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Original Research

Effects of Radiotherapy and Chemotherapy on Platelet in Patients with Lung Cancer

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Abstract

Background: An animal study has shown that platelets form are formed in the lungs. Therefore, we wanted to study the relationship between lung radiation dose and platelet count in lung cancer patients receiving radiation therapy. **Methods**: This retrospective study included 93 patients with lung cancer who received radical thoracic radiation therapy. The correlation between pulmonary dose-volume histogram (DVH) parameters and thrombocytopenia during radiotherapy (RT) was evaluated by chi-square test, logistic regression analysis, Spearman and Pearson correlation analysis, etc. **Results**: Thrombocytopenia occurred in 17 of 93 patients (18.3%). Chi-square test and logistic regression analysis showed that chemotherapy ($p = 0.038$), MLD (mean lung dose, $p = 0.001$), V_5 ($p = 0.008$), V_{10} ($p = 0.004$), AND V_{20} ($p = 0.003$) were important independent predictors of thrombocytopenia. Using the chi-square test, increased MLD ($p = 0.002$), V_5 ($p = 0.021$), V_{10} ($p = 0.008$), and V_{20} ($p = 0.006$) were associated with increased risk of thrombocytopenia. Receiver operating characteristic (ROC) curve was used to analyze the thresholds of MLD, V_5, $V_{10,}$ and V_{20}, which showed high sensitivity and specificity for distinguishing between non-thrombocytopenia and thrombocytopenia. **Conclusions**: Higher doses of radiation to the lung are associated with an increased risk of thrombocytopenia. Moreover, optimization of treatment plans via the control of DVH parameters may reduce treatment interruptions and improve outcomes in lung cancer patients treated with RT.

Keywords: lung; radiotherapy; thrombocytopenia

1. Introduction

Until recently, it was widely accepted that megakaryocytes mainly reside in the bone marrow, and thus, the bone marrow is the site of platelet production. However, in 2017, Lefrançais *et al.* [1] published a groundbreaking study demonstrating blood formation in the lungs of mice. Using lung microcirculation imaging, they showed that a large number of megakaryocytes circulate through the lungs, where they dynamically release platelets. Their observation that megakaryocytes produce more than 10 million platelets per hour in the blood vessels of the lungs suggests that more than half of the mouse's platelet production occurs in the lungs, instead of the bone marrow. Together, their results provided strong evidence that the lungs play a key role in blood formation in mice.

Megakaryocytes are a special type of hematopoietic cell, the grandmother cell that produces platelets [2–4]. Ionizing radiation causes a decrease in megakaryocytes and platelets [5,6]. In a previous study, megakaryocyte progenitors were found to be more sensitive to X-rays than other hematopoietic cells [7]. *In vitro* studies revealed that platelets exposed to gamma rays are ultimately damaged under storage conditions, leading to shortened life after transfusion; this is due to increased clearance of the reticuloendothelial system, resulting in decreased survival after 24-hour commodity channel index (CCI) and platelet transfusion [8–10]. When a lesion of a lung cancer patient is treated with radiation, the rest of the normal lung tissue is also exposed to radiation. Here, we investigated the consequence of radiation exposure of the lung tissues to platelets in the human body. Specifically, we investigated the relationships between dose-volume histogram (DVH) parameters and the incidence of thrombocytopenia in lung cancer patients treated with radiotherapy (RT).

2. Material and Methods

2.1 Patient Selection

This retrospective study was approved by the Ethics Committee of Shandong Cancer Research Institute (SDTHEC2020004042). Patients included in this retrospective study had: (1) pathologically or cytologically confirmed lung cancer; (2) received chest RT between 2015 and 2017; and (3) a platelet count of 100,000/μL or greater at the time that chest RT was initiated. The exclusion criteria were: (1) evidence of hematologic malignancy; (2) treatment with molecular targeted therapy, interferon, or secondary RT; (3) evidence of liver, kidney, and spleen diseases. Blood count data were extracted retrospectively from an electronic medical records database. For blood biochemical examination, we apply the principle of de-

