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Does the high dose to the vertebral body in the treatment of esophageal cancer lead to increased hematological toxicity?

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ABSTRACT

Background: To investigate the effect of radiation dose to thoracic vertebrae (TV) on the development of hematologic toxicity in esophageal cancer patients treated with intensity-modulated radiotherapy. ***Materials and Methods:*** We identified 28 patients with esophageal cancer treated with chemoradiotherapy between 2014-2021.Vertebral volumes receiving 5-50 Gy (TV5-50) and the mean vertebral and thoracic blood pool dose were collected from the dose-volume-histogram. Complete blood cell counts were analyzed and hematologic toxicities were graded according to the Common Terminology Criteria for Adverse Events version5.0 (CTCAE v5.0). ***Results:*** TV50 was negatively linearly associated with mean lymphocyte nadir by percentage. TV20 was negatively linearly associated with mean platelet nadir by cc. Planning Target Volume (PTV) length was negatively linearly associated with mean hemoglobin nadir. The optimal threshold dose values for avoiding grade ≥4 lymphopenia was TV40 of <22.3%, TV50 of <9.09%, mean thoracic blood pool dose of < 16.9 Gy, PTV volume of <652 cc and PTV length of <16.7 cm. The optimal threshold dose values for avoiding grade ≥3 leukopenia were TV10 of <47.6%, TV20 of <39.7%, TV30 of< 34.69%,and mean vertebral dose of <17.7Gy. ***Conclusion:*** This study demonstrated a statistically significant negative correlation between vertebral doses and hematologic parameters. The optimal threshold dose values for avoiding grade ≥3 leukopenia were TV10 of <47.6% and mean vertebral dose of <17.7Gy.

INTRODUCTION

At present, concurrent chemotherapy and radiotherapy (CRT), with or without surgical resection, is widely used for the treatment of advanced esophageal cancer, with 2-year overall survival rates of 56% [1]. Despite the use of modern, advanced radiotherapy techniques for treatment, acute adverse events (≥ grade 3) still occur in around half of patients. The most common types of these events are dysphagia and hematological toxicities (HTs), which include leukopenia and neutropenia in up to one-third of patients [2]. HTs often lead to dose reductions and treatment discontinuation [3]. According to a multicenter randomized trial, only 53% of patients were able to complete the full course of treatment [1]. Moreover, toxicity increases the risk of infection, hospitalization, and transfusion requirements. Survival can also be adversely affected by unplanned treatment interruptions with serious consequences [4]. In this respect, a recent meta-analysis has shown a negative prognostic relationship between HT and survival [5].

Reasons for HT other than chemotherapy-mediated toxicity, such as the radiotherapy technique, irradiation of the bone marrow, and irradiation of the circulating blood pool, have been investigated in various studies. In this context, pelvic bone marrow dose has been the most studied and the link with bone marrow dose and HT has been shown in studies of gynecological and anal malignancies [6, 7].

Nowadays, it is possible to reduce the dose delivered to bone structures using intensity-modulated radiotherapy (IMRT). To prevent leukopenia, lymphopenia, and neutropenia, numerous research studies have examined the association between HT and bone marrow irradiation in patients undergoing pelvic or thoracic radiotherapy. These studies have produced a variety of cutoff values. However, there is wide variations in the definition of these thresholds reported in the literature [8-10]. To reduce the incidence of severe HT, there is currently no defined upper dose limit for bone marrow exposure. In addition, most studies of esophageal cancer use various radiotherapy modalities, including IMRT and three-dimensional

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conformal radiotherapy (3-DCRT), of a heterogeneous group of patients. Furthermore, these studies only consider the dose received by bony structures with HT, ignoring the dose received by circulating blood cells.

This study investigated whether there is an association between vertebral dose-volume histogram (DVH) parameters and blood count nadirs in patients with esophageal cancer who were treated with IMRT. The study will also examine the effects of radiation dose on the thoracic vertebrae (TV) and the thoracic blood pool on the development of HT. Thus, it might be possible to improve treatment planning and reduce the incidence of HT if these structures are considered when optimizing treatment.

