

Association Between Thoracic Radiotherapy and Severity of Coronary Artery Calcification in Lung Cancer: A Retrospective Cohort Study

Xue Zhang¹, Qiang Liu²

¹Department of Traditional Chinese Medicine, First Hospital of Qiqihar, Qiqihar 161000, Heilongjiang, China

²Department of Cardiothoracic Surgery, Qiqihar Traditional Chinese Medicine Hospital, Qiqihar 161000, Heilongjiang, China

Corresponding author: Qiang Liu (e-mail: xssxb007@163.com).

ABSTRACT Objective To investigate the association between thoracic irradiation (TIR) and the severity of coronary artery calcification (CAC) in patients with lung cancer, and to provide evidence-based basis for cardiovascular risk stratification and early intervention in lung cancer patients undergoing radiotherapy. **Methods** A retrospective cohort study design was adopted. A total of 126 patients with primary lung cancer who received thoracic radiotherapy in the oncology department of a tertiary hospital from January 2018 to December 2023 were consecutively enrolled as the radiotherapy group, and 126 lung cancer patients diagnosed during the same period but without radiotherapy were matched at a 1:1 ratio as the non-radiotherapy group. Propensity score matching was performed for baseline characteristics including age, sex, smoking history, hypertension, diabetes, dyslipidemia and tumor stage. The CAC score was semiquantitatively calculated by the Agatston method based on follow-up chest CT images obtained at least 12 months after radiotherapy, and the severity was classified into three grades according to the number of involved vessels: no calcification, single-vessel calcification and multi-vessel calcification. Dosimetric parameters of the radiotherapy group were collected, including mean heart dose (MHD), heart V₃₀ and left anterior descending artery (LAD) dose. Inter-group differences were compared using t-test, χ^2 test and rank-sum test. Multivariate ordinal Logistic regression was used to analyze the independent influencing factors of CAC severity.

Results The median CAC score in the radiotherapy group was significantly higher than that in the non-radiotherapy group [426.3 (IQR: 118.5–982.7) AU vs. 187.6 (IQR: 42.3–563.2) AU, $Z=-4.215$, $P<0.001$]. The proportion of multi-vessel calcification in the radiotherapy group was significantly higher than that in the non-radiotherapy group (46.0% vs. 27.0%, $\chi^2=10.286$, $P=0.006$). Multivariate ordinal Logistic regression analysis showed that after adjusting for age, hypertension, diabetes, dyslipidemia and smoking history, thoracic radiotherapy was an independent risk factor for increased CAC severity (OR=2.87, 95%CI: 1.64–5.02, $P<0.001$). In the subgroup analysis of the radiotherapy group, MHD ≥ 10 Gy (OR=2.31, 95%CI: 1.12–4.76, $P=0.023$) and LAD maximum dose ≥ 35 Gy (OR=2.05, 95%CI: 1.03–4.08, $P=0.041$) were independently associated with more severe CAC.

Conclusion Thoracic radiotherapy in lung cancer patients is independently associated with increased severity of coronary artery calcification, and patients with higher cardiac radiation dose tend to have greater CAC severity. Routine baseline CAC assessment before radiotherapy, optimization of cardiac dose constraints during treatment, and strengthened cardiovascular event monitoring and early intervention during follow-up are recommended.

INDEX TERMS lung neoplasms; radiotherapy; coronary artery calcification; Agatston score; retrospective cohort study; heart dose

I. INTRODUCTION

LUNG cancer is one of the malignant tumors with the highest morbidity and mortality worldwide. Radiotherapy is an important component of its comprehensive

treatment, especially for locally advanced non-small cell lung cancer (NSCLC), for which definitive chemoradiotherapy is the standard treatment regimen [1]. However, while killing tumor cells, thoracic radiotherapy inevitably

exposes the heart and coronary arteries to varying degrees of radiation, thereby inducing radiation-induced heart disease (RIHD) [2]. In recent years, with the prolongation of survival in lung cancer patients, radiotherapy-related cardiovascular complications have become an important cause affecting long-term quality of life and non-cancer mortality [3].

Coronary artery calcification (CAC) is an important marker of atherosclerosis, and its severity is closely related to the degree of coronary stenosis and the risk of future cardiovascular events [4]. As the gold standard for semi-quantitative assessment of CAC, the Agatston score has been widely used for cardiovascular risk stratification [5]. Previous studies have shown that the incidence of coronary artery disease (CAD) is significantly increased in patients with thoracic tumors after radiotherapy, and this increased risk is related to cardiac radiation dose [6-7]. A study by van der Palen *et al.* [8] found that the proportion of newly developed CAC in lung cancer patients after thoracic irradiation was significantly higher than that in matched non-irradiated controls, and radiation exposure was the only independent predictor of new calcification (OR=3.1, 95%CI: 1.09–9.2). However, existing studies have mostly focused on the incidence of new CAC, and there is still a lack of systematic investigation on the dose-response relationship between radiotherapy and CAC severity (including calcification score and number of involved vessels), particularly in domestic studies.