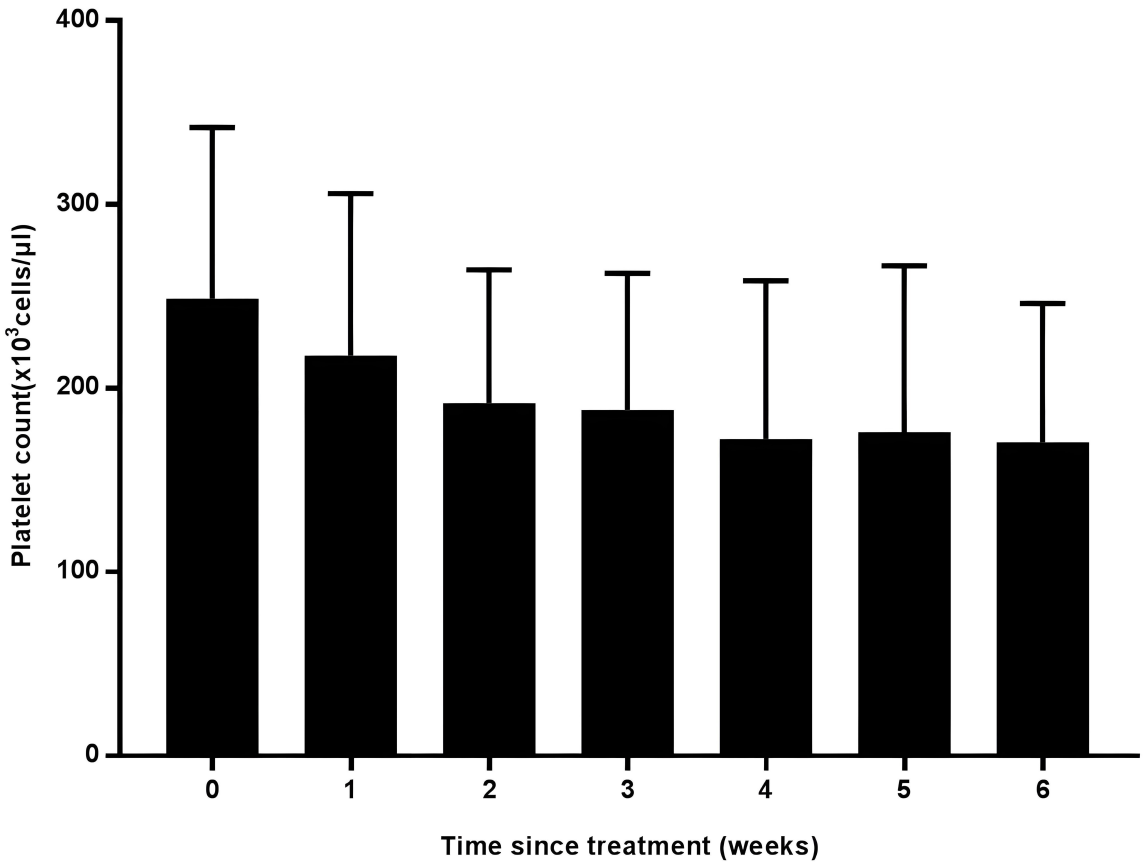

Fig. 1. The dynamic changes of platelet counts during 6 weeks after thoracic radiation.

tecting blood cells by resistance. The resistance method quantifies and detects the properties and form of a substance based on the change of its resistance to the current. After a series of treatments, the blood samples were placed between electrodes. By applying a certain frequency and alternating current to the samples, the current and voltage were measured, and the shape, quantity, and nature of the blood cells were obtained according to the impedance changes. Similarly, platelets possess capacitive properties, and their charge distribution produces the impedance change to the transmission of current. DVH data were collected for calculating the mean lung dose (MLD) and the lung V_5, $V_{10,}$and V_{20}, where MLD (mean lung dose) refers to the average radiation dose received by lung cancer patients in both lungs during radiation therapy, and Vx is defined as the percentage of the volume of the whole lung receiving x Gray (Gy) of radiation.