MATERIALS AND METHODS

Patients

Patients with esophageal cancer who were treated with IMRT and concurrent chemotherapy at our institution between 2014 and 2021, were retrospectively evaluated. The study included patients treated with curative intent (preoperative or definitive), with complete blood count (CBC) data (within 10 days before the start of treatment), accessible DVH parameters, and blood values suitable for treatment (eg, hemoglobin [Hgb] ≥10 k/μL, white blood cells (WBC) ≥4 k/μL, neutrophils ≥2 k/μL, platelets (Plt) ≥150 k/μL, and lymphocytes ≥0.8 k/μL). Patients receiving postoperative or palliative radiotherapy and not receiving concurrent chemoradiotherapy were excluded from the study. 28 patients participated in the analyses. Pre-treatment evaluation included physical examination, laboratory tests, endoscopy, and biopsy. Staging was performed with initial imaging using the American Joint Committee on Cancer TNM (ie, tumor size and spread, lymph node spread, and metastasis) staging system.

Treatment planning and delivery

The patients were immobilized in a supine position on a wing board with their arms elevated and underwent a computed tomography (CT) scan (GE Lightspeed 16, USA). PET fusion was used to identify regions of the tumor. Target volumes were delineated according to the contouring guidelines for IMRT in esophageal and gastroesophageal junction cancer [11]. The radiation dose was 41.4–50.4 Gy administered in 1.8 Gy daily fractions. The vertebra was not included as the organs at risk (OAR) and was not considered during the planning process. An image-guided IMRT approach was used to deliver radiotherapy. The radiotherapy was performed using the RapidArc (Varian Medical Systems, Palo Alto, CA, USA) linac device. During radiotherapy, the concomitant chemotherapy protocol consisted of carboplatin (AUC 2 mg/m^2/min) and paclitaxel (50 mg/m^2) weekly or cisplatin (75–100 mg/m^2) and 5-FU (750–1000 mg/m^2) every 28 days.

Blood counts

Blood cell counts were collected from patients' medical records, including baseline (before the start of CRT), during CRT, and before each post-treatment visit. The cell count nadir was defined as the lowest value within 60 days of treatment initiation. The Common Terminology Criteria for Adverse Events (CTCAE) version 5 was used to grade treatment-related HTs.

Data collection

To obtain TV and thoracic blood pool values, all vertebral bodies from C2 to L2 or to the lowest vertebra visible on planning CT scans were contoured by the same radiation oncologist using bone window on CT sections. Vertebral bodies, pedicles, laminae, transverse, and spinous processes were all included in each contour. In addition, great vessels, the heart, and the whole lungs were defined up to the upper part of the aortic arch to create the thoracic blood pool (figure 1). The spinal canal was excluded from the vertebral volume. Vertebral volumes receiving 5–50 Gy (TV_5, TV_{10}, TV_{20}, TV_{30}, TV_{40}, and TV_{50}; figure 2) with a mean dose, thoracic blood pool, and planning target volume (PTV) data were collected via DVH.

The study was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, and was conducted in accordance with the tenets of the Helsinki Declaration. In addition, each patient provided written informed consent before treatment given the possibility of their files and treatment data being used in any study.

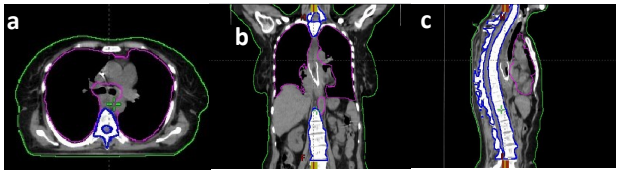

Figure 1. Axial **(a)**, coronal **(b)**, sagittal **(c)** images of the thoracic vertebrae from C2 to L2 (dark blue contour) and thoracic blood pool (magenta contour) structures.