In addition, as a traditional cardiac dosimetric indicator, the value of mean heart dose (MHD) in predicting cardiac toxicity has been questioned, and an increasing number of studies have

emphasized the importance of radiation dose to cardiac substructures, especially coronary artery branches [9-10]. As one of the most important blood supply vessels of the heart, the relationship between the radiation dose of the left anterior descending artery (LAD) and radiation-induced coronary injury warrants in-depth investigation [11].

Accordingly, this study adopted a retrospective cohort study design, balanced baseline differences between groups through propensity score matching, systematically investigated the association between thoracic radiotherapy and CAC severity in lung cancer, and further analyzed the dose-response relationship between cardiac dosimetric parameters (MHD, heart V_{30} , LAD maximum dose) and CAC severity, aiming to provide a scientific basis for cardiovascular risk assessment, radiotherapy plan optimization and follow-up strategy development in lung cancer patients undergoing radiotherapy.

II. MATERIALS AND METHODS

A. STUDY DESIGN

This was a single-center retrospective cohort study, approved by the Hospital Ethics Committee, with waiver of informed consent. The technical route of the study is shown in Figure 1.

B. STUDY SUBJECTS

1) Radiotherapy Group

Patients with primary lung cancer who were diagnosed in the oncology department of our hospital and received thoracic radiotherapy from January 2018 to December 2023 were consecutively enrolled.

Inclusion criteria:

- ① Pathologically or cytologically confirmed primary bronchogenic carcinoma;
- ② Received thoracic radiotherapy (including definitive radiotherapy, palliative radiotherapy, or postoperative adjuvant radiotherapy; among them, 89 cases received definitive radiotherapy, 24 cases received postoperative adjuvant radiotherapy, and 13 cases received palliative radiotherapy);
- ③ Available follow-up chest CT images for CAC assessment at least 12 months after the end of radiotherapy;
- ④ Complete clinical data.

Exclusion criteria:

- ① Previous history of coronary stent implantation or coronary artery bypass grafting;
- ② Previous history of thoracic radiotherapy;
- ③ Concomitant other malignant tumors;
- ④ Poor CT image quality precluding CAC assessment;
- ⑤ Missing clinical data.

2) Non-Radiotherapy Group

Patients were selected from lung cancer patients diagnosed during the same period in our hospital but who did not receive radiotherapy, matched by propensity score matching at a 1:1 ratio.

Inclusion criteria:

- ① Pathologically or cytologically confirmed primary bronchogenic carcinoma;
- ② Did not receive any form of thoracic radiotherapy;
- ③ Available follow-up chest CT images for CAC assessment at least 12 months after diagnosis, with CT assessment time matched to the follow-up time of the radiotherapy group;
- ④ Complete clinical data.

Exclusion criteria: Same as the exclusion criteria for the radiotherapy group.

C. PROPENSITY SCORE MATCHING

Propensity score matching (PSM) was used to balance baseline characteristics between the two groups. With whether to receive radiotherapy as the dependent variable, and age, sex, smoking history, hypertension history, diabetes history, dyslipidemia, body mass index (BMI), tumor pathological type and tumor stage as independent variables, a Logistic regression model was constructed to calculate the propensity score. The nearest-neighbor matching method was adopted with a caliper value of 0.05 and a matching ratio of 1:1. A standardized mean difference (SMD) <0.1 after matching

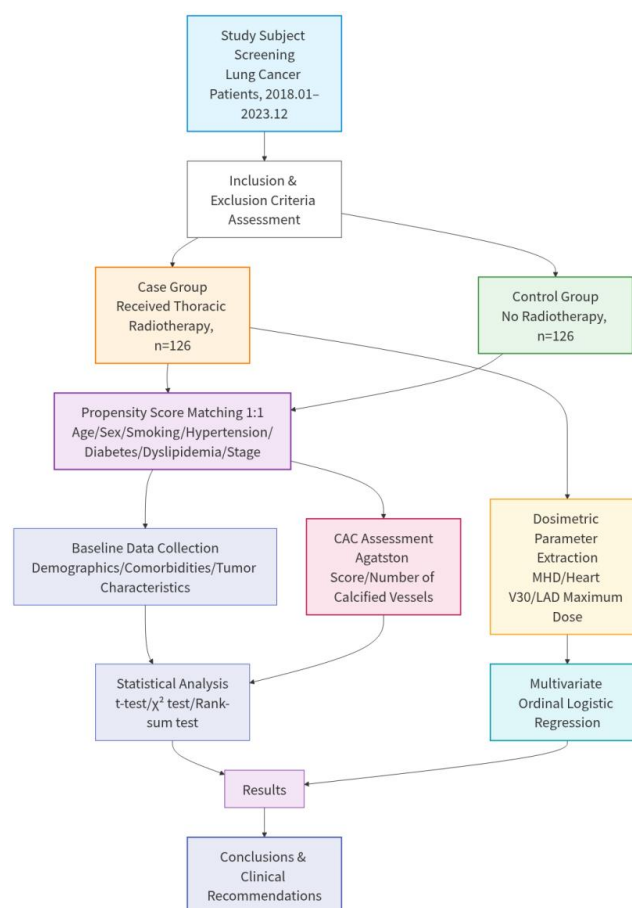


FIGURE 1. Technical route of the study

was considered to indicate good balance. The original radiotherapy group included 218 cases and the non-radiotherapy group included 356 cases; after 1:1 nearest-neighbor matching, 126 cases were included in each group, with matching efficiencies of 57.8% and 35.4%, respectively.