2.2 Radiotherapy and Multimodality Therapy

For treatment, patients were positioned in a supine position with their arms above their heads. The patients were trained to breathe as shallowly as possible. All gross tumor volumes (GTVs) were contoured on intravenous contrast-enhanced lesions. The clinical target volume (CTV) was defined as the GTV with a surrounding margin of 5 mm. The planning target volume (PTV) included 5–10 mm margins to account for the effects of setup error and internal organ motion on the CTV. RT was administered using 6 MV photons by a Oncor Impression linear accelerator (Siemens, Erlangen, Germany). The administration dosage for organs at risk was defined according to the Radiation Therapy Oncology Group (RTOG) contouring atlas of the lung. A total of 38 patients (41%) received first-line chemotherapy before receiving RT, and 32 patients (34%) received concurrent chemotherapy.

2.3 Evaluation

Complete platelet counts were collected weekly during RT. The primary endpoint was the absolute platelet count nadir during treatment. Thrombocytopenia was graded according to the Common Terminology Criteria for Adverse Events, version 4.0. The assessment of the tumor node metastasis (TNM) stage was based on computed tomography (CT) scans of the thorax and upper abdomen, magnetic resonance imaging (MRI) or CT scans of the brain, and bone emission CT scans.

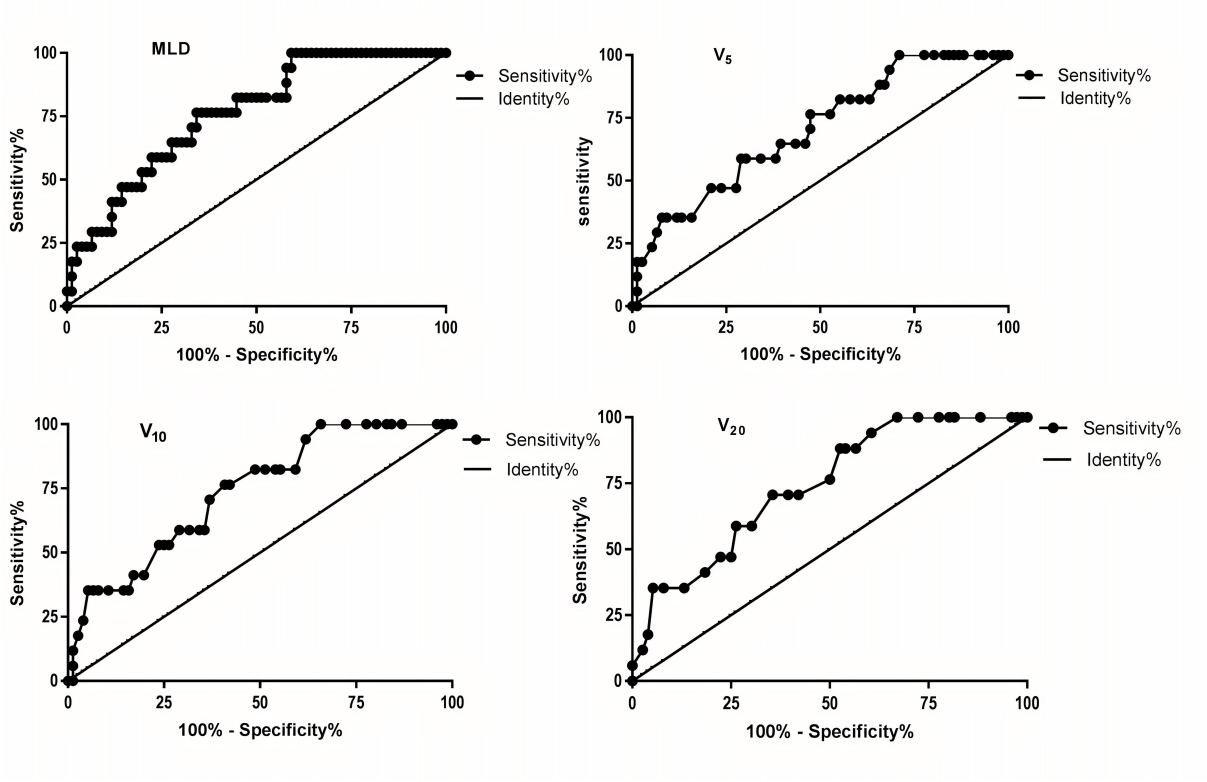

Fig. 2. ROC curves for thrombocytopenia according to dosimetric parameters of MLD, V_5, V_{10}, and V_{20}. ROC, receiver operating characteristic; MLD, mean lung dose.