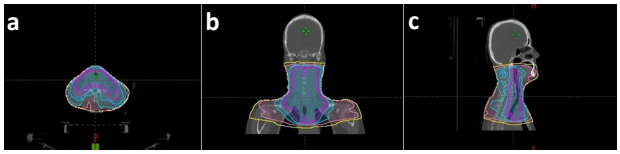

Figure 2. Isodose lines of 5 (yellow), 10 (orange), 20 (green), 30 (blue), 40 (red), and 50 (magenta) Gy in a sample patient's axial **(a)**, coronal **(b)**, and sagittal **(c)** sections.

Statistical analysis

SPSS 22.0 software was used for statistical analyses (SPSS Inc., Chicago, IL), and a p value of <0.05 was considered statistically significant. The normalization of hematological cell counts was

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performed using the Shapiro–Wilk test. Linear regression analyses examined the associations between Hgb, WBC, neutrophil, lymphocyte, platelet nadirs, and DVH parameters. The change in mean hematological cell count for each unit increase in the associated DVH parameters was represented by the regression coefficient β. Logistic regression analyses were performed to assess the risk of HTs with increasing DVH parameters. The Chi-squared test or Fisher's exact test was used to compare HTs. Univariate analyses of time from diagnosis to death from any cause were performed using Kaplan–Meier plots and log–rank tests. Receiver operating characteristic (ROC) curves were calculated to evaluate dose thresholds for DVH parameters to avoid grade ≥3 leukopenia and grade ≥4 lymphopenia.

RESULTS

Patients

Patient characteristics are shown in table 1. Of the patients enrolled, 16 (57.1%) were male, and 78.6% had squamous cell carcinoma. The median age was 56.5 (range 37–74) years. Most patients (92.9%) were diagnosed at stage T3–T4; 71.4% had positive lymph nodes and were treated with a dose of 50.4 Gy (75%). 61% of patients received carboplatin/paclitaxel, and 39% were treated with platinum/5-FU. Mean PTV volume and length were 677.22 (range 170.45–2450.11) cc and 16.95 (range 12.4–22.95) cm, respectively. Treatment was interrupted for a median of 4 (range 1–18) days in 22 patients. The main reason for interruption of treatment was HTs in six patients. The 2-year overall survival rate was 41.4%. When evaluating the effect of treatment interruptions on survival, no statistically significant difference was found between a break of less than 4 days and 4 days and longer (p=0.169).

Table 1. Patient baseline characteristics.

Characteristic	n	%
Gender		
Male	16	57.1
Female	12	42.9
Histology		
SCC	22	78.6
AC	6	21.6
T Stage		
T1 or T2	2	7.1
T3 or T4	26	92.9
N Stage		
N0	8	28.6
N+	20	71.4
AJCC Stage		
Stage I-II	7	25
Stage III	21	75
Chemotherapy regimens		
Carboplatin/paclitaxel	17	60.7
Platinum/5FU	11	39.3
Total radiotherapy dose, Gy		
50.4	21	75
<50.4	7	25

SCC, squamous cell carcinoma; AC, adenocarcinoma; AJCC, American Joint Committee on Cancer; 5FU, 5,fluorouracil.

Hematological toxicities (HTs)

Descriptive characteristics of hematological and dosimetric parameters are summarized in tables 2 and 3. Mean baseline blood count values were Hgb of 13.1 k/μL, WBC of 8.3 k/μL, neutrophil of 5.4 k/μL, Plt of 278.3 k/μL, and lymphocyte of 1.9 k/μL. Acute HT rates are shown in table 4. Of the 28 patients in this study, 89% (n=25) developed grade 3–4 lymphocytopenia. Neither thrombocytopenia nor grade 4 anemia occurred in any of the patients.

