% when V_{20} was 50% (OR 1.968 [95% CI 1.03–3.07]; $P = .038$), whereas it increased by more than 2-fold when V_5 was 65% (OR 2.222 [95% CI 1.254–3.937]; $P = .006$) or V_{10} was 60% (OR 2.352 [95% CI 1.317–4.202]; $P = .004$).

Discussion

This is the largest study analyzing acute HT3+ as a function of radiation dose to the TVB BM in lung cancer patients. We demonstrate that TVB mean dose and low dose parameters (V_5 – V_{20}) correlate with clinically significant HT in a diverse lung cancer cohort treated with curative CRT. Patients with a variety of histologies and stages but all treated with once-daily radiation to 60 Gy with concurrent platinum-based chemotherapy regimens were included to best represent the wide spectrum of lung cancers and methods for treatment delivery in this population. For further practicality, we: (1) developed an NTCP model and (2) identified potential cut-points for HT3+, which can guide prospective trials aimed at evaluating this endpoint. Specifically, we found that constraining the TVB to mean dose 23.5 Gy, V_5 65%, V_{10} 60%, and/or V_{20} 50% may result in an approximately 2-fold decrease in HT3+ when compared with exceeding these threshold values. The NTCP modeling expectedly yielded an n parameter value of 1; this implies that the TVB BM behaves as a parallel organ

and that the mean TVB dose is a useful predictor for toxicity, which is consistent with past NTCP studies of pelvic BM (13).

Deek et al (11) reported similar results for leukopenia in a cohort ($n = 52$) of NSCLC patients receiving CRT with combination carboplatin and paclitaxel. The authors found that RT dose to other sites of thoracic BM (scapulae, ribs, and clavicles) did not significantly correlate with HT, whereas dose to the TVB was associated with HT. Their reported TVB mean dose and V_{20} cut-points for grade 3 leukopenia were 23.9 Gy and 56%, respectively, which are comparable to our values of 23.5 Gy and 50% for HT3+.

The contribution of RT dose to BM suppression in sites outside the thorax has been well established, and advanced radiation techniques have been used in an effort to reduce HT (13–15). Some studies suggest that the use of pelvic BM-sparing IMRT may help reduce rates of clinically significant HT in cervical cancer (16–18). Specific to the vertebral column, craniospinal irradiation has been associated with high rates of HT3+ in the past. However, Brown et al (19, 20) showed that BM-sparing proton RT reduced HT in adult patients receiving craniospinal irradiation for medulloblastoma. This reduction in HT was achieved by placing the distal edge of the proton beam at the anterior border of the thecal sac, thus largely sparing the vertebral bodies from the anterior exit dose typically seen in photon radiation.

The use of alternative treatment planning techniques, including IMRT or particle therapy, could also be applied to reduce dose to the TVB in patients receiving CRT in lung cancer. Although IMRT was associated with increased low-dose bath to the TVB in our study, this trend can be reversed by applying TVB dose constraints in treatment planning. Such planning modifications, however, cannot be applied without proper consideration. For example, TVB-sparing IMRT may result in higher dose to the esophagus, lungs, and/or heart, which can also be associated with clinically significant toxicities (3,21–23). The feasibility of TVB-sparing IMRT at our institution was tested in 11 previously treated lung cancer patients who had an elevated TVB mean dose. Plans were retrospectively reoptimized with the addition of TVB mean dose constraints. This reoptimization reduced the TVB mean dose by a median of 10.2 Gy (range, –16.7 to –1.0 Gy) without significantly impacting target coverage, lung V_{20} , or mean dose to the heart, lungs, and esophagus (24). Further study is needed to confirm the clinical effects of such modifications.

The potential benefits of reducing HT3+ with TVB-sparing RT are wide ranging. As in other studies, HT was the major factor limiting our patients from receiving a full course of chemotherapy during CRT (9, 25, 26). In one retrospective analysis of CRT for NSCLC, missed chemotherapy administrations were found to negatively impact progression-free and overall survival (9). The combination of these data and our study results suggests that minimizing RT dose to the TVB may reduce HT and improve chemotherapy compliance during CRT, leading to improved cancer control. Furthermore, reducing higher doses of radiation to BM has been associated with more complete long-term recovery from marrow injury (27). This would potentially allow better tolerance of chemotherapy given after CRT. It is possible that such an effect could also have an impact on long-term disease outcomes.