2.4 Statistical Analysis

The categorical variables included age, gender, Karnofsky Performance Scale (KPS) score, smoking history, stage, histological feature, and chemotherapy, and differences between the two groups were analyzed by Chi-square test. For lung DVH parameters which were considered continuous variables, the logistic regression analysis was performed. Logistic regression analysis, Spearman, and Pearson correction analysis were used to test the correlations between thrombocytopenia and DVH parameters. Receiver operating characteristic (ROC) curves were employed to evaluate cutoff DVH values for avoiding thrombocytopenia. These cutoffs were determined by finding the point closest to the upper left of the ROC curve, which represents the highest accuracy of predicting thrombocytopenia. All statistical analyses were performed using SPSS software package version 22.0 (IBM SPSS, Armonk, NY, USA), and $p < 0.05$ was considered significant.

3. Results

3.1 Patient Characteristics

The baseline characteristics of 93 patients included in this study are summarized in Table 1. Their median age was 64 years (range, 38–80 years), and the median dose of radiation to the tumor site was 58 Gy (range, 40–75 Gy). The mean and standard deviation of the DVH variables in the lungs are MLD (972.4; 426.8), V_5 (37.97%; 15.9), V_{10} (26.6%; 12.1), and V_{20} (16.6%; 8.0). Thrombocytopenia occurred in 17 (18.3%) cases, including 5 cases of grade 1, 8 cases of grade 2, 2 cases of grade 3, and 2 cases of grade 4. The dynamic platelet (PLT) counts during 6 weeks of thoracic RT are shown in Fig. 1. Chemotherapy is the only clinical factor found to be associated with thrombocytopenia ($p = 0.038$; Table 1).

3.2 DVH Parameters Associated with Risk of Thrombocytopenia

Simple logistic regression analysis showed that increasing MLD ($p = 0.001$), V_5 ($p = 0.008$), V_{10} ($p = 0.004$), and V_{20} ($p = 0.003$) were significant predictors of thrombocytopenia (Table 2). When using the cutoff point obtained in the ROC curves analysis, the χ^2 test demonstrated that increasing MLD ($p = 0.002$), V_5 ($p = 0.021$), V_{10} ($p = 0.008$), and V_{20} ($p = 0.006$) were independently associated with an increased risk of thrombocytopenia (Table 3).

3.3 DVH Toxicity Threshold for Thrombocytopenia

To identify thresholds for dosimetric planning, we analyzed the ROC curves for thrombocytopenia according to MLD, V_5, V_{10}, and V_{20} (Fig. 2). The area under the curve (AUC) values for MLD, V_5, V_{10}, and V_{20} are presented in Table 4 and the cutoff values for avoiding thrombocytopenia were MLD $\leq$10.6 Gy, V_5 $\leq$44.5%, V_{10} $\leq$27.5%, and V_{20} $\leq$14.5%. These cutoffs represent the DVH values

Table 1. Patient's characteristics and corresponding incidence of thrombocytopenia.