D. RADIOTHERAPY REGIMEN AND DOSIMETRIC PARAMETERS

All patients in the radiotherapy group received intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). The definitive radiotherapy dose was 60–66 Gy/30–33 fractions, the postoperative adjuvant radiotherapy dose was 50–54 Gy/25–27 fractions, and the palliative radiotherapy dose was 30–45 Gy/10–15 fractions.

The following dosimetric parameters were extracted from the treatment planning system (TPS):

- ① Mean heart dose (MHD);
- ② Heart V₃₀ (percentage of heart volume receiving ≥ 30 Gy);
- ③ LAD maximum dose (Dmax). The delineation of the heart and LAD was independently performed by two senior radiation oncologists on the planning CT, and consensus was reached through discussion when opinions differed.

E. CAC ASSESSMENT METHOD

All chest CT images were acquired using a 64-slice or higher spiral CT scanner with a slice thickness ≤ 3 mm. Two radiologists blinded to group assignment independently calculated the CAC score using the Agatston method [12]: calcified lesions (CT value ≥ 130 HU, area ≥ 1 mm²) were identified on CT images; the score of each calcified lesion = lesion area $\times$ density weighting factor (1 for 130–199 HU, 2 for 200–299 HU, 3 for 300–399 HU, 4 for ≥ 400 HU); the sum of scores of all calcified lesions was the total CAC score (unit: Agatston Unit, AU).

According to the CAC score, the degree of calcification was classified as [13]: 0 (no calcification), 1–10 (minimal calcification), 11–100 (mild calcification), 101–400 (moderate calcification), >400 (severe calcification). Meanwhile, according to the number of coronary artery branches involved by calcification, patients were classified as: no calcification, single-vessel calcification (involving one of the LAD, left circumflex artery, or right coronary artery), and multi-vessel calcification (involving ≥ 2 branches). The intraclass correlation coefficient (ICC) of the assessment results between the two physicians was 0.92 (95%CI: 0.88–0.95), indicating good consistency.

F. OUTCOME MEASURES

Primary outcome measures:

- ① Comparison of CAC scores between the two groups;
- ② Comparison of calcification severity grades and number of involved vessels between the two groups;
- ③ Analysis of independent influencing factors of CAC severity;
- ④ Relationship between cardiac dosimetric parameters and CAC severity in the radiotherapy group.

Secondary outcome measures:

- ① Comparison of baseline characteristics between the two groups;
- ② Distribution of calcification in each coronary artery branch.

G. STATISTICAL METHODS

Statistical analysis was performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA) and R 4.3.1 software. Normally distributed measurement data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and inter-group comparisons were performed using the independent samples t-test; non-normally distributed measurement data were expressed as median (interquartile range) [M (IQR)], and inter-group comparisons were performed using the Mann-Whitney U test. Categorical data were expressed as number (percentage) [n (%)], and inter-group comparisons were performed using the χ^2 test or Fisher's exact test. Rank-sum test was used for inter-group comparison of ordinal data.

With CAC severity (no calcification/single-vessel calcification/multi-vessel calcification) as the dependent variable, and variables with $P < 0.10$ in univariate analysis as well as clinically meaningful variables as independent variables, a multivariate ordinal Logistic regression model (proportional odds model) was constructed to calculate OR values and 95%CI. The proportional odds assumption was verified by the parallel lines test.

To further explore the relationship between dose and CAC severity, MHD was divided into 4 grades by quartiles (<7.2 , $7.2-11.8$, $11.8-16.5$, ≥ 16.5 Gy), and the Cochran-Armitage trend test was used to analyze the trend association between dose grade and CAC severity. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

III. RESULTS

A. COMPARISON OF BASELINE DATA BETWEEN THE TWO GROUPS

After propensity score matching, 126 patients were included in each of the radiotherapy group and the non-radiotherapy group. After matching, there were no statistically significant differences in baseline characteristics such as age, sex, smoking history, hypertension, diabetes, dyslipidemia, tumor pathological type and tumor stage between the two groups ($P > 0.05$), and the SMD of all variables was < 0.1 , indicating good balance. See Table 1.

B. COMPARISON OF CAC SCORES AND CALCIFICATION SEVERITY BETWEEN THE TWO GROUPS

The median CAC score in the radiotherapy group was 426.3 AU, which was significantly higher than 187.6 AU in the non-radiotherapy group, with a statistically significant difference ($Z = -4.215$, $P < 0.001$). According to CAC score grading, the proportion of severe calcification (> 400 AU) in the radiotherapy group was 38.1%,

which was significantly higher than 20.6% in the non-radiotherapy group ($\chi^2 = 10.052$, $P = 0.007$). According to the number of vessels involved by calcification, the proportion of multi-vessel calcification in the radiotherapy group was 46.0%, which was significantly higher than 27.0% in the non-radiotherapy group ($\chi^2 = 10.286$, $P = 0.006$). See Table 2 and Figure 2.