When comparing the effects of two different chemotherapy regimens on the development of HT, 35.3% of patients receiving carboplatin/paclitaxel had grade 3 or higher HTs compared with 36.4% of patients receiving platinum/5FU. Nevertheless, there was no statistically significant difference between the two chemotherapy regimens (p=1.0). 29.4% of patients receiving carboplatin/paclitaxel had grade 4 or higher lymphocytopenia compared with 45.5% of patients receiving platinum/5FU. Similarly, no statistically significant difference was found between the two chemotherapy regimens (p=0.444). When the effect of grade 3 and higher HTs and grade 4 and higher lymphocytopenia on overall survival was evaluated, no statistical significance was found (p=0.228 and p=0.802, respectively).

Table 2. Summary of pre-treatment and lowest post-treatment hematological parameters.

Parameter	Mean	Standard deviation
Baseline blood count (k/μL)		
Hemoglobin	13.1	1.5
Leukocyte	8.3	2.3
Neutrophil	5.4	1.9
Platelet	278.3	65.5
Lymphocyte	1.9	0.8
Blood cell nadir (k/μL)		
Hemoglobin	9.9	0.8
Leukocyte	2.7	1.5
Neutrophil	1.9	1.3
Platelet	131.5	57.6
Lymphocyte	0.3	0.4

Table 3. Summary of dosimetric parameters including thoracic vertebrae and thoracic blood pool.

Parameter	Mean	Standard deviation
Vertebral body DVH (%; cc)		
TV_5	49.2; 51.8	6.9; 3.3
TV_{10}	44; 51.3	7.1; 3.4
TV_{20}	35.8; 50.1	8.5; 3.3
TV_{30}	28.9; 48.5	9.5; 3.7
TV_{40}	19.8; 46.7	11.4; 4.3
TV_{50}	11.1; 44.9	9.9; 4.7
Mean vertebral dose (Gy)	17.9	5.5
Mean thoracic blood pool dose (Gy)	16.9	4.27

DVH, dose-volume histogram; TV, thoracic vertebrae.

Table 4. Acute hematologic toxicities observed in cohort.

Toxicity	CTCAE grade, n (%)				
	0	1	2	3	4
Anemia	1 (3.6)	15 (53.6)	9 (32.1)	3 (10.7)	0
Leukopenia	3 (10.7)	6 (21.4)	11 (39.3)	7 (25)	1 (3.6)
Thrombocytopenia	7 (25)	19 (67.9)	2 (7.1)	0	0
Neutropenia	5 (17.9)	13 (46.4)	4 (14.3)	5 (17.9)	1 (3.6)
Lymphocytopenia	1 (3.6)	0	2 (7.1)	15 (53.6)	10 (35.7)

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Association of dosimetric parameters and HTs

The mean log-transformed lymphocyte nadir was inversely linearly correlated with TV_{50} (β=0.007, p=0.006) by the percentage on linear regression analysis. The mean log-transformed lymphocyte nadir inversely linearly correlated with TV_5 (β=-0.06, p=0.024), TV_{10} (β=-0.009, p=0.031), TV_{30} (β=-0.01, p=0.031), and TV_{40} (β=-0.048, p=0.034) by cc. The mean log-transformed platelet nadir was inversely linearly correlated with TV_5 (β=-0.118, p=0.05) and TV_{20} (β=-0.301, p=0.044) by cc. Furthermore, the mean Hgb nadir was negatively linearly correlated with PTV length (β=-0.281, p=0.04; table 5). Logistic regression analysis for grade 3 and higher HT, grade 4 and higher lymphopenia, and grade 3 and higher leukopenia were not statistically significant.

Table 5. Linear regression analysis of dosimetric factors associated with hematologic parameters.