Variables	n (%)	Thrombocytopenia		*p*
		Grade 0	≥ Grade 1	
Age (years)				0.780
<60	32 (34.4)	27	5	
≥60	61 (65.6)	49	12	
Gender				0.257
Female	28 (30.1)	25	3	
Male	65 (69.9)	51	14	
KPS score				0.791
≤80	36 (38.7)	30	6	
>80	57 (61.3)	46	11	
Smoking history				0.604
Never smoker	44 (47.3)	37	7	
Former/current smoker	49 (52.7)	39	10	
Stage				0.556
I	21 (22.6)	19	2	
II	3 (3.2)	2	1	
III	56 (60.2)	44	12	
IV	13 (14.0)	11	2	
Histology				0.541
Adenocarcinoma	28 (30.1)	24	4	
Squamous	25 (26.9)	20	5	
SCLC	32 (34.4)	27	5	
Other	8 (8.6)	5	3	
Chemotherapy				0.038
Concurrent CRT and prior chemotherapy	70 (75.3)	54	16	
No chemotherapy	23 (24.7)	22	1	

Abbreviations: SCLC, small cell lung cancer; CRT, chemoradiotherapy; KPS, Karnofsky Performance Scale.

Table 2. The simple logistic regression analysis of predictors of thrombocytopenia.

DVH parameters	Thrombocytopenia	
	HR (95% CI)	*p*
MLD	1.001–1.004	0.001
V_5	1.013–1.091	0.008
V_{10}	1.025–1.134	0.004
V_{20}	1.040–1.221	0.003

Abbreviations: DVH, dose-volume histogram; HR, hazard ratio; CI, confidence interval; MLD, mean lung dose.

with the highest accuracy for predicting thrombocytopenia. For example, patients who received a MLD >10.6 Gy were more likely to develop thrombocytopenia (33%) than those who received a MLD <10.6 Gy (7%; $p = 0.002$). Additionally, patients with V_5 >44.5%, V_{10} >27.5%, and V_{20} >14.5% were more likely to develop thrombocytopenia (31%, 30%, and 27%, respectively) than with V_5 <44.5%, V_{10} <27.5%, and V_{20} <14.5% (11%, 8%, and 5%, respectively; $p = 0.021$, $p = 0.008$, $p = 0.006$; Table 3).

3.4 Factors Associated with Platelet Nadir

According to Spearman and Pearson correlation analysis, chemotherapy (r = –0.385, $p = 0.000$) and DVH parameters including MLD (r = –0.353, $p = 0.001$), V_5 (r = –0.342, $p = 0.001$), V_{10} (r = –0.350, $p = 0.001$), and V_{20} (r = –0.336, $p = 0.001$), were negatively correlated with platelet nadir. Increasing chemotherapy and DVH parameters were associated with lower platelet nadir. Chemotherapy (r = –0.385) trended toward significance.

4. Discussion

In observing the platelet changes in patients with lung radiation exposure, we found that 18.3% of patients developed thrombocytopenia during lung cancer radiation therapy, and increased lung radiation dose was closely associated with decreased platelet count. *In vitro* studies have also found that when human megakaryocytes are exposed to radiation, the DNA structure inside the cells is damaged, resulting in decreased numbers of megakaryocytes and platelets produced.

From the logistic regression analysis in the present study, the MLD, V_5, V_{10}, and V_{20} were associated with

Table 3. Incidence of thrombocytopenia according to MLD, V_5, V_{10}, and V_{20}.

DVH parameters	Category	Thrombocytopenia (≥ Grade 1)	*p*
MLD	>1059 cGy	13/39	0.002
	≤1059 cGy	4/54	
V_5	>44.5%	10/32	0.021
	≤44.5%	7/61	
V_{10}	>27.5%	13/44	0.008
	≤27.5%	4/49	
V_{20}	>14.5%	15/55	0.006
	≤14.5%	2/38	

Abbreviations: DVH, dose-volume histogram; MLD, mean lung dose.

Table 4. AUC values for the prediction of thrombocytopenia according to the MLD, V_5, V_{10}, and V_{20}.