In addition to impacting disease control, a reduction in HT3+ may decrease the need for related medical interventions that are costly and diminish patient quality of life. For example, 49% of our study cohort developed HT3+ during CRT, ultimately necessitating transfusion support (packed red blood cells, platelets, or both) in 46 different patients (23%). Likewise, leukopenia and neutropenia can increase the risk of serious infection and often require hospitalization. Although the details of such events are not within the scope of our study, reducing HT3+ would theoretically decrease the frequency of such events and the need for intervention, likely improving quality of life and reducing costs of care. Further research is needed to test this hypothesis.

This study is limited by biases inherent in retrospective studies and can be viewed as hypothesis generating. We included a wide spectrum of patients to allow for a more broad and practical application of our study results; however, this can also introduce additional confounding factors not present in more homogenous cohorts. For example, we did allow induction chemotherapy when blood counts had recovered before CRT. However, we did limit our study population to those who received either cisplatin/etoposide or carboplatin/paclitaxel, which have become standard in CRT for lung cancer. In this regard there are conflicting data in terms of which of those regimens is associated with more HT in the treatment of lung cancer (28, 29). In a multicenter, randomized, controlled trial in unresectable stage III NSCLC comparing CRT with cisplatin/etoposide versus carboplatin/paclitaxel, Liang et al (30) showed no differences in HT3+ between the 2 regimens (30.5% vs 27.0%, respectively). Our data are consistent with these findings: we also found that concurrent cisplatin/etoposide was not significantly associated with increased odds of developing HT3+ compared with other chemotherapy regimens. It should be noted that the use of cisplatin/etoposide and induction chemotherapy were associated with increased odds of developing grade 4 HT, though the fact that all TVB dose parameters were also significantly associated with grade 4 HT suggests that limiting TVB dose may help reduce this toxicity.

Histology is also a potential confounder, because the frequency and intensity of cisplatin/etoposide in patients with SCLC is higher compared with those receiving cisplatin/etoposide for NSCLC. We took this into account in our sensitivity analysis in which SCLC patients were removed, and we found that TVB dosimetric parameters remained correlated with HT3+. We also recognize that multiple factors other than radiation dose contribute to BM suppression (age, BMI, gender), and this likely explains the low AUC found with each dosimetric parameter in receiver operating characteristic analysis. Nonetheless, radiation dose to the TVB is a modifiable factor, particularly with the use of IMRT, and efforts to use IMRT to reduce dose to the TVB may result in lower rates of acute HT. We believe that our results represent a starting point for future confirmatory studies (in particular, the non-cetuximab arms of the Radiation Therapy Oncology Group 0617 trial, in which patients were uniformly treated with carboplatin/paclitaxel to doses of 60 Gy or 74 Gy, represent an excellent data set to independently verify our findings) and also for prospective trials incorporating functional imaging modalities to potentially identify and spare active BM regions in an effort to potentially reduce acute HT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Normal tissue complication probability (NTCP) for acute grade 3 hematologic toxicities (HT3+) per the Lyman-Kutcher-Burman model. Patients who experienced HT3+ during chemoradiation for lung cancer are represented by red asterisks; patients without HT3+ are represented by green circles. *Abbreviations:* EUD = equivalent uniform dose; TD_{50} = the uniform organ at risk dose that results in a 50% complication risk. (A color version of this figure is available at www.redjournal.org.)

Table 1

Patient, tumor, and treatment characteristics

Characteristic	Value
Male	105 (52.2)
Female	96 (47.8)
BMI (kg/m ²)	25.6 (22.1–31.7)
Age (y)	63 (57–71)
Pathology	
NSCLC	162 (80.6)
SCLC	39 (19.4)
TNM stage	
IB	2 (1.0)
IIA	5 (2.5)
IIB	15 (7.5)
IIIA	109 (54.2)
IIIB	45 (22.4)
IV	25 (12.4)
ECOG performance status	
0–1	178 (88.6)
>1	23 (11.4)
Radiation therapy technique	
3D conformal	46 (22.9)
IMRT	155 (77.1)
Chemotherapy	
Cisplatin + etoposide	107 (53.2)
Carboplatin + paclitaxel	94 (46.8)
Induction	42 (20.9)

Abbreviations: 3D Z 3-dimensional; BMI Z body mass index; ECOG Z Eastern Cooperative Oncology Group; IMRT Z intensity modulated radiation therapy; NSCLC Z non-small cell lung cancer; SCLC Z small cell lung cancer.

Values are number (percentage) or median (interquartile range).