C. MULTIVARIATE ORDINAL LOGISTIC REGRESSION ANALYSIS OF CAC SEVERITY

With CAC severity (no calcification=0, single-vessel calcification=1, multi-vessel calcification=2) as the dependent variable, variables with $P < 0.10$ in univariate analysis (age, hypertension, diabetes, dyslipidemia, smoking history, whether to receive thoracic radiotherapy) were included in the multivariate ordinal Logistic regression model. The parallel lines test $P = 0.326$, satisfying the proportional odds assumption.

The results showed that after adjusting for age, hypertension, diabetes, dyslipidemia and smoking history, thoracic radiotherapy was an independent risk factor for increased CAC severity (OR=2.87, 95%CI: 1.64–5.02, $P < 0.001$). In addition, age (OR=1.04, 95%CI: 1.01–1.07, $P = 0.012$), hypertension (OR=1.85, 95%CI: 1.06–3.23, $P = 0.031$) and diabetes (OR=1.92, 95%CI: 1.03–3.58, $P = 0.040$) were also

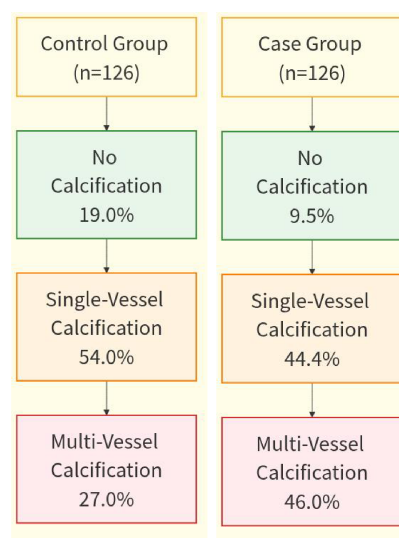


FIGURE 2. Comparison of the distribution of the number of coronary artery branches involved by calcification between the two groups

TABLE 1. Comparison of baseline data between the two groups of patients

Variable	Radiotherapy Group (n = 126)	Non-Radiotherapy Group (n = 126)	Statistic	P value	SMD
Age (years, $\bar{x} \pm s$)	62.3 $\pm$ 8.5	61.8 $\pm$ 8.9	$t = 0.462$	0.644	0.058
Sex [male, n (%)]	82 (65.1)	79 (62.7)	$\chi^2 = 0.155$	0.694	0.050
Smoking history [n (%)]			$\chi^2 = 0.071$	0.790	0.024
Never smoker	38 (30.2)	40 (31.7)			
Former smoker	52 (41.3)	50 (39.7)			
Current smoker	36 (28.6)	36 (28.6)			
Hypertension [n (%)]	45 (35.7)	42 (33.3)	$\chi^2 = 0.168$	0.682	0.051
Diabetes [n (%)]	28 (22.2)	25 (19.8)	$\chi^2 = 0.219$	0.640	0.059
Dyslipidemia [n (%)]	36 (28.6)	33 (26.2)	$\chi^2 = 0.180$	0.671	0.053
BMI (kg/m ² , $\bar{x} \pm s$)	23.8 $\pm$ 3.2	23.5 $\pm$ 3.4	$t = 0.728$	0.467	0.091
Pathological type [n (%)]			$\chi^2 = 0.312$	0.855	0.042
Adenocarcinoma	68 (54.0)	70 (55.6)			
Squamous cell carcinoma	45 (35.7)	43 (34.1)			
Small cell carcinoma	13 (10.3)	13 (10.3)			
Tumor stage [n (%)]			$\chi^2 = 0.526$	0.913	0.038
Stage I–II	32 (25.4)	34 (27.0)			
Stage III	68 (54.0)	66 (52.4)			
Stage IV	26 (20.6)	26 (20.6)			
Chemotherapy history [n (%)]	89 (70.6)	85 (67.5)	$\chi^2 = 0.286$	0.593	0.067
Follow-up time (months, M (IQR))	28.5 (16.2–42.3)	26.8 (15.5–40.1)	$Z = -0.684$	0.494	0.085

Note: SMD, standardized mean difference; BMI, body mass index.