Variable	nadirHgb		nadirWBC		nadirNeu		nadirPlt		nadirLymp	
	β	p	β	p	β	p	β	p	β	p
DVH by %										
TV5	-0.23	0.15	0.04	0.43	0.06	0.,47	-0.038	0.306	-0.009	0.402
TV10	0.52	0.16	-0.09	0.30	-0.10	0.26	0.054	0.328	-0.016	0.308
TV20	-0.03	0.22	0.08	0.27	0.08	0.20	-0.039	0.394	0.015	0.113
TV30	0.19	0.10	-0.06	0.37	-0.06	0.28	0.017	0.491	-0.010	0.086
TV40	-0.01	0.06	0.002	0.43	80.00	0.37	-0.009	0.372	-0.011	0.083
TV50	0.04	0.23	-0.01	0.23	-0.002	0.31	-0.017	0.072	-0.007	**0.006**
DVHby cc										
TV5	-2.49	0.14	-0.045	0.09	0.062	**0.05**	-0.118	**0.050**	-0.060	**0.024**
TV10	1.59	0.12	-0.11	0.11	-0.101	0.07	0.235	0.059	-0.009	**0.031**
TV20	3.07	0.25	0.26	0.18	0.087	0.14	-0.301	**0.044**	0.084	**0.018**
TV30	-3.33	0.47	-0.306	0.33	-0.06	0.30	0.281	0.056	-0.010	**0.031**
TV40	-0.92	0.33	0.24	0.39	0.008	0.39	-0.147	0.051	-0.048	**0.034**
TV50	4.54	0.22	0.02	0.35	-0.002	0.36	0.039	**0.043**	0.110	**0.033**
Vertebra mean	-1.12	0.15	0.056	0.33	0.021	0.46	0.025	0.096	0.063	**0.003**
PTV volume	-0.01	0.07	-2.64	0.33	-3.43	0.40	<0.001	0.163	-5.324	0.092
PTV lenght	-0.281	**0.04**	-0.005	0.14	-0.007	0.12	0.022	0.243	0.006	0.175
Thoracic blood pool mean	0.284	0.14	-9.07	0.17	7.26	0.23	-6.23	0.054	-2.74	0.08

DVH, dose-volume histogram; TV, thoracic vertebrae; PTV, planning target volume.

Determination of threshold values to avoid lymphopenia and leukopenia

We calculated the cutoff values predicting the risk of developing grade 3 and higher HT, grade 4 and higher lymphopenia, and grade 3 and higher leukopenia using ROC curves. The optimal thresholds for avoiding grade 3 and higher HTs could not be determined due to low discriminatory power. However, the optimal dose thresholds for avoiding grade 4 and higher lymphopenia were as follows: TV_{40} of less than 22.3% [area under curve (AUC) =0.706, sensitivity=70%, specificity=67%], TV_{50} of less than 9.09% (AUC=0.706, sensitivity=70%, specificity=72.2%), TV_{50} of less than 45.1 cc (AUC=0.7, sensitivity=80%, specificity=61.1%), mean thoracic blood pool dose of less than 16.9 Gy (AUC=0.711, sensitivity=80%, specificity=66.7%), PTV volume of less than 652 cc (AUC=0.828, sensitivity=80%, specificity=77.8%), and PTV length less than 16.7 cm (AUC=0.761, sensitivity=90%, specificity=72.2%) (Figure 3).

The optimal dose thresholds to avoid grade 3 and higher leukopenia were as follows: TV_{10} less than 47.6% (AUC=0.681, sensitivity=62.5%, specificity=75%), TV_{20} less than 39.7% (AUC=0.7, sensitivity=62.5%, specificity=75%), TV_{30} less than 34.69% (AUC=0.681, sensitivity=62.5%, specificity=85%), and mean vertebral dose less than 17.7 Gy (AUC=0.669, sensitivity=62.5%, specificity=60%) (Figure 4).