Table 2

Thoracic vertebral body dosimetric parameters

Parameter	3D conformal, median (IQR)	IMRT, median (IQR)	<i>P</i>
V ₅ (%)	56.5 (48.1–66.1)	63.0 (52.0–74.3)	.007
V ₁₀ (%)	48.3 (40.7–59.1)	56.2 (47.1–68.2)	<.001
V ₂₀ (%)	38.3 (27.5–50.4)	46.2 (34.9–59.5)	.003
V ₃₀ (%)	33.1 (17.9–42.3)	35.7 (20.3–49.0)	.388
V ₄₀ (%)	23.1 (10.6–30.2)	20.4 (6.7–29.7)	.543
V ₅₀ (%)	7.2 (2.5–12.7)	7.3 (0.5–13.3)	.837
V ₆₀ (%)	1.1 (0.0–5.2)	0.9 (0–3.7)	.711
Mean (Gy)	18.2 (14.2–24.6)	20.8 (15.8–26.6)	.060

Abbreviation: IQR = interquartile range. Other abbreviations as in Table 1.

Table 3

Acute hematologic toxicities

Toxicity	Value
WBC	
Nadir ($10^3/\mu\text{L}$)	2.3 (1.5–3.3)
Grade 0–2	114 (56.7)
Grade 3	87 (43.3)
ANC	
Nadir ($10^3/\mu\text{L}$)	1.5 (0.8–2.4)
Grade 0–2	137 (68.2)
Grade 3	64 (31.8)
Platelets	
Nadir ($10^3/\mu\text{L}$)	135 (95–187)
Grade 0–2	179 (89.1)
Grade 3	22 (10.9)
Hemoglobin	
Nadir (g/ μL)	10.0 (8.3–11.1)
Grade 0–2	161 (80.1)
Grade 3	40 (19.9)

Abbreviations: ANC = absolute neutrophil count; WBC = white blood cells.

Values are median (range) or number (percentage).

Table 4

Simple logistic regression for parameters associated with HT3+

Parameter	OR (95% CI)	P
Mean dose (per Gy)	1.041 (1.004–1.080)	.032
V ₅ (per %)	1.023 (1.005–1.042)	.012
V ₁₀ (per %)	1.025 (1.007–1.043)	.008
V ₂₀ (per %)	1.019 (1.003–1.036)	.022
V ₃₀ (per %)	1.014 (0.999–1.030)	.072
V ₄₀ (per %)	1.015 (0.998–1.033)	.083
V ₅₀ (per %)	1.024 (0.993–1.057)	.131
V ₆₀ (per %)	1.003 (0.937–1.074)	.933
Age	1.015 (0.986–1.046)	.314
BMI	0.961 (0.921–1.002)	.064
IMRT vs 3D-CRT	1.703 (0.871–3.330)	.120
Cisplatin/etoposide vs other	1.411 (0.809–2.462)	.225
Induction chemotherapy	1.914 (0.954–3.842)	.068
Initial WBC	0.948 (0.892–1.009)	.092
Initial ANC	0.961 (0.898–1.027)	.241
Initial platelet count	1.056 (0.538–2.072)	.875
Initial hemoglobin	0.331 (0.033–3.286)	.345

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; CI = confidence interval; HT3+ = grade 3 hematologic toxicity; OR = odds ratio. Other abbreviations as in Tables 1 and 3.

Table 5

Multivariate logistic regression of parameters associated with HT3+

Parameter	OR (95% CI)	P
Mean dose (per Gy)	1.042 (1.002–1.083)	.039
Age (per y)	1.029 (0.997–1.063)	.078
BMI	0.962 (0.921–1.005)	.080
Induction chemotherapy	1.805 (0.873–3.774)	.117
Initial WBC	0.947 (0.889–1.009)	.093
V ₅ (per %)	1.023 (1.004–1.042)	.018
Age (per y)	1.025 (0.993–1.058)	.121
BMI	0.962 (0.921–1.005)	.086
Induction chemotherapy	1.762 (0.842–3.688)	.133
Initial WBC	0.943 (0.885–1.006)	.075
V ₁₀ (per %)	1.025 (1.006–1.044)	.010
Age (per y)	1.026 (0.994–1.059)	.106
BMI	0.962 (0.921–1.005)	.085
Induction chemotherapy	1.757 (0.837–3.690)	.136
Initial WBC	0.943 (0.884–1.005)	.072
V ₂₀ (per %)	1.019 (1.002–1.037)	.029
Age (per y)	1.028 (0.996–1.061)	.085
BMI	0.961 (0.920–1.004)	.075
Induction chemotherapy	1.829 (0.874–3.829)	.109
Initial WBC	0.949 (0.890–1.011)	.103

Abbreviations as in Tables 1, 3, and 4.