DVH parameters	Area	Asymptotic Sig.[a]	Asymptotic 95% CI	
			Lower bound	Upper bound
MLD	0.761	0.001	0.647	0.875
V_5	0.704	0.009	0.573	0.853
V_{10}	0.738	0.002	0.618	0.858
V_{20}	0.740	0.002	0.621	0.858

[a]Null hypothesis: true area = 0.5. Abbreviations: DVH, dose-volume histogram; CI, confidence interval; MLD, mean lung dose.

thrombocytopenia (all $p < 0.05$). Presently in our hospital, the maximum limit dose for the normal part of both lung organs for patients with chest radiotherapy is MLD ≤20 Gy, V_5 ≤65%, V_{20} ≤35%. However, we determined the threshold values for these DVH parameters that best predict thrombocytopenia: MLD ≤10.6 Gy, V_5 ≤44.5%, V_{10} ≤27.5%, and V_{20} ≤14.5%. For each parameter, the incidence of thrombocytopenia was greater when the radiation doses to the lung exceeded the threshold value. Clinically, severe thrombocytopenia can require RT treatment interruptions and/or a reduction in radiation dose and even lead to shortened survival time. Unscheduled interruptions in potentially curative treatments have been related to a reduced probability of local control of lung cancer [11,12]. In addition, severe thrombocytopenia can cause bleeding problems and reduce the quality of life for patients. Therefore, in clinical practice, the ability to protect the lungs by controlling the value of DVH parameters and thereby reducing the risk of thrombocytopenia could offer great benefits to lung cancer patients receiving RT.

Our study shows that chemotherapy is associated with thrombocytopenia. Simultaneously, DVH parameters also have an association with thrombocytopenia. This indicates that the increase in lung radiation dosage was an important factor causing platelet reduction, in the context of chemotherapy-induced myelosuppression ($p < 0.05$). However, some studies also found that the number of megakaryocytes in the peripheral blood of patients increased after chemotherapy and growth factory-induced mobilization [13,14]. Because the patients in this study were treated based on chemotherapy, they could not be analyzed separately. Nonetheless, regardless of the increase or decrease of megakaryocytes after chemotherapy, we analyzed the decrease of platelets in the peripheral blood after receiving radiation in human lungs based on chemotherapy.

The association between thrombocytopenia and radiation dose to thoracic bone marrow (sternum, ribs, scapula) was not analyzed in this study, because these patients adopted the precise radiotherapy technology in our hospital. The radiotherapy dose is mainly concentrated on the lung tumor tissue and the surrounding lung tissue, and the irradiation dose to the chest bone marrow is very small. And previous studies have also shown that there is no significant correlation between radiation dose to thoracic bone marrow (sternum, ribs, scapula) and thrombocytopenia [15]. In addition, more than one-half of the body's bone marrow is located in the pelvic bone marrow (os coxae, sacrum, proximal femora, and lower lumbar spine) [16], however, there is no significant correlation between dosimetric parameters and platelet count nadirs [17]. Furthermore, only 25% of the bone marrow in the human body is located in the thoracic bone marrow (sternum, ribs, scapula), thus thoracic bone marrow irradiation does not affect platelets. The treatments that patients received before RT were not homogeneous due to the retrospective study design. In the future, a well-designed prospective study is needed to overcome the limitations of the present study and to confirm the correlation between radiation dose to the lung and thrombocytopenia, as well as provide insight into the underlying mechanisms, particularly the production of platelets within the human.

5. Conclusions

Higher doses of radiation to the lung are associated with an increased risk of thrombocytopenia. Moreover, optimization of treatment plans via the control of DVH parameters may reduce the risk of bleeding and improve the quality of life in lung cancer patients treated with RT.

Abbreviations

RT, radiotherapy; DVH, dose-volume histogram; MLD, mean lung dose; GTVs, gross tumor volumes; CTV, clinical target volume; PTV, planning target volume; RTOG, Radiation Therapy Oncology Group; TNM, tumor node metastasis; CT, computed tomography; MRI, magnetic resonance imaging; KPS, Karnofsky Perormance Scale; ROC, Receiver operating characteristic; PLT, platelet.

Availability of Data and Materials

Reasonable requests for data and materials will be considered and should be made in writing to the corresponding author.

Author Contributions

SHY designed the study; SST collected the patients' clinical data and SST, LL analyzed the data, SST wrote the paper. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study has been approved by the Ethics Committee of Shandong Cancer Research Institute (SDTHEC2020004042). The patients enrolled all presented written informed consent.

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Conflict of Interest

The authors declare no conflict of interest.

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