TABLE 2. Comparison of CAC scores and calcification severity between the two groups

Variable	Radiotherapy Group (n = 126)	Non-Radiotherapy Group (n = 126)	Statistic	P value
CAC score [AU, M (IQR)]	426.3 (118.5–982.7)	187.6 (42.3–563.2)	$Z = -4.215$	< 0.001
CAC score grading [n (%)]			$\chi^2 = 17.836$	0.001
0 (no calcification)	12 (9.5)	24 (19.0)		
1–10 (minimal)	8 (6.3)	14 (11.1)		
11–100 (mild)	22 (17.5)	28 (22.2)		
101–400 (moderate)	36 (28.6)	34 (27.0)		
> 400 (severe)	48 (38.1)	26 (20.6)		
Number of calcified vessels [n (%)]			$\chi^2 = 10.286$	0.006
No calcification	12 (9.5)	24 (19.0)		
Single-vessel calcification	56 (44.4)	68 (54.0)		
Multi-vessel calcification	58 (46.0)	34 (27.0)		
LAD involvement [n (%)]	86 (68.3)	68 (54.0)	$\chi^2 = 5.584$	0.018
LCx involvement [n (%)]	52 (41.3)	38 (30.2)	$\chi^2 = 3.360$	0.067
RCA involvement [n (%)]	48 (38.1)	36 (28.6)	$\chi^2 = 2.562$	0.109

Note: CAC, coronary artery calcification; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; AU, Agatston Unit.

independently associated with increased CAC severity. See Table 3.

D. RELATIONSHIP BETWEEN DOSIMETRIC PARAMETERS AND CAC SEVERITY IN THE RADIOTHERAPY GROUP

Among the 126 patients in the radiotherapy group, the median MHD was 11.8 Gy (IQR: 7.2–16.5 Gy), the median heart V_{30} was 8.5% (IQR: 3.2–15.8%), and the median LAD maximum dose was 32.6 Gy (IQR: 18.5–45.2 Gy).

Comparison of dosimetric parameters by CAC severity groups showed that MHD, heart V_{30} and LAD maximum dose in the multi-vessel calcification group were significantly higher than those in the no calcification group and

the single-vessel calcification group ($P < 0.05$). See Table 4.

Furthermore, in the radiotherapy group, with CAC severity as the dependent variable, and MHD (< 10 Gy vs. ≥ 10 Gy), heart V_{30} ($< 10\%$ vs. $\geq 10\%$), LAD maximum dose (< 35 Gy vs. ≥ 35 Gy), as well as age, hypertension and diabetes as independent variables, a multivariate ordinal Logistic regression model was constructed. The results showed that $MHD \geq 10$ Gy (OR=2.31, 95%CI: 1.12–4.76, $P=0.023$) and LAD maximum dose ≥ 35 Gy (OR=2.05, 95%CI: 1.03–4.08, $P=0.041$) were independently associated with more severe CAC, while heart $V_{30} \geq 10\%$ did not reach statistical significance (OR=1.68, 95%CI: 0.86–3.28, $P=0.126$).

After dividing MHD into 4 grades by quartiles, the Cochran-Armitage trend test showed that with the in-

TABLE 3. Multivariate ordinal Logistic regression analysis of CAC severity

Variable	β	SE	Wald χ^2	P value	OR	95%CI
Age (years)	0.039	0.016	6.125	0.013	1.04	1.01–1.07
Hypertension	0.615	0.281	4.786	0.029	1.85	1.06–3.23
Diabetes	0.652	0.318	4.201	0.040	1.92	1.03–3.58
Dyslipidemia	0.412	0.276	2.228	0.136	1.51	0.88–2.59
Smoking history						
Never smoker	Reference				1.00	
Former smoker	0.328	0.305	1.158	0.282	1.39	0.76–2.53
Current smoker	0.486	0.324	2.251	0.134	1.63	0.86–3.08
Received thoracic radiotherapy	1.054	0.284	13.762	< 0.001	2.87	1.64–5.02

Note: Model goodness-of-fit test, Pearson $\chi^2 = 168.32$, $P=0.215$; Parallel lines test $P=0.326$. SE, standard error; OR, odds ratio; CI, confidence interval.

TABLE 4. Comparison of dosimetric parameters in patients with different CAC severity in the radiotherapy group

Dosimetric parameter	No Calcification (n = 12)	Single-Vessel Calcification (n = 56)	Multi-Vessel Calcification (n = 58)	Statistic	P value
MHD (Gy, M (IQR))	7.2 (4.5–10.1)	10.5 (6.8–14.8)	14.8 (9.5–20.2)	$H = 18.632$	< 0.001
Heart V ₃₀ (% M (IQR))	3.8 (1.2–7.5)	7.2 (2.8–13.5)	12.8 (5.6–20.5)	$H = 15.287$	0.001
LAD maximum dose (Gy, M (IQR))	22.5 (12.8–32.6)	28.6 (16.5–40.2)	38.5 (25.8–52.6)	$H = 12.856$	0.002
Prescribed dose (Gy, $\bar{x} \pm s$)	56.8 $\pm$ 8.5	58.2 $\pm$ 7.9	59.5 $\pm$ 7.2	$F = 1.025$	0.361
Radiotherapy technique [n (%)]				$\chi^2 = 1.286$	0.526
IMRT	8 (66.7)	38 (67.9)	36 (62.1)		
VMAT	4 (33.3)	18 (32.1)	22 (37.9)		

Note: MHD, mean heart dose; LAD, left anterior descending artery; IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy. Inter-group comparisons were performed using the Kruskal-Wallis H test or one-way analysis of variance.

crease of MHD grade, the proportion of multi-vessel calcification showed a significant upward trend (the proportions of no calcification/single-vessel/multi-vessel in Q1–Q4 were 16.7%/53.3%/30.0%, 12.9%/48.4%/38.7%, 6.5%/41.9%/51.6%, 3.2%/32.3%/64.5%, respectively; trend $\chi^2=11.82$, $P<0.001$), suggesting a dose-response trend between MHD and CAC severity.