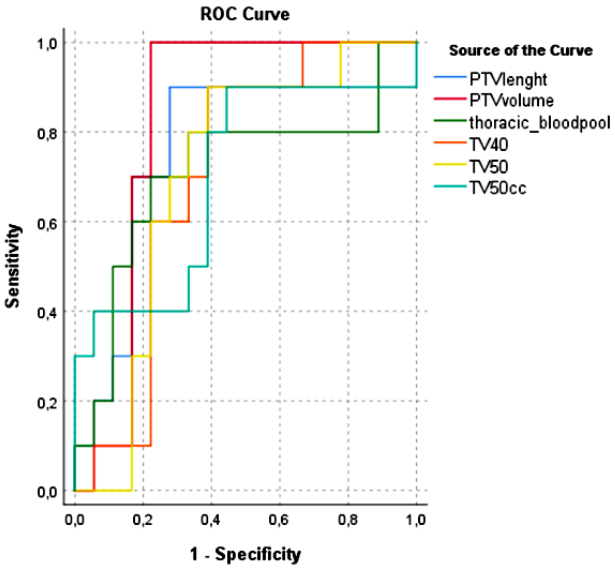

Figure 3. Receiver operating characteristics curve for grade ≥4 lymphopenia.

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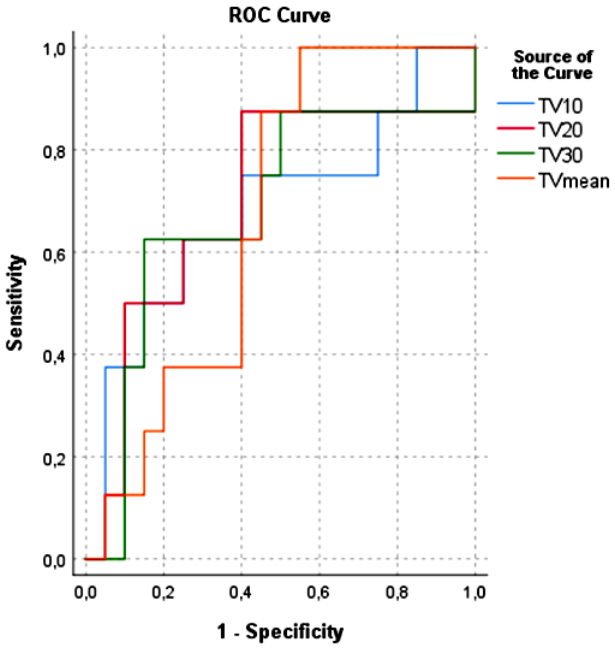

Figure 4. Receiver operating characteristics curve for grade ≥3 leukopenia.

DISCUSSION

The study of radiation dose effects on the TV and thoracic blood pool has received increasing attention, particularly following the widespread use of IMRT for esophageal cancer. There are numerous studies in the literature that explore the relationship between exposure to radiation and the mechanisms that lead to the development of HT. Most of these trials were conducted in patients with lung and esophageal cancers. However, to date, the optimal dose–volume restriction of the bone marrow to prevent the development of HT has not been recommended as a standard. The only information available is that the potential dose restrictions recommended for patients undergoing pelvic irradiation are a mean dose of less than 28 Gy, V_{10} less than 90%, and V_{20} less than 75% [12].

Deek *et al*. showed the potential benefit of preserving TV in patients receiving CRT for non-small cell lung cancer. They also reported that TV_5, TV_{20}, TV_{30}, and mean vertebral dose were associated with HT [8]. Lee et al. evaluated dosimetric predictors of HT in 41 patients with esophageal cancer receiving CRT and found that higher TV and rib irradiation were associated with grade 3 leukopenia [9]. Fabian *et al*. further contributed to this discourse by providing empirical evidence that high radiation doses to the thoracic bone marrow correlated with increased rates of grade 3 and higher HTs in patients with esophageal cancer undergoing CRT. Their analysis of 137 cases emphasized the importance of specific dose metrics related to the vertebral body and rib subsites, reinforcing the notion that radiation exposure to these regions is a crucial factor in the development of acute toxicity. In particular, patients with thoracic marrow V_{30} of 14% and higher had a 5.7-fold increased risk of grade 3 and higher HTs [13].