IV. DISCUSSION

This study systematically investigated the association between thoracic radiotherapy and the severity of coronary artery calcification in lung cancer through a retrospective cohort design combined with propensity score matching. The results showed that lung cancer patients who received thoracic radiotherapy had significantly higher CAC scores than matched non-radiotherapy patients, a significantly higher proportion of multi-

vessel calcification, and radiotherapy was an independent factor associated with increased CAC severity. Further dosimetric analysis showed that MHD and LAD maximum dose were independently associated with CAC severity. These findings provide important clinical evidence for understanding the pathological mechanism of radiation-induced coronary injury and optimizing radiotherapy strategies for lung cancer.

A. ASSOCIATION BETWEEN RADIOTHERAPY AND CORONARY ARTERY CALCIFICATION

Coronary artery calcification is a product of atherosclerosis progressing to a certain stage, and its formation is a chronic and progressive process involving multiple links such as vascular endothelial injury, inflammatory response, smooth muscle cell apoptosis and calcium-phosphorus metabolism disorder [14]. This study found that the median CAC score in lung cancer patients who received thoracic radiotherapy was 2.3 times that of the non-radiotherapy group, and the proportion of severe calcification was nearly twice that of the non-radiotherapy group, suggesting that radiotherapy is significantly associated with increased severity of coronary atherosclerosis. This result is consistent with previous studies. A study by van der Palen et al. [8] in lung cancer patients found that the proportion of newly developed CAC in the thoracic irradiation group was significantly higher than that in the non-irradiation group ($P=0.007$), and calcification extension in the LAD region was more pronounced ($P=0.003$); multivariate analysis showed that radiation exposure was the only independent predictor of new calcification (OR=3.1, 95%CI: 1.09–9.2). The OR value of radiotherapy in this study was 2.87, which is close to the association strength between radiation exposure and new calcification reported in that study (OR=3.1), further supporting the independent association between radiotherapy and CAC severity. It should be noted that the outcome definitions of the two studies differ: van der Palen et al. focused on the risk of new calcification after radiotherapy, whereas this study

investigated the cross-sectional association of CAC severity, and the two cannot be directly equated.

The mechanisms by which radiotherapy may lead to coronary artery calcification include the following aspects [15-16]:

- ① Ionizing radiation directly damages vascular endothelial cells, leading to endothelial dysfunction and increased permeability, promoting lipid deposition and inflammatory cell infiltration;
- ② Radiation-induced chronic inflammatory response continuously activates macrophages and vascular smooth muscle cells, promoting cytokine release and oxidative stress, accelerating plaque formation;
- ③ Radiation induces phenotypic transformation and apoptosis of vascular smooth muscle cells, releasing vesicles and alkaline phosphatase, promoting hydroxyapatite crystal deposition and calcification;
- ④ Radiation damages collagen and elastic fibers in the vascular wall, disrupting the normal structure of the vascular wall and providing conditions for calcium deposition. A scientific statement from the American Heart Association (AHA) also noted that therapeutic radiation can lead to plaque rupture, thrombosis and accelerated atherosclerosis through the generation of free radicals and a pro-inflammatory state [17].

B. DOSE-RESPONSE RELATIONSHIP BETWEEN CARDIAC DOSIMETRIC PARAMETERS AND CAC

An important finding of this study is that MHD and LAD maximum dose are independently associated with CAC severity. Dichotomized analysis showed that when $MHD \geq 10$ Gy, the risk of increased CAC severity was elevated by 2.31 times; when LAD maximum dose ≥ 35 Gy, the risk was elevated by 2.05 times. Further dose-grade trend analysis showed that with the increase of MHD quartile grade, the proportion of multi-vessel calcification showed a significant upward trend (trend $\chi^2 = 11.82$, $P < 0.001$), suggesting a dose-response trend between MHD and CAC severity. This result emphasizes the importance of strictly limiting the radiation dose to the heart, especially the coronary arteries, in lung cancer radiotherapy planning.

As a traditional cardiac dosimetric indicator, MHD has long been used to predict radiation-induced heart injury. Multiple previous studies have shown that for every 1 Gy increase in MHD, the risk of major coronary events increases by approximately 7%–16% [18-19]. A secondary analysis of the RTOG 0617 study showed that survival in patients with locally advanced NSCLC was significantly associated with cardiac radiation dose [20]. However, in recent years, an increasing number of studies have questioned the predictive value of MHD, arguing that as a whole-heart average dose, MHD cannot reflect the dose distribution differences of cardiac substructures, especially the coronary arteries [9,21]. This study found that LAD maximum dose (a coronary-specific parameter) was independently associated

with CAC severity, while heart V_{30} (a whole-heart high-dose volume parameter) did not reach statistical significance. It is worth noting that MHD, as a whole-heart average dose parameter, was also independently associated with CAC, suggesting that the whole-heart average exposure level has strong collinearity with coronary dose. These results suggest that when assessing radiation-induced coronary injury, focusing on coronary-specific dose (especially LAD dose) may be more valuable than simply focusing on whole-heart high-dose volume (V_{30}). This is consistent with the findings of Gondi *et al.* [22], who found that a mean coronary dose > 7 Gy was associated with an increased risk of major adverse cardiovascular events and all-cause mortality.