Conversely, Zhang *et al*. investigated the threshold dose levels to prevent grade 3 and higher leukopenia. They showed that V_{10} higher than 49.1%, V_{20} higher than 45.6%, and mean dose higher than 17.2 Gy to the vertebral body were closely associated with the risk of developing grade 3 and higher leukopenia [10]. In our study, ROC analyses showed that the optimal dose thresholds to avoid grade 3 and higher leukopenia were less than 47.6% TV_{10} and less than 17.7 Gy mean dose to the vertebral body, which were similar values reported by Zhang *et al.*

It has been reported that lymphocytes in particular, are sensitive to low radiation doses [14]. Lymphocytopenia has been shown to be a prognostic factor for survival in several malignancies, including esophageal carcinoma [15, 16]. In patients treated with neoadjuvant or definitive CRT for esophageal cancer, Xu *et al*. showed that radiation-induced lymphopenia was associated with worse clinical outcomes [17]. Previously published studies indicate that larger treatment volumes are associated with lymphocytopenia in patients with esophageal cancer and that reducing the irradiated volumes might decrease the probability of lymphocytopenia [18, 19]. Tseng *et al*. showed that the probability of grade 4 lymphopenia following curative CRT for esophageal cancer was reduced by lower radiation dose to bone marrow and the spleen [20]. According to Wang et al, peripheral blood lymphocytes are affected by the V_{20} of the sternum [21]. In Davuluri *et al*.'s study, it was shown that mean body dose was significantly associated with grade 4 lymphocytopenia, and it was emphasized that grade 4 lymphocytopenia during CRT for esophageal cancer was associated with worse overall survival, progression-free survival, local recurrence-free survival, and disease-specific survival [15]. In another study, Newman *et al*. investigated the relationship between radiation doses to vertebral bone marrow and the incidence of lymphopenia during CRT for esophageal cancer. Their results showed a significant correlation between dose metrics and grade 4 lymphopenia, establishing the vertebral bone marrow as a potential OAR during treatment. This study highlighted the effect of lymphopenia on treatment efficacy and suggested that adopting spinal marrow-sparing techniques could improve patient outcomes by minimizing treatment interruptions [22]. Similarly, our study showed a strong negative correlation between TV doses and lymphocyte count. However, the effect of cytopenias on survival was not established in this study.

In a recent study investigating the relationship between HT and vertebral doses in patients with locally advanced gastric cancer who received preoperative CRT, vertebral V_5 values were closely

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associated with grade 3 and higher leukopenia, thrombocytopenia, and HTs, and the optimal cutoff value for V_5 was reported as less than 88.75% from ROC analysis [23]. On the other hand, the analyses performed for the TV_5 value in our study were not significant.

Some limitations should be considered when evaluating this study. First, these are retrospective results from a single center, and the sample size is small. Second, two different chemotherapy regimens were administered, which caused heterogeneity among patients. Third, bone structures were contoured on CT imaging without functional imaging modalities. Some studies have indicated that the relationships between TV radiation exposure and cell count troughs might be stronger if functional imaging approaches such as 18F-fluorodeoxyglucose (FDG)-PET/CT are used to identify active bone marrow [24, 25]. Lastly, treatment outcomes and the effect of toxicity on survival were not reported.

In conclusion, our study showed a statistically significant negative correlation between TV doses and hematological parameters, lymphopenia, and leukopenia. It is important to determine and implement bone marrow dose restrictions to reduce the incidence of HT during chemoradiation. Similar to previous studies, we found the optimal dose thresholds for grade 3 and higher leukopenia to be less than 47.6% for TV_{10} and less than 17.7 Gy for the mean vertebral dose. However, these values require further investigation and validation in larger patient groups. Thus, compliance with chemotherapy and radiotherapy can be increased by reducing HTs and survival outcomes can be improved.

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Authors' contribution: Study conception and design: C.B., D.Ç.Ö.; Data collection: C.B., E.S.A., T.K.Ç., S.Ç.K.; Analysis and interpretation of results: C.B., Ş.A.E., H.C.Y.; Draft manuscript preparation: C.B., Ş.A.E., D.Ç.Ö.; All authors reviewed the results and approved the final version of the manuscript.

Data Availability: For data availability, please contact the corresponding author.

Artificial Intelligence: AI was not used in this study

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