As the main branch of the left coronary artery, the LAD supplies the anterior wall of the left ventricle, the anterior 2/3 of the interventricular septum and the apex, and is the most commonly involved vessel in coronary heart disease; its lesions often lead to severe clinical consequences. This study found that the proportion of LAD involvement in the radiotherapy group (68.3%) was significantly higher than that in the non-radiotherapy group (54.0%, $P = 0.018$), and LAD maximum dose ≥ 35 Gy was independently associated with more severe CAC, suggesting that special attention should be paid to LAD dose constraints in lung cancer radiotherapy planning. At present, there is no unified standard for dose limits of coronary artery branches. Some scholars have suggested that LAD V_{15} Gy should be $< 10\%$ or the mean dose should be < 5 – 10 Gy [23]. More large-sample prospective studies are needed in the future to establish dose constraints based on cardiac substructures.

C. CLINICAL SIGNIFICANCE AND RESEARCH IMPLICATIONS

The results of this study have important clinical significance. First, for lung cancer patients planned to receive thoracic radiotherapy, routine CAC score assessment before radiotherapy is recommended to identify populations at high cardiovascular risk. For patients with high baseline CAC scores, cardiac dose should be more strictly limited in the radiotherapy plan, and combined cardiovascular drug prophylaxis (such as statins, aspirin, etc.) should be considered [24]. Second, in radiotherapy plan design, in addition to the traditional MHD and heart V_{30} , dose parameters of coronary artery branches (especially LAD) should be incorporated into the plan

optimization objectives, and advanced radiotherapy techniques (such as IMRT, VMAT, proton therapy, etc.) should be used to minimize coronary radiation dose [25]. Finally, for lung cancer patients who have received thoracic radiotherapy, cardiovascular event monitoring should be strengthened during long-term follow-up, with regular electrocardiography, echocardiography and CAC score re-examination to achieve early detection and early intervention.

It is worth noting that age, hypertension and diabetes in this study were also independently associated with CAC

severity, which is consistent with the traditional understanding of cardiovascular risk factors [26]. This suggests that when assessing radiotherapy-related cardiovascular risk, patients' baseline cardiovascular risk factors should be comprehensively considered for individualized risk stratification and management. The 2023 expert consensus of the Society of Cardiovascular Computed Tomography (SCCT) also supports the use of CAC scoring for cardiovascular risk assessment and guidance of preventive therapy in cancer patients [27].

V. CONCLUSION

This study found through a retrospective cohort design and propensity score matching that thoracic radiotherapy in lung cancer patients is independently associated with increased severity of coronary artery calcification, and patients with higher cardiac radiation dose (especially MHD and LAD maximum dose) tend to have greater CAC severity, with dose-grade trend analysis supporting a dose-response trend between the two. These findings suggest that routine baseline CAC assessment should be performed before lung cancer radiotherapy, cardiac dose constraints should be optimized during radiotherapy (with special attention to LAD dose), and cardiovascular event monitoring and early intervention should be strengthened after radiotherapy, to reduce the risk of radiation-induced heart injury and improve the long-term quality of life of lung cancer patients.

REFERENCES

- [1] Chinese Society of Oncology and Chinese Medical Association Publishing House, "Chinese Medical Association clinical guidelines for the diagnosis and treatment of lung cancer (2024 edition)," National Medical Journal of China, vol. 104, no. 16, pp. 1169–1201, 2024.
- [2] M. X. Yang, W. T. Xu, R. R. Dai, et al., "Imaging manifestations and research progress of radiotherapy-related cardiovascular injury," Journal of Clinical Cardiology, vol. 40, no. 8, pp. 625–630, 2024.
- [3] W. Zhang, G. F. Li, and J. J. Wang, "Research progress on heart injury caused by radiotherapy for thoracic tumors," Chinese Journal of Radiation Oncology, vol. 32, no. 5, pp. 435–440, 2023.
- [4] J. Liu, Y. Zhang, and M. Zhang, "Clinical application value of coronary artery calcium scoring," Chinese Journal of Cardiology, vol. 50, no. 3, pp. 295–300, 2022.
- [5] A. S. Agatston, W. R. Janowitz, F. J. Hildner, et al., "Quantification of coronary artery calcium using ultrafast computed tomography," J Am Coll Cardiol, vol. 15, no. 4, pp. 827–832, 1990.
- [6] S. C. Darby, M. Ewertz, P. McGale, et al., "Risk of ischemic heart disease in women after radiotherapy for breast cancer," N Engl J Med, vol. 368, no. 11, pp. 987–998, 2013.
- [7] M. Chen, X. L. Fu, and G. L. Jiang, "Relationship between cardiac dose and cardiac complications in lung cancer radiotherapy," China Oncology, vol. 31, no. 8, pp. 745–752, 2021.
- [8] R. L. J. van der Palen, C. M. R. Zegers, E. C. Schimmel, et al., "Heart dose and coronary artery calcification in patients receiving thoracic irradiation for lung cancer," J Thorac Dis, vol. 12, no. 5, pp. 2256–2266, 2020.
- [9] J. J. Wang, H. Z. Zhang, and J. R. Dai, "Research progress on cardiac substructure dose in predicting radiation-induced heart injury," Chinese Journal of Radiological Medicine and Protection, vol. 43, no. 10, pp. 793–800, 2023.
- [10] A. McWilliam, E. Spezi, R. Pai, et al., "Moving beyond mean heart dose: The importance of cardiac substructures in radiation therapy toxicity," Acta Radiol, vol. 68, no. 5, pp. 974–986, 2024.
- [11] N. Yegya-Raman, M. Simon, S. Ganti, et al., "Understanding cardiac toxicity and immune responses to thoracic radiation therapy in non-small cell lung cancer – implications for future research," Cancers (Basel), vol. 14, no. 15, p. 3685, 2022.
- [12] B. He and C. Wang, "Application of chest CT in coronary artery calcification assessment," Chinese Journal of Tuberculosis and Respiratory Diseases, vol. 45, no. 6, pp. 580–585, 2022.
- [13] P. Greenland, M. J. Blaha, M. J. Budoff, et al., "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines," Circulation, vol. 139, no. 25, pp. e1082–e1143, 2019.
- [14] J. Li and Y. Zhang, "Pathogenesis and clinical significance of coronary artery calcification," Chinese Journal of Cardiology, vol. 51, no. 2, pp. 185–190, 2023.
- [15] F. Liu, J. Zhu, and L. H. Wang, "Research progress on pathophysiological mechanisms of radiation-induced heart injury," Chinese Journal of Radiation Oncology, vol. 31, no. 11, pp. 1098–1103, 2022.
- [16] A. Seaward, J. J. Kengwoung-Keumo, D. Gadi, et al., "Radiation-induced heart disease: current status and challenges," Cells, vol. 12, no. 15, p. 1994, 2023.
- [17] F. Rodriguez, K. J. Lavine, S. Ormaza, et al., "Coronary atherosclerosis in patients with cancer and survivors: a scientific statement from the American Heart Association," J Am Heart Assoc, vol. 15, no. 3, p. e031245, 2026.
- [18] L. H. Wang, X. L. Fu, M. Chen, et al., "Expert consensus on cardiac dose constraints in radiotherapy for locally advanced nonsmall cell lung cancer," Chinese Journal of Radiation Oncology, vol. 32, no. 3, pp. 185–192, 2023.
- [19] C. W. Taylor, Y. Zheng, P. Hall, et al., "Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous dose-response relationships," Int J Radiat Oncol Biol Phys, vol. 99, no. 4, pp. 927–935, 2017.
- [20] J. D. Bradley, R. Paulus, R. Komaki, et al., "Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-smallcell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study," Lancet Oncol, vol. 16, no. 2, pp. 187–199, 2015.
- [21] G. F. Li, J. J. Wang, and W. Zhang, "Limitations of mean heart dose in predicting cardiac toxicity of lung cancer radiotherapy and alternative indicators," Chinese Journal of Lung Cancer, vol. 26, no. 7, pp. 485–493, 2023.
- [22] V. Gondi, C. Shah, S. Hardy, et al., "Mean heart dose is an inadequate surrogate for left anterior descending coronary artery dose and the risk of major adverse cardiac events in lung cancer radiation therapy," Int J Radiat Oncol Biol Phys, vol. 111, no. 3, pp. 680–690, 2021.
- [23] H. Z. Zhang, J. J. Wang, and J. R. Dai, "Radiation dose constraints for cardiac substructures and radiotherapy plan optimization strategies," Chinese Journal of Radiological Medicine and Protection, vol. 44, no. 6, pp. 455–462, 2024.
- [24] Y. D. Chen and Q. H. Jin, "Prevention and management of cancer therapy-related cardiovascular toxicity," Chinese Journal of Cardiology, vol. 51, no. 4, pp. 345–352, 2023.
- [25] J. R. Dai and Y. M. Hu, "Progress and clinical application of intensity-modulated radiotherapy technology," Chinese Journal of Radiation Oncology, vol. 31, no. 9, pp. 825–832, 2022.
- [26] Y. Huo, J. B. Ge, and W. Y. Fang, "Chinese expert consensus on clinical application of coronary artery calcium scoring," Chinese Journal of Interventional Cardiology, vol. 31, no. 4, pp. 181–190, 2023.
- [27] J. Li, Y. Zhang, and Y. D. Chen, "Cardiovascular risk assessment and intervention of coronary calcification in elderly cancer patients," Chinese Circulation Journal, vol. 39, no. 8, pp. 785–792, 